Chemical Communications

Supplementary Information

A reactive nitrone-based organogel that self-assembles from its constituents in chloroform

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General Procedures

Chemical and experimental details

All chemicals and solvents were purchased from Alfa Aesar, Apollo Scientific Ltd., Fisher Scientific UK Ltd., TCI UK Ltd., or Sigma-Aldrich Company Ltd. and purified by standard techniques where necessary. Where appropriate, non-aqueous reactions were carried out under inert atmosphere of nitrogen or Argon gas. $Pd(PPh_3)_4$ was prepared from $PdCl_2$ according to standard procedure[1]. Brine refers to a saturated solution of sodium chloride. Dry THF and toluene were obtained using and MBraun MS SPS-800 solvent purification system, where solvents are dried by passage through filter columns and dispensed under argon atmosphere. Thin layer chromatography (TLC) analysis was performed using MACHEREY-NAGEL GmbH & Co. POLYGRAM SIL G/UV254 plates. Developed plates were air-dried and visualised under a UV lamp (λ_{max} 254 or 366 nm). Flash column chromatography was performed using Apollo Scientific Ltd. silica gel 40–63 micron or Silicycle SiliaFlash P60 silica gel (230–400 mesh).

Melting points were determined using a Stuart SMP30 melting point apparatus and are reported uncorrected.

Electrospray ionisation (ES) and chemical ionisation (CI) spectra were performed on a Micromass LCT spectrometer operating in positive or negative mode from solutions of methanol, acetonitrile or water.

FTIR spectra were gathered on a Shimadzu IRAffinity-1s IR spectrometer with a gladiATR-10 attachment. Absorbance peaks are described as strong (s), medium (m), weak (w) or broad (br). Multiple overlapping peaks in a narrow region are noted with an asterisk*.

XRD data was collected at RT on a Panalytical Empyrean diffractometer using Cu $K_{\alpha 1}$ radiation, operating in reflection mode.

SEM samples were air-dried and coated with gold (Quorum Q150R ES) at 10 mA for 60 seconds, images were taken on a Jeol JSM-6700F Scanning Electron Microscope with a field emission gun (FEG) electron source running at 5 kV

NMR spectroscopy details

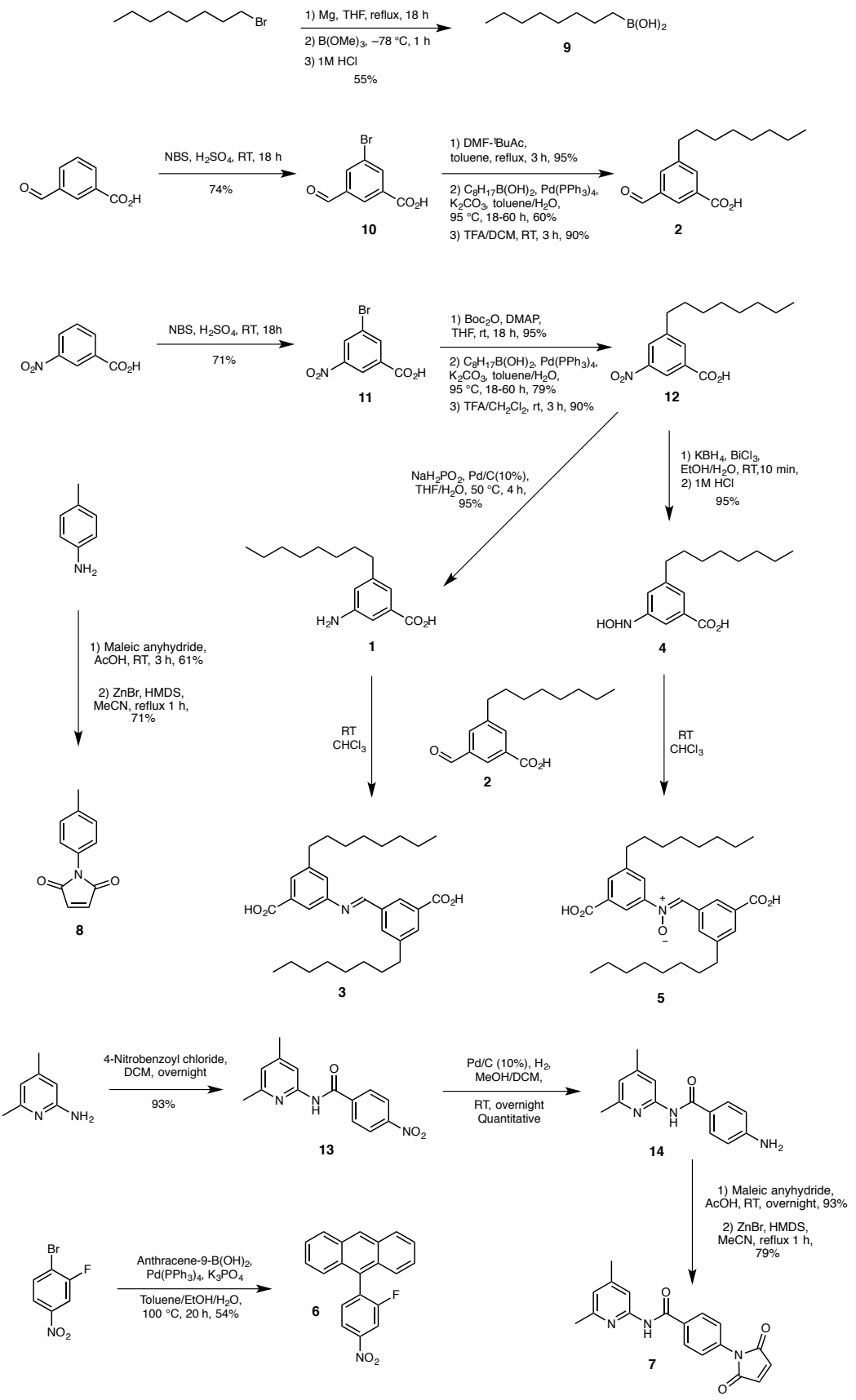
^{1}H NMR spectra were recorded on either a Bruker Avance III-HD 700 (700.1 MHz), Bruker Avance III-HD 500 (499.9 MHz), a Bruker Avance III 500 (500.1 MHz), a Bruker Avance 400 (400.3 MHz), or a Bruker Avance II 400 (400.1 MHz) spectrometer using the deuterated solvent as the lock and the residual non-deuterated solvent as the internal reference in all cases. In the assignment of ^{1}H NMR spectra the chemical shift information (δ_H) for each resonance signal is given in units of parts per million (ppm) relative to the residual non-deuterated solvent resonance where δ_H $CHCl_3$ = 7.26 ppm, δ_H MeOH = 3.31 ppm, and δ_H DMSO = 2.50 ppm. The number of protons (n) for reported signals is indicated as nH from their integral value and their multiplicity by the symbol in parentheses. Their coupling constants (J) are determined by analysis using the iNMR software (Version 5.3.0, Mestrelab Research, 2013) quoted to the nearest 0.1 Hz.

^{19}F NMR spectra were recorded on either a Bruker Avance III-HD 500 (470.4 MHz), a Bruker Avance III 500 (470.5 MHz) or a Bruker Avance II 400 (376.6 MHz) spectrometer using a broadband proton decoupling pulse sequence with the deuterated solvent as the lock. The chemical shift information (δ_F) for each resonance signal is given in units of parts per million (ppm) relative to CCl_3F where δ_F CCl_3F = 0.00 ppm.

^{13}C NMR spectra were recorded on either a Bruker Avance III-HD 700 (176.1 MHz), Bruker Avance III-HD 500 (125.7 MHz), Bruker Avance III 500 (125.7 MHz), Bruker Avance 400 (100.7 MHz), or a Bruker Avance II 400 (100.6 MHz) spectrometer using the DEPTQ pulse sequence, the deuterated solvent as the lock, and the residual non-deuterated solvent as the internal reference in all cases. The chemical shift information (δ_C) for each resonance signal is given in units of parts per million (ppm) relative to the residual non-deuterated solvent resonance where δ_C $CHCl_3$ = 77.16 ppm, δ_C MeOH = 49.00 ppm, and δ_C DMSO = 39.52 ppm. All signals are singlets unless stated otherwise, multiple overlapping peaks are noted with an asterisk*.

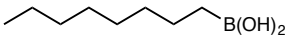
Pseudo 2D DOSY spectra were acquired using a Bruker Avance III-HD 700 instrument equipped with Prodigy TCI CryoProbe (for the nitrone **5** DOSY experiments), and a Bruker Avance III-HD 500 (for the dye **6** DOSY experiments), using a stimulated echo pulse sequence with bipolar gradients (ledbpgp2s). The diffusion time (big delta) of 50 ms was set constant for all experiments. The diffusion gradient length (small delta) was optimised using 1D version of the DOSY pulse sequence in order to detect the whole decay properly. Accordingly, the gradient lengths 700, 800, 1200 and 1200 µs were used for the 1 mM, 2 mM, 5 mM and 10 mM samples of nitrone **5**, respectively, and 1000 µs for the samples with dye **6**. The decay curves were fitted and the diffusion constants were extracted using Bruker Dynamics Center 2.2.

Synthesis and characterisation



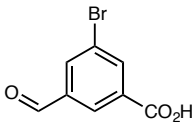
Scheme S1 – Synthetic overview

1-Octylboronic acid[2] (9)



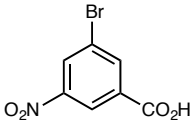
1-Bromooctane (10.0 g, 52 mmol) is added to a flask containing magnesium turnings (1.41 g, 58 mmol) and a few crystals of iodine in dry THF (100 mL), under an argon atmosphere. The mixture was heated to reflux for 18 hours, then cooled to –78 °C before addition of trimethylborate (8.8 mL, 78 mmol) to the newly formed Grignard reagent. The cooling was maintained for 1 h whilst stirring and then removed, allowing warming to RT. The reaction was quenched by the addition of 1M HCl and THF was removed *in vacuo*. The compound was extracted with Et_2O, and the organic layer was washed with brine, dried over $MgSO_4$, and solvent removed *in vacuo* to give the crude product. Purification was achieved by recrystallisation from hexane, giving a white crystalline solid. Yield: 4.47 g (55%); mp: 86 – 88 °C (Lit[3]: 83 – 84 °C); ^{1}H NMR (400.1 MHz; DMSO-d_6): δ_H 7.33 (s, 2H), 1.34-1.19 (m, 12H), 0.85 (t, J = 6.9 Hz, 3H), 0.56 (t, J = 7.7 Hz, 2H); ^{13}C NMR (100.6 MHz; DMSO-d_6): δ_C 32.1, 31.4, 29.0, 28.7, 24.2, 22.1, 15.4 (br), 14.0.

3-Bromo-5-formylbenzoic acid[4] (10)



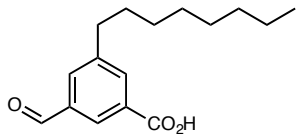
N-Bromosuccinimide (6.77 g, 38 mmol) was added portion-wise to a solution of 3-formylbenzoic acid (5.20 g, 35 mmol) in concentrated H_2SO_4 (50 mL), and the mixture was stirred at RT for 18 h. The solution was added to ice-water (200 mL), and the resulting white precipitate was filtered and washed with water. The product was recrystallised from boiling water (1.1 L) to afford a white solid, yield: 5.90 g (74%); mp: 170 – 171 °C (Lit[4]: 166 °C); ^{1}H NMR (400.1 MHz; DMSO-d_6): δ_H 10.05 (s, 1H), 8.40 (t, J = 1.4 Hz, 1H), 8.30 (d, J = 1.4 Hz, 2H); ^{13}C NMR (100.6 MHz; DMSO-d_6): δ_C 191.6, 165.2, 138.2, 136.8, 135.6, 133.9, 128.8, 122.6.

3-Bromo-5-nitrobenzoic acid[5] (11)



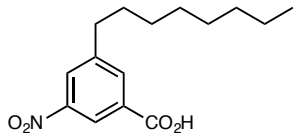
Synthesis of **11** used the same method employed in the synthesis of **10** but using 3-nitrobenzoic acid. Off-white solid, yield: 5.23 g (71%); mp: 160.5 – 161.5 °C (Lit[5]: 161 °C); ^{1}H NMR (400.3 MHz; DMSO-d_6): δ_H 8.63 (t, J = 2.0 Hz, 1H), 8.55 (m, 1H), 8.42 (m, 1H); ^{13}C NMR (100.7 MHz; DMSO-d_6): δ_C 164.4, 148.7, 137.6, 134.2, 130.0, 122.8, 122.4.

