Electronic Supplementary Information

Radiofluorination of diaryliodonium tosylates under aqueous-organic and cryptand-free conditions

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Experimental

1 Materials

DMF (99%, anhydrous), water (HPLC grade), K_2CO_3 (99%), K 2.2.2 (4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane), Koser's reagent, 4-anisole, 4-iodobiphenyl, diphenyliodonium tosylate (**1**) and reference fluoroarenes were purchased from either Sigma-Aldrich (Milwaukee, WI) or Alfa Aesar (Ward Hill, MA). 4-Bromo-4'-iodobenzophenone was obtained from Rieke Metals, Inc. (Lincoln, NE). The following diaryliodonium tosylates were prepared as described previously: (2-methylphenyl)(phenyl)iodonium tosylate (**2**) [1], (2-bromophenyl)(phenyl)iodonium tosylate (**3**) [1], (3-ethoxycarbonylphenyl)(4'-methoxyphenyl)iodonium tosylate (**9**) [2], (4-methoxyphenyl)[3‘-(trifluoromethyl)phenyl]iodonium tosylate (**10**) [3], (4-methoxyphenyl)(3‘-nitrophenyl)iodonium tosylate (**11**) [3], and (3-cyanophenyl)(4‘-methoxyphenyl)iodonium tosylate (**13**) [3].

2 General methods

^{1}H (400 MHz), ^{13}C (100 MHz), and ^{19}F (376 MHz) NMR spectra were recorded at room temperature on an Avance-400 spectrometer (Bruker; Billerica, MA). ^{1}H and ^{13}C chemical shifts are reported in δ units downfield from the chemical shift for tetramethylsilane and ^{19}F NMR chemical shifts in δ units downfield from the chemical shift for $CFCl_3$. Abbreviations br, s, d, t, and m denote broad, singlet, doublet, triplet and multiplet, respectively.

High resolution mass spectra (HRMS) were obtained from the Mass Spectrometry Laboratory, University of Illinois at Urbana-Champaign (Urbana, IL) under electron ionization conditions using a double-focusing high-resolution mass spectrometer (Autospec; Micromass Inc., USA). Melting points were measured with a Mel-Temp melting point apparatus (Electrothermal; Fisher Scientific).

3 Syntheses of reagents for making diaryliodonium salts

*3.1 4-Cyano(diacetoxyiodo)benzene (**A**)*

Peracetic acid in acetic acid (32 wt.%, 10 mL) was added drop-wise to cooled (~ 0 °C) 4-iodobenzonitile (1.15 g, 5 mmol). The temperature was gradually raised to rt and the reaction mixture was stirred overnight (*ca*. 14 h) to give a white precipitate. Water (20 mL) was added to the mixture and the resultant solid was filtered off, washed with Et_2O (30 mL × 3), and dried *in vacuo* for 4 h to give **A** as a white solid (1.12 g, 65%); mp 171−173 ^{o}C; ^{1}H-NMR ($CDCl_3$) δ 8.21 (2 H, d, J = 8.8 Hz, ArH), 7.78 (2 H, d, J = 8.8 Hz, ArH), 2.03 (6 H, s, Me); ^{13}C-NMR ($CDCl_3$) δ 176.9, 135.8, 134.3, 125.4, 117.3, 115.9, 20.6.

*3.2 1-Cyano-4-[hydroxy(tosyloxy)iodo]benzene (**B**)*

A (1.04 g, 3 mmol) in MeCN (20 mL) was added in one portion to a heated (~ 60 ^{o}C) bright yellow solution of *p*-TsOH·H_2O (0.63 g, 3.3 mmol). The reaction mixture was cooled to rt. The precipitate was filtered off and washed with Et_2O (30 mL × 3) to give **B** as a white solid (0.95 g, 76%); mp 138−139 ^{o}C; ^{1}H-NMR (DMSO-d_6) δ 10.04 (1 H, br s, O*H*), 8.34 (2 H, d, J = 7.6 Hz, ArH), 8.07 (2 H, d, J = 7.6 Hz, ArH), 7.47 (2 H, d, J = 7.6 Hz, ArH), 7.12 (2 H, d, J = 7.6 Hz, ArH), 2.29 (3 H, s, Me); ^{13}C-NMR (DMSO-d_6) δ 145.3, 137.9, 134.6, 134.5, 128.2, 125.5, 117.6, 114.6, 20.8.

*3.3 1-Fluoro-4-[hydroxy(tosyloxy)iodo]benzene (**C**)*

m-Chloroperbenzoic acid (*m*-CPBA; 77% max.; 1.73 g, 7.7 mmol) was added portion-wise to a solution of 4-fluoroiodobenzene (1.55 g, 7 mmol) in $CHCl_3$ (30 mL). *p*-TsOH·H_2O (1.47 g, 7.7 mmol) was added to the pale yellow solution and the temperature was raised to 40 ^{o}C. The reaction mixture was stirred for 1 h and then cooled to rt. The resultant precipitate was filtered off, washed with Et_2O (50 mL × 3), and dried *in vacuo* for 6 h to give **C** as a white solid (1.96 g, 68%); mp 145−146 °C; ^{1}H-NMR (DMSO-d_6) δ 9.89 (1 H, br s, O*H*), 8.29 (2 H, dt, J = 1.6, 3.6 Hz, ArH), 7.50−7.45 (4 H, m, ArH), 7.12 (2 H, d, J = 8 Hz, ArH), 2.29 (s, 3H, Me); ^{19}F-NMR (DMSO-d_6) δ −105.86.

3.4 4-(Diacetoxyiodo)biphenyl (***D***)

Peracetic acid (32 wt.% diluted in acetic acid, 12 mL) was added drop-wise to a mixture of 4-iodobiphenyl (1.96 g, 7 mmol) in acetic acid (5 mL). The reaction was gradually heated to 50 °C and stirred for 5 h. Consumption of 4-iodobipenyl was monitored with TLC. The yellow solution was cooled to rt and water (30 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (30 mL × 2), dried over $MgSO_4$, and concentrated under reduced pressure. The resulting oil was triturated with Et_2O and then the solid was filtered off and recrystallized from acetic acid to give **D** as a pale yellow solid (0.62 g, 22%); mp 155−159 °C; ^{1}H-NMR ($CDCl_3$) δ 7.86 (2 H, d, J = 8.4 Hz, ArH), 7.45 (2 H, d, J = 8.4 Hz, ArH), 7.55−7.51 (5 H, m, Ph), 1.94 (6 H, s, Me); ^{13}C-NMR ($CDCl_3$) δ 175.6, 142.0, 133.2, 131.6, 127.4, 126.8, 126.2, 125.1, 124.9, 120.1, 19.2.

4. Syntheses of diaryliodonium salts

*4.1 (2-Cyanophenyl)(4'-methoxyphenyl)iodonium tosylate (**4**).*

m-CPBA (0.49 g, 2.3 mmol, 77% max. content) was added to a solution of 2-iodobenzonitrile (0.46 g, 2 mmol) in CH_2Cl_2 (10 mL) and the mixture was stirred for 15 min. *p*-TsOH·H_2O (0.38 g, 2.0 mmol) was added to the colorless solution and the resulting pale yellow solution was stirred for 10 min. Anisole (0.33 g, 3 mmol) was then added and the resulting mixture was stirred for 14 h. Solvent was removed *in vacuo* and the crude product was sonicated for 5 min in Et_2O (25 mL). Et_2O was decanted off and the residual solid was washed with water to remove tosic acid and then dissolved in MeCN. Et_2O was added slowly to precipitate **4** slowly (~15 min) as a white solid (0.68 g, 67%); mp 173−176 °C (decomp.); ^{1}H-NMR (DMSO-d_6) δ 8.67−8.59 (1 H, m, ArH), 8.19−8.11 (3 H, m, ArH), 7.90−7.83 (2 H, m, ArH), 7.46 (2 H, d, J = 8.0 Hz, ArH), 7.11 (4 H, overlappping doublets, ArH), 3.80 (3 H, s, OMe), 2.29 (3 H, s, Me); ^{13}C-NMR (DMSO-d_6) δ 162.2, 145.6, 137.7, 137.2, 136.3, 135.4, 132.9, 128.1, 125.5, 120.7, 118.0, 117.8, 116.4, 106.3, 91.7, 55.8, 20.8; LC-MS (ESI, *m/z*) $[M-OTs]^+$ Calc'd. for $C_{14}H_{11}ONI$: 335.99, Found: 336.10. HRMS $[M-OTs]^+$ Calc'd. for $C_{14}H_{11}OIN$: 335.9885, Found: 335.9881.

