Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

A Small Molecule Sensor for Fluoride Based on an Autoinductive, Colorimetric Signal Amplification Reaction

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Supporting Information

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Materials:

All reactions were performed in flame-dried glassware under a positive pressure of argon. Air- and moisture-sensitive liquids were transferred by syringe or stainless steel cannula. Organic solutions were concentrated by rotary evaporation (25–40 mmHg) at ambient temperature, unless otherwise noted. *p*-Difluoromethylbenzoic acid, 4-formylbenzoic acid, and all other reagents were purchased commercially and were used as received unless otherwise noted. Flash-column chromatography was performed as described by Still et al.,[1] employing silica gel (60-Å pore size, 32–63 μm, standard grade, Dynamic Adsobents). Thin layer chromatography was carried out on Dynamic Adsorbants

silica gel TLC (20 × 20 cm w/h, F-254, 250 μm). Deionized water was purified with a Millipore-purification system (Barnstead EASYpure® II UV/UF). Kinetics experiments were carried out in 1.7 mL VWR microcentrifuge tubes.

Instumentation:

Photographs were taken with a Nikon digital camera (D40). Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded using a Bruker CDPX-300 (300 MHz) NMR spectrometer at 25 °C. Proton chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to residual protium in the NMR solvent ($CDCl_3$, δ 7.26 ppm). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and/or multiple resonances), integration, and coupling constant (*J*) in Hertz. Carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded on a Bruker AMX-360 (75 MHz) NMR spectrometer at 25 °C. Carbon chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to the carbon resonances of the NMR solvent ($CDCl_3$, δ 77.0).

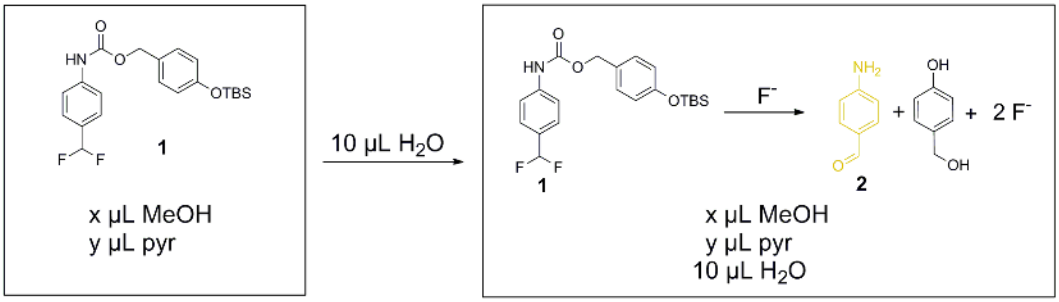
Synthesis of Amplification Reagent 1:

Amplification Reagent 1.
p-Difluoromethylbenzoic acid (**2**) (0.2 g, 1.2 mmol, 1.0 equiv) was dissolved in dichloromethane (5.8 mL), and the resulting solution was cooled to 0 °C. Oxalyl chloride (0.12 mL, 1.4 mmol, 1.2 equiv) was added dropwise to the ice-cold solution, followed by 5 drops of *N,N*-dimethylformamide. The reaction mixture was heated to 100 °C and was stirred for 1 h. The solution was removed from heat and allowed to cool to 23 °C, at which point the solution was concentrated under reduced pressure. The resulting residue was re-dissolved in acetone (2.9 mL) and was cooled to 0 °C. A solution of sodium azide (0.23 g, 3.5 mmol, 3 equiv; dissolved in 2.9 mL water) was added dropwise, and the reaction solution was stirred at 0 °C for 1 h. The solution was diluted with ethyl acetate (50 mL) and the layers were separated. The organic layer was dried over sodium sulfate, the solids were filtered through a fritted Büchner funnel, and the remaining liquid was concentrated under reduced pressure. The residue was dissolved in toluene (5.8 mL), and this solution was heated to 100 °C for 1 h. The reaction mixture was allowed to cool to room temperature, and *p*-[(*tert*-butyldimethylsilyl)oxy]benzyl alcohol (0.33 g, 1.4 mmol, 1.2 equiv) was added in one portion. The reaction mixture was heated to 100 °C, and was stirred at this temperature for 3 h. The solution was cooled to room temperature and concentrated, and the resulting residue was purified via column chromatography (elution with 5% EtOAc–hexanes) to afford compound **1** as a white solid (0.41 g, 1.0 mmol, 87%). ^{1}H NMR ($CDCl_3$): δ 7.51 (d, 2 H, *J* = 9), 7.46 (d, 2 H, *J* = 9), 7.31 (d, 2 H, *J* = 9), 6.88 (d, 2 H, *J* = 9), 6.63 (t, 1 H, *J* = 57), 4.92 (s, 2 H), 1.02 (s, 9 H), 0.24 (s, 6 H). This ^{1}H NMR data matches previously published data for **1**.[2]

Synthesis of Control Reagent 3:

