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A chemiluminescence sensor with signal amplification based on a self-immolative reaction for the detection of fluoride ion at low concentrations

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ABSTRACT

A sensory system incorporated with an amplification function was developed for the detection of trace-level fluoride ions. This sensory system comprises two steps: amplification and chemiluminescence. These steps were linked with chemical reactions and were induced continuously. The process from amplification to chemiluminescence was accomplished in this system using fluoride ions. The amplification is based on a self-immolative system that permits the detection of emissions even at low fluoride ion concentrations for systems in which chemiluminescence cannot be induced in the absence of fluoride ions. The optimal ratio of the chemiluminescent compound and the amplifier was calculated to achieve efficient amplification.

1. Introduction

Technology for the detection of trace-level substances is useful and has been applied in various fields. Specifically, convenient detection of specific harmful materials, such as fluoride ions, is very valuable. Fluoride ions cause diseases of the teeth and bones. For example, the U.S. Environmental Protection Agency recommends a fluoride concentration of 2.0 ppm in drinking water and has mandated an upper limit of 4.0 ppm.[1] Therefore, sensors and probes for detecting trace-level fluoride ions are needed in the food, farming, and environmental research industries.

Inductively coupled plasma mass spectrometry is generally used to detect trace-level substances. Signal amplification plays an important role in highly sensitive detection tools such as photomultipliers and secondary electron multipliers. However, these devices require electricity to operate, and they should not be moved frequently because movement affects their precision. Therefore, a chemical sensor that can detect objective substances on site would be very convenient. In particular, luminescent sensors are a clear and highly recommended method of visual detection.

Chemiluminescence is an attractive option for visual detection of trace-level fluoride ions. Chemiluminescence is induced by the decomposition of energized compounds, such as peroxides; it can be controlled using chemical reactions and by changing the reaction conditions. In addition, the induction of chemiluminescence does not require electricity or excitation light. Emission, including chemiluminescence, is generally a more sensitive detection method than absorption, reflection, and light scattering. However, at extremely low sensor concentrations, even effective emissive sensors almost fail to detect objective substances. Therefore, signal amplification via substrate recognition is necessary for these sensory systems.

Recently, in terms of amplification based on chemical reactions, much attention[2–9] has been paid to sequential disaggregative reactions, known as self-immolation. Self-immolative reactions have been applied in luminescent sensors and probes,[10–15] release and amplification of low molecular weight compounds,[16–19] and drug delivery systems.[20–23] For example, Shabat's group reported the fluorescence amplification of low-molecular weight compounds by disaggregation of dendritic compounds or polymers.[24–26] Attention has been focused on signal amplification by cyclical reactions with

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fluoride ions or hydrogen peroxide.[27–31] Phillips's group reported the amplification of chromophore concentration by cyclical reactions with fluoride ions or piperidine and the release of alcoholic compounds from acetals.[32–35] Furthermore, Huang's group[36] and Gabrielli's group[37] recently reported fluorescent probes with fluoride ion amplification functions.

Our idea was to fabricate a sensory system comprising two distinct steps. The resulting sensory system is based on a self-immolative system, as shown in Fig. 1, into which the function of amplifying fluoride ions is incorporated. The two steps are linked with chemical reactions and are induced continuously. The first step involves the recognition of trace-level fluoride ions and the amplification of fluoride ions. In this step, the amplifier recognizes trace-level fluoride ions as initiators and self-destructs to release several fresh fluoride ions. This self-destruction is caused repeatedly by the generated fluoride ions, resulting in the creation of more fluoride ions. This cyclical reaction involving self-destruction and recombination with fluoride ions leads to amplification of the fluoride ions. The second step involves the induction of chemiluminescence by the amplified fluoride ions. In this second step, the deprotection of the luminophore precursor by fluoride ions induces chemiluminescence.

In this work, as a chemiluminescence source, we applied compound **1**, which was reported previously (Scheme 1).[38–41] Compound **1** contains a phenol group protected with *tert*-butyldimethylsilyl ether and a dioxetane unit stabilized with a bulky adamantyl group. Compound **1** was deprotected by fluoride ion to induce chemiluminescence. However, the chemiluminescence of **1** is so weak that it can not be detected by the analyzer or by the naked eye at very low fluoride ion concentrations. Therefore, at sufficiently low fluoride ion concentrations, the detection of the chemiluminescence of **1** requires appropriate signal amplification. Compound **2** was prepared as the amplifier of fluoride ions in the developed sensory system. Fluoride ion amplification was achieved by disaggregation of **2**. Compound **2** was prepared from 4-cresol by protection with *tert*-butyldimethylsilyl ether as the triggering group for fluoride ions and was equipped with fluoromethyl groups at its 2- and 6-positions. The protecting group of **2** was cleaved by a fluoride ion, leading to disaggregation of **2** and the release of two fluoride ions through 1,4-elimination. The freshly released fluoride ions again reacted with **2**. When this cyclical reaction is performed N times (N: natural number), 2^N fresh fluoride ions are released. Finally, compound **2** was fully consumed and converted into an equivalent amount of fluoride ions. Using this amplified amount of fluoride ions, chemiluminescence of **1** was induced. Compounds **1** and **2** were prepared on the basis of literature reports, as shown in Schemes 2 and 3, respectively.[15,30]