*4.2 (4-Methoxycarbonylphenyl)(4'-methoxyphenyl)iodonium tosylate (**5**).*

The method described for **4** was used with methyl-4-iodobenzoate (0.53 g, 2 mmol). The process gave crude product (0.72 g) that contained about 10% tosic acid and 10% unreacted methyl-4-iodobenzoate. A portion (0.15 g) of this material was washed with water to remove tosic acid. Then the solid was dissolved in CH_2Cl_2 (0.5 mL). Diethyl ether was added slowly to precipitate **5** as white solid (80 mg, 36%). mp 179−181 ^{o}C; ^{1}H-NMR ($CDCl_3$) δ 7.97 (d, J = 8.4 Hz, 2H, ArH), 7.90−7.86 (m, 4H, ArH), 7.47 (d, J = 8 Hz, 2H, ArH), 7.01 (d, J = 8.0 Hz, 2H, ArH), 6.83 (d, J = 8.8 Hz, 2H, ArH), 3.91 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 2.31 (s, 3H, CH_3); ^{13}C-NMR ($CDCl_3$) δ 165.2, 162.1, 145.7, 137.6, 137.5, 135.1, 132.4, 131.8, 128.1, 125.5, 121.8, 117.6, 105.5, 55.8, 52.7, 20.8; LC-MS (ESI, *m/z*) $[M-OTs]^+$ Calc'd. for $C_{15}H_{14}O_3I$: 369.00, Found: 368.90. HRMS $[M-OTs]^+$ Calc'd. for $C_{15}H_{14}O_3I$: 368.9988, Found: 368.9991.

*4.3 (4-Cyanophenyl)(4'-methoxyphenyl)iodonium tosylate (**6**).*

Anisole (0.7 g, 6.4 mmol) was added to a suspension of **B** (0.13 g, 0.3 mmol) in $CHCl_3$ (7 mL). The reaction mixture was then refluxed for 5 h. The obtained light brown solution was concentrated under reduced pressure and the residual light brown oil was triturated with Et_2O. The solid was filtered off, and washed with Et_2O/hexane to give **6** as a beige solid (0.12 g, 80%). mp 188−191 °C; ^{1}H-NMR (DMSO-d_6) δ 8.36 (2 H, d, J = 8.4 Hz, ArH), 8.21 (2 H, d, J = 8.4 Hz, ArH), 7.98 (2 H, d, J = 8.4 Hz, ArH), 7.47 (2 H, d, J = 8 Hz, ArH), 7.12−7.07 (4 H, m, ArH), 3.80 (3 H, s, OMe), 2.28 (3 H, s, Me); ^{13}C-NMR (DMSO-d_6) δ 162.2, 145.7, 137.7, 137.3, 135.4, 134.9, 128.1, 125.5, 121.9, 117.6, 114.4, 105.6, 55.8, 20.8. HRMS [M−OTs]$^+$ Calc'd. for $C_{14}H_{11}OIN$: 335.9885, Found: 335.9876.

*4.4 (2-Methylphenyl)(4'-methoxyphenyl)iodonium tosylate (**7**).*

The method described for **4** was used with iodotoluene (0.53 g, 2 mmol) to give **7** as a white solid (0.43 g, 43%). mp 157−159 °C; ^{1}H-NMR (CDCl$_3$) δ 8.01 (1 H, dd, J = 8.0 and 1.2 Hz, ArH), 7.79 (2 H, d, J = 9.2 Hz, ArH), 7.54 (2 H, d, J = 8.0 Hz, ArH), 7.46 (1 H, dt, J = 7.6 and 0.8 Hz, ArH), 7.37 (1 H, dd, J = 7.6 and 0.8 Hz, ArH), 7.17 (1 H, dt, J = 8.0 and 1.2 Hz, ArH), 7.04 (2 H, d, J = 8.0 Hz, ArH), 6.85 (2 H, d, J = 9.2 Hz, ArH), 3.76 (3 H, s, OMe), 2.55 (3 H, s, Me), 2.30 (3 H, s, Me); ^{13}C-NMR (CDCl$_3$) δ 162.0, 142.8, 141.1, 139.1, 137.3, 136.5, 132.5, 131.4, 129.1, 128.4, 126.0, 120.8, 117.3, 103.3, 55.6, 25.6, 21.3; LCMS (ESI, m/z) [M−OTs]$^+$ Calc'd. for $C_{14}H_{14}OI$: 325.01, Found: 324.90. HRMS [M−OTs]$^+$ Calc'd. for $C_{14}H_{14}OI$: 325.0089, Found: 325.0089

*4.5 (4-(4''-Bromophenylcarbonyl)phenyl)(4'-methoxyphenyl) tosylate (**8**).*

m-CPBA (0.26 g, 1.5 mmol, 77% max. content) was added in portions to a solution of 4-bromo-4'-iodobenzophenone (0.58 g, 1.5 mmol) in CHCl$_3$ (20 mL). The mixture was stirred until it became a pale yellow solution (~ 15 min). *p*-TsOH·H$_2$O (0.29 g, 1.5 mmol) was added, followed by anisole (1.08 g, 10 mmol). The resulting mixture was gradually heated to 40 °C and held at this temperature for about 2 h while the mixture became a yellow solution. Full consumption of the *in situ* generated [hydroxy(tosyl)iodo]arene was verified with KI starch paper. Reaction solvent was then removed *in vacuo* and the residual yellow oil was triturated with Et$_2$O. The generated solid was washed with Et$_2$O and recrystallized from MeOH-Et_2O to give **8** as a white solid (0.53 g, 53%). mp = 165−167 °C; ^{1}H-NMR (MeOD-d_4) δ 8.19 (4 H, dd, J = 8.4, 28.4 Hz, ArH), 7.81 (2 H, d, J = 8.4 Hz, ArH), 7.72−7.65 (6 H, m, ArH), 7.21 (2 H, d, J = 7.6 Hz, ArH), 7.08 (2 H, d, J = 8.8 Hz, ArH), 3.85 (3 H s, OMe), 2.35 (3 H, s, Me); ^{13}C-NMR (MeOD-d_4) δ 195.5, 164.9, 143.8, 141.9, 141.8, 139.1, 136.7, 136.2, 133.7, 133.3, 133.0, 130.0, 129.6, 127.2, 120.4, 119.2, 104.6, 56.5, 21.5; HRMS $[M{-}OTs]^+$ Calc'd. for $C_{20}H_{15}O_2BrI$: 492.9300, Found: 492.9298.

*4.6 (4-Biphenyl)(4'-methoxyphenyl)iodonium tosylate (**12**).*

p-TsOH·H_2O (0.12 g, 0.6 mmol), was added to a suspension of **D** (0.26 g, 0.6 mmol) in MeCN (3 mL). A bright yellow solution developed instantly. Anisole (0.21 g, 2.0 mmol) in $CHCl_3$ (20 mL) was added and the reaction mixture was refluxed for 4 h. Consumption of in situ generated 4-[hydroxy(tosyloxy)iodo]biphenyl was monitored with KI starch paper. The reaction mixture was cooled to rt and concentrated under reduced pressure. The residual yellow oil was triturated with Et_2O and the solid filtered off, washed with Et_2O (20 mL x 3), and dried *in vacuo* for 6 h to give **12** as a white solid (0.19 g, 56%); mp 178−181 °C; ^{1}H-NMR (MeOD-d_4) δ 8.17 (2 H d, J = 8.4 Hz, ArH), 8.11 (2 H d, J = 9.2 Hz, ArH), 7.74 (2 H, d, J = 8.4 Hz, ArH), 7.69 (2 H, d, J = 8.0 Hz, ArH),7.62 (2 H, d, J = 7.2 Hz, ArH), 7.49−7.41 (3 H, m, ArH), 7.21 (2 H, d, J = 7.6 Hz, ArH), 7.06 (2 H, d, J = 8.8 Hz, ArH), 3.85 (3 H, s, OMe), 2.35 (3 H, s, Me); ^{13}C-NMR (MeOD-d_4) δ 164.6, 146.7, 143.6, 141.7, 140.0, 138.6, 136.5, 131.4, 130.2, 129.9, 128.3, 127.0, 118.9, 114.8, 104.7, 56.4, 21.3; HRMS $[M{-}OTs]^+$ Calc'd. for $C_{19}H_{16}OI$: 387.0246, Found: 387.0236.

*4.7 (4-Fluorophenyl)(4'-methoxyphenyl)iodonium tosylate (**14**).*

Anisole (0.86 g, 8 mmol) was added to a suspension of **C** (0.67 g, 1.6 mmol) in $CHCl_3$ (20 mL) and mixture was refluxed for 2 h. Solvent was removed under reduced pressure and the crude oil was triturated with Et_2O (20 mL). The resultant solid was filtered off, washed with Et_2O (20 mL × 2), and dried *in vacuo* for 4 h to give **14** as a white solid (0.55 g, 68%); mp 138−140 °C; ^{1}H-NMR ($CDCl_3$) δ 8.01−7.93 (2 H, m) 7.90 (2 H, d, J = 8.8 Hz, ArH), 7.39 (2 H, d, J = 7.6 Hz, ArH), 6.98 (2 H, d, J = 7.6 Hz, ArH), 6.93 (2 H, t, J = 8.8 Hz, ArH), 6.77 (2 H, d, J = 8.8 Hz, ArH), 3.76 (3 H, s, OMe), 2.30 (3 H, s, Me); ^{13}C-NMR ($CDCl_3$) δ 165.1, 163.0, 162.2, 142.4, 139.5, 128.5, 125.9, 118.7 (d, $J_{C\text{-}F}$ = 24.1 Hz), 117.3, 109.7, 104.7, 55.5, 21.2; ^{19}F-NMR (decoupled, $CDCl_3$) δ −107.0; HRMS $[M-OTs]^+$ Calc'd. for $C_{13}H_{11}OIF$: 328.9839, Found: 328.9839.

