

## Ratiometric sensing of fluoride ions using Raman spectroscopy

*Electronic Supplementary Information*

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## Materials and Methods

### Raman spectroscopy

Raman spectra were acquired on a Renishaw InVia Raman microscope equipped a 785 nm diode laser providing a maximum power of 300 mW using a 1200 l/mm grating.

*Neat samples:* A small amount of sample compounds **1** or **2** was transferred onto a CaF<sub>2</sub> window and Raman spectra were acquired using  $\lambda_{\text{ex}} = 785$  nm and a 20× NA 0.4 NPlanEPI objective (~95 mW, Leica) for 10 s.

*Reaction monitoring:* The reaction mixture was prepared in a quartz cuvette (500  $\mu\text{L}$ ) and Raman spectra were acquired using a 5× NA 0.12 NPlanEPI objective (Leica) or a 20× NA 0.4 NPlanEPI objective (Leica). Spectra were acquired continuously using either a 0.5 s or 1 s acquisition time.

*Paper test strips:* Whatman™ Qualitative Filter Paper: Grade 1 Circles were cut into 1 cm × 1 cm squares and treated with sensor **1** (100 mM in THF; 10  $\mu\text{L}$ ). The strips were air-dried (~5 min at r.t.) and subsequently treated with TBAF (0 – 5 mM in THF up to 300  $\mu\text{L}$ ). The test strips were air-dried (~5 min at r.t.) and analysed as per Figure legend.

*Handheld detection:* Raman spectra were acquired using a handheld CBEx spectrometer with 785 nm laser excitation wavelength, from Snowy Range Instruments (now Metrohm). Measurements were acquired using a 10 s integration time. A point and shoot adaptor with a single element lens (N.A. 0.5) was fitted for detection of the filter paper samples which gave an average laser power of ~55 mW at the focus. Individual spectra were acquired from randomly selected points on the test paper sample.

### UV-Visible spectrometry

UV-visible spectra were acquired using a Cary 60 (Agilent Technologies) UV-Vis spectrometer. The reaction mixture was prepared in a plastic cuvette (1.5 mL) and sequential UV-Vis spectra across the range 200 – 800 nm were acquired.

### Data processing

*Raman spectra of reaction mixtures.* All spectra were processed in WiRE 4.4™ software enabling cosmic ray removal and baseline subtraction. Peak normalisation (1450  $\text{cm}^{-1}$ ) was performed in OriginPro2018 software and the peak areas determined using the Integrate tool (Sensor **1** 2140–2185  $\text{cm}^{-1}$ ; desilylated product **2** 2085 –2130  $\text{cm}^{-1}$  and nitrile peak 2205–2255  $\text{cm}^{-1}$ ).

*Raman maps on paper test strips:* All Raman maps were processed in WiRE 4.4™ software enabling cosmic ray removal, noise filtering and baseline subtraction. A custom MATLAB® script was then used to perform ratiometric analysis on the Raman spectral map (20  $\mu\text{m}$  × 20  $\mu\text{m}$ ; 400 spectra). False-colour images for the test paper strips were created based on the peak intensity ratio: 2105  $\text{cm}^{-1}$ / 2160  $\text{cm}^{-1}$  and 2231  $\text{cm}^{-1}$ / 2237  $\text{cm}^{-1}$ . The images were scaled between 0–0.2 (alkyne) or 0–1.0 (nitrile) and are presented in the Parula LUT available in MATLAB®.

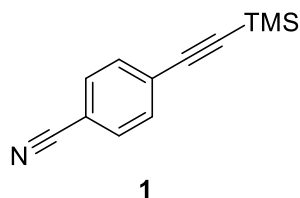
## Chemical Synthesis

### General Procedures

All reagents were obtained from commercial sources, including Sigma-Aldrich, Alfa Aesar and Fluorochem and used without purification unless otherwise stated. The abbreviations Et<sub>2</sub>O and NEt<sub>3</sub> refer to diethyl ether and triethylamine, respectively. The term “*in vacuo*” refers to evaporation under reduced pressure using a rotary evaporator connected to a diaphragm pump, followed by the removal of trace volatiles using a high vacuum (oil) pump. The term “purged” refers to atmospheric exchange *via* 3 evacuation/refill cycles using a Schenck line fitted to a cylinder of inert gas and a high vacuum (oil) pump. Flash chromatography was carried out using Fischer Scientific chromatography grade silica 60 Å particle size 35–70 micron. Analytical thin layer chromatography was carried out using aluminium-backed plates coated with Machery-Nagel pre-coated TLC sheets, coated in 0.20 mm silica gel 60 with UV<sub>254</sub> fluorescent indicator. Sheets were visualized under UV light (at 254 nm) or stained using *p*-anisaldehyde. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance

500 spectrometer, operating at 500 MHz ( $^1\text{H}$ ) and 125 MHz ( $^{13}\text{C}$ ). Chemical shifts were reported in parts per million (ppm) in the scale relative to  $\text{CDCl}_3$ , 7.26 ppm for  $^1\text{H}$  NMR and 77.16 for  $^{13}\text{C}$  NMR. Multiplicities are abbreviated as: s, singlet; d, doublet. Coupling constants are measured in Hertz (Hz). Melting points were obtained on a Stuart SMP11 device. Infrared spectra were recorded in the range 4000–600  $\text{cm}^{-1}$  on a Shimadzu IRAffinity-1 equipped with an ATR accessory.

