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Oxidation State-Specific Fluorescent Method for Palladium(II) and Platinum(IV) Based on the Catalyzed Aromatic Claisen Rearrangement

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Pd contamination in active pharmaceutical ingredients (APIs) and their synthetic intermediates is a severe problem in the pharmaceutical industry, because substantial efforts are needed to analyze and remove the residual metal.[1] Since Pd^0 and Pd^{II} bind to scavengers differently, it is informative to separately quantify these Pd species in synthetic samples to effectively remove these impurities.[2] Currently available analytical methods are not capable of quantifying residual Pd species in APIs in native oxidation states;[3] therefore, it is difficult, if not impossible, to troubleshoot the nonreproducible Pd scavenging without addressing oxidation states during API purifications. Thus, the development of methods to monitor Pd in an oxidation state-specific manner without altering oxidation states is warranted. Moreover, such methods would facilitate studies on Pd materials including colloid and polymer-bound catalysts.[4]

We previously demonstrated that the transformation of nonfluorescent compound **1** to green fluorescent compound **2** is highly specific for Pd and Pt and capable of sensitively detecting these metals by means of Tsuji−Trost type reactions.[5] We also noted the noncatalyzed Claisen rearrangement from **1** to fluorescent green-yellow compound **3** at 150 °C in organic solvents[6] and 100 °C in water (unpublished results). Since **3** is nearly as fluorescent as **2** and distinct spectral differences exist between them (**2**, $\lambda_{max} = 523$ nm; **3**, $\lambda_{max} = 535$ nm), we asked if this transformation could be catalyzed by metals in water at a lower temperature.

Although numerous metal species catalyze the aromatic Claisen rearrangement in organic solvents,[7] only in rare examples have metal species been shown to catalyze this transformation in water; therefore, we were unable to expect particular metal species to do so a priori. As such, we proceeded to screen for metals. Among the metal reagents tested, only $PdCl_2$ promoted this rearrangement at 50 °C after 4 h in 1:4 DMSO/pH 10 buffer, while none of the other reagents afforded **2** or **3** (Figure 1a). This reaction may proceed through the mechanism shown in Scheme 1,[8] indicating that this detection method is fundamentally different from our previous method. Although Pd^0 species should afford **2** rather than **3**, this needed to be confirmed.[9] Toward this end, we screened Pd reagents with various oxidation states. As Figure 1b shows, our detection method is oxidation state-specific and each Pd^{II} reagent and a Pd^{IV} reagent successfully performed the conversion from **1** to **3**[10] while Pd^0 and insoluble Pd species did not.[11]

Using $PdCl_2$, we examined the initial rate and the sensitivity of our method. The initial rate was measured in 1:1 DMSO/pH 10 buffer (Figure S2). The reaction continued to proceed even after 24 h (data not shown), indicating that longer incubation time would increase the sensitivity of this detection method proportionally since the fluorescence signal is generated catalytically with respect to the analyte.[10] The fluorescence intensity correlated to the concentration of Pd^{II} in the 0.5−50 μM (50 ppb−5 ppm) range (Figure 1b). The detection limit under these conditions was calculated as 3.9 μM (390 ppb) with a signal-to-background ratio (S/B) of 3. The S/B increased at a lower buffer concentration (Figure 1c).

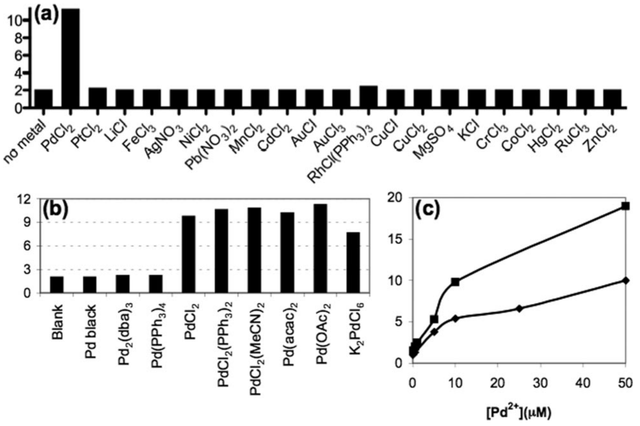
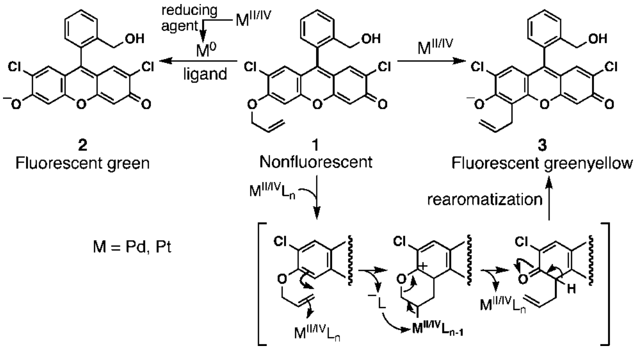


Figure 1. Fluorescence analysis after 4 h at 50 °C. [**1**] = 12.5 μM. The *y*-axis is fluorescence intensity (au × 10^5) at 535 nm. For example, “2” means 2 × 10^5. (a) Metal specificity. [metal] = 10 μM. (b) Pd species at various oxidation states. [Pd] = 10 μM. (c) Correlation between fluorescence intensity and [Pd^{II}]. ◆ = in buffer ([K^+] = 114 mM). ■ = in buffer ([K^+] = 11.4 mM).