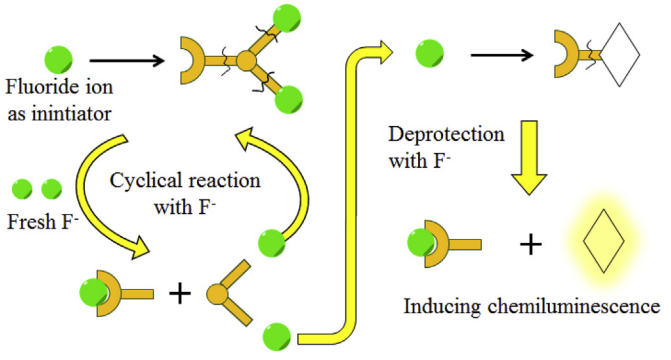
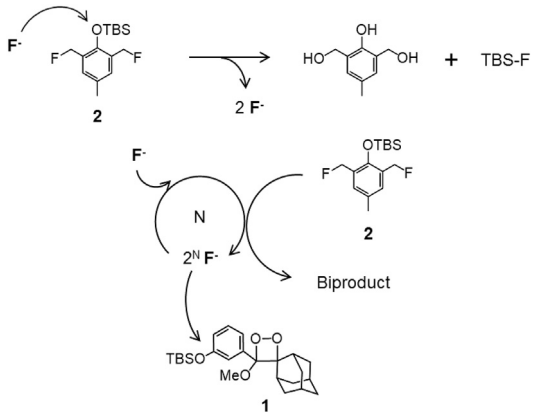
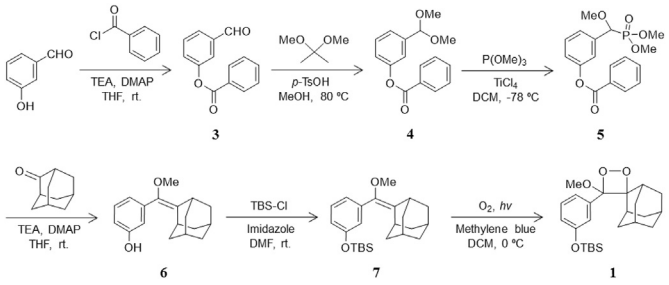


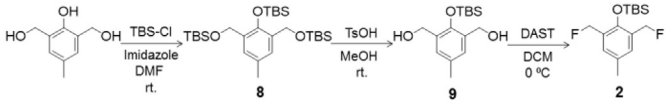
Fig. 1. Induced chemiluminescence with signal amplification of fluoride ions in the developed sensory system.



Scheme 1. Reaction sequence of amplification of the chemiluminescence **1** by **2**.



Scheme 2. Synthesis of chemiluminescent compound **1**.



Scheme 3. Synthesis of compound **2** as the amplifier of fluoride ions.

2. Results and discussion

The chemiluminescence performance of **1** was investigated to determine the lowest amount of fluoride ions required to induce chemiluminescence of **1**. Compound **1** shows blue chemiluminescence, with a peak emission at 471 nm in dichloromethane (DCM), as shown in Fig. 2a. This result is similar to a previously reported result for another solvent.[15,38–40] Time-resolved chemiluminescence spectra of **1** were measured by monitoring the luminescence intensity at the wavelength of 471 nm (Fig. 2b). It was found that the luminescence intensity depended on the amount of tetrabutylammonium fluoride (TBAF) added as a fluoride ion initiator. The addition of 2.1 mM (0.21 μmol) of TBAF to **1** caused no detectable chemiluminescence; however, the addition of 0.53 mM (0.53 μmol) of TBAF to **1** caused detectable chemiluminescence. Therefore, more than 0.53 mM of fluoride ions from the initiator or the amplifier is required to maintain constant intensity of the chemiluminescence of **1**. Conversely, inducing chemiluminescence of **1** with the amplifier **2** resulted in improved detectability of fluoride ions in the sensory system, despite the addition of less than 0.21 mM of fluoride ions from the initiator.

