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ARTICLE TYPE

A Depropargylation-Triggered Spontaneous Cyclization Based Fluorescent "Turn-On" Chemodosimeter for the Detection of Palladium Ions and Its Application in Live-Cell Imaging

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A novel depropargylation-triggered spontaneous cyclization reaction based fluorescent turn-on chemodosimeter for the detection of palladium ions has been reasonably designed and developed. Based on the specific reactivity of palladium promoted hydrolysis reaction, the probe exhibited a high selectivity and sensitivity for palladium ions. Furthermore, the probe was successfully used for fluorescence imaging of Pd^{2+} in living cells.

Palladium, which is widely distributed in the environment due to its use in alloys, jewellery, dental crowns, fuel cells, chemical catalysts and especially in automobile catalytic converters.[1] Palladium are not biodegradable, and hence can be concentrated through the food chain. Excess palladium accumulation may result in degradation of DNA and cell mitochondria, allergic reactions, and also enzyme inhibition.[2] Therefore, the determination of palladium in environmental and biological samples is crucial both to the monitoring of environmental pollution and to the diagnosis of clinical disorders.

Whereas conventional techniques used for quantification of palladium species, such as atomic absorption spectroscopy, inductively coupled plasma atomic emission spectroscopy, and solid-phase microextraction high-performance liquid chromatography, usually suffer from the expensive and sophisticated instrumentation, and/or complicated sample preparation, and are therefore not suitable for real-time and in situ analysis.[3] In comparison with those conventional methods for palladium species, fluorescent probe techniques display apparent advantages because of their ease of application in solution as well as their high sensitivity to and selectivity for trace analytes with spatial and temporal resolution.[4]

Over the past several years, considerable efforts have been made to develop fluorescent probe for palladium ions based on the coordination of Pd^{2+} to heteroatom-based ligands, Pd^{2+} catalyzed ring-opening reaction, Pd^{2+} catalyzed oxidative cyclization reaction, and palladium catalyzed depropargylation and deallylation reaction (Fig. 1).[5] However, many of them still have limitations such as interference from other coexisting metal ions, long response time, and need additional reagents. Therefore, for practical applications, it is still strongly desirable to develop novel fluorescent probes

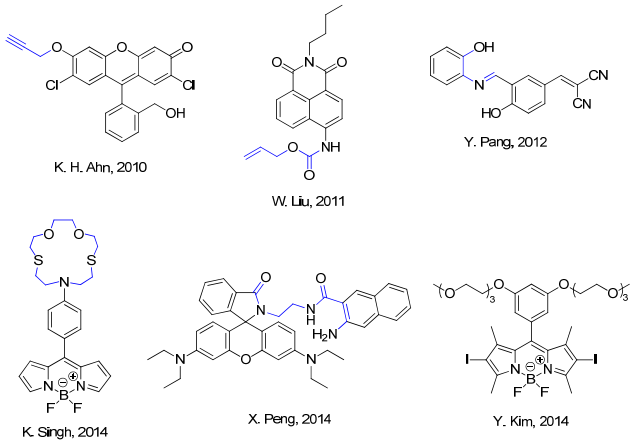
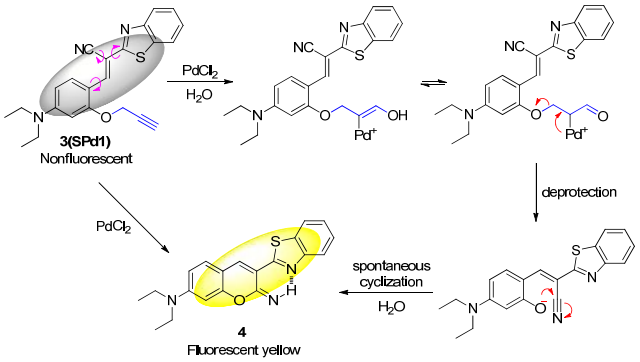


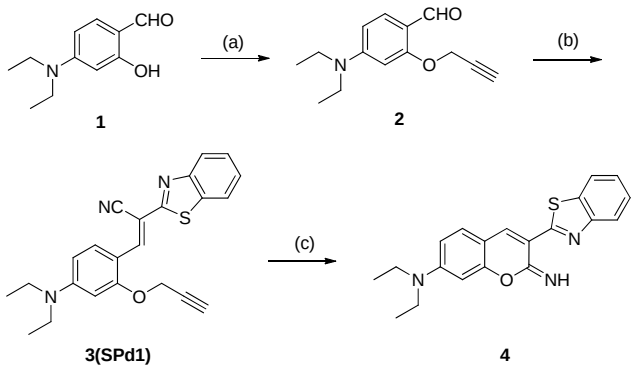
Fig. 1 Some reported palladium probes.

with high sensitivity, and quick response for real-time detection of palladium ions.

