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A sensitive and selective chemiluminogenic probe for palladium†

Ilke Simsek Turan,[a] Ozge Yilmaz,[b] Betul Karatas[b] and Engin U. Akkaya*[ac]

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Palladium triggered removal of a propargyl group leads to the cleavage of the 1,2-dioxetane ring, leading to bright chemiluminescence. The reaction of the probe is highly specific for the Pd species, thus the probe described here has considerable potential for practical utility.

Introduction

Optical sensing of palladium ions has attracted considerable attention due to their serious environmental and health problems. Water resources, soil, dust and natural flora have been contaminated by increased palladium emissions which are caused by a wide spectrum of applications such as the electrical and electronic industries, catalytic converters, dental appliances, fuel cells and jewellery. In addition, it is also exploited as catalyst in many cross-coupling reactions such as Buchwald–Hartwig, Heck, Sonogashira and Suzuki–Miyura, leading to the formation of difficult bonds for the synthesis of complex molecules involving many clinical drugs.[1] Fruitful use of Pd-catalysed reactions in pharmaceutical industry increases the risk of Pd-contamination in active pharmaceutical ingredients because a high level of residual palladium is often found in final products, despite rigorous purification steps and thus, it can cause harm to human body.[2] Traditional methods like atomic absorption spectroscopy (AAS), solid-phase microextraction high performance liquid chromatography (SPME-HPLC), inductively coupled plasma atomic emission spectrometry (ICP-AES), X-ray fluorescence, *etc.*, can be applied for the detection of palladium ions, however they all suffer from complicated sample preparation procedures, expensive experimental setup and the requirement for highly-trained individuals.[3] Therefore, development of analytical techniques with selective and sensitive detection of palladium ions is urgently needed in a high-throughput fashion. As a new insights into the optical sensing systems, chemiluminescence based ones would be promising due to their superior advantages such as operational simplicity, cost effectiveness, rapid and high sensitivity of the target, free from interferences caused by light scattering and reduced background noise due to the absence of photonic excitation.[4] Since light emission occurs as a result of a specific chemical reaction which is unique to the analyte of interest, it is significant to develop chemiluminogenic systems for detection of palladium ions with high sensitivity and selectivity.[5] Until now, to the best of our knowledge, no reports based on the chemiluminescence detection of palladium ions employing 1,2-dioxetanes have been published.

As a chemiluminogenic unit, our choice was a stable 1,2-dioxetane which is a four-membered cyclic peroxide usually implicated as the reactive intermediates in bioluminescence as well as oxalate esters, luminol and acridinium esters. Use of 1,2-dioxetane derivatives as chemiluminogenic unit is a very promising alternative strategy since their luminescence can be triggered by the cleavage of a chemical bond under mild reaction conditions.[6] The chemical reaction can be chosen specific to analyte of interest by designing the chemiluminogen accordingly. When triggering moiety is cleaved *via* chemical reaction leads to the release of electronically excited *m*-oxybenzoate anion which undergoes an electron transfer according to CIEEL (Chemically Initiated Electron Exchange Luminescence) mechanism and eventually relaxes radiatively with a peak emission at 466 nm.[7] Recently, reaction based fluorescent probes have been designed to sense palladium ions *via* either depropargylation reaction[8] or Tsuji–Trost allylic oxidative insertion mechanism.[9]

Results and discussions

In this work, we wanted to design two different 1,2-dioxetane derivatives by incorporating propargyl and allyl ether moieties which are expected to luminesce *via* two different palladium catalysed reactions.

