Self-immolative systems for the disclosure of reactive electrophilic alkylating agents

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Materials

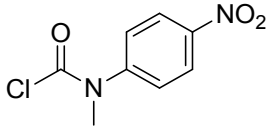
All chemical reagents were purchased from Sigma Aldrich and were used as received without purification with the exception of *N*-methyl-*N*-(4-nitrophenyl)carbamoyl chloride[1] and 2-diphenylphosphinoethanol[2,3] **6**, which were synthesised by modifications of literature procedures. Solvents were purchased from Fisher Scientific except for ethyl acetate and hexane which were purchased from Sigma Aldrich. All solvents were used as supplied with the exception of THF that was distilled under argon from sodium and benzophenone prior to use. Fisher Scientific Silica 60A (particle size 35-70 micron) was used to perform column chromatography. Thin-layer chromatography (TLC) was performed on aluminium sheets coated with Merck 5735 Kieselgel 60 F_{254}. Developed plates were air-dried and stained using a potassium permanganate solution.

Characterisation

^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded at 20 °C on a Bruker Nano 400 (9.39 T) or Bruker DPX 400 (9.39 T) instrument with tetramethylsilane (TMS) used as the internal standard. Chemical shifts (δ) are reported in parts per million from low to high field and referenced to residual solvent. Coupling constant (*J*) are reported in Hertz (Hz). Standard abbreviations indicating multiplicity are used as follows: b = broad, s = singlet, d = doublet, t = triplet, m = multiplet. Fourier transform infrared spectroscopy (FTIR) spectra were recorded on a PerkinElmer Spectrum FT-IR in transmission mode, all of the samples were analysed directly using a diamond ATR sampling accessory. Mass spectrometry was conducted using ThermoFisher Scientific Orbitrap XL LCMS. The sample was introduced by liquid chromatography and sample ionisation was achieved by electrospray ionisation (ESI). Melting points were recorded using a Stuart MP10 melting point apparatus and are uncorrected. UV−visible spectra were measured with a Varian Cary 300 spectrophotometer, using 4 mm inner width Quartz cuvette, in the wavelength range 250−800 nm.

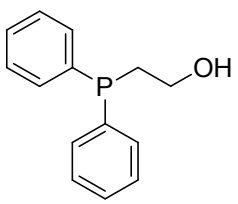
Synthesis

Synthesis of *N*-methyl-*N*-(4-nitrophenyl)carbamoyl chloride[1]



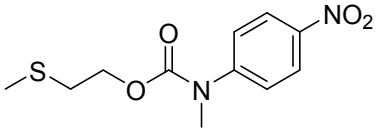
To a solution of triphosgene (3.00 g, 10.11 mmol) in dry hexane (10 mL) was added Aliquat® 336 (1.00 g, 2.53 mmol). After stirring the solution at room temperature for 16 hours, a solution of *N*-methyl-4-nitroanaline (0.77 g, 5.05 mmol) and triethylamine (1.41 mL, 10.11 mmol) in THF (20 mL) was added dropwise at 0 °C. After stirring the solution at room temperature for 2 hours the precipitate was filtered and the solvent removed *in vacuo*. The crude product was further purified by column chromatography (10→20 % EtOAc/hexane) followed by a recrystallization from EtOAc/hexane (9/1 V/V) to afford the product (0.91 g, 84 %) as a white solid. δ_H ($CDCl_3$, 400 MHz) 3.48 (3H, s, C*H*$_3$N), 7.48 (2H, d, *J* = 8.8 Hz, Ar*H*), 8.31 (2H, d, *J* = 8.8 Hz, Ar*H*) ppm. δ_C ($CDCl_3$, 100 MHz) 35.3 (br.), 119.7, 122.5, 141.6 (br.), 142.9, 143.3 ppm. FTIR (ATR/ν max) 3111-3081 (C-H), 1726 (C=O), 1594 (C=C), 1512 (N=O), 1495 (C=C), 1418, 1342 (N=O), 1255 cm^{-1}. M.p. = 102 °C.

Synthesis of 2-(diphenylphosphino)ethanol **6**[2,3]



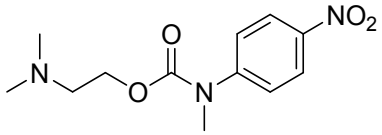
To a solution of diphenylphosphine (1.00g, 5.37mmol) and 2-bromoethanol (0.671g, 5.37mmol) in THF (20mL) was added *n*-butyl lithium (7.1 mL, 1.6 M in hexanes). The mixture was stirred for 6 hours at 0 °C. The THF was evaporated and the residue extracted in CH_2Cl_2 (2 × 20 mL). The resulting solution was treated with an excess of solid NH_4Cl in CH_2Cl_2 and the suspension was filtered and the solution evaporated. The remaining residue was extracted with Et_2O (2 × 15mL), and the volatiles were removed. The crude residue was further purified via column chromatography (hexane/CH_2Cl_2 1/1→CH_2Cl_2/EtOAc 7/3) to yield the product (0.750g, 61%) as a colorless oil. δ_H ($CDCl_3$, 400 MHz) 1.63 (1H, br. s, CH_2OH), 2.40 (2H, t, J = 7.2 Hz, CH_2P), 3.80 (2H, dt, J = 9.6 Hz, J = 7.2 Hz, CH_2OH), 7.28-7.39 (6H, m, Ar*H*), 7.39-7.49 (4H, m, Ar*H*) ppm. δ_C ($CDCl_3$, 100 MHz) 32.3 (d, $^1J_{CP}$ = 12.5 Hz), 60.2 (d, $^2J_{CP}$ = 22.1 Hz), 128.6 (d, $^3J_{CP}$ = 6.7 Hz), 128.8, 132.7 (d, $^2J_{CP}$ = 18.8 Hz), 137.9 (d, $^1J_{CP}$ = 11.6 Hz) ppm. δ_P ($CDCl_3$, 162 MHz) -24.13 ppm. FTIR (ATR/ν max) 3324 (O-H), 3051-2875 (C-H), 1584 (C=C), 1480 (C=C), 1432, 1037 cm^{-1}. ESI-MS m/z calculated for $[C_{14}H_{16}OP]^+$: 231.0933, found m/z 231.0928.

Synthesis of 2-(methylthio)ethyl methyl(4-nitrophenyl)carbamate **1**



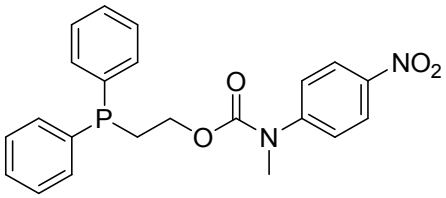
Methyl(4-nitrophenyl)carbamic chloride (0.50 g, 2.33 mmol), 2-(methylthio)ethanol (0.20 mL, 2.33 mmol), 4-dimethylaminopyridine (0.14 g, 1.165 mmol) and triethylamine (0.65 mL, 4.66 mmol) were dissolved in THF (10 mL) and the solution was heated under reflux overnight. The solvent was removed *in vacuo* and the crude product purified via column chromatography (5 % MeOH/$CHCl_3$) to afford the product (0.34 g, 54 %) as a white solid. δ_H ($CDCl_3$, 400 MHz) 2.13 (3H, s, SCH_3), 2.75 (2H, t, J = 6.8 Hz, SCH_2), 3.39 (3H, s, NCH_3), 4.33 (2H, t, J = 6.8 Hz, CH_2O), 7.49 (2H, AA'XX', Ar*H*), 8.21 (2H, AA'XX', Ar*H*) ppm. δ_C ($CDCl_3$, 100 MHz) 15.7, 32.8, 37.1, 64.6, 124.3, 124.7, 144.5, 148.8, 154.6 ppm. FTIR (ATR/ν max) 2919 (C-H), 1705 (C=O), 1593 (C=C), 1513 (N=O), 1498 (C=C), 1325 (N=O), 1256, 1151, 1103 cm^{-1}. M.p. = 43 °C. We were unable to obtain a mass ion of **1** and so measured the mass ion of the sulfonium ion arising from its methylation. ESI-MS m/z calculated for $[C_{12}H_{17}N_2O_4S]^+$: 285.0904, found m/z 285.0909.

Synthesis of 2-(dimethylamino)ethyl methyl(4-nitrophenyl)carbamate **2**



Methyl(4-nitrophenyl)carbamic chloride (0.20g, 0.93 mmol), 2-dimethylaminoethanol (0.094 mL, 0.93 mmol), 4-dimethylaminopyridine (0.057 g, 0.465 mmol) and triethylamine (0.26 mL, 1.86 mmol) were dissolved in THF (10 mL) and the solution was heated under reflux overnight. The solvent was removed *in vacuo* and the crude product purified via column chromatography (5→10 % MeOH/$CHCl_3$) to afford the product (0.138 g, 55 %) as a colourless oil. δ_H ($CDCl_3$, 400 MHz) 2.27 (6H, s, 2 × CH_2NCH_3), 2.59 (2H, t, J = 6.0 Hz, NCH_2), 3.39 (3H, s, CH_3), 4.28 (2H, t, J = 6.0 Hz, CH_2O), 7.50 (2H, AA'XX', Ar*H*), 8.20 (2H, AA'XX', Ar*H*) ppm. δ_C ($CDCl_3$, 100 MHz) 37.0, 45.8, 57.9, 64.3, 124.2, 124.5, 144.3, 149.0, 154.8 ppm. FTIR (ATR/ν max) 2946-2822-2771 (C-H), 1706 (C=O), 1593 (C=C), 1514 (N=O), 1499 (C=C), 1323 (N=O), 1258, 1154, 1104 cm^{-1}. ESI-MS m/z calculated for $[C_{12}H_{18}O_4N_3]^+$: 268.1292, found m/z 268.1293.

Synthesis of 2-(diphenylphosphino)ethyl methyl(4-nitrophenyl)carbamate **3**



Methyl(4-nitrophenyl)carbamic chloride (0.15 g, 0.70 mmol), 2-(diphenylphosphino)ethanol (0.16 g, 0.70 mmol), 4-dimethylaminopyridine (0.009 g, 0.07 mmol) and triethylamine (0.19 mL, 1.40 mmol) were dissolved in THF (10 mL) and the solution was heated under reflux overnight. The solvent was removed *in vacuo* and the crude product purified via column chromatography (25 % EtOAc/hexane) to afford the product (0.20 g, 70 %) as a colourless oil. δ_H ($CDCl_3$, 400 MHz) 2.48 (2H, t, J = 7.2 Hz, PCH_2), 3.25 (3H, s, NCH_3), 4.35 (2H, dt, J = 9.6 Hz, J = 7.2 Hz, CH_2O), 7.28-7.38 (6H, m, ArH), 7.38-7.48 (6H, m, ArH), 8.18 (2H, AA'XX', ArH) ppm. δ_C ($CDCl_3$, 100 MHz) 28.1 (d, $^1J_{CP}$ = 14.4 Hz), 36.8, 64.2 (d, $^2J_{CP}$ = 23.3 Hz), 124.2, 124.4, 128.6 (d, $^3J_{CP}$ = 7.0 Hz), 128.9, 132.6 (d, $^2J_{CP}$ = 19.0 Hz), 137.6 (d, $^1J_{CP}$ = 12.1 Hz), 144.3, 148.8, 154.5 ppm. δ_P ($CDCl_3$, 162 MHz) -22.3 ppm. FTIR (ATR/ν max) 3051-2954 (C-H), 1705 (C=O), 1593 (C=C), 1513 (N=O), 1498 (C=C), 1433, 1325 (N=O), 1254, 1151, 1103 cm^{-1}. ESI-MS m/z calculated for $[C_{22}H_{22}N_2O_4P]^+$: 409.1312, found m/z 409.1304.

NMR spectrum ($CDCl_3$)