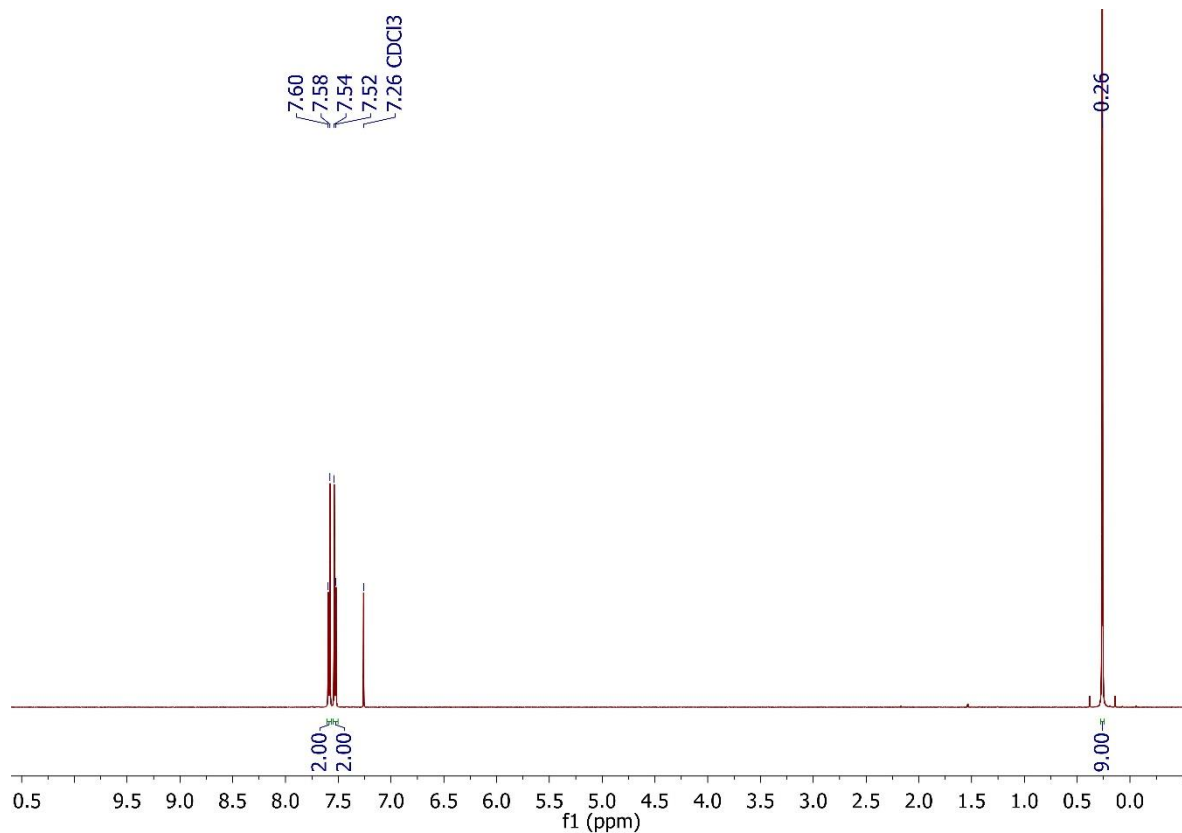
### Synthesis of Sensor 1, 4-((trimethylsilyl)ethynyl)benzonitrile



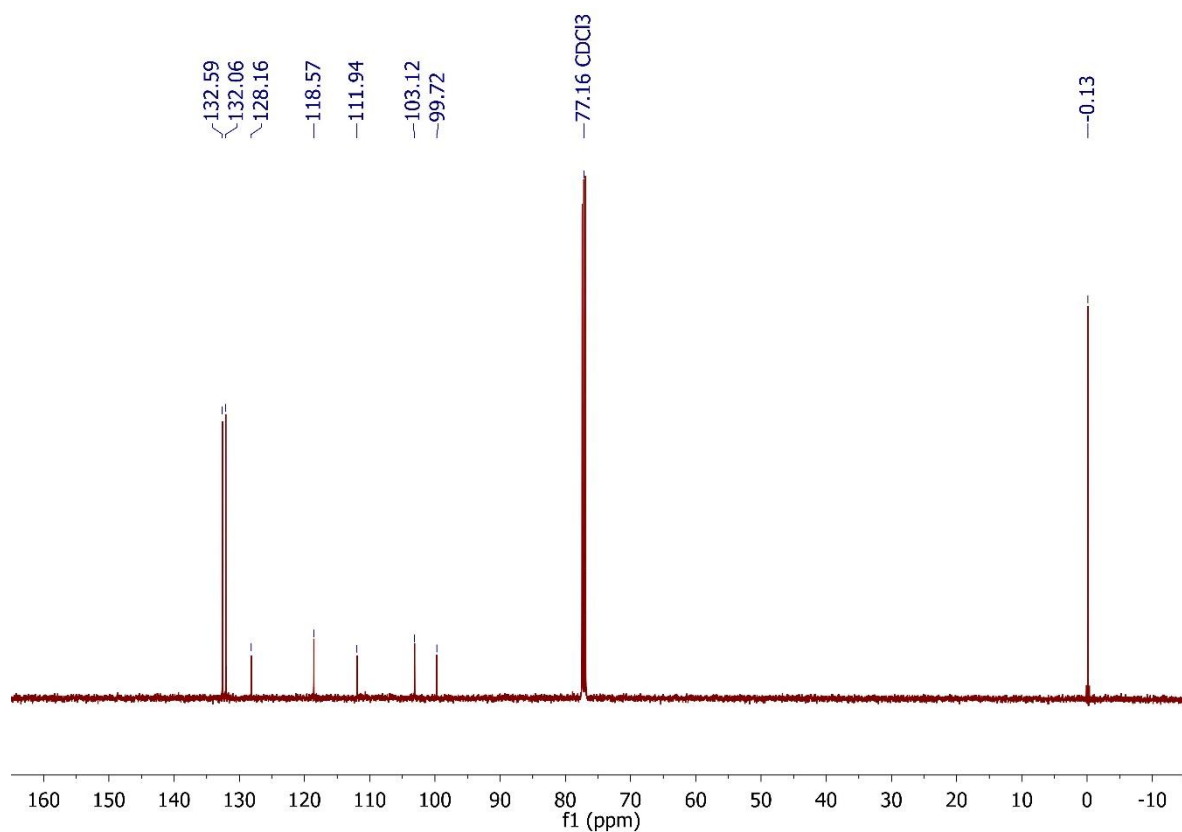
A flame dried 20 mL reaction vial was charged with 4-bromobenzonitrile (273 mg, 1.50 mmol, 1.0 eq), bis(triphenylphosphine)palladium (II) dichloride (10.5 mg, 0.015 mmol, 1 mol%) and copper (I) iodide (3.0 mg, 0.015 mmol, 1 mol%), then sealed purged with nitrogen.  $\text{NEt}_3$  (degassed by 3 freeze-pump-thaw cycles, 6 mL) was added to the reaction vial *via* syringe, followed by (trimethylsilyl)acetylene (230  $\mu\text{L}$ , 1.65 mmol, 1.1 eq) and the reaction was heated to 80  $^\circ\text{C}$  with stirring for 4 h. After cooling to ambient temperature, the reaction mixture was diluted with  $\text{Et}_2\text{O}$  (20 mL), filtered through a pad of celite $^\circledR$  and evaporated *in vacuo*. Purified by silica flash chromatography (3%  $\text{Et}_2\text{O}$ /petroleum ether 40–60) to yield the title compound **1** as a white solid (285 mg, 1.43 mmol, 95%).