Aldehyde 2; *3-Formyl-5-octylbenzoic acid*



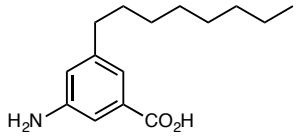
i) Protection: *N,N*-Dimethylformamide di-tert-butyl acetal (21.1 g, 104 mmol) was added drop-wise to a solution of **10** (5.75 g, 25 mmol) in dry toluene (120 mL) heated to reflux. The solution was refluxed for 3 h before cooling and washing sequentially with water, $NaHCO_3$ solution, then brine. The solution was dried over $MgSO_4$ and solvent was removed *in vacuo* resulting in an orange oil. Yield: 6.78 g (95%), the product was used without any purification.
ii) Suzuki coupling: The acid-protected formyl-bromide (3.39 g, 12 mmol), 1-octylboronic acid **9** (1.87 g, 12 mmol), and K_2CO_3 (5.18 g, 38 mmol) were dissolved in toluene/H_2O (100 mL, 3:1), and the solution was degassed with argon. $Pd(PPh_3)_4$ (0.36 g, 0.31 mmol) was added and the mixture heated at 95 °C for 3 days. The reaction was cooled and then concentrated under reduced pressure. The compound was extracted with EtOAc, and washed with brine, dried over $MgSO_4$ and solvent was removed *in vacuo*. The crude product was purified by column chromatography (3:2 CH_2Cl_2/hexane), to afford a colourless oil. Yield: 2.28 g (60%).
iii) Deprotection: The alkylated product (2.28 g, 7.2 mmol) was dissolved in TFA/CH_2Cl_2 (30 mL, 1:2) and stirred at RT for 3 h. The solution was washed with water, then brine, and dried over $MgSO_4$ before the solvent was removed *in vacuo* to give the desired product as an off-white solid. Yield: 1.67 g (89%, overall: 51%); mp: 87 – 89 °C; FTIR: 2955 (w), 2920 (m), 2850 (m), 2600 (br), 2362 (w), 1684 (s), 1599 (m), 1462 (m), 1424 (m), 1313-1237* (m), 1149 (m), 1125 (m), 1010 (w), 933 (br), 922 (m), 896 (m), 773 (m), 741 (w), 724 (w), 687 (s), 611 (w), 564 (m); ^{1}H NMR (400.1 MHz; $CDCl_3$): δ_H 10.08 (s, 1H), 8.43 (t, J = 1.7 Hz, 1H), 8.20 (t, J = 1.7 Hz, 1H), 7.97 (t, J = 1.7 Hz, 1H), 2.77 (t, J = 7.8 Hz, 2H), 1.72-1.65 (m, 2H), 1.37-1.24 (m, 10H), 0.88 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100.6 MHz; $CDCl_3$): δ_C 191.7, 171.0, 145.0, 136.9, 136.0, 133.7, 130.3, 130.0, 35.6, 32.0, 31.3, 29.5, 29.3*, 22.8, 14.3; HRMS-ES: calcd for $[M-H]^-$ ($C_{16}H_{21}O_3$): m/z 261.1491, found: m/z 261.1493.
[synthesis adapted from ref[2]]

Nitro 12; *3-Nitro-5-octylbenzoic acid*



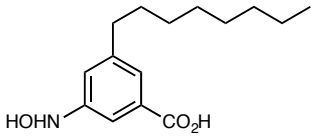
i) Protection: Di-*tert*-butyl dicarbonate (14.0 g, 64 mmol) was added to a solution of **11** (5.16 g, 21 mmol) and DMAP (0.59 g, 4.8 mmol) in dry THF (40 mL). The solution was stirred at RT for 18 h before pouring into ice-water and adjusting pH to ~10 with Na_2CO_3 solution. The compound was extracted with EtOAc, washed with brine, dried over $MgSO_4$ and solvent was removed *in vacuo* resulting in a yellow oil. Yield: 6.03 g (95%), the product was used without any purification.
ii) Suzuki coupling: The acid-protected nitro-bromide (4.01 g, 13 mmol), 1-octylboronic acid **9** (2.51 g, 16 mmol), and K_2CO_3 (5.86 g, 42 mmol) were dissolved in toluene/H_2O (100 mL, 3:1), and the solution was degassed under Argon. $Pd(PPh_3)_4$ (0.77 g, 0.66 mmol) was added and the mixture heated at 95 °C for 3 days. The reaction was then cooled and concentrated under reduced pressure. The compound was extracted with EtOAc, and washed with brine, dried over $MgSO_4$ and solvent was removed *in vacuo*. The crude product was purified by column chromatography (3:2 CH_2Cl_2/hexane) to afford a light yellow oil. Yield: 3.51 g (79%).
iii) Deprotection: The alkylated product (3.51 g, 10 mmol) was dissolved in TFA/CH_2Cl_2 (30 mL, 1:2) and stirred at RT for 3 h. The solution was washed with water, then brine, and dried over $MgSO_4$ before the solvent was removed *in vacuo* to give the desired product as an off-white solid. Yield: 2.62 g (90%, overall: 68%); mp: 83 – 84 °C; FTIR: 3084 (w), 2921 (m), 2856 (m), 2558 (w), 2360 (w), 1693 (s), 1621 (w), 1586 (w), 1534 (s), 1465 (m), 1413 (m), 1352 (m), 1288 (s), 1218 (m), 1130 (w), 1108 (w), 1090 (w), 1002 (w), 951 (w), 935 (w), 912 (m), 784 (m), 739 (m), 703 (m), 681 (m), 595 (m); ^{1}H NMR (500.1 MHz; DMSO-d_6): δ_H 8.44 (s, 1H), 8.30 (s, 1H), 8.17 (s, 1H), 2.79 (t, J = 7.7 Hz, 2H), 1.61 (m, 2H), 1.28-1.23 (m, 10H), 0.84 (t, J = 6.7 Hz, 3H); ^{13}C NMR (125.7 MHz; DMSO-d_6): δ_C 165.7, 148.0, 145.6, 135.2, 132.3, 126.9, 121.3, 34.3, 31.3, 30.6, 28.7, 28.6, 28.5, 22.1, 14.0; HRMS-ES: calcd for $[M\text{-}H]^-$ ($C_{15}H_{20}NO_4$): m/z 278.1392, found: m/z 278.1392.
[synthesis adapted from ref[2]]

Amine 1; *3-Amino-5-octylbenzoic acid*



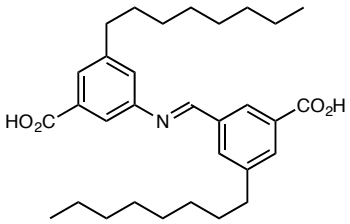
A solution of sodium hypophosphite monohydrate (190 mg, 1.79 mmol) in water (5 mL) was added to a solution of nitro **12** (100 mg, 0.36 mmol) in THF (5 mL). Palladium (10%) on carbon (15 mg) was added and the resulting mixture was stirred at 50 °C for 4 h. The cooled mixture was filtered through celite, washing with EtOAc. The organic solution was washed with water, then brine, dried over $MgSO_4$, and the solvent was removed *in vacuo* resulting in a light yellow solid, further purification was not necessary. Yield: 85 mg (95%); mp: 112 – 113 °C; FTIR: 3251 (w), 2919 (s), 2848 (m), 2574 (br), 2362 (w), 1684 (s), 1628 (w), 1603 (m), 1560 (m), 1459 (s), 1383 (s), 1336 (m), 1320 (m), 1260 (m), 1166 (w), 1123 (w), 875 (m), 795 (m), 776 (m), 756 (m), 726 (m), 691 (m), 566 (m), 523 (w), 497 (w), 443 (s); ^{1}H NMR (500.1 MHz; DMSO-d_6): δ_H 12.52 (br, 1H), 6.98 (m, 1H), 6.91 (m, 1H), 6.59 (m, 1H), 5.21 (br, 2H), 2.45 (t, J = 7.6 Hz, 2H), 1.52-1.50 (m, 2H), 1.26-1.23 (m, 10H), 0.85 (t, J = 6.9 Hz, 3H); ^{13}C NMR (125.7 MHz; DMSO-d_6): δ_C 168.0, 148.7, 143.0, 131.2, 118.0, 116.9, 112.2, 35.1, 31.3, 30.8, 28.9, 28.7*, 22.1, 14.0; HRMS-ES: calcd for $[M\text{-}H]^-$ ($C_{15}H_{22}NO_2$): m/z 248.1651, found: m/z 248.1655, calcd for $[MH]^+$ ($C_{15}H_{24}NO_2$): m/z 250.1807, found: m/z 250.1796.

Hydroxylamine 4; *3-(Hydroxyamino)-5-octylbenzoic acid*



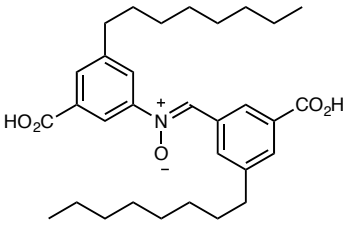
$BiCl_3$ (44 mg, 0.14 mmol) was added to a solution of nitro **12** (100 mg, 0.36 mmol) in EtOH/H_2O (13 mL, 4:1). To this white suspension, KBH_4 (78, 1.44 mmol) was added in a single portion. The resulting black mixture was stirred at RT for 10 minutes before addition of H_2O, then 1M HCl to quench the reaction. The compound was extracted by EtOAc and washed with brine, dried over $MgSO_4$, and solvent was removed *in vacuo* (maintaining the temperature <30 °C), to afford a white solid. Yield: 90 mg (95%). (If necessary, purification can be achieved through recrystallization with EtOAc/hexane although may result in significant loss to yield). mp: 87 – 89 °C; FTIR: 2920 (m), 2850 (m), 1690 (s), 1637 (w), 1600 (m), 1458 (m), 1420 (m), 1314 (s), 1290 (m), 1256 (s), 1121 (w), 1030 (w), 929 (m), 885 (m), 770 (m), 730 (m) 688 (m), 568 (w); ^{1}H NMR (400.1 MHz; DMSO-d_6): δ_H 12.68 (br, 1H), 8.40 (br, 2H), 7.25 (t, J = 1.7 Hz, 1H), 7.16 (t, J = 1.7 Hz, 1H), 6.86 (t, J = 1.7 Hz, 1H), 2.54 (t, J = 7.7 Hz, 2H), 1.50-1.56 (m, 2H), 1.30-1.19 (m, 10H), 0.85 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100.6 MHz; DMSO-d_6): δ_C 167.7, 152.3, 142.8, 130.9, 120.3, 116.9, 111.3, 35.1, 31.3, 30.8, 28.8, 28.7, 28.6, 22.1, 14.0; HRMS-ES: calcd for $[M\text{-}H]^-$ ($C_{15}H_{22}NO_3$): m/z 264.1600, found: m/z 264.1602.

Imine 3; *3-((3-carboxy-5-octylbenzylidene)amino)-5-octylbenzoic acid*



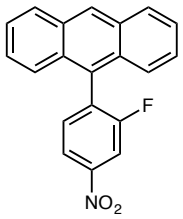
Amine **1** and aldehyde **2** and were dissolved (in a 1:1 ratio) in $CHCl_3$, sonicated for 10 min and left standing at RT. mp: 152 – 154 °C; FTIR: 2924 (s), 2855 (m), 2592 (br), 1686 (s), 1630 (w), 1601 (m), 1458 (m), 1416 (m), 1296 (m), 1240 (s), 928 (br), 895 (m), 773 (w), 721 (w), 692 (w) cm^{-1}; ^1H NMR (400.1 MHz; $CDCl_3$): δ_H 8.58 (s, 1H), 8.39 (s, 1H), 8.08 (s, 1H), 8.04 (s, 1H), 7.83 (s, 2H), 7.36 (s, 1H), 2.73 (m, 4H), 1.70 (s, 4H), 1.35-1.28 (m, 20H), 0.89 (m, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ_C 172.4, 172.0, 160.1, 151.5, 144.7, 144.4, 136.5, 133.3, 132.9, 130.4, 130.1, 129.4, 128.2, 128.0, 119.0, 35.9, 35.8, 32.0, 31.5, 31.4, 29.6*, 29.5*, 29.4*, 22.8*, 14.3*; HRMS-ES: calcd for $[M-H]^-$ ($C_{31}H_{42}NO_4$): m/z 492.3114, found: m/z 492.3120.

Nitrone gelator 5; *N,1-bis(3-carboxy-5-octylphenyl)methanimine oxide*



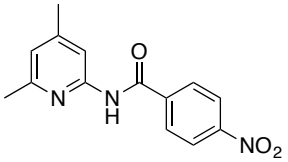
Aldehyde **2** and hydroxylamine **4** were dissolved (in a 1:1 ratio) in $CHCl_3$, sonicated for 10 min and left standing at RT. mp: 179 – 180 °C; FTIR: 2924 (m), 2853 (m), 2582 (br), 1682 (s), 1589 (w), 1458 (m), 1418 (m), 1302 (m), 1246 (m), 1177 (m), 1123 (w), 1092 (w), 897 (m), 800 (w), 772 (w), 724 (w), 685 (m), 629 (w), 567 (w), 523 (w) cm^{-1}; ^1H NMR (700.1 MHz; MeOD-d_4): δ_H 8.92 (s, 1H), 8.58 (s, 1H), 8.45 (s, 1H), 8.29 (s, 1H), 8.01 (d, J = 5.0 Hz, 2H), 7.92 (s, 1H), 2.77 (dt, J = 19.1, 7.7 Hz, 4H), 1.70 (m, 4H), 1.38-1.25 (m, 20H), 0.88 (t, J = 7.0 Hz, 6H). ^{13}C NMR (176.1 MHz; MeOD-d_4): δ_C 169.1, 168.3, 149.6, 146.4, 145.0, 138.3, 134.8, 133.7, 133.2, 132.4, 132.3, 131.7, 130.0, 126.9, 121.4, 36.6, 36.5, 32.9, 32.3, 32.2, 30.4*, 30.2*, 30.1*, 23.6*, 14.5*; HRMS-ES: calcd for $[MH]^+$ ($C_{31}H_{44}NO_5$): m/z 510.3214, found: m/z 510.3194, calcd for $[M+Na]^+$ ($C_{31}H_{43}NNaO_5$): m/z 532.3039, found: m/z 532.3010.