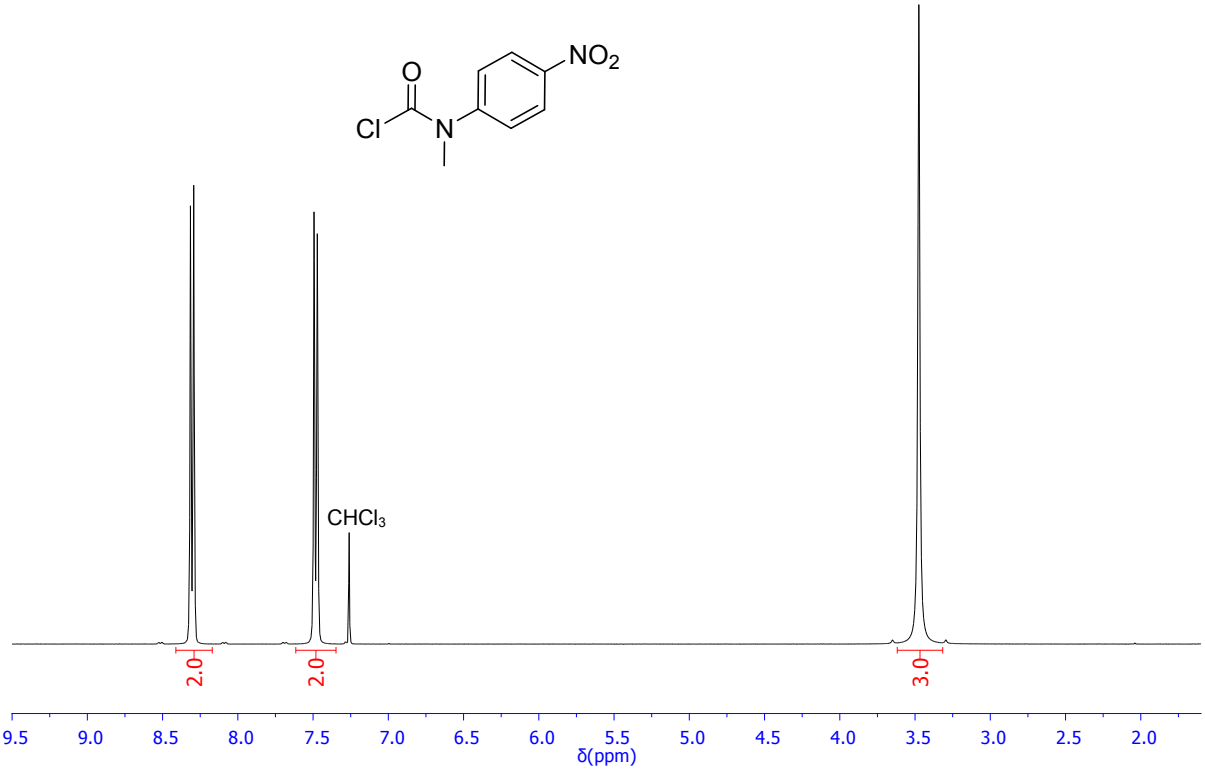


Fig. S1 ^{1}H NMR spectrum of *N*-methyl-*N*-(4-nitrophenyl)carbamoyl chloride

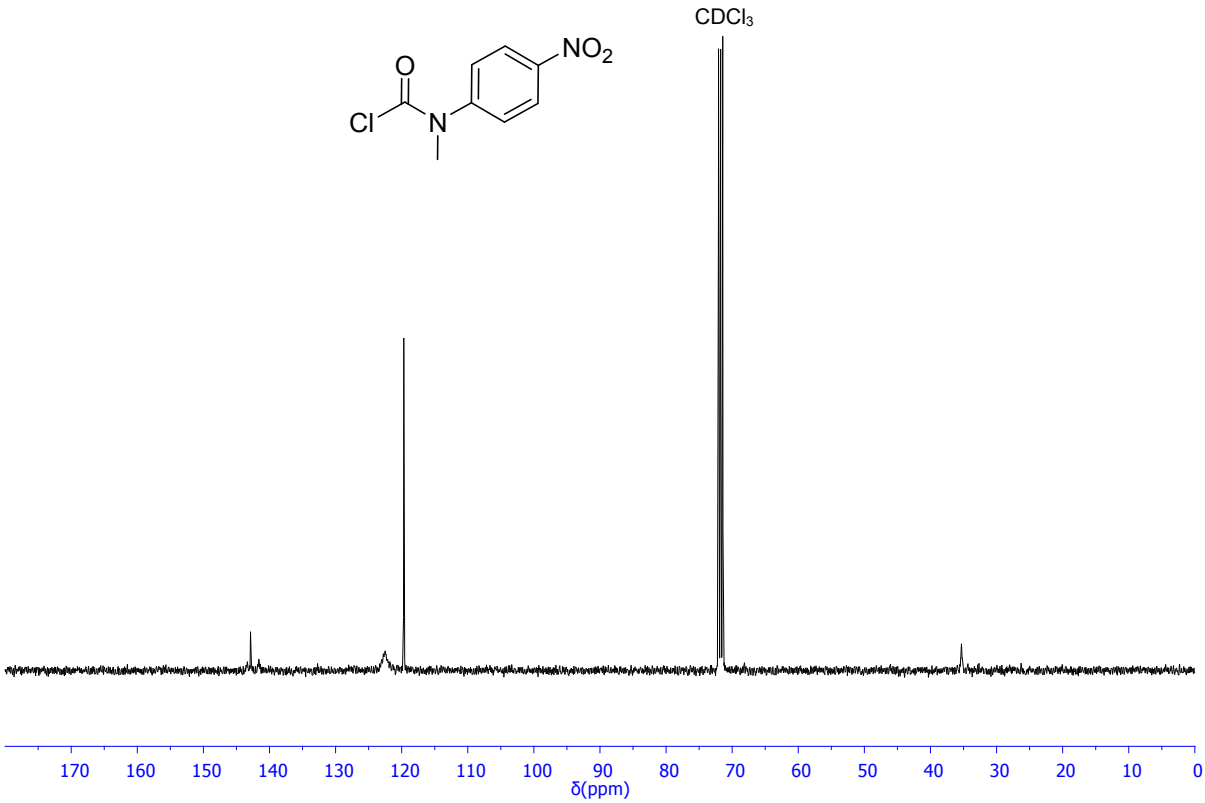


Fig. S2 ^{13}C NMR spectrum of *N*-methyl-*N*-(4-nitrophenyl)carbamoyl chloride

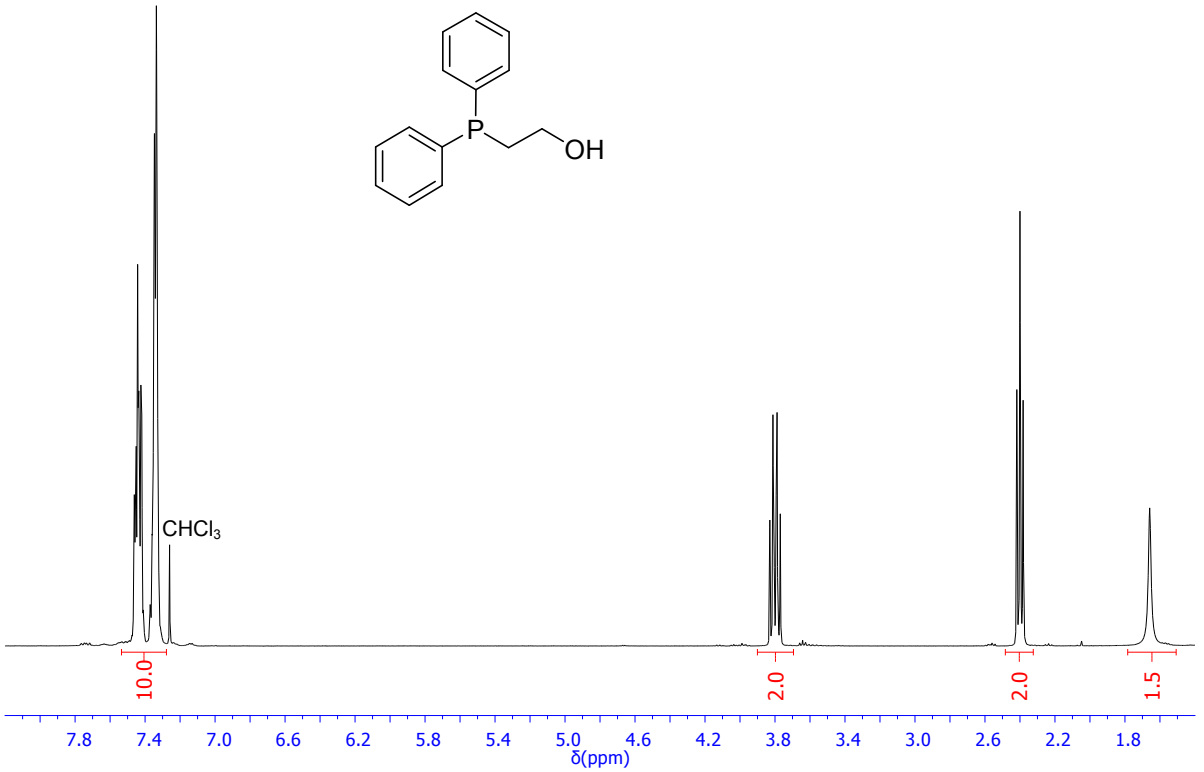


Fig. S3 ^{1}H NMR spectrum of 2-(diphenylphosphino)ethanol **6**

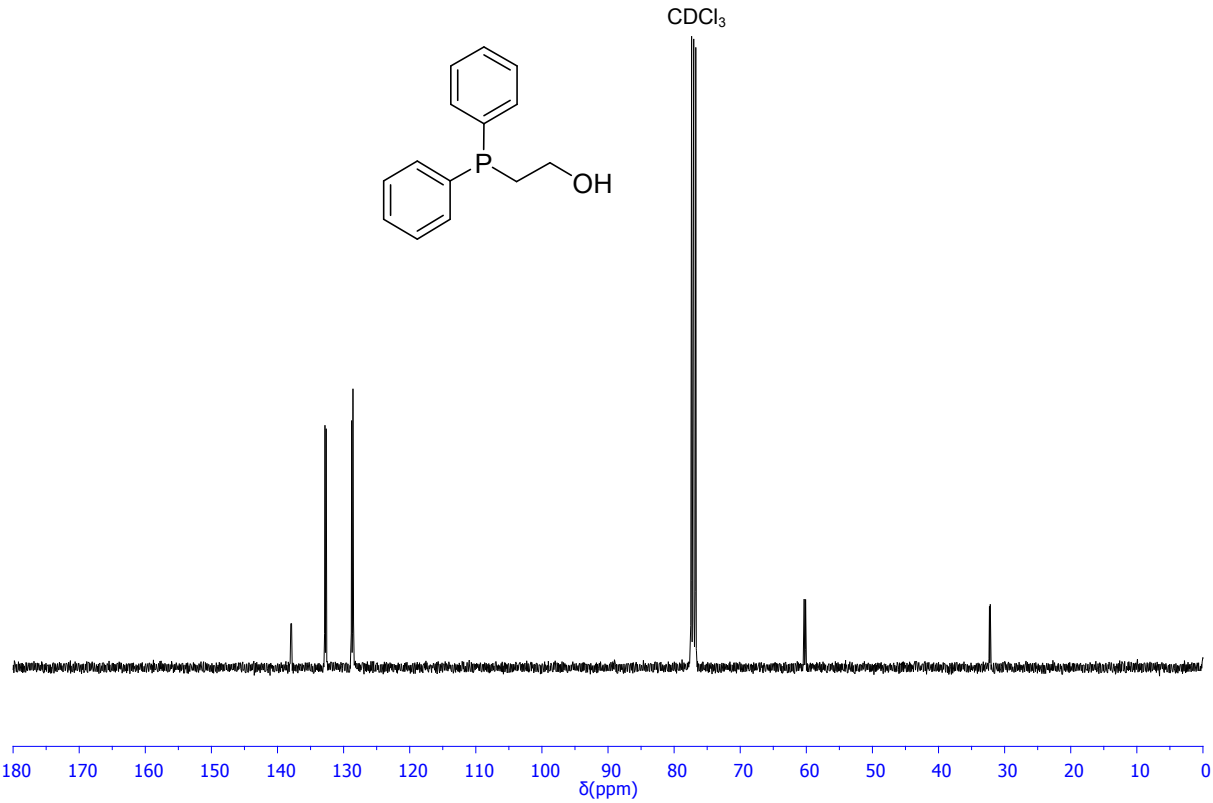


Fig. S4 ^{13}C NMR spectrum of 2-(diphenylphosphino)ethanol **6**

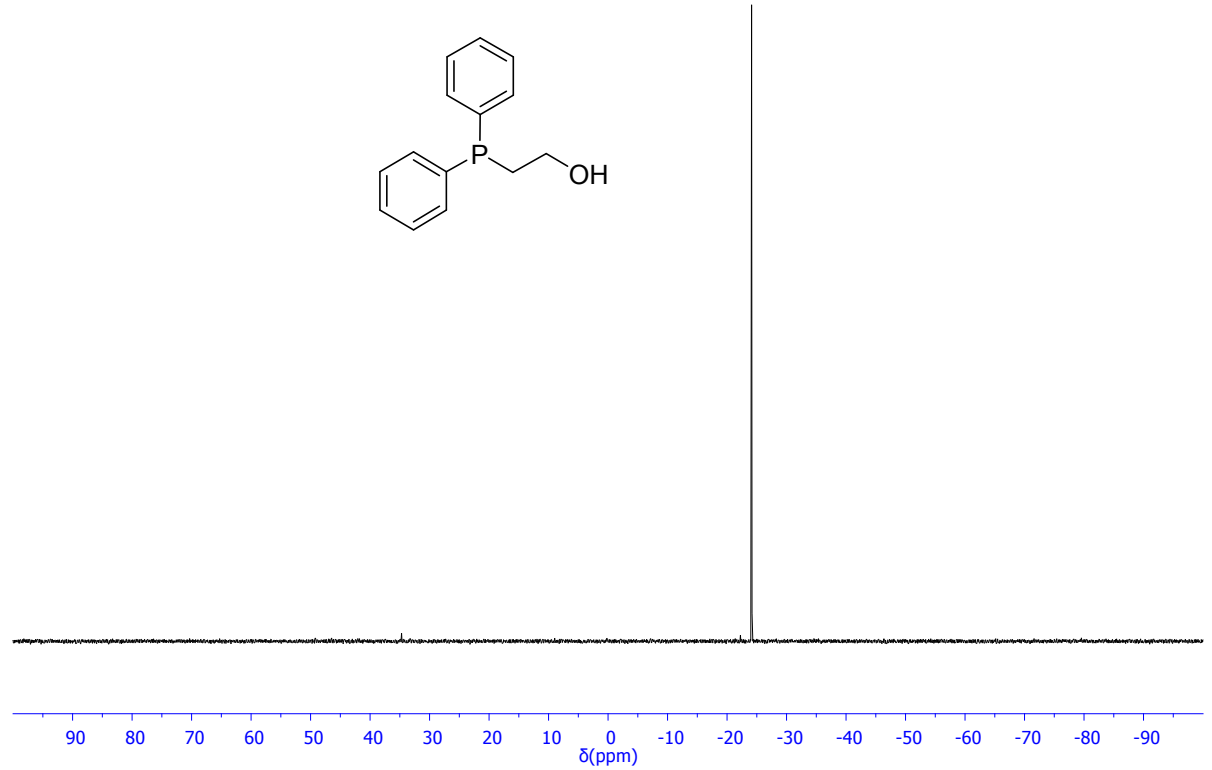


Fig. S5 ^{31}P NMR spectrum of 2-(diphenylphosphino)ethanol **6**

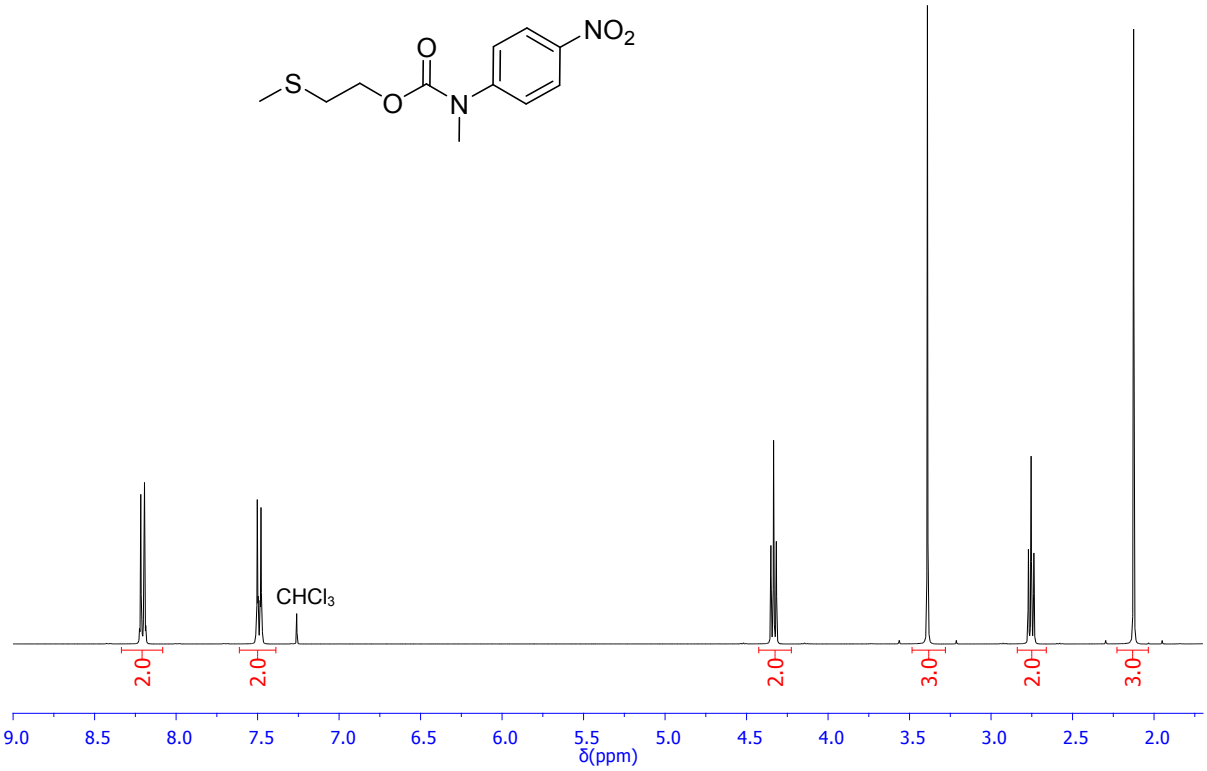


Fig. S6 ^{1}H NMR spectrum of 2-(methylthio)ethyl methyl(4-nitrophenyl)carbamate **1**

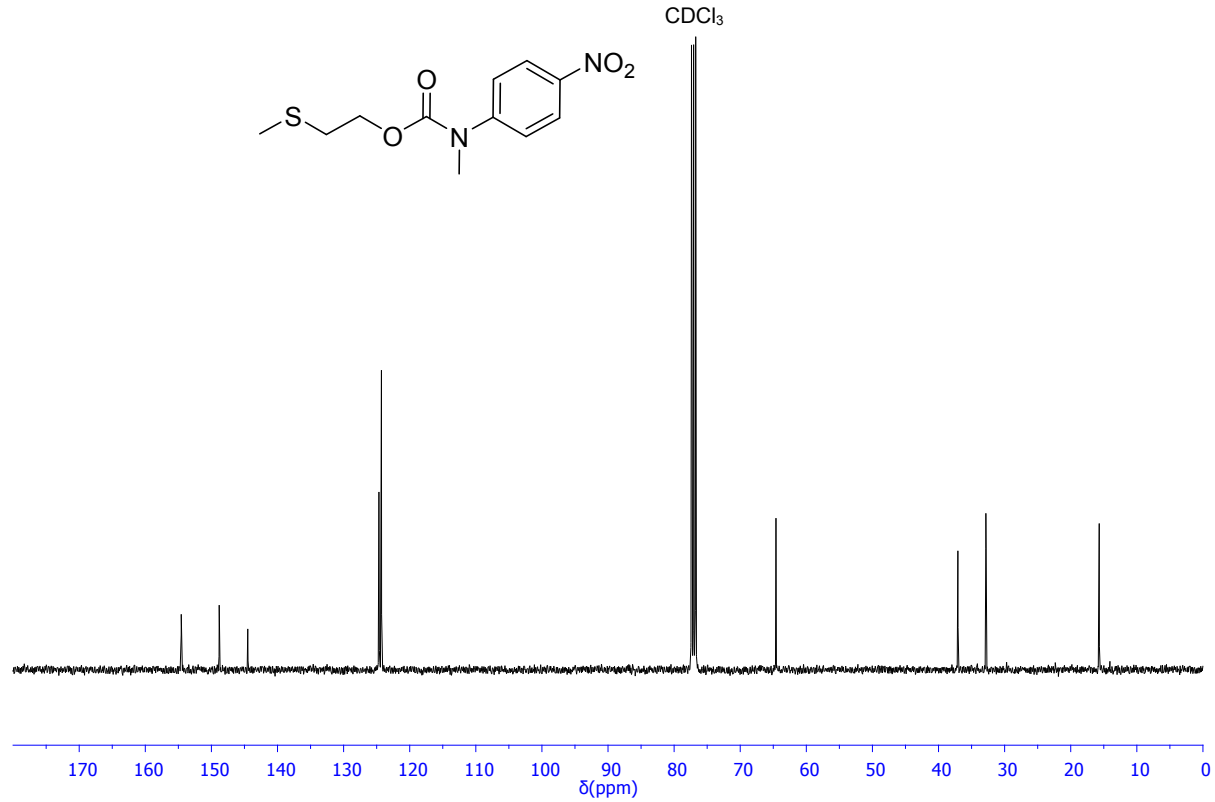


Fig. S7 ^{13}C NMR spectrum of 2-(methylthio)ethyl methyl(4-nitrophenyl)carbamate **1**

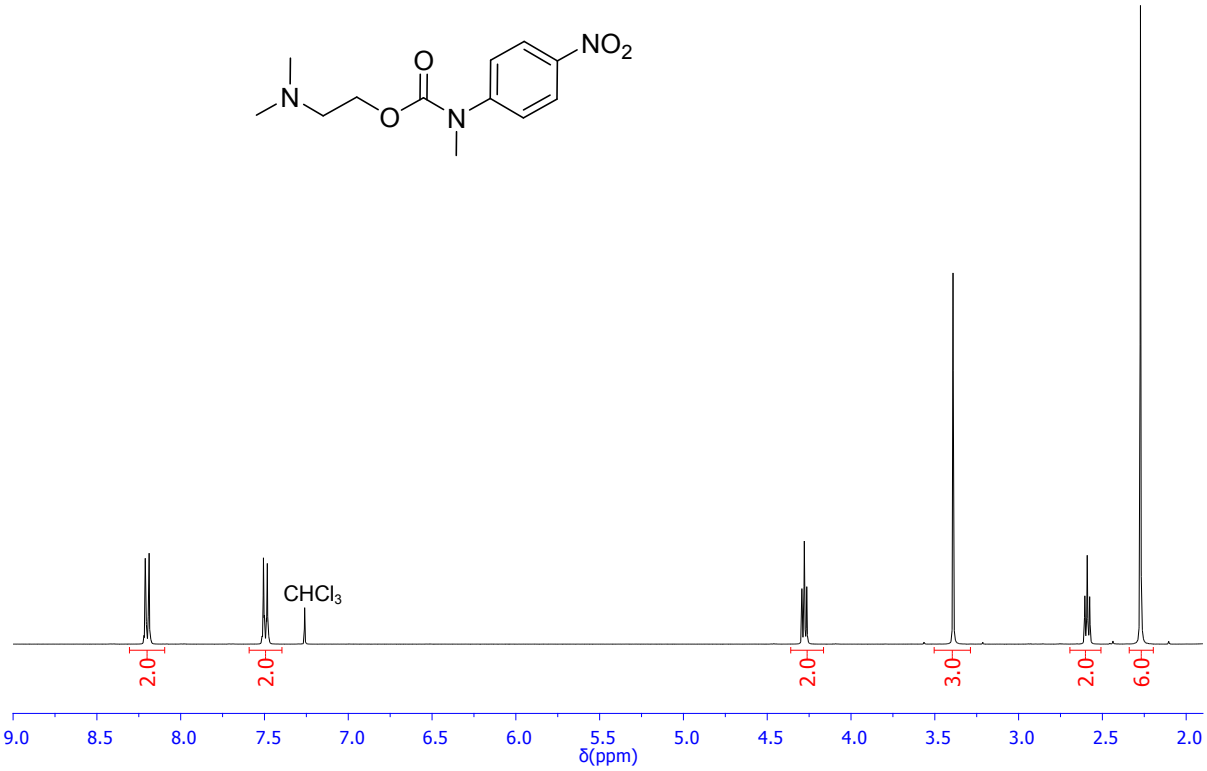


Fig. S8 ^{1}H NMR spectrum of 2-(dimethylamino)ethyl methyl(4-nitrophenyl)carbamate **2**

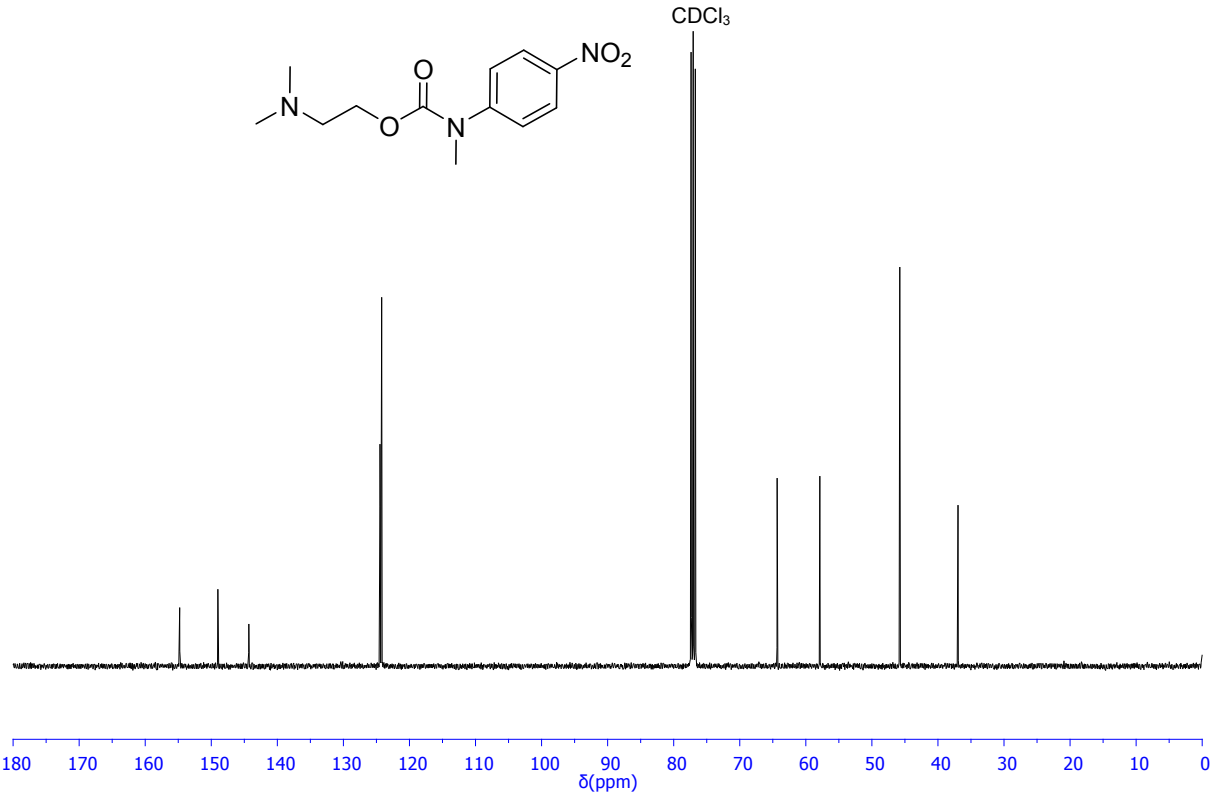


Fig. S9 ^{13}C NMR spectrum of 2-(dimethylamino)ethyl methyl(4-nitrophenyl)carbamate **2**

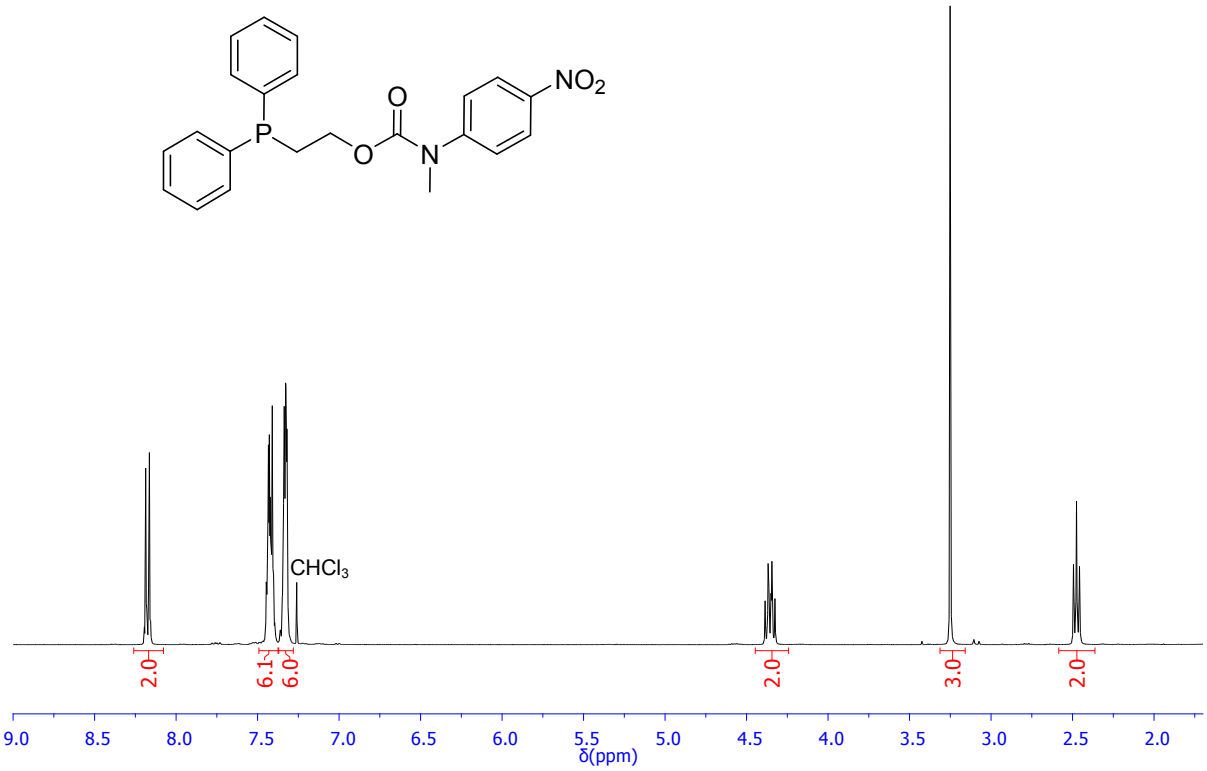


Fig. S10 ^{1}H NMR spectrum of 2-(diphenylphosphino)ethyl methyl(4-nitrophenyl)carbamate **3**

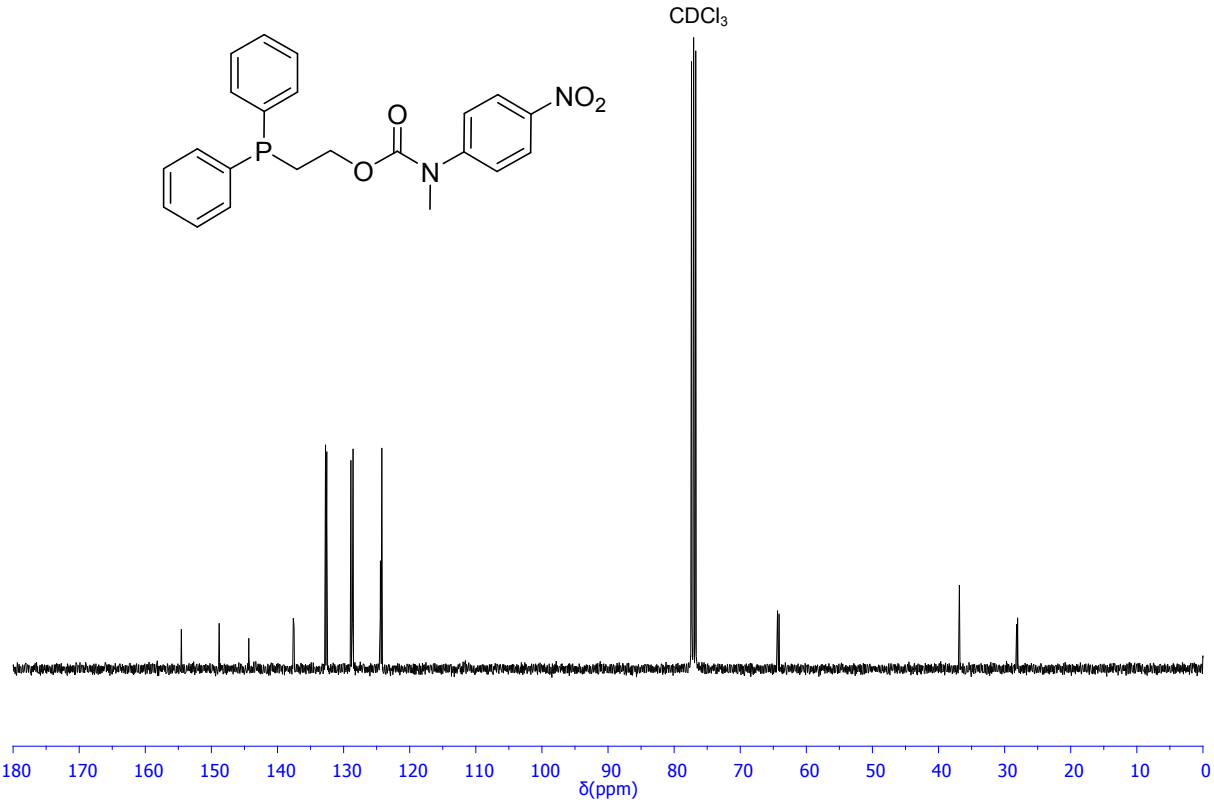


Fig. S11 ^{13}C NMR spectrum of 2-(diphenylphosphino)ethyl methyl(4-nitrophenyl)carbamate **3**