Scheme 1. Pd/Pt Species-Dependent Deallylation or Claisen Rearrangement of **1**



We next examined the detection of Pd^{II} contamination in the presence of Pd^0 in functionalized organic compounds. Since this process requires the detection of Pd^{II} in the presence of a large excess of synthetic compound (500, 50, 5 ppm = 2000, 20 000, 200 000 equiv of compound with respect to Pd^{II}), we were originally skeptical about our own method because of such stoichiometry. Nonetheless, each compound (12.5 mg/mL) was spiked with Pd^0 (6 μM in solution) and varying amounts of Pd^{II} ([Pd^{II}] = 5−500 ppm relative to each compound; 0.6−60 μM in solution), treated with **1** and heated at 50 °C for 4 h in 1:4 DMSO/pH 10 buffer. Figure 2a shows that, although the absolute fluorescence fluctuated among samples (Figures S3a and S3c), for each organic compound the relative contents of Pd^{II} can be rapidly monitored to prioritize

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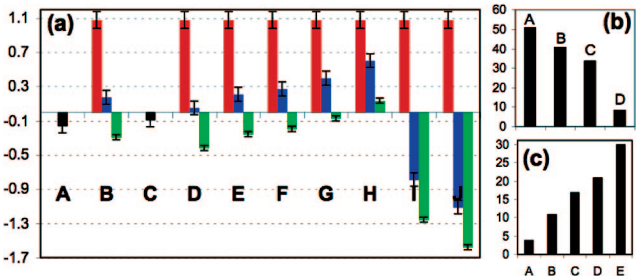

Figure 2. Pd^{II}-specific detection in the presence of synthetic samples and Pt^{IV} detection in water. For details, see text and Figure S3. (a) The *y*-axis is $\log_{10}$(fluorescence intensity (au × 10^5) at 535 nm) (normalized).[12] B, D-J: $[Pd^{II}] = 60$ μM (red), 6 μM (blue), 0.6 μM (green). A = background, B = Pd^{II} only, C = Pd^0 only, D = $Pd^{II} + Pd^0$. All organic compounds contain both Pd^{II} and Pd^0: E = thioanisole, F = cholesterol, G = 2-carboxy-7-hydroxycoumarin, H = morpholine, I = indole, J = *N*-methylephedrine. (b, c) The *y*-axis is fluorescence intensity (au × 10^5) at 535 nm. (b) Monitoring of Pt^{IV} (1 mM) reduction to Pt^0. Reduction time = 0 (A), 10 (B), 20 (C), 30 min (D). (c) Detection of Pt^{IV} in Pt^0-containing drinking water ($[Pt^0] = 250$ μM). $[Pt^{IV}] = 0$ (A), 0.5 (= 0.0975 ppb) (B), 5 (C), 50 (D), 500 nM (E).

scavenging methods and optimize the protocol in a high throughput manner without pretreatment. While indole at 12.5 mg/mL was found to quench the fluorescence signal of **3** (note: it does not quench at <1.3 mg/mL; see Figure S4), an electron-deficient indole was found to be compatible with this method (Figure S5). *N*-Methylephedrine presumably binds to Pd^{II} strongly and retards the metal-catalyzed Claisen rearrangement (example J).[10] Even with these types of compounds, the relative Pd concentrations can still be monitored during Pd scavenging because the relative fluorescence signal decreases as the Pd content decreases.[10]

On the basis of the similar π-electrophilicity between cationic Pd and Pt species, we asked if this method could be extended to Pt^{n+} detection. Pt^0 has been shown to be beneficial for human health due to its ability to catalytically quench reactive oxygen species to less toxic materials and is used in many health-related products including commercially bottled drinking water.[13] However, a major concern in manufacturing these products is contamination with Pt^{IV} because it is produced through the reduction of the more stable Pt^{IV} species and Pt^{IV} is highly toxic.