The target molecules were synthesized (Scheme 1) in a few steps from commercially available materials, some in close analogy to the literature procedures. The synthesis starts with the protection of 3-hydroxybenzaldehyde as benzoyl ester derivative **1** in order to prevent polymerization reaction during *p*-toluenesulfonic acid catalysed addition of 2,2-dimethoxypropane to yield

[a]*UNAM-National Nanotechnology Research Center, Bilkent University, Ankara 06800, Turkey. E-mail: eua@fen.bilkent.edu.tr*

[b]*Department of Chemistry, Ahi Evran University, Kirsehir, 40100, Turkey*

[c]*Department of Chemistry, Bilkent University, Ankara 06800, Turkey*

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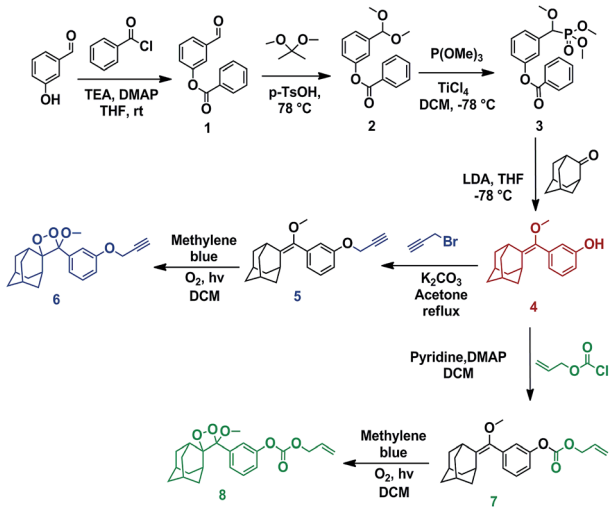
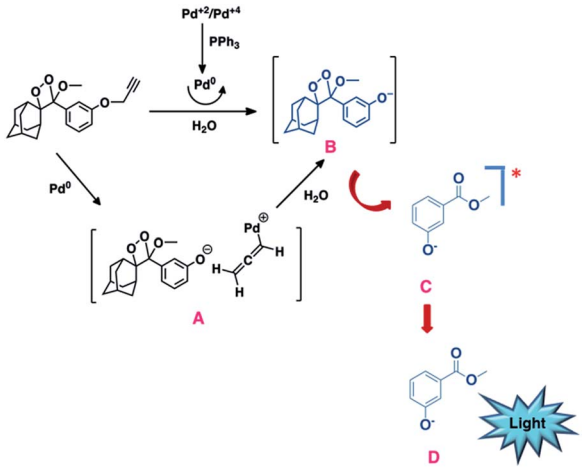


Scheme 1 Synthesis of chemiluminogenic palladium sensors (TEA: triethylamine, DMAP: 4-dimethylaminopyridine, *p*-TsOH: *p*-toluenesulfonic acid).



Scheme 2 Proposed chemiluminescent depropargylation process catalysed by Pd ions.

acetal derivative **2**, which was then reacted with trimethyl phosphite using $TiCl_4$ as the catalyst to give corresponding phosphonate **3**. Subsequent treatment of phosphonate **3** to the Wadsworth–Emmons coupling with 2-adamantanone proceeded to give vinyl ether **4** which was further reacted either with propargyl bromide to yield compound **5** or with allyl chloroformate to yield compound **7**. In the final step, the electron-rich enol ethers are efficiently photooxygenated to yield 1,2-dioxetane derivatives **6** and **8**. The chemical structures of all compounds were verified analytically.

We initially tested the chemiluminescent response of **6** toward palladium in DMSO–H_2O (95 : 5, v/v) buffered with Na_2CO_3–$NaHCO_3$ buffer (50 mM, pH: 9.0). In order to identify the mechanism operates through depropargylation reaction leading to light emission; $PdCl_2$ was selected as representative palladium species in titration experiments since it is the most toxic one among all. Based on titration experiment results (Fig. 1), we have proposed that chemiluminescent depropargylation reaction was proceeded *via* an allenyl-Pd intermediate which is resulted from the oxidative addition of Pd(0) to the alkyne moiety (Scheme 2) and thus, in the act of water molecules as nucleophile, allenyl-Pd intermediate **A** leads to the formation of activated form of 1,2-dioxetane **B** due to the pK_a of the medium. Activated 1,2-dioxetane transfers electron to the four membered ring to initiate its decomposition for the generation of excited state *m*-oxybenzoate anion **C** while it relaxes back to ground state, resulting in the emission of photon.