4-(tert-Butyldimethylsilyloxy)benzyl 4-Formylphenylcarbamate (3).
4-Formylbenzoic acid (0.33 g, 2.18 mmol, 1.0 equiv) was added to dichloromethane (11 mL) and the resulting solution was cooled to 0 °C. Oxalyl chloride (0.37 mL, 4.36 mmol, 2.0 equiv) was added dropwise to the ice-cold solution, followed by 4 drops of *N,N*-dimethylformamide. The reaction mixture was stirred at 0 °C for 1 h. The solution was allowed to warm to 23 °C, at which point the solution was concentrated under reduced pressure. The resulting residue was re-dissolved in acetone (5.5 mL) and was cooled to 0 °C. A solution of sodium azide (0.28 g, 4.36 mmol, 2 equiv; dissolved in 5.5 mL water) was added dropwise, and the reaction solution was stirred at 0 °C for 1 h. The solution was diluted with ethyl acetate (15 mL) and the layers were separated. The organic layer was dried over sodium sulfate, the solids were filtered through a fritted Büchner funnel, and the remaining liquid was concentrated under reduced pressure. The residue was dissolved in toluene (11 mL), and this solution was heated to 100 °C for 1 h. The reaction mixture was allowed to cool to room temperature, and *p*-[(*tert*-butyldimethylsilyl)oxy]benzyl alcohol (0.52 g, 2.18 mmol, 1.0 equiv) was added in one portion. The reaction mixture was heated to 100 °C, and was stirred at this temperature for 3 h. The solution was cooled to room temperature and concentrated, and the resulting residue was purified via column chromatography (elution with 10% EtOAc–benzene) to afford compound **5** as a white solid (0.72 g, 1.87 mmol, 86%). NMR ($CDCl_3$): δ 9.85 (s, 1 H), 7.79 (m, 3 H,), 7.61 (d, 2 H, J = 8), 7.26 (d, 2 H, J = 8), 6.83 (d, 1 H, J = 8), 5.14 (s, 2 H), 1.00 (s, 9 H), 0.21 (s, 6 H). This ^{1}H NMR data matches previously published data for **3**.[3]

Procedure for Pyridine Solvent Screen



Scheme S1. Aliquots (10 µL) of aqueous CsF (0.62 M) were added to separate 0.12 M solutions of compound **1**. The ratios of methanol–pyridine–water tested are shown in Table S1. At hour intervals, photographs were obtained and analyzed using Adobe®Photoshop®. The digital images were cropped just above and below the solution in the centrifuge tube. The image was magnified six times and the color was inverted using the inversion setting. Using the circular marquee tool, a section of approximately 300 pixels just below the meniscus of the solution was highlighted. The mean intensity in the blue channel on the histograph function was recorded. The mean intensities were subtracted from the mean intensities for the centrifuge tubes at time 0.

Table of time to reach maximum colorimetric signal with the volume of pyridine

Table S1. Rates of colorimetric production resulting from the reaction of **1** with fluoride under varying ratios of methanol to pyridine.

MeOH (μL)	Pyridine (μL)	Time to reach max signal (h)
95	0	8
94	1	5
93	2	5
92	3	5
91	4	5
90	5	5
80	25	6
70	35	7
60	45	10

Tables of Color Intensity for Pyridine Solvent Screen

Table S2. Intensities of color for 95:10 MeOH–H_2O

Time (h)	Trial 1	Trial 2	Trial 3
1	39	36	41
2	67	65	65
3	78	78	77
4	82	82	85
5	88	86	90
6	93	91	93
7	96	96	96
8	100	100	100

Table S3. Intensities of color for 94:1:10 MeOH–pyr–H_2O

Time (h)	Trial 1	Trial 2	Trial 3
1	50	51	50
2	73	73	73
3	86	86	85
4	93	95	94
5	100	100	100

Table S4. Intensities of color for 93:2:10 MeOH–pyr–H_2O

Time (h)	Trial 1	Trial 2	Trial 3
1	51	50	50
2	74	73	74
3	86	87	85
4	97	95	94
5	100	100	100

Table S5. Intensities of color for 92:3:10 MeOH–pyr–H_2O

Time (h)	Trial 1	Trial 2	Trial 3
1	49	50	48
2	74	71	73
3	86	87	85
4	96	94	95
5	100	100	100

Table S6. Intensities of color for 91:4:10 MeOH–pyr–H_2O

Time (h)	Trial 1	Trial 2	Trial 3
1	47	46	46
2	70	72	73
3	88	84	87
4	96	96	94
5	100	100	100

Table S7. Intensities of color for 90:5:10 MeOH–pyr–H_2O

Time (h)	Trial 1	Trial 2	Trial 3
1	50	49	47
2	73	71	72
3	87	86	88
4	97	96	96
5	100	100	100

Table S8. Intensities of color for 80:15:10 MeOH–pyr–H_2O

Time (h)	Trial 1	Trial 2	Trial 3
1	37	37	37
2	67	65	64
3	82	81	80
4	90	90	89
5	98	97	96
6	100	100	100