To investigate the self-immolative reaction of **2**, fluorine-19 nuclear magnetic resonance (^{19}F NMR) spectroscopy was conducted with the addition of various amounts of chloroform-*d* solutions of TBAF; the conversion was then calculated. Fig. 3 indicates that the self-immolative reaction of **2** completed within a short

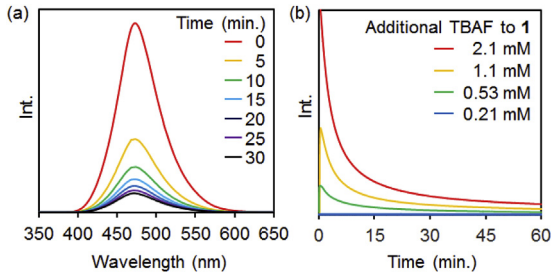


Fig. 2. Chemiluminescence performance of **1**. (a) Time-resolved chemiluminescence spectra of **1** (9.0 mg, 22 μmol) in DCM (ca. 1 mL). Chemiluminescence was induced with a dichloromethane solution of TBAF (2.1 mM, 2.1 μmol). The lines with different colors correspond to respective measurement times. (b) Time-resolved chemiluminescence spectra monitored at 471 nm, which is the maximum intensity of the spectrum of **1** (9.0 mg, 22 μmol) in DCM (ca. 1 mL). The red, yellow, green, and blue lines correspond to 2.1 mM (2.1 μmol), 1.1 mM (1.1 μmol), 0.53 mM (0.53 μmol), and 0.21 mM (0.21 μmol) of TBAF added to a solution of **1**, respectively.

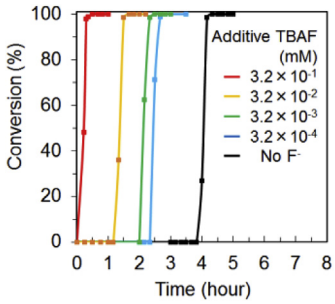


Fig. 3. Conversion of **2** versus reaction time during the self-immolative reaction. The conversions were calculated from the ^{19}F NMR spectra of **2**. The red, orange, green, blue, and black lines indicate the conversion patterns of 0.32 mM (0.20 μmol), 32 μM (20 nmol), 3.2 μM (2.0 nmol), and 0.32 μM (0.20 nmol) of TBAF and the solution without fluoride ions, respectively. The sample solution was prepared by mixing **2** (25 mg, 0.087 mmol), triethylamine (6% solution in $CDCl_3$, 0.35 mL, 0.15 mmol), and $CDCl_3$ (0.25 mL). An appropriate amount of chloroform-*d* solution (20 μL) of TBAF was added to each solution as a fluoride ion initiator.

period (15–30 min) because of the exponential release of fluoride ions. Furthermore, it shows that the reaction of **2** completed even with a small amount of TBAF (0.32 μM, 0.20 nmol), although the reaction required a long time to start. The reason for the long delay of the reaction with **2** is that the amplification of fluoride ions occurs exponentially. The amplification of fluoride ions can be divided into two phases. The first phase is the initial reaction phase, which occurs immediately after the start of amplification. In this phase, the fluoride ions from the TBAF initiator account for the majority of the fluoride ions in the system. The chain reaction involved in the amplification of fluoride ions is the intermolecular reaction between **2** and a fluoride ion. Therefore, in the initial-reaction phase, the rate of the chain reaction is slow; the fluoride ions gradually increase exponentially (2^N). The second phase is the state in which the quantity of fluoride ions is sufficient to react with **2**. In this phase, the rate of the chain reaction increases. Therefore, the chain reaction depends on the amount of initiator in the first phase; thus, the smaller the amount of initiator added, the slower the rate of amplification of fluoride ions, and the more time required to reach the second phase. Meanwhile, **2** was consumed rapidly by the chain reaction regardless of the amount of initiator. Therefore, in all cases, **2** was consumed completely within a short period (15–30 min), as shown in Fig. 3. This result also indicates that the amplification of fluoride ions with **2** can occur even with a lower amount of initiator (0.32 μM) than the amount of fluoride ions (0.21 mM, see Fig. 2) that causes no detectable chemiluminescence of **1**.

The selectivity of **2** for other anions was also investigated (Fig. 4). The investigation was performed under the same conditions as with TBAF. A series of tetrabutylammonium compounds were used as sources of other anions instead of TBAF. The concentration of each anion used was 0.032 mM. This is the concentration that initiates the reaction of **2** and consumes **2** completely within 2 h when the anion source is TBAF. However, in each case, the reaction of **2**, which was monitored by ^{19}F NMR spectroscopy was not initiated 2 h after the addition of each anion. This result was very similar to previously reported data for analogous compounds.[30,37]

Considering the chemical properties of **1** and **2**, the fluoride ion generation was amplified to induce subsequent chemiluminescence with the generated fluoride ions. To clarify whether the reaction was influenced by either **1** or **2**, their amounts were varied, and the induced chemiluminescence intensities were measured by monitoring the intensity at 471 nm. Fig. 4 shows the time-dependent chemiluminescence intensities with the addition of (5a) 21–63 μmol and (5b) 63–349 μmol of **2**. When the amount of **2** was increased, the luminescence intensity tended to increase within the 21–63 μmol range of added **2** (Fig. 5a). In contrast, when the amount of **2** exceeded this range, the luminescence intensity began to decrease (Fig. 5b). Fig. 5c shows plots of the relative emission yields against the amount of **2** during the initial 2 h after addition. The yields were calculated by integrating the luminescence intensity at the wavelength of 471 nm. The profile indicates that 1.9 equivalent amounts of **2** to **1** induced the maximum luminescence intensity; an excessive amount of **2** caused the intensity to decrease.