The response of chemiluminescent probe toward palladium ion was studied in the presence of PPh_3 which reduces metal species such as M^{II} to M^0 *in situ*, enabling the determination of total palladium ion quantity regardless of the oxidation states. The amount of PPh_3 is critical since elevated concentrations leads to decrease in the concentration of reactive palladium species and thus, retards the depropargylation reaction (Fig. 2a). Bright blue chemiluminescence is triggered *via* the catalytic action of Pd(0) whose larger concentrations progressively resulted in the stronger emission (Fig. 1). The effect of

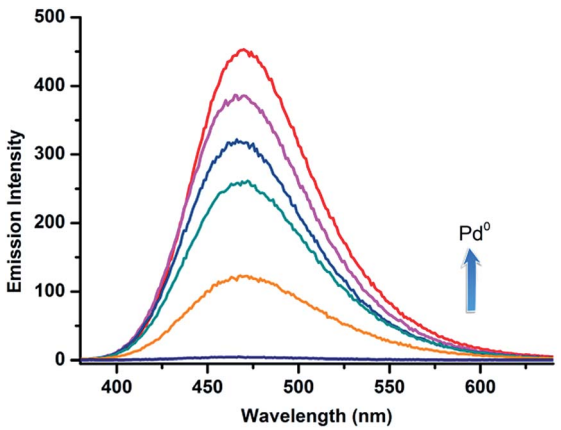


Fig. 1 Chemiluminescence spectra of dioxetane **6** (200 μM) in the presence of increasing concentrations of $PdCl_2$ (concentrations: 0.1, 0.2, 0.3, 0.4, 0.5, 0.6 mM) in DMSO–H_2O (95 : 5, v/v) solution with Na_2CO_3–$NaHCO_3$ buffer (50 mM, pH: 9.0) involving PPh_3 (1.0 mM) at 70 °C.

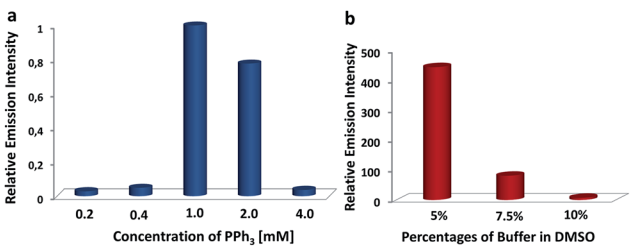


Fig. 2 Chemiluminescence emission data for dioxetane **6** (200 μM) in the presence of $PdCl_2$ (0.4 mM) ions in DMSO–H_2O (95 : 5, v/v) solution with Na_2CO_3–$NaHCO_3$ buffer (50 mM, pH: 9.0) (a) with varying concentrations of PPh_3 at 70 °C, (b) with varying percentages of buffer in DMSO involving PPh_3 (1.0 mM) at 70 °C.

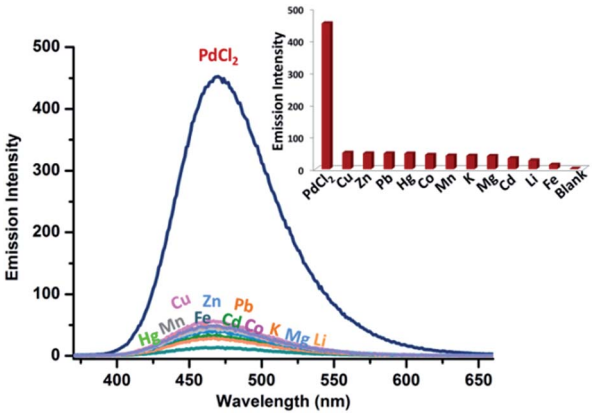


Fig. 3 Chemiluminescence emission intensity of dioxetane **6** (200 μM) upon addition of different metal ions in DMSO–H_2O (95 : 5, v/v) solution with Na_2CO_3–$NaHCO_3$ buffer (50 mM, pH: 9.0) involving PPh_3 (1.0 mM) at 70 °C.

water content is critical due to the possibility of protonation of phenoxide ion responsible for the emissive fragmentation process that was also investigated by varying the percentage of buffer in DMSO (Fig. 2b).