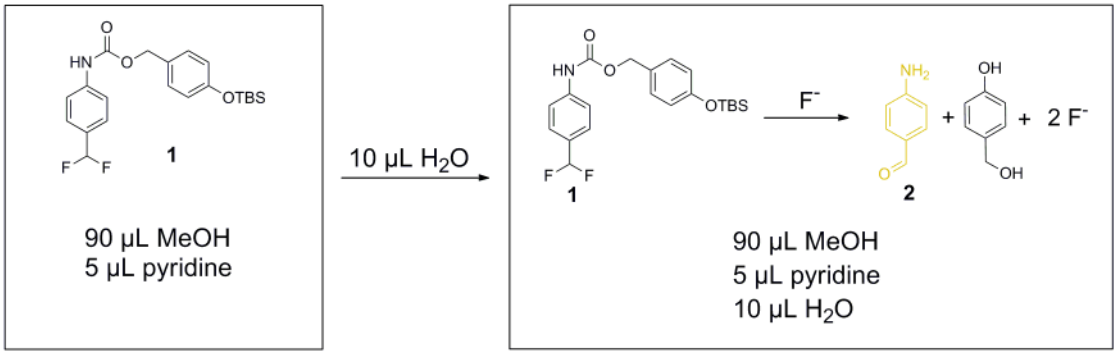
Table S9. Intensities of color for 70:25:10 MeOH–pyr–H_2O

Time (h)	Trial 1	Trial 2	Trial 3
1	30	29	31
2	59	58	57
3	73	71	74
4	82	81	84
5	90	90	88
6	96	97	97
7	100	99	99

Table S10. Intensities of color for 60:35:10 MeOH–pyr–H_2O

Time (h)	Trial 1	Trial 2	Trial 3
1	21	26	24
2	45	49	47
3	61	66	67
4	70	77	75
5	79	81	83
6	85	89	87
7	89	92	92
8	95	94	94
9	94	96	95
10	99	100	99

Procedure for Figure 3a: Measuring the Autoinductive Colorimetric Readout Provided by Reagent 1 in Methanol.



Scheme S2. Aliquots (10 µL) of solutions of CsF (610 µM – 1.22 M) were added to separate 0.12 M solutions of compound **1** in 18:1 MeOH–pyridine (95 µL). At hour intervals, photographs were obtained and analyzed using Adobe®Photoshop®. The digital images were cropped just above and below the solution in the centrifuge tube. The image was magnified six times and the color was inverted using the inversion setting. Using the circular marquee tool, a section of approximately 300 pixels just below the meniscus of the solution was highlighted. The mean intensity in the blue channel on the histograph function was recorded. The mean intensities were subtracted from the mean intensities for the centrifuge tubes at time 0.

Tables of Color Intensity for Figure 3a

Table S12. Intensities of color for 23,000 ppm fluoride

Time (h)	Trial 1	Trial 2	Trial 3
0.25	41	39	40
0.5	65	64	66
0.75	77	76	79
1	96	93	95
1.25	101	101	101

Table S13: Intensities of color for 2,300 ppm fluoride

Time (h)	Trial 1	Trial 2	Trial 3
1	54	53	51
2	73	75	73
3	88	86	86
4	101	101	101

Table S14. Intensities of color for 230 ppm fluoride

Time (h)	Trial 1	Trial 2	Trial 3
1	13	10	11
2	25	26	24
3	40	41	39
4	56	56	55
5	66	68	65
6	76	76	75
7	84	87	84
8	90	88	87
9	95	95	95
10	101	101	101

Table S15. Intensities of color for 23 ppm fluoride

Time (h)	Trial 1	Trial 2	Trial 3
1	1	2	2
3	8	6	8
5	12	9	11
7	25	19	22
9	45	36	39
11	67	61	62
13	84	76	81
15	92	92	88
17	100	98	99

Table S16. Intensities of color for 11.5 ppm fluoride

Time (h)	Trial 1	Trial 2
11	3	2
13	6	5
15	7	4
17	12	8
19	28	16
21	48	35
23	58	68
25	82	76
27	99	87
29	101	99
31	101	101

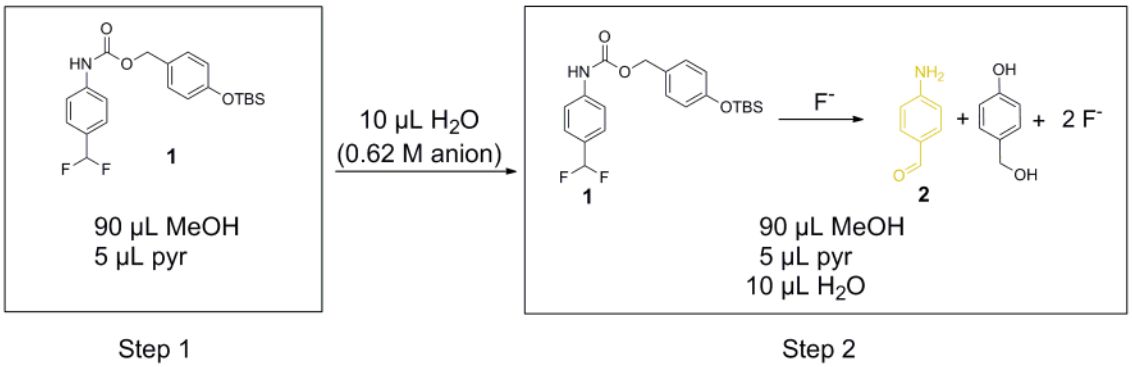
Table S17. Intensities of color for 2.3 ppm fluoride