Similar luminescence behavior was observed as a function of the amount of **1**. An increase in the amount of **1** within the range of 7.2–36 μmol led to intensification of the luminescence (Fig. 6a). From the time-dependent intensities of **1**, a profile was plotted using the integrated values of luminescence intensity for 2 h for each amount of **1** added (Fig. 6b). The profile indicates that 2.4 equivalent amounts of **2** to **1** induces the maximum luminescence intensity, and further addition of **1** (36–86 μmol) causes the luminescence intensity to decrease.

Considering the results of these two cases, we deduced that the optimum ratio of **2** to **1** is 1.9–2.4 for efficient amplification of chemiluminescence. The existence of an optimum mixture ratio during the addition of **1** and **2** to the sensory system may be due to chemiluminescence quenching caused by the byproducts of **1** or **2** or by the radical coupling reaction of **1** when its amount is increase in the amount of **1**. Therefore, when a large excess of **1** was used, the chemiluminescence intensity decreased due to the byproducts of **1** and the radical coupling reaction of **1**. In contrast, when a large

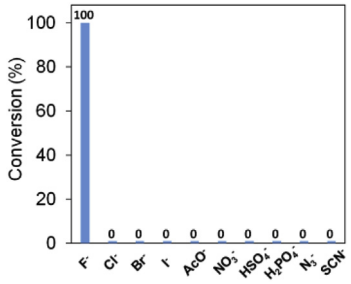


Fig. 4. Selectivity of the amplifier **2** for other anions. The conversions were calculated from the ^{19}F NMR spectra of **2** 2 h after the addition of each anion. The sample solution was prepared by mixing **2** (25 mg, 0.087 mmol), triethylamine (6% solution in $CDCl_3$, 0.35 mL, 0.15 mmol), and $CDCl_3$ (0.25 mL). Chloroform-*d* solutions (0.032 mM, 20 μL) of the tetrabutylammonium series (Cl^-, Br^-, I^-, AcO^-, NO_3^-, HSO_4^-, $H_2PO_4^-$, N_3^-, and SCN^-) were added to each solution instead of TBAF as the initiator.

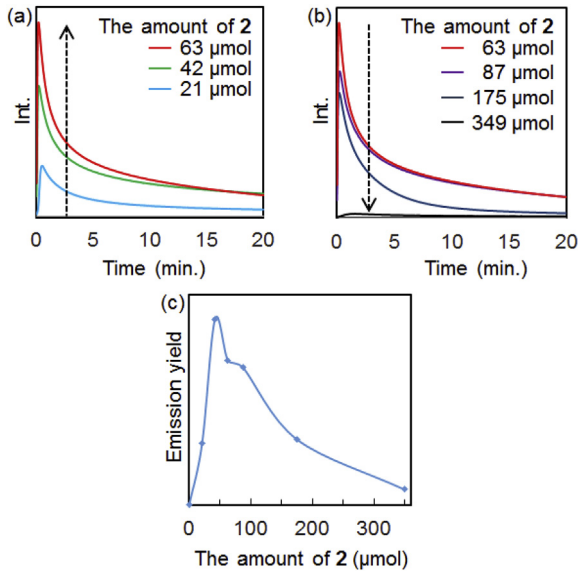


Fig. 5. Chemiluminescence performance of **1** with varying amounts of **2**. The amounts of **1**, triethylamine, and TBAF were fixed as follows: **1** (9.0 mg, 22 μmol), triethylamine (0.22 mmol) and TBAF (20 μM, 20 nmol). (a) Time-resolved chemiluminescence spectra of **1** monitored at 471 nm while varying the amount of **2** (21–63 μmol). The color of the line corresponds to the amount of **2** added. (b) Time–resolved chemiluminescence spectra of **1** monitored at 471 nm by varying the amount of **2** (63–349 μmol). The color of the line corresponds to the amount of **2** added. (c) Plots of emission yields during the initial 2 h versus the amount of **2**.

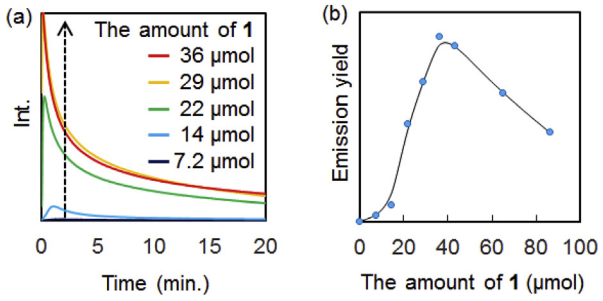


Fig. 6. Chemiluminescence performance of **1** with varying amounts of **1**. The amounts of **2**, triethylamine, and TBAF were fixed as follows: **2** (25 mg, 87 μmol), triethylamine (0.22 mmol), and TBAF (20 μM, 20 nmol). (a) Time-resolved chemiluminescence spectra of **1** monitored at 471 nm with varying amounts of **1** (7.2–36 μmol). The color of the line corresponds to the amount of **2** added. (b) Plots of emission yields during the initial 2 h versus the amount of **1**.

excess of **2** was used, the chemiluminescence intensity also decreased due to the byproducts of **2**.

