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A Rationally Designed Fluorescence Turn-On Probe for the Gold(III) Ion

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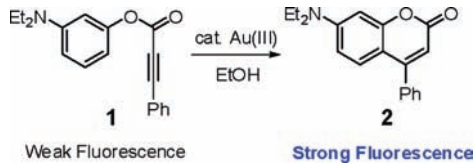
ABSTRACT



A latent fluorophore (1) was rationally designed to give rise to strong fluorescence through a selective gold ion-mediated hydroarylation reaction by a catalytic amount of the gold(III) ion. It is a highly selective and sensitive fluorescence turn-on probe for gold(III) ions and is operative even in protic solvents.

There is much current interest in gold with respect to its chemical properties. Gold ions are known to activate carbon−carbon multiple bonds, especially alkynes, toward nucleophilic addition. Owing to the characteristic alkynophilicity of the gold ion, a variety of organic transformations have been investigated by employing gold ions.[1] Gold ions also have anti-inflammatory properties and are used as pharmaceuticals in the treatment of arthritis and tuberculosis.[2]

Despite the interesting chemical and medicinal properties of gold ions, soluble gold salts such as gold chloride are known to cause damage to the liver, kidneys, and the peripheral nervous system.[3] Some gold ions, especially Au(III), are so tightly bound to a certain enzyme that they are reported to cause cell toxicity in living organisms.[4] Therefore, it is of great importance to develop gold ion probes to assess the quantity of environmental gold ions by luminescence methods. However, a few fluorescence probes for gold metal ions have been reported very recently using a propagylamide-derived rhodamine.[5] Herein, we report on a rationally designed latent fluorescence probe based on an apocoumarin,[6] which has shown an excellent selectivity and sensitivity toward the gold(III) ion with fluorescence turn-on in protic solvents.

In order to develop a fluorescent probe for gold ions, we designed an aryl alkyne compound (**1**), which is weakly fluorescent

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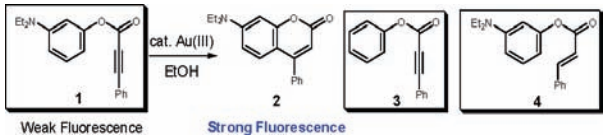
or nonfluorescent. The dialkylamino group is located for the intramolecular hydroarylation reaction in the para position of **1** with a Michael acceptor, and the phenyl ester functionality is introduced to cause a proper push−pull electronic effect on the fluorophore **2**. Therefore, the latent fluorophore (**1**) can be rearranged into the fluorescent **2** with strong fluorescence by a gold ion-mediated hydroarylation reaction (Scheme 1).[7]

Scheme 1. Latent Fluorophore (**1**) and Control Compounds



The syntheses of **1** and its analogues (**3** and **4**) were accomplished through EDC coupling reactions of each acid and the corresponding phenols (see the Supporting Information). The hydroarylation of **1** was monitored in ethanol[8] by applying a catalytic amount of Au(III) ion under a hand-held UV−vis lamp. A new thin-layer chromatography (TLC) spot at R_f 0.30 (EtOAc/Hex, 1:4, v/v) below that of **1** (R_f 0.57) appeared upon the addition of 10 mol % of Au(III) ion to **1** (Figure 1A). The TLC chromatogram displayed

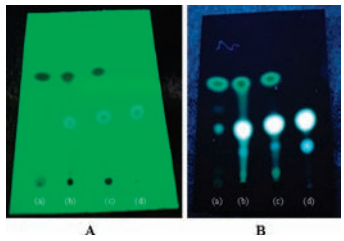


Figure 1. Time-dependent UV−vis (A) and fluorescence (B) chromatograms of **1** (0.20 M) in ethanol with 10 mol % of Au(III) ions: (a) 0 min, (b) 10 min, (c) 30 min, and (d) **2**.

bright fluorescence under the UV−vis light at λ_{ex}365 nm (Figure 1B). After the reaction was complete, the fluorescent compound was separated by column chromatography and proven to be a hydroarylation product (**2**), whose structure was confirmed by ^{1}H and ^{13}C NMR and mass spectral analyses (Figure S2 in the Supporting Information). Noticeably, the hydroarylation reaction was not undergone with compound **4** with an alkene moiety, nor did the alkyne ester analogue (**3**) show any detectable transformation in the presence of Au(III) ions (Figure S5, Supporting Information). These control experiments indicate that both the alkyne and the diethylamino groups of **1** are important for the gold(III)-catalyzed hydroarylation.