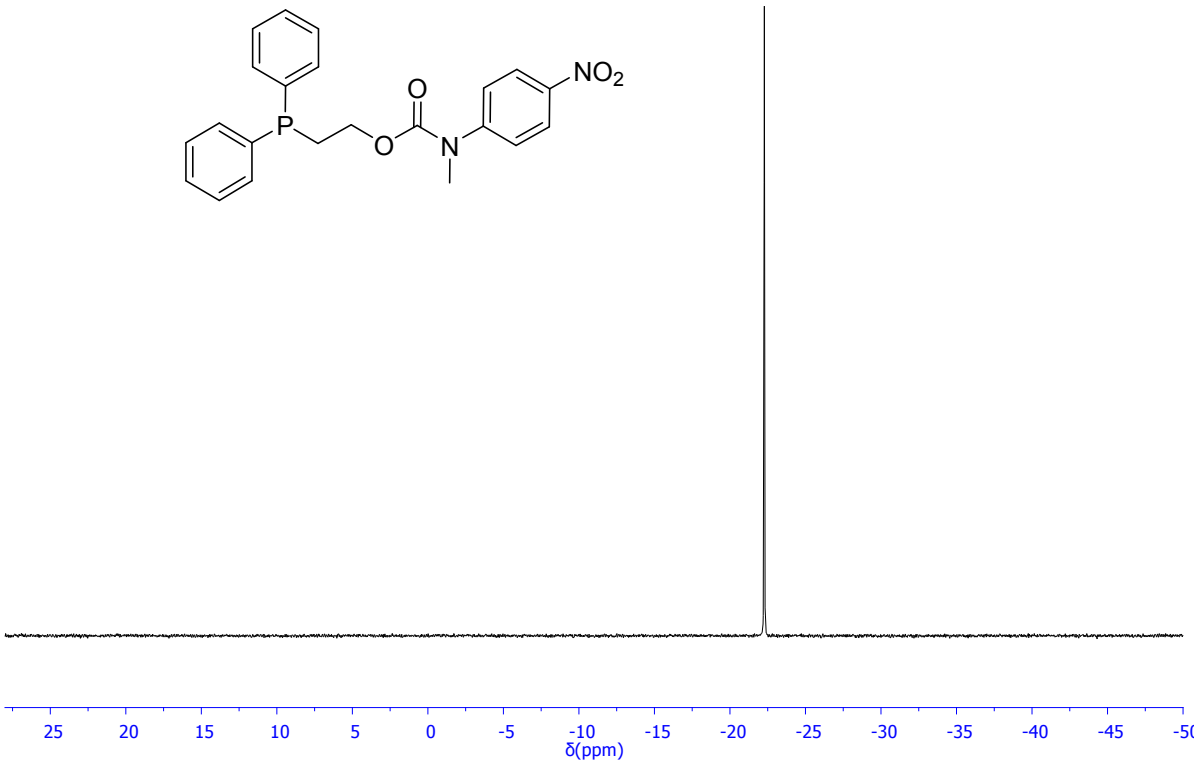


Fig. S12 ^{31}P NMR spectrum of 2-(diphenylphosphino)ethyl methyl(4-nitrophenyl)carbamate **3**

Alkylation/β-elimination reactions for the detectors 1-3, Degradation study for the detector 3 and *"One pot"* alkylation/β-elimination reaction using the detector 3

Alkylation reactions

^{1}H NMR spectroscopic studies were conducted by dissolution of the various detectors (**1**, **2** and **3**) in MeCN-d_3 (0.5 mL, [detector] = 0.025 mol.L^{-1}), followed by the addition of 10 molar equivalents of the corresponding alkylating agent (methyl iodide: MeI, benzyl bromide: BnBr, benzyl chloride: BnCl, 2-methylbenzyl bromide: 2-Me-BnBr, 3-methylbenzyl bromide: 3-Me-BnBr, 4-methylbenzyl bromide: 4-Me-BnBr, allyl Bromide: allyl-Br, allyl chloride: allyl-Cl or trityl chloride) directly to the NMR tube. The ^{1}H NMR spectra were recorded at regular time intervals. The area of the triplet resonance CH_2S of **1**, CH_2N of **2** and doublet of triplets resonance CH_2P of **3** or singlet resonance CH_3N of **3** was standardised to the area of the MeCN solvent resonance at 1.969 ppm and was used to calculate the percentage of the detector that remained non-alkylated over time with respect to the initial area of the methylene resonance (*i.e.* before the addition of the alkylating agent, time point = 0).

β-elimination studies

^{1}H NMR spectroscopic studies were conducted by addition of 2 molar equivalents of *N*,*N*-diidopropylethylamine (DIPEA) of the corresponding alkylated detector (**1**, **2** and **3**) directly to the NMR tube. The ^{1}H NMR spectra were recorded at regular time intervals. For the alkylated detector **1** and **2**, the area of the multiplet resonance CH_2S$^+$ and CH_2N$^+$ were standardised to the area of the MeCN solvent resonance at 1.969 ppm and were used to calculate the percentage of the alkylated detector that remained non-degraded over time with respect to the initial area of the methylene resonance. The percentage of alkylated detector **3** remaining over time was calculated by comparison of the integrations of the apparent doublet resonance C*H* e' and e'' (see Fig. S18) corresponding to the alkylated detector and the reporter group (r.g.) *N*-methyl-4-nitroaniline, respectively. (*i.e.* before the addition of DIPEA, time point = 0).

Degradation study

^{1}H NMR spectroscopic study was conducted by dissolution of detector **3** in a mixture of MeCN-d_3 + 10 % D_2O (0.5 mL, [detector] = 0.025 mol.L^{-1}). The ^{1}H NMR spectra were recorded at regular time intervals.

"*One pot*" alkylation/β-elimination reaction using 2-(diphenylphosphino)ethyl methyl(4-nitrophenyl)carbamate 3

^{1}H NMR spectroscopic studies were conducted by addition of 10 molar equivalents of benzyl bromide to a solution of the corresponding detector **3** (V = 0.5 mL, [detector] = 0.025 mol.L^{-1}) and 2 molar equivalent of DIPEA directly to the NMR tube. The ^{1}H NMR spectra were recorded at regular time intervals. The area of the singlet CH_3N of the detector **3**, the area of the multiplet resonance CH_2P$^+$ of the alkylated detector as well as the area of the singlet CH_3N of the reporter group (r.g.: *N*-methyl-4-nitroaniline) were used to calculate the percentage of the different species remaining over time (*i.e.* before the addition of BnBr, time point = 0).

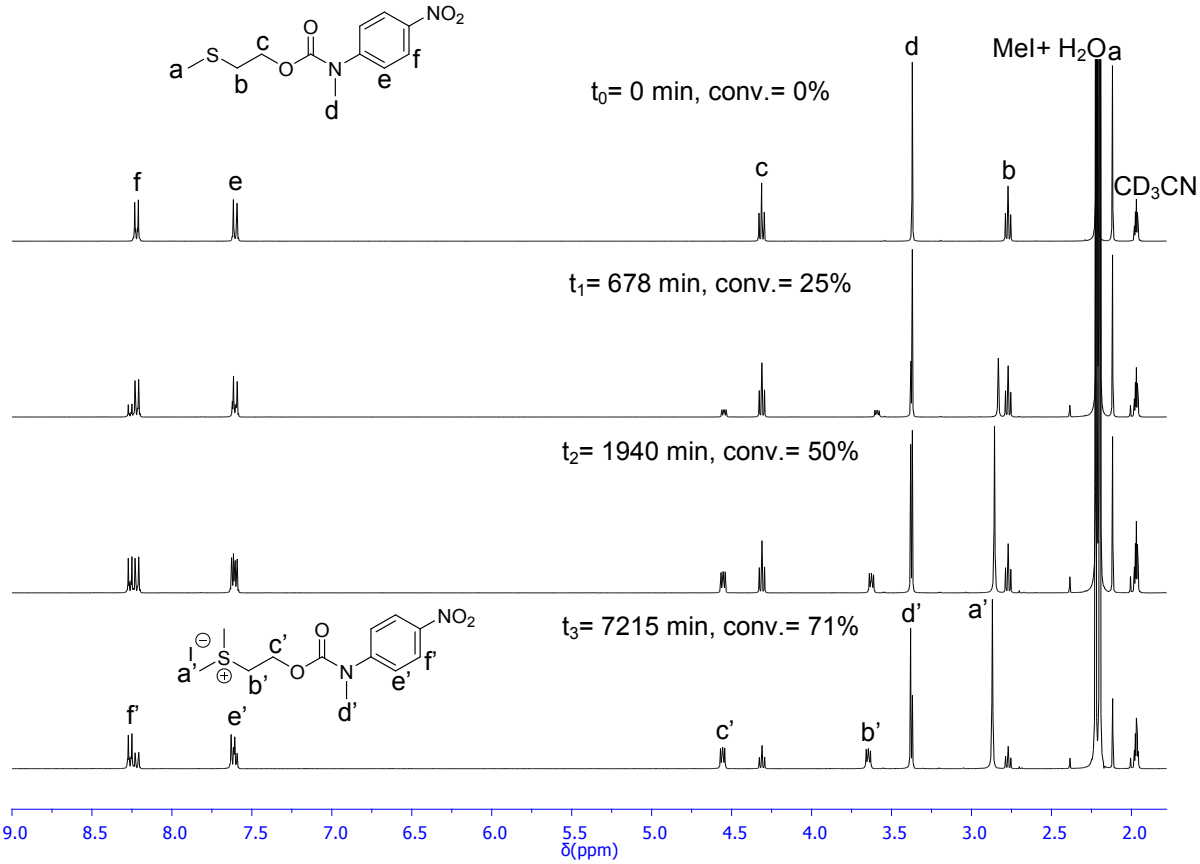


Fig. S13 ^{1}H NMR spectrum recorded overtime following the addition of 10 equivalents of MeI to a solution of **1** in MeCN-d_3

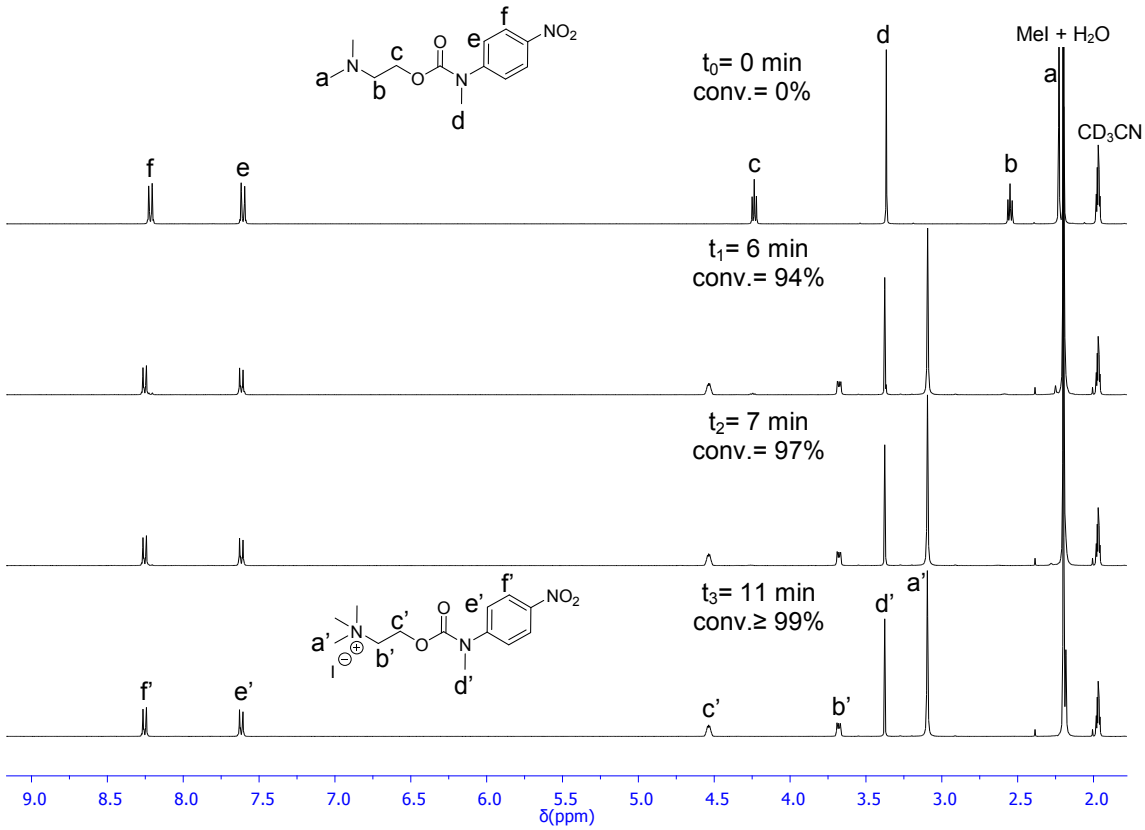


Fig. S14 ^{1}H NMR spectrum recorded overtime following the addition of 10 equivalents of MeI to a solution of **2** in MeCN-d_3

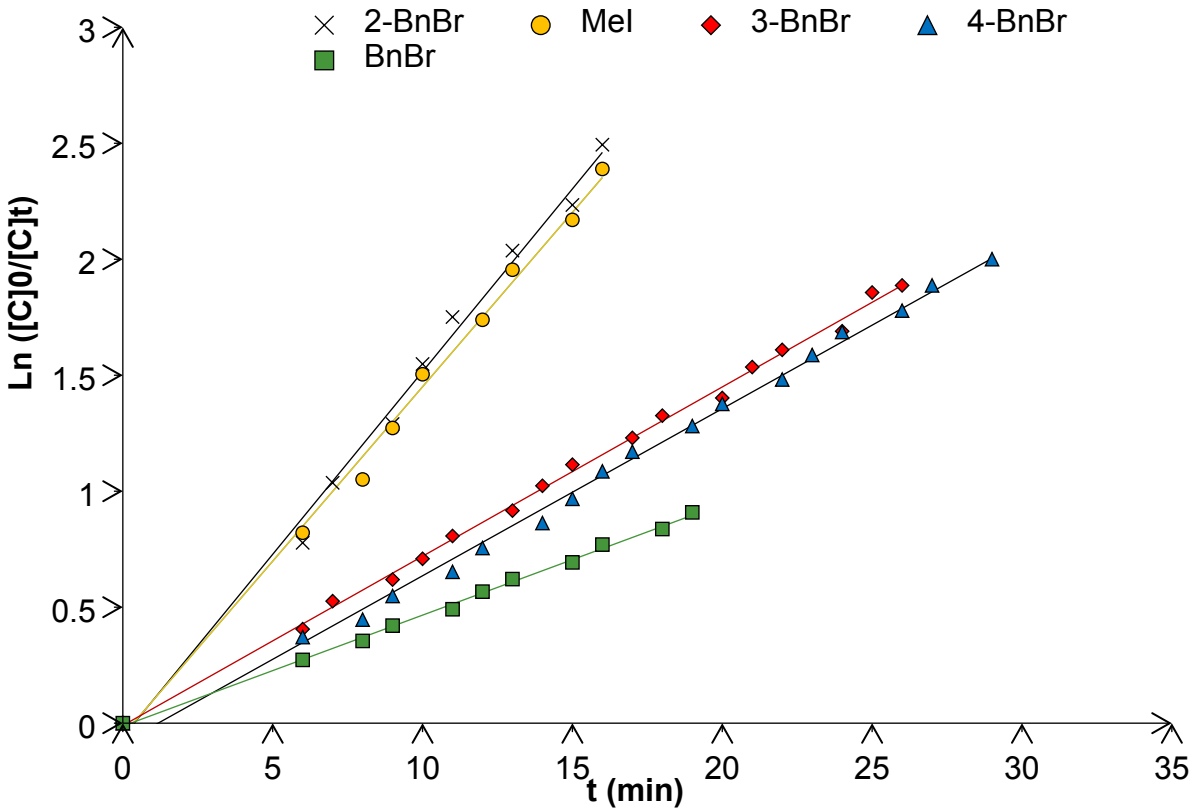


Fig. S15 Kinetic plot of ln([C]$_0$/[C]$_t$) versus reaction time for the alkylation of 2-(diphenylphosphino)ethyl methyl(4-nitrophenyl)carbamate **3** in MeCN-d_3 at 20 °C

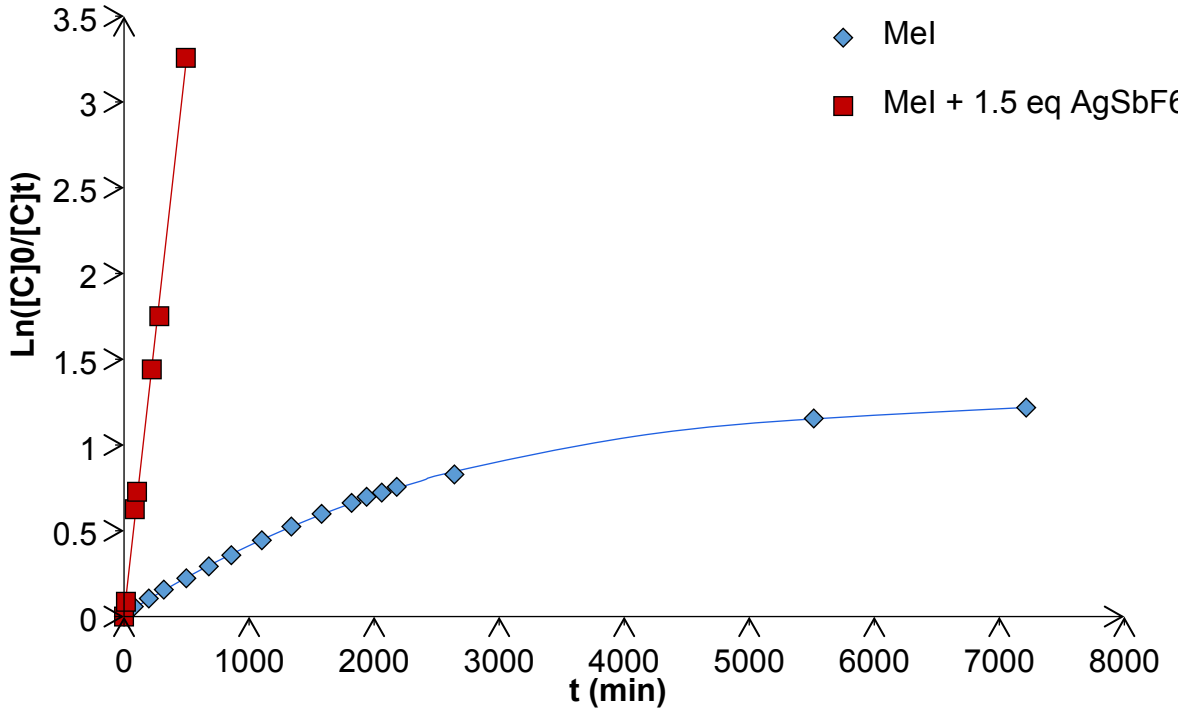


Fig. S16 Kinetic plot of $\ln([C]_0/[C]_t)$ versus reaction time for the alkylation 2-(methylthio)ethyl methyl(4-nitrophenyl)carbamate **1** using 10 equivalents of MeI in MeCN-d_3 at 20 °C

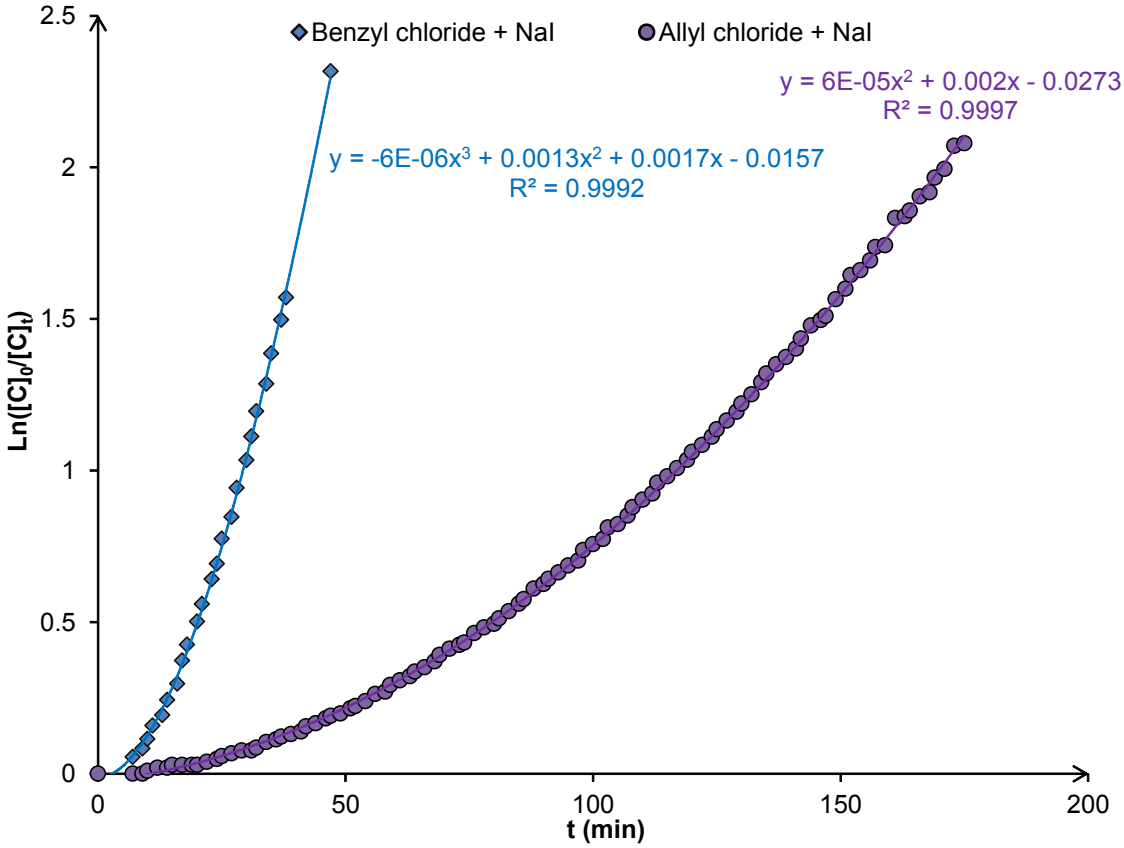


Fig. S17 Kinetic plot of $\ln([C]_0/[C]_t)$ versus reaction time for the alkylation of 2-(diphenylphosphino)ethyl methyl(4-nitrophenyl)carbamate **3** using 10 equivalents of BnCl or Allyl-Cl and 10 equivalents of NaI in MeCN-d_3 at 20 °C