Herein, the aim of this work is to develop a new fluorescent probe with novel response mechanism for palladium ions. As shown in Scheme 1, probe **SPd1** was developed with coumarin precursor derivative and a terminal propargyl ether moiety. It is well known that the terminal propargyl ether can be cleaved by palladium-catalyzed hydrolysis reaction to generate the corresponding free hydroxyl group.[5d, 5m] We envisioned that the fluorescent intensity of the **SPd1** is greatly reduced due to the effect of intramolecular rotation. However, the deprotection of the propargyl ether group of **SPd1** by



Scheme 1 The "deprotection-cyclization" strategy for the design of **SPd1**.



Scheme 2 Synthesis of **SPd1**: (a) 3-bromopropyne/K_2CO_3, acetone, reflux, 12 h, 93%; (b) Et_3N, EtOH, rt, 12 h, 65%; (c) $PdCl_2$, THF-H_2O (1:1), rt, 3 h, 72%.

palladium ions promoted hydrolysis reaction would releases the hydroxy intermediate, which wills readily spontaneous cyclize to form a highly fluorescent coumarin derivative **4** (Scheme 1). To the best of our knowledge, this is the first example of depropargylation-triggered spontaneous cyclization based fluorescent chemodosimeter for the detection of palladium ions. Furthermore, **SPd1** can be successfully applied for Pd^{2+} imaging in living cells.

As shown in Scheme 2, **SPd1** can be readily prepared in two convenient steps under facile conditions with high yield starting with commercially available 4-(diethylamino)-2-hydroxybenzaldehyde. The product (**SPd1**) was well characterized by ^1H, ^{13}C NMR, and HR-MS (ESI†).

We firstly assessed the UV-vis spectroscopic properties of **SPd1** in PBS buffer solution (10 mM, pH 7.4, containing 50% EtOH). **SPd1** (20.0 μM) displayed a moderate UV-vis absorption around 474 nm. Upon incremental addition of Pd^{2+} (0-10.0 equiv.), the peak at 474 nm slightly decreased, and the absorption at 350 and 555 nm increased instantly with two clear isosbestic points at 452 and 502 nm, respectively, indicating that compound **4** was formed in the present of Pd^{2+} (Fig. 2). Furthermore, a good linear relationship was observed between the changes in the absorbance at 452 and 520 nm with Pd^{2+} in the range of 0-10.0 equiv. (Fig. S1, ESI†).

The emission spectra of **SPd1** and its fluorescent titration

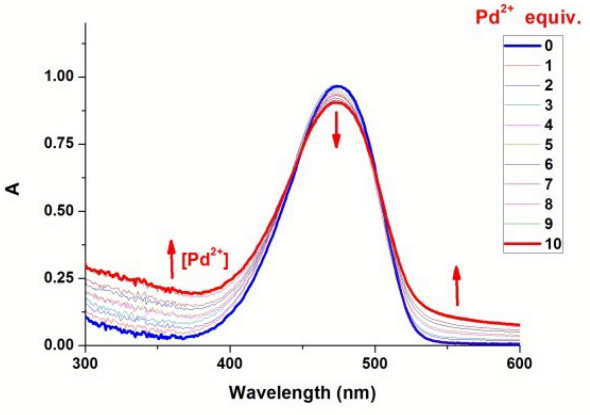


Fig. 2 Absorption spectra of **SPd1** (20.0 μM) in PBS buffer solution (10 mM, pH 7.4, containing 50% EtOH) in the presence of different concentrations of Pd^{2+} (0-10.0 equiv.).

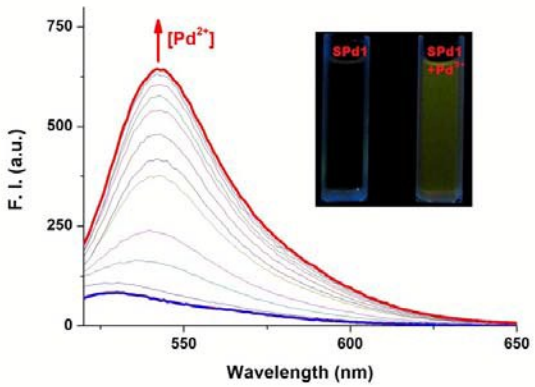


Fig. 3 Fluorescence spectra of **SPd1** (10.0 μM) in PBS buffer solution (10 mM, pH 7.4, containing 50% EtOH) in the presence of different concentrations of Pd^{2+} (0-150.0 μM) (λ_{ex} = 510 nm). Inset: cuvette images of probe **SPd1** before and after addition of $PdCl_2$ taken under a hand held UV-lamp (λ_{ex} = 365 nm).