*4.8 Bis(4-methoxyphenyl)iodonium tosylate (**15**).*

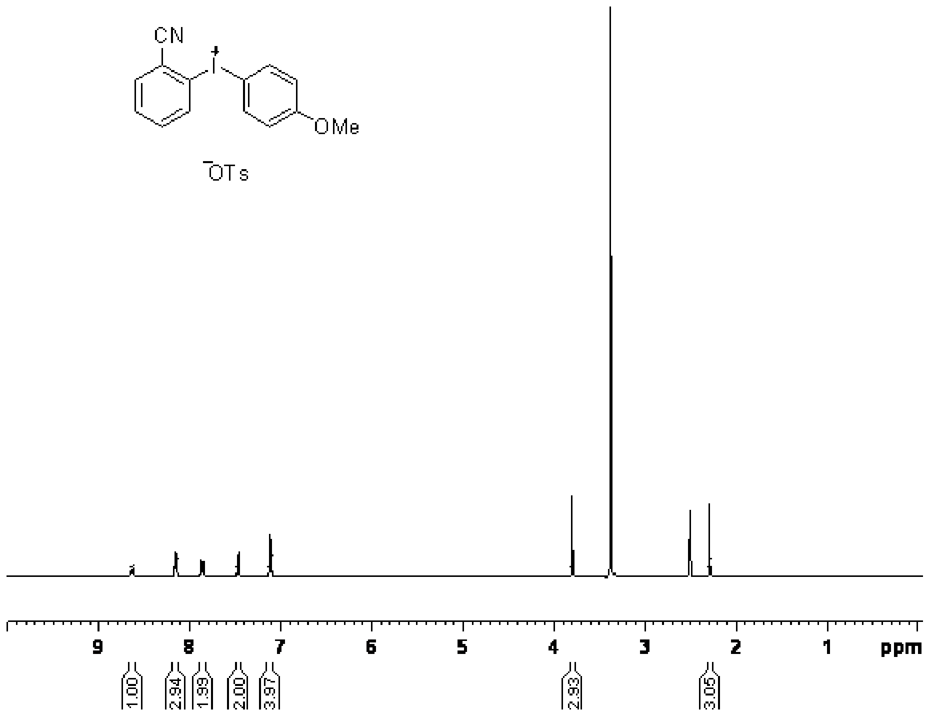
m-CPBA (0.74 g, 3.3 mmol, 77% max. content) was added to a solution of 4-iodoanisole (0.33 g, 3.0 mmol) in $CHCl_3$ (30 mL). *p*-$TsOH{\cdot}H_2O$ (0.63 g, 3.3 mmol) was added to the pale yellow solution, followed by anisole (1.62 g, 15 mmol). The resultant mixture was heated to 40 °C and held at this temperature for 4 h. Solvent was removed *in vacuo* and the resultant yellow oil was triturated with Et_2O. The obtained solid was washed with Et_2O and recrystallized from MeOH-Et_2O to give **15** as a white solid (1.14 g, 74%). mp 158−160 °C; ^{1}H-NMR ($CDCl_3$) δ 7.86 (4 H, d, J = 8.8 Hz, ArH), 7.51 (2 H, d, J = 8 Hz, ArH), 7.01 (2 H, d, J = 8 Hz, ArH), 6.79 (4 H, d, J = 9.2 Hz, ArH), 3.76 (6 H, s, OMe), 2.30 (3 H, s, Me); ^{13}C-NMR ($CDCl_3$) δ 162.4, 143.2, n139.4, 137.1, 128.6, 126.2, 117.5, 104.7, 55.8, 21.4. HRMS $[M-OTs]^+$ Calc'd. for $C_{14}H_{14}O_2I$: 341.0039, Found: 325.0038

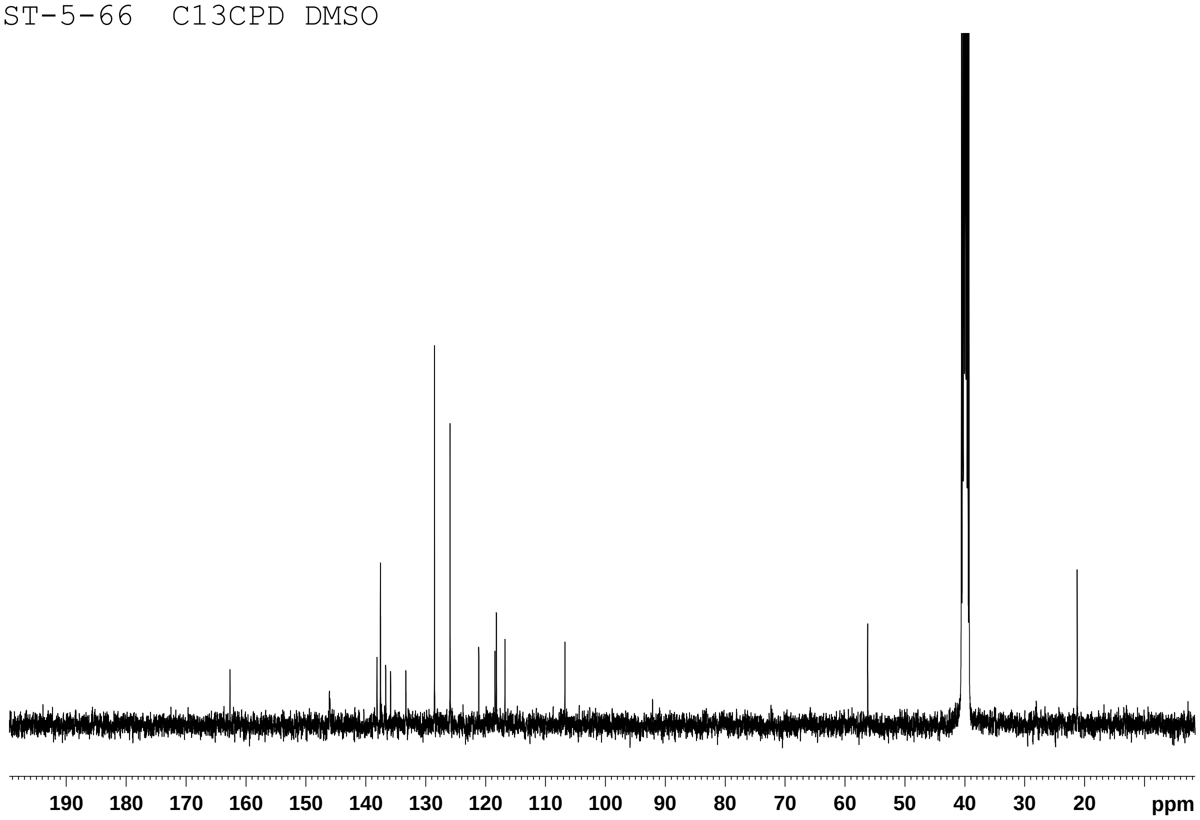
References

1 J.-H. Chun, S. Lu, Y.-S. Lee and V. W. Pike, *J. Org. Chem.*, 2010, **75**, 3332–3338.
2 J.-H. Chun and V. W. Pike, *J. Org. Chem.*, 2012, **77**, 1931−1938.
3 J.-H. Chun, S. Lu and V. W. Pike, *Eur. J. Org. Chem.*, 2011, 4439–4447.

Appendix 1. ^{1}H (400 MHz), ^{13}C (100 MHz) and ^{19}F (376 MHz) NMR spectra of diaryliodonium tosylates

1.1 Compound **4**





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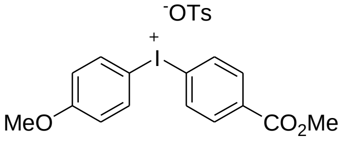

