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COMMUNICATION

Furanyl Bis(indolyl)methane as a Palladium Ion-Selective Chromogenic Agent

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The colorless solution of furan-2-yl bis(indolyl)methanes (BIMs) were newly reveled to work as palladium (Pd^{2+}) ion-selective chromogenic agent to turn orange. 5-(*N*-methyl-*N*-phenyl-aminomethyl)-furan-2-yl BIM could be synthesized from 5-chloromethylfurfural as a biorenewable feedstock via one pot and double functionalizations, and a mixture of its solution and Pd^{2+} ion indicated the highest absorbance at 465 nm in UV-Vis analysis. On the other hand, other metal ions (Cu^{2+}, Cr^{2+}, Cr^{3+}, Fe^{2+}, Fe^{3+}, Ni^{2+}, Zn^{2+}, In^{2+}, Pt^{2+}, or Ce^{3+}) possessed no response.

Divalent palladium salts ($PdCl_2$ etc.) are widely utilized as catalysts, precursors, or precatalysts for organic reactions, such as cross-coupling reactions,[1] C-H activation,[2] deuterations,[3] and so on.[4] However, the Pd residues in the products may be problematic because of their biotoxicity.[5] Although Pd residues can be detected using atomic absorption spectroscopy,[6] total reflection X-ray fluorescence,[7] HPLC,[8] capillary zone electrophoresis,[9] and inductively coupled plasma mass spectrometry[10], specific analytical devices and cumbersome pretreatments are usually required. Therefore, the chromogenic (visualizing) agents that can detect palladium (Pd^{2+}) ions via changes visible by the naked eye have attracted attention as convenient materials.[11]

Bis(indolyl)methanes (BIMs) are the fundamental backbones that function as colorimetric anion-selective sensors,[12] bioactive compounds,[13] heterogeneous catalysts,[14] and other materials.[15] As a chromogenic agent, phenyl BIM solution has been reported to possess Cu^{2+} ion-selective property, while Li^+, Na^+, K^+, Mg^{2+}, Ca^{2+}, Ni^{2+}, Zn^{2+}, Cd^{2+}, Hg^{2+}, Pb^{2+}, Sm^{3+}, Eu^{3+}, Yb^{3+}, and Lu^{3+} ions were insensitive to the solution (Figure 1A; Pd^{2+} ion was not tested).[16] Additionally, Hg^{2+} ion was selectively responsive when using 5-(4-methoxyphenyl)-furan-2-yl BIM solution and no response toward Ca^{2+}, Cr^{3+}, Fe^{2+}, Fe^{3+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+}, and Pd^{2+} ions was observed.[17] Herein, we demonstrate that the colorless solution of 5-(*N*-methyl-*N*-phenyl-aminomethyl)-furan-2-yl BIM (**4a**) can function as a Pd^{2+} ion-selective chromogenic agent, turning orange (Figure 1B). **4a** was easily synthesized from 5-chloromethylfurfural (**1**; 5-CMF) as a biorenewable feedstock by acid-catalyzed nucleophilic addition of indole (**2a**) to the formyl group on **1** and the subsequent nucleophilic substitution of *N*-methylaniline (**3a**) with the chloromethyl group on **1** in a one-pot manner.

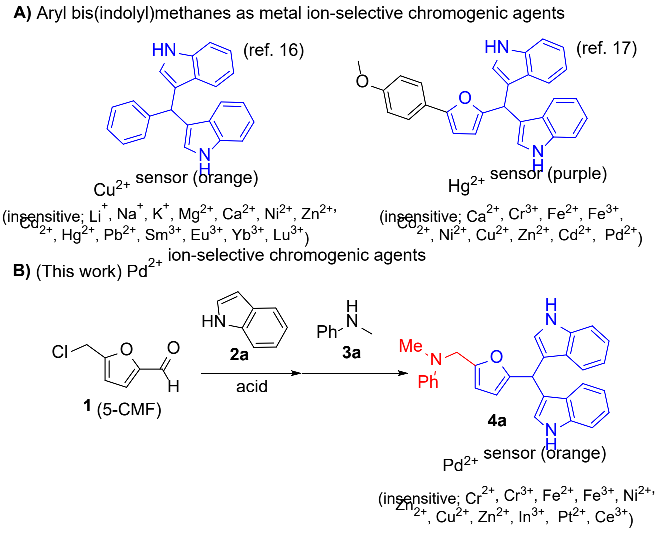

Figure 1. Aryl bis(indolyl)methanes as metal ion-selective chromogenic agents

In organic chemistry, recently, the development of functional materials using biorenewable feedstocks are spotlighted.[18] 5-CMF (**1**), industrially prepared from cellulose, glucose, fructose etc., are recognized as useful and natural