with Pd^{2+} were recorded in PBS buffer solution (10 mM, pH 7.4, containing 50% EtOH) (Fig. S2, ESI†). As expected, **SPd1** alone is almost non-fluorescent (λ_{ex} = 510 nm, Φ = 0.004, Table S1, ESI†) due to the effect of intramolecular rotation (Scheme 1). However, upon progressive addition of Pd^{2+}, the emission band at 542 nm rapidly increased (Fig. 3), which was attributed to the cleavage of propargyl ether group by palladium ions-promoted hydrolysis followed by spontaneous cyclization reaction to form the highly fluorescent coumarin derivative **4** (Scheme 1). Moreover, the fluorescence titration curve revealed that the fluorescence intensity at 542 nm increased linearly with increasing concentration of Pd^{2+} (R^2 = 0.99213) (Fig. S3 and S4, ESI†) and further smoothly increased until a maximum was reached up to 100.0 μM Pd^{2+} (λ_{ex} = 510 nm, Φ = 0.023, Table S1, ESI†). Based on these results, the detection limit of **SPd1** for Pd^{2+} was calculated to be 9.3×10^{-8} M.[6] Owing to the specific reactivity of palladium ions-promoted hydrolysis reaction, **SPd1** displayed a high sensitivity toward Pd^{2+}.

The plausible mechanism of the palladium ions induced fluorescence response is shown in Scheme 1. Efforts were

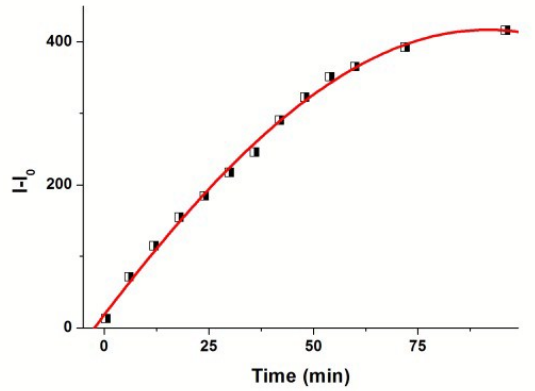


Fig. 4 Time-dependent fluorescence intensity changes of **SPd1** (10.0 μM) upon addition of Pd^{2+} (10.0 equiv.) in PBS buffer solution (10 mM, pH 7.4, containing 50% EtOH) (λ_{ex} = 510 nm).

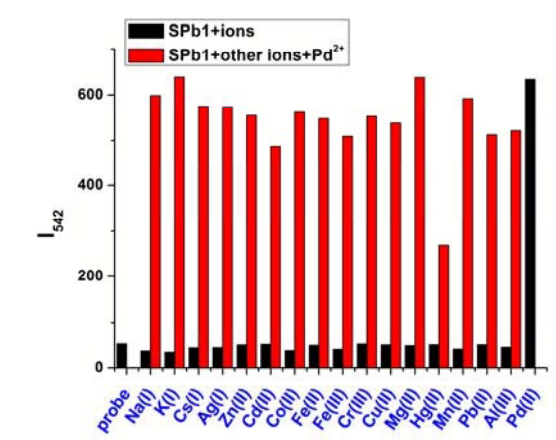


Fig. 5 Fluorescence responses of **SPd1** to various metal ions (including Na^+, K^+, Ag^+, Co^{2+}, Mn^{2+}, Al^{3+}, Cd^{2+}, Cr^{3+}, Cs^+, Cu^{2+}, Fe^{2+}, Fe^{3+}, Hg^{2+}, Mg^{2+}, Zn^{2+}, Pb^{2+}, and Pd^{2+}). Black bars represent the addition of 10.0 equiv. of the appropriate metal ions to a 10.0 μM solution of **SPd1** (in PBS buffer solution, 10 mM, pH 7.4, containing 50% EtOH). Red bars represent the addition of 10.0 equiv. of Pd^{2+} to the solutions containing **SPd1** (10.0 μM) and the appropriated metal ions (10.0 equiv.) (λ_{ex} = 510 nm).

then made to explore the nature of the palladium ions induced response. To this end, a comparison of fluorescent spectra between the **SPd1**-Pd^{2+} system and compound **4** was made to confirm the generation of **4** after treatment with Pd^{2+} (Fig. S5, ESI†). The ^{1}H NMR spectra of the isolated product of the **SPd1**-Pd^{2+} solution were also measured to support the depropargylation-triggered spontaneous cyclization of **SPd1** (see ESI†).