Considering the optimum ratio of **2** to **1** of 1.9–2.4 for efficient amplification of chemiluminescence, it was verified that the inducement of chemiluminescence was possible via amplification with the lowest amount of fluoride ions (0.32 μM 0.20 nmol) detectable by ^{19}F NMR. Fig. 7 shows time-resolved chemiluminescence spectra of **1** in the presence and absence of the amplifier **2**. When the amplifier **2** was present, the induced chemiluminescence was clearly detected, in contrast to the absence of amplifier **2**. Therefore, fluoride ions were detectable by the chemiluminescence of **1** using amplifier **2** even for very low amounts such as 0.20 μM (0.20 nmol). Recently, Gabrielli's group[37] and Akkaya's group[15] reported a self-immolative probe for fluoride, respectively. The probe of Gabrielli's group was a multimodal detection probe with two modes: UV–vis absorption and fluorescence. Furthermore, their probe can detect amounts of fluoride ions

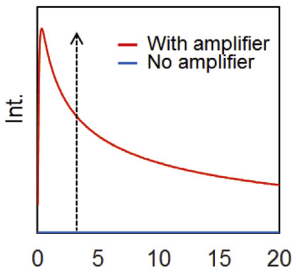


Fig. 7. Chemiluminescence performance of **1** with amplified F^- from a small amount of TBAF (0.20 μM 2.0 nmol) as the initiator. Time-resolved chemiluminescence spectra of **1** monitored at 471 nm. The red and blue lines correspond to the spectra with and without amplifier, respectively. The amounts of **1**, **2**, and triethylamine were fixed as follows: **1** (15 mg, 36 μmol), **2** (25 mg, 87 μmol), and triethylamine (0.22 mmol) in DCM solution (1 mL).

(100 μM) and is synthesized in two steps. While, the probe of Akkaya's group was a chemiluminescence sensor for fluoride ions. Their probe was equipped with two 1,2-dioxetane units as a chemiluminescence source. Therefore, the chemiluminescence quantum yield of their probe was almost twice that of the single 1,2-dioxetane unit. Furthermore, their probe can detect a low concentration of fluoride ions. The detection limit of their probe was determined to be 47 μM in DMSO and 0.67 μM in DMSO/aqueous buffer mixture (90/10, pH 7.2). Compared to the probe of Gabrielli's group, our sensory system is superior in the following two ways. One is that our probe can detect fluoride ions in lower amounts i.e., 0.20 μM (0.20 nmol), than their probe. The other is that our probe can detect fluoride ions by chemiluminescence without electricity or excitation light. On the other hand, compared to the probe of Akkaya's group, our sensory system is superior slightly in terms of the detectable concentration for fluoride ions and further improvement is possible with modification of each the steps. However, in this work, a series of process from amplification of fluoride ions to inducement of chemiluminescence was performed in non-protonic solvents rather than mixed aqueous solvents used by Gabrielli's group and Akkaya's group. The reason is to prevent the chemiluminescence of **1** from being quenched by a protonic solvent such as water and alcohol. Using a mixed solvent used by Akkaya's group or an enhancer reported in the past[39] may reduce the quenching of chemiluminescence of **1**. However, the factors involved in our sensory system increase and it led to become complicated our sensory system. We focused on the process from the amplification of fluoride ions to inducement of chemiluminescence in this work and therefore we performed with non-protonic solvents in order to simplify the sensor system.

3. Conclusions

We accomplished the processes of amplification and chemiluminescence in a sensory system. Using signal amplification, the developed system can detect fluoride ions at extremely low concentrations, even lower than those required to observe the chemiluminescence of **1**. We determined an optimum mixture ratio of **2** and **1**, which are the fluoride ion amplifier and the chemiluminescence source, respectively. In addition to functioning as a fluoride ion sensor, the processes of amplification and chemiluminescence in the developed sensory system can be applied to the detection of various substances involved in the disaggregation process in which fluoride ions are released when an objective substance is recognized. In our laboratory, further study of this sensory system for recognition of radioactive nuclides is underway. We believe that the present concept of linking two or more

reactions, such as amplification and chemiluminescence, is highly useful for detecting trace-level substances.

