

Supporting Information

Continuous flow solvent free organic synthesis involving solids (reactants/products) using a screw reactor

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Experimental Section

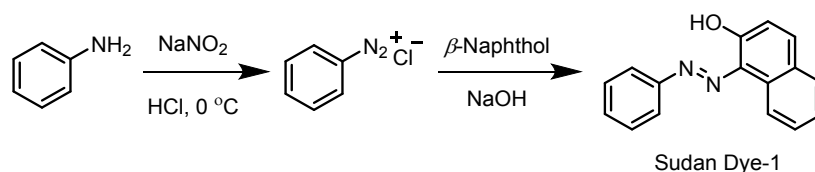
General (Information) Method:

All the reagents and solvents were used as a commercial grade. All the reactions were carried out in a solid screw feeder. All the reaction was monitored by thin layer chromatography (TLC) on Merck silica gel 60-F254 coated 0.25 mm plates, detected by UV. Flash chromatography was performed with the indicated solvents on silica gel (particle size 0.064–0.210 mm). Yields reported are for isolated, spectroscopically pure compounds. ¹H and ¹³C NMR spectra were recorded on a Bruker -200 MHz instrument with TMS as the internal standard. Chemical shifts are given in ppm (δ), referenced to tetramethylsilane (TMS) for ¹H NMR and the ¹³C-resonances of CDCl₃ (δ = 77.0 ppm) for ¹³C NMR as internal standards. Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, m = multiples, b=broad, respectively) coupling constant (*J*, Hz), and integration.

General procedure for the synthesis of products (Representative Examples)-

Note: After the reaction was over as monitored by TLC, the remained product in the grooves of screw was removed by using respective solvents used for the particular reaction followed by vacuum evaporation so as to avoid the loss in product yields.

1a. Protocol for 10g synthesis of Sudan dye



The generation of benzenediazonium chloride was done as per batch protocol.

Batch Protocol: To a solution of NaNO₂ (112.7 mmol, 7.8 g) in 10 mL water was added dropwise ice-cooled solution of aniline (107.4 mmol, 9.8 mL), HCl (35% wt. /wt.) (322.1 mmol, 28.6 mL) and 50 mL H₂O. The clear solution was stirred for 10 min at 0 °C.

Flow Protocol: The above generated benzenediazonium chloride was fed from solid dosing 1 and the mixture of β-naphthol (112.7 mmol, 16.2 g), NaOH (322.1 mmol, 12.8 g) and 60 mL water was fed from solid dosing 2 in a screw feeder reactor rotating at the 120-150 rpm, maintained at 0°C. The total residence time for azo dye formation was only 20 sec. The red coloured slurry of the formed dye was collected and checked for the presence of unreacted diazonium salt using H-acid. Since there was no colour change which indicated the complete conversion of diazonium salt. Then product was filtrated using Whatman filter under the suction pump and dries at 50 °C to afford reddish orange solid product in (95%, 25.4g) yield and requires no further purification. The product was analysed by NMR spectroscopy.¹H NMR (200 MHz, CDCl₃) δ = 8.54 (d, *J* = 8.2 Hz, 1 H), 7.76 - 7.65 (m, 3 H), 7.60 - 7.29 (m, 6 H), 6.85 (d, *J* = 9.4 Hz, 1 H); ¹³C NMR (50 MHz, CDCl₃) δ = 172.0, 144.7, 140.1, 133.6, 130.0, 129.6, 128.8, 128.6, 128.0, 127.4, 125.7, 124.8, 121.7, 118.5.

1a. **Protocol for 1 kg synthesis of Sudan Dye:**

The procedure for 1 kg synthesis is also similar to that used for 10 kg synthesis of Sudan dye. The quantity of starting material taken are mentioned below. Only in this case peristaltic pumps were used to feed the diazonium salt flow rates 20 mL/min and β-naphthol in NaOH solution flow rate 20 ml/min into the screw feeder at a 0 °C and the screw is rotating at an 80-200 rpm.

Diazonium salt: NaNO₂ (4509 mmol, 311.0 g) in 420 mL water, aniline (4295 mmol, 392 mL), HCl (35% wt. /wt.) (1289 mmol, 1147 mL) and 900 mL H₂O.

Coupling Partner: β-naphthol (4510 mmol, 650.0 g) in NaOH (1289 mmol, 516.0 g) dissolved in 3400 mL water. The residence time for azo dye formation was only 20 sec. The separation process is same as mentioned above. To afford reddish orange solid product in 95% (0.98 kg) yield. The product was analysed by NMR spectroscopy.

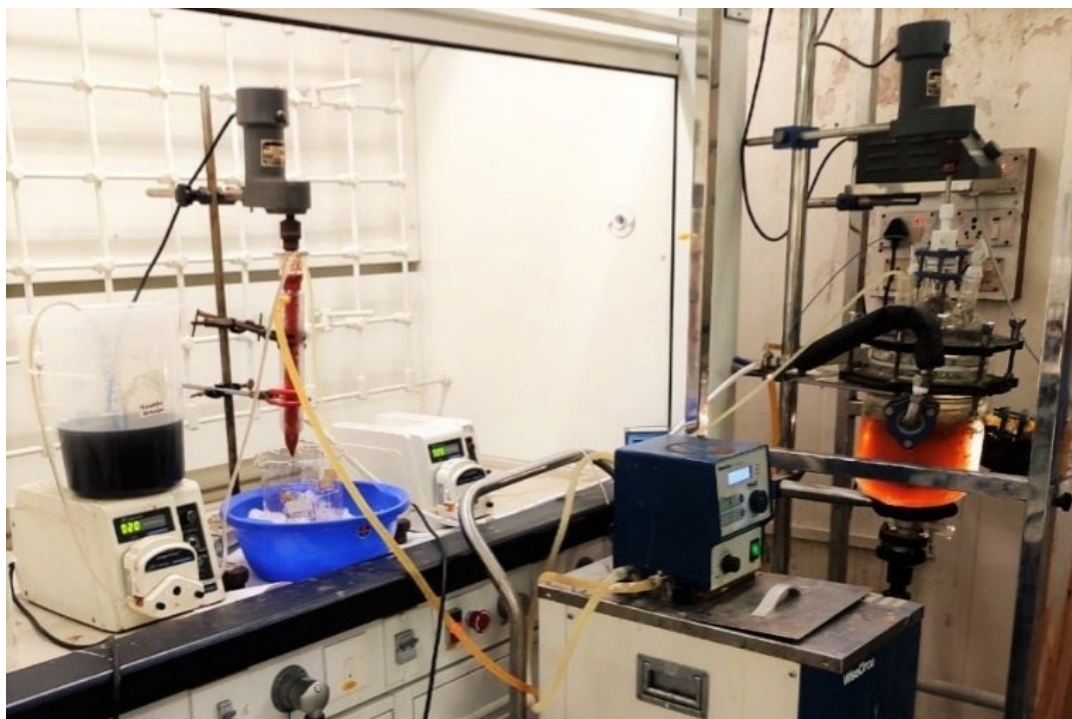
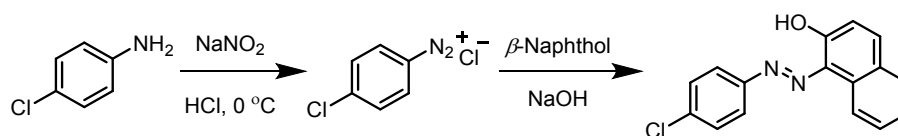


Figure S1: Setup for continuous synthesis of azo-dyes on kilogram scale using screw reactor



Figure- S2: 1 kg Sudan dye synthesized using the screw reactor

1b. Protocol for 10 g synthesis of Sudan dye of 4-chloroaniline

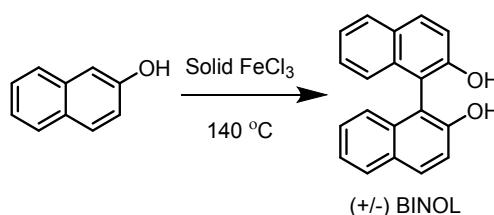


The generation of 4-chlorobenzenediazonium chloride was done as per batch protocol.

Batch Protocol: To a solution of NaNO₂ (82.3 mmol, 5.7 g) in 10 mL water was added dropwise ice-cooled solution of aniline (78.4 mmol, 7.0 mL), HCl (35% wt. /wt.) (235 mmol, 23.7 mL) and 50 mL H₂O. The clear solution was stirred for 10 min at 0 °C.

Flow Protocol: The above generated 4-chlorobenzenediazonium chloride was fed from solid dosing 1 and the mixture of β-naphthol (82.3 mmol, 11.9 g), NaOH (235.1 mmol, 9.4 g) and 60 mL water was fed from solid dosing 2 in a screw feeder reactor rotating at the 90-150 rpm, maintained at 0 °C. The total residence time for azo dye formation was only 24 sec. The red coloured slurry of the formed dye was collected and checked for the presence of unreacted diazonium salt using H-acid. Since there was no colour change which indicated the complete conversion of diazonium salt. Then products was filtrated using whatman filter under the suction pump and dry at 50 °C to afford reddish orange solid product in 94% (21g) yield and requires no further purification. The product was analysed using NMR spectroscopy. ¹H NMR (400 MHz, CDCl₃) δ = 16.02 (s, 1 H), 8.52 (d, *J* = 8.5 Hz, 1 H), 7.71 (d, *J* = 9.8 Hz, 1 H), 7.66 (d like, *J* = 8.5 Hz, 2 H), 7.60 (d, *J* = 7.3 Hz, 1 H), 7.55 (t, *J* = 7.3 Hz, 1 H), 7.46 - 7.36 (m, 3 H), 6.86 (d, *J* = 9.2 Hz, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ = 170.6, 143.8, 140.1, 133.3, 132.9, 130.2, 129.7, 128.9, 128.6, 128.1, 125.8, 124.3, 121.7, 119.9.

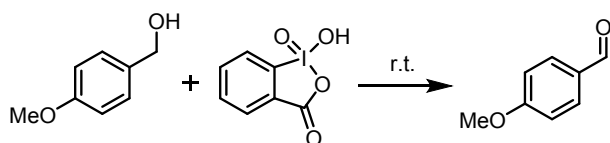
2. Synthesis of (±)-BINOL



The mixture of β-Naphthol (34.7 mmol, 5.0 g) and FeCl₃ (97.1 mmol, 18.8 g) were fed by making paste using 10 mL (1:1, H₂O: MeOH) in a screw feeder rotating at 250-300 rpm. The reaction temperature was maintained to 90-100 °C by using Julabo. The residence time of 300 sec was sufficient for the completion of the reaction as monitored using TLC and blackish yellow solid was collected from the bottom of the reactor. The reaction mass was quenched using 1M HCl (1.8 mL 35% HCL dissolved in 50 mL water) and extracted with ethyl acetate

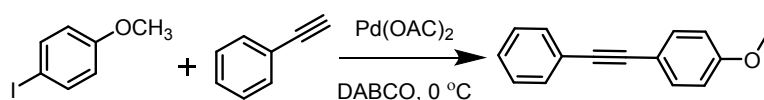
(25 x 3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum to give the crude product. The crude product on flash column chromatography purification using (petroleum ether: ethyl acetate = 9:1) as eluent afforded the pure BINOL product 52% (5.15g) as a pale yellow solid. The product was characterized using NMR spectroscopy. ^1H NMR (200 MHz, CDCl_3) δ = 8.01 - 7.83 (m, 4 H), 7.41 - 7.24 (m, 6 H), 7.19 - 7.09 (m, 2 H), 5.05 (s, 2 H); ^{13}C NMR (50 MHz, CDCl_3) δ = 152.7, 133.4, 131.4, 129.4, 128.4, 127.5, 124.2, 124.0, 117.7, 110.8.

3. Oxidation of Alcohol to Aldehyde:



2-Iodoxybenzoic acid (IBX, 72.4 mmol, 20.3 g) in 5 mL ethyl acetate was mixed so as to make the paste which was fed along with 4-methoxybenzyl alcohol (36.2 mmol, 5.0 g) in a screw feeder reactor rotating at 300-450 rpm, maintained at 65 °C. By providing the residence time of 60 sec the reaction was completed as confirmed from TLC. After completion of the reaction the product was filtered through the celite filled in G3-glass sintered funnel connected to the vacuum pump kept at the bottom of the reactor. The reaction mixture was concentration under vacuum to afford the product in 93% (4.57 g) yield as a pale-yellow liquid without any further purification. The product was analysed using NMR spectroscopy. ^1H NMR (400 MHz, CDCl_3) δ = 9.79 (s, 1H), 7.74 (d, J = 8.5 Hz, 2H), 6.91 (d, J = 8.5 Hz, 2 H), 3.78 (s, 3 H) ^{13}C NMR (100 MHz, CDCl_3) 190.83, 164.61, 131.95, 129.95, 114.31, 55.53.