**M.P:** 100–102  $^\circ\text{C}$  [Lit:<sup>[1]</sup> 102–103  $^\circ\text{C}$ ]; **FTIR (ATR,  $\text{cm}^{-1}$ ):** 3063.0, 2955.0, 2897.1, 2233.6, 2156.4, 1602.9, 1498.7, 1408.0, 2146.0, 1176.6;  **$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):**  $\delta$  7.59 (d,  $J$  = 8.6 Hz, 2H), 7.53 (d,  $J$  = 8.6 Hz, 2H), 0.26 (s, 9H);  **$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):**  $\delta$  132.6, 132.1, 128.2, 118.6, 111.9, 103.1, 99.7, -0.13.

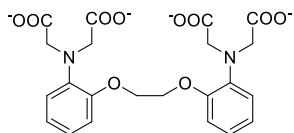
**<sup>1</sup>H NMR Spectrum of Sensor 1 (500 MHz, CDCl<sub>3</sub>)**



**<sup>13</sup>C NMR Spectrum of Sensor 1 (126 MHz, CDCl<sub>3</sub>)**

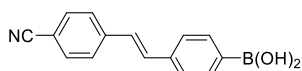


### Metal-chelation sensor

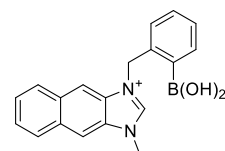


MW: 476.43 g/mol  
*Chem. Commun.* **2011**, 47, 4391

### Boronic acid sensors

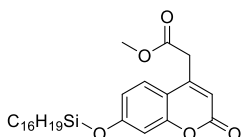


MW: 249.08 g/mol  
*Anal. Biochem.* **2002**, 301, 111

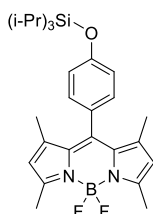


MW: 317.17 g/mol  
*Eur. J. Org. Chem.* **2009**, 3058

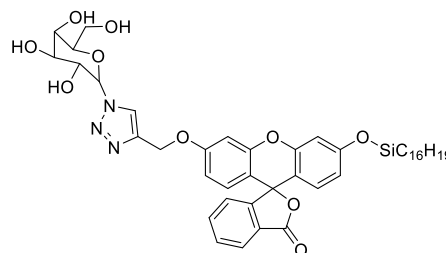
### Fluorescent sensors based on Si-O bond cleavage



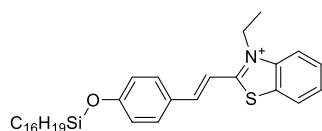
MW: 472.61 g/mol  
*Chem. Commun.* **2009**, 4735



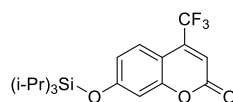
MW: 496.52 g/mol  
*Org. Lett.* **2010**, 12, 1400



MW: 813.94 g/mol  
*Anal. Chim. Acta* **2011**, 703, 219

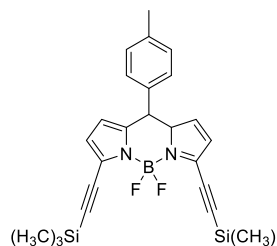


MW: 520.79 g/mol  
*Chem. Commun.* **2011**, 47, 7098

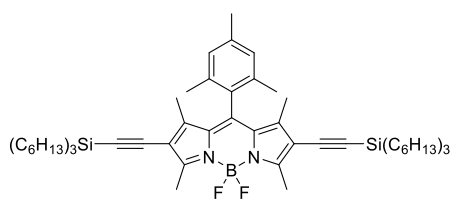


MW: 386.49 g/mol  
*J. Org. Chem.* **2011**, 76, 3820

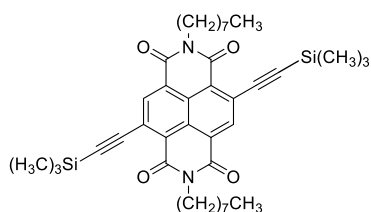
### Fluorescent sensors based on Si-C bond cleavage