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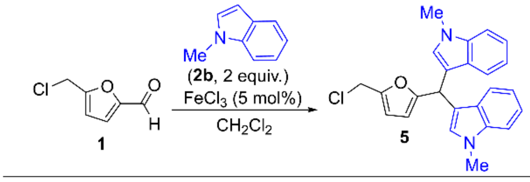
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x resources to synthesize raw materials for polymers, bioactive compounds and so on.[19] However, the reactive control toward the nucleophiles would be difficult, because **1** possesses two electrophilic moieties; formyl and chloromethyl groups. To evaluate this novel chromogenic agent, 5-amine unit-substituted furan-2-yl BIM derivatives that coordinate with metal ions were designed. The reaction of **1** with *N*-methyl indole (**2b**; 2 equiv.) to the BIM skeleton (**5**) were examined (Figure 2A; Table 1). $FeCl_3$-catalyzed nucleophilic addition of **2b** to formyl group on **1** proceeded at -20 °C to yield 66% NMR yield of **5** (entry 2; **5** could not be isolated probably due to instability of chloromethyl group), while the reaction occurring at 0 °C led complex mixture owing to no selectivity between formyl or chloromethyl group as nucleophilic positions (entry 1). A decrease in the reaction temperature to -40 °C slightly improved the yield of **5** to 71% (entry 3). During the nucleophilic addition of the two indoles to the formyl group of **1**, H_2O was generated via the formation of iminium intermediate **B**[20] (Figure 2B). A concerted reaction mechanism via S_N2-type's direct nucleophilic substitution of **A** with **2b** is also considerable. This generation of H_2O causes the hydrolysis of the chloromethyl group, decreasing the yield of **5**. Therefore, the addition of molecular sieves to capture H_2O improved reaction efficiency, affording **5** in 83% yield (Table 1, entry 4; The results using other drying reagents were described in Table S3). **5**, generated in entry 4, underwent further nucleophilic addition of *N*-methyl aniline (**3a**) to afford 5-(*N*-methyl-*N*-phenyl-aminomethyl)-furan-2-yl bis(*N*-methylindolyl) methane (**4b**) in 80% yield in a one-pot manner (Figure 2C).

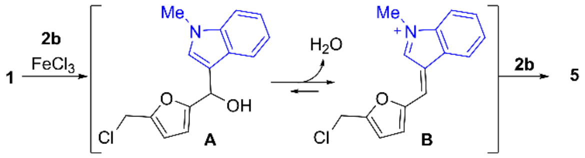
A) Table 1. Construction of BIM skeleton from **1**.



entry	conditions	Yield (%)[a]	
		1	5
1	0 °C (2 h)	Complex mixture	
2	-20 °C (3 h)	6	66
3	-40 °C (2 h) to -20 °C (1 h)	2	71
4[b]	-40 °C (4 h)	1	83

[a] The yield was determined by ^1H NMR using dibromomethane as an internal standard. [b] MS 4A were added.

B) Proposed pathway in transformation of **1** and **2b** to **5**.



C) One-pot transformation of **1** to **4b**.

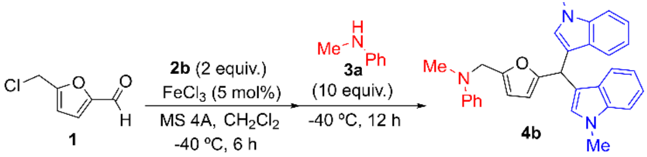
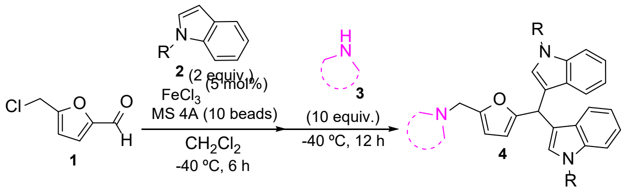
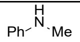
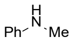
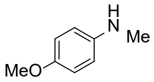
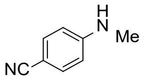
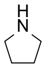


Figure 2. Transformation of **1**.