Probe **1** has a UV absorption maximum centered at 263 nm ($\varepsilon = 4.29 \times 10^4$ M^{-1} cm^{-1}) and exhibits negligible fluorescence. The addition of the Au(III) ion triggers a prominent bathochromic shift (ca. 130 nm) to λ_{max} 390 nm ($\varepsilon = 1.98 \times 10^4$ M^{-1} cm^{-1}) with an apparent isosbestic point at 333 nm (Figure 2). The rate constant for the conversion of **1** (30 μM) to **2** in ethanol was measured in the presence of the gold(III) ion (10 equiv) and estimated to be $k_{obs} = (3.31 \pm 0.62) \times 10^{-5}$ s^{-1}, whereas other metal ions such as Hg(II), Pd(II), Pt(II), Cd(II), Cu(II), Zn(II), Cu(I), Ag(I), and Au(I) did not induce any significant spectral changes even in the presence of 100 equiv of metal ions.

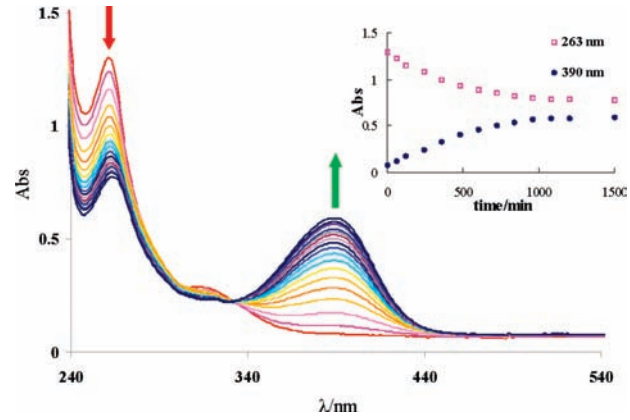


Figure 2. UV−vis spectral changes and its kinetics (inset) upon addition of 10 equiv of Au(III) to **1** (30 μM) in EtOH.

The fluorescence responses of the latent fluorophore **1** (30 μM in EtOH) were examined after each addition of various metal ions. The fluorescence spectra have shown a large Stokes shift (~100 nm), enough to block the spectral cross talk between **1** and **2**.[9] Fluorescence intensity at 488 nm was dramatically increased ca. 60 times by the Au(III) ion and 4.6 times by the Ag(I) ion, whereas other metal ions did not induce any significant fluorescence changes (Figure 3). Competitive fluorescence experiments have also corroborated the selectivity of **1** toward the Au(III) ion. The fluorescence was turned on again when the gold(III) ions were added to the nonfluorescent mixtures of **1** and other metal ions (Figure S7, Supporting Information). It is noticeable that **1** is inert to the Lewis acids like copper(II) or zinc(II) ions as well as other electrophilic metal ions such as Pd(II), Pt(II), and Cu(I). To our surprise, the Au(I) ion did not turn on the fluorescence of **1** even though 10 equiv of PPh_3AuCl was added to **1** in ethanol. This suggests the latent fluorophore **1** can be a useful probe for the gold(III) chloride without any activation of gold ions[10] because there is possibly a significant interaction between the more highly charged gold(III) ion and the alkyne

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(8) The Au(III)-catalyzed reaction was dependent on solvents. The initial rate analysis showed that the rate in dichloromethane was about 2-fold slower than ethanol (Figure S6 in the Supporting Information).

(9) Anslyn, E. V.; Dougherty, D. A. *Modern Physical Organic Chemistry*; University Science Books: Sausalito, 2006.

1 compared to gold(I) in a protic solvent as similarly observed in the gold ion−enzyme interaction.[11] The fluorescence turn-on of **1** was apparently observed to the naked eye for the gold(III) ion under a UV lamp (λ_{ex} 365 nm), whereas the fluorescence for other metal ions was not clearly observed (Figure S8, Supporting Information).