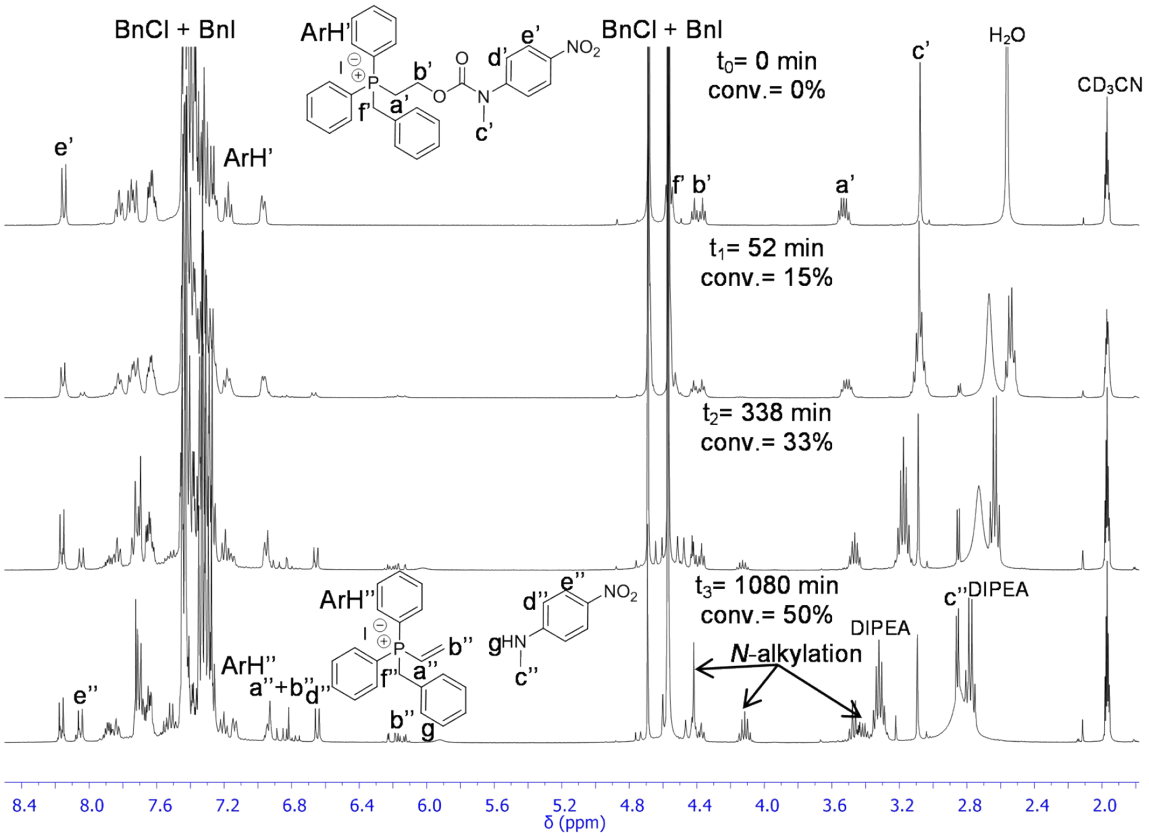


Fig. S18 ^{1}H NMR spectrum recorded overtime following the addition of DIPEA to a solution of alkylated **3** (BnCl) in MeCN-d_3

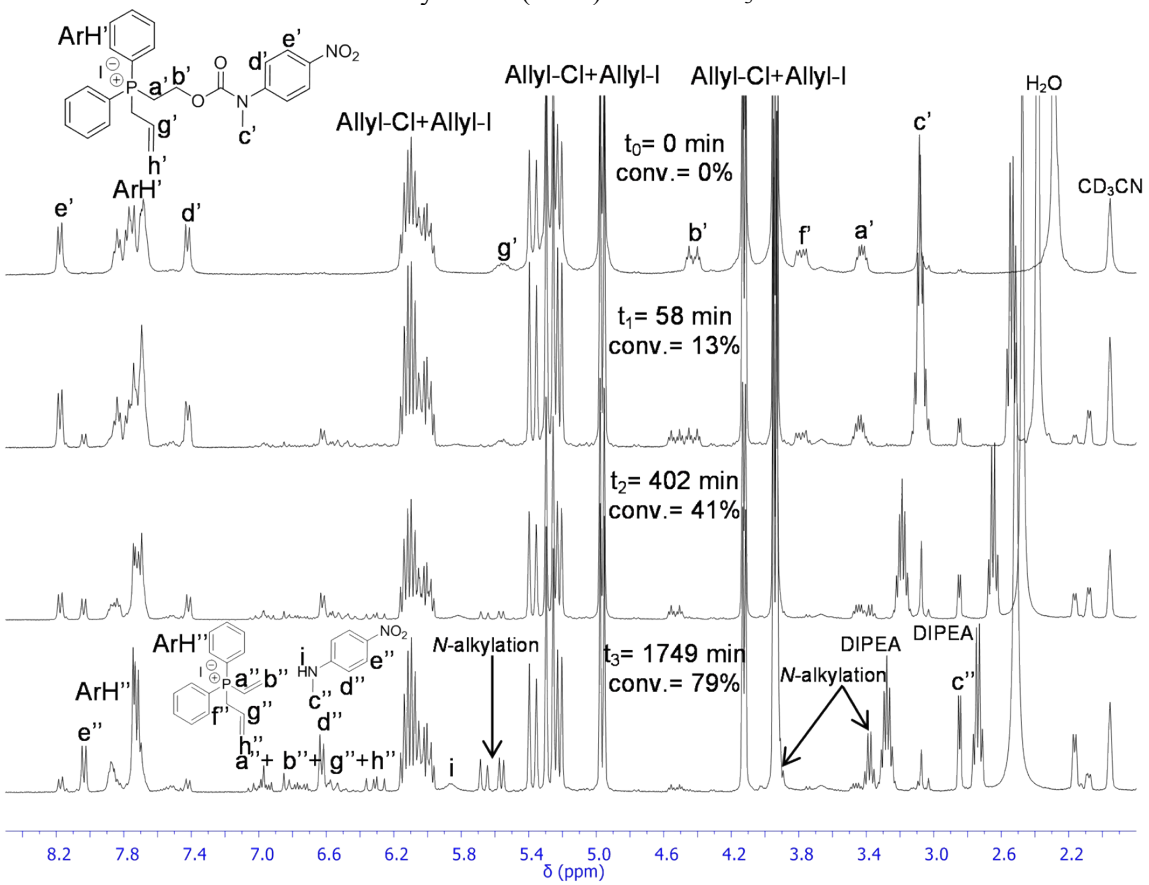


Fig. S19 ^{1}H NMR spectrum recorded overtime following the addition of DIPEA to a solution of alkylated **3** (Allyl-Cl) in MeCN-d_3

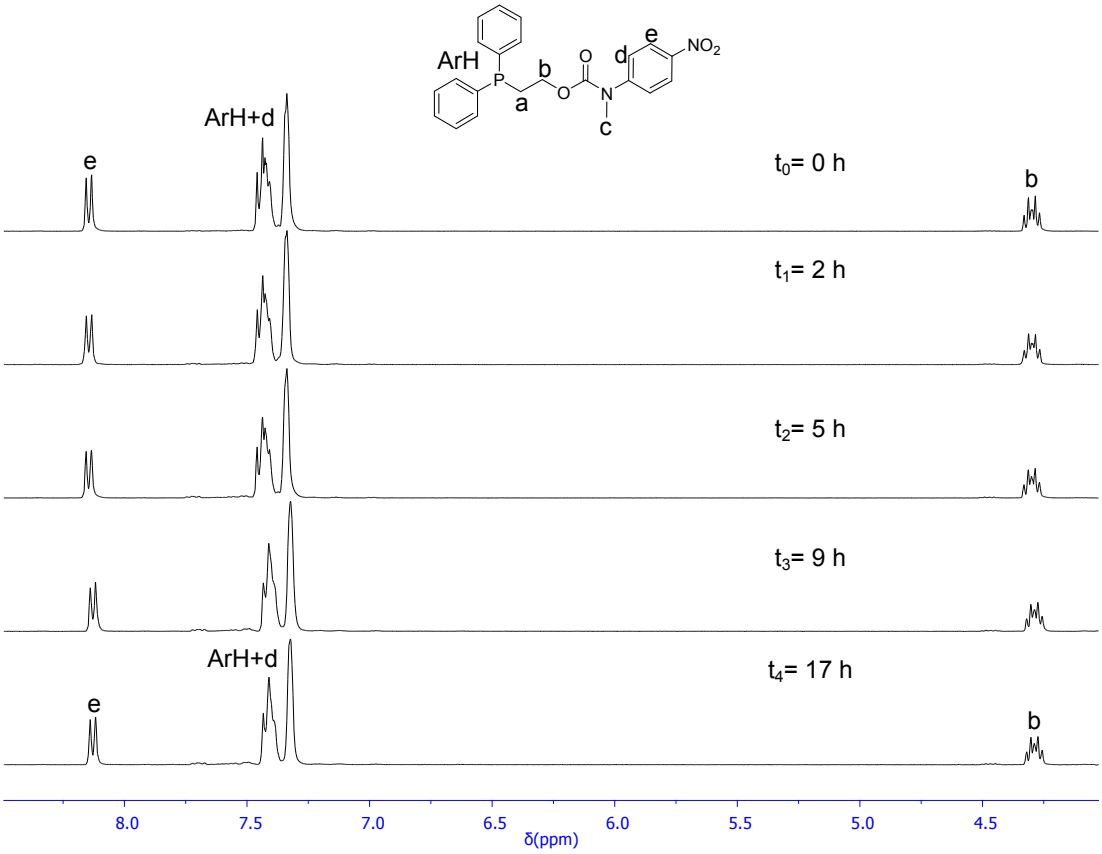


Fig. S20 ^{1}H NMR spectrum of **3** (MeCN-d_3 + 10 % D_2O) over time

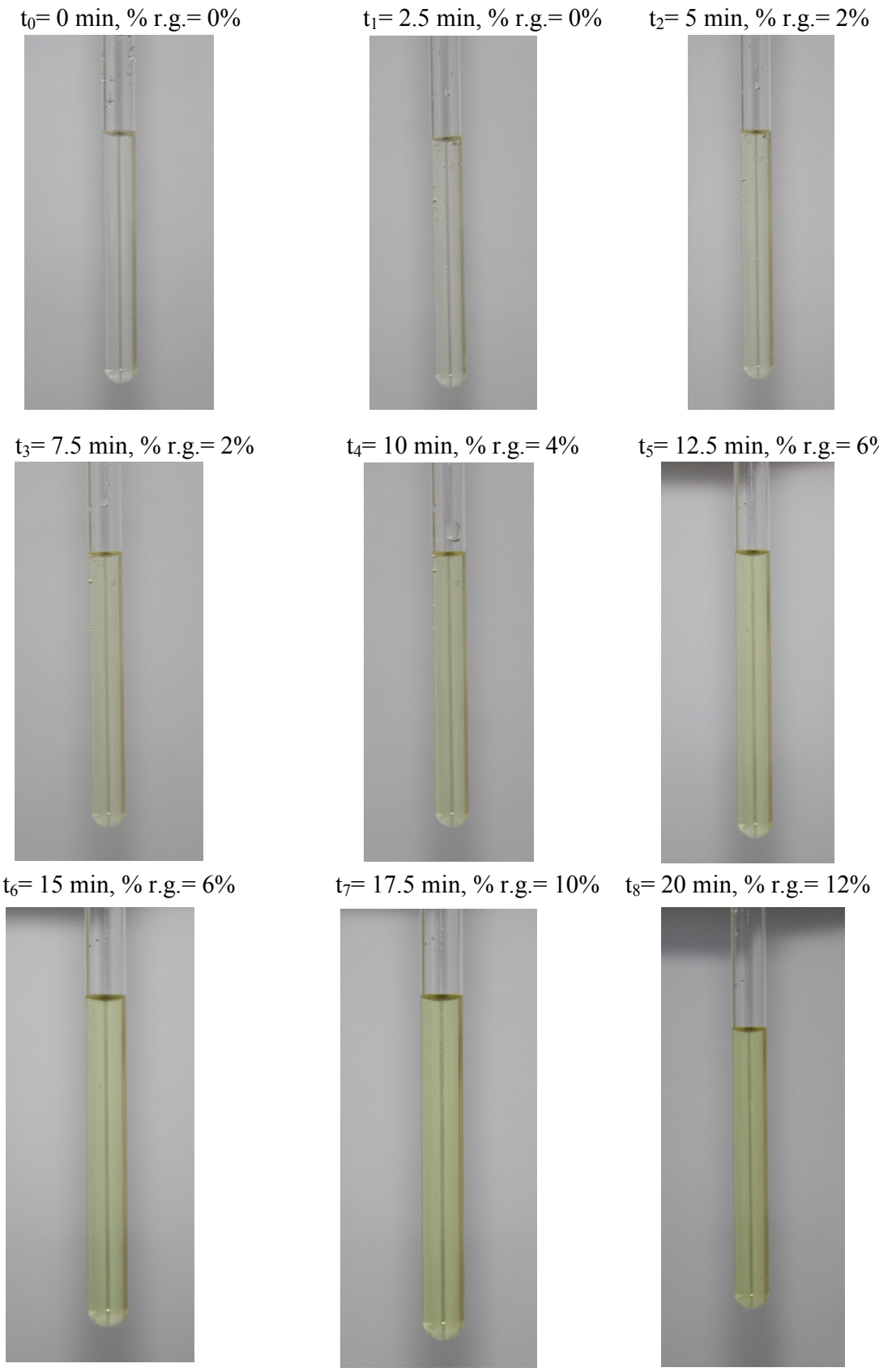


Fig. S21.1 Visualisation of yellow colour experiment for the "*one pot*" reaction following the addition of 10 equivalents of BnBr to a solution of **3** and 2 equivalents of DIPEA in MeCN-d_3 at 20 °C

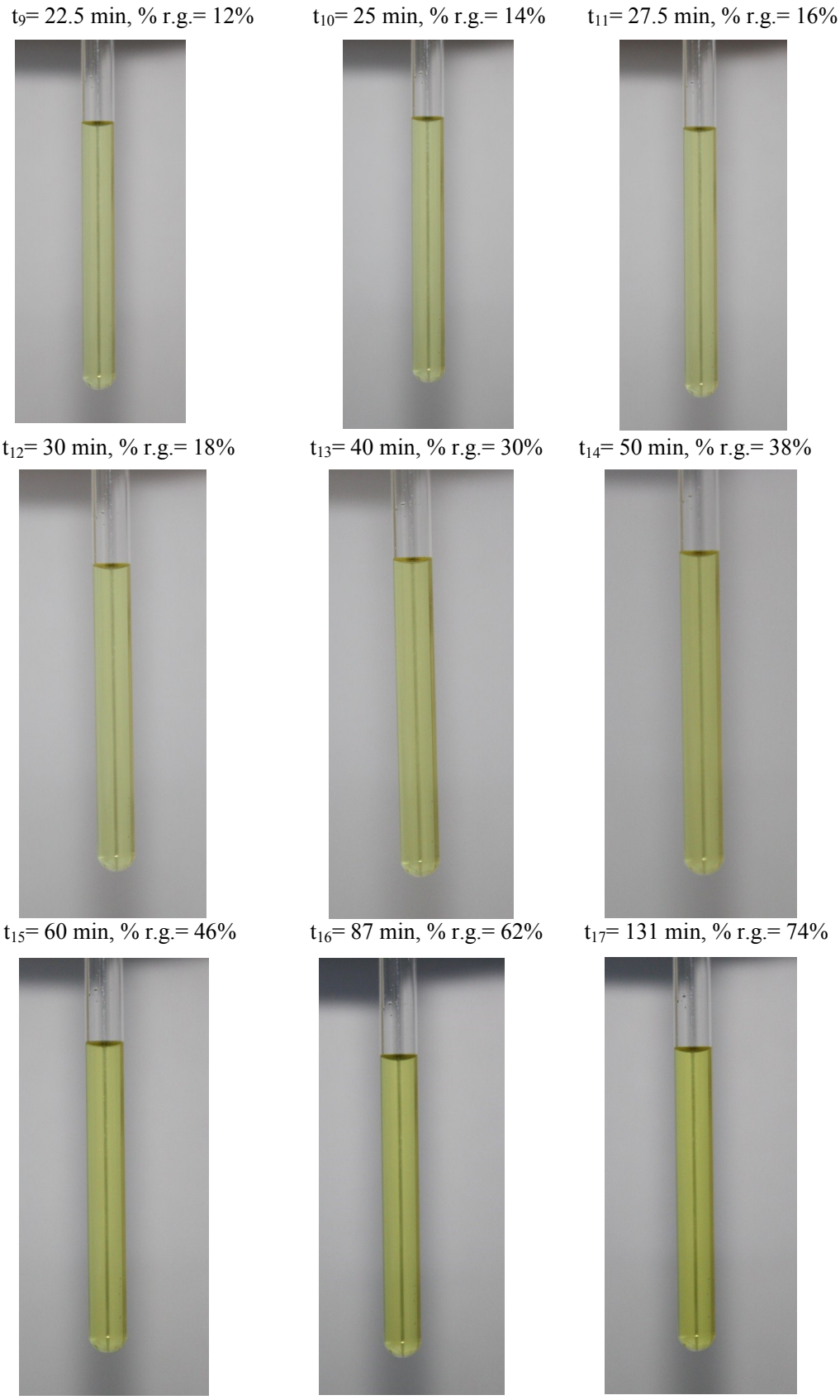


Fig. S21.2 Visualisation of yellow colour experiment for the "*one pot*" reaction following the addition of 10 equivalents of BnBr to a solution of **3** and 2 equivalents of DIPEA in MeCN-d_3 at 20 °C

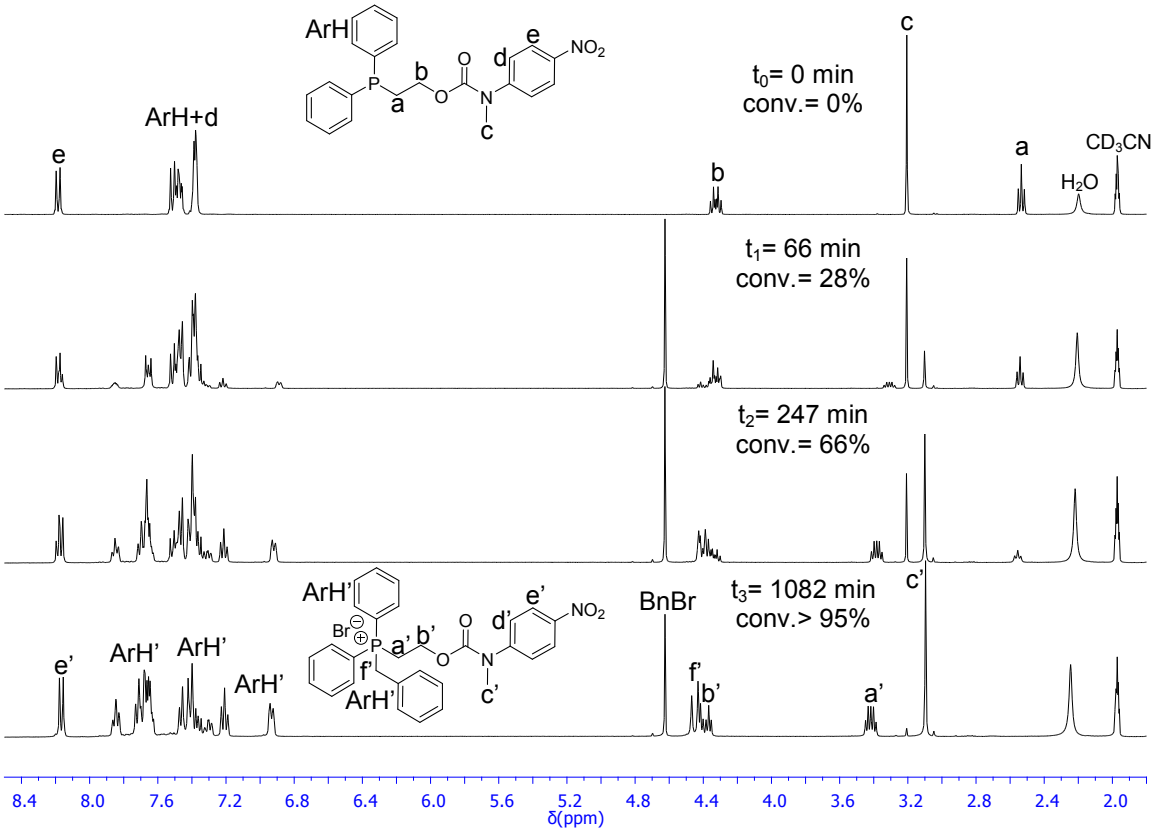
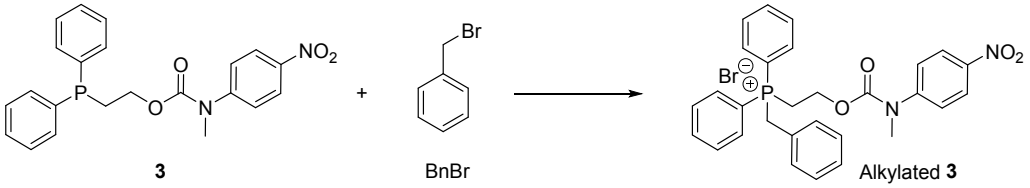


Fig. S22 ^{1}H NMR spectrum recorded overtime following the addition of 1.85 equivalents of BnBr to a solution of **3** in MeCN-d_3



Bimolecular SN_2 Type II reaction:

-Initial concentrations: $[\mathbf{3}]_0$; $[BnBr]_0$, with $\Delta = [BnBr]_0 - [\mathbf{3}]_0$.