As mentioned later (Figure 5), **4b**, derived from *N*-methyl indole (**2b**), could not be used as a Pd^{2+} ion sensor, and *N*-free indole (**2a**) have to be introduced into the furan-2-yl BIM skeleton. Although **2b** was the first nucleophile to afford **4b** in high yield in the presence of $FeCl_3$ (Table 2, entry 1 (Figure 1A and 1C)), the reactions using **2a** did not proceed smoothly to afford **4** in low yields (entries 2-5). However, the corresponding 5-amine unit-substituted furan-2-yl BIM derivatives (**4a, 4c**-**4e**) were obtained from **3a**, *N*-methyl-4-methoxyaniline (**3b**), *N*-methyl-4-cyanoaniline (**3c**), and pyrrolidine (**3d**) to evaluate the chromogenic properties (**4c**-**4e** possessed the least chromogenic properties, see Figure S4). The yield of **4a** could be improved by using montmorillonite K10 instead of $FeCl_3$ as the acidic catalyst (the screening results are shown in Table S1 and S2). The use of other nucleophiles (NaOMe or aniline) for the second step gave no desired products. As comparative control compounds to evaluate the chromogenic properties, furan-2-yl bis(indolyl)methane (**6a**), 5-hydroxymethyl-furan-2-yl bis(indolyl)methane (**6b**), phenyl bis(indolyl)methane (**6c**), 1,1-bis(indolyl)hexane (**6d**), and diindolylmethane (**6e**), shown in Figure 4, were respectively prepared by the reported methods (See ESI).

Table 2. Substrate scope



entry	R	3	yield (%)
1	Me (**2b**)	 (**3a**)	80 (**4b**)
2	H (**2a**)	 (**3a**)	35 (55)[a](**4a**)
3	H (**2a**)	 (**3b**)	30 (**4c**)
4	H (**2a**)	 (**3c**)	17 (**4d**)
5	H (**2a**)	 (**3d**)	27 (**4e**)

[a] montmorillonite K10 (10 mg) was used instead of $FeCl_3$ as acid catalyst.

The chromogenic property of **4a** in MeCN/H_2O (7:3) solution was evaluated by the addition of a solution of various metal salts ($PdCl_2$, $CuCl_2$, $CrCl_2$, $CrCl_3$, $FeCl_2$, $FeCl_3$, $NiCl_2$, $ZnCl_2$, $InCl_2$, $PtCl_2$, or $CeCl_3$) at the ratio of 1/4 for **4a**/metal ion. After 1 h, a significant color change was observed by the naked eye when mixing **4a** and $PdCl_2$ (Figure 3A). The colorless solution of **4a** turned orange. UV-Vis analysis also observed an absorbance peak at 465 nm only for $PdCl_2$ [Figure 3B; The UV-Vis absorption using a lower concentration of Pd^{2+} ion solution with **4a** was also investigated (Figure S3)].

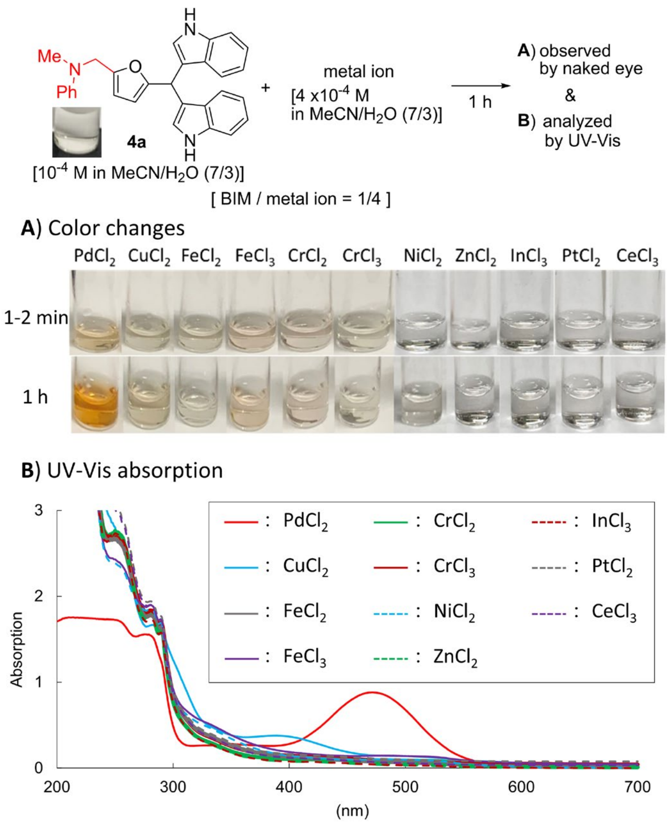


Figure 3. Chromogenic property of **4a** toward various metal ion.