Although in our metal screening studies Pt^{II} did not produce fluorescence signal, we hypothesized that Pt^{IV} would be a more efficient catalyst because it is presumably more π-electrophilic.[14] Indeed, unlike $Pt^{0/II}$, Pt^{IV} catalyzed the Claisen rearrangement in water.[15] We applied this reaction for the Pt^0 manufacturing process to monitor the progress of the electrochemical reduction of Pt^{IV} to Pt^0 in water. As Figure 2b shows, our detection method is successful for fluorescently monitoring this reduction. We next used this fluorescence method to detect Pt^{IV} contamination in a Pt^0-containing drink. As Figure 2c shows, spiked Pt^{IV} was successfully detected by fluorescence in a concentration-dependent manner with a detection limit of 0.54 nM (0.11 ppb) with S/B of 3 in the presence of Pt^0 at 250 μM, which is 3-orders of magnitude more sensitive than that currently employed.[16]

In summary, we have demonstrated that fluorogenic probe **1** can detect $Pd^{II/IV}$ and Pt^{IV} via Claisen rearrangement to **3** even in functionalized compounds and Pt^0-water, each without sample preparation steps. This method may find application in the pharmaceutical industry, the environment, and Pd/Pt quality control.

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Supporting Information Available: Details of all fluorescence analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Garrett, C. E.; Prasad, K. *Adv. Synth. Catal.* **2004**, *346*, 889.
(2) (a) Galaffu, N.; Man, S. P.; Wilkes, R. D.; Wilson, J. R. H. *Org. Process Res. Dev.* **2007**, *11*, 406. (a) Welch, C. J.; Albaneze-Walker, J.; Leonard, W. R.; Biba, M.; DaSilva, J.; Henderson, D.; Laing, B.; Mathre, D. J.; Spencer, S.; Bu, X.; Wang, T. *Org. Process Res. Dev.* **2005**, *9*, 198. (b) Urawa, Y.; Miyazawa, M.; Ozeki, N.; Ogura, K. *Org. Process Res. Dev.* **2003**, *7*, 191.
(3) Electrochemical methods require chromatographic separation, during which Pd^0 can be oxidized to Pd^{II}. ICP−MS analysis and a method by the Anslyn group require acid treatment of samples. Houk, R. J. T.; Wallace, K. J.; Hewage, H. S.; Anslyn, E. V. *Tetrahedron* **2008**, *64*, 8271.
(4) (a) MacQuarrie, S.; Horton, J. H.; Barnes, J.; McEleney, K.; Loock, H.-P.; Crudden, C. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3279. (b) Köhler, K.; Kleist, W.; Pröckl, S. S. *Inorg. Chem.* **2007**, *46*, 1876. (c) Crudden, C. M.; Sateesh, M.; Lewis, R. *J. Am. Chem. Soc.* **2005**, *127*, 10045.
(5) (a) Song, F.; Garner, A. L.; Koide, K. *J. Am. Chem. Soc.* **2007**, *129*, 12354. For the absorption and emission spectra of **1** and **2**, see ref 6 and (b) Garner, A. L.; Koide, K. *Chem. Commun.*, in press. For the application of **1** for Pt detection, see: (c) Garner, A. L.; Koide, K. *Chem. Commun.*, in press.
(6) Koide, K.; Song, F.; de Groh, E. D.; Garner, A. L.; Mitchell, V. D.; Davidson, L. A.; Hukriede, N. A. *ChemBioChem* **2008**, *9*, 214.
(7) Majumdar, K. C.; Alam, S.; Chattopadhyay, B. *Tetrahedron* **2008**, *64*, 597.
(8) (a) van der Baan, J. L.; Bickelhaupt, F. *Tetrahedron Lett.* **1986**, *27*, 6267. (b) Schenck, T. G.; Bosnich, B. *J. Am. Chem. Soc.* **1985**, *107*, 2058.
(9) Itami, K.; Yamazaki, D.; Yoshida, J.-I. *Org. Lett.* **2003**, *5*, 2161.
(10) See Supporting Information.
(11) A similar observation was also made in organic solvent.[10]
(12) The data are normalized for 500 ppm Pd^{II} analogously to ICP−MS analysis, in which a standard curve is generated for Pd in each organic molecule separately. For more detail, see Supporting Information.
(13) (a) http://www.apt-ca.com. (b) Kajita, M.; Hikosaka, K.; Iitsuka, M.; Kanayama, A.; Toshima, N.; Miyamoto, Y. *Free Radical Res.* **2007**, *41*, 615.
(14) Barluenga, J.; Diéguez, A.; Fernández, A.; Rodríguez, F.; Fañanás, F. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 2091.
(15) There is one example from the literature reporting the Pt^{IV}-catalyzed Claisen rearrangement: Stewart, H. F.; Seibert, R. P. *J. Org. Chem.* **1968**, *33*, 4560.
(16) In a manufacturing facility, Pt^{IV} can be detected at 500 nM and above in the presence of Pt^0 at 250 μM. Minenobu Okayama, APt Co., personal communication; April 1 and May 16, 2008.

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