Dye 6; *(9-(2-fluoro-4-nitrophenyl)anthracene)*



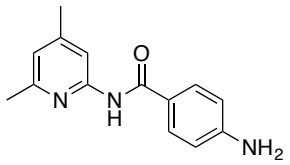
3-Fluoro-4-bromonitrobenzene (0.88 g, 4.0 mmol), anthracene-9-boronic acid (1.07 g, 4.8 mmol) and tripotassium phosphate (2.55 g, 12.0 mmol) were dissolved in were dissolved in toluene/EtOH/H_2O (13.5/13.5/9 mL) and the mixture was degassed with argon. $Pd(PPh_3)_4$ (0.23 g, 0.20 mmol) was added and the mixture was heated at 100 °C for 20 h. The reaction was then cooled and concentrated under reduced pressure. The compound was extracted with EtOAc, and then washed with brine, dried over $MgSO_4$ and the solvent was removed *in vacuo*. The crude product was purified through column chromatography (3:1 hexane/CH_2Cl_2), to afford an orange solid. Yield: 0.69 g (54%); mp: 182 – 183 °C; ^{1}H NMR (499.9 MHz; $CDCl_3$): δ_H 8.61 (s, 1H), 8.29 (dd, J = 8.3, 2.1 Hz, 1H), 8.22 (dd, J = 8.5, 2.1 Hz, 1H), 8.10 (d, J = 8.3 Hz, 2H), 7.64 (dd, J = 8.1, 7.2 Hz, 1H), 7.53-7.49 (m, 4H), 7.45-7.42 (m, 2H); ^{19}F-NMR (470.4 MHz; $CDCl_3$): δ_F 170.99; ^{13}C NMR (125.7 MHz; $CDCl_3$): δ_C 161.3, 159.3, 148.7*, 134.4, 134.3, 133.8, 133.6, 131.2, 129.9, 128.8, 128.7, 127.3, 126.6, 125.4, 125.2, 119.4*, 112.1, 111.8; HRMS-CI: calcd for M^+ ($C_{20}H_{12}FNO_2$): m/z 317.0852, found: m/z 317.0876, calcd for $[MH]^+$ ($C_{20}H_{13}FNO_2$): m/z 318.0930, found 318.0929. [synthesis adapted from ref[6]]

Nitro 13;[7] *N-(4,6-dimethylpyridin-2-yl)-4-nitrobenzamide*



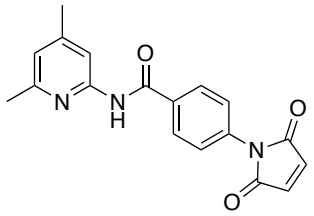
4-nitrobenzoyl chloride (2.13 g, 11.5 mmol) was suspended in dry DCM (25 mL) and cooled to 0 °C. A solution of 4,6-dimethylpyridin-2-amine (3.05 g, 25.0 mmol) in dry DCM (25 mL) was slowly added drop-wise. The addition resulted in the formation of a clear solution, which was stirred overnight whilst warming to RT. Work-up included extraction of excess amine from the organic layer with 1M HCl solution, re-extracting the aqueous layer with DCM, washing the combined organic layers with sat. aqueous NaHCO3 solution, drying over $MgSO_4$, filtration and concentration *in vacuo* to furnish the desired product as a white powder (2.89 g, 93%). mp: 206 – 207 °C (lit.[7]: 163 °C); ^{1}H NMR (300.1 MHz, $CDCl_3$): δ_H 8.83 (s, 1H), 8.30 (d, *J* = 9.0 Hz, 2H), 8.06 (d, *J* = 9.0 Hz, 2H), 8.00 (s, 1H, 6.79 (s, 1H), 2.36 (s, 3H), 2.36 (s, 3H);^{13}C NMR (75.5 MHz, $CDCl_3$): δ_C 163.8, 156.7, 150.6, 150.4, 150.0, 140.1, 128.5 , 124.1, 121.4, 112.1, 23.8, 21.5; MS (ES+): *m/z* 272 (100%, $[MH]^+$); HRMS-ES: calcd for $[MH]^+$ ($C_{14}H_{14}N_3O_3$): m/z 272.1035, found: m/z 272.1037.

Amine 14;[7] *4-amino-N-(4,6-dimethylpyridin-2-yl)benzamide*



Nitro **13** (1.20 g, 4.98 mmol) was dissolved in a 9:1 MeOH/DCM mixture (50 mL). Palladium (120 mg, 10 wt.% on carbon, dry) was added carefully. The solution was purged with hydrogen and kept under a hydrogen atmosphere at RT overnight using hydrogen filled balloons. The following day, the solution was filtered through celite and concentrated in vacuo to yield the desired product in sufficient quality for further conversion. The obtained spectrum is in accordance with the literature[7]. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ_H 8.49 (s, 1H), 8.04 (s, 1H), 7.77 (d, J = 8.7 Hz, 2H), 6.74 (s, 1H), 6.69 (d, J = 8.6 Hz, 2H), 2.42 (s, 3H), 2.34 (s, 3H).

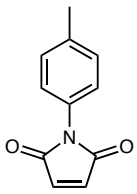
Maleimide 7; *N-(4,6-dimethylpyridin-2-yl)-4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)benzamide*



i) Amine **14** (1.11g, 4.6 mmol) was dissolved in acetic acid (30 mL) and maleic anhydride (0.59 g, 5.98 mmol) was added neat. The reaction was left to stir overnight at RT before the precipitate was filtered and thoroughly washed with Et_2O to yield the desired product as a light yellow solid (1.57 g, 93%) and was used without further purification.

ii) The crude intermediate (1.19 g, 3.50 mmol) was suspended in dry MeCN (30 mL). $ZnBr_2$ (0.79 mg, 3.50 mmol) and hexamethyldisilazane (2.82 g, 17.5 mmol) were added at RT. The reaction was refluxed at 90 °C for 1 h. After cooling to RT, the precipitate was filtered and the filtrate was reduced to roughly 10% of its original volume. Water was added and a pH of 1 was adjusted using 1M HCl. The solution was extracted with DCM. The combined organic layers were subsequently washed with an aqueous 0.1M EDTA solution, H_2O and brine, then dried over $MgSO_4$, filtered and concentrated to yield the desired product as a light yellow solid. Recrystallised from CH_2Cl_2, Yield: 890 mg (79%, overall: 73%). mp: 226 – 227 °C; ^{1}H NMR (400.1 MHz, $CDCl_3$): δ_H 8.48 (br, 1H), 8.03 (m, 3H), 7.56 (d, J = 8.9 Hz, 2H), 6.90 (s, 2H), 6.79 (s, 1H), 2.43 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ_C 169.0, 164.8, 154.5, 153.0, 150.2, 135.2, 134.6, 132.6, 128.6, 125.7, 120.9, 112.6, 29.8, 21.9; MS (ES+): m/z 322 (100%, $[MH]^+$); HRMS-ES: calcd for $[MH]^+$ ($C_{18}H_{16}N_3O_3$): m/z 322.1180, found: m/z 322.1192.

Maleimide 8;[8] *1-(4-Methylphenyl)-1H-pyrrole-2,5-dione*



i) *p*-Toluidine (2.14 g, 20.0 mol) in acetic acid (50 mL) was reacted with maleic anhydride (1.96 g, 20.0 mmol) at room temperature for 3 hours. The yellow precipitate formed during the reaction was filtered, washed with Et_2O (10 mL) and dried under vacuum to yield an intermediate (2.52 g, 61%).

ii) The intermediate (771 mg, 3.76 mmol) was dissolved in MeCN (40 mL), then zinc bromide (850 mg, 3.76 mmol) and hexamethyldisilazane (4 ml, 18.8 mmol) were added to the solution. The reaction mixture was refluxed at 70 ˚C for one hour, before being quenched with water (50 mL). The organic layer was treated with conc. HCl (5 mL) and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo, affording the product as yellow solid. Yield: 0.50 g (71%, overall: 43%); mp: 148 ˚C (Lit.[8]: mp 151–153 °C); ^{1}H NMR (400.1 MHz, $CDCl_3$): δ_H 7.27 (d, *J* = 8.4 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 6.85 (s, 2H), 2.38 (s, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ_C 169.7, 138.1, 134.2, 129.8, 128.5, 126.1, 21.2; HRMS-CI: calcd for $[MH]^+$ ($C_{11}H_{10}NO_2$): m/z 188.0712, found: m/z 188.0715.

Comparison of gelation in different solvents

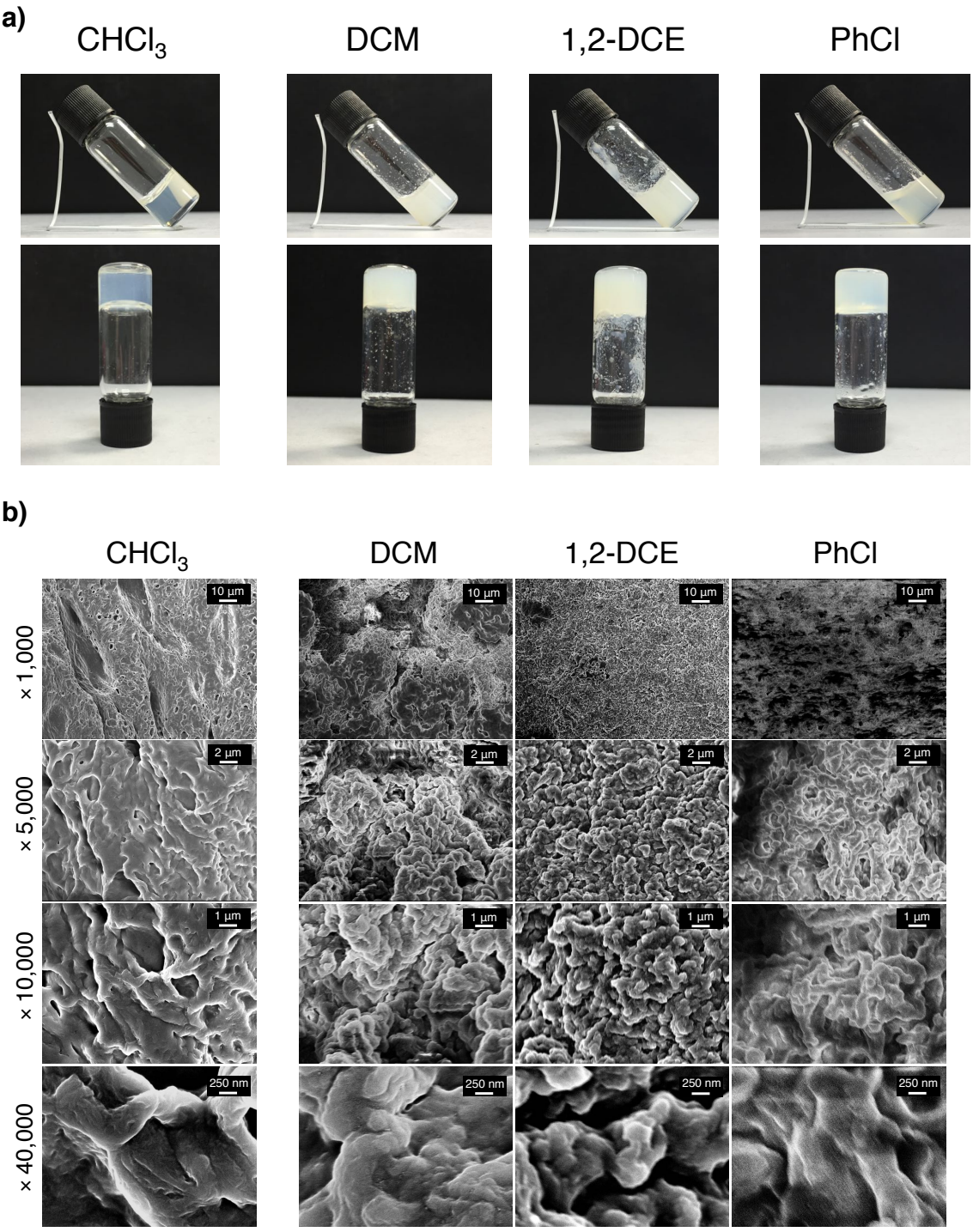
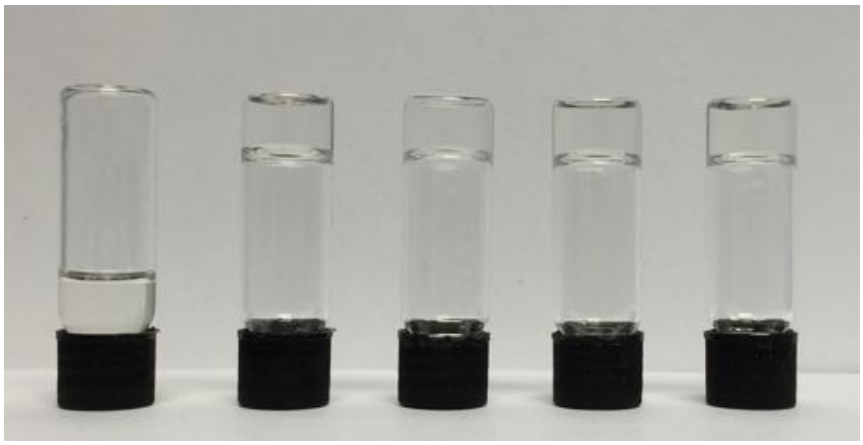


Figure S2 a) Photographs of nitrone **5** gels in different solvents (chloroform, dichloromethane, 1,2-dichloroethane, chlorobenzene) each made at 40 mM. b) SEM image comparison of nitrone **5** xerogels made from the different solvents (chloroform, dichloromethane, 1,2-dichloroethane, chlorobenzene) shown at a range of length scales: ×1,000, ×5,000, ×10,000, ×40,000 magnification.