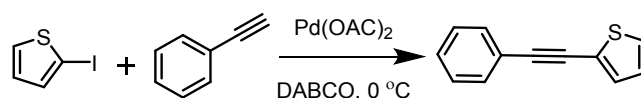
4a. Sonogashira Coupling Reaction:



The mixture of 4-iodo anisole (42.7 mmol, 10.0 g), DABCO (53.4 mmol, 6.0 g), $\text{Pd}(\text{OAc})_2$ (2.13 mmol, 0.48 g) was fed together along with phenyl acetylene (53.4 mmol, 5.9 mL) in a screw feeder reactor maintained at 0 °C, rotating at 400-500 rpm. The total residence time of 180 sec was required for the completion of the reaction as checked by TLC. Finally, the black solid mass collected at the bottom of the reactor, without any workup was directly subjected

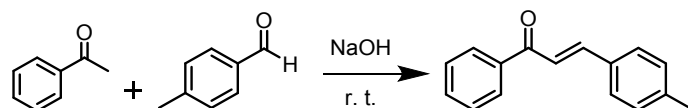
to flash column chromatography purification (petroleum ether: ethyl acetate = 97:3) to afford the pure product in (79%, 7.02g) yield as a pale yellow solid. The product was characterized using NMR spectroscopy. ^1H NMR (400 MHz, CDCl_3) δ = 7.53 - 7.45 (m, 4 H), 7.37 - 7.29 (m, 3 H), 6.88 (d, J = 8.5 Hz, 2 H), 3.83 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ = 159.6, 133.0, 131.4, 128.3, 127.9, 123.6, 115.4, 114.0, 89.3, 88.0, 55.3.

4b. Sonogashira Coupling Reaction:



The mixture of 2-iodothiophene (23.8 mmol, 5.0 g), DABCO (29.7 mmol, 3.3 g), Pd (OAc)₂ (1.19 mmol, 0.27 g) was fed together along with phenyl acetylene (29.7 mmol, 3.0 mL) in a screw feeder reactor maintained at 0 °C, rotating at 350-450 rpm. The total residence time of 65 sec was required for the completion of the reaction as checked by TLC. Finally, the black solid mass collected at the bottom of the reactor, without any workup was directly subjected to flash column chromatography purification (petroleum ether: ethyl acetate = 97:3) to afford the pure product in (85%, 3.71g) yield as a yellowish liquid. The product was analysed using NMR spectroscopy. ^1H NMR (400 MHz, CDCl_3) δ = 7.57 - 7.46 (m, 2 H), 7.37 - 7.35 (m, 3 H), 7.31-7.30(m 2H), 7.03 (dd, J = 3.7, 5.0 Hz, 1 H). ^{13}C NMR (100 MHz, CDCl_3) δ = 132.8, 132.19, 131.70, 128.67, 127.55, 127.39, 123.60, 123.20, 93.30, 82.88.

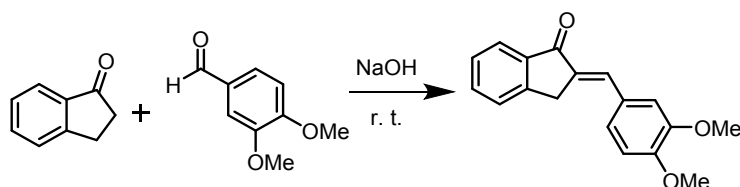
5a. Synthesis of chalcone:



Acetophenone (83.3 mmol, 9.7 mL), 4-methyl benzaldehyde (83.3 mmol, 9.8 mL) and sodium hydroxide (83.3 mmol, 3.3 g) were fed in the form of solid (no solvent) into the screw feeder reactor rotating at 180-200 rpm at room temperature. After the residence time of 89 sec the greenish solid obtained was analysed by TLC which marked the completion of the reaction. The crude product thus obtained was given water wash to remove inorganic impurities and without any further purification the chalcone was obtained in 92% (17 g) yield

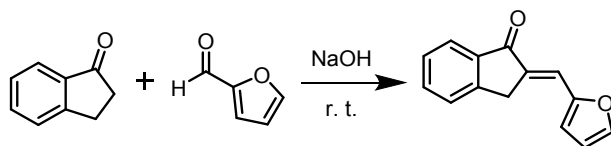
as a green solid. The product was analysed using NMR spectroscopy. ^1H NMR (200 MHz, CDCl_3) $\delta = 8.01$ (d, $J = 6.9$ Hz, 2 H), 7.80 (d, $J = 15.8$ Hz, 1 H), $7.70 - 7.34$ (m, 6 H), 7.25 (s, 2 H), 2.39 (s, 3 H); ^{13}C NMR (50 MHz, CDCl_3) $\delta = 190.6, 144.9, 141.0, 138.3, 132.6, 132.1, 129.7, 128.5, 128.4, 121.1, 21.5$.

5b. Synthesis of chalcone



1-Indanone (60.2 mmol, 7.95 g), veratraldehyde (60.2 mmol, 10.0 g) and sodium hydroxide (60.2 mmol, 2.4 g) were fed in the form of solid (no solvent) into the screw feeder reactor rotating at 300-400 rpm at room temperature. After the residence time of 68 sec pale greenish solid obtained was analysed by TLC which marked the completion of the reaction. The crude product thus obtained was given water wash to remove inorganic impurities and without any further purification the chalcone was obtained in 88% (14.8 g) yield as a pale green solid. The product was analysed using NMR spectroscopy. ^1H NMR (400 MHz, CDCl_3) $\delta = 7.91$ (d, $J = 7.8$ Hz, 1 H), $7.65 - 7.63$ (m, 1 H), $7.62 - 7.59$ (m, 1 H), $7.58 - 7.55$ (m, 1 H), $7.46 - 7.40$ (m, 1 H), 7.32 (dd, $J = 1.8, 8.5$ Hz, 1 H), 7.19 (d like, $J = 1.8$ Hz, 1 H), 6.96 (d, $J = 8.7$ Hz, 1 H), $4.04 - 4.02$ (m, 2 H), 3.97 (s, 3 H), 3.95 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3) $\delta = 194.3, 150.6, 149.4, 149.0, 138.2, 134.4, 134.1, 132.6, 128.4, 127.6, 126.1, 124.6, 124.3, 113.4, 111.2, 56.0, 32.3$.

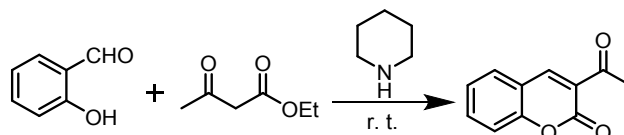
5c. Synthesis of chalcone



1-Indanone (104.1 mmol, 13.8 g), furfural (104.1 mmol, 8.6 mL) and sodium hydroxide (104.1 mmol, 4.2 g) were fed in the form of solid (no solvent) into the screw feeder reactor rotating at 250-350 rpm at room temperature. After the residence time of 62 sec grey solid obtained was analysed by TLC which marked the completion of the reaction. The crude product thus obtained was given water wash to remove inorganic impurities and without any further purification the chalcone was obtained in 90% (19.6 g) yield as a pale grey solid. The

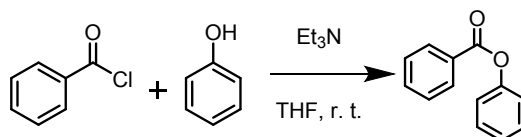
product was analysed using NMR spectroscopy. ^1H NMR (400 MHz, CDCl_3) $\delta = 7.89$ (d, $J = 7.3$ Hz, 1 H), 7.65 - 7.63 (m, 1 H), 7.63 - 7.59 (m, 1 H), 7.58 - 7.54 (m, 1 H), 7.47 (t, $J = 2.3$ Hz, 1 H), 7.42 (t, $J = 7.8$ Hz, 1 H), 6.78 (d, $J = 3.2$ Hz, 1 H), 6.56 (dd, $J = 1.8, 3.7$ Hz, 1 H), 4.08 - 4.04 (m, 2 H); ^{13}C NMR (100 MHz, CDCl_3 -d) $\delta = 193.7, 151.9, 149.5, 145.0, 138.1, 134.1, 132.2, 127.1, 125.8, 123.9, 119.7, 116.3, 112.3, 32.0$

6. Synthesis of Coumarins



Salicylaldehyde (81.9 mmol, 8.7 mL), ethyl acetoacetate (98.3 mmol, 12.5 mL) and piperidine (16.4 mmol, 1.6 mL) were fed in the form of liquid (no solvent) into the screw feeder reactor rotating at 95-150 rpm at 0 °C. After the residence time of 30 sec the yellow orange solid was obtained and the completion of the reaction was monitored by TLC. In order to remove the impurities of ethyl acetoacetate and piperidine the crude product was further purified by recrystallization from 95% ethanol and the coumarin was obtained in 97% (14.9g) yield as an orange solid. The product was analysed using NMR spectroscopy. ^1H NMR (400 MHz, CDCl_3) $\delta = 8.49$ (s, 1 H), 7.68 - 7.62 (m, 2 H), 7.37 - 7.31 (m, 2 H), 2.71 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3) $\delta = 195.4, 159.2, 155.2, 147.4, 134.4, 130.2, 124.9, 124.4, 118.2, 116.6, 30.5$.

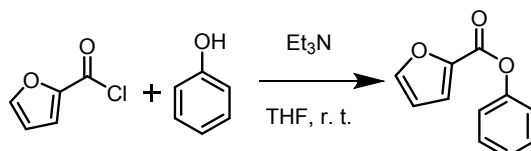
7a. Synthesis of benzoyl ester



Benzoyl chloride (71.1 mmol, 8.3 mL) dissolved in 5 mL THF was fed with mixture of phenol (71.1 mmol, 6.3 mL) and triethyl amine (106.7 mmol, 14.9 mL) in a screw feeder reactor rotating at 150-210 rpm maintained at 0 °C. After the residence time of 25 sec, white slurry was formed indicating the completion of the reaction since all the reactants were in liquid form as also checked by TLC. The reaction was quenched by addition of water so as to dissolve the salt formed during the reaction and extracted with ethyl acetate (30 x 3). The

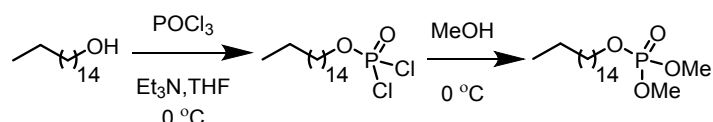
removal of solvent under vacuum afforded the pure product in (90%, 12.7g) yield as a colourless solid without any purification. The product was analysed using NMR spectroscopy. ^1H NMR (200 MHz, CDCl_3) δ = 8.25 - 8.14 (m, 2 H), 7.66 - 7.33 (m, 5 H), 7.30 - 7.14 (m, 3 H); ^{13}C NMR (50 MHz, CDCl_3) δ = 165.1, 150.9, 133.5, 130.1, 129.4, 128.5, 125.8, 121.6.

7b. Synthesis of 2-Furoyl ester



2-Furoyl chloride (76.6 mmol, 7.6 mL) dissolved in 10 mL THF was fed with mixture of phenol (76.6 mmol, 6.7 mL) and triethyl amine (114.9 mmol, 16 mL) in a screw feeder reactor rotating at 150-210 rpm maintained at 0 °C. After the residence time of 15 sec, white slurry was formed indicating the completion of the reaction since all the reactants were in liquid form as also checked by TLC. The reaction was quenched by addition of water so as to dissolve the salt formed during the reaction and extracted with ethyl acetate (30 x 3). The removal of solvent under vacuum afforded the pure product in (95%, 13.7g) yield as a grey liquid without any purification. The product was analysed using NMR spectroscopy. ^1H NMR (400 MHz, CDCl_3) δ = 7.64 (s, 1 H), 7.45 - 7.35 (m, 3 H), 7.28 - 7.16 (m, 3 H), 6.60 - 6.51 (m, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ = 156.8, 150.1, 147.0, 143.8, 129.4, 125.9, 121.5, 119.3, 112.1.