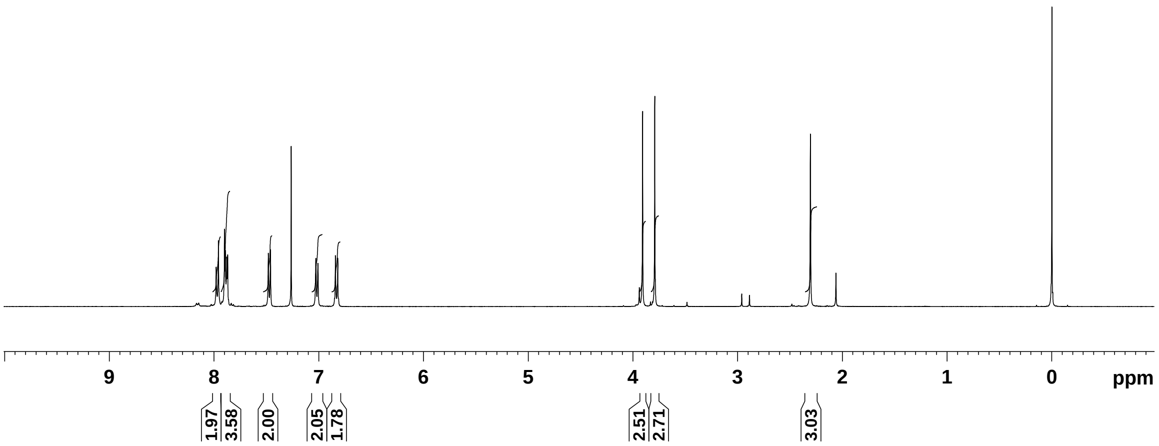

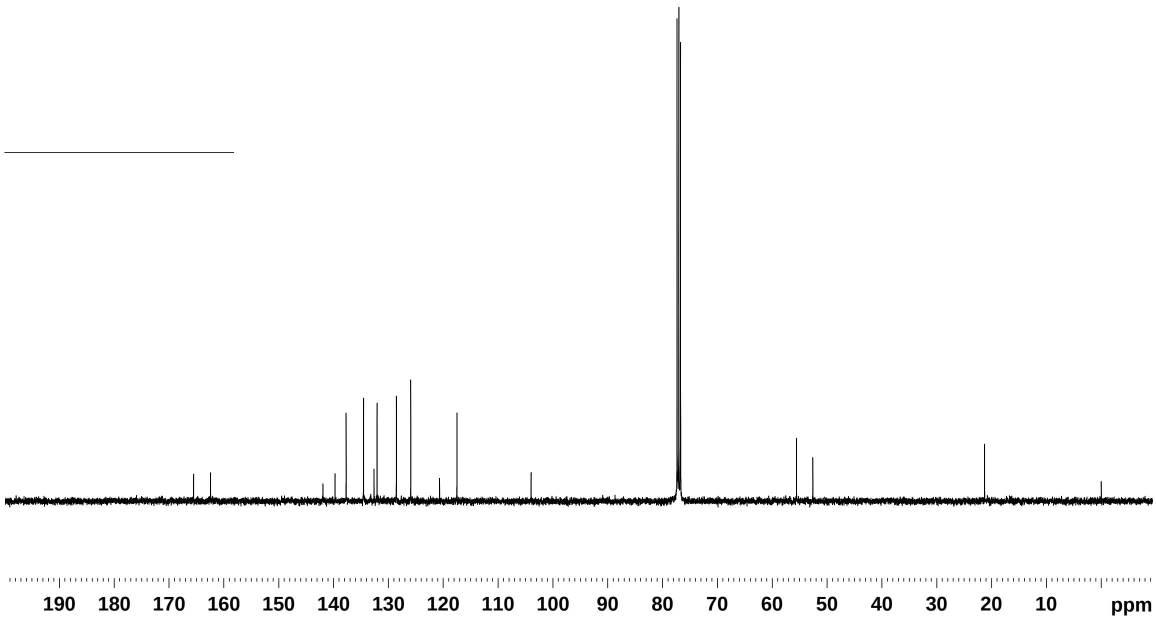

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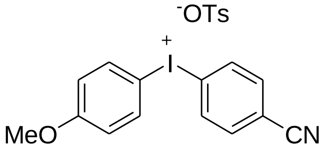

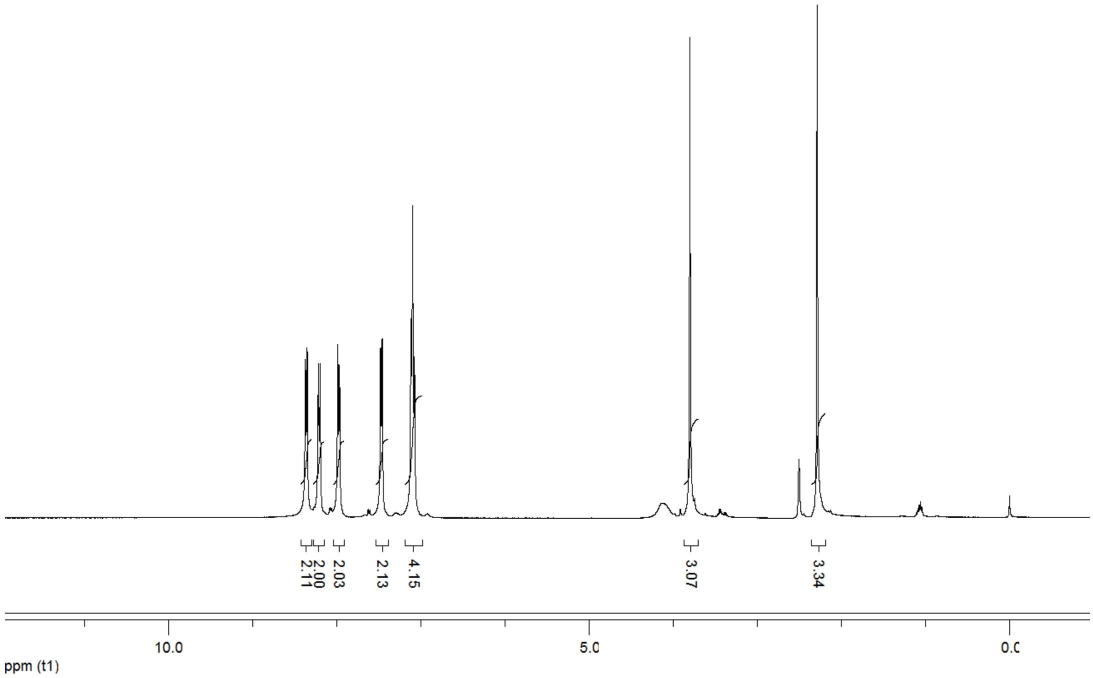

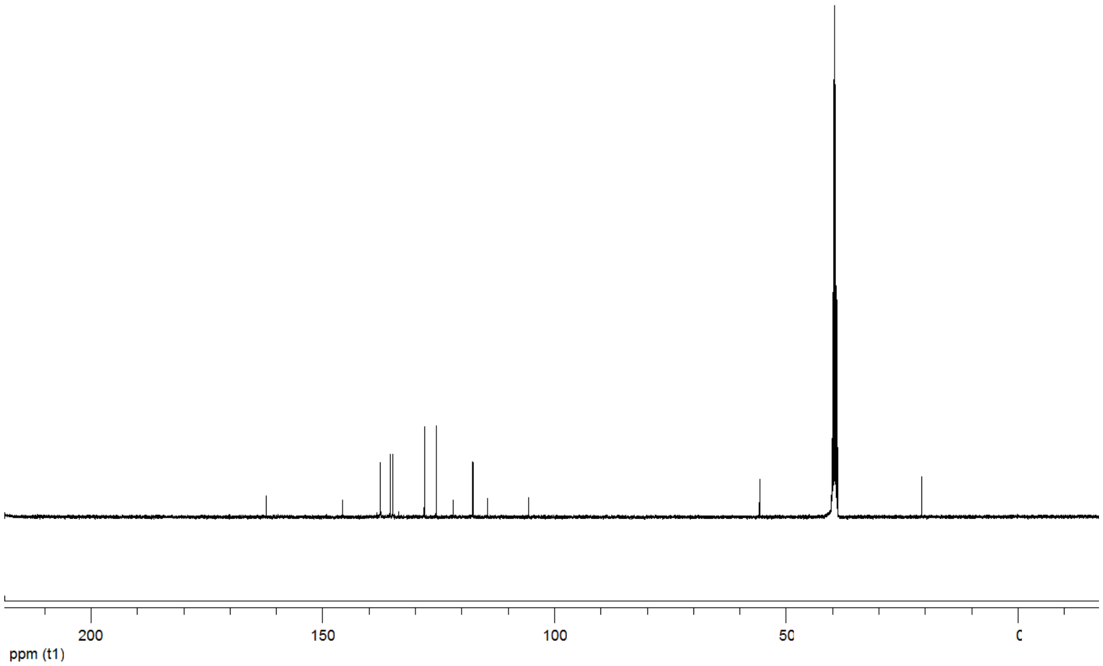

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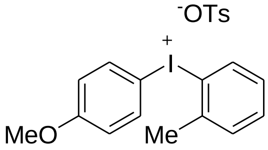