-The difference between [BnBr] and [**3**] remains constant since **3** and BnBr are consumed at the same rate. Thus at any time: $[BnBr] = [\mathbf{3}] + \Delta$.

- Kinetic equation: *Equation 1*

$$\frac{d[\mathbf{3}]}{dt} = -k[\mathbf{3}]([\mathbf{3}]+\Delta) \qquad \text{with } [BnBr] = [\mathbf{3}]+\Delta$$

- After integration: *Equation 2*

$$[\mathbf{3}] = \frac{\Delta}{\frac{[BnBr]_0}{[\mathbf{3}]_0} \times e^{\Delta kt} - 1}$$

- Expression of [**3**] versus reaction time: *Equation 3*

$$kt = Ln\left[\frac{\Delta+[\mathbf{3}]}{\frac{[BnBr]_0}{[\mathbf{3}]_0} \times [\mathbf{3}]}\right] \times \frac{1}{\Delta}$$

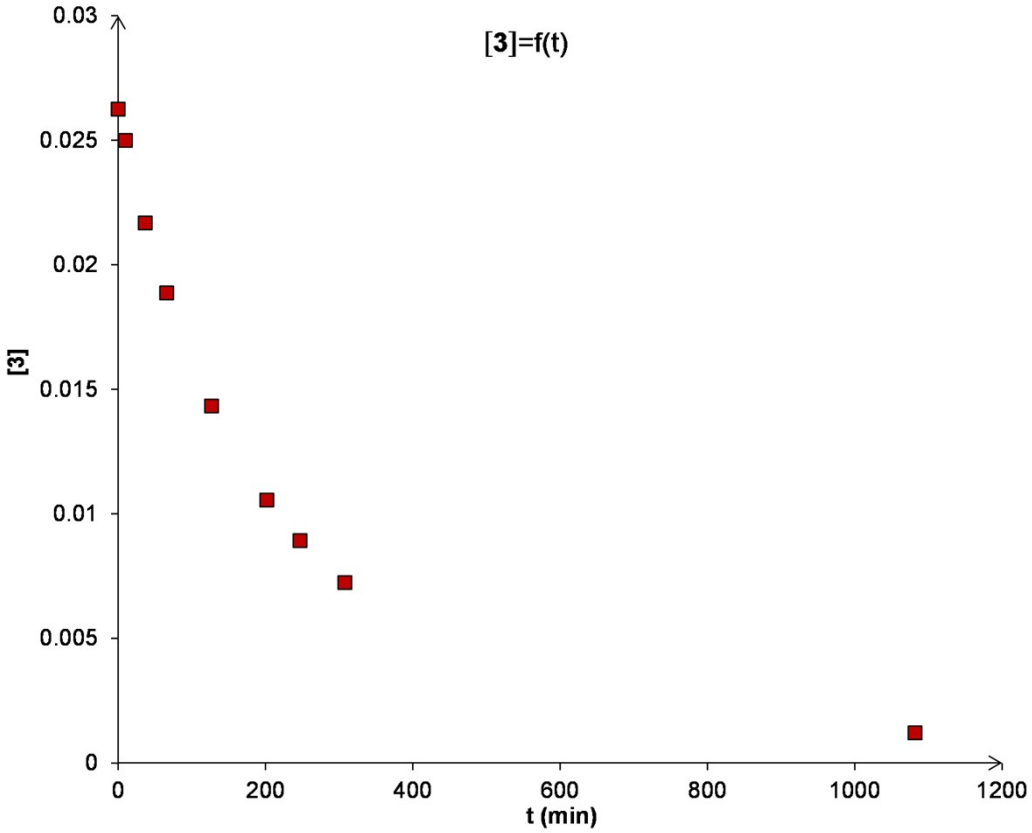


Fig. S23 Concentration of [**3**] versus reaction time for the alkylation of 2-(diphenylphosphino)ethyl methyl(4-nitrophenyl)carbamate **3** using 1.85 equivalents of BnBr in MeCN-d_3 at 20 °C

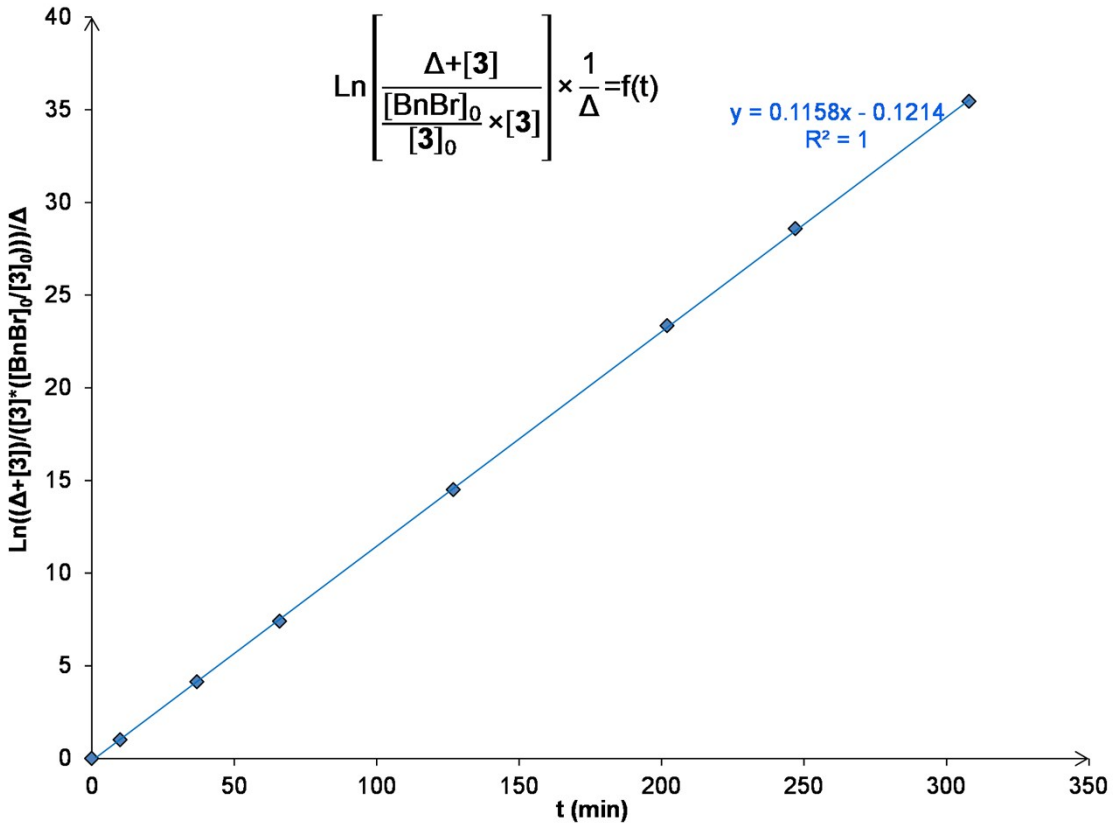


Fig. S24 Kinetic plot of kt = Ln[(Δ+[**3**])/([BnBr]$_0$/[**3**]$_0$×[**3**])]×(1/Δ) versus reaction time for the alkylation of 2-(diphenylphosphino)ethyl methyl(4-nitrophenyl)carbamate **3** using 1.85 equivalents of BnBr in MeCN-d_3 at 20 °C

Table. S1 Alkylation rate data obtained following the addition of 1.85 equivalents of BnBr to a solution of **3** in MeCN-d_3 at 20 °C calculated using ^{1}H NMR spectroscopy

$[BnBr]_0$ (mol.L^{-1})	$[\mathbf{3}]_0$ (mol.L^{-1})	Δ (mol.L^{-1})	k (L.mol^{-1}.min^{-1})	$t_{1/2}$ (min)
0.04625	0.025	0.02125	0.1158	144.9

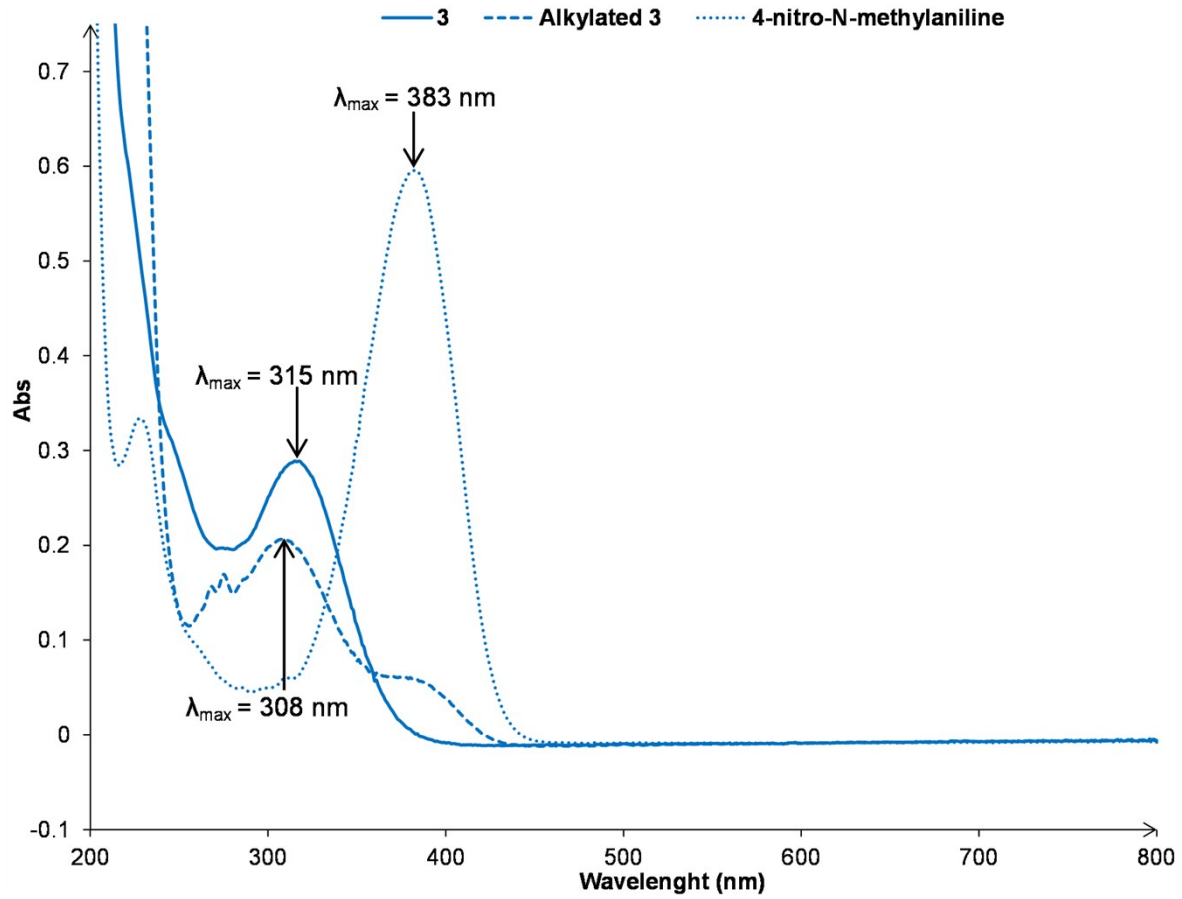


Fig. S25 UV-visible spectra of **3**, Alkylated **3** and the reporter group 4-nitro-*N*-methylaniline individually in MeCN at C = 2.64.10^{-5} mol.L^{-1}

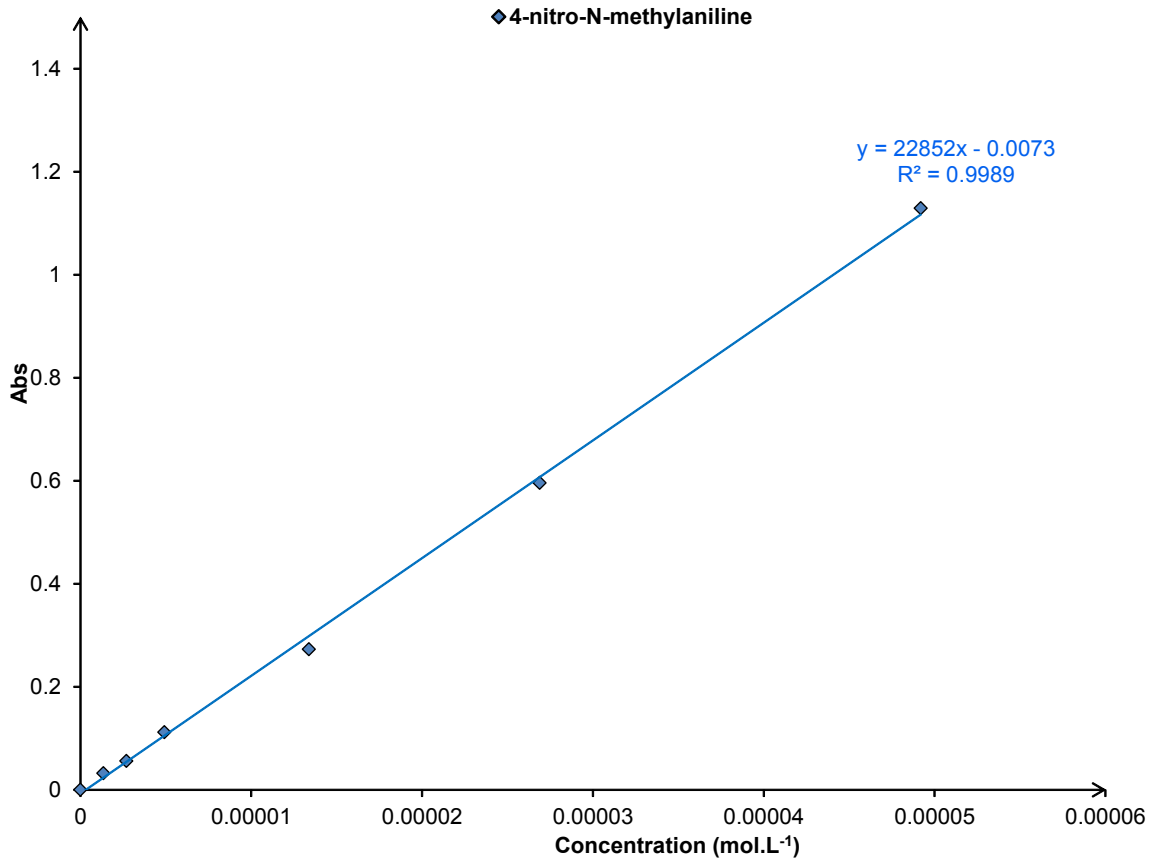


Fig. S26 UV spectroscopy calibration curve for the reporter group 4-nitro-*N*-methylaniline in MeCN

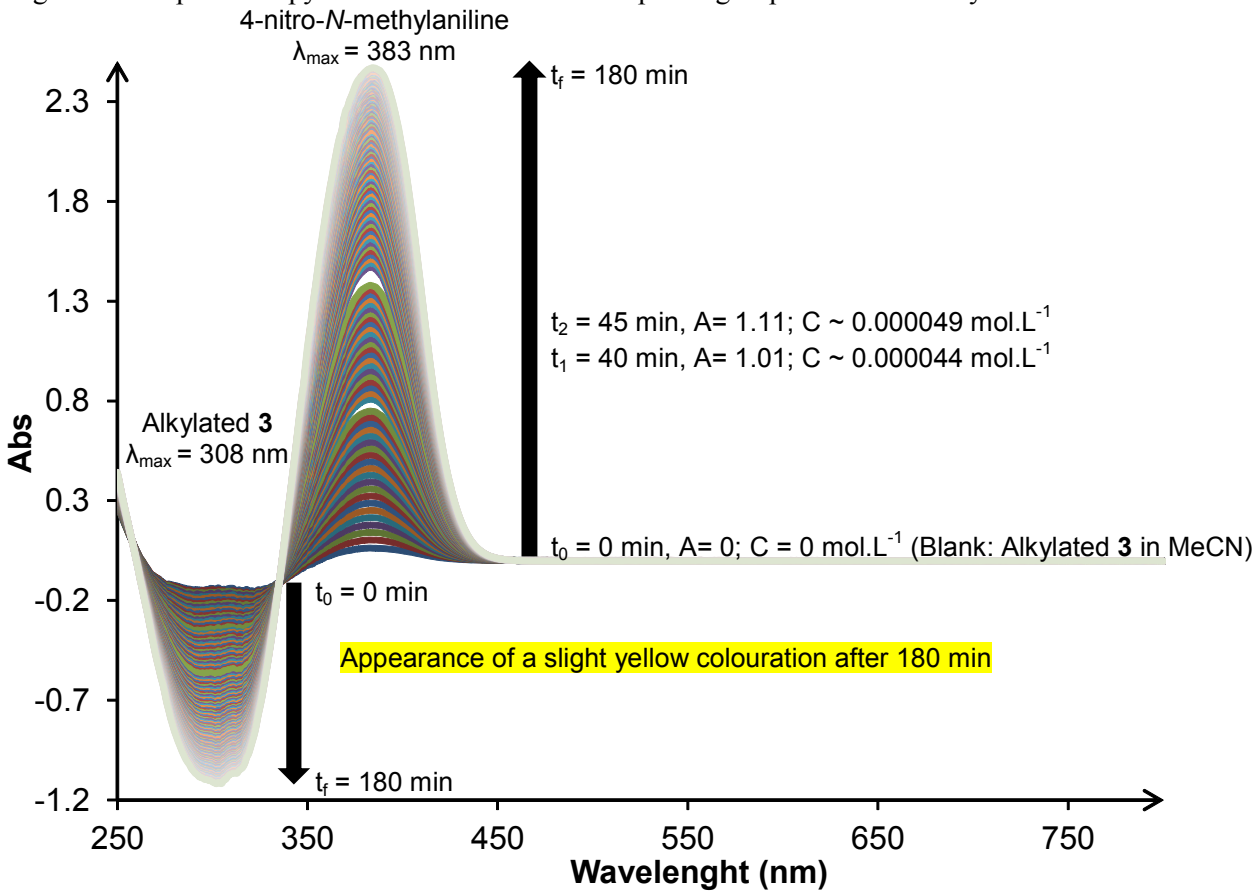


Fig. S27 UV-visible spectra displaying the release of 4-nitro-*N*-methylaniline from alkylated **3** in MeCN ([alkylated **3**]$_0$ = 2.5.10^{-4} mol.L^{-1}) upon the addition of 2 equivalent of DIPEA

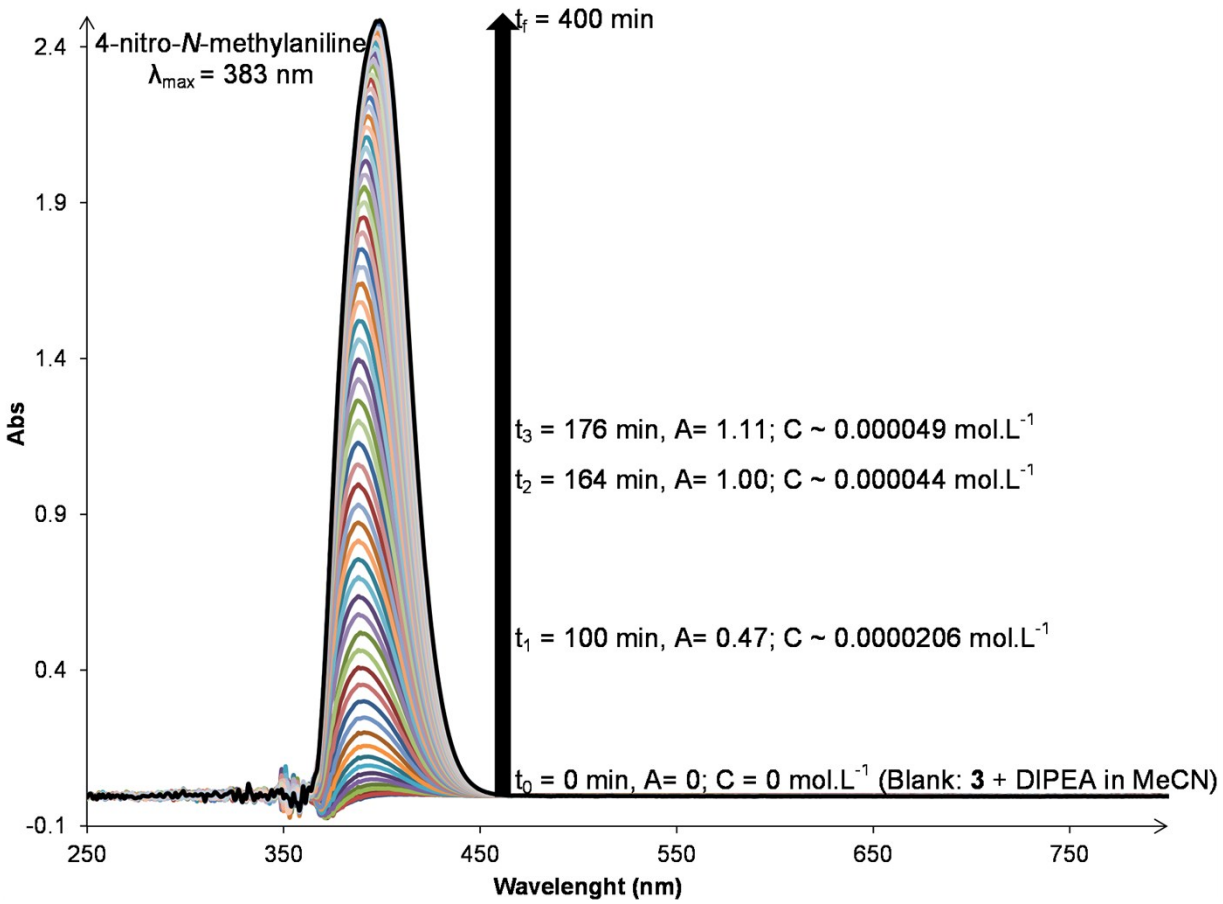


Fig. S28 UV-visible spectra displaying the release of 4-nitro-*N*-methylaniline following the addition of 1.85 equivalents of BnBr to a solution of **3** and 2 equivalents of DIPEA in MeCN ($[\mathbf{3}]_0 = 2.5.10^{-3}$ mol.L^{-1})