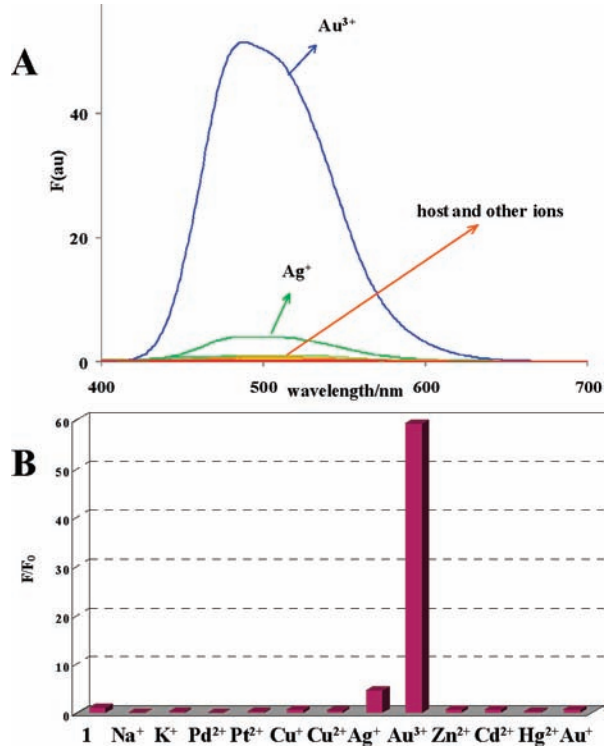

Figure 3. (A) Fluorescence spectra of **1** (30 μM, λ_{ex} 390 nm) in EtOH upon addition of various metal ions (10 equiv of Au^{3+} and Au^{+}, whereas 100 equiv of other ions). (B) Relative fluorescence responses at λ_{em}488 nm, where F_0 is the intensity of **1** only.

A sensitivity curve of **1** toward gold(III) ions was obtained by measuring the emission spectra of **1** (10 μM in EtOH, λ_{em} 488 nm) according to the varying concentrations of gold ions. The fluorescence intensity of **1** was almost *fully expressed* even in the presence of 0.1 equiv of Au(III) ions. It increases linearly over the concentration ranges from 20 to 100 ppb of gold(III) ions, with a limit of detection (LOD) of 64 ppb of the Au(III) ion (Figure S9, Supporting Information[12] Gold(III) ions are reported as toxic as over 90% of K562 human cells are dead at a concentration of 40 ppm.[4c] Therefore, probe **1** is sensitive enough to distinguish the toxic levels of gold.

Fluorescence microscopic imaging for the Au(III) ion-mediated hydroarylation of **1** was successful using the HaCaT cells in a PBS buffer (Figure 4). Cells exposed to 10 μM of the Au(III) ion and stained with **1** (50 μM) were clearly observed as fluorescent in the cytoplasm when viewed through a confocal microscope, whereas those treated with the Au(III) ions or **1** only were not fluorescent.

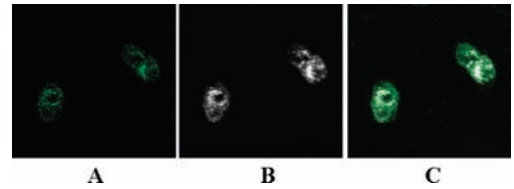

Figure 4. Fluorescence images of HaCaT cells (×600) after 30 min incubation with Au(III) ions (10 μM) and 10 min with **1** (50 μM) in PBS buffer: (A) fluorescence images (λ_{ex}= 405 nm, λ_{em} = 505−530 nm); (B) bright field images; (C) their overlay images.

From the chromatographic and spectroscopic evidence (TLC, NMR,and fluorescence data), we propose a plausible mechanism for the gold-catalyzed hydroarylation (Figure 5). Latent fluorophore **1** is activated by a reactive and alkynophilic Au(III) ion, followed by the intramolecular electrophilic aromatic substitution with a Michael acceptor, and will complete the hydroarylation reaction to afford a fluorescent probe **2**, where the gold(III) ion is regenerated.

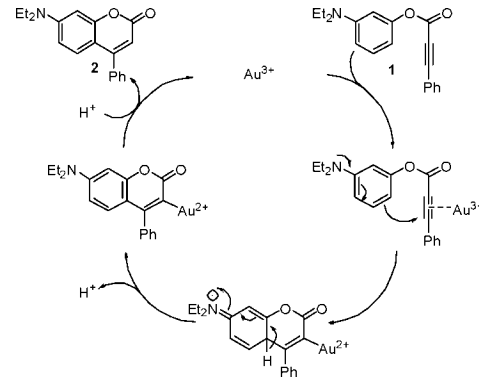

Figure 5. Proposed gold-mediated hydroarylation of **1**.

In conclusion, we have rationally designed a highly selective and sensitive fluorescent probe for the gold(III) ion using a latent fluorophore, which is operating in protic solvents and shows a fluorescence turn-on property through a selective gold(III)-mediated hydroarylation reaction. The application of the latent fluorophore to an effective catalyst screening is the subject of ongoing research.

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Supporting Information Available: Experimental procedure and selected spectral data for compounds **1**−**4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Most of the gold(I) ions are used by the in situ activation of Ph_3PAuCl with $AgSbF_6$.

(11) Lee, M.-T.; Ahmed, T.; Haddad, R.; Friedman, M. E *J. Enzyme Inhibition* **1989**, *3*, 35.

(12) We obtained the LOD as the concentration of gold ions at F/F_0 = 3, which is similar to the analytical definition of 1.