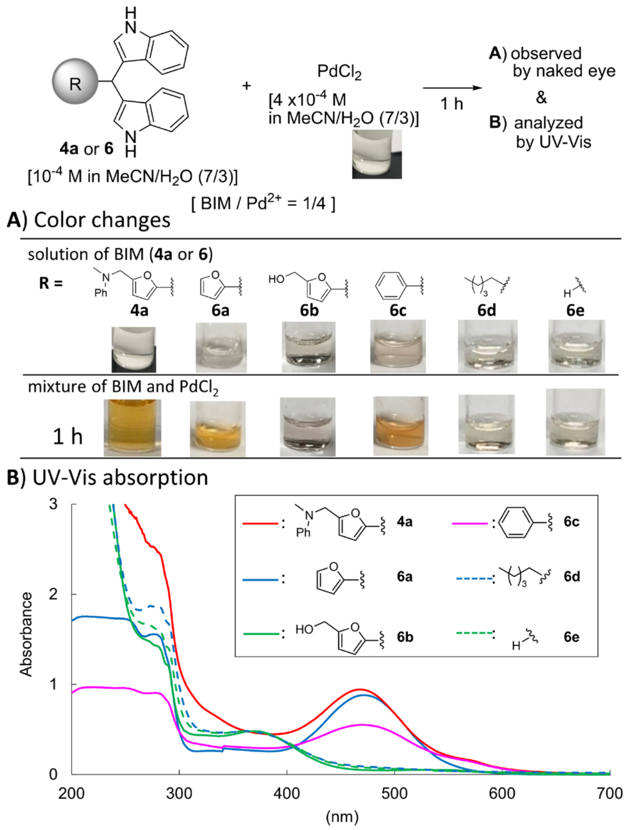


Figure 4. Substituent effects on BIMs

The substituent effects on BIMs were further evaluated by mixing the solution of **4a** or **6a**-**6e** with $PdCl_2$. Color changes were visually observed when using compounds **4a**, **6a**, and **6c**, while **6b**, **6d**, and **6e** were ineffective in exhibiting visual color change (Figure 4A). These results indicate that aromatic moieties substituted into the BIM skeleton are important for chromogenic properties, similar to the reported compounds shown in Figure 1A. In the case of **6b**, the free hydroxy group may strongly coordinate with the Pd^{2+} ion to inhibit the chromogenic property of the BIM skeleton. UV-Vis analysis clearly indicated a difference in color contrast upon the addition of each compound (Figure 4B). The absorbance intensity of **4a** was the highest, and the intensity decreased in the order **4a** (465 nm) > **6a** (472 nm) > **6c** (470 nm) > **6b**, **6d**, and **6e**. The furanyl group was important for increasing the chromogenic properties, and 5-(*N*-methyl-*N*-phenyl-aminomethyl) group of **4a** slightly enhanced the intensity compared to that of **6a** (**6a** also has Pd^{2+} ion selectivity, see Figure S4). The absorption maxima of **4a**, **6a** and **6c** shown in Figure 4b are identical, which assumes that similar types of complexes were formed. However, the reason for the enhancement by 5-(*N*-methyl-*N*-phenyl-aminomethyl furan-2yl group is unclear at this stage, and elucidation using time-dependent density functional theory calculations is currently underway.

The *N*-free indole moiety of **4a** was essential for its chromogenic properties (Figure 3). By contrast, the *N*-methyl compound **4b** exhibited chromogenic properties toward Cu^{2+} ions by turning pale red (Figure 5). UV-Vis analysis when mixing $PdCl_2$, $CuCl_2$, $CrCl_2$, $CrCl_3$, $FeCl_2$, $FeCl_3$, $NiCl_2$, $ZnCl_2$, $InCl_2$, $PtCl_2$, or $CeCl_3$ is shown in Figure S6.

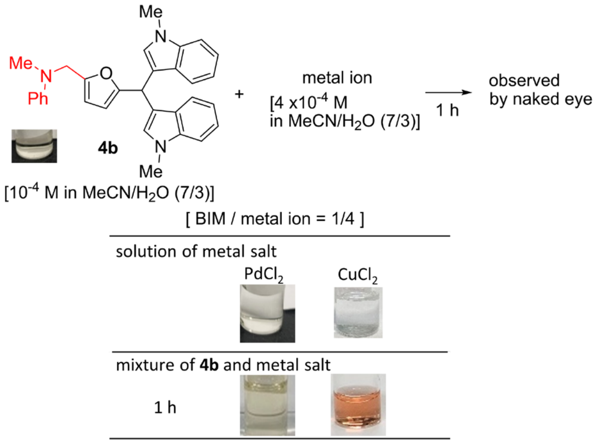


Figure 5. Chromogenic property of **4b**

Conclusions

We developed 5-(*N*-methyl-*N*-phenyl-aminomethyl)-furan-2-yl BIM **4a** as a novel chromogenic agent for Pd^{2+} ion. **4a** was easily synthesized from 5-CMF as a biorenewable feedstock. Furan-2-yl moiety was important for observing the color change upon mixing with the Pd^{2+} ion solution. This novel phenomenon is expected to contribute to Pd residue detection in the future.

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Conflicts of interest

There are no conflicts to declare.

Author Contributions

K.B., S.N., T.A. S.O. and S.A. contributed to organic synthesis. H.T. analyzed UV-Vis. Y.K. contributed to compound design. Y.S. directed the project. K.B. and Y.S. wrote the manuscript.

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