Clear gel	Turbid, partial gel	Soluble	Insoluble
Chloroform	Chlorobenzene Dichloromethane 1,2-DCE 1,2-DCB	1,1,2,2-TCE THF Acetone* Methanol Ethanol DMSO	Hexane Toluene Diethyl ether Ethyl acetate Acetonitrile Water

Table S3 Gelation solvent screening results. Samples were prepared from mixtures of **2** and **4**, those that did not produce a gel were tested again by adding preformed nitrone **5** to the solvent, this still did not produce a gel, resulting in either solution or precipitation. (*Acetone reacts with hydroxylamine **2**).



[5] / mM	5	6	7	8	9
wt%	0.17	0.20	0.24	0.27	0.31

Figure S4 Photographs of a more accurate CGC measurement, at 5 mM the gel held only several seconds before collapse into a viscous solution/partial gel. We therefore determine the CGC of nitrone **5** in $CHCl_3$ to be 6 mM (0.2 wt%).

Triethylamine exposure to the nitrone gel

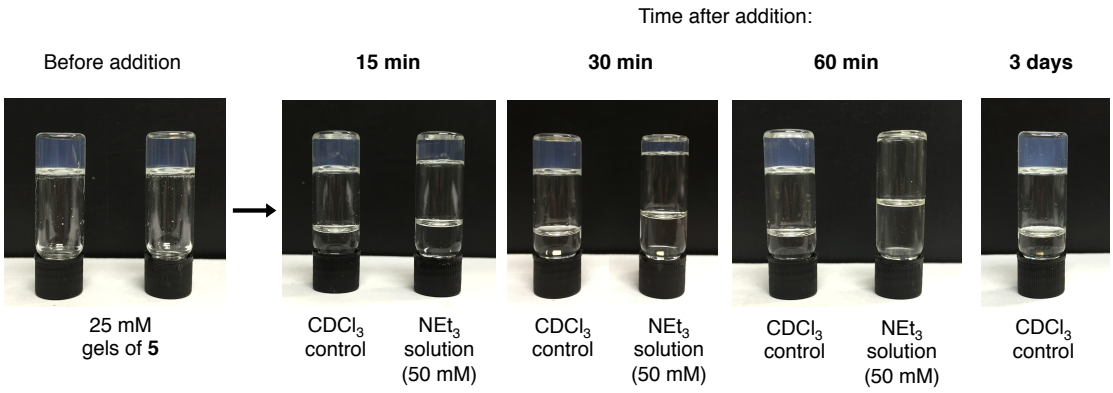
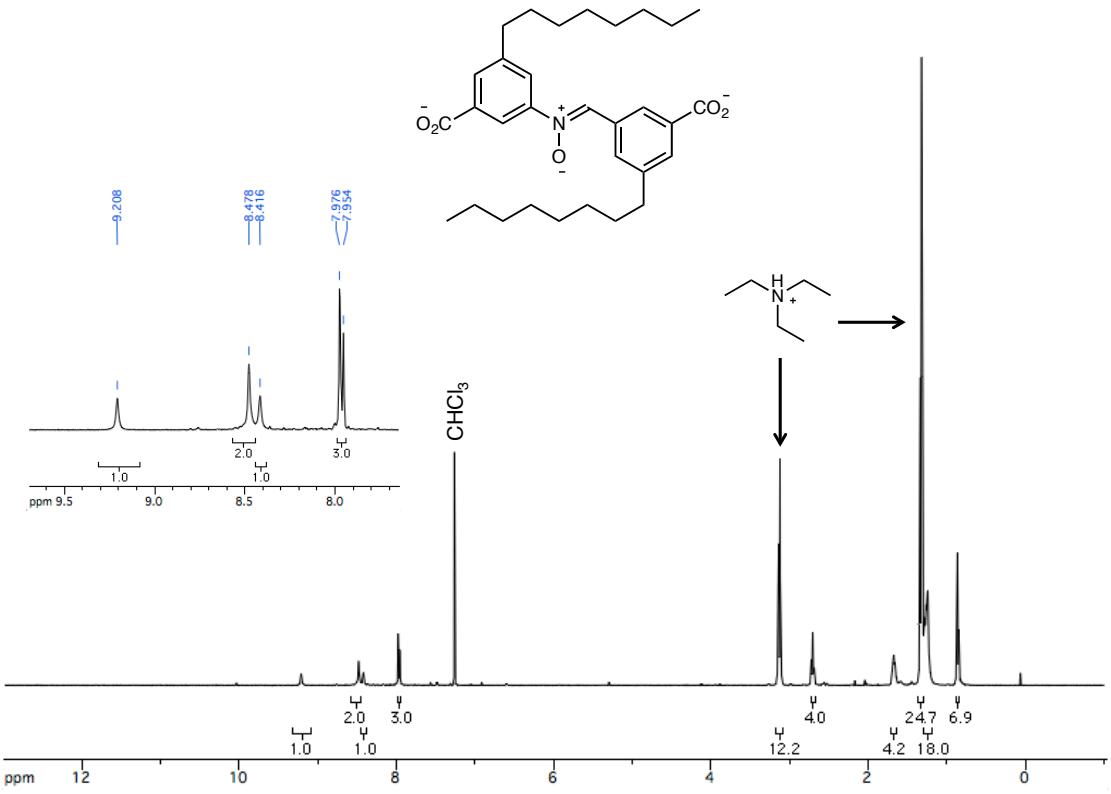


Figure S5 A Series of photos showing condition of gels at several times after the addition of $CDCl_3$ (left) and a 50 mM solution of NEt_3 in $CDCl_3$ (right) to gels of nitrone **5** prepared at 25 mM in $CDCl_3$ (sample vials are inverted just before each photo is taken). Gel is stable to addition of more solvent, but will dissolve readily with added triethylamine (NMR of the resulting solution after 60 minutes is shown below). Addition of pTSA to the NEt_3 mixture results in hydrolysis of **5** and precipitation.



^{1}H NMR spectrum (500.1 MHz, RT, $CDCl_3$) of **5** after deprotonation and subsequent dissolution by NEt_3

Reaction of the nitrone gel

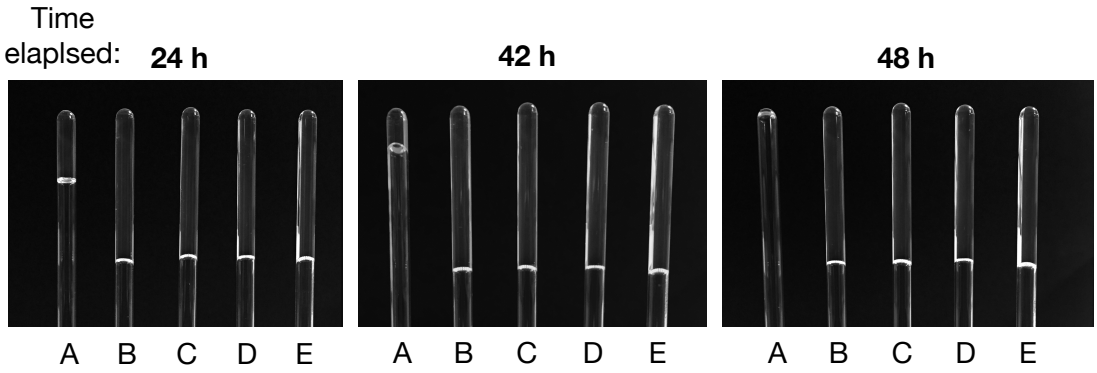
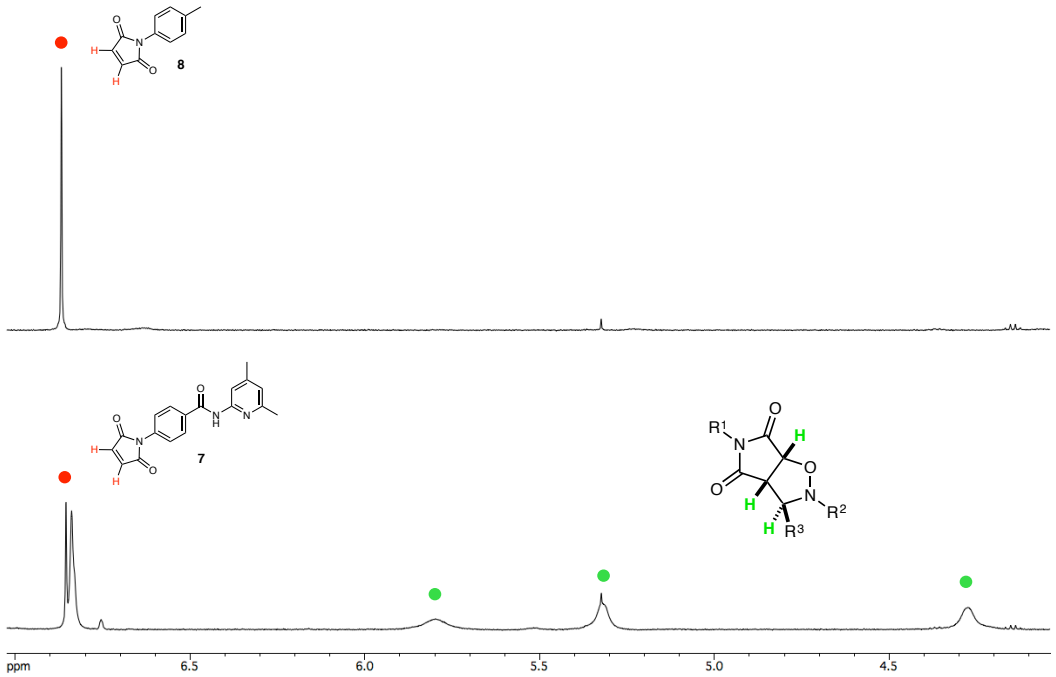


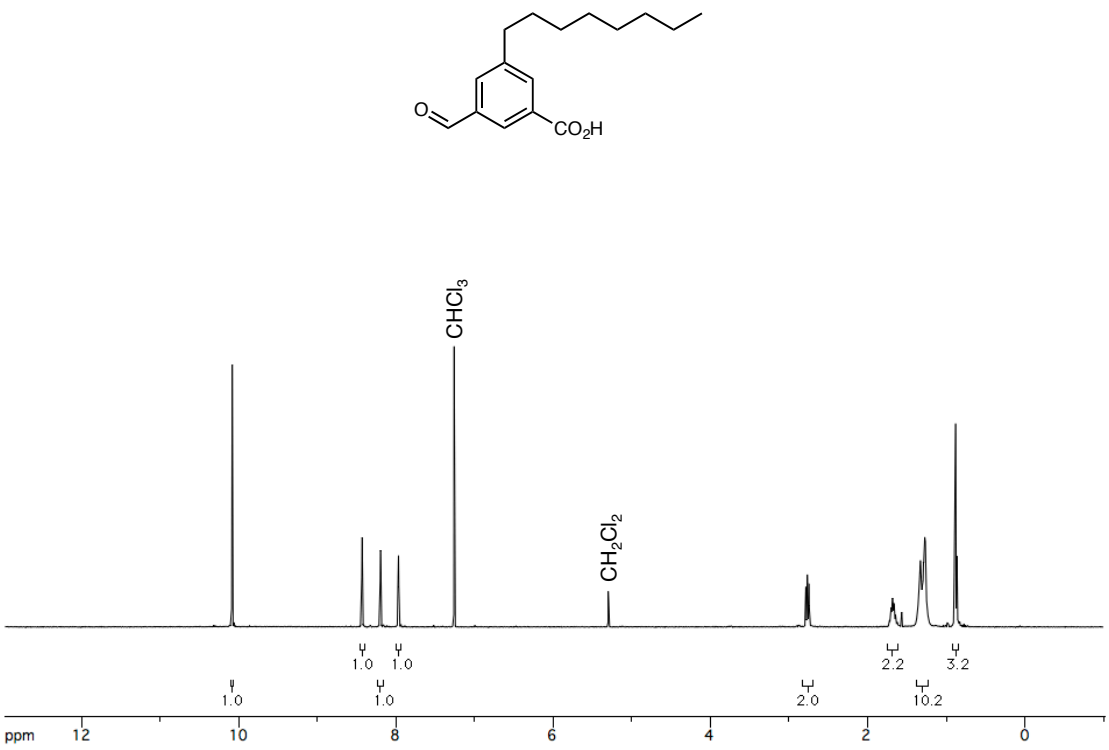
Figure S6 A Series of photos showing the gel composition for several samples over the course of 48 h. In each NMR tube a 0.5 mL $CDCl_3$ solution containing a 20 mM mixture of **2** and **4** were added. The tubes were sonicated for 10 mins and kept upright allowing the nitrone gel **5** to form. Over an hour later, 0.5 mL of one of five other solutions (20 mM in $CDCl_3$) was layered on top of the gel and the vials were sealed. The solutions added consisted of: A = Maleimide **7**, B = Maleimide **8**, C = Nitro **13**, D = Maleimide **8** + Nitro **13**, E = just $CDCl_3$ control. Only sample A showed signs of degradation of gel, caused by reaction of nitrone **5** with maleimide **7**.