The selective nature of chemiluminogenic probe was demonstrated with a number of potential competitor cations and the results revealed that chemiluminogenic probe possess high selectivity toward palladium in the presence of other metal ions (Fig. 3). The detection limit of the probe was determined as 88 μM.

Optimal pH of the depropargylation reaction was examined by varying the pH of chemiluminogenic fragmentation reaction. Intense emission was observed at pH 9 (Fig. 4a) and when the pH was either below or above 9, the emission intensity was reduced due to the possibility of protonation of phenoxide or the chelation of palladium ion. The reactivity of the probe toward other palladium reagents with oxidation states of 0, II and IV were investigated. The results (Fig. 4b) indicates that our method was both general for many different palladium sources and successful in the conversion of all palladium to reactive

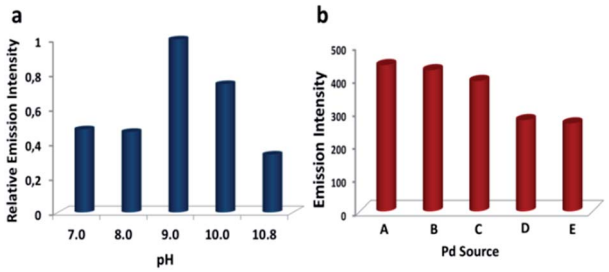


Fig. 4 (a) Chemiluminescence emission intensity data in pH dependent deallylation of dioxetane **6** (200 μM) in the presence of $PdCl_2$ (0.4 mM), PPh_3 (1.0 mM) in DMSO–H_2O (95 : 5, v/v) solution with phosphate buffer (50 mM for pH: 7.0, 8.0) or Na_2CO_3–$NaHCO_3$ buffer (50 mM for pH: 9.0–10.8) with added PPh_3 (1.0 mM) at 70 °C. (b) Chemiluminogenic response of the probe **6** toward various Pd species and oxidation states. A = $PdCl_2$, B = Na_2PdCl_4, C = Na_2PdCl_6, D = $Pd(OAc)_2$, E = $Pd(PPh_3)$.

$Pd(PPh_3)_n$ species even in the presence of other ligands in solution. Dioxetane **8** is supposed to decompose *via* Tsuji–Trost allylic oxidation reaction. Unfortunately, we have not observed any specific chemiluminogenic response against the palladium ion due to the lability of carbonate functionality toward strong base.

Conclusions

In conclusion, we proposed a new approach for the sensing of Pd ions by using 1,2-dioxetane based chemiluminogenic probes. Considering the fact that chemiluminescence in principle can provide a rapid, qualitative and/or quantitative test for analytes of interest, we are confident that other probes exploiting the superior qualities of chemiluminescence will emerge. Chemiluminogenic assessment of Pd concentrations in pharmaceuticals, water and soil could be a possible application, and the bright chemiluminescence of the probe or structurally related derivatives could provide a promising alternative. We believe that this study is expected to be inspirational in the development of chemiluminescence based Pd(0) sensors due to its analytical importance.

Experimental section

General

All chemicals and solvents obtained from suppliers were used without further purification. ^1H NMR and ^{13}C NMR spectra were recorded on Bruker Spectrospin Avance DPX 400 spectrometer using $CDCl_3$ as the solvent. Chemical shifts values are reported in ppm from tetramethylsilane as internal standard. Spin multiplicities are reported as the following: s (singlet), d (doublet), m (multiplet). HRMS data were acquired on an Agilent Technologies 6530 Accurate-Mass Q-TOF LC/MS. Chemiluminescence measurements were done on a Varian Eclipse spectrofluorometer. Spectrophotometric grade solvents were used for spectroscopy experiments. Flash column chromatography (FCC) was performed by using glass columns with a flash grade silica gel (Merck Silica Gel 60 (40–63 μm)). Reactions were monitored by thin layer chromatography (TLC) using precoated silica gel plates (Merck Silica Gel PF-254), visualized by UV-vis light. All organic extracts were dehydrated over anhydrous Na_2SO_4 and concentrated by using rotary evaporator before being subjected to FCC.