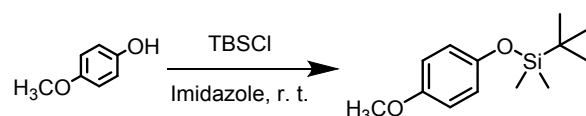
8. Synthesis of Phosphate:



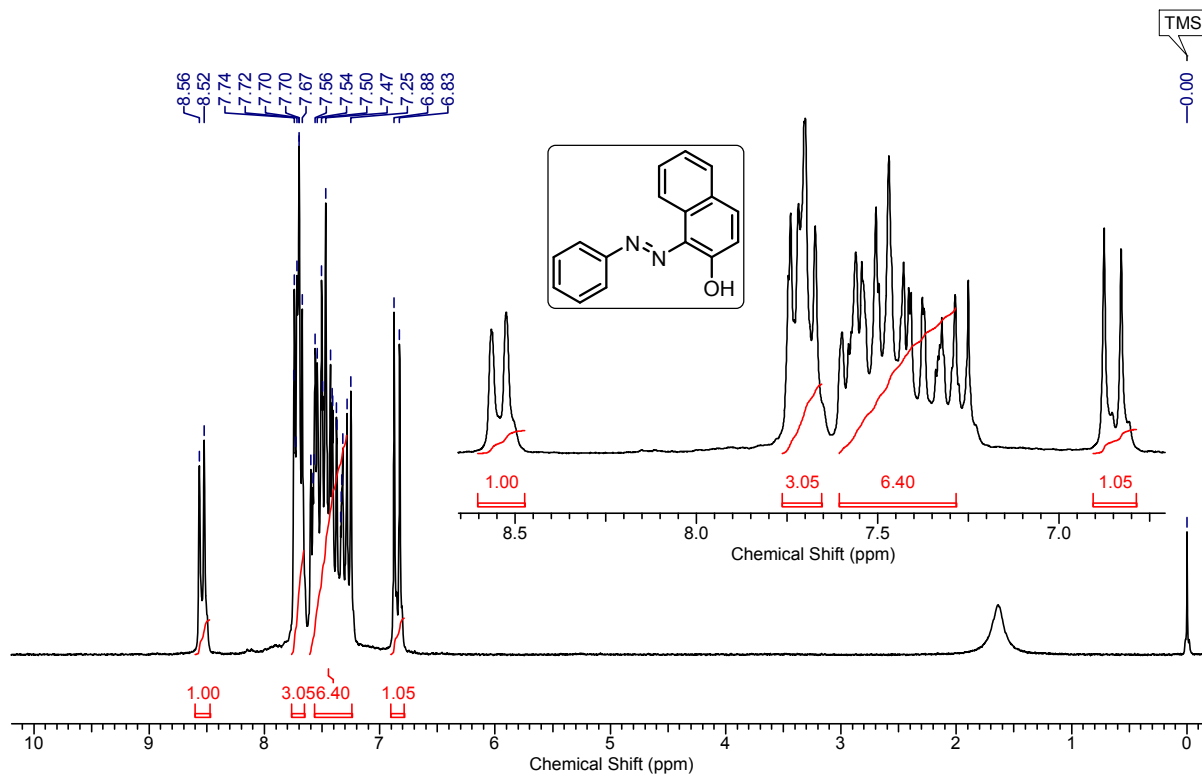
The mixture of hexadecanol (41.2 mmol, 10.0 g) and triethyl amine (49.5mmol, 6.9 mL) dissolved in 3 mL THF were fed along with POCl_3 (45.4 mmol, 4.2 mL) dissolved in 2 mL THF in a screw feeder reactor rotating at 160-180 rpm, maintained at 0 °C. As the reaction progressed, it resulted in the formation of thick white $\text{HCl}\cdot\text{Et}_3\text{N}$ slurry along with dichloro-intermediate in a residence time of 18 sec indicating the completion of the reaction as also monitored by TLC. The reaction mixture on quenching with 20 mL of methanol gave the dimethoxy Phosphate which on concentration under vacuum gave the crude residue. The

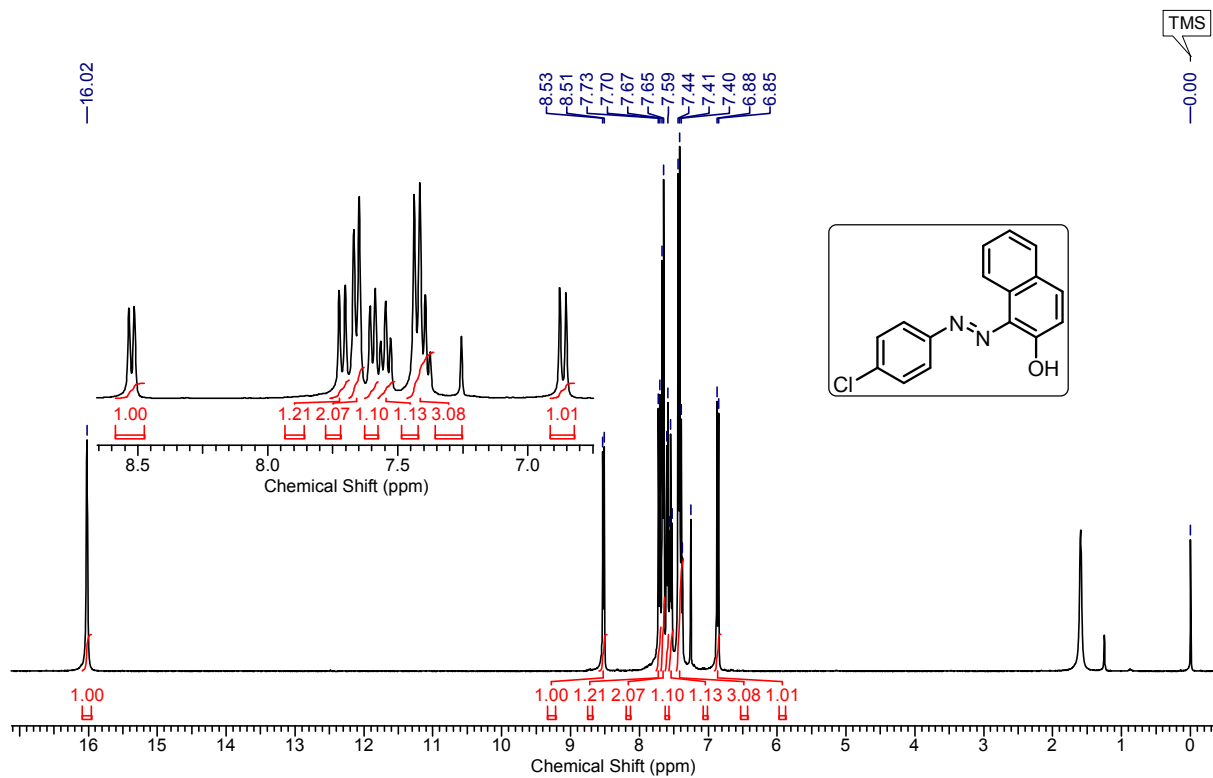
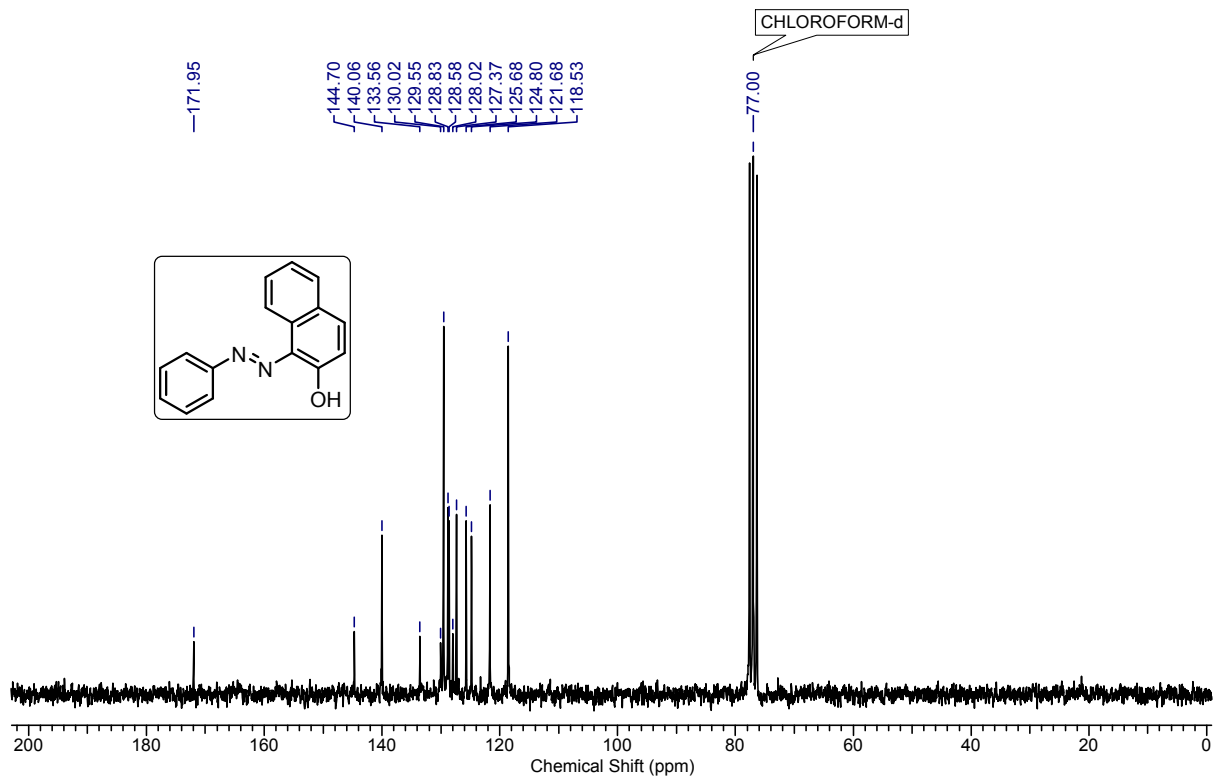
crude residue was purified by flash column chromatography (petroleum ether: ethyl acetate =9:1) to afford pure product in (85%, 12.3g) yield as a colourless liquid. The product was analysed by NMR spectroscopy. ^1H NMR (200 MHz, CDCl_3) δ = 4.04 (q, J = 6.7 Hz, 2 H), 3.79 (s, 3 H), 3.73 (s, 3 H), 1.76 - 1.60 (m, 2 H), 1.25 (s, 26 H), 0.87 (t, J = 6.7 Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ = 68.0, 67.9, 54.2, 54.1, 31.9, 30.3, 30.2, 29.7, 29.6, 29.6, 29.5, 29.4, 29.3, 29.1, 25.4, 22.7, 14.1; ^{31}P NMR (162 MHz, CDCl_3) δ = 1.31.

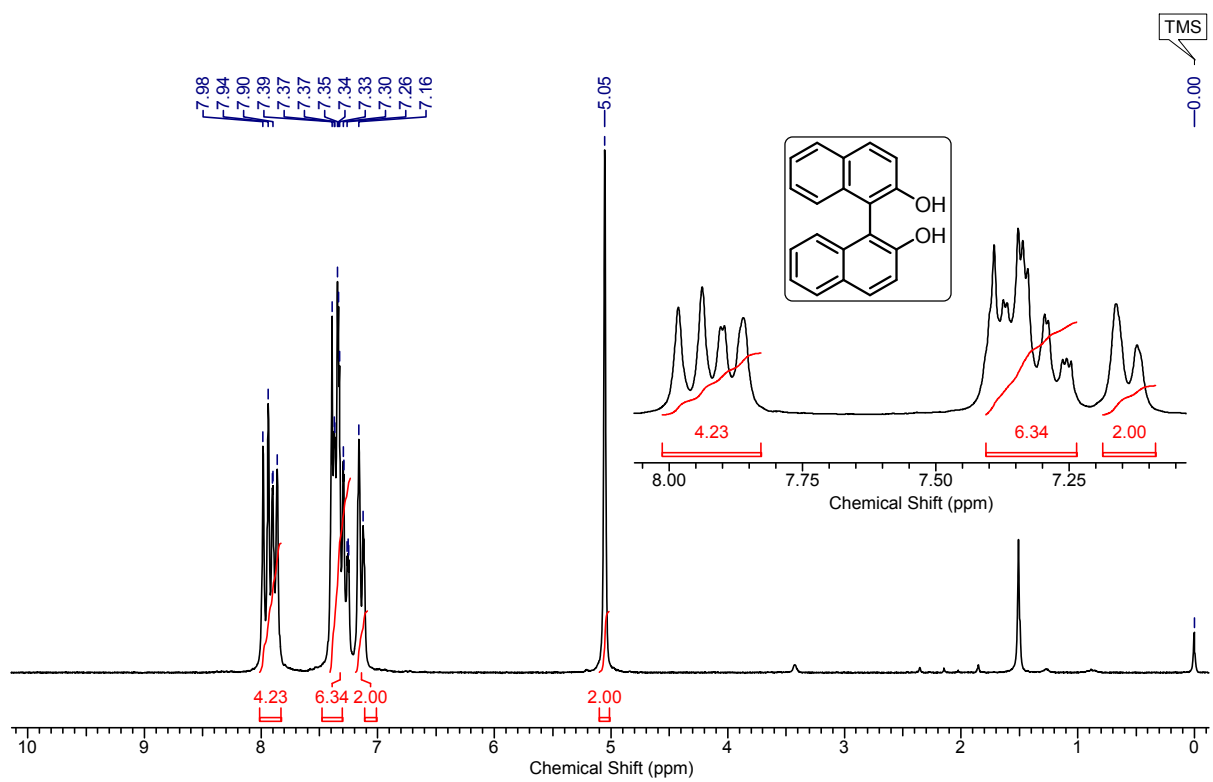
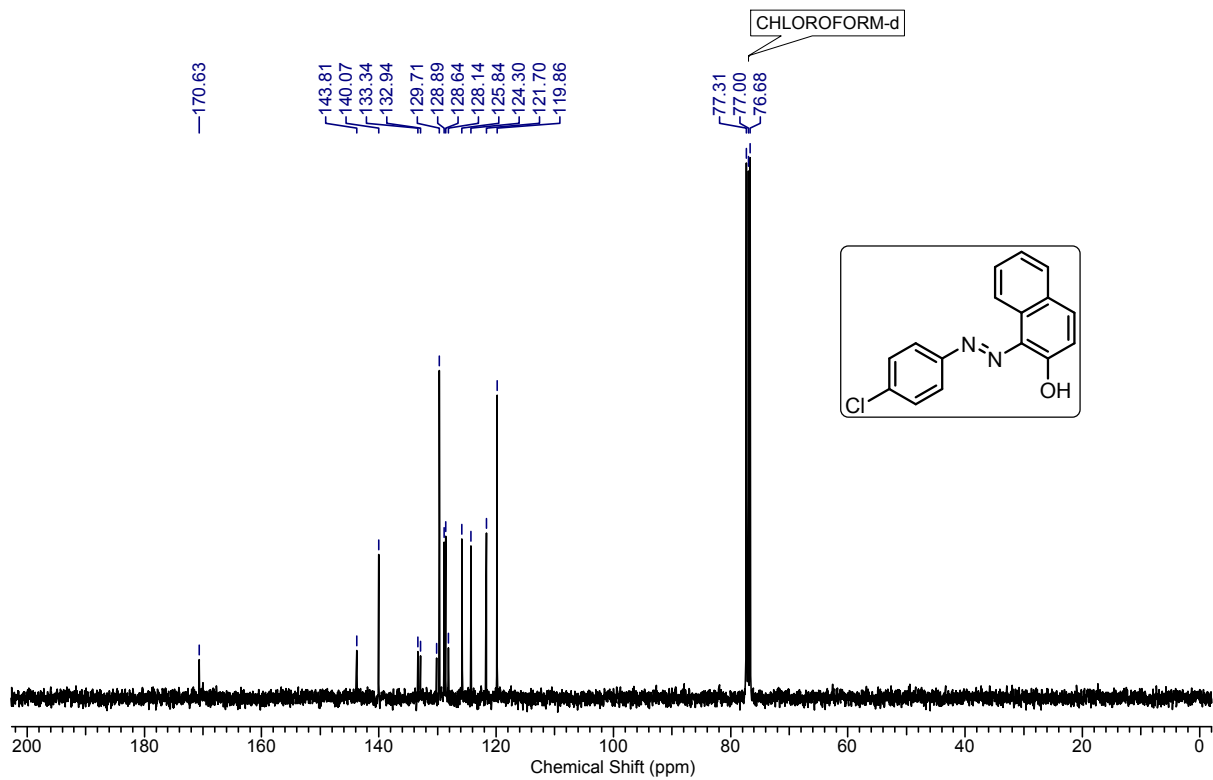
9. Synthesis of silyl-protected phenol