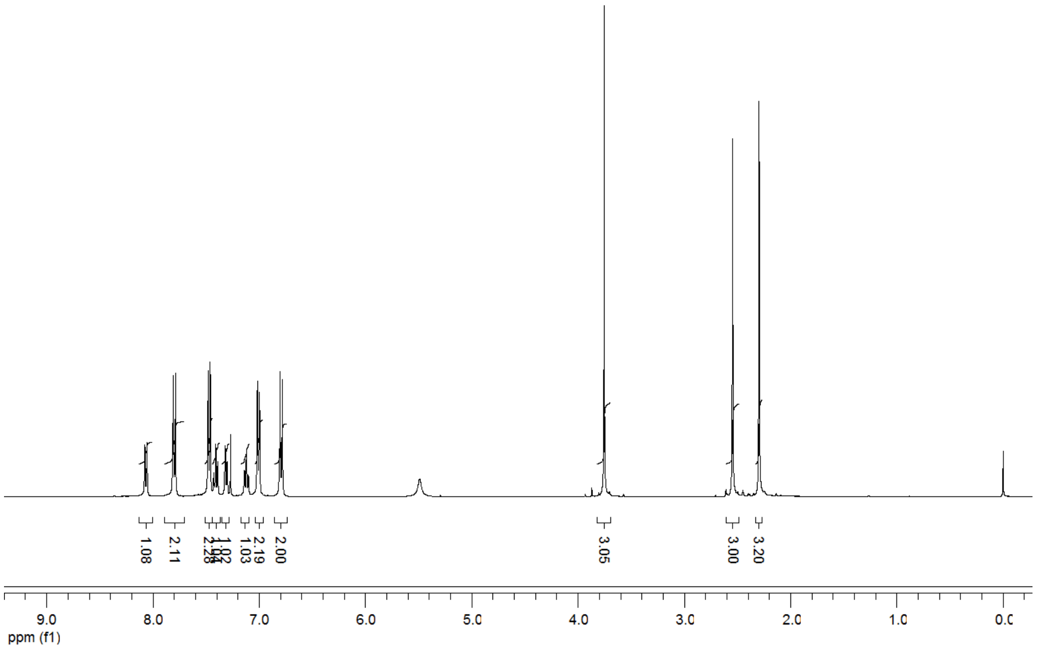

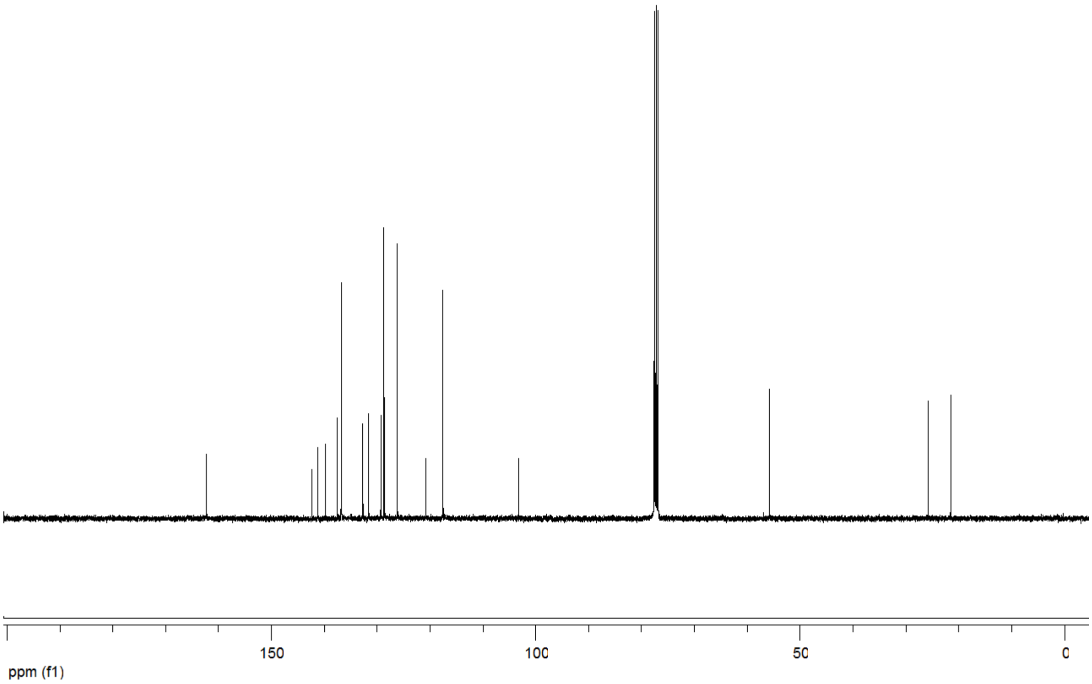

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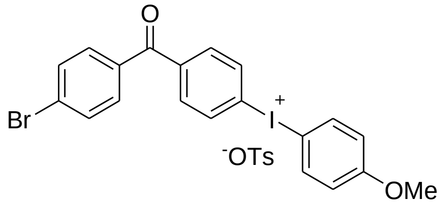

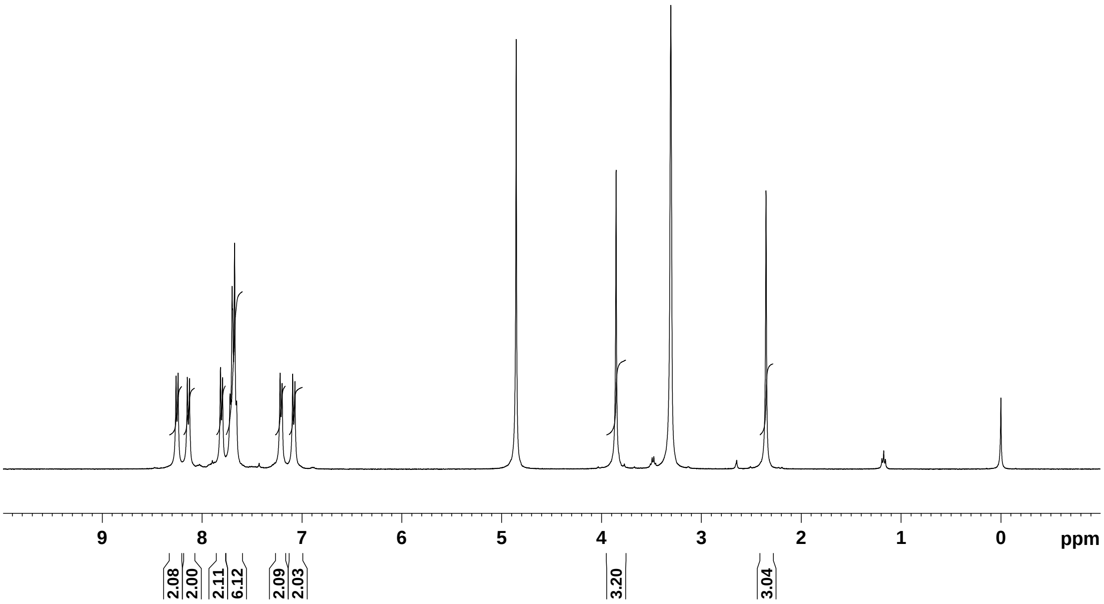

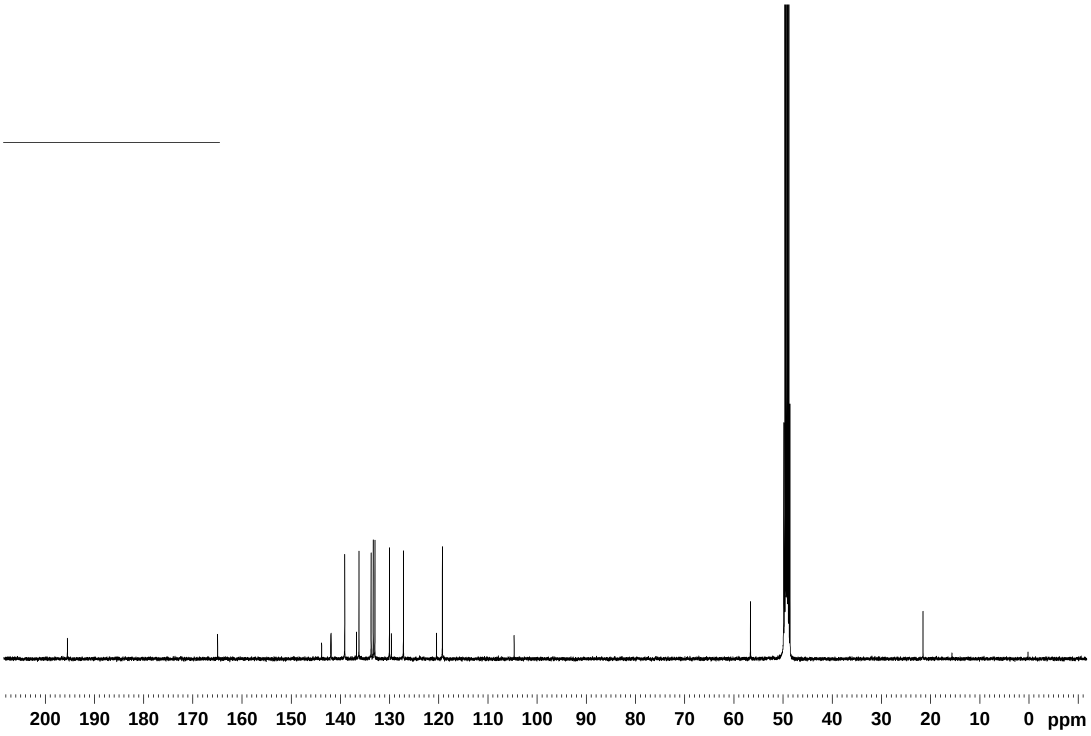

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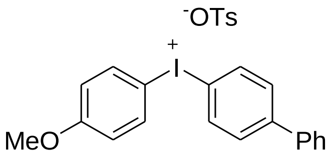