Subsequently, the time-dependence of fluorescence was also evaluated in the presence of Pd^{2+} in PBS buffer solution (10 mM, pH 7.4, containing 50% EtOH) (Fig. 4, ESI†). The result shows that the fluorescence of the tested solutions remarkably increased to the maximum value within 70 minutes. Accordingly, the observed rate constant (k_{obs}) for the formation of compound **4** has been calculated to be 2.4×10^{-2} min^{-1} (Fig. S6, ESI†).[7]

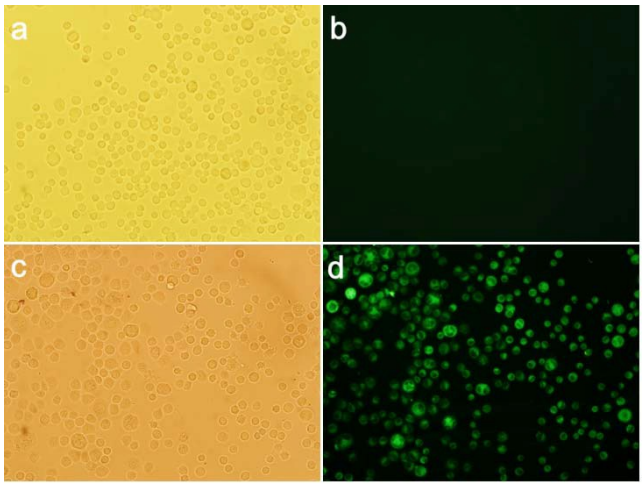


Fig. 6 Fluorescence image of HeLa cells incubated with **SPd1** (10.0 μM) for 0.5 h, and then washed quickly with PBS for imaging (b). The cells were then treated with $PdCl_2$ (30.0 μM) for 0.5 h which resulted in a dramatic increase in intracellular green fluorescence (d). (a) and (c) Bright-field images of live cells in (b) and (d).

Further, the fluorescence titration of **SPd1** with various metal ions was conducted to examine the selectivity (Fig. 5, and S7, ESI†). Much to our delight, the examined alkali, alkaline-earth metal ions, transition metal ions, and even Hg^{2+} showed nominal changes to the fluorescence spectra of **SPd1**. It should be mentioned that **SPd1** still responded to palladium ions sensitively even in the presence of other relevant competing ions (Fig. 5, and S8, ESI†). Therefore, these results suggest that **SPd1** displays high selectivity toward palladium ions in neutral aqueous solution.

Moreover, the palladium ions sensing ability of **SPd1** at a wide range of pH values was investigated. As depicted in Fig. S9, ESI†, **SPd1** alone was inert to pH in the range of 5.5-9.8. On the other hand, it readily reacted with palladium ions within the biologically relevant pH rang (6.5-8.5). These results indicate that **SPd1** could be used in living cells without interference from pH effects.

Due to the favorable properties of **SPd1** in vitro, the potential utility of **SPd1** in living cells was studied. HeLa cells were incubated with 10.0 μM of **SPd1** for 30 min at 37 ^{o}C and exhibited only weak fluorescence (Fig. 6b). The cells were then treated with $PdCl_2$ (30.0 μM) for 30 min at 37 ^{o}C, which resulted in a dramatic increase of intracellular green fluorescence (Fig. 6d). These obvious changes indicated that **SPd1** was cell membrane permeable and capable of image Pd^{2+} in living cells.

In conclusion, we have rationally developed a novel and simple depropargylation-triggered spontaneous cyclization based fluorescent chemodosimeter for the detection of palladium ions. The probe displayed a specific fluorescence response towards palladium ions under mild conditions with a low detection limit. Furthermore, fluorescence imaging of Pd^{2+} in living cells indicated that this probe might be favorable for biological applications.

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Notes and references

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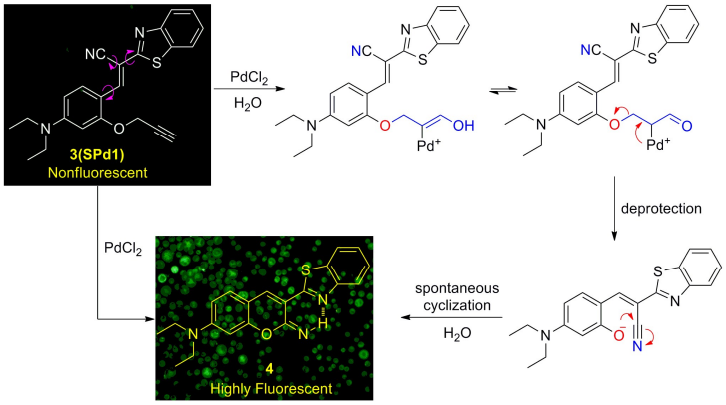

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