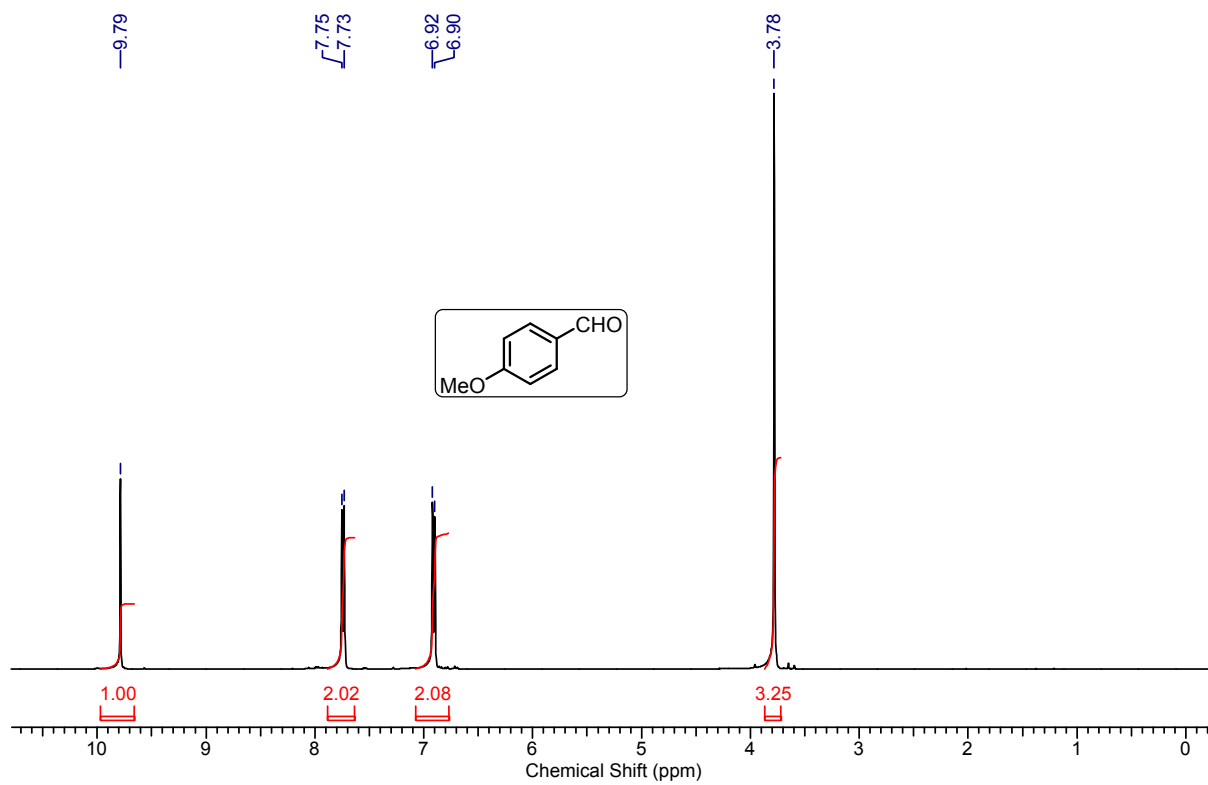
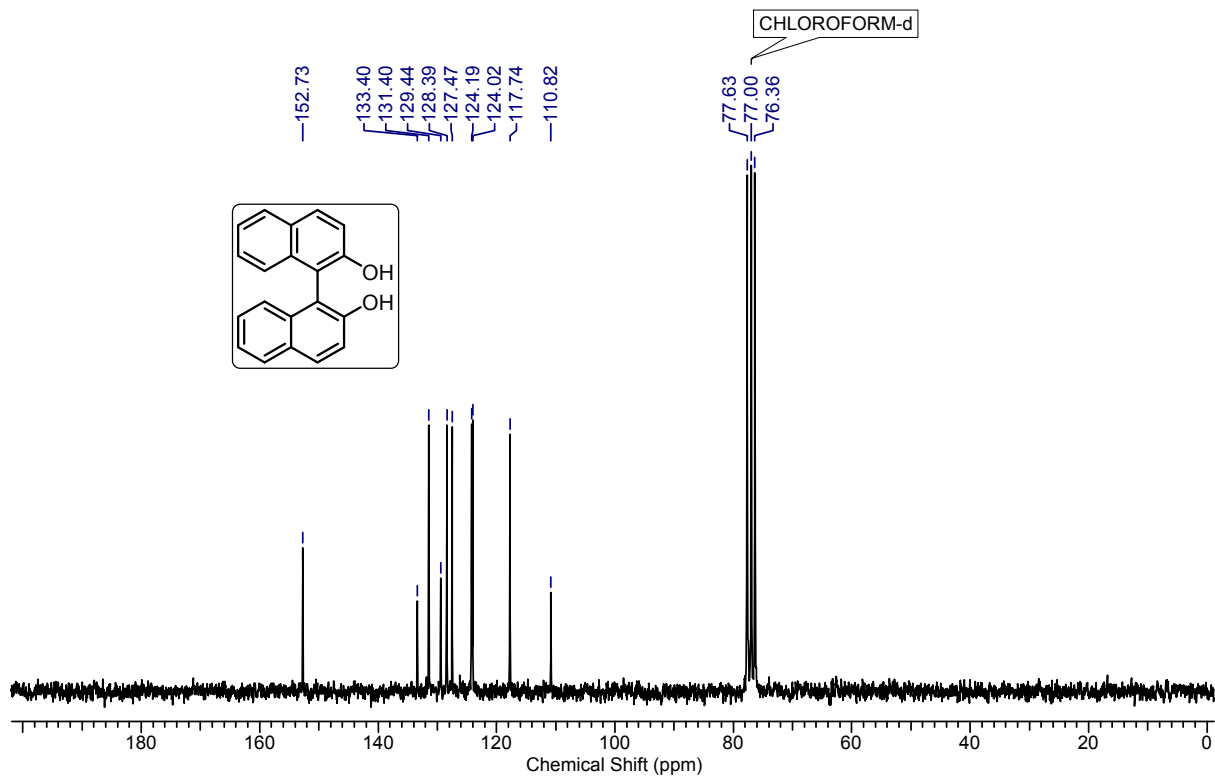


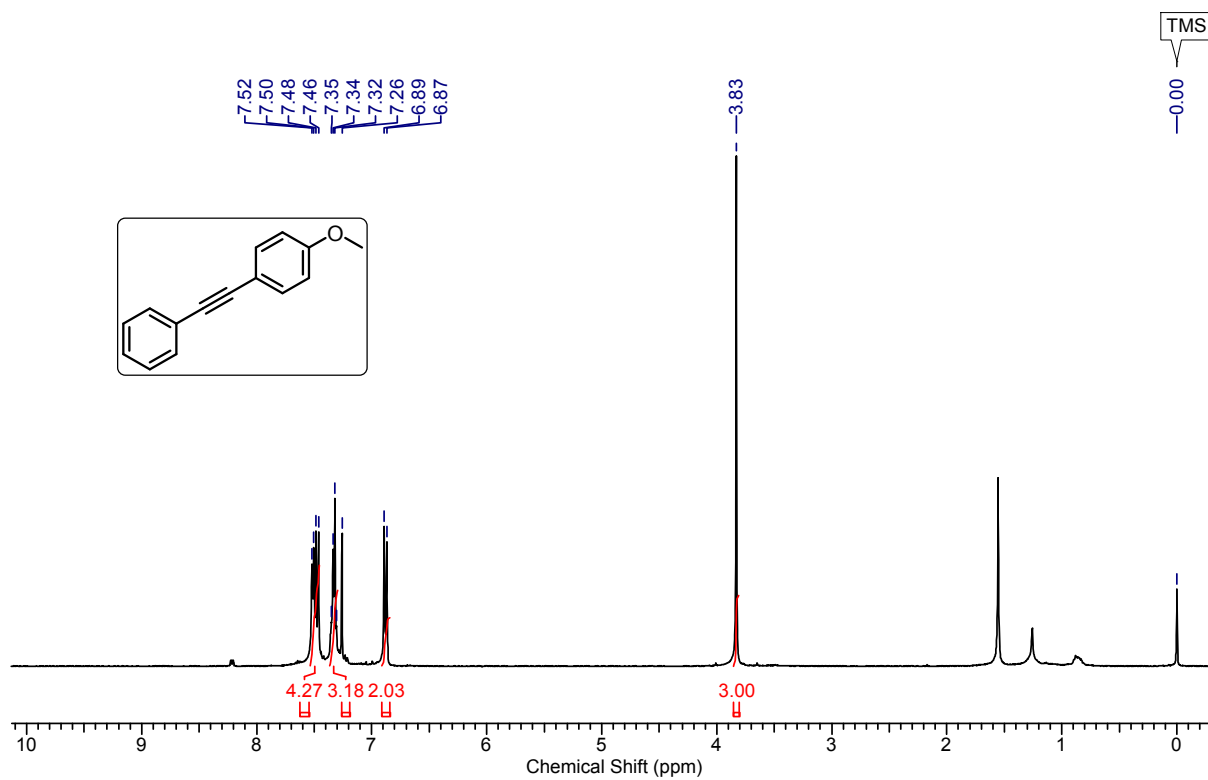
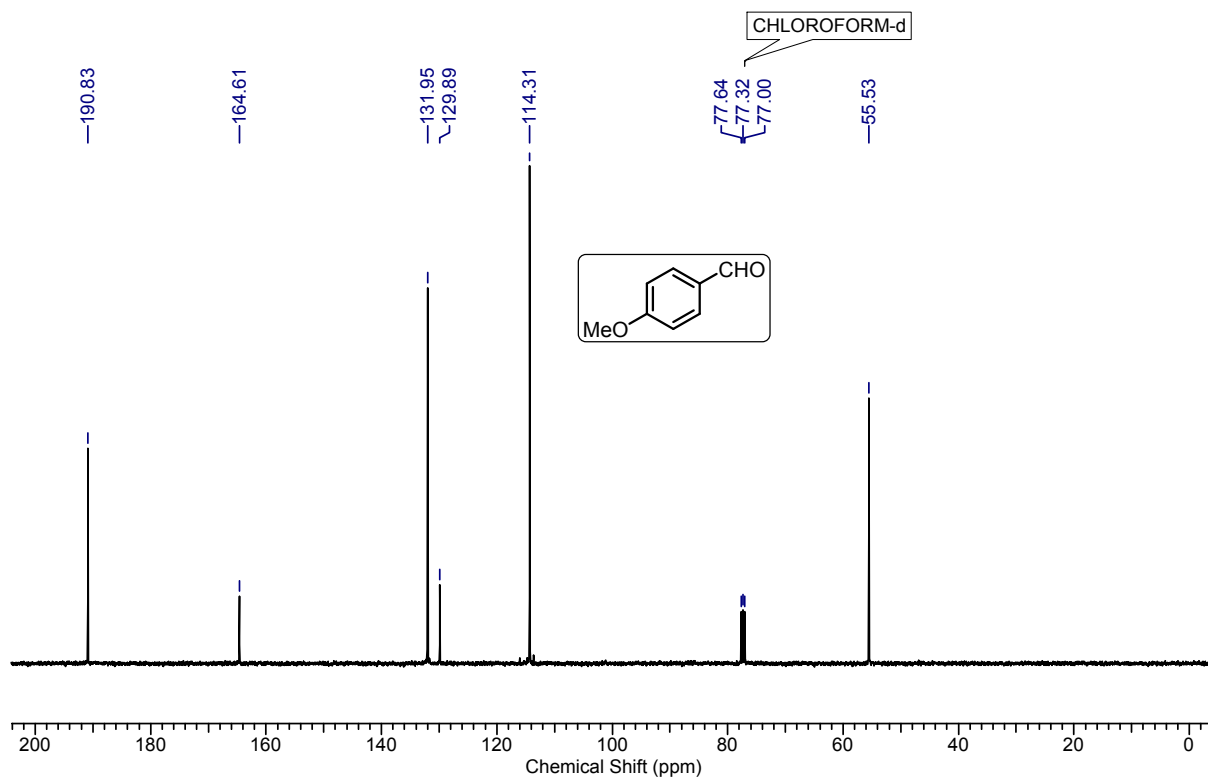
4-methoxy phenol (80.6 mmol, 10.0 g), TBSCl (96.7 mmol, 14.5 g) and imidazole (161.1mmol, 11.0 gm) were fed directly as a solid (no solvent) in a screw feeder reactor rotating at 130-150 rpm maintained at room temp. The total residence time required was only 15 sec and it resulted in formation of creamy white paste. After completion of reaction as monitored by TLC the reaction was quenched with water and the aqueous layer was extracted with EtOAc (50 x 3), and the organic layer was dried with Na_2SO_4 and concentration under vacuum to afford silyl-protected phenol as a colourless liquid in (94%, 17.12g) yield without any purification. The product was analysed by NMR spectroscopy. ^1H NMR (400 MHz, CDCl_3) δ = 6.80 (s, 4 H), 3.78 (s, 3 H), 1.03 (s, 9 H), 0.21 (s, 6 H); ^{13}C NMR (100 MHz, CDCl_3) δ = 154.1, 149.3, 120.6, 114.4, 55.5, 25.7, 18.1, -4.6.