Synthesis of compound 1. 3-Hydroxybenzaldehyde (1.0 g, 8.19 mmol) was dissolved in dry THF. When reaction mixture was cooled to 0 °C, TEA (1.71 mL, 12.2 mmol) was added and mixed for 20 min. After the addition of catalytic amount of DMAP, benzoyl chloride (1.38 mL, 12.2 mmol) was added dropwise to the reaction mixture and it was left to stir at room temperature. The progress of the reaction was monitored by TLC. When TLC showed no starting material, reaction was concentrated to half of it. The residue was diluted with EtOAc and extracted with brine. Combined organic phases were dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was purified by silica gel flash column chromatography using EtOAc/hexane (1 : 5, v/v) as the eluent. Compound **1** was

obtained as white solid (1.41 g, 76%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.04 (s, 1H), 8.23 (d, J = 8.4 Hz, 2H), 7.78–7.82 (m, 2H), 7.57–7.69 (m, 2H), 7.51–7.57 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.1, 164.8, 151.5, 137.8, 133.9, 130.24, 130.21, 129.0, 128.71, 128.69, 127.9, 127.3, 122.5 ppm.

Synthesis of compound 2. Compound **1** (1.0 g, 4.42 mmol), 2,2-dimethoxypropane (1.2 mL) and catalytic amount of *p*-toluenesulfonic acid was mixed at 78 °C. The progress of the reaction was monitored by TLC. When TLC showed no starting material, reaction was concentrated to half of it. The residue was diluted with EtOAc and extracted with brine. Combined organic phases were dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was purified by silica gel flash column chromatography using EtOAc/hexane (1 : 5, v/v) as the eluent. Compound **2** was obtained as white solid (0.745 g, 62%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (d, J = 8.5 Hz, 2H), 7.65 (t, J = 7.4 Hz, 1H), 7.39–7.55 (m, 5H), 7.23 (d, J = 8.0 Hz, 1H), 5.48 (s, 1H), 3.37 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1, 151.0, 140.0, 133.6, 130.1, 129.5, 129.3, 128.6, 124.2, 121.7, 120.2, 102.2, 52.5 ppm. HRMS *m*/*z*: calcd: 295.09408, found: 295.09078 $[M + Na]^+$, Δ = 11.18 ppm.

Synthesis of compound 3. Trimethylphosphite (0.3 mL, 2.58 mmol) was added to the solution of compound **2** (0.5 g, 1.84 mmol) in DCM at −78 °C under Ar. 15 min later, $TiCl_4$ (0.3 mL, 2.58 mmol) was added dropwise to the reaction mixture at −78 °C. The mixture was stirred for 30 min before allowing it to room temperature and stirred at room temperature for further 1 hour. After the addition of aqueous methanol (2 : 1), reaction mixture was diluted with DCM and extracted first with saturated solution of $NaHCO_3$ then with brine. Combined organic phases were dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was purified by silica gel flash column chromatography using EtOAc as the eluent. Compound **3** was obtained as white solid (0.583 g, 91%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (d, J = 8.3 Hz, 2H), 7.66–7.68 (m, 1H), 7.52–7.55 (m, 2H), 7.48 (t, J = 7.9 Hz, 1H), 7.38 (d, J = 7.7 Hz, 1H), 7.34 (s, 1H), 7.24 (d, J = 8.0 Hz, 1H), 4.60 (d, J = 15.8 Hz, 1H), 3.74 (dd, J = 7.1 Hz, 6H), 3.45 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.0, 151.19, 151.16, 136.1, 133.6, 130.1, 129.6, 129.5, 128.6, 125.4, 125.3, 121.97, 121.94, 121.19, 121.14, 80.7, 79.0, 59.0, 58.8, 53.98, 53.92, 53.8, 53.7 ppm. HRMS *m*/*z*: calcd: 373.07657, found: 373.07657, $[M + Na]^+$, Δ = 12.27 ppm.