4. Experimental section

4.1. General procedures

4.1.1. Materials and methods

All reagents employed here were obtained commercially and were used as received without further purification. All solvents used were of special grade. Column chromatography was performed with silica gel (0.063–0.2 mm). Melting points were determined by introducing a tiny amount into a small capillary tube, attaching this tube to MEL-TEMP II (LABORATORY DEVICE INC, USA), heating the bath slowly, and observing the temperatures at which melting begins and is complete. IR spectra were recorded on a JASCO FT-IR spectrometer with polytetrafluoroethylene (PTFE) plates. Preparative GPC was performed using GPC columns (JAIGEL 1H-40 and 2H-40, Japan Analytical Industry Co., Ltd). ^{1}H NMR spectra were recorded on a JEOL JNM-ECA600 spectrometer in $CDCl_3$ with Me_4Si as an internal standard. Chemiluminescence spectra were recorded on a HITACHI F-7000 fluorescence spectrophotometer in DCM. High-resolution ESI mass spectra were measured using a Thermo Fisher Exactive mass spectrometer.

4.2. Synthesis

4.2.1. Synthesis of the chemiluminescence source (compound **1**)

Compound **3**. To a solution of 3-hydroxybenzaldehyde (3.00 g, 25 mmol), triethylamine (10 mL, 74 mmol), and DMAP (50 mg, 0.41 mmol) in THF (60 mL) was added benzoyl chloride (3.2 mL, 28 mmol) at room temperature. The resulting mixture was stirred at room temperature for 18 h. After the reaction, the resulting solution was diluted with ethyl acetate (60 mL) and washed with water (40 mL × 3), aqueous 1 M HCl solution (20 mL × 2) and saturated aqueous solution of $NaHCO_3$ (40 mL). Organic layer was dried over anhydrous magnesium sulfate. After evaporation of solvent, the residue was purified by chromatography on silica gel (hexane/ethyl acetate, 5:1) to afford **3** (5.47 g, 98%) as a white solid; mp 136–137 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.03 (s, 1H), 8.21 (dd, J = 8.4 Hz, 1.8 Hz, 2H), 7.80 (d, J = 7.8 Hz, 1H), 7.75 (t, J = 1.8 Hz, 1H), 7.66 (t, J = 7.2 Hz, 1H), 7.61 (t, J = 7.2 Hz, 1H), 7.53 (t, J = 7.8 Hz, 1H), 7.51–7.49 (m, 1H); HRMS (ESI), calcd for $C_{14}H_{11}O_3$ $[M + H]^+$ 227.0703, found 227.0709.

Compound **4**. A solution of **3** (3.83 g, 17 mmol), *p*-toluenesulfonic acid monohydrate (583 mg, 3.4 mmol) in methanol (100 mL) and 2,2-dimethoxypropane (20 mL) was dehydrated with 4A molecular sieves. The molecular sieves were removed from the mixture solution by filtration. The filtrate was stirred at 80 °C for 27 h. After the reaction, the resulting solution was concentrated and diluted with ethyl acetate (120 mL). The solution was filtered and washed with water (50 mL × 4). Organic layer was dried over anhydrous magnesium sulfate. After evaporation of solvent, the residue was purified by chromatography on silica gel (hexane/ethyl acetate, 5:1) to afford **4** (3.29 g, 71%) as a yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.20 (d, J = 7.2 Hz, 2H), 7.63 (t, J = 7.2 Hz, 1H), 7.51 (t, J = 7.2 Hz, 2H), 7.43 (t, J = 8.4 Hz, 1H), 7.36 (d, J = 7.2 Hz, 1H), 7.34 (s, 1H), 7.19 (dm, J = 6.6 Hz, 1H), 5.44 (s, 1H), 3.36 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.2, 151.0, 140.1, 133.7, 130.3, 129.6, 129.4, 128.7, 124.3, 121.8, 120.3, 102.3, 52.7; HRMS (ESI), calcd for $C_{16}H_{16}O_4Na$ $[M + Na]^+$ 295.0941, found 295.0938.

Compound **5**. To a solution of **4** (1.60 g, 1.7 mmol) and trimethyl phosphite (1.0 mL, 8.8 mmol) in DCM (17 mL) was added $TiCl_4$ (1.0 M solution in DCM, 8.7 mL, 8.8 mmol) at −78 °C. After stirring at −78 °C for 30 min, the resulting mixture was allowed to warm to room temperature and was stirred at room temperature for 23 h. After the addition of 15 mL aqueous methanol (2:1, v/v), the resulting solution was diluted with water (100 mL) and extracted with chloroform (20 mL × 2). Organic layer was washed with a saturated aqueous solution of $NaHCO_3$ (20 mL × 2). Organic layer was dried over anhydrous sodium sulfate. After evaporation of solvent, the residue was purified by chromatography on silica gel using hexane/ethyl acetate (3:1, v/v) and with continuous supply of ethyl acetate as the eluent to afford **5** (1.98 g, 97%) as a pale yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.19 (d, J = 8.4 Hz, 2H), 7.63 (t, J = 7.8 Hz, 1H), 7.50 (t, J = 7.5 Hz, 2H), 7.44 (t, J = 7.8 Hz, 1H), 7.35 (d, J = 7.8 Hz, 1H), 7.31 (s, 1H), 7.20 (d, J = 7.2 Hz, 1H), 4.57 (d, J = 16.2 Hz, 2H), 3.71 (dd, J = 12.3 Hz, 10.5 Hz, 6H), 3.42 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.1, 151.2, 136.2, 133.8, 130.2, 129.7, 129.5, 128.7, 125.5 (d, J = 5.7 Hz, P-C coupling), 122.1 (d, J = 2.9 Hz, P-C coupling), 121.2 (d, J = 5.7 Hz, P-C coupling), 80.5, 79.3, 59.0 (d, J = 16 Hz, P-C coupling), 54.0 (dd, J = 24 Hz, J = 5.8 Hz, P-C coupling); HRMS (ESI), calcd for $C_{17}H_{20}O_6P$ $[M + H]^+$ 351.0992, found 351.0992.