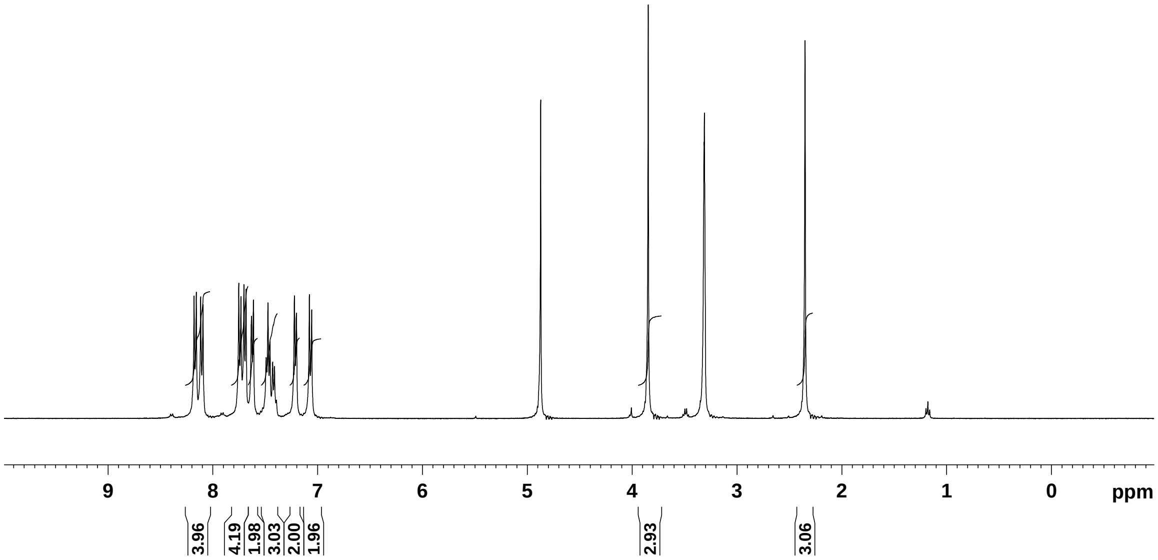

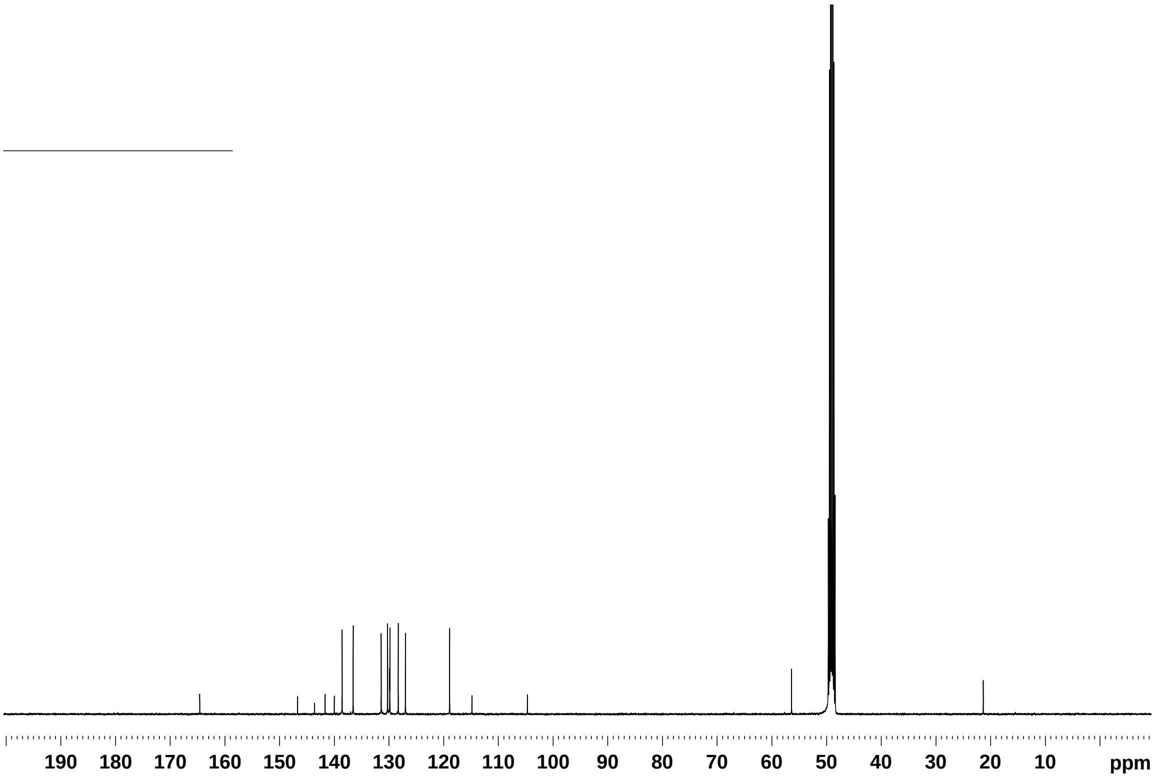

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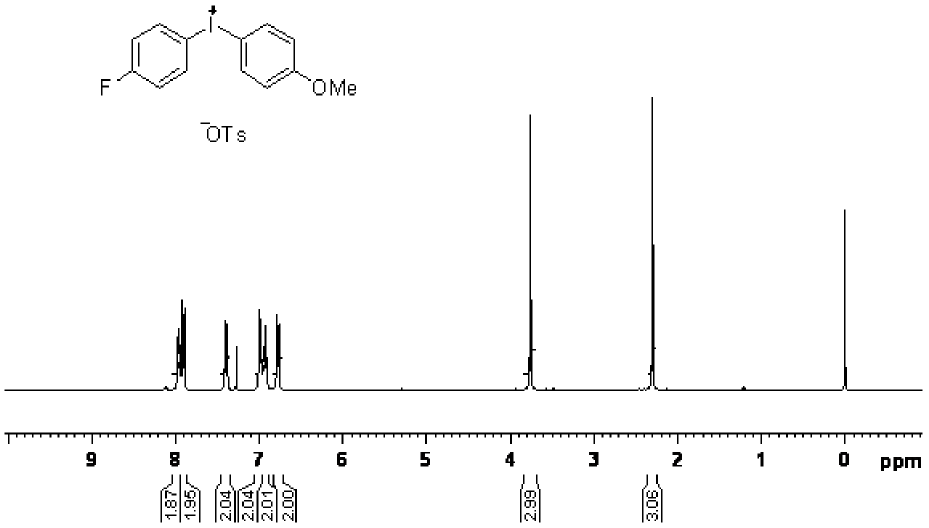
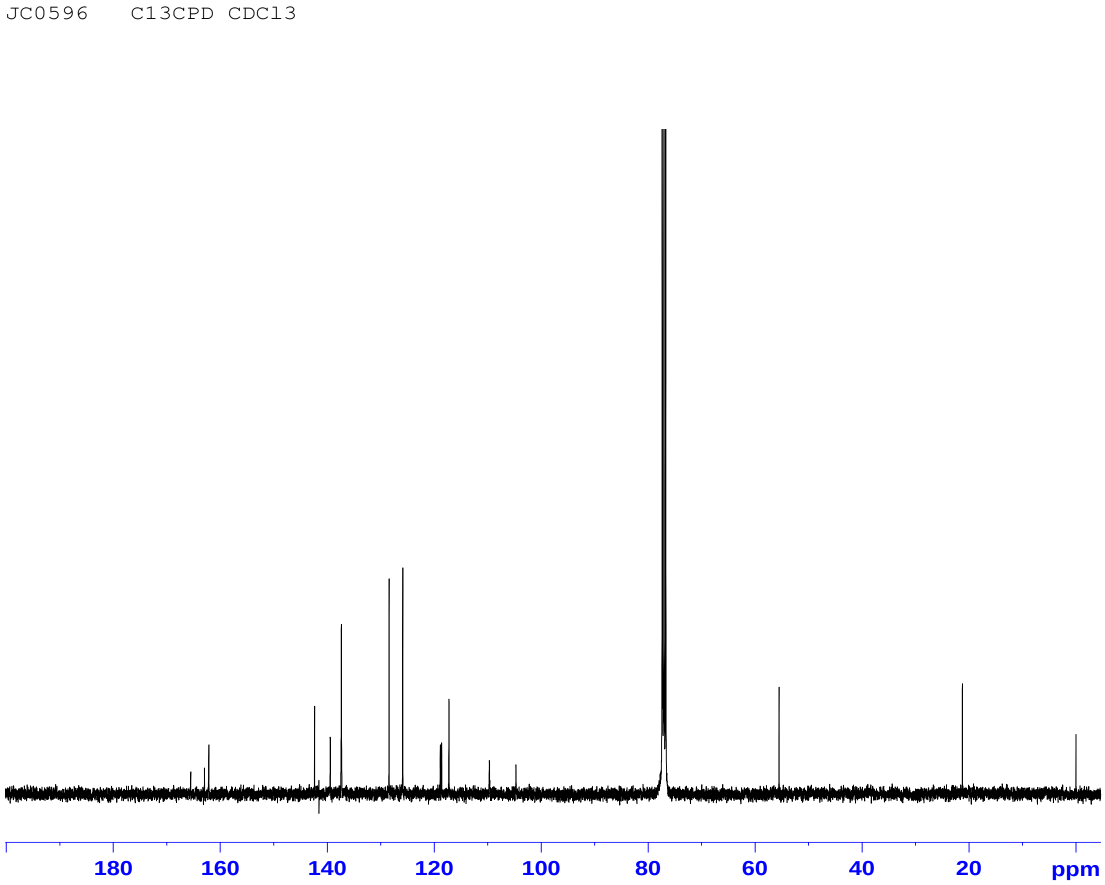
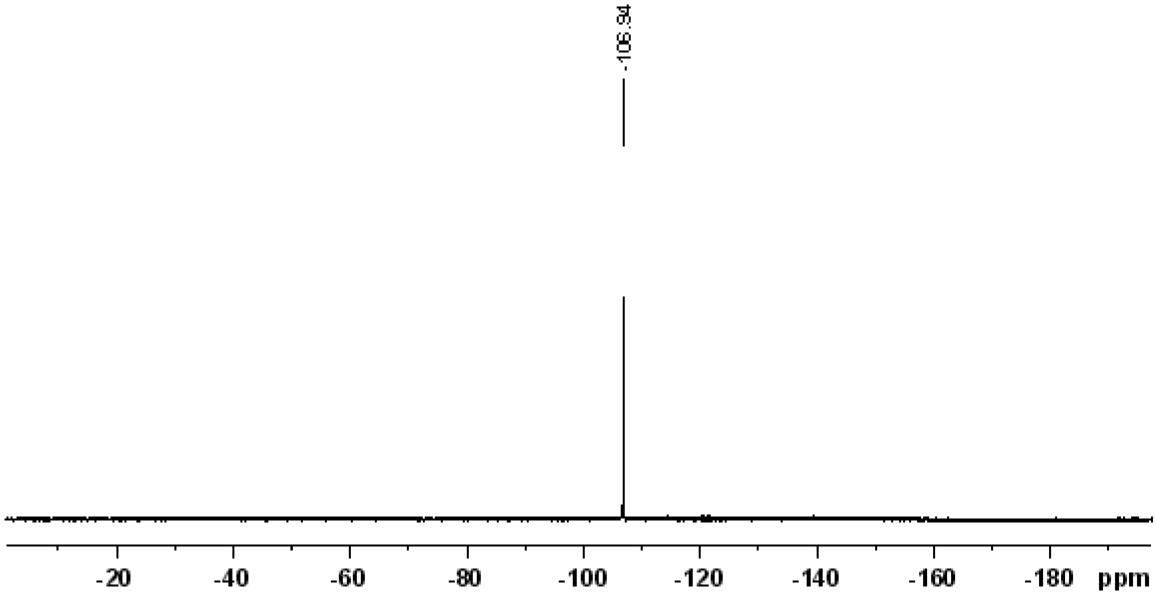
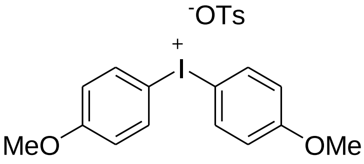