NMR spectra were taken for each sample (A to E) at each of these times showing diffusion of compounds into the gel (apparent by appearance of sharp peaks). Only sample A, containing maleimide **7**, with both a recognition and reactive element, produced the cycloadduct. The other controls demonstrate that both recognition and reactive elements are required, and connected in a single entity. (B = reactive component with no recognition, C = recognition but not reactive, D = combination of B and C but disconnected, E = neither component). An overlay of spectra from samples A and B after 48 h is shown below with indicative reaction product peaks labelled.

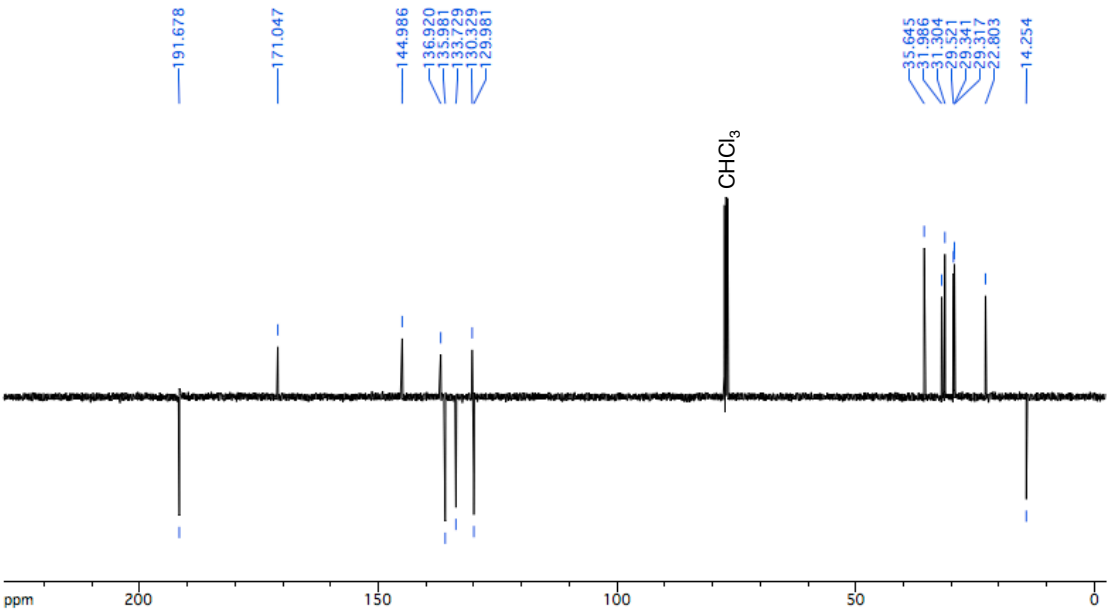


Overlaid ^{1}H NMR spectra (500.1 MHz, RT, $CDCl_3$) of **5** 48 h after addition of solution of: maleimide **7** bottom, maleimide **8** top

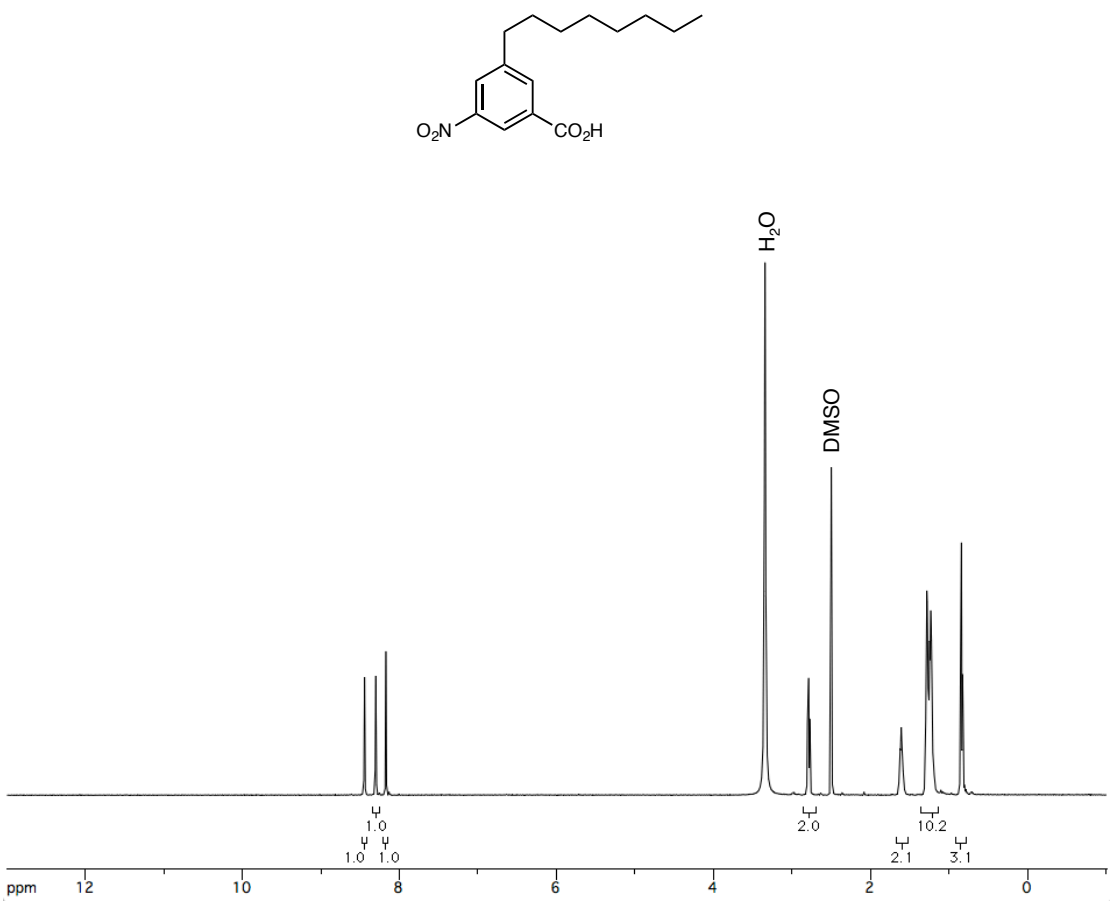
NMR Spectra of important compounds



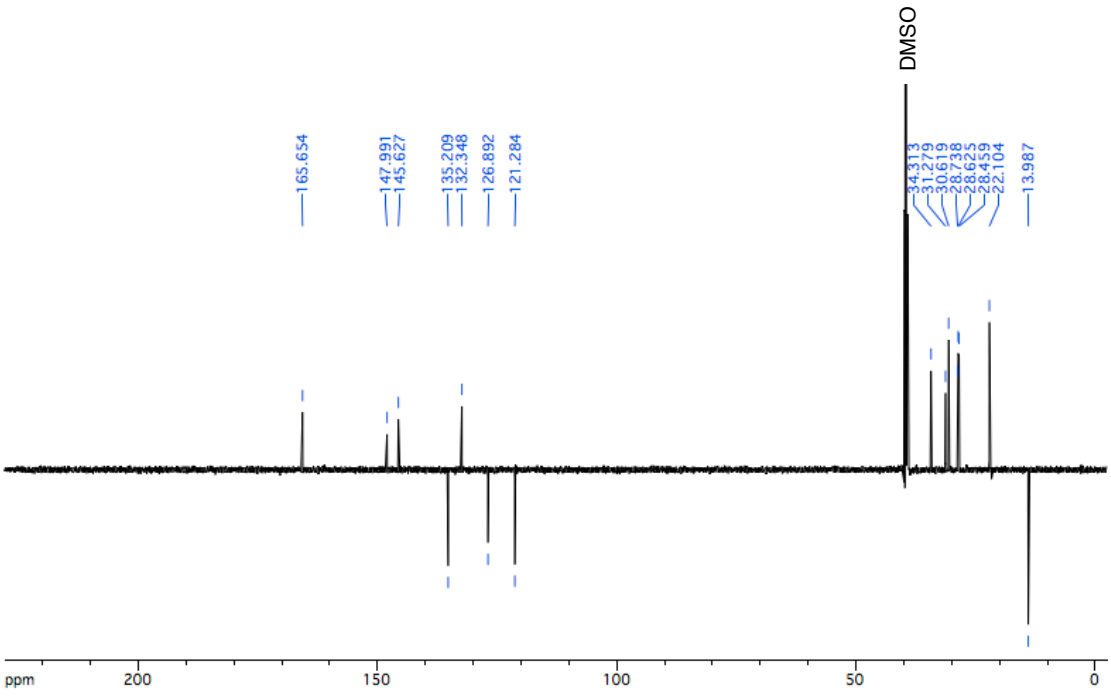
^{1}H NMR spectrum (400.1 MHz, RT, $CDCl_3$) of **2**



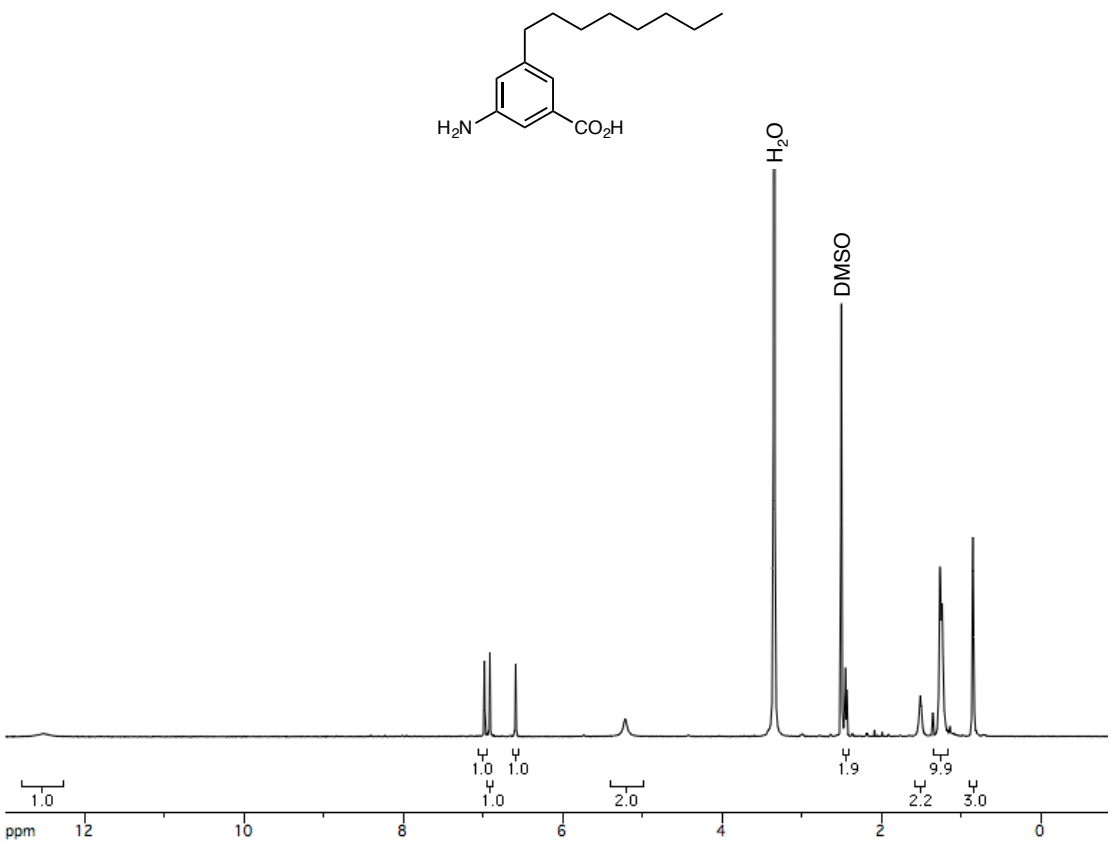
^{13}C NMR spectrum (100.6 MHz, RT, $CDCl_3$) of **2**



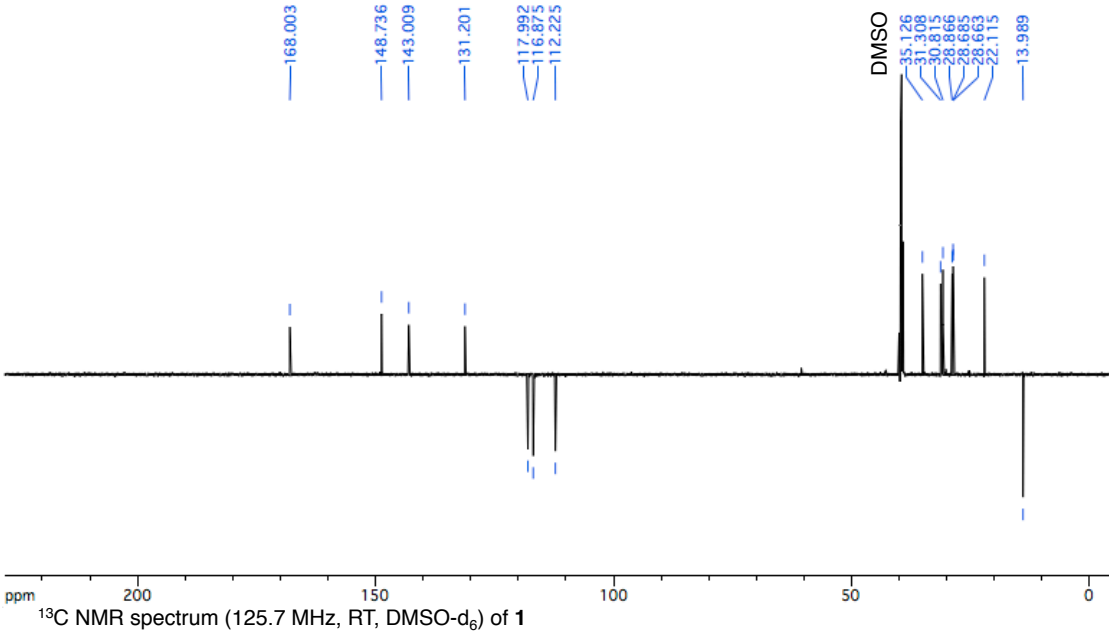
^{1}H NMR spectrum (500.1 MHz, RT, DMSO-d_6) of **12**