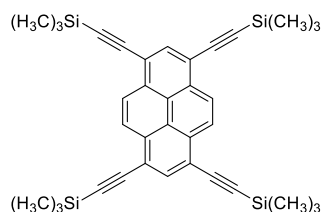
MW: 446.45 g/mol  
*Tetrahedron* **2010**, 66, 1728



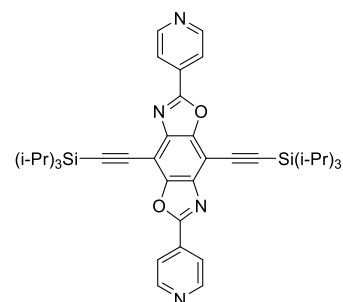
MW: 979.46 g/mol  
*Chem. Commun.* **2011**, 47, 5503



MW: 683.05 g/mol  
*Tetrahedron Lett.* **2011**, 52, 1990

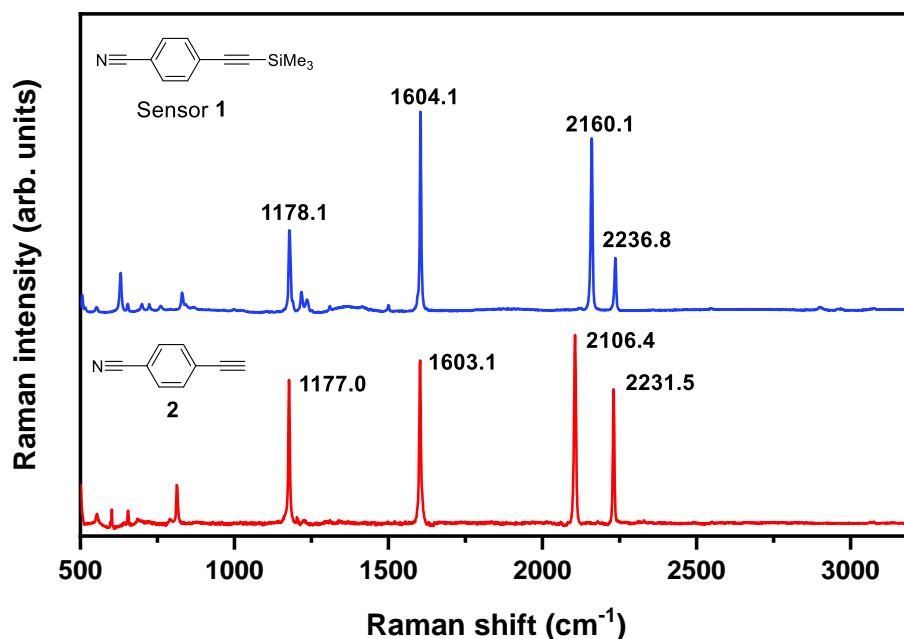


MW: 587.07 g/mol  
*Org. Biomol. Chem.* **2011**, 9, 4558

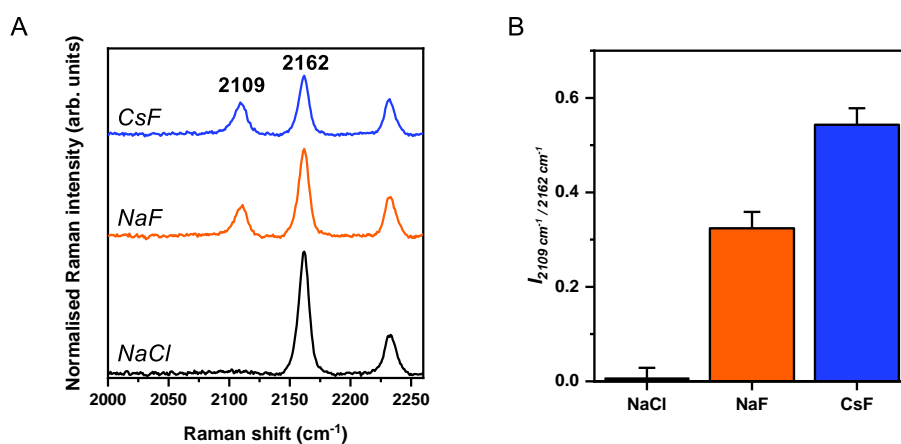


Molecular Weight: 675.04  
*Org. Lett.* **2013**, 15, 3518

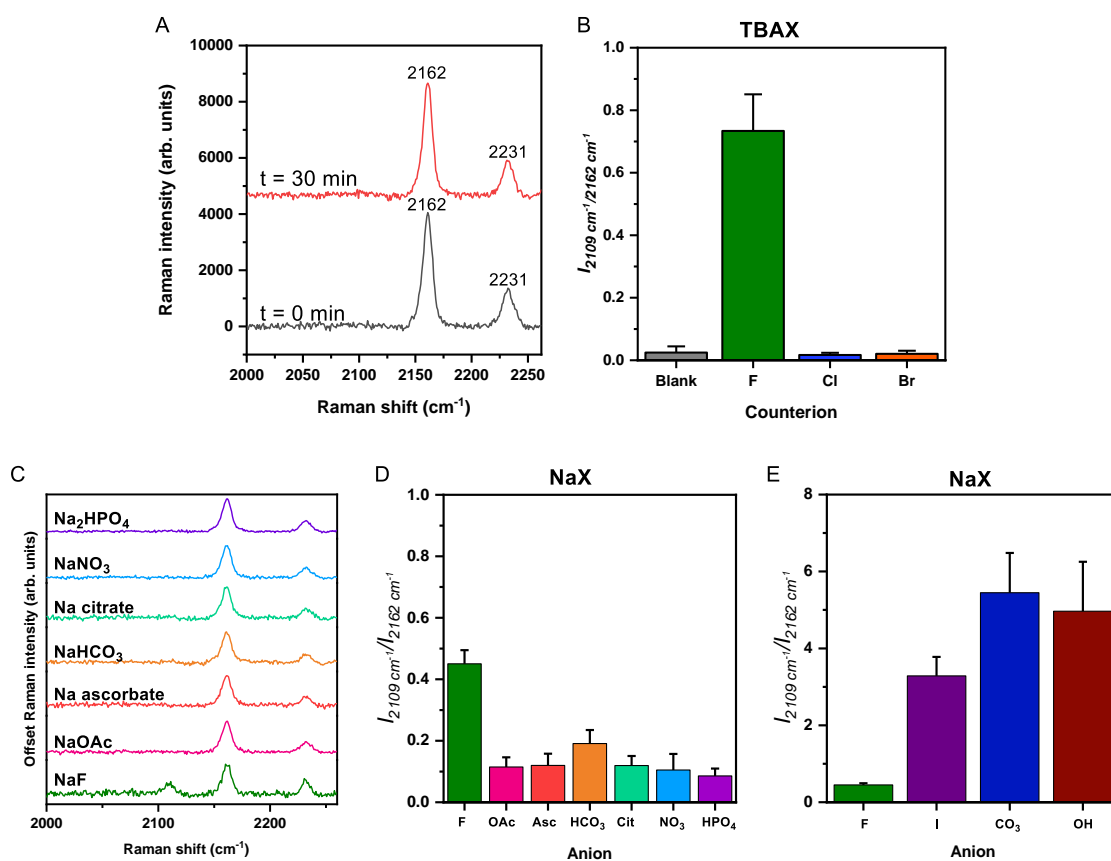
**Figure S1** Previously reported fluorescent fluoride sensors. The sensors are grouped by function: a metal chelation sensor, boronic acid fluoride sensors, fluoride sensors based on Si-O bond cleavage and fluoride sensors based on Si-C bond cleavage.



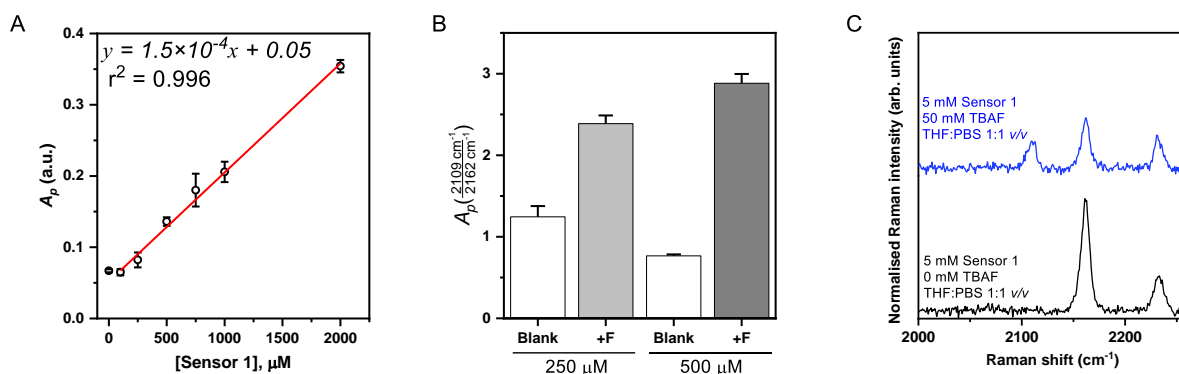