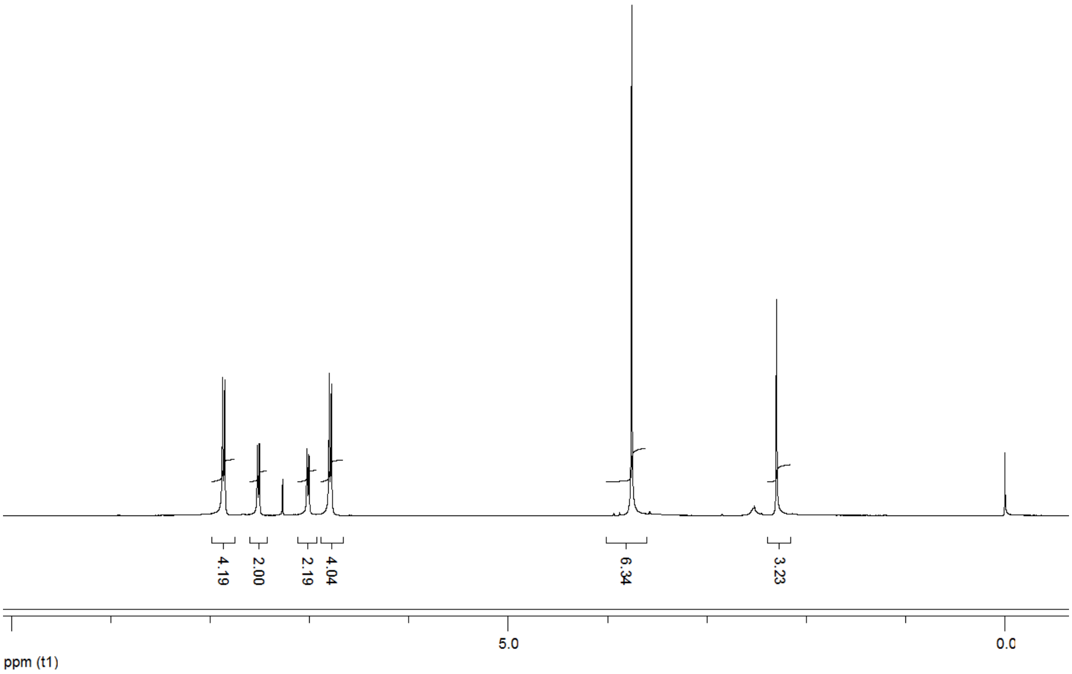


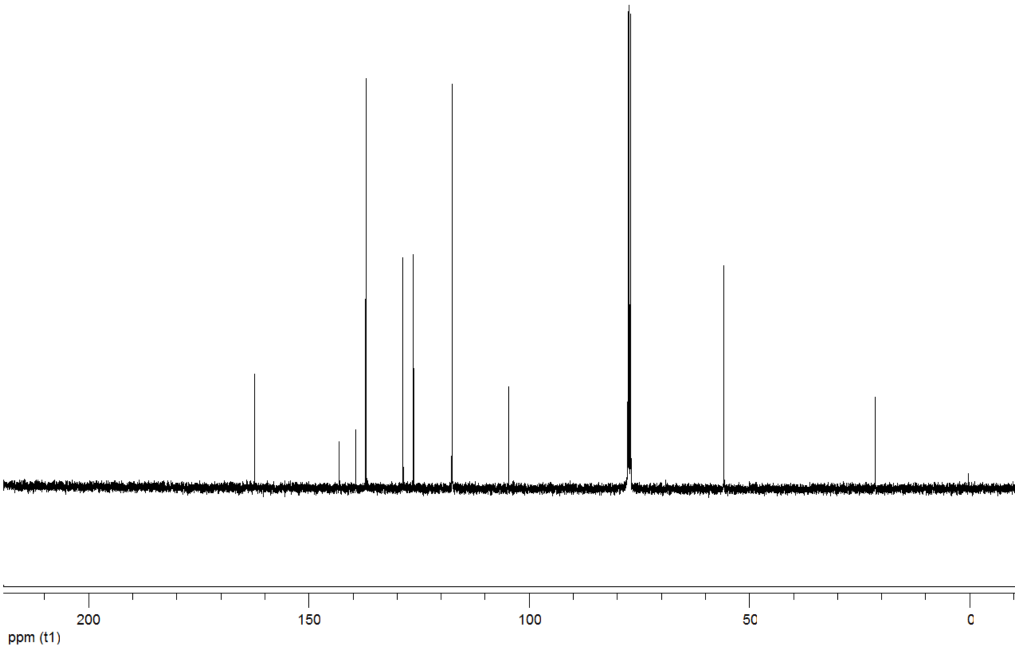
^{19}F NMR



1.8 Compound **15**



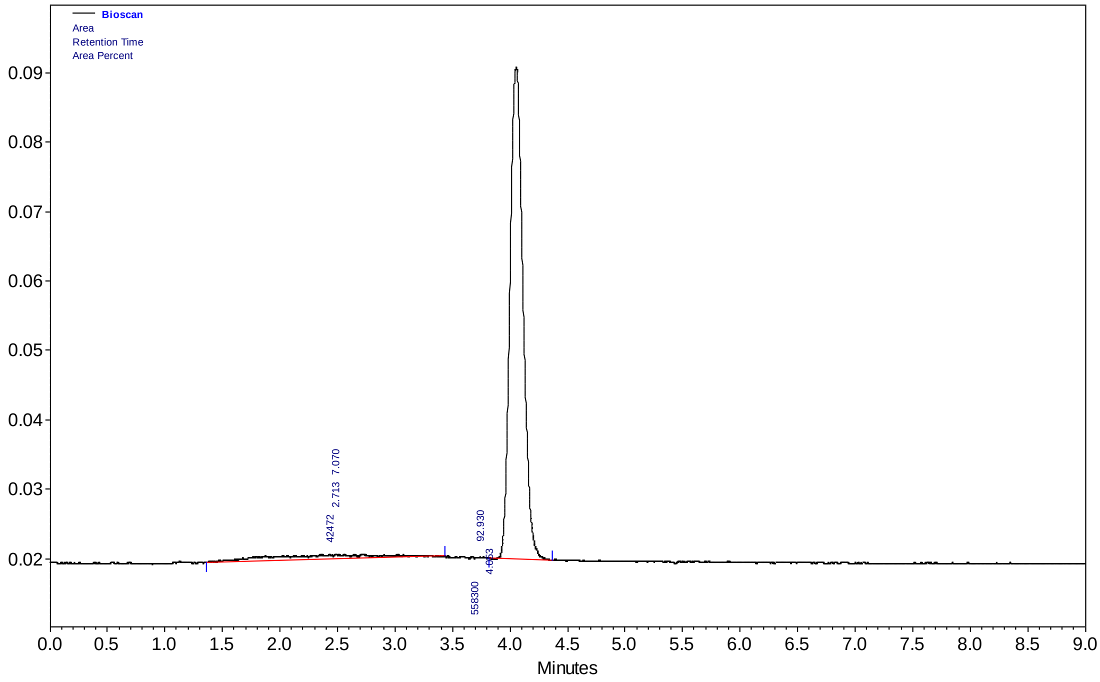




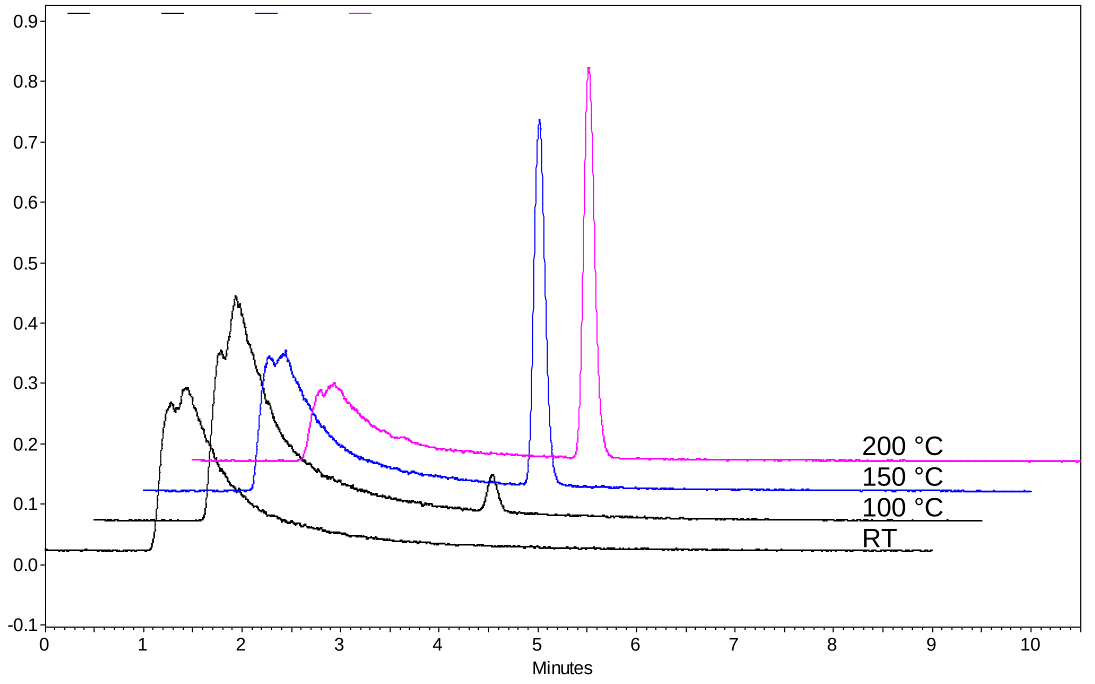
Appendix 2. Selected radio-HPLC chromatograms
(Volts represent output of radioactivity detector, and this is proportional to radioactivity detected)

2.1 Example of high yield radiofluorination of **5** in micro-reactor