Synthesis of compound 4. Lithiumdiisopropyl amide (1.8 mL, 3.07 mmol) was added dropwise to the reaction mixture of compound **3** (0.43 g, 1.23 mmol) dissolved in 1 mL dry THF at −78 °C under Ar. After stirring of the reaction mixture for 45 min, 2-adamantanone (0.166 g, 1.11 mmol) dissolved in dry THF was added dropwise to the reaction mixture at −78 °C under Ar. Reaction was left to stir at room temperature overnight. After pouring it into phosphate buffer (0.2 M, pH 7), it was extracted with EtOAc. Combined organic phases were dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was purified by silica gel flash column chromatography using EtOAc/hexane (1 : 5, v/v) as the eluent. Compound **4** was obtained as white solid (0.312 g, 94%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (t, J = 7.8 Hz, 1H), 6.88–6.91 (m, 2H), 6.80–6.83 (m, 1H), 6.11 (s, br, 1H), 3.36 (s, 3H), 3.27 (s, 1H), 2.68 (s, 1H), 1.80–1.98 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.8, 142.8, 136.7, 132.4, 129.1, 121.8, 115.9, 114.6, 57.7, 39.1, 39.0, 37.1, 32.2, 30.3, 28.2 ppm. HRMS *m*/*z*: calcd: 271.16926, found: 271.16357, $[M + H]^+$, Δ = 13.59 ppm.

Synthesis of compound 5. K_2CO_3 (0.107 g, 0.78 mmol) was added to the reaction mixture of compound **4** (0.07 g, 0.26 mmol) and propargyl bromide (45 μL, 0.52 mmol) dissolved in 5 mL acetone. After the addition of catalytic amount of KI, reaction mixture was refluxed at 65 °C. The progress of the reaction was monitored by TLC. When TLC showed no starting material, the reaction was extracted with water (3 × 100 mL) and combined organic phases were dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was purified by silica gel flash column chromatography using EtOAc/hexane (1 : 5, v/v) as the eluent. Compound **5** was obtained as colorless solid (0.075 g, 94%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (td, J = 8.1, 1.1 Hz, 1H), 6.99–6.97 (m, 2H), 6.94–6.91 (m, 1H), 4.72 (s, 2H), 3.32 (s, 1H), 3.28 (s, 1H), 2.65 (s, 1H), 2.55–2.54 (m, 1H), 2.00–1.81 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.3, 143.2, 136.9, 131.7, 128.9, 122.7, 115.6, 114.0, 75.5, 57.7, 55.7, 39.25, 39.07, 37.2, 32.2, 30.2, 28.3 ppm. HRMS *m*/*z*: calcd: 309.18491, found: 309.18983 $[M + H]^+$, Δ = −1.68 ppm.

Synthesis of compound 6. Compound **5** (0.10 g, 0.32 mmol) was dissolved in DCM. Methylene blue (5 mg) was added to the reaction mixture which was irradiated while oxygen gas was passing through it. The progress of the reaction was monitored by TLC. When TLC showed no starting material, the mixture was concentrated under vacuo and the residue was subjected to the silica gel flash column chromatography by using DCM as the eluent. Compound **6** was obtained as white solid (0.108 g, 98%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.13 (br, m, 3H), 7.05–7.02 (m, 1H), 4.74 (s, 2H), 3.24 (s, 3H), 3.04 (s, 1H), 2.52 (s, 1H), 2.22 (s, 1H), 1.92–1.01 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.5, 136.3, 129.3, 122.8, 121.3, 120.2, 119.1, 116.2, 111.9, 95.4, 75.7, 55.8, 49.9, 36.4, 34.7, 33.1, 32.9, 32.3, 31.6, 31.5, 26.0, 25.9 ppm.