**Figure S2** Analysis of sensor 1 and desilylated product 2 in solid form. Raman spectra were acquired from solid samples of sensor 1 (top, blue trace) and desilylated alkyne 2 (bottom, red trace) using  $\lambda_{\text{ex}} = 785 \text{ nm}$  for 10 s with a 20x objective lens ( $\sim 95 \text{ mW}$ ). Peak assignments are in  $\text{cm}^{-1}$ .



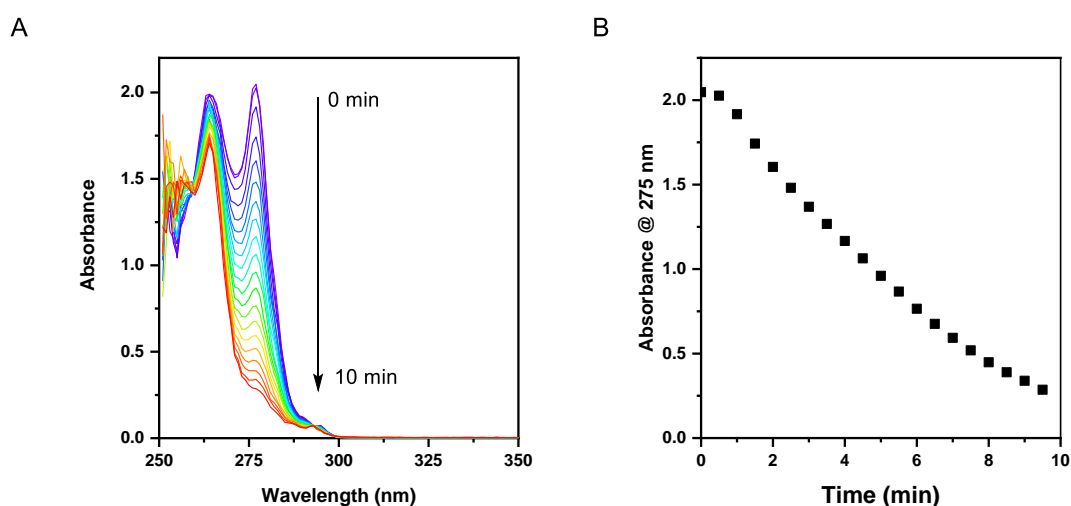
**Figure S3** Analysis of the desilylation of sensor 1 using different fluoride sources. Sensor 1 (5 mM) was treated with NaCl, NaF or CsF at a concentration of 50 mM (10 equiv.) in THF:Water (1:1 v/v). Raman spectra were acquired after 30 min at  $20 \text{ }^\circ\text{C}$  using 785 nm for 10s with a 20x objective lens ( $\sim 180 \text{ mW}$ ). **A** Average Raman spectra acquired from 6 replicates normalised to the THF peak at  $1450 \text{ cm}^{-1}$ . **B** Ratio analysis of the  $2109 / 2162 \text{ cm}^{-1}$  peaks from the 6 replicates in **A**. Error bars:  $\pm$ S.D.