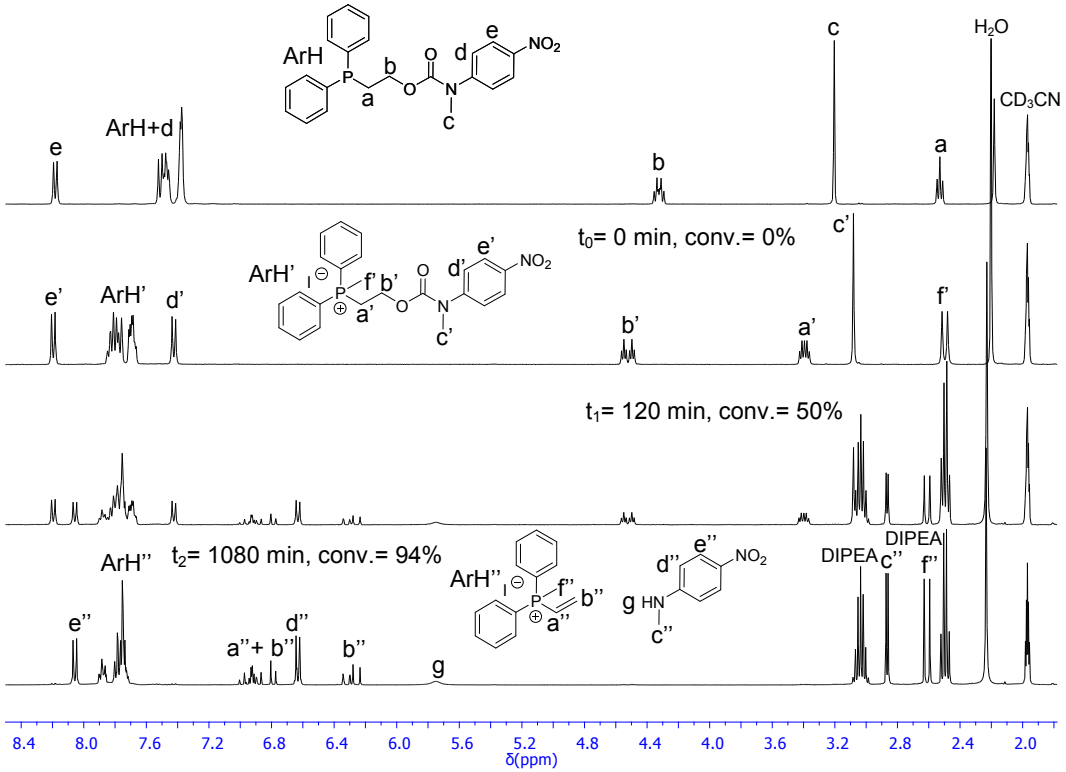


Fig. S29 ^{1}H NMR spectrum recorded overtime following the addition of DIPEA to a solution of alkylated **3** (MeI) in MeCN-d_3

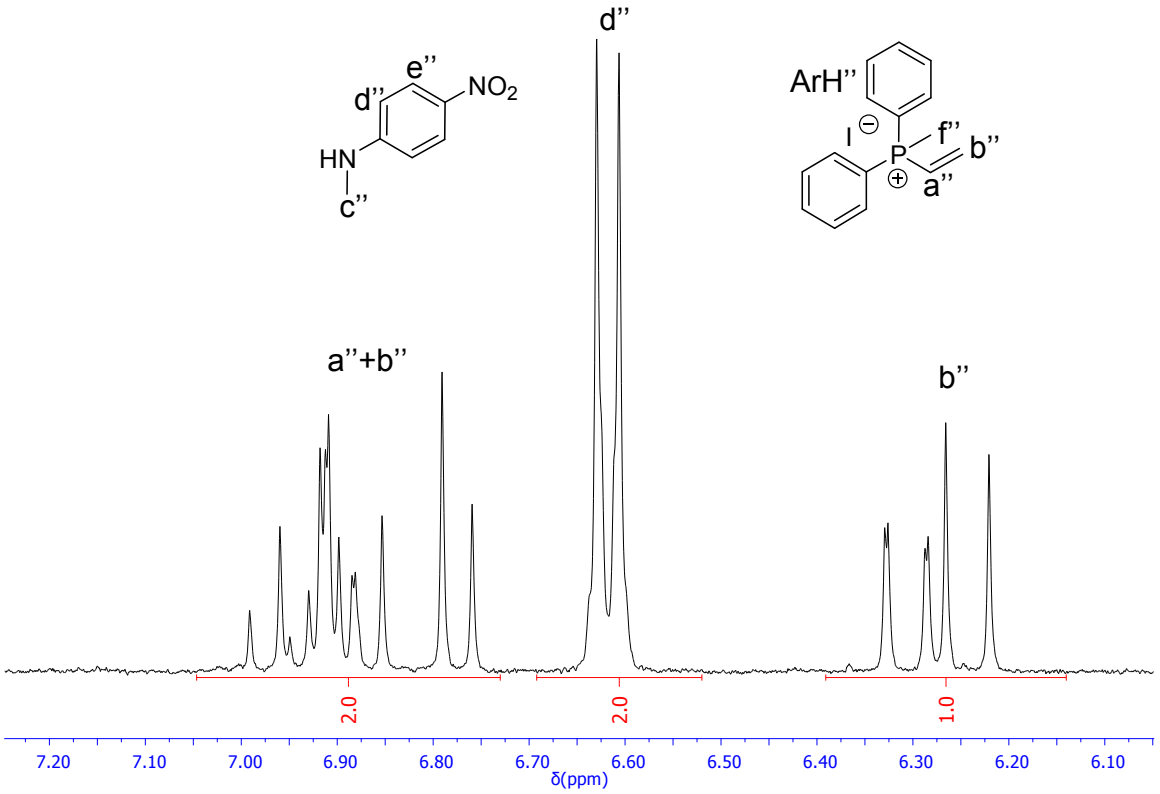


Fig. S30 Enlargement of the ^{1}H NMR spectrum recorded 1080 minutes following the addition of DIPEA to a solution of alkylated **3** (MeI) in MeCN-d_3

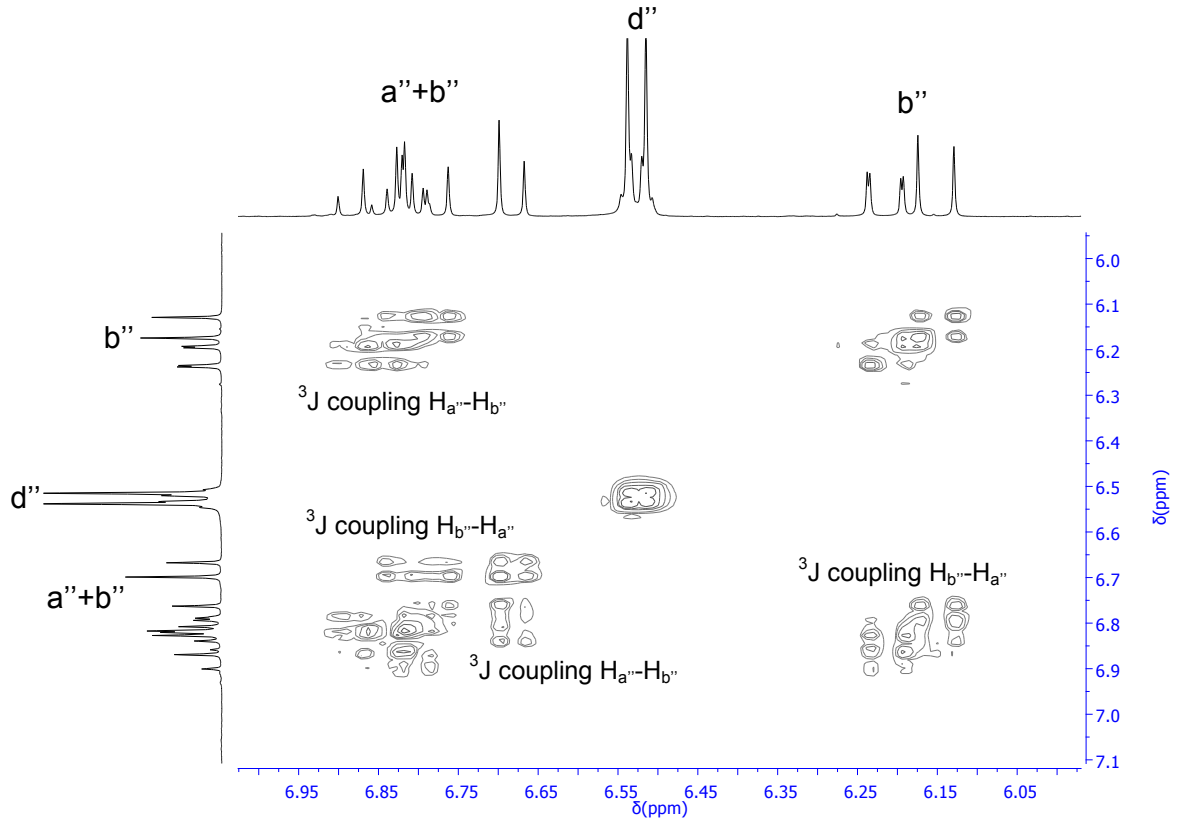


Fig. S31 COSY spectrum recorded 1080 minutes following the addition of DIPEA to a solution of alkylated **3** (MeI) in MeCN-d_3

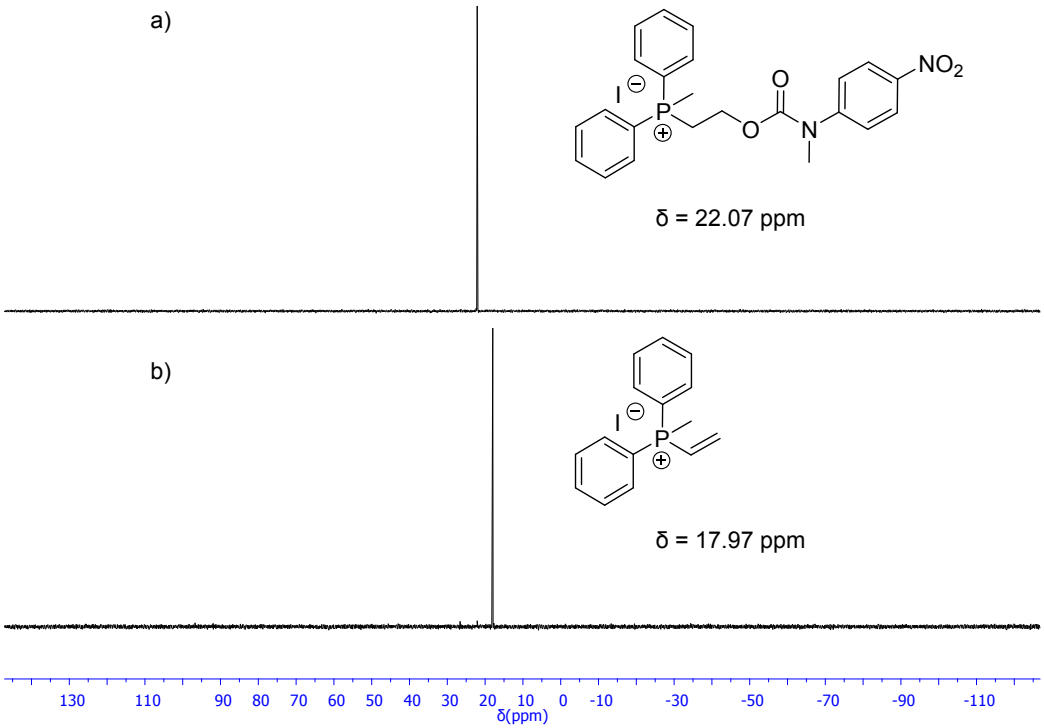


Fig. S32 ^{31}P NMR spectrum recorded in MeCN-d_3 a) before the addition of DIPEA to a solution of alkylated **3** (MeI) and b) 1080 minutes following the addition of DIPEA

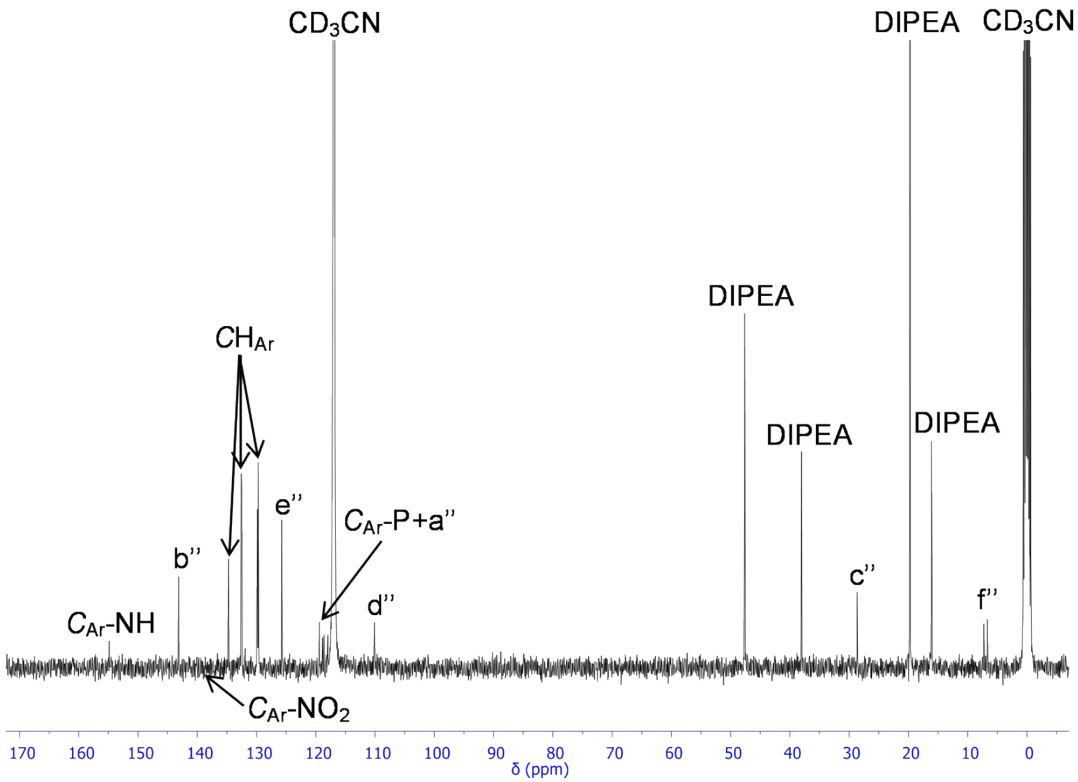


Fig. S33 ^{13}C NMR spectrum recorded 1080 minutes following the addition of DIPEA to a solution of alkylated **3** (MeI) in MeCN-d_3

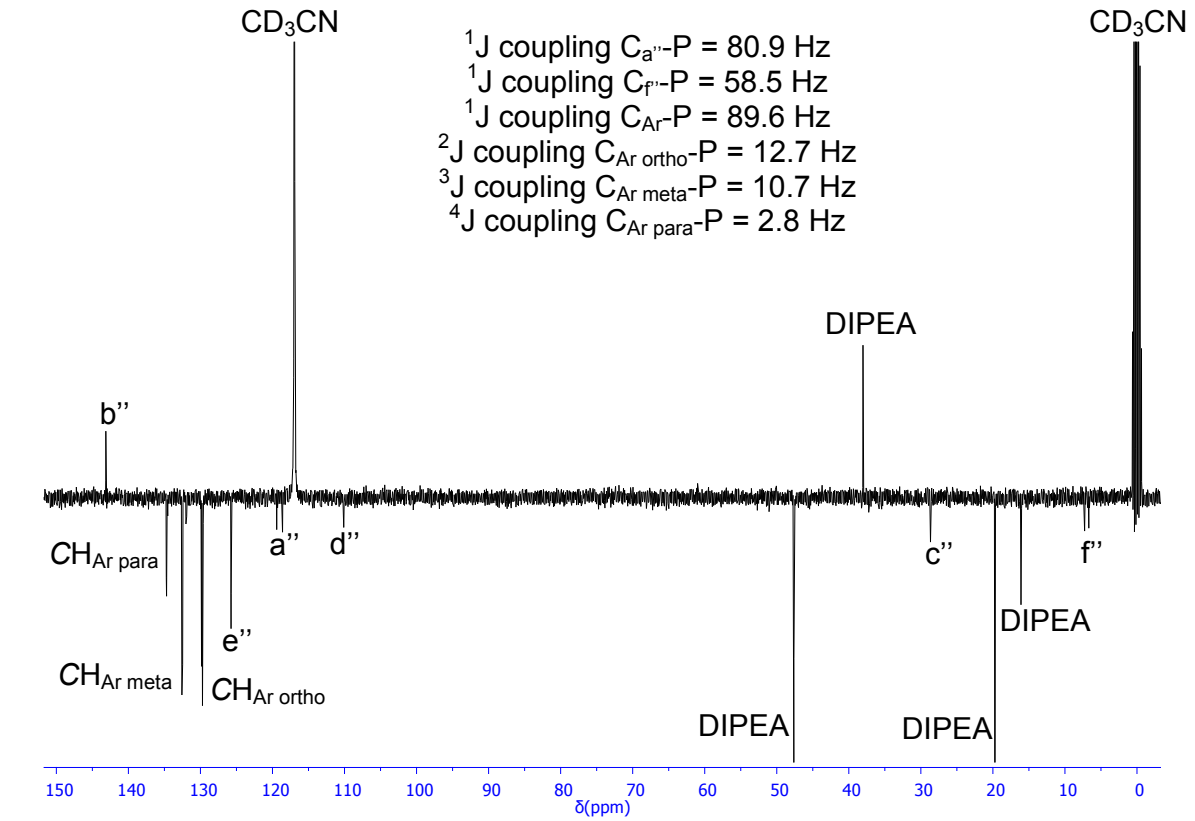


Fig. S34 DEPT-135 spectrum recorded 1080 minutes following the addition of DIPEA to a solution of alkylated **3** (MeI) in MeCN-d_3

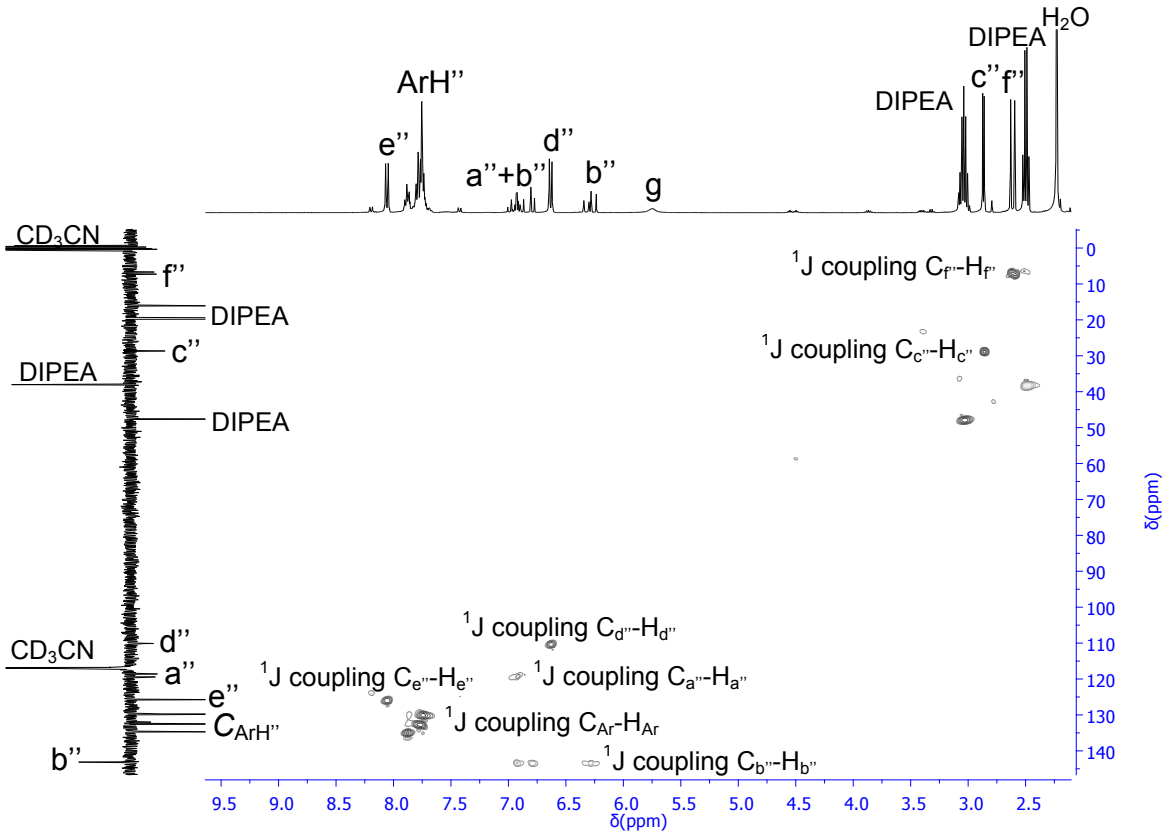


Fig. S35 HSQC spectrum recorded 1080 minutes following the addition of DIPEA to a solution of alkylated **3** (MeI) in MeCN-d_3