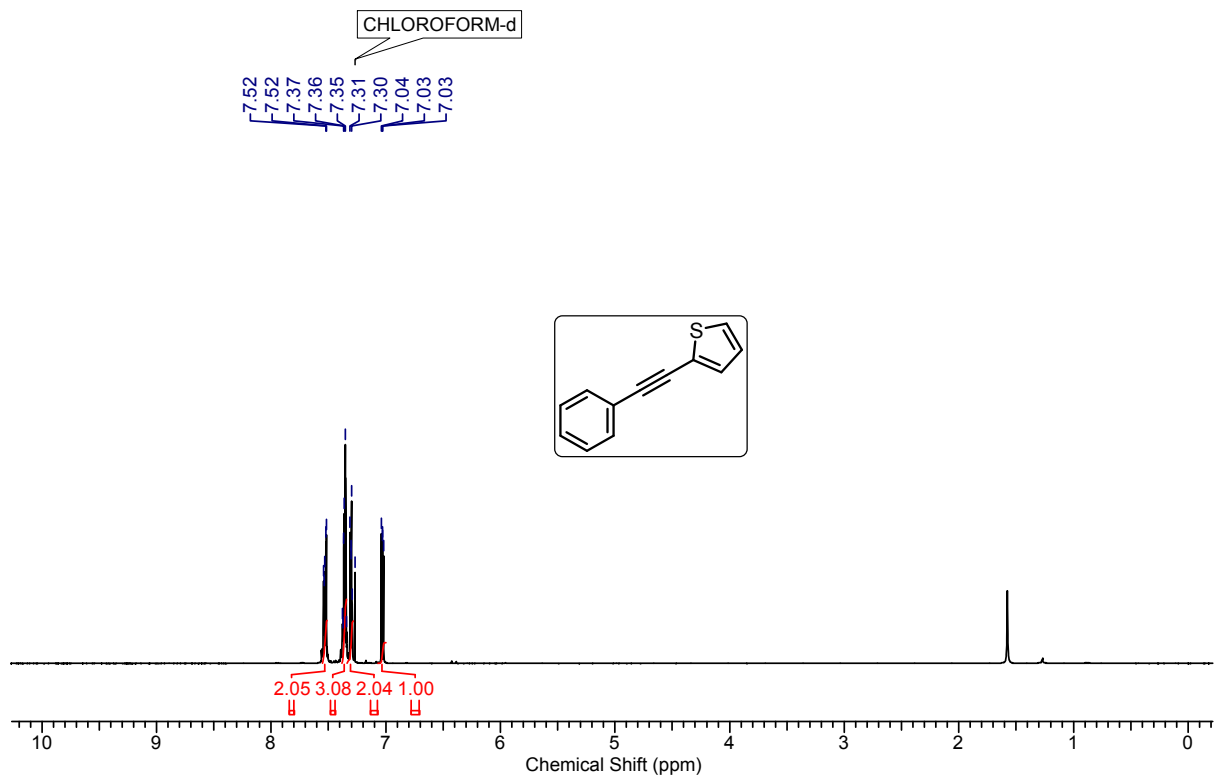
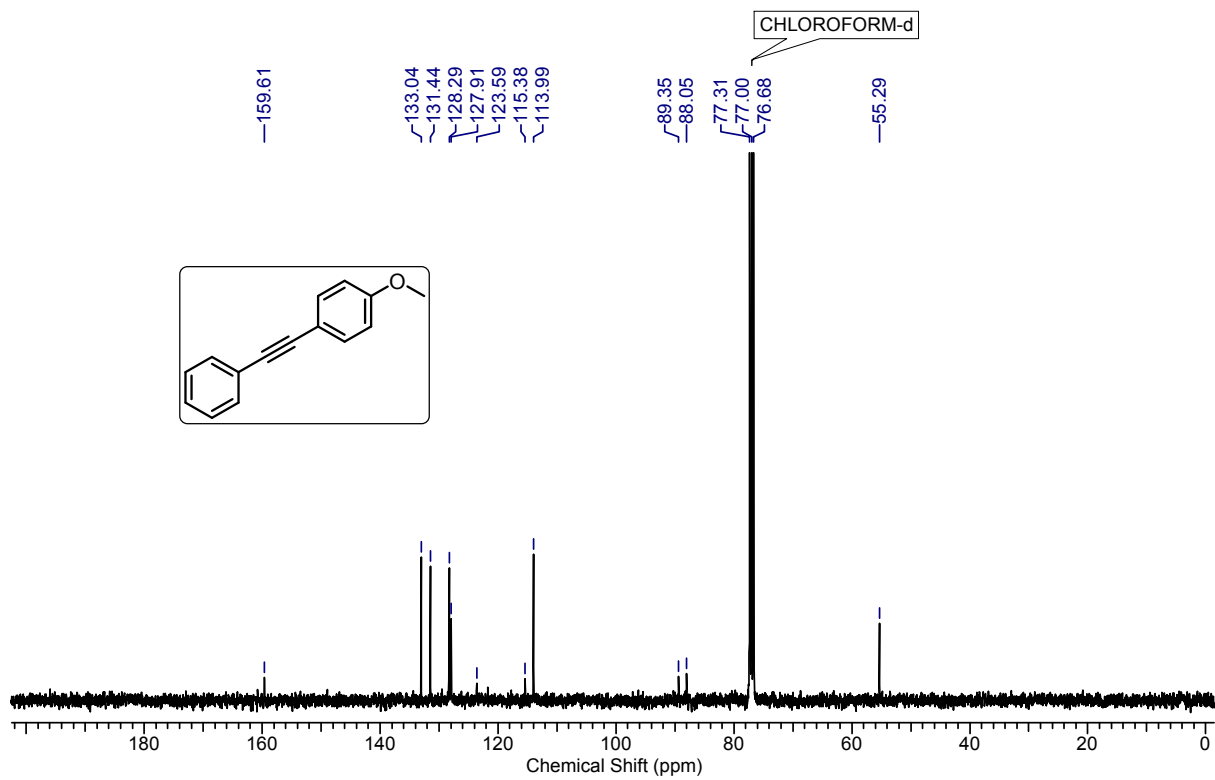


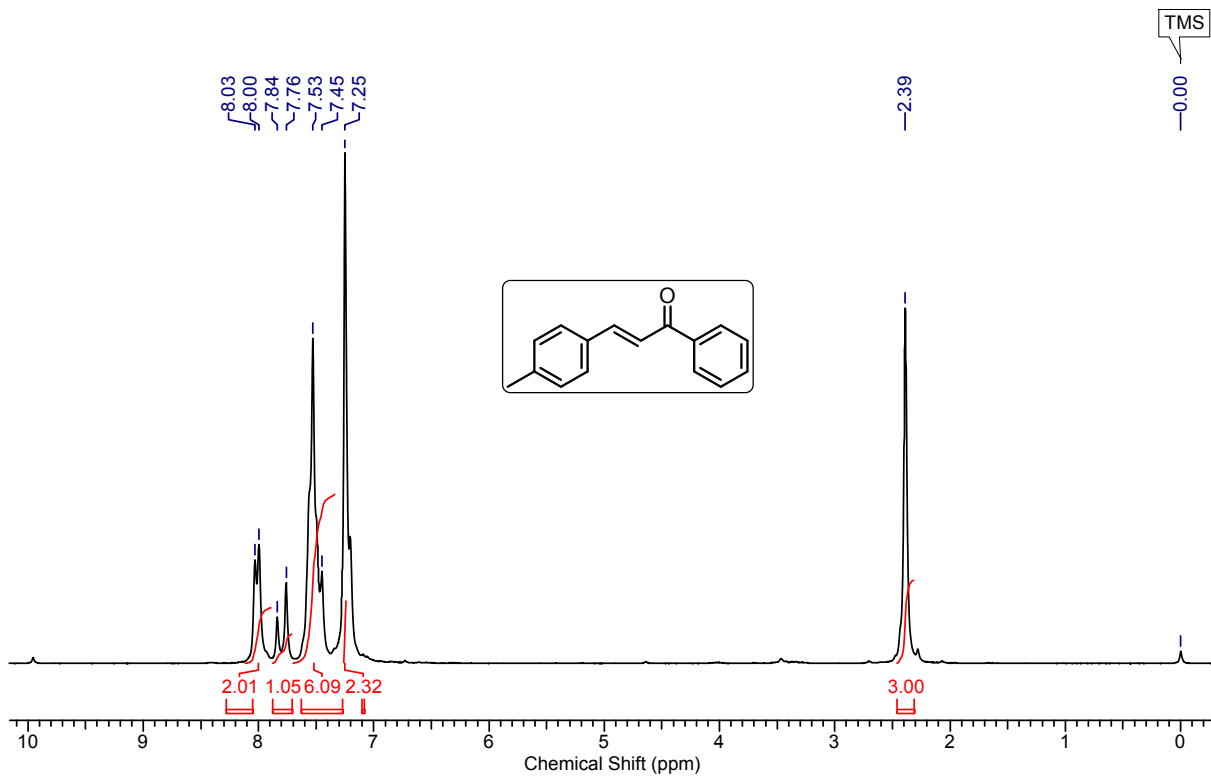
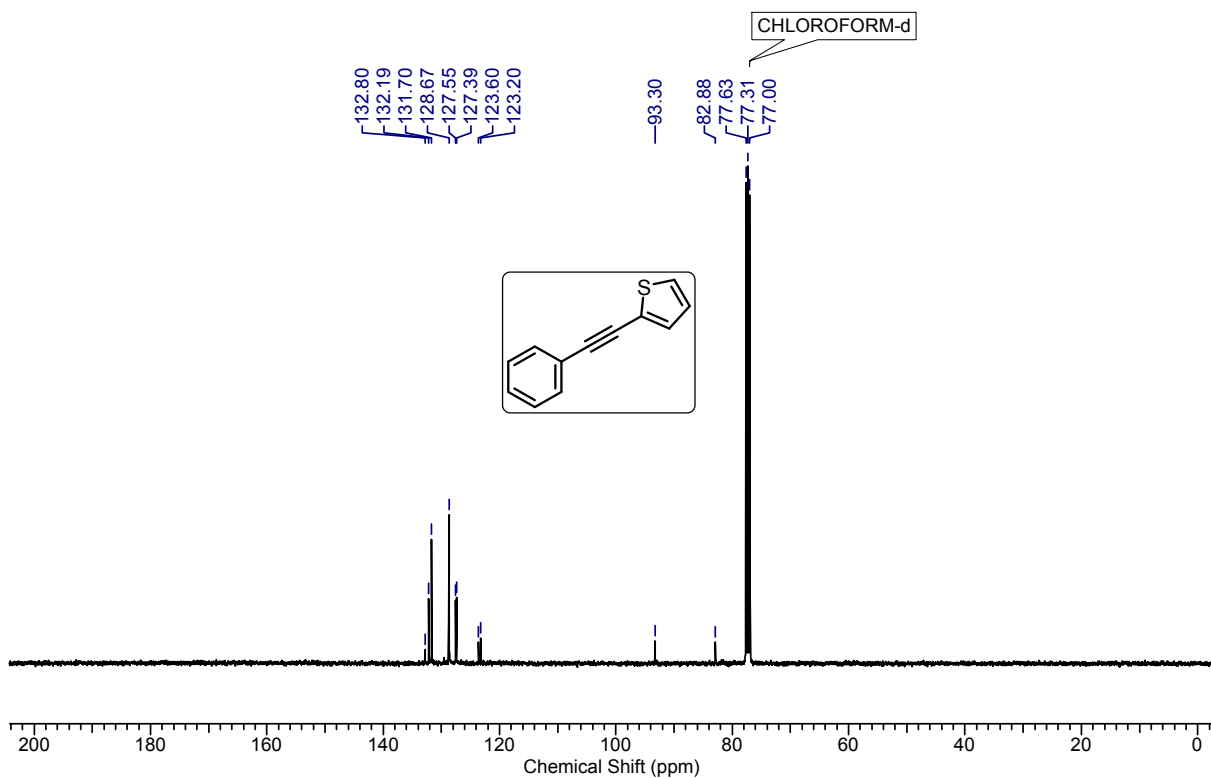