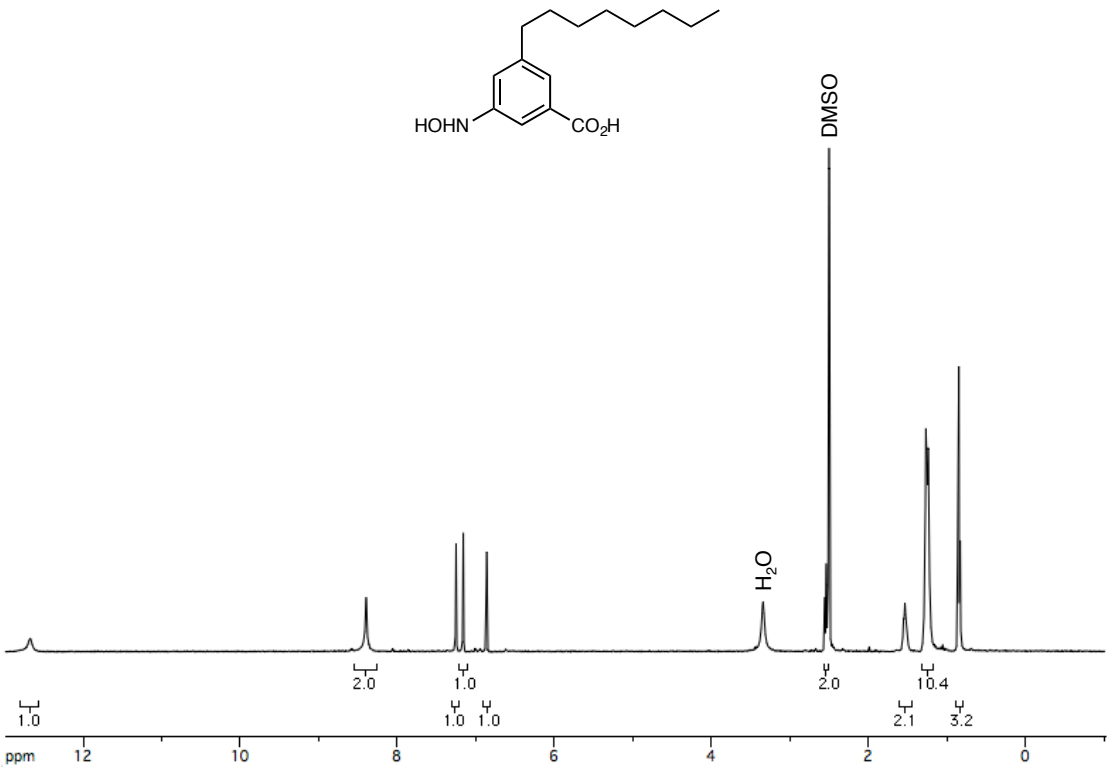
^{13}C NMR spectrum (125.7 MHz, RT, DMSO-d_6) of **12**



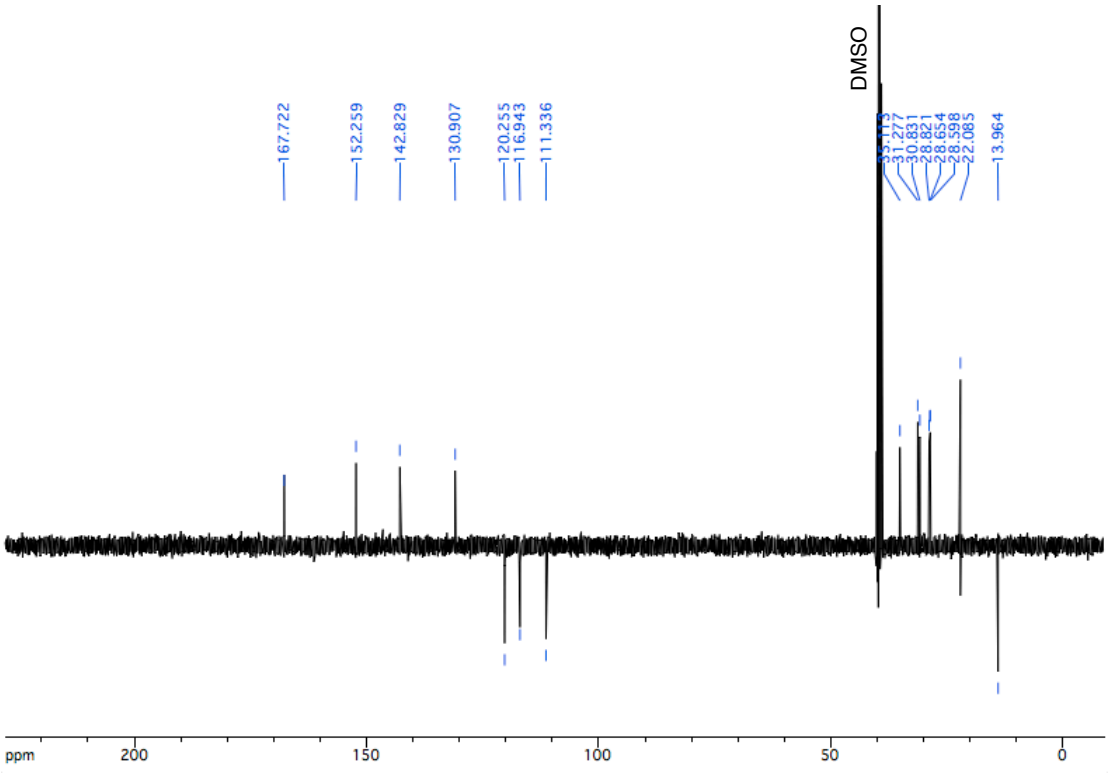
^{1}H NMR spectrum (500.1 MHz, RT, DMSO-d_6) of **1**



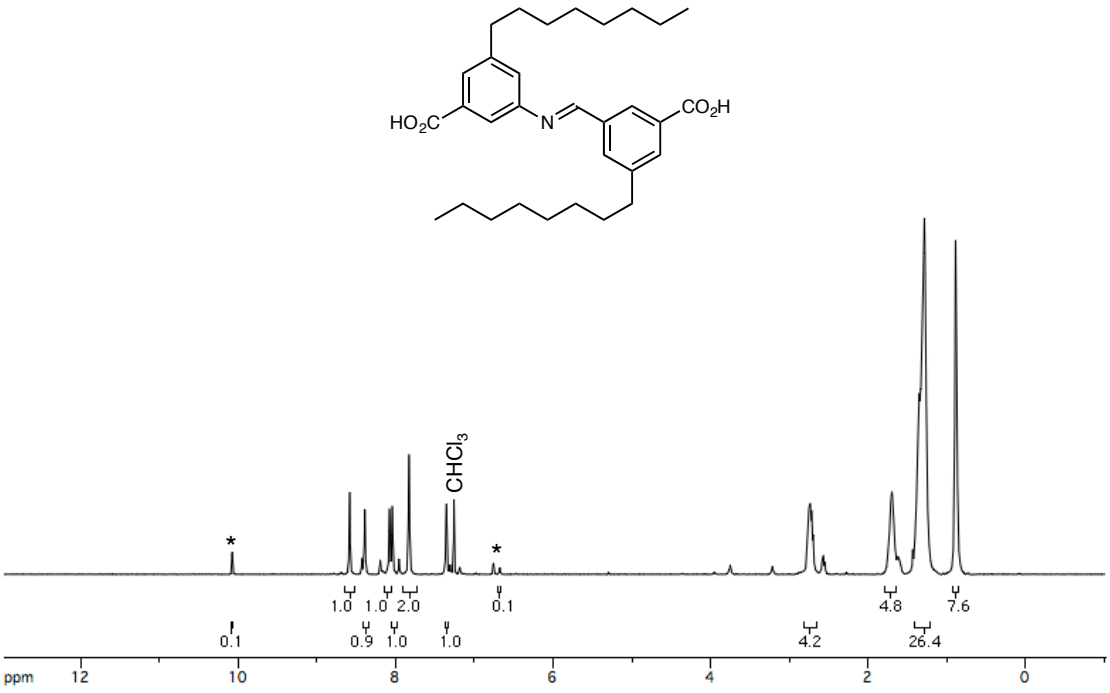
^{13}C NMR spectrum (125.7 MHz, RT, DMSO-d_6) of **1**



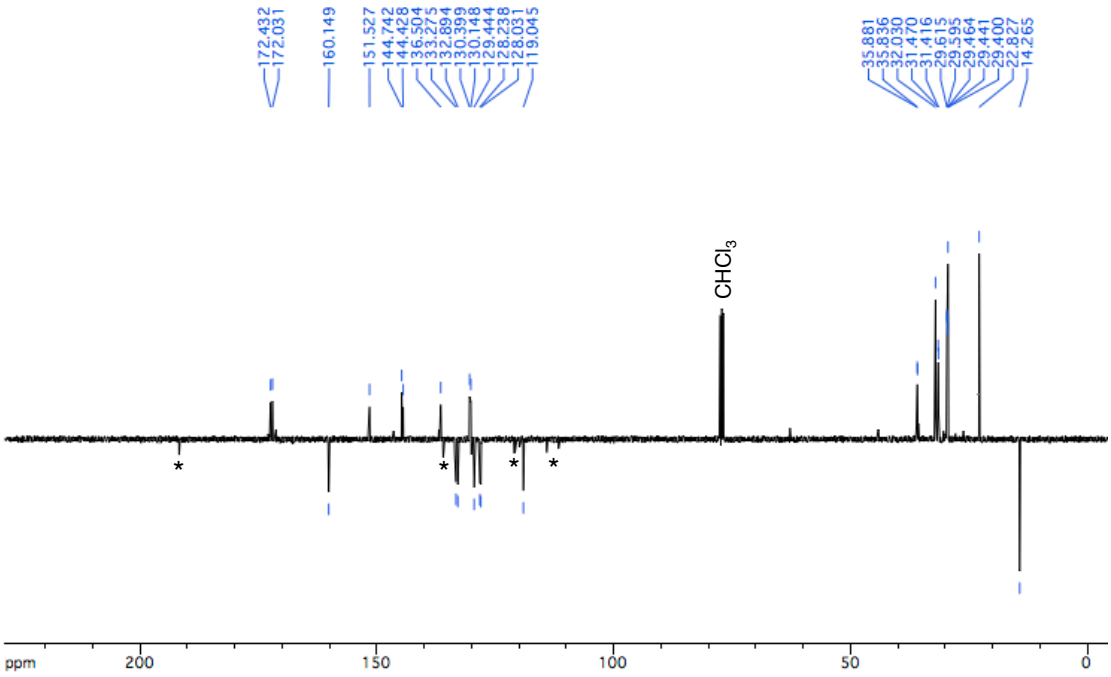
^{1}H NMR spectrum (400.1 MHz, RT, DMSO-d_6) of **4**