Compound **6**. To a solution of **5** (1.05 g, 3.0 mmol) in THF (18 mL) was added LDA (1.5 M solution in THF, 10 mL, 15 mmol) at −78 °C. After stirring of the reaction mixture for 30 min at −78 °C, 2-adamantanone (495 mg, 3.3 mmol) was added to the reaction mixture at −78 °C. The reaction mixture was allowed to warm to room temperature and stirred at room temperature for 24 h. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (130 mL). The resulting solution was extracted with ethyl acetate (20 mL × 6). Organic layer was dried over anhydrous sodium sulfate. After evaporation of solvent, the residue was purified by chromatography on silica gel (hexane/ethyl acetate, 5:1). Furthermore, the crude was purified by preparative GPC (in chloroform, 65 min) to afford **6** (231 mg, 28%) as a colorless oil. IR (PTFE) 3347 (m), 3063 (w), 2905 (s), 2846 (m), 1580 (m), 1445 (m), 1306 (m), 1230 (m) cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.22 (t, J = 7.8 Hz, 1H), 6.89 (dd, J = 7.8 Hz, 1H), 6.81–6.80 (m, 1H), 6.77 (dd, J = 8.4 Hz, 2.4 Hz, 2H), 4.84 (s, 1H), 3.30 (s, 3H), 3.24 (s, 1H), 2.66 (s, 1H), 1.98–1.76 (m, 12H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.9, 143.0, 136.9, 132.4, 129.2, 121.9, 116.0, 114.7, 57.9, 39.3, 39.1, 37.2, 32.3, 30.4, 28.4; HRMS (ESI), calcd for $C_{18}H_{23}O_2$ $[M + H]^+$ 271.1693, found 271.1694.

Compound **7**. To a solution of **6** (205 mg, 0.76 mmol) and imidazole (67 mg, 0.99 mmol) in DCM (6.0 mL) was added tert-butyldimethylsilyl chloride (149 mg, 0.99 mmol) at room temperature. The resulting mixture was stirred at room temperature for 17 h. After the reaction, the resulting solution was diluted with chloroform (40 mL) and washed with water (20 mL × 4). Organic layer was dried over anhydrous magnesium sulfate. After evaporation of solvent, the residue was purified by chromatography on silica gel by using hexane/ethyl acetate (5:1, v/v) as the eluent to afford **7** (242 mg, 83%) as a colorless oil. IR (PTFE) 3062 (w), 2907(s), 2848 (s), 1597 (m), 1578 (m), 1480 (m), 1286 (m) cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.20 (t, J = 7.8 Hz, 1H), 6.91 (d, J = 7.2 Hz, 1H), 6.81–6.79 (m, 1H), 6.78–6.75 (m, 1H), 3.29 (s, 3H), 3.24 (s, 1H), 2.63 (s, 1H), 1.97–1.75 (m, 12H), 0.98 (s, 9H), 0.20 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.4, 143.4, 136.9, 131.3, 129.0, 122.6, 121.2, 119.4, 57.7, 39.3, 39.1, 37.3, 32.3, 30.2, 28.4, 25.8, 18.3, −4.4; HRMS (ESI), calcd for $C_{24}H_{37}O_2Si$ $[M + H]^+$ 385.2557, found 385.2557.

Compound **1**. A solution of **7** (178 mg, 0.46 mmol) and methylene blue (7.0 mg, 0.022 mmol) in DCM (11 mL) was irradiated with a halogen lamp at 0 °C while oxygen gas was passed through it; the reaction was monitored by TLC. When the TLC showed no presence of compound **7**, the resulting solution was concentrated. The residue was purified by chromatography on silica gel by using hexane/ethyl acetate (20:1, v/v). Furthermore, the crude residue was purified by preparative GPC (in chloroform, 59 min) as the eluent to afford **1** (151 mg, 78%) as a colorless oil. IR (PTFE) 3365 (w), 3066

(w), 2934 (s), 2858 (s), 1601 (m), 1584 (m), 1472 (m), 1291 (m) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.50–6.70 (br, 3H), 6.87 (d, J = 6.6 Hz, 1H), 3.22 (s, 3H), 3.01 (s, 1H), 2.23 (s, 1H), 1.91 (d, J = 13 Hz, 1H), 1.79–1.46 (m, 10H), 1.23 (d, J = 15 Hz, 1H), 0.97 (s, 9H), 0.18 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.7, 136.2, 129.3, 121.4, 112.1, 95.6, 50.0, 36.5, 34.8, 33.2, 32.5, 31.7, 31.6, 26.1, 26.0, 25.8, −4.3; HRMS (ESI), calcd for $C_{24}H_{37}O_4Si$ $[M + H]^+$ 417.2456, found 417.2455.