**Figure S4** Control reactions for the desilylation reaction of sensor **1**. **A** A mixture of sensor **1** (5 mM in THF:water 1:1 *v/v*) was analysed using Raman spectroscopy at *t* = 0 min and *t* = 30 min. The acquisitions show no peak at 2109 cm<sup>-1</sup> (i.e. no desilylated product **2** was observed). Raman spectra were acquired using 785 nm excitation and a 20x objective lens (~180 mW) for 10 s. **B** Analysis of sensor **1** with different counter anions. Sensor **1** (5 mM in THF) was treated with either THF (Blank) or TBAX (X= F, Cl, Br; 50 mM prepared from a 100 mM stock in water). Raman spectra were acquired after 30 min at 20 °C using 785 nm for 10s using a 20x objective lens (~180 mW). Data represents the mean peak area ratio at 2109/2162 cm<sup>-1</sup> from three replicates with error bars ± S.D. **C** and **D** Analysis of sensor **1** with different counter anions. Sensor **1** (5 mM in THF) was treated with NaX (X= fluoride, acetate, ascorbate, hydrogen carbonate, citrate, nitrate and phosphate; 50 mM prepared from a 100 mM stock in water). Raman spectra were acquired after 30 min at 20 °C using 785 nm for 10 s using a 20x objective lens (~180 mW). Data represents the mean peak area ratio at 2109/2162 cm<sup>-1</sup> from three replicates with error bars ± S.D. **E** As per **C** and **D**, but using NaI and at high pH using NaX (X = carbonate and hydroxide) showing decomposition of the sensor occurs.