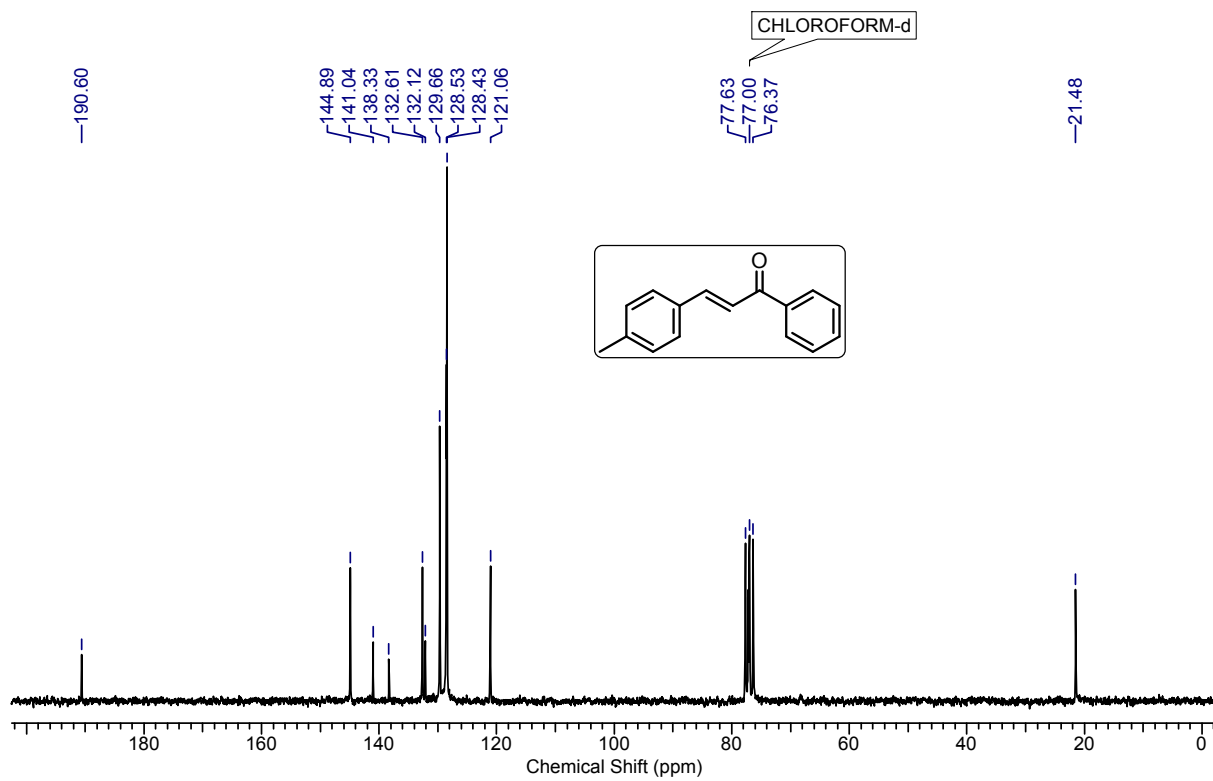


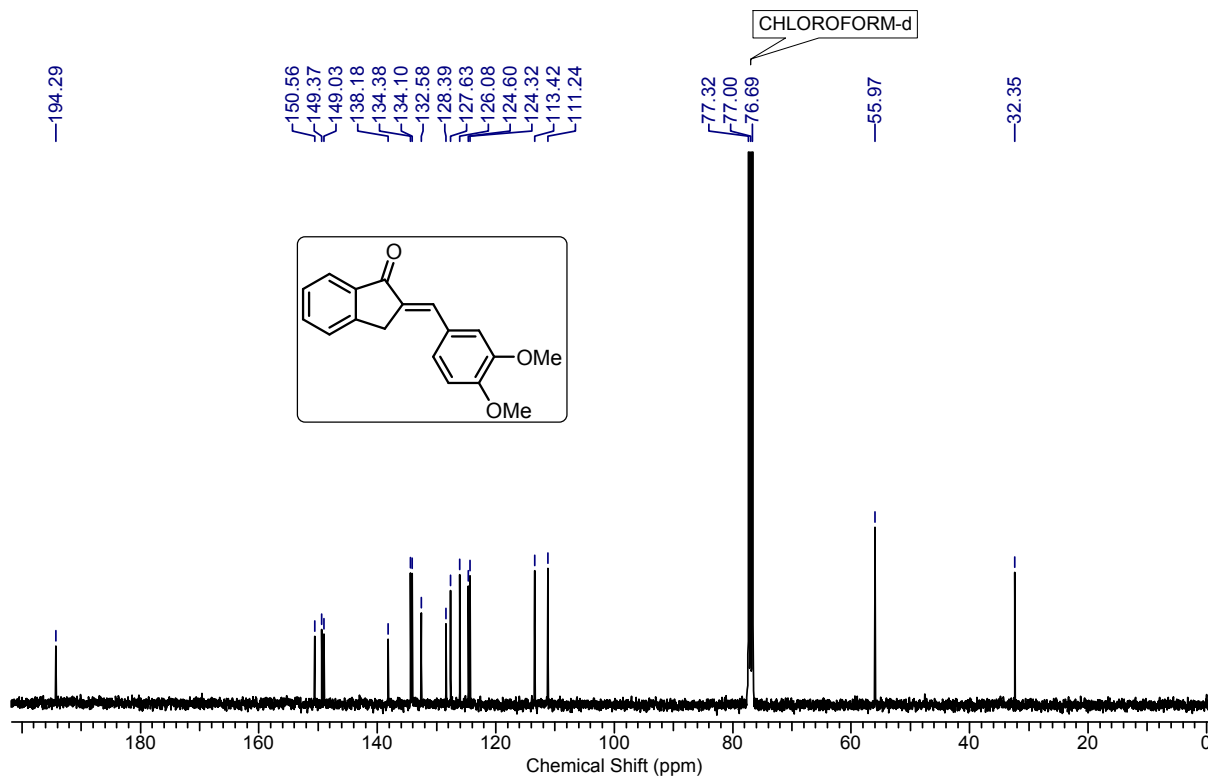
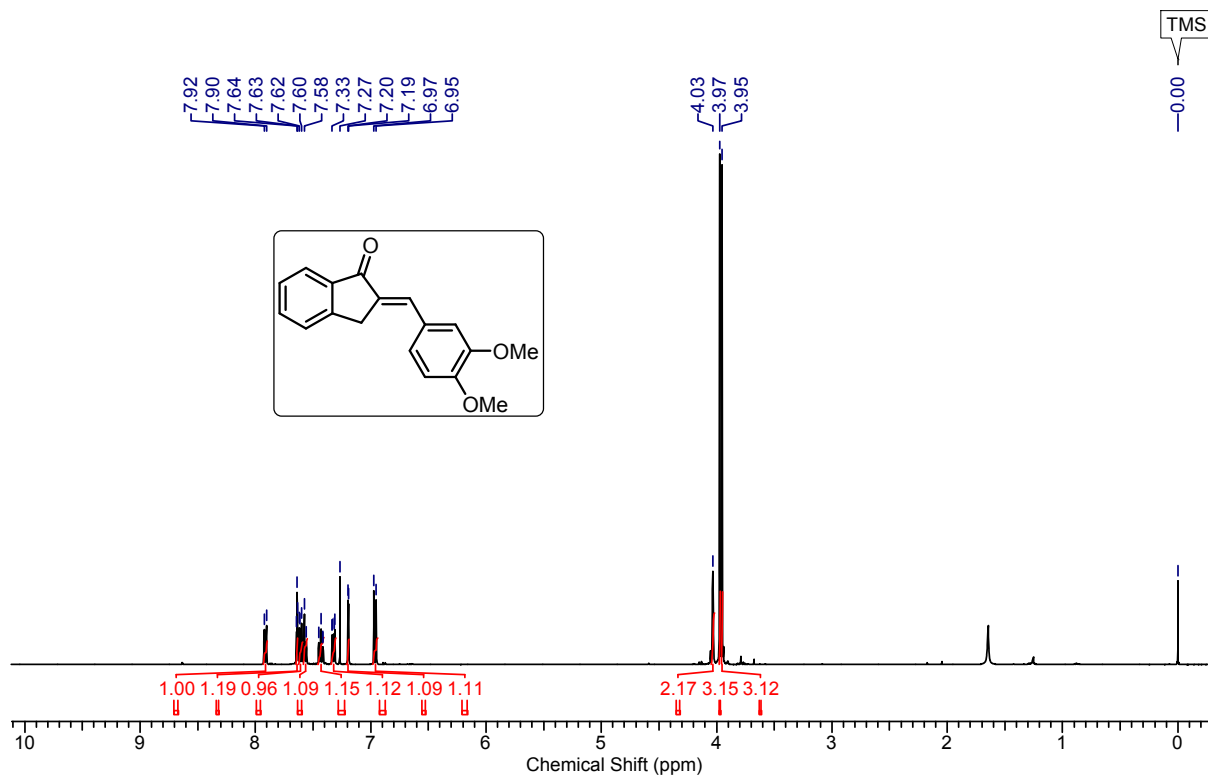


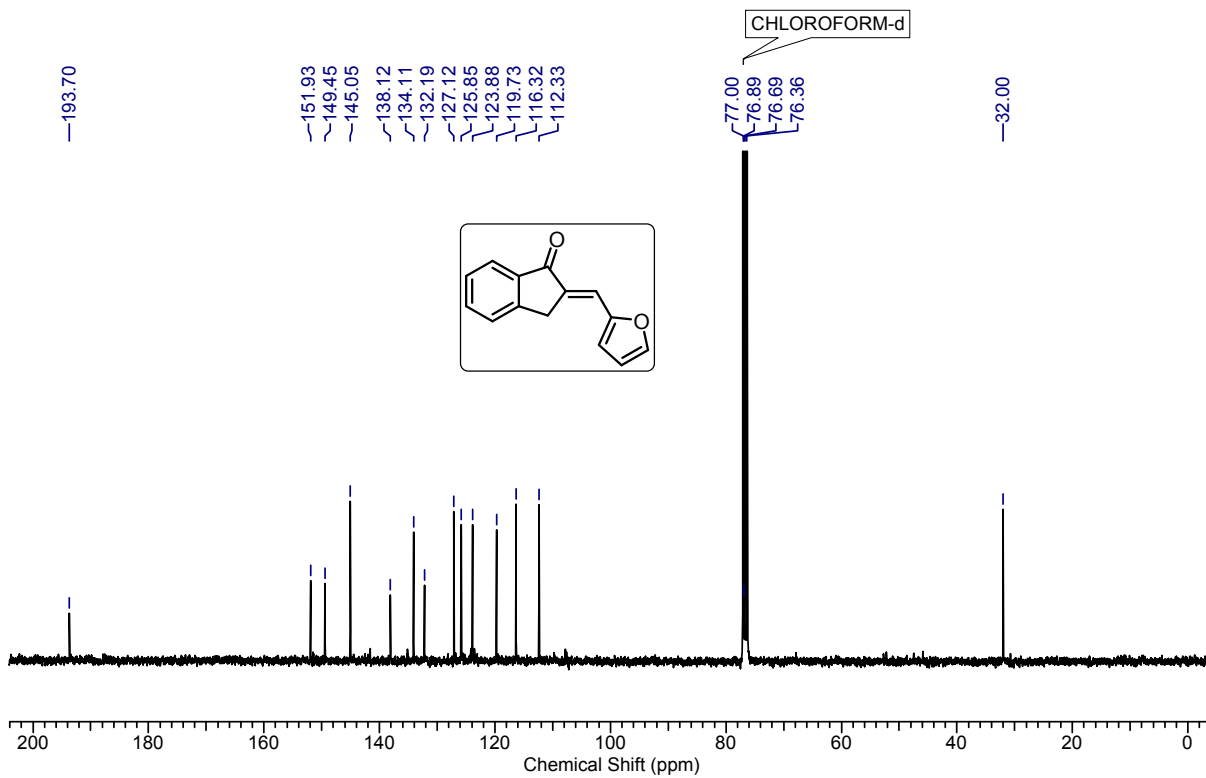
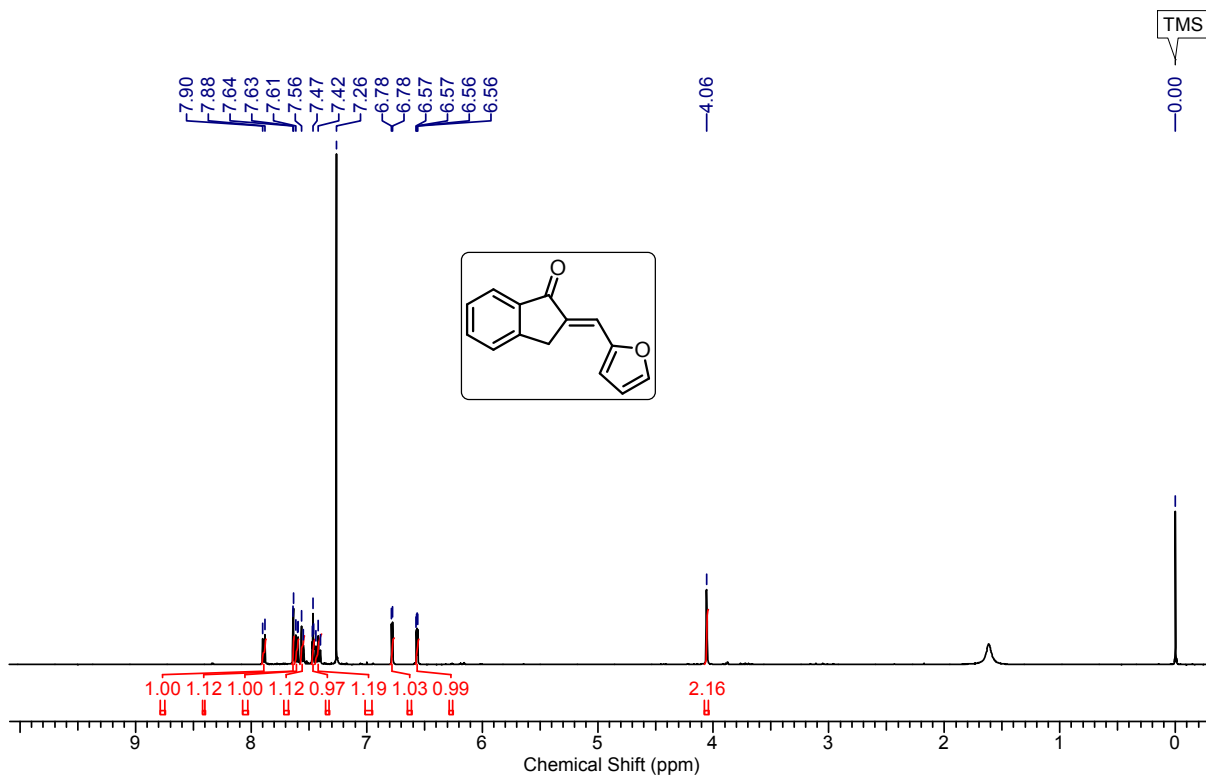