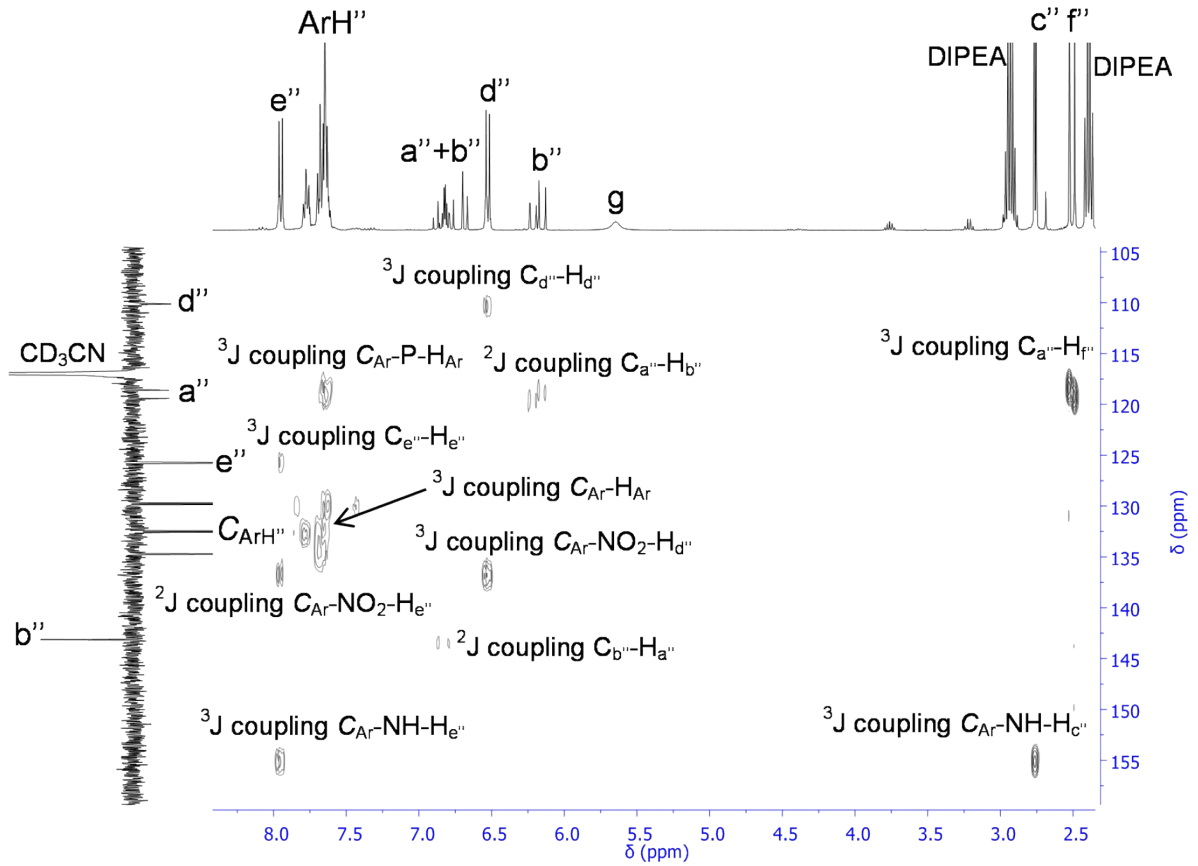


Fig. S36 HMBC spectrum recorded 1080 minutes following the addition of DIPEA to a solution of alkylated **3** (MeI) in MeCN-d_3

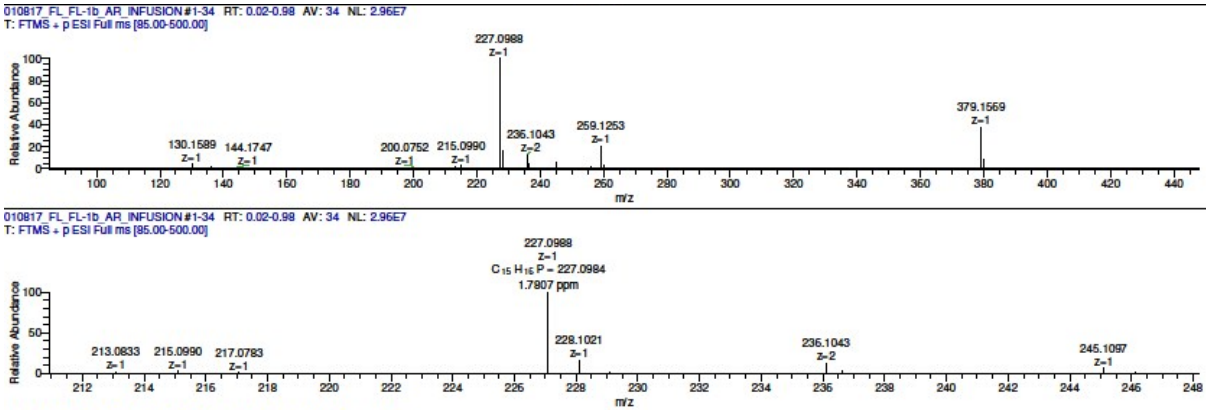


Fig. S37 HR-MS spectrum recorded 1080 minutes following the addition of DIPEA to a solution of alkylated **3** (MeI) in MeCN-d_3

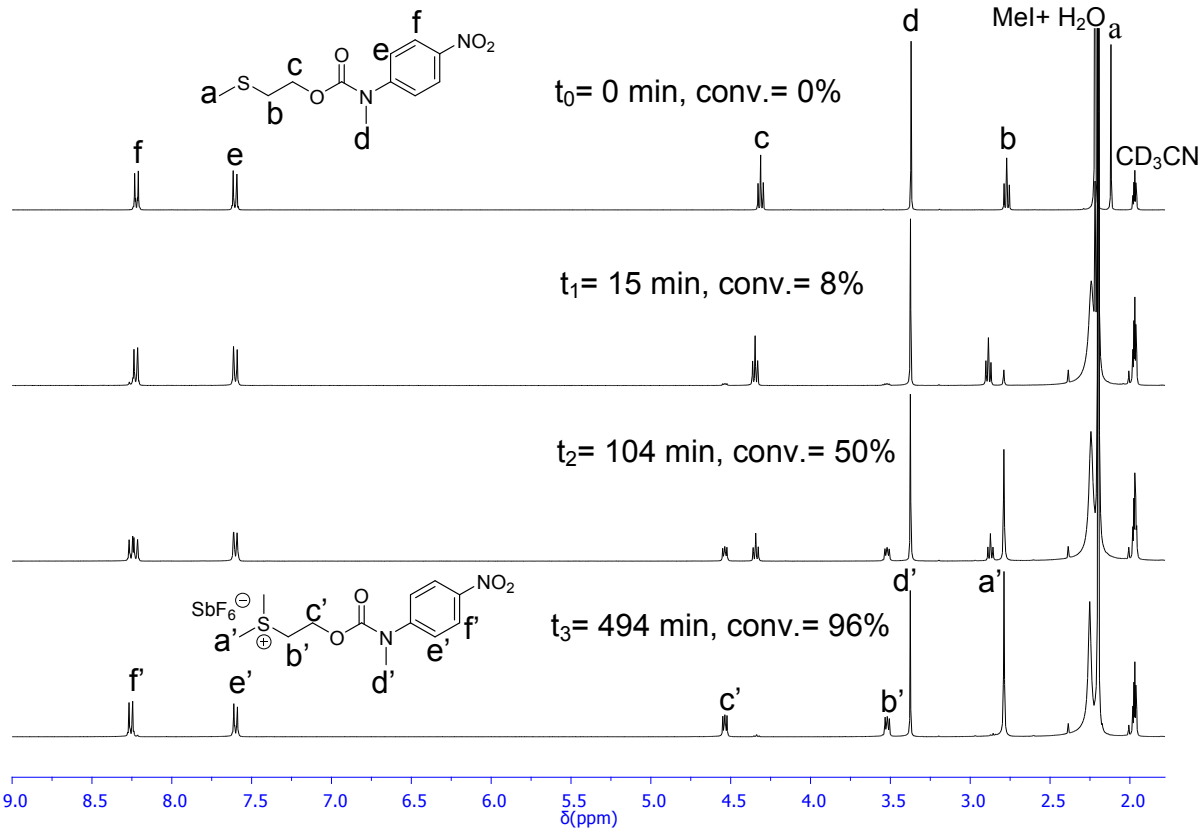


Fig. S38 ^{1}H NMR spectrum recorded overtime following the addition of 10 equivalents of MeI to a solution of **1** and 1.5 equivalent of $AgSbF_6$ in MeCN-d_3

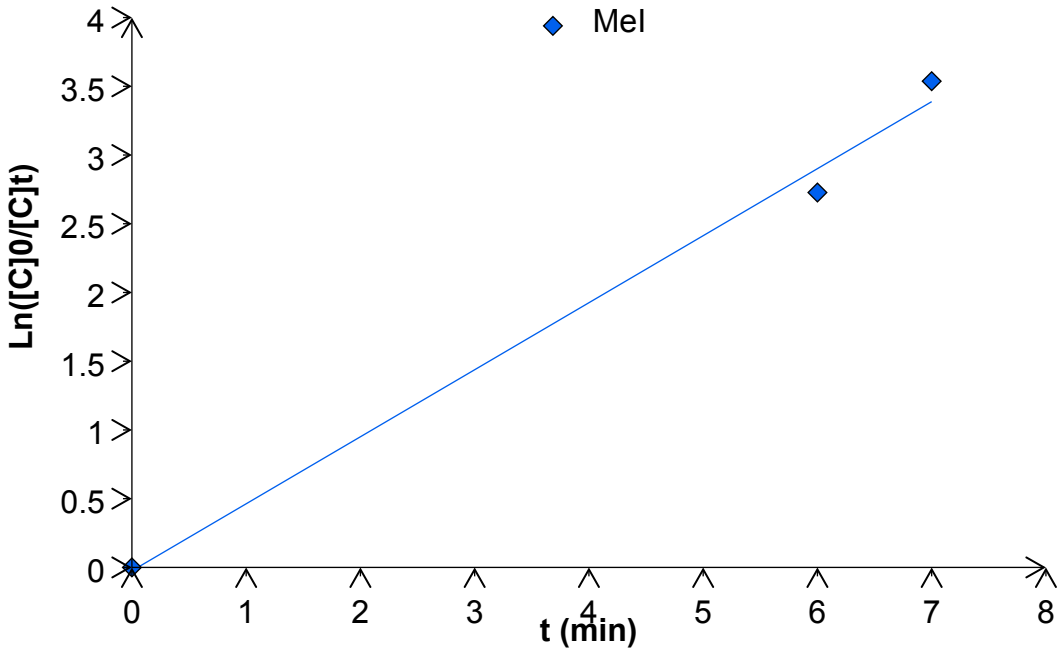


Fig. S39 Kinetic plot of $\ln([C]_0/[C]_t)$ versus reaction time for the alkylation 2-(dimethylamino)ethyl methyl(4-nitrophenyl)carbamate **2** using 10 equivalents of MeI in MeCN-d_3 at 20 °C

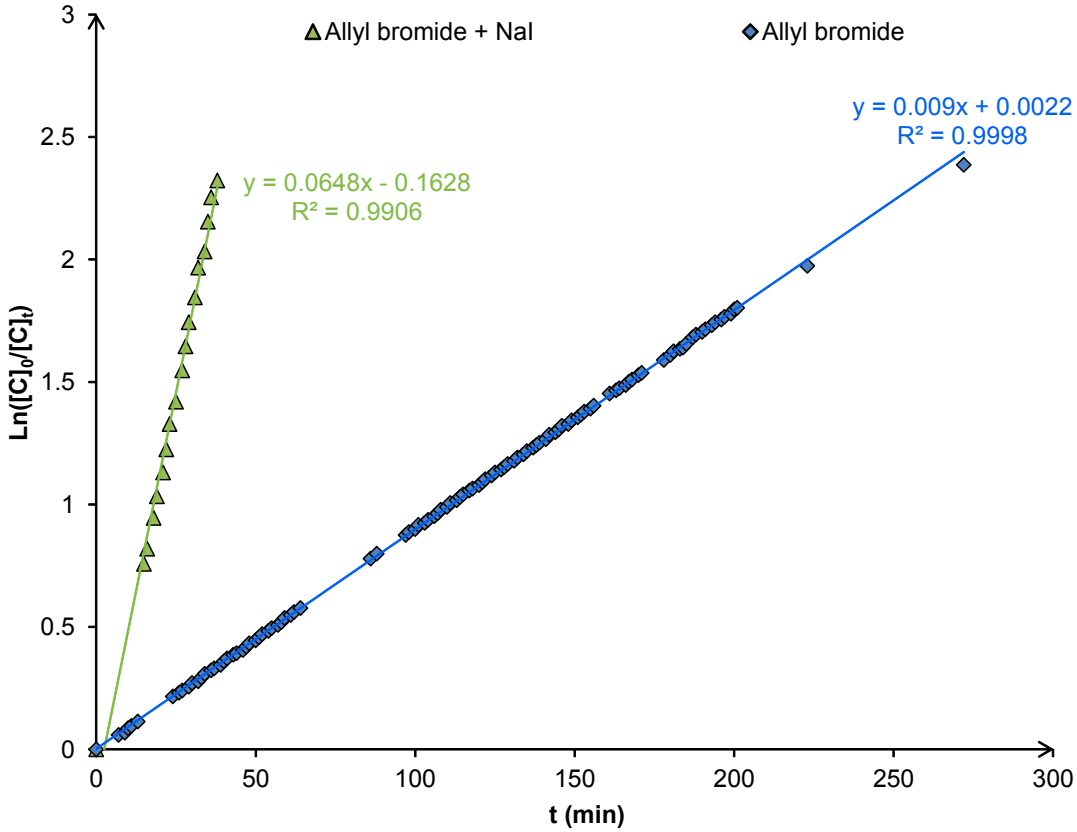


Fig. S40 Kinetic plot of $\ln([C]_0/[C]_t)$ versus reaction time for the alkylation of 2-(diphenylphosphino)ethyl methyl(4-nitrophenyl)carbamate **3** using 10 equivalents of Allyl-Br in MeCN-d_3 at 20 °C

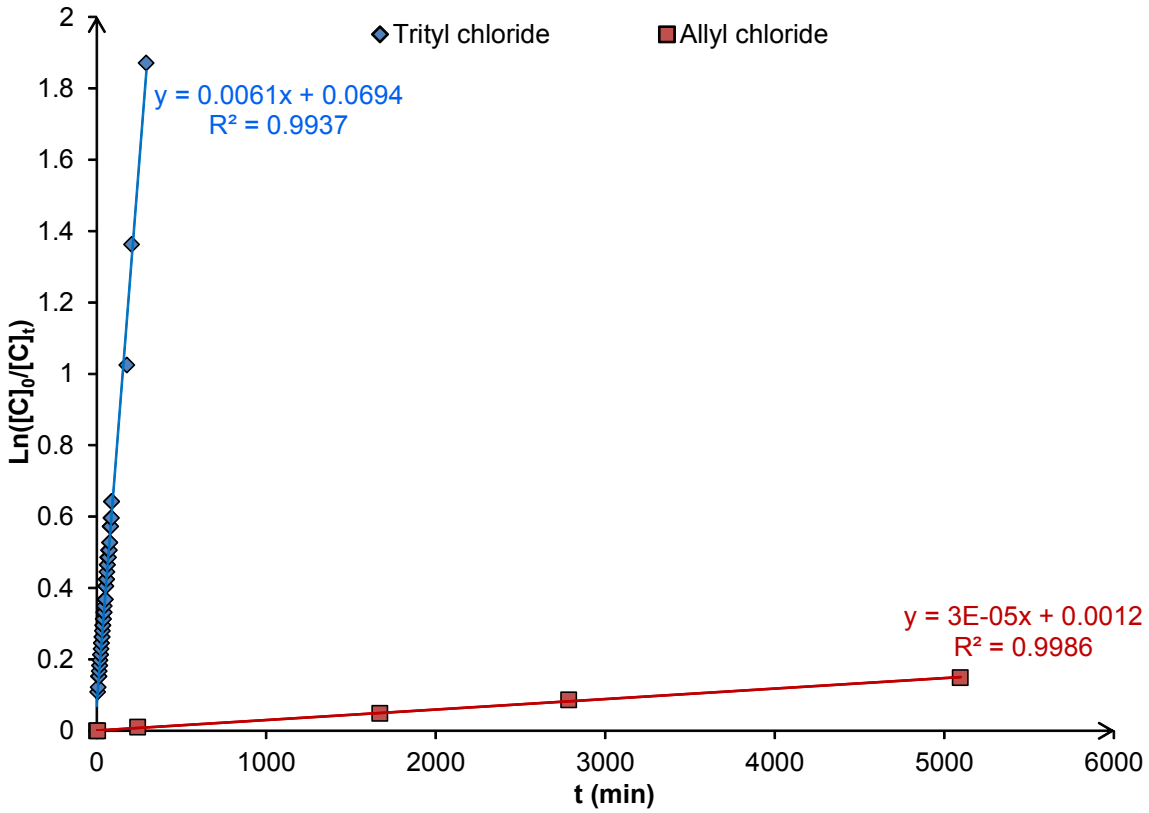


Fig. S41 Kinetic plot of $\ln([C]_0/[C]_t)$ versus reaction time for the alkylation of 2-(diphenylphosphino)ethyl methyl(4-nitrophenyl)carbamate **3** using 10 equivalents of alkylating agents Trityl chloride or Allyl-Cl in MeCN-d_3 at 20 °C

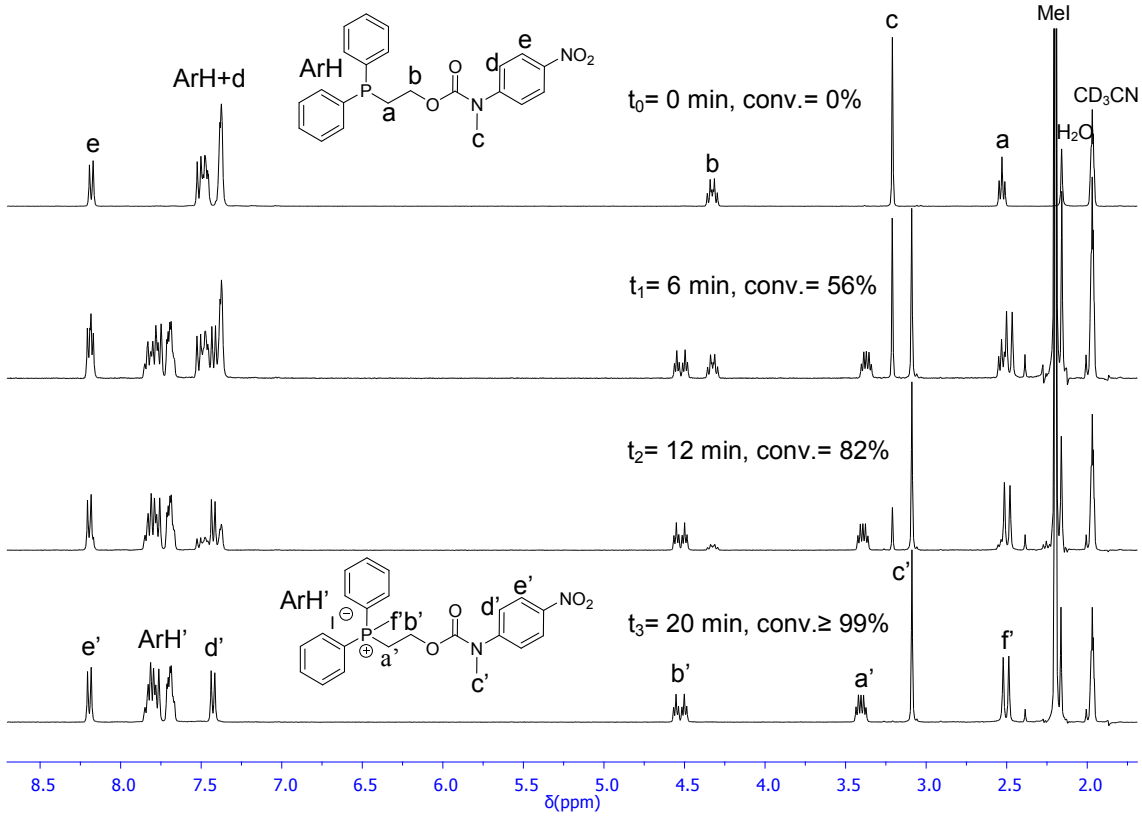


Fig. S42 ^{1}H NMR spectrum recorded overtime following the addition of 10 equivalents of MeI to a solution of **3** in MeCN-d_3

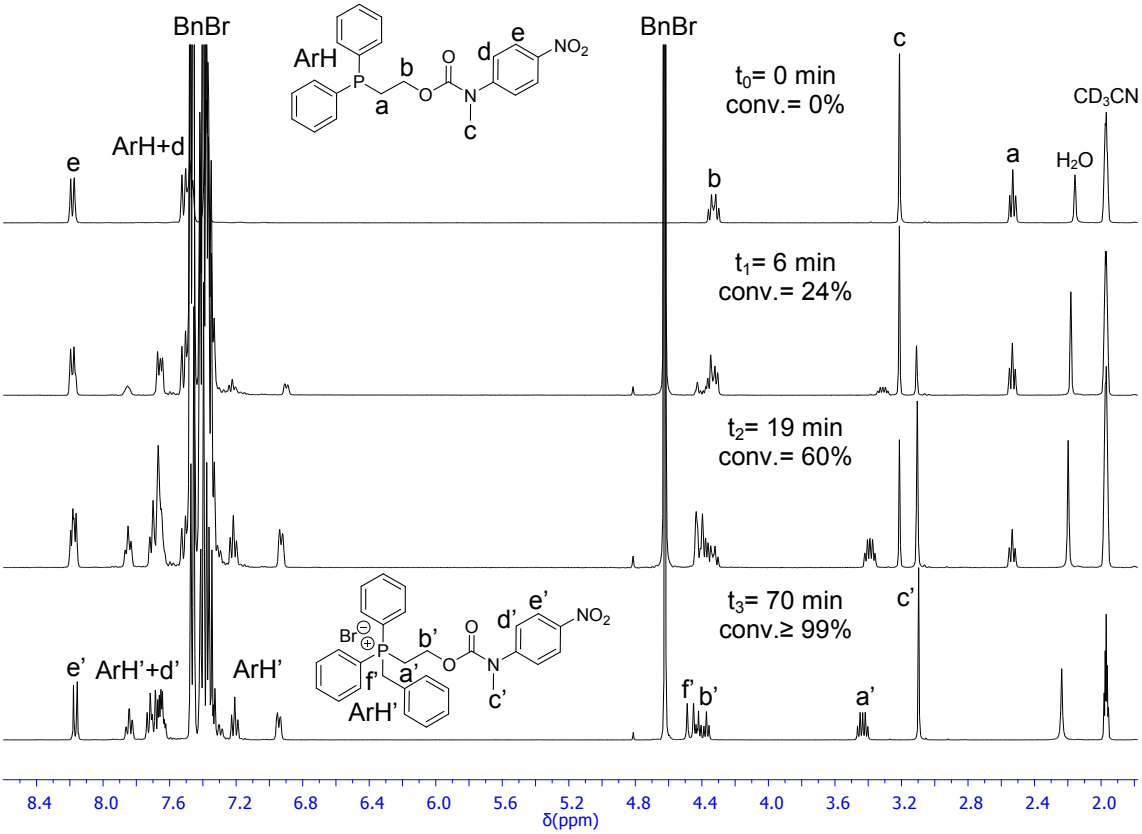


Fig. S43 ^{1}H NMR spectrum recorded overtime following the addition of 10 equivalents of BnBr to a solution of **3** in MeCN-d_3