Synthesis of compound 7. Pyridine (56 μL, 0.7 mmol) was added to the reaction mixture of compound **4** (0.135 g, 0.5 mmol) dissolved in DCM and the reaction mixture was stirred at room temperature for 10 min. After the addition of catalytic amount of DMAP, allyl chloroformate (0.072 g, 0.6 mmol) dissolved in DCM was added dropwise to the reaction mixture while it was kept at 0 °C and left to stir at room temperature overnight. When TLC shows no starting material, the reaction mixture was concentrated under vacuo and crude product was subjected to the flash column chromatography by using EtOAc/hexane (1 : 5, v/v) as the eluent. Compound **7** was obtained as colorless solid (0.15 g, 85%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (t, J = 7.8 Hz, 1H), 7.22 (d, J = 7.6 Hz, 1H), 7.16 (s, 1H), 7.12 (d, J = 8.1 Hz, 1H), 6.07–5.99 (m, 1H), 5.45 (d, J = 14.4 Hz, 1H), 5.34 (d, J = 9.2 Hz, 1H), 4.77 (m, 2H), 3.32 (s, 3H), 3.27 (s, 1H), 2.68 (s, 1H), 2.00–1.81 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.4, 150.9, 142.5, 137.1, 132.6, 131.1, 128.9, 126.9, 121.7, 119.8, 119.4, 69.1, 57.8, 39.1, 39.0, 37.1, 32.1, 30.2, 26.2 ppm. HRMS *m*/*z*: calcd: 355.19039, found: 355.19886 $[M + H]^+$, Δ = −1.52 ppm.

Synthesis of compound 8. Compound **7** (0.12 g, 0.34 mmol) was dissolved in DCM. Methylene blue (5 mg) was added to the

reaction mixture which was irradiated while oxygen gas was passing through it. The progress of the reaction was monitored by TLC. When TLC showed no starting material, the mixture was concentrated under vacuo and the residue was subjected to the silica gel flash column chromatography by using DCM as the eluent. Compound **8** was obtained as white solid (0.124 g, 95%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (br, m, 3H), 7.25 (dd, J = 9.1, 2.40 Hz, 1H), 6.06–5.96 (m, 1H), 5.47–5.41 (m, 1H), 5.36–5.33 (m, 1H), 4.76 (d, J = 5.8 Hz, 2H), 3.23 (s, 3H), 3.04 (s, 1H), 2.15 (s, 1H), 1.82–0.99 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.2, 151.1, 136.6, 131.0, 129.3, 127.2, 125.6, 122.3, 122.0, 119.5, 117.5, 95.3, 69.2, 49.9, 36.3, 34.7, 33.1, 32.8, 32.2, 31.7, 31.5, 26.0, 25.8 ppm.

Chemiluminescent spectroscopic analysis

Chemiluminescence measurements were performed as follows: Pd(0) was added to vial which contains PPh_3 (1.0 mM) and dioxetane **6** or **8** (200 μM) in DMSO–H_2O (95 : 5, v/v) solution with Na_2CO_3–$NaHCO_3$ buffer (50 mM, pH: 9.0). Chemiluminescence was measured for every 2 °C from 60 °C to 80 °C by transferring 1.0 mL solution to the cell and chemiluminescence emission was managed with the addition of NaOH (10 μL) from 10.0 N stock solution. Blank was measured as above in the absence of Pd(0). Stock solutions were prepared according to the literature.

Detection limit measurements

The detection limit for probe and reference compound was calculated based on chemiluminescence titration. In order to determine the S/N ratio, the chemiluminescence emission intensity of the blanks without Pd was measured 10 times and standard deviation of these blanks was calculated. Chemiluminescence emission intensities of the probe in the presence of Pd ions were plotted as a concentration of Pd in order to determine the slopes. The linear relationship between emission intensity and Pd(0) concentration were determined and detection limits were calculated according to the equation: $3\sigma/m$, where σ represents the standard deviation of the blank measurements, m represents the slope between intensity *versus* sample concentration. Standard deviation was determined as 0.026268 and the slope of the graph as 885.92.

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