Time (h)	Trial 1	Trial 2
31	2	0
33	4	5
35	5	8
37	14	18
39	31	37
41	58	62
43	79	79
45	91	95
47	99	101

Table S18. Intensities of color for 0.0 ppm fluoride

Time (h)	Trial 1	Trial 2	Trial 3
35	2	2	1
37	5	3	3
39	15	6	4
41	31	19	10
43	56	44	24
45	77	69	55
47	87	81	71
49	101	97	88
51	101	101	101

Selectivity of Compound 1 for Fluoride over Other Anions in Methanol (Figure 3c)



Scheme S4. In separate experiments, CsF, KCl, KBr, KI, KNO_3, KSCN, KO_2CCH_3, tetrabutylammonium phosphate and tetrabutylammonium sulfate (0.5 equivalents) were added to a 0.12 M solution of compound **1** (105 µL) in 18:1:2 MeOH–pyridine–H_2O at 23 °C. Photographs were obtained after 3 h of amplification using the procedure described in Scheme S1.

Table S26. Intensities of color for the selectivity study in Figure 3c.

anion	Trial 1	Trial 2	Trial 3
Cl^-	4	3	2
Br^-	1	0	0
I^-	1	0	3
NO_3^-	2	1	2
$H_2PO_4^-$	0	1	0
SO_4^{2-}	1	0	1
SCN^-	0	1	4
$CH_3CO_2^-$	3	4	4
F^-	97	97	97
No Ions	3	2	1

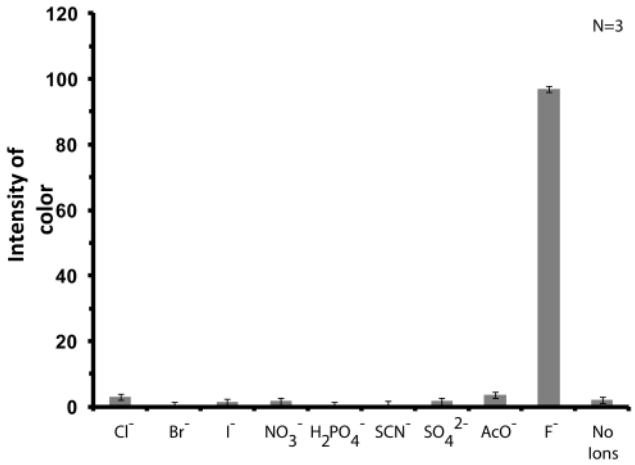
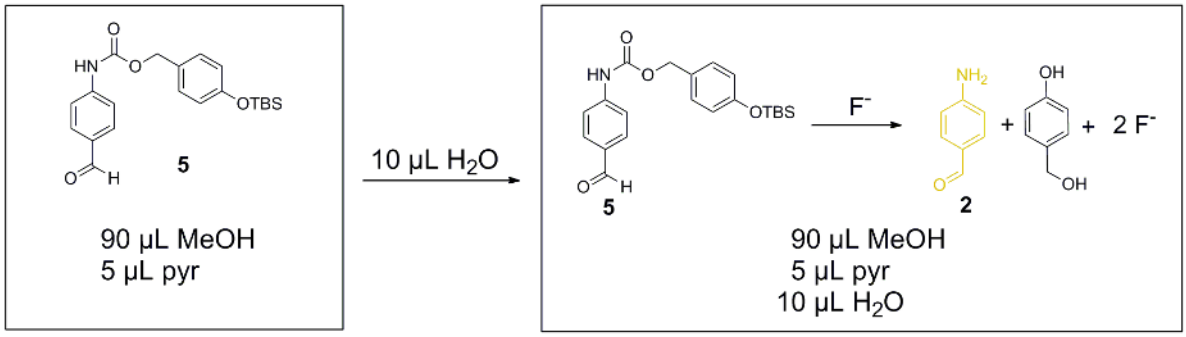


Figure S1. In separate experiments nine different anions (0.5 equiv, 10 µL H_2O) were added to a 0.13 M solution of compound **1** (95 µL) in 18:1 MeOH/pyr. Photographs were taken after 3 h of amplification. Error bars reflect the standard deviations from the average value.