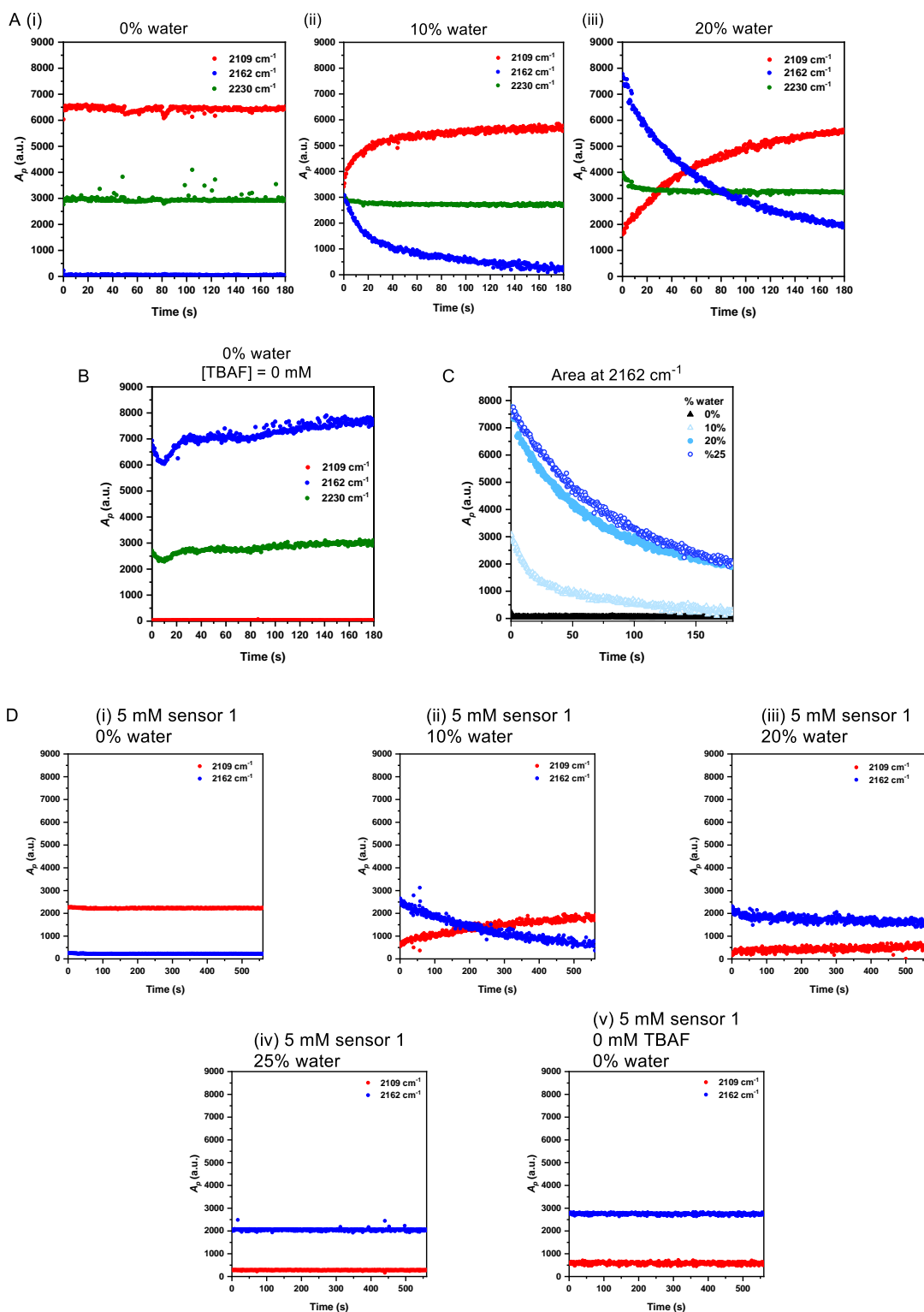


**Figure S5** Solution phase analysis of sensor **1** in THF. **A** Calibration curve of sensor **1** in THF. Solutions of sensor **1** were analysed by Raman spectroscopy using  $\lambda_{\text{ex}} = 785 \text{ nm}$  using a 5x lens ( $\sim 180 \text{ mW}$ ) for 30 s (3 accumulations). A linear fitting is applied. **B** Analysis of the reaction of sensor **1** with 1 equiv. TBAF at (i) Sensor **1** (250  $\mu\text{M}$ ) + TBAF (250  $\mu\text{M}$ ) and (ii) Sensor **1** (500  $\mu\text{M}$ ) + TBAF (500  $\mu\text{M}$ ). In the samples labelled 'Blank', TBAF was replaced with an equal volume of THF. Raman spectra were acquired as per **A**. Data represent the mean peak area ( $A_p$ ) ratio at 2109/2162  $\text{cm}^{-1}$  from three repeats with error bars  $\pm$  S.D. **C** Analysis of sensor **1** in THF:PBS (1:1 v/v). A 5 mM solution of sensor **1** was treated with (i) THF:PBS (1:1 v/v) (blank) or (ii) TBAF (50 mM in THF:PBS (1:1 v/v)). Raman spectra were acquired after 15 min at RT using  $\lambda_{\text{ex}} = 785 \text{ nm}$  using a 5x lens ( $\sim 180 \text{ mW}$ ) for 10 s. Spectra representative of 3 repeats.



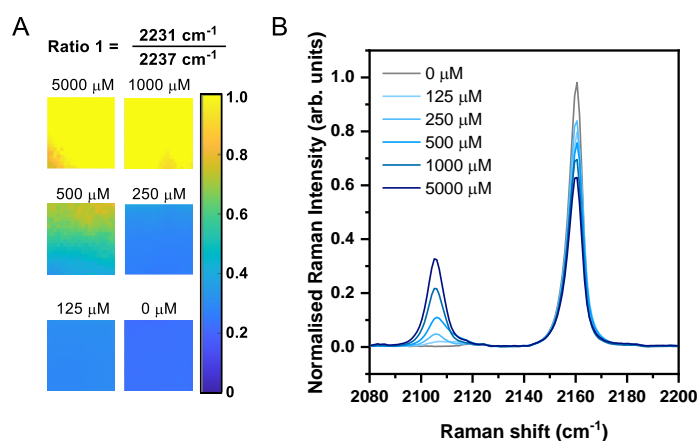
**Figure S6** Analysis of the desilylation of sensor **1** using UV-Vis spectrometry. **A** Sensor **1** (50  $\mu\text{M}$ ) was mixed with TBAF (50  $\mu\text{M}$ ) in THF and sequentially analysed by UV-Vis spectrometry for 10 min. **B** A plot of absorbance at 275 nm as a function of time for the reaction in **A**. This reaction shows a decrease in absorbance at  $\sim 280 \text{ nm}$  which is in good agreement with a similar TMS-protected alkyne – see Supplementary Information File Ref. [2].



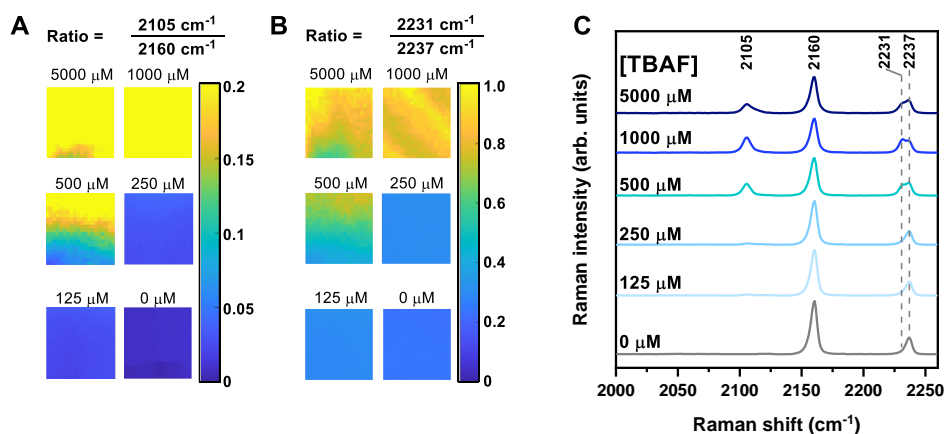


**Figure S7** Analysing the effect of water upon the desilylation reaction of sensor 1. **A** Reaction profiles for the desilylation reaction of **1** (50 mM) with TBAF (75 mM) in (i) THF, (ii) THF:water (90:10 v/v) and (iii) THF:water (80:20 v/v). The peak areas ( $A_p$ ) at 2162  $\text{cm}^{-1}$  (C≡C-TMS, **1**), 2109  $\text{cm}^{-1}$  (desilylated alkyne, **2**) and 2230  $\text{cm}^{-1}$  (C≡N) are plotted as a function of time. **B** Control reaction of sensor **1** (50 mM) in the absence of TBAF in THF solution. **C** Reaction profiles for the decrease in the 2162  $\text{cm}^{-1}$  signal (sensor **1**) when the %water is varied in the reaction mixture.  $A_p$  = peak area at 2162  $\text{cm}^{-1}$ . Raman spectra were acquired using 785 nm