^{13}C NMR spectrum (100.6 MHz, RT, DMSO-d_6) of **4**

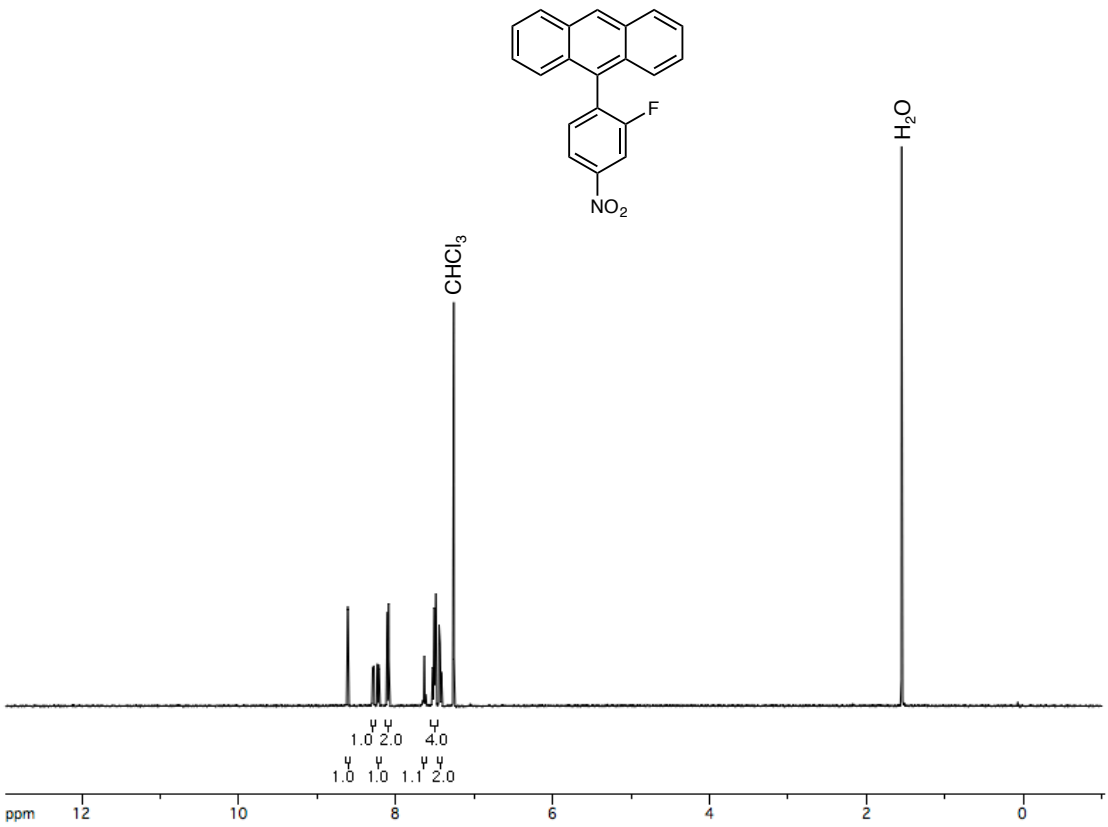


^{1}H NMR spectrum (400.1 MHz, RT, MeOD-d_4) of **3**

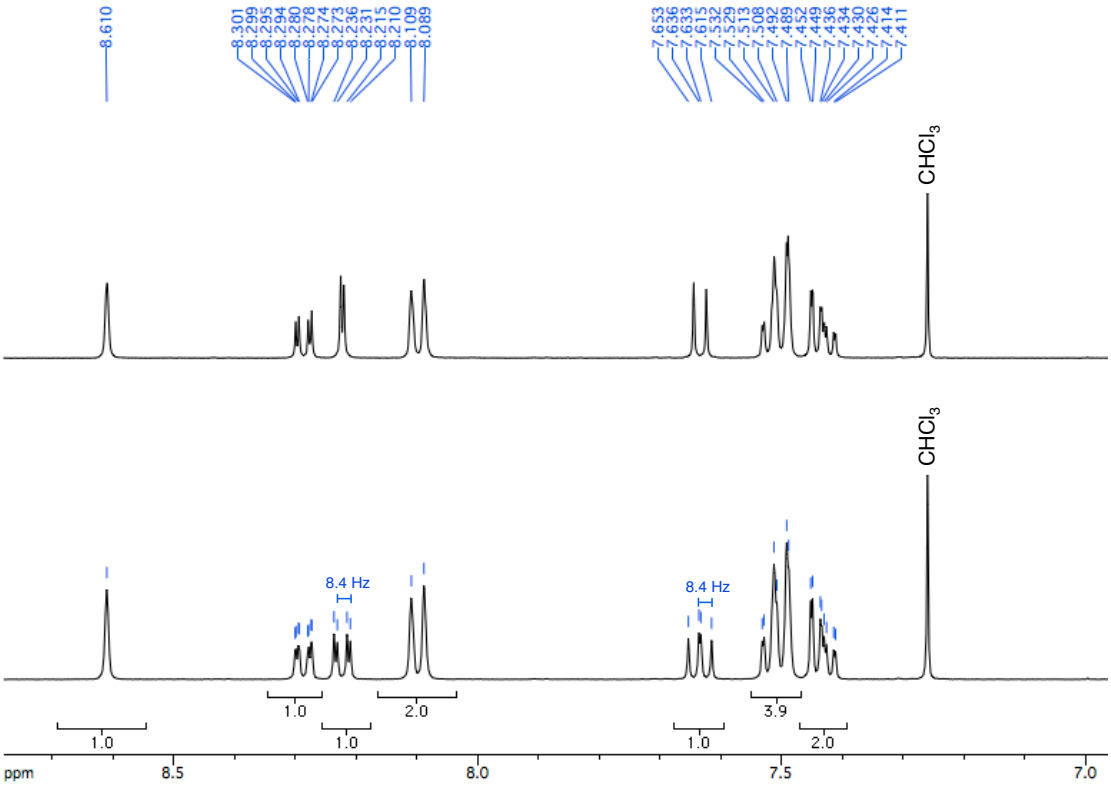


^{1}H NMR spectrum (100.6 MHz, RT, MeOD-d_4) of **3**

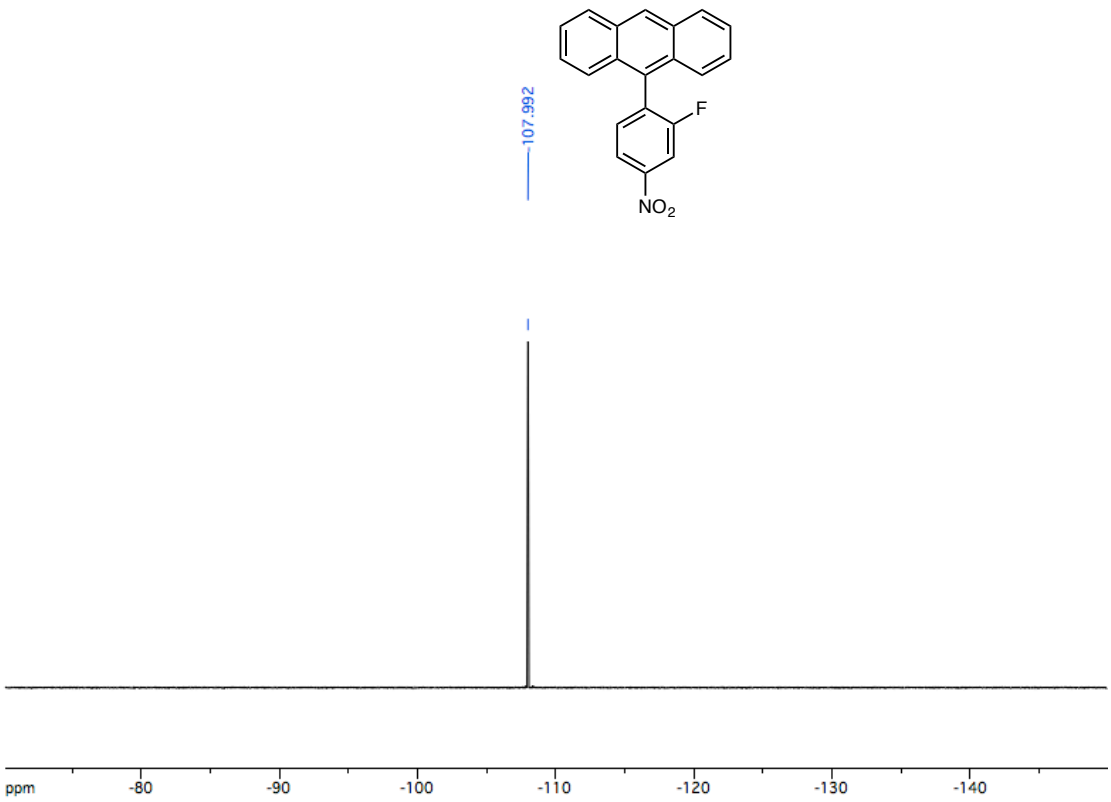
* = A small amount of hydrolysis products are visible due to incomplete conversion. These minor impurities affect the integrals of overlapping alkyl chains.



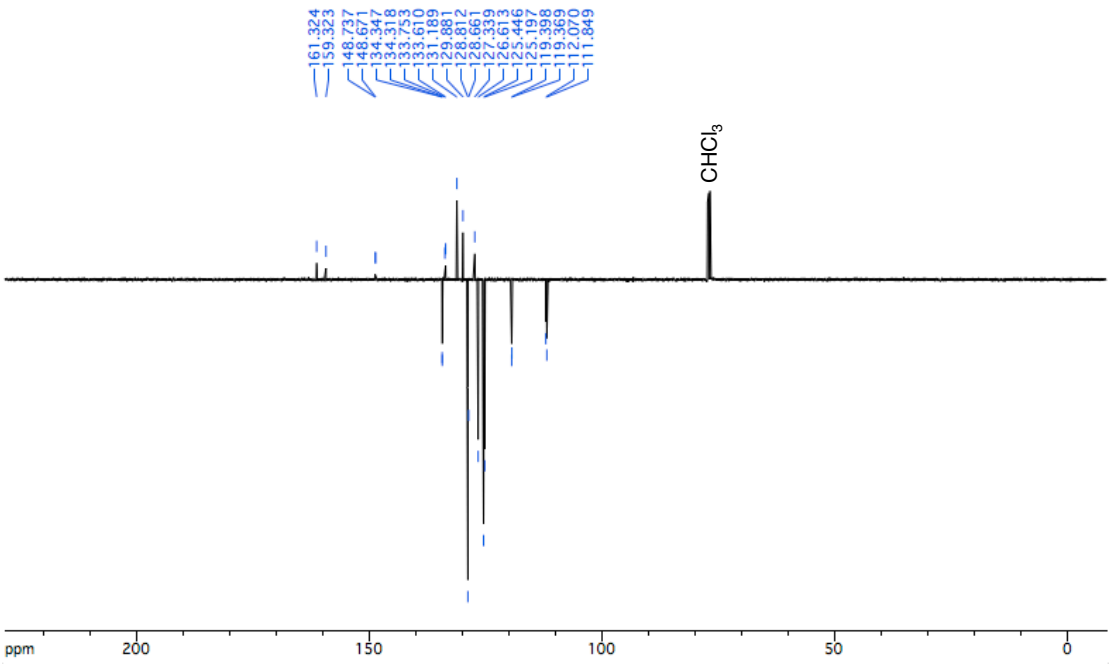
^{1}H NMR spectrum (500.1 MHz, RT, $CDCl_3$) of **6**



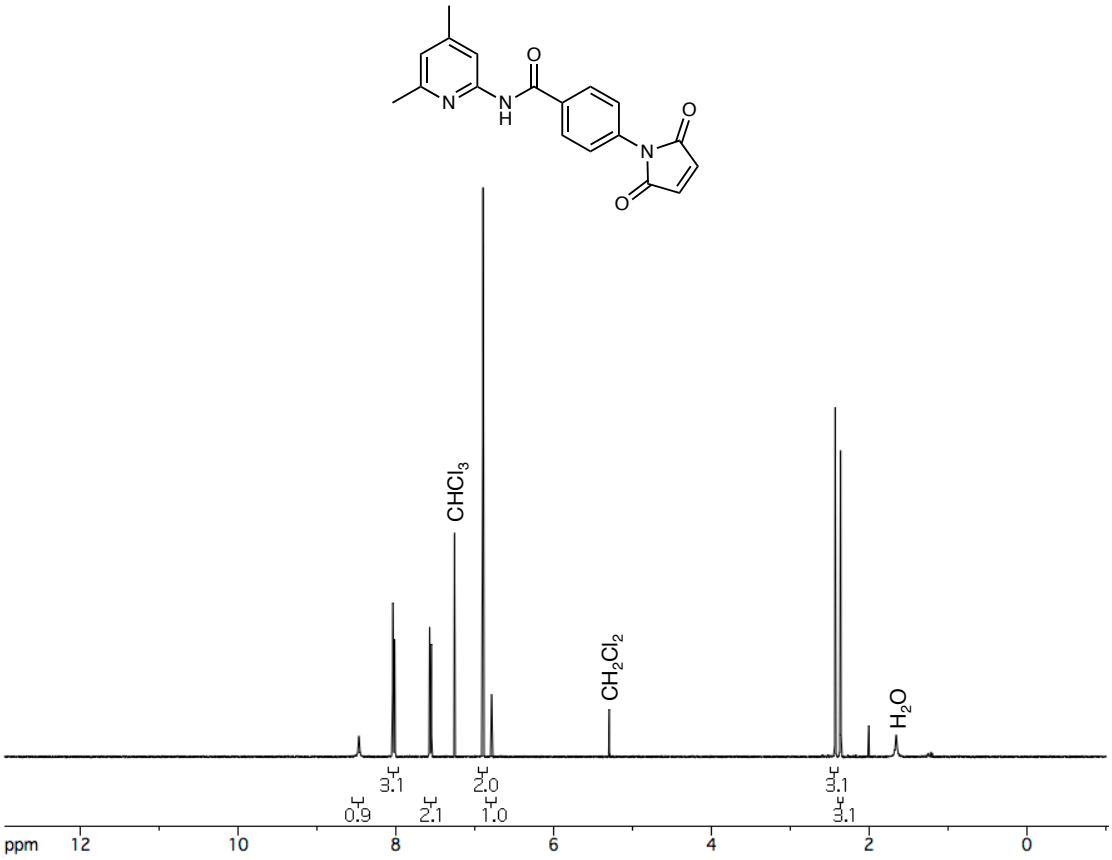
Overlaid partial ^{1}H NMR spectra (500.1 MHz, RT, $CDCl_3$) of **6**, top = ^{1}H {^{19}F}, bottom = ^{1}H without decoupling