Procedure for Measuring the Colorimetric Readout Provided by Reagent 3 (Figure 4b)



Scheme S3. Aliquots (10 µL) of solutions of CsF (610 µM – 1.22 M) were added to separate 0.12 M solutions of compound **5** in 18:1 MeOH–pyridine (95 µL). At hour intervals, photographs were obtained and analyzed using Adobe®Photoshop®. The digital images were cropped just above and below the solution in the centrifuge tube. The image was magnified six times and the color was inverted using the inversion setting. Using the circular marquee tool, a section of approximately 300 pixels just below the meniscus of the solution was highlighted. The mean intensity in the blue channel on the histograph function was recorded. The mean intensities were subtracted from the mean intensities for the centrifuge tubes at time 0.

Tables of Color Intensity for Figure 4b

Table S19. Intensities of color for 23,000 ppm fluoride

Time (h)	Trial 1	Trial 2	Trial 3
1	61	60	59
4	60	59	58
8	54	53	53
12	56	55	54
16	55	55	55
22	53	53	51
30	55	56	55
38	56	55	56
46	57	55	57
51	58	58	57

Table S20. Intensities of color for 2,300 ppm fluoride

Time (h)	Trial 1	Trial 2	Trial 3
1	30	32	26
4	30	32	31
8	31	33	33
12	30	30	31
16	33	33	33
22	31	31	31
30	32	34	34
38	30	32	30
46	29	30	31
51	29	31	28

Table S21. Intensities of color for 230 ppm fluoride

Time (h)	Trial 1	Trial 2	Trial 3
1	7	6	7
4	9	5	4
8	8	6	9
12	8	5	5
16	11	9	10
22	8	7	8
30	12	9	8
38	9	7	7
46	9	7	8
51	7	4	5

Table S22. Intensities of color for 23 ppm fluoride

Time (h)	Trial 1	Trial 2	Trial 3
1	3	4	4
4	4	3	4
8	4	3	4
12	1	2	1
16	5	5	5
22	2	2	2
30	4	7	7
38	3	3	4
46	4	4	5
51	2	3	3

Table S23. Intensities of color for 11.5 ppm fluoride

Time (h)	Trial 1	Trial 2	Trial 3
1	2	3	3
4	3	4	3
8	2	2	2
12	0	1	1
16	4	4	6
22	2	4	3
30	7	1	6
38	3	3	4
46	2	5	3
51	2	3	3

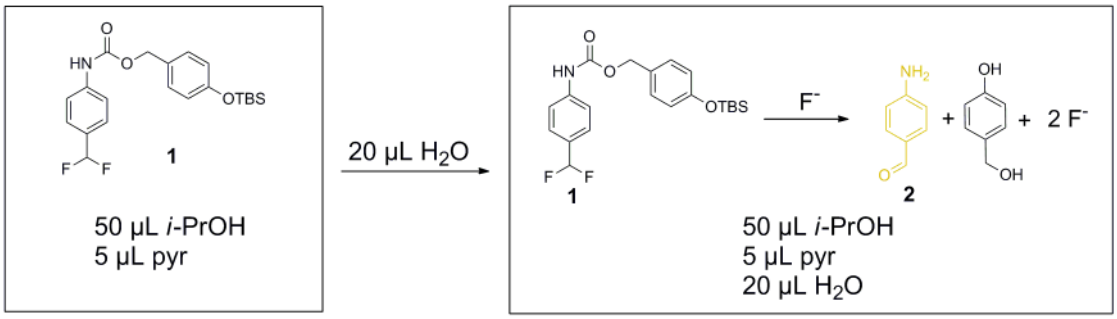
Table S24. Intensities of color for 2.3 ppm fluoride

Time (h)	Trial 1	Trial 2	Trial 3
1	4	3	5
4	1	5	4
8	1	3	3
12	2	1	1
16	5	5	7
22	3	3	3
30	6	7	5
38	4	5	5
46	5	7	2
51	2	3	3

Table S25. Intensities of color for 0.0 ppm fluoride

Time (h)	Trial 1	Trial 2	Trial 3
1	4	3	4
4	3	1	2
8	2	1	3
12	1	0	1
16	5	5	5
22	2	3	3
30	7	4	8
38	3	2	4
46	4	4	2
51	3	2	4

Procedure for Measuring the Autoinductive Colorimetric Readout Provided by Reagent 1 in Isopropyl Alcohol (Figure 5a)



Scheme S5. Aliquots (20 µL) of solutions of CsF (610 µM – 1.22 M) were added to separate 0.22 M solutions of compound **1** in 10:1 isopropyl alcohol–pyridine (55 µL). At hour intervals, photographs were obtained and analyzed using Adobe®Photoshop®. The digital images were cropped just above and below the solution in the centrifuge tube. The image was magnified six times and the color was inverted using the inversion setting. Using the circular marquee tool, a section of approximately 300 pixels just below the meniscus of the solution was highlighted. The mean intensity in the blue channel on the histograph function was recorded. The mean intensities were subtracted from the mean intensities for the centrifuge tubes at time 0.