*4.2.2. Synthesis of the amplifier (compound **2**)*

Compound **8**. To a solution of 2,6-bis(hydroxymethyl)-p-cresol (2.00 g, 12 mmol) and imidazole (2.67 g 39 mmol) in DMF (15 mL) was added tert-butyldimethylsilyl chloride (5.91 g, 39 mmol) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction, the resulting solution was diluted with ethyl acetate (100 mL) and washed with water (50 mL × 4). Organic layer was dried over anhydrous magnesium sulfate. After evaporation of solvent, **8** was obtained as a colorless oil (6.14 g). The crude product was used in subsequent reactions without further purification. ^1H NMR (600 MHz, $CDCl_3$) δ 7.15 (s, 1H), 4.68 (s, 4H), 2.32 (s, 3H), 1.02 (s, 9H), 0.94 (s, 18H), 0.15 (s, 6H), 0.08 (s, 12H); HRMS (ESI), calcd for $C_{27}H_{54}O_3NaSi_3$ $[M + Na]^+$ 533.3269, found 533.3273.

Compound **9**. To a solution of **8** (6.14 g, 12 mmol) in MeOH (25 mL) was added *p*-toluenesulfonic acid monohydrate (69 mg, 0.36 mmol) at room temperature. The resulting mixture was stirred at room temperature; the reaction was monitored by TLC. When TLC showed no presence of compound **8**, the resulting solution was diluted with ethyl acetate (100 mL) and neutralized with a saturated aqueous solution of $NaHCO_3$ (20 mL × 3). Organic layer was washed with water (40 mL × 4) and dried over anhydrous sodium sulfate. After evaporation of solvent, the residue was purified by chromatography on silica gel (hexane/ethyl acetate, 5:1) to afford **9** (2.19 g, 65%) as a white solid; mp 80–81 °C. IR (PTFE) 3245 (w), 2926 (w), 2883 (w), 2855 (w), 1459 (m), 1200 (s) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.12 (s, 1H), 4.61 (d, J = 4.8 Hz, 4H), 2.28 (s, 3H), 1.02 (s, 9H), 0.17 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 147.8, 131.8, 131.7, 129.1, 61.1, 26.1, 20.7, 18.7, −3.6; HRMS (ESI), calcd for $C_{15}H_{26}O_3NaSi$ $[M + H]^+$ 305.1543, found 305.1540.

Compound **2**. To a solution of 4 (711 mg, 2.5 mmol) in DCM (5.0 mL) was added (diethylamino)sulfur trifluoride (0.99 mL, 7.5 mmol) at 0 °C. The resulting mixture was stirred at 0 °C; the reaction was monitored by TLC. When TLC showed no presence of compound **9**, the reaction was quenched with water (10 mL). Organic layer was washed with a saturated aqueous solution of $NaHCO_3$ (20 mL) and brine (20 mL × 2) and subsequently dried over anhydrous sodium sulfate. After evaporation of solvent, the residue was purified by preparative GPC (in chloroform, 62 min) to afford **2** (268 mg, 37%) as a colorless oil. IR (PTFE) 2956 (s), 2932 (s), 2898 (m), 2860 (s), 1479 (s), 1464 (s), 1257 (s) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.21 (s, 2H), 5.35 (d, J = 48.0 Hz, 4H), 2.31 (s, 3H), 1.04 (s, 9H), 0.18 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 148.9, 131.6, 127.3, 127.2, 80.2 (d, J = 165 Hz, C-F coupling), 26.0, 20.6, 18.8, −4.0; ^{19}F NMR (565 MHz, $CDCl_3$) −206.9 (t, J = 47.7); HRMS (ESI), calcd for $C_{15}H_{24}OFSi$ $[M - F]^+$ 267.1575, found 267.1556; calcd for $C_{15}H_{24}OF_2NaSi$ $[M + Na]^+$ 309.1457, found 309.1486.

4.3. Amplification of fluoride ions and inducement of chemiluminescence

The amplification of fluoride ions with **2** and inducement of chemiluminescence of **1** was performed as follows.

Appropriate amounts of **2** and triethylamine (6% solution in DCM, 0.50 mL, 0.22 mmol) were added to a fluoropolymer tube. To this mixture solution was added TBAF (1.0×10^{-3} M solution in DCM, 0.020 mL, 0.020 μmol). The resulting mixture was stirred at room temperature for 2–4 h; the reaction was monitored by TLC. When TLC showed no presence of compound **2**, the mixture was added to a solution with an appropriate amount of **1** in DCM (0.48 mL). Immediately, thereafter, the chemiluminescence spectra of **1** were recorded.

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