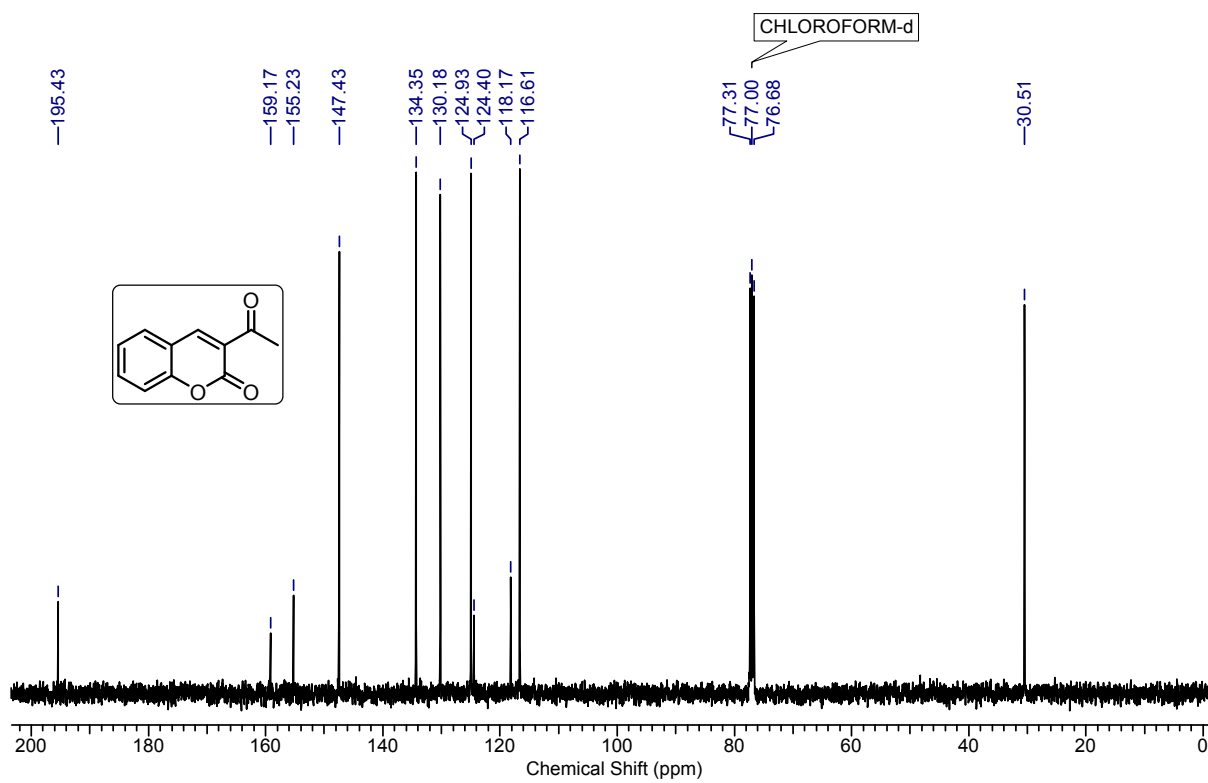
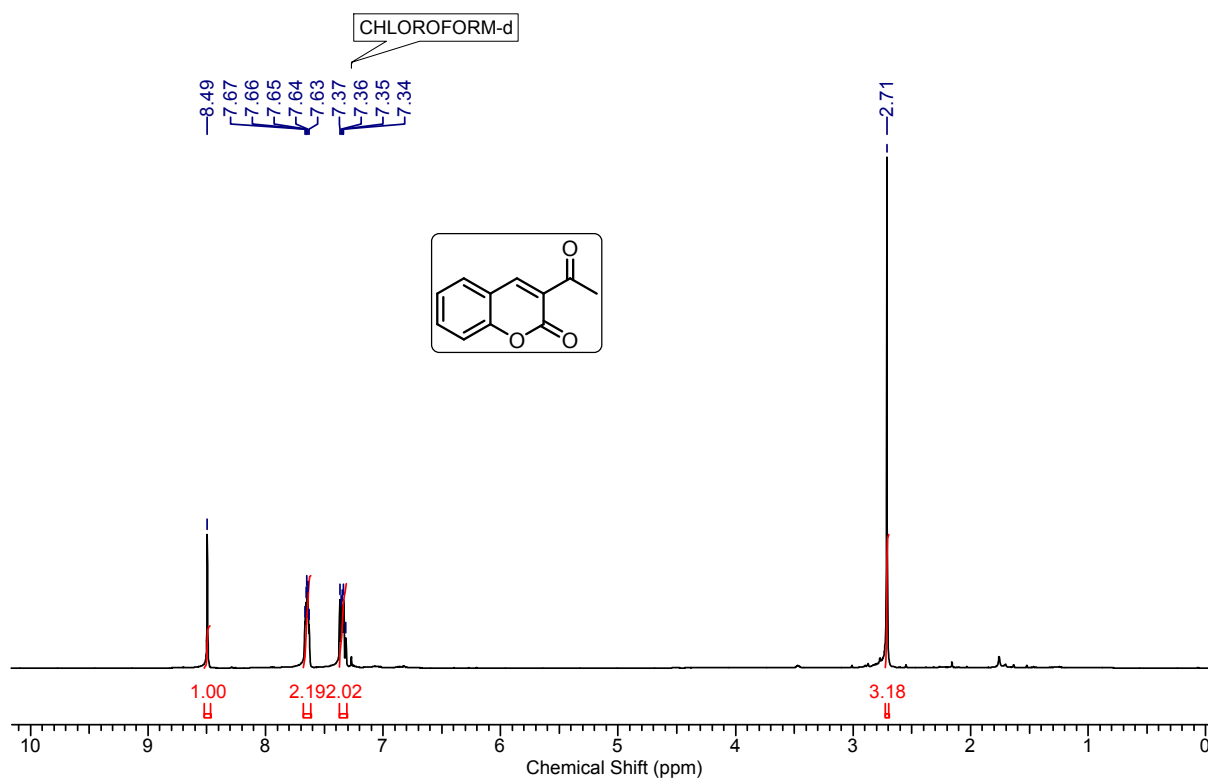


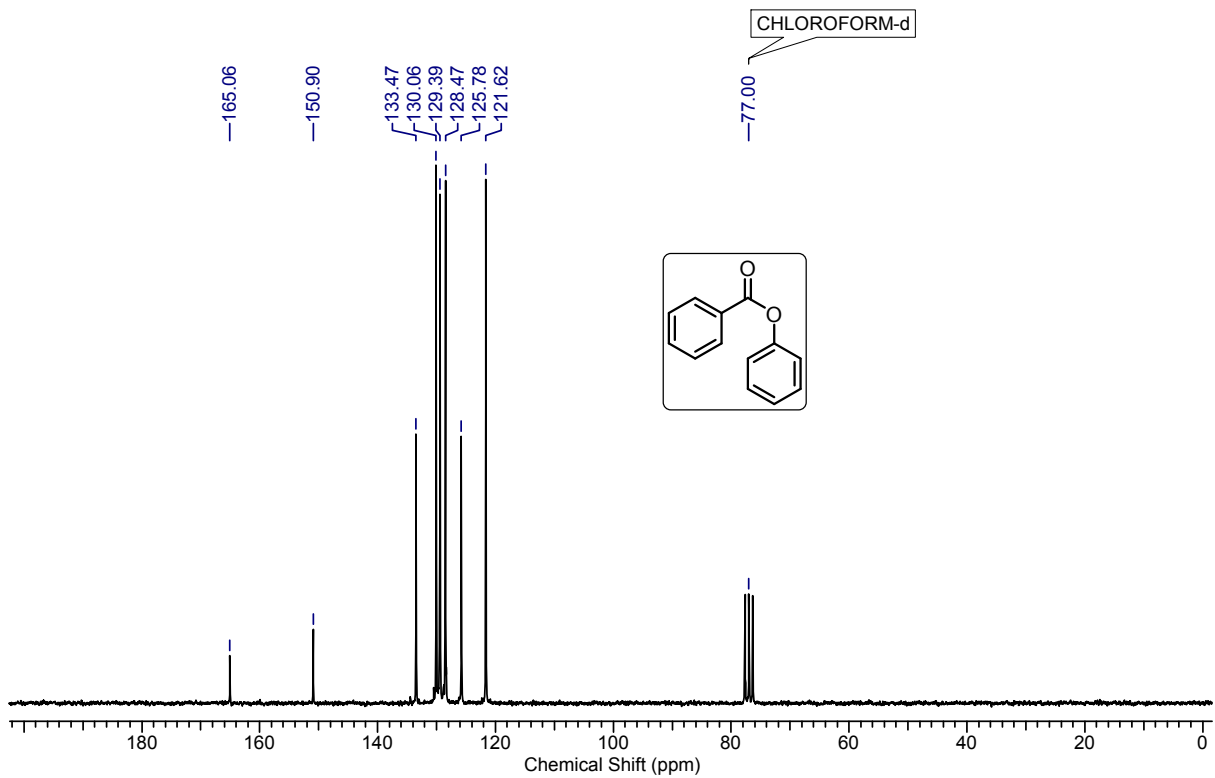
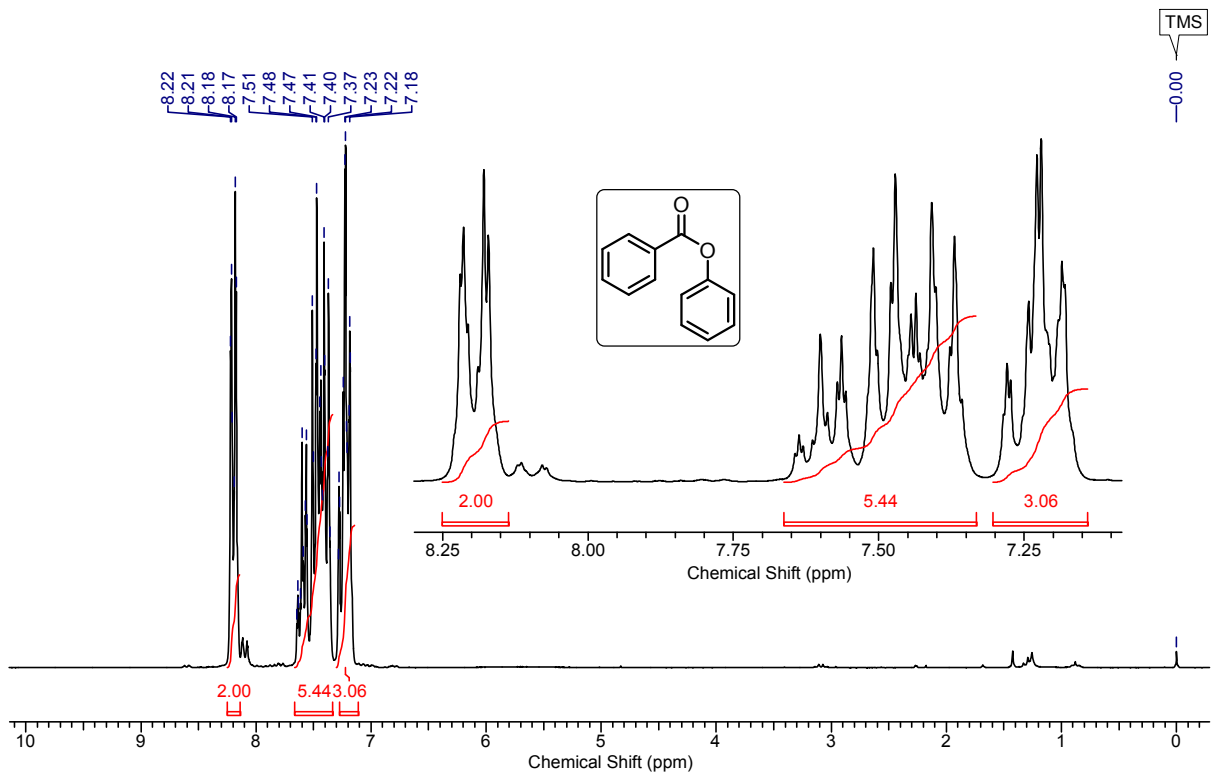