(A) in DMF-0.25% H_2O containing K 2.2.2-K_2CO_3 at 150 °C

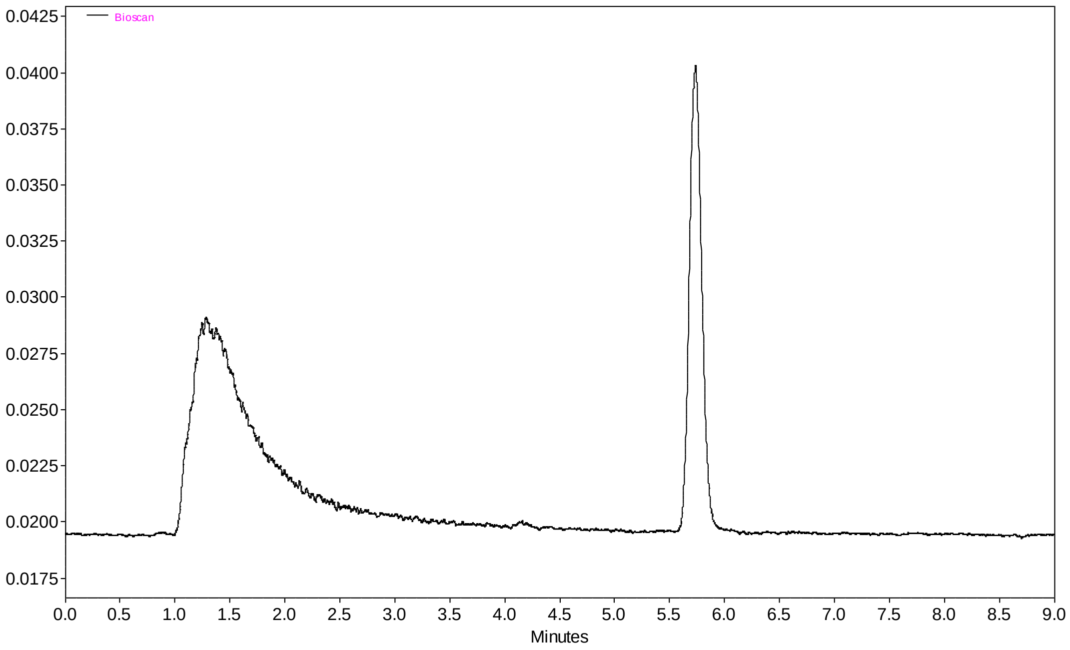


(B) in DMF-28% H_2O containing K_2CO_3 only and at different temperatures

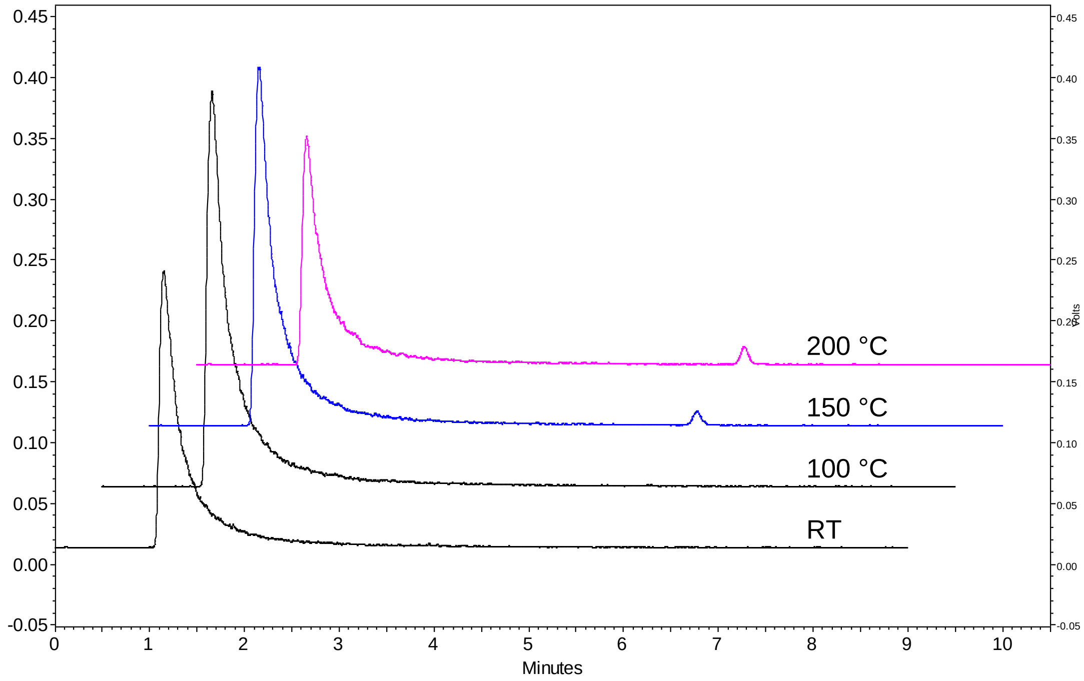


2.2 Example of low yield radioflourination of **10** in micro-reactor

(A) in DMF-0.25% H_2O containing K 2.2.2-K_2CO_3 at 150 °C



(B) in DMF-28% H_2O containing K_2CO_3 only and at different temperatures



Appendix 3. Configuration of the microfluidic apparatus