Tables of Color Intensity for Figure 5a

Table S27: Intensities of color for 2,300 ppm fluoride

Time (min)	Trial 1	Trial 2	Trial 3
0	169	169	168
10	198	196	193
20	228	225	225
30	246	245	246
40	251	250	251
50	253	252	254
60	254	253	252
80	254	253	254

Table S28. Intensities of color for 230 ppm fluoride

Time (min)	Trial 1	Trial 2	Trial 3
0	169	170	170
20	200	201	202
40	238	238	238
60	248	247	248
80	251	250	251
100	252	252	252
120	254	253	253
140	255	254	254
160	254	253	253

Table S29. Intensities of color for 23 ppm fluoride

Time (min)	Trial 1	Trial 2	Trial 3
0	171	169	170
20	169	167	168
40	185	182	184
60	199	197	198
80	211	208	211
100	221	220	221
120	230	228	229
140	232	232	233
160	237	236	237
180	240	239	240
200	242	242	241
220	245	244	245
240	248	247	248
260	251	248	250
280	250	250	250
300	251	251	251
320	251	251	251

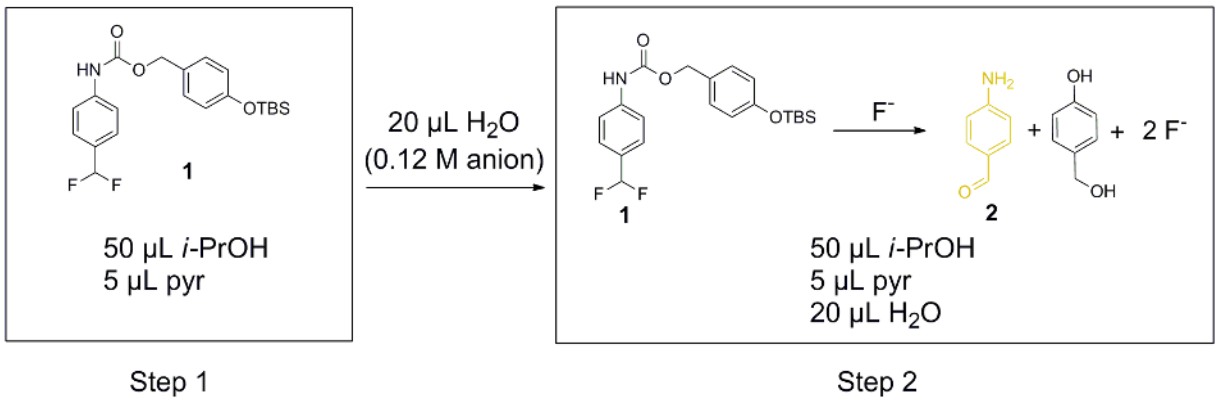
Table S30. Intensities of color for 2.3 ppm fluoride

Time (h)	Trial 1	Trial 2	Trial 3	Trial 4
0	171	168	171	169
2	167	167	168	169
4	169	174	174	173
6	176	173	174	172
7	177	180	180	179
8	187	187	189	190
9	207	210	212	211
10	221	224	227	228
11	235	236	238	239
12	242	244	244	245
13	249	249	250	250
14	252	252	252	252
15	253	252	252	252
16	255	254	255	254
17	255	255	254	254

Table S31. Intensities of color for 0.0 ppm fluoride

Time (h)	Trial 1	Trial 2	Trial 3	Trial 4
0	169	168	169	171
2	164	164	165	165
4	173	172	174	173
6	166	166	167	169
8	169	168	170	169
10	172	171	170	170
11	173	174	172	173
12	177	174	174	174
13	184	178	176	183
14	193	187	185	198
15	202	188	187	203
16	226	220	218	233
17	237	231	241	230
18	244	241	241	247
19	249	243	245	250
20	252	249	250	251
21	254	253	253	254
22	255	252	252	253

Selectivity of Compound 1 for Fluoride over Other Anions in Isopropanol (Figure 5c)



Scheme S6. In separate experiments, CsF, KCl, KBr, KI, KNO_3, KSCN, KO_2CCH_3, tetrabutylammonium phosphate and tetrabutylammonium sulfate (0.2 equivalents, 20 µL) were added to a 0.22 M solution of compound **1** (55 µL) in 10:1 *i*-PrOH–pyridine at 23 °C. Photographs were obtained after 2 h of amplification using the procedure described in Scheme S2.

Table S32. Intensities of color for the selectivity study in Figure 5c.