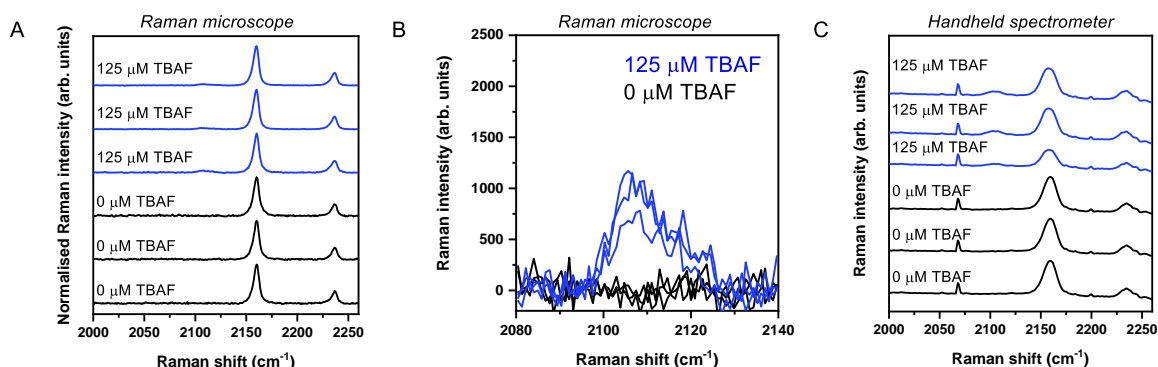
for 0.5 s using a 5× objective lens (~180 mW) and normalised to the intensity of the THF solvent peak at 1450 cm<sup>-1</sup> (CH<sub>2</sub> def). The reaction monitoring started ~5 s after the addition of TBAF. **D** Reaction profiles for the desilylation reaction of **1** (5 mM) with TBAF (7.5 mM) in (i) THF, (ii) THF:water (90:10 v/v), (iii) THF:water (80:20 v/v), (iv) THF:water (75:25 v/v) and (v) is a control reaction where [TBAF] = 0 mM. The peak areas ( $A_p$ ) at 2162 cm<sup>-1</sup> (C≡C-TMS, **1**) and 2109 cm<sup>-1</sup> (desilylated alkyne, **2**) are plotted as a function of time. Raman spectra were acquired using 785 nm for 1 s using a 5× objective lens (~180 mW) and normalised to the intensity of the THF solvent peak at 1450 cm<sup>-1</sup> (CH<sub>2</sub> def).



**Figure S8** Paper-based detection of fluoride using Raman sensor **1** using the ratio of the nitrile band. **A** These maps accompany those acquired in Figure 4. Filter paper was pre-treated with sensor **1** (100 mM in THF, 10  $\mu\text{L}$ ) before air-drying and subsequent treatment with TBAF in THF at the indicated concentrations. Raman maps were acquired across 20  $\mu\text{m}$   $\times$  20  $\mu\text{m}$  (1  $\mu\text{m}$  pixel size; 400 spectra) using 785 nm laser excitation with a 20× objective lens (~180 mW) for 0.5 s. The maps represent the ratio of the nitrile band at 2231 cm<sup>-1</sup>/2237 cm<sup>-1</sup> (for desilylated product/sensor **1**). **B** Expanded view of the Raman spectra presented in Figure 4B, indicating signal at 2109 cm<sup>-1</sup> when 125  $\mu\text{M}$  TBAF is added.



**Figure S9** Repeat analysis of the paper-based detection of fluoride using Raman sensor **1**. Filter paper was pre-treated with sensor **1** (100 mM in THF, 10  $\mu$ L) before air-drying and subsequent treatment with TBAF in THF at the indicated concentrations. Raman maps were acquired across 20  $\mu$ m  $\times$  20  $\mu$ m (1  $\mu$ m pixel size; 400 spectra) using 785 nm laser excitation with a 20 $\times$  objective lens ( $\sim$ 180 mW) for 0.5s. The maps represent the following ratios: **A** 2105  $\text{cm}^{-1}$ /2160  $\text{cm}^{-1}$ ; **B** 2231  $\text{cm}^{-1}$ /2237  $\text{cm}^{-1}$  (for desilylated product/sensor **1**) and **C** the average Raman spectra from the maps presented in **A** and **B**.



**Figure S10** Paper-based detection of fluoride using a Raman microscope and a handheld spectrometer. Filter paper was pre-treated with sensor **1** (100 mM in THF, 10  $\mu$ L) before air-drying and subsequent treatment with TBAF in THF (either 125  $\mu$ M or 0  $\mu$ M). Point spectra were acquired using either (**A**) – (**B**) a Raman microscope (785 nm laser excitation with a 20 $\times$  objective lens ( $\sim$ 180 mW) for 10s) or (**C**) a handheld spectrometer (785 nm laser excitation for 10s ( $\sim$ 55 mW)). Three repeat spectra from the same paper test strip are provided in each case.

## References

1. M. Valášek, K. Edelmann, L. Gerhard, O. Fuhr, M. Lukas and M. Mayor, *J. Org. Chem.*, 2014, **79**, 7342-7357.
2. M. Jo, J. Lim and O. Š. Miljanić, *Org. Lett.*, 2013, **15**, 3518-3521.