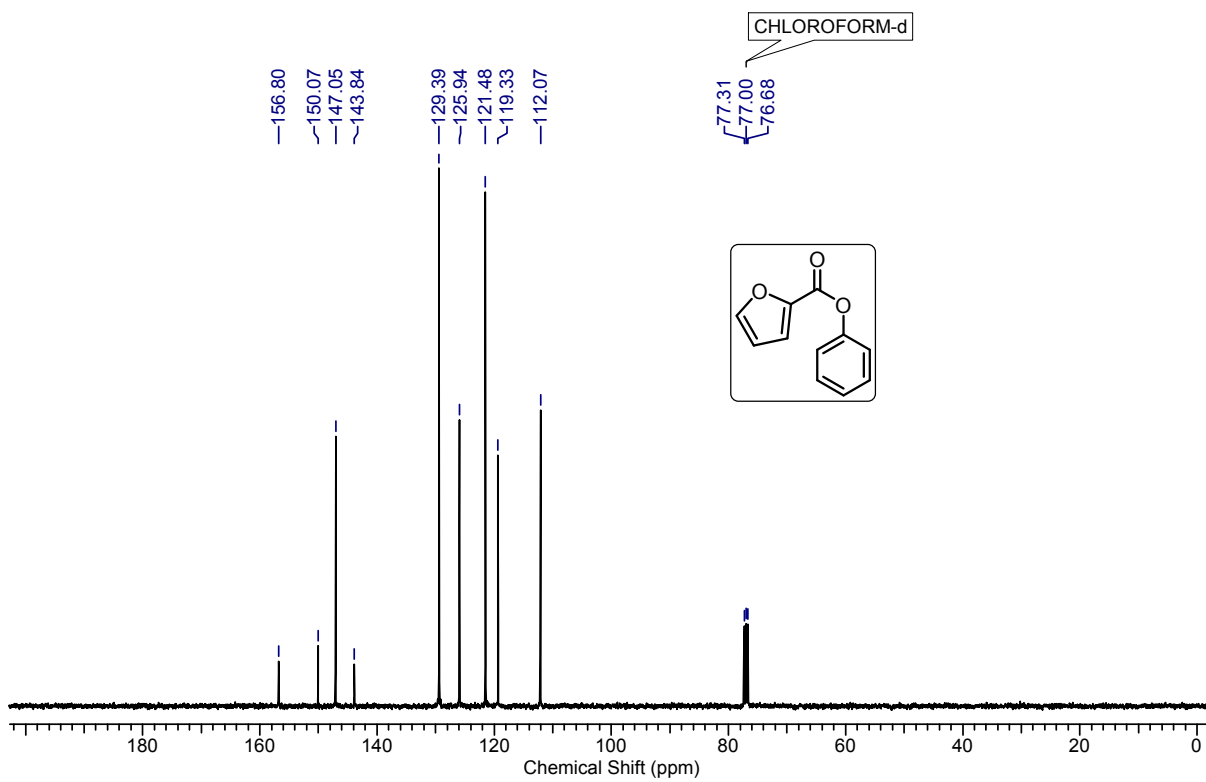
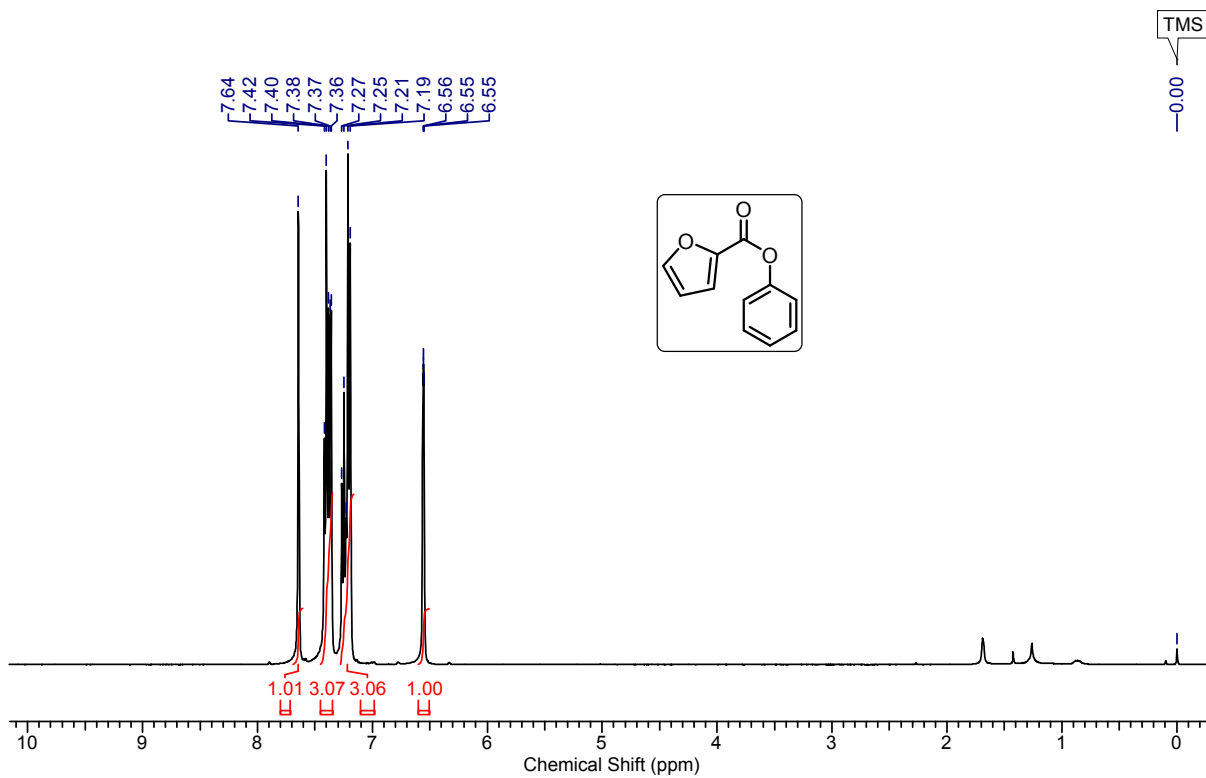


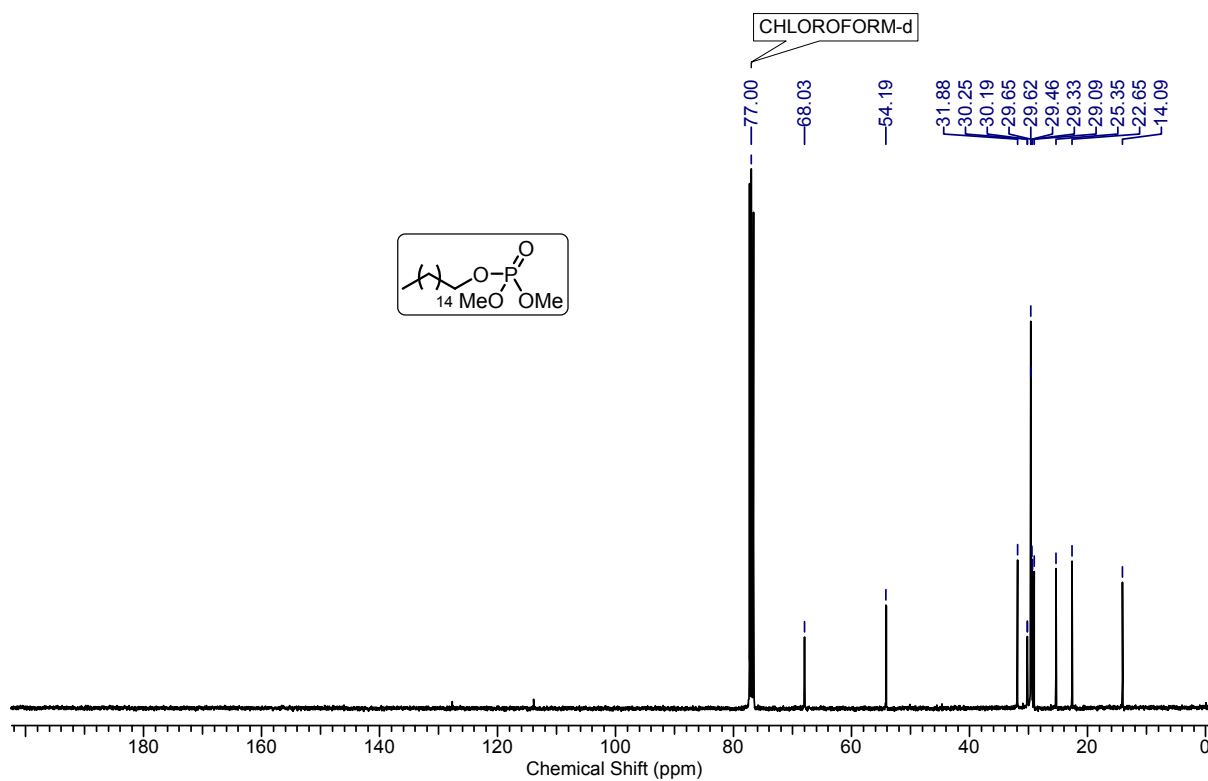
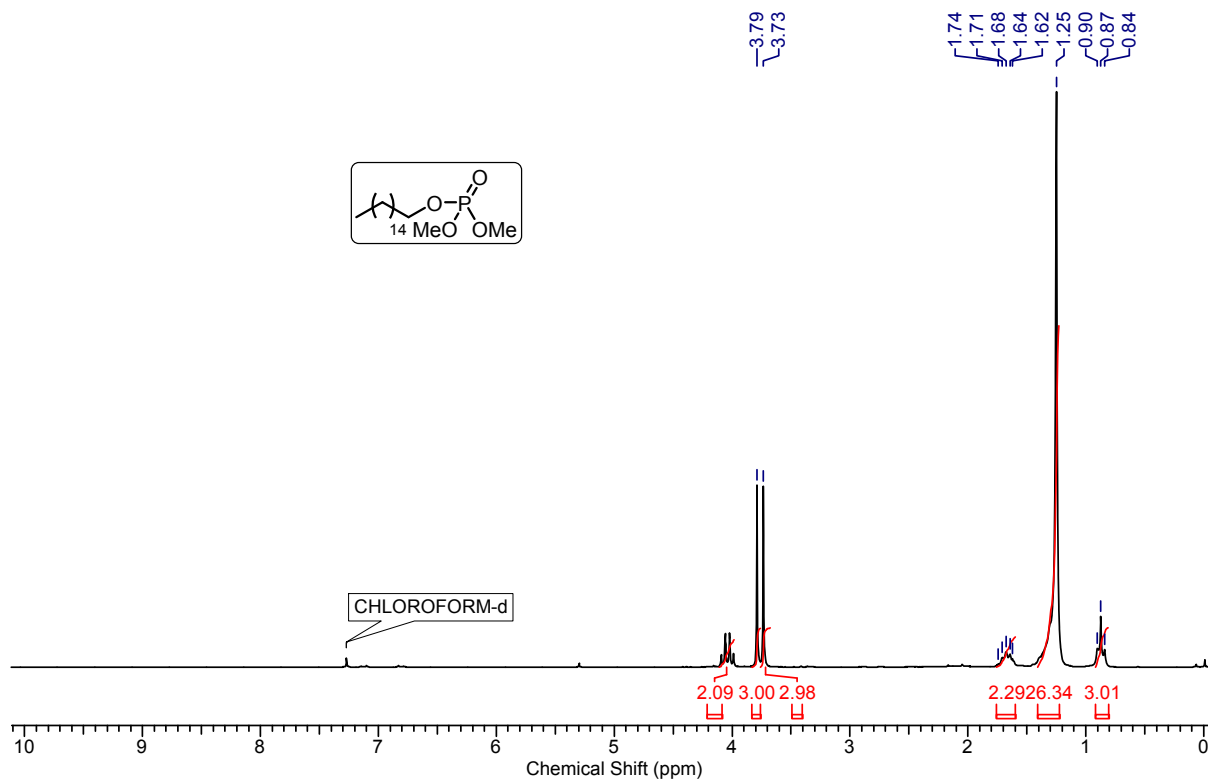


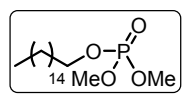












^{31}P -NMR, 162 MHz