Anion	Trial 1	Trial 2	Trial 3
Cl^-	1	1	1
Br^-	0	0	0
I^-	1	1	0
NO_3^-	0	0	0
$H_2PO_4^-$	0	0	1
SO_4^{2-}	2	3	1
SCN^-	0	0	0
$CH_3CO_2^-$	0	0	0
F^-	86	86	86
No Ions	0	0	0

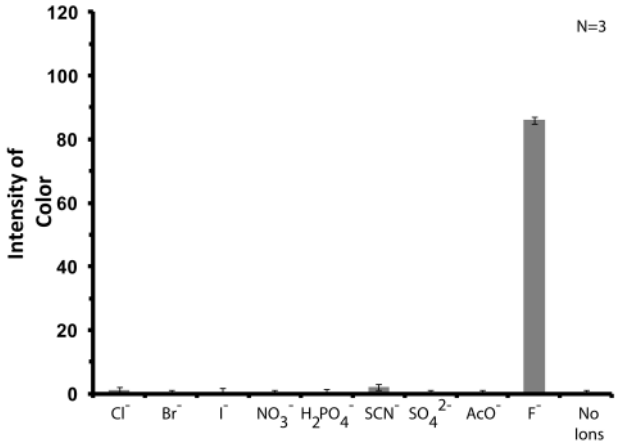
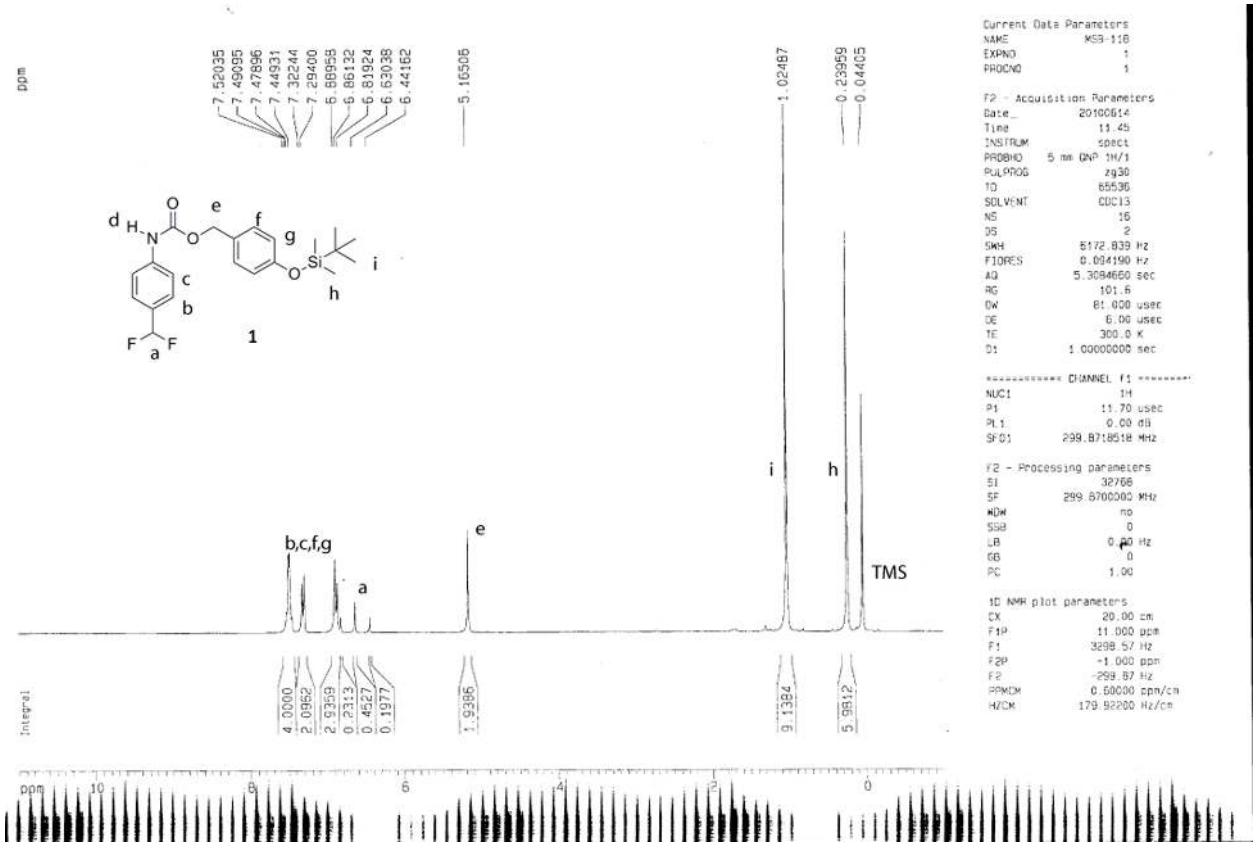


Figure S2. In separate experiments nine different anions (0.2 equiv, 20 µL H_2O) were added to a 0.22 M solution of compound **1** (55 µL) in 10:1 *i*-PrOH/pyr. Photographs were taken after 2 h of amplification. Error bars reflect the standard deviations from the average value.