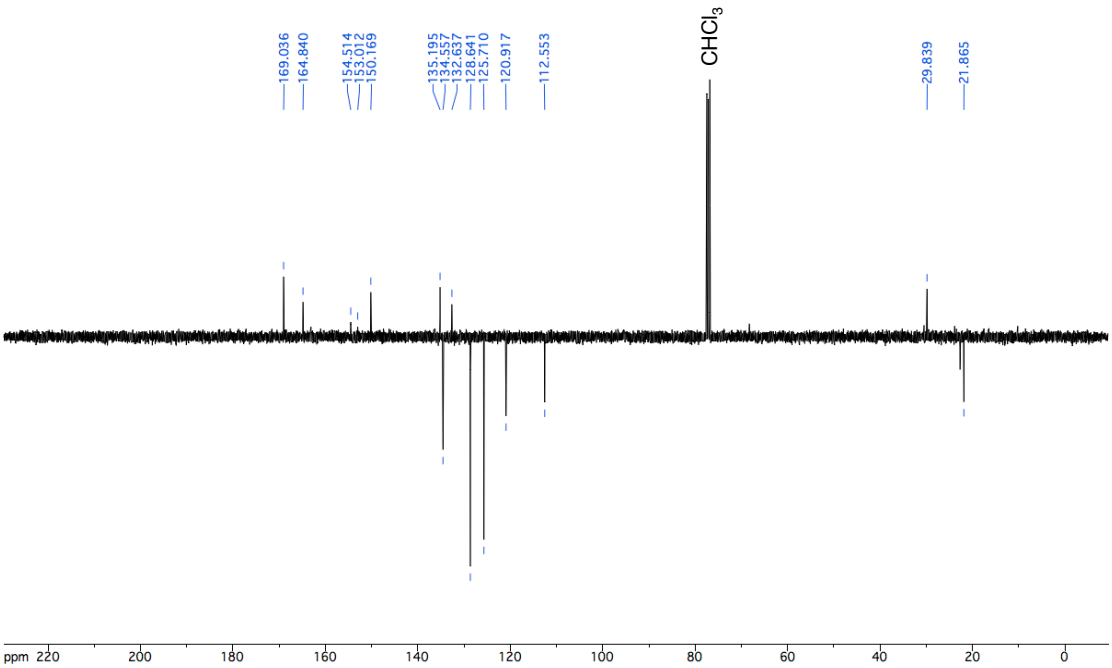
^{19}F {^{1}H} NMR spectrum (470.5 MHz, RT, $CDCl_3$) of **6**



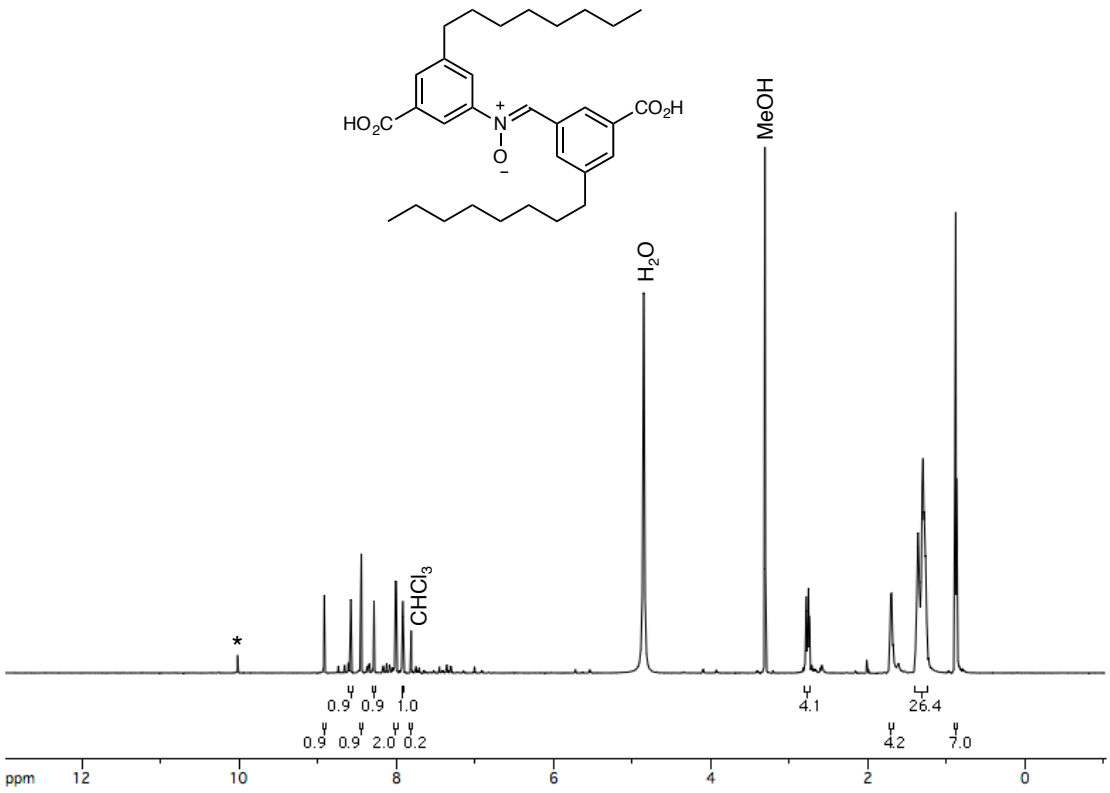
^{13}C NMR spectrum (125.7 MHz, RT, $CDCl_3$) of **6**



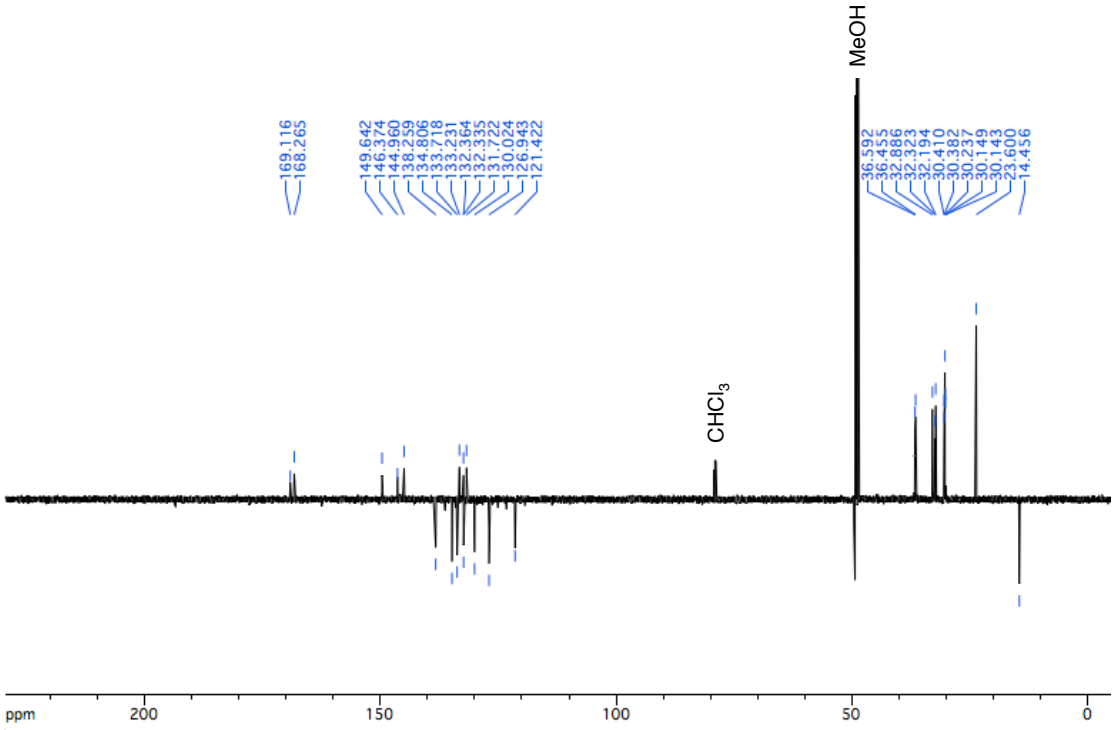
^{1}H NMR spectrum (400.1 MHz, RT, MeOD-d_4) of **7**



^{1}H NMR spectrum (100.6 MHz, RT, MeOD-d_4) of **7**

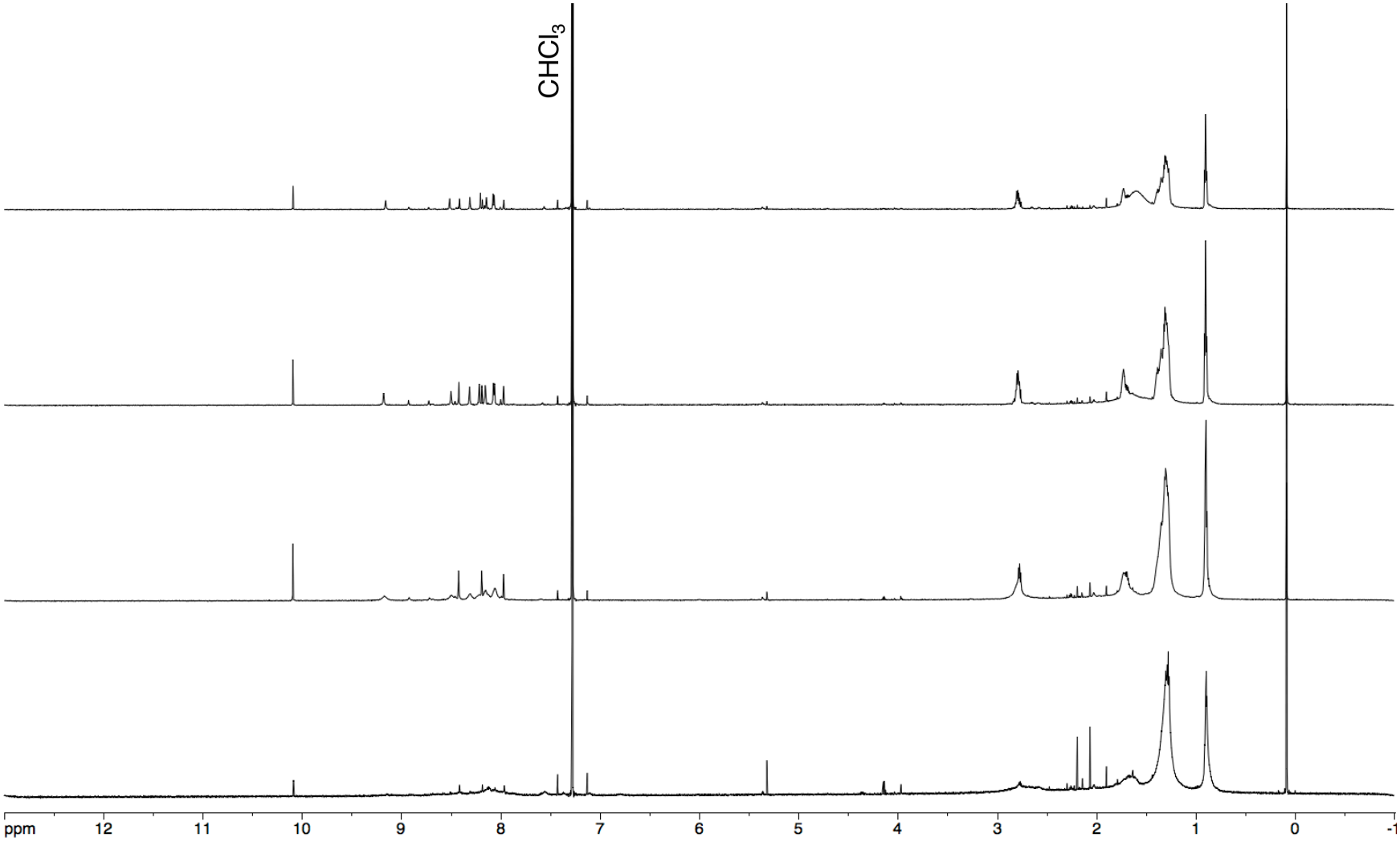


^{1}H NMR spectrum (700.1 MHz, RT, MeOD-d_4) of **5**



^{1}H NMR spectrum (176.1 MHz, RT, MeOD-d_4) of **5**

* = A small amount of hydrolysis products are visible due to water present in the solvent. These minor impurities affect the integrals of overlapping alkyl chains.



Overlaid ^{1}H NMR spectra (700.1 MHz, RT, $CDCl_3$) of **2** + **4** mixtures, prepared at 1, 2, 5, and 10 mM (from top to bottom)

Supporting information references

1. R. F. Heck, *Palladium Reagents in Organic Syntheses*, Academic Press, 1985, pp 2-3
2. Changliang Ren, Shengyu Xu, Jun Xu, Hongyu Chen, and Huaqiang Zeng, *Org. Lett.,* 2011**, 13** (15), 3840-3843
3. W. Gerrard, E. F. Mooney and R. G. Rees, *J. Chem. Soc.*, 1964, 740-745
4. Dahui Zhao and and Jeffrey S. Moore, *J. Org. Chem.,* 2002**, 67** (11), 3548-3554
5. K. Rajesh, M. Somasundaram, R. Saiganesh, and K. K. Balasubramanian, *J. Org. Chem.,* 2007, **72** (15), 5867-5869
6. Y.-X. Gao, L. Chang, H. Shi, B. Liang, K. Wongkhan, D. Chaiyaveij, A. S. Batsanov, T. B. Marder, C.-C. Li, Z. Yang, and Y. Huang, *Adv. Synth. Catal.* 2010, **352**, 1955 – 1966
7. S. Bouhayat, S. Piessard, G. Le Baut, L. Sparfel, J.-Y. Petit, F. Piriou, L. Welin, *J. Med. Chem.,* 1985, **28**, 555-559.
8. B.J. Davie, C. Valant, J.M. White, P.M. Sexton, B. Capuano, A. Christopoulos, and P.J. Scammells, *J. Med. Chem.* 2014, **57**, 5405–5418