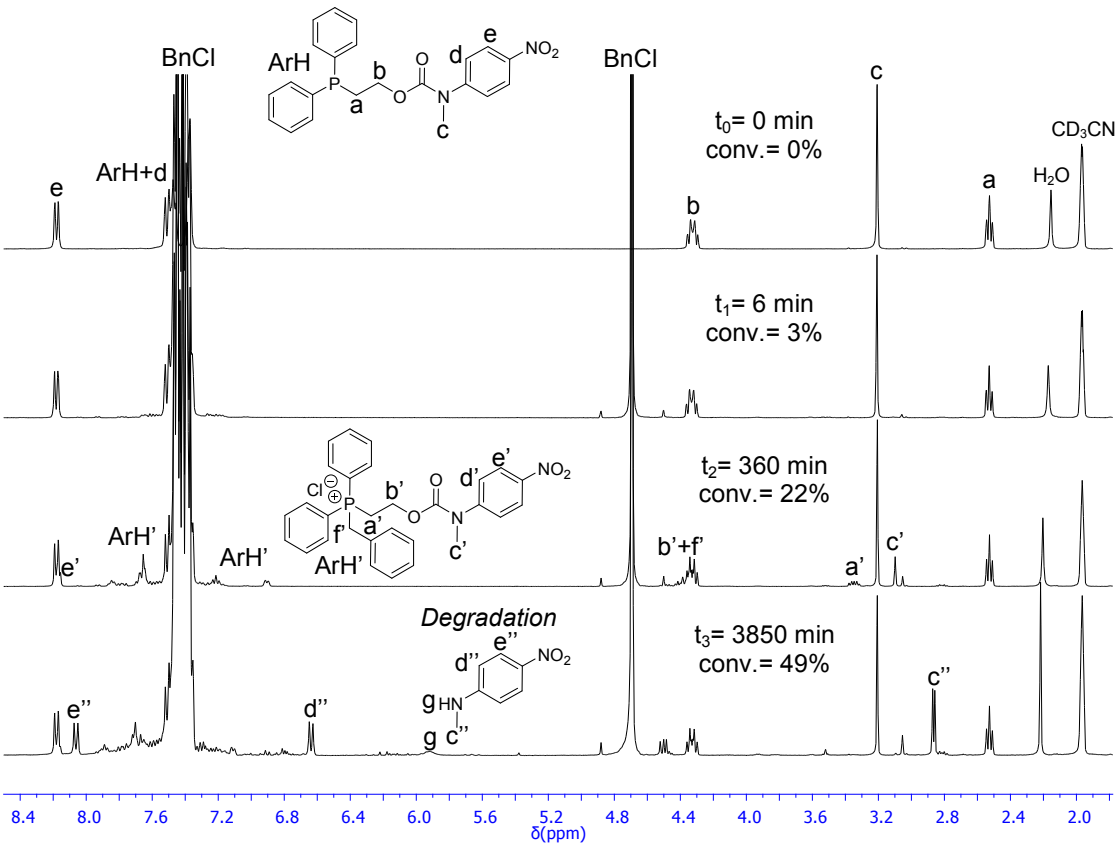


Fig. S44 ^{1}H NMR spectrum recorded overtime following the addition of 10 equivalents of BnCl to a solution of **3** in MeCN-d_3

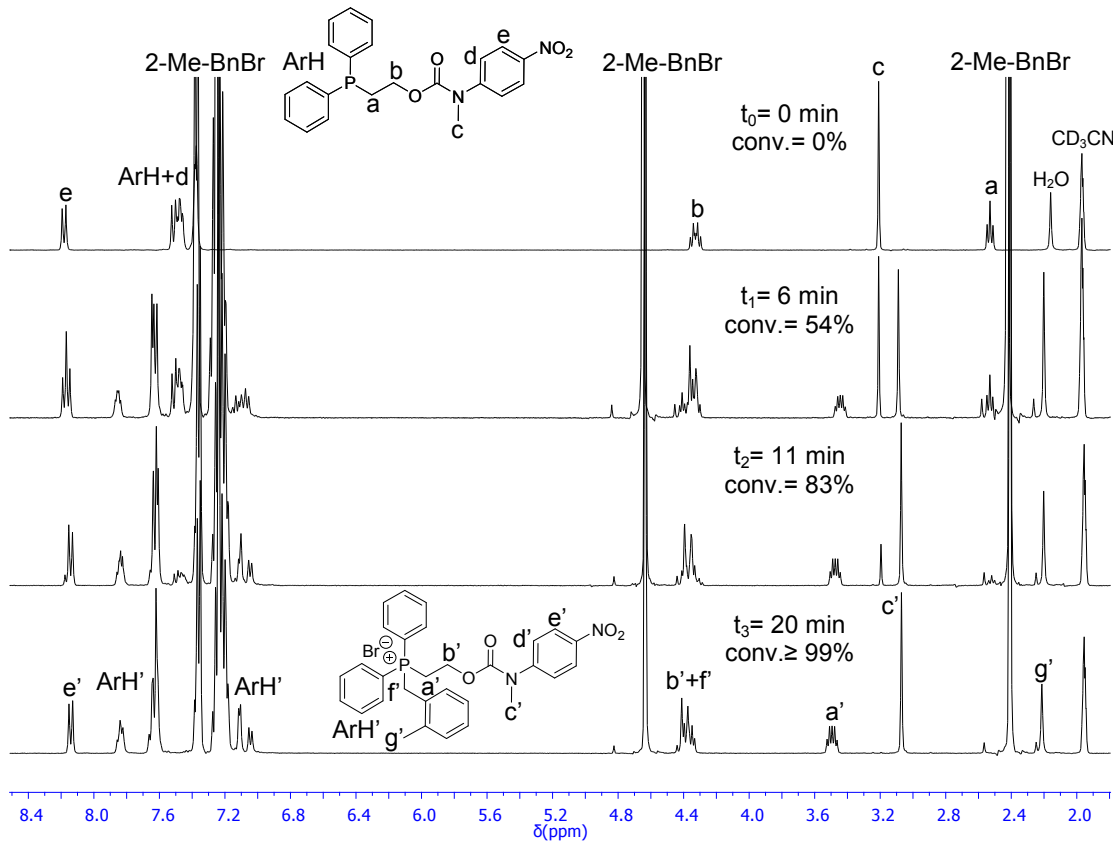


Fig. S45 ^{1}H NMR spectrum recorded overtime following the addition of 10 equivalents of 2-Me-BnBr to a solution of **3** in MeCN-d_3

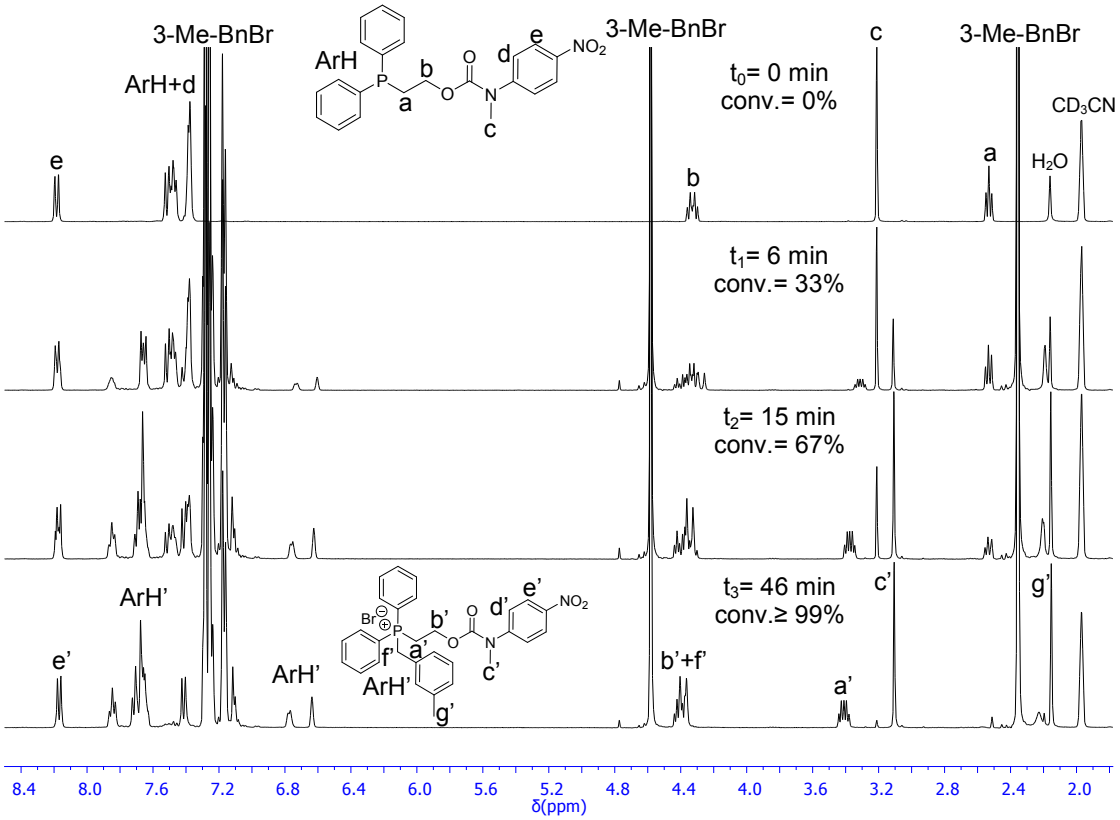


Fig. S46 ^{1}H NMR spectrum recorded overtime following the addition of 10 equivalents of 3-Me-BnBr to a solution of **3** in MeCN-d_3

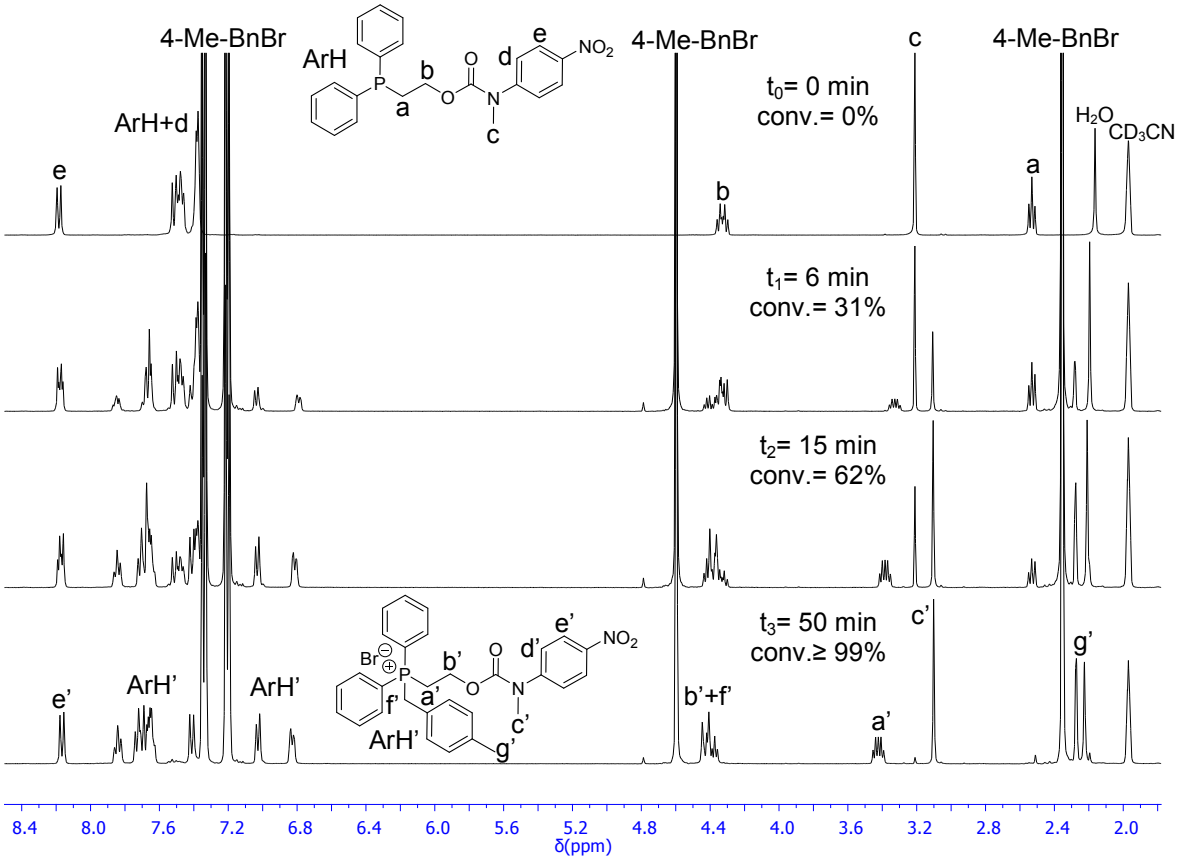


Fig. S47 ^{1}H NMR spectrum recorded overtime following the addition of 10 equivalents of 4-Me-BnBr to a solution of **3** in MeCN-d_3

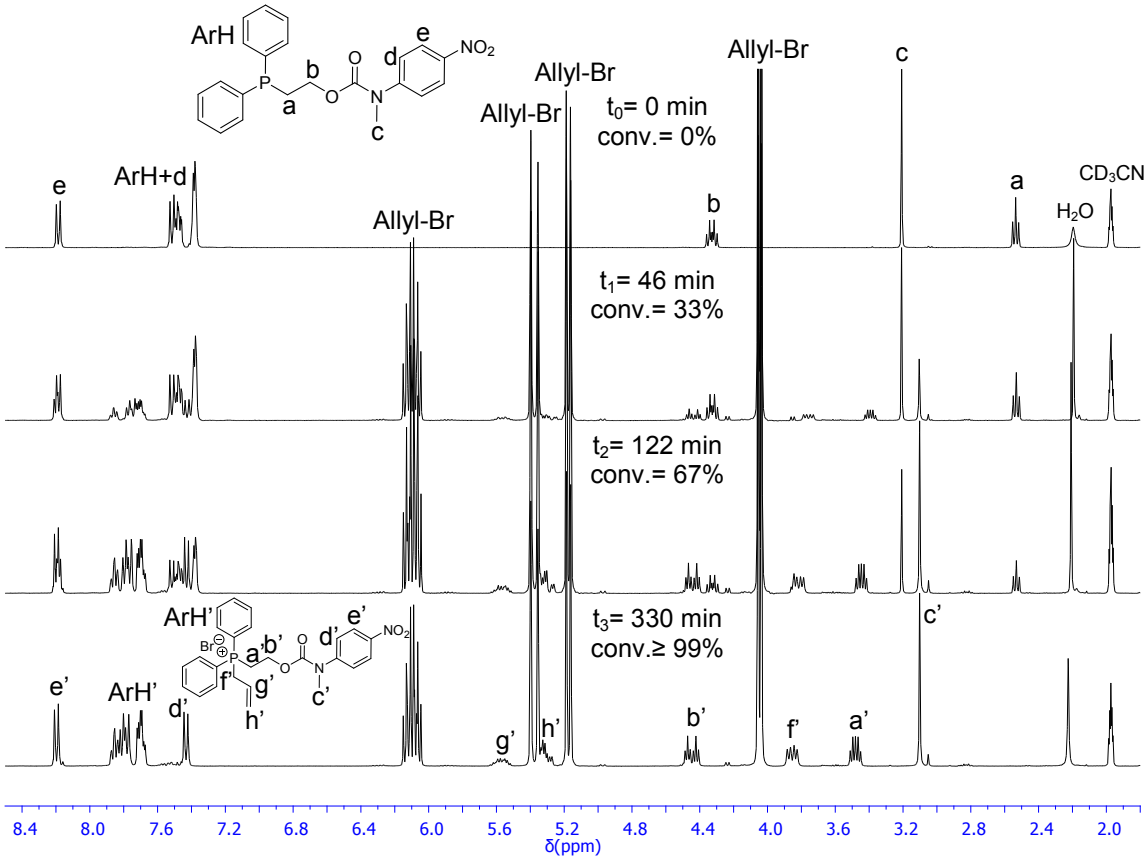


Fig. S48 ^{1}H NMR spectrum recorded overtime following the addition of 10 equivalents of Allyl-Br to a solution of **3** in MeCN-d_3

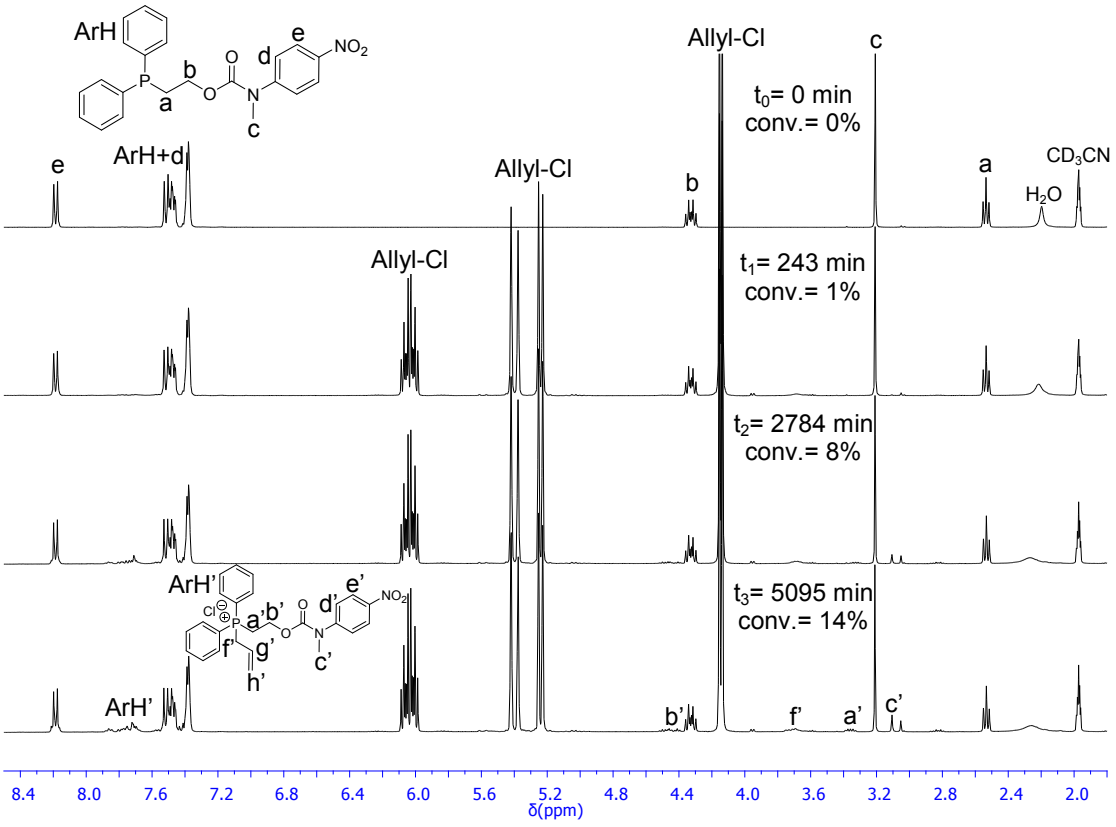


Fig. S49 ^{1}H NMR spectrum recorded overtime following the addition of 10 equivalents of Allyl-Cl to a solution of **3** in MeCN-d_3

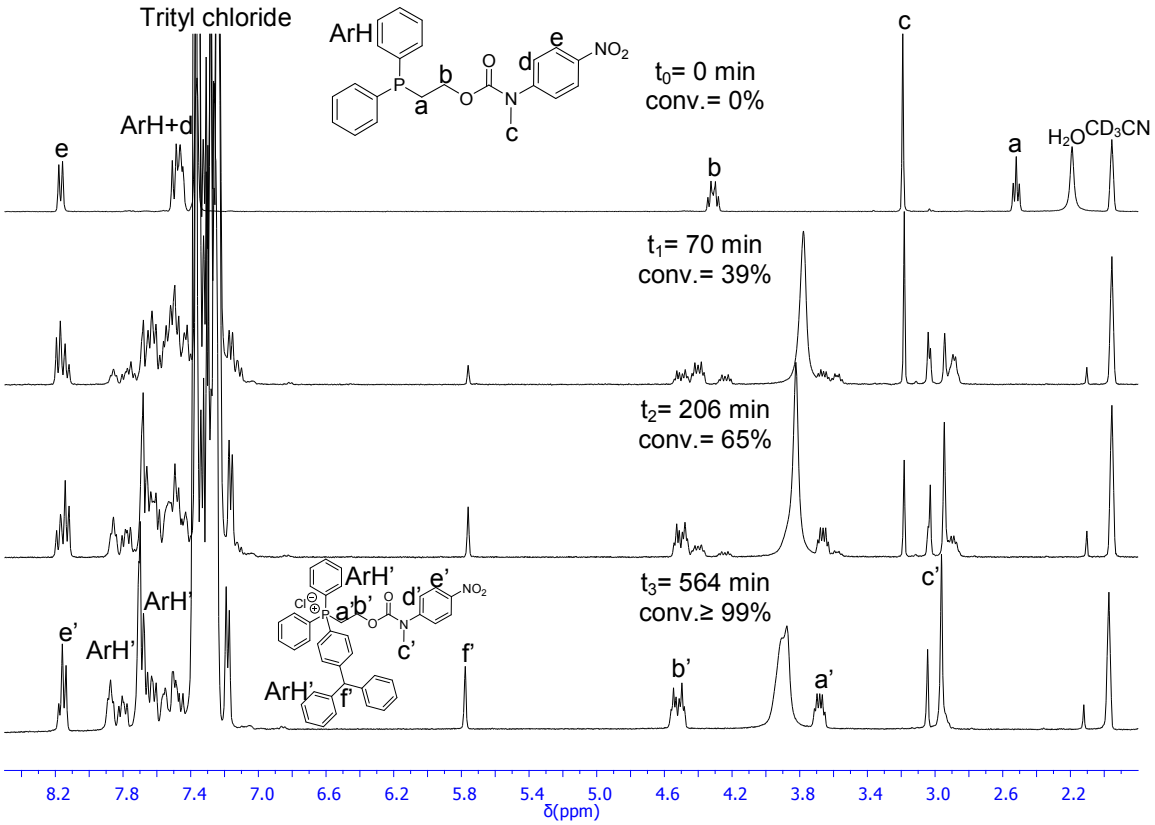


Fig. S50 ^{1}H NMR spectrum recorded overtime following the addition of 10 equivalents of Trityl chloride to a solution of **3** in MeCN-d_3