References

1)Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.
2)Baker, M. S.; Phillips, S. T. *J. Am. Chem. Soc.* **2011**, 133, 5170–5173.
3)Nuñez, S. A.; Yeung, K.; Fox, N. S.; Phillips, S. T. *J. Org. Chem.* **2011**, 76, 10099–10113.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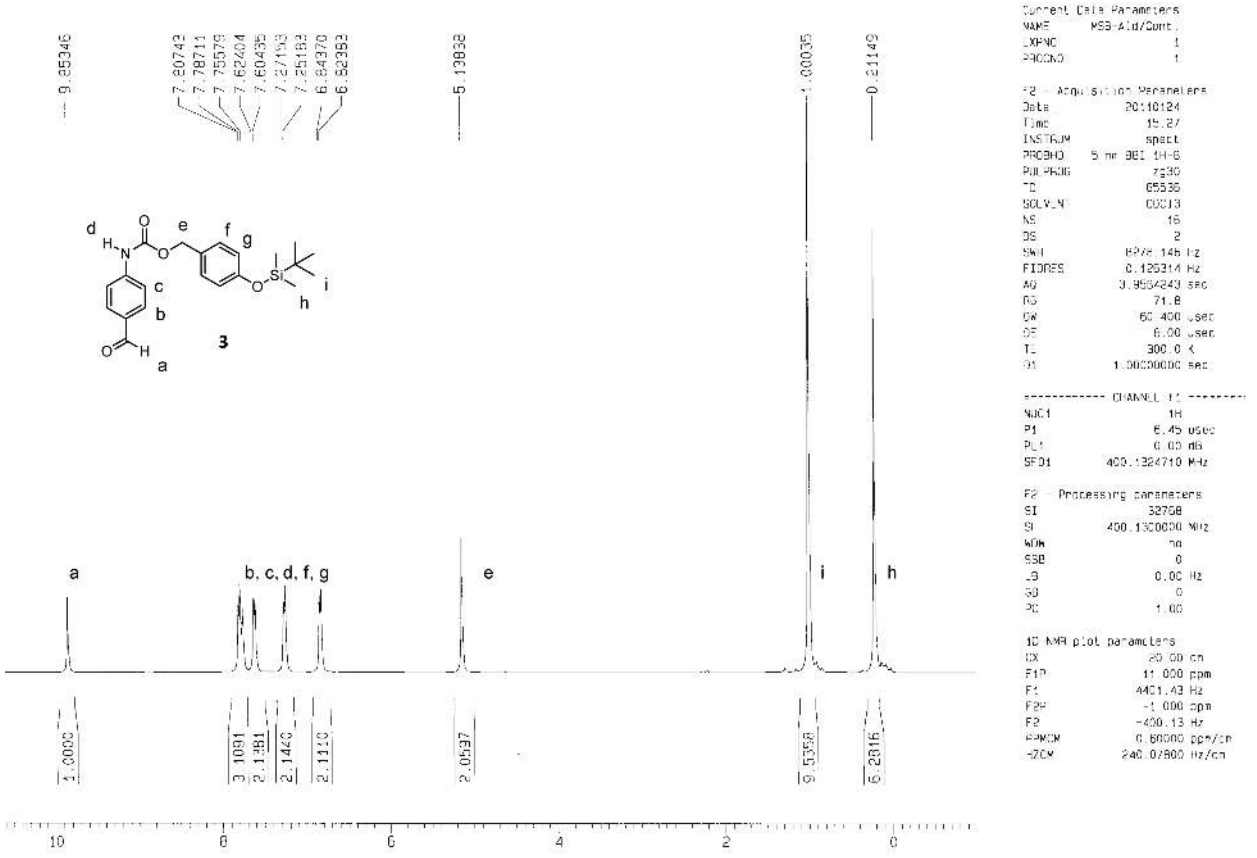
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 6172.839 Hz
FIDRES 0.094190 Hz
AQ 5.3084660 sec
RG 101.6
DW 81.000 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
CHANNEL f1
NUC1 1H
P1 11.70 usec
PL1 0.00 dB
SFO1 299.8718518 MHz
F2 - Processing parameters
SI 32768
SF 299.8700000 MHz
WDW no
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 20.00 cm
F1P 11.000 ppm
F1 3298.57 Hz
F2P -1.000 ppm
F2 -299.87 Hz
PPMCM 0.60000 ppm/cm
HZCM 179.92200 Hz/cm


9.85346
7.80743
7.78711
7.75578
7.62404
7.60435
7.25183
6.84370
6.82383
5.13838
1.00035
0.21149
d
e
f
g
c
b
O
H
a
3
i
h
a
b, c, d, f, g
e
i
h
1.0000
3.1091
2.1381
2.1445
2.1119
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9.5358
6.2916
Current Data Parameters
NAME MSB-Ald/Conf
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20110124
Time 15.27
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PROBHD 5 mm BBI 1H-B
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 71.8
DW 60.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
CHANNEL f1
NUC1 1H
P1 8.45 usec
PL1 0.00 dB
SFO1 400.1324710 MHz
F2 - Processing parameters
SI 32768
SF 400.1300000 MHz
WDW no
SSB 0
LB 0.00 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 20.00 cm
F1P 11.000 ppm
F1 4401.43 Hz
F2P -1.000 ppm
F2 -400.13 Hz
PPMCM 0.60000 ppm/cm
HZCM 240.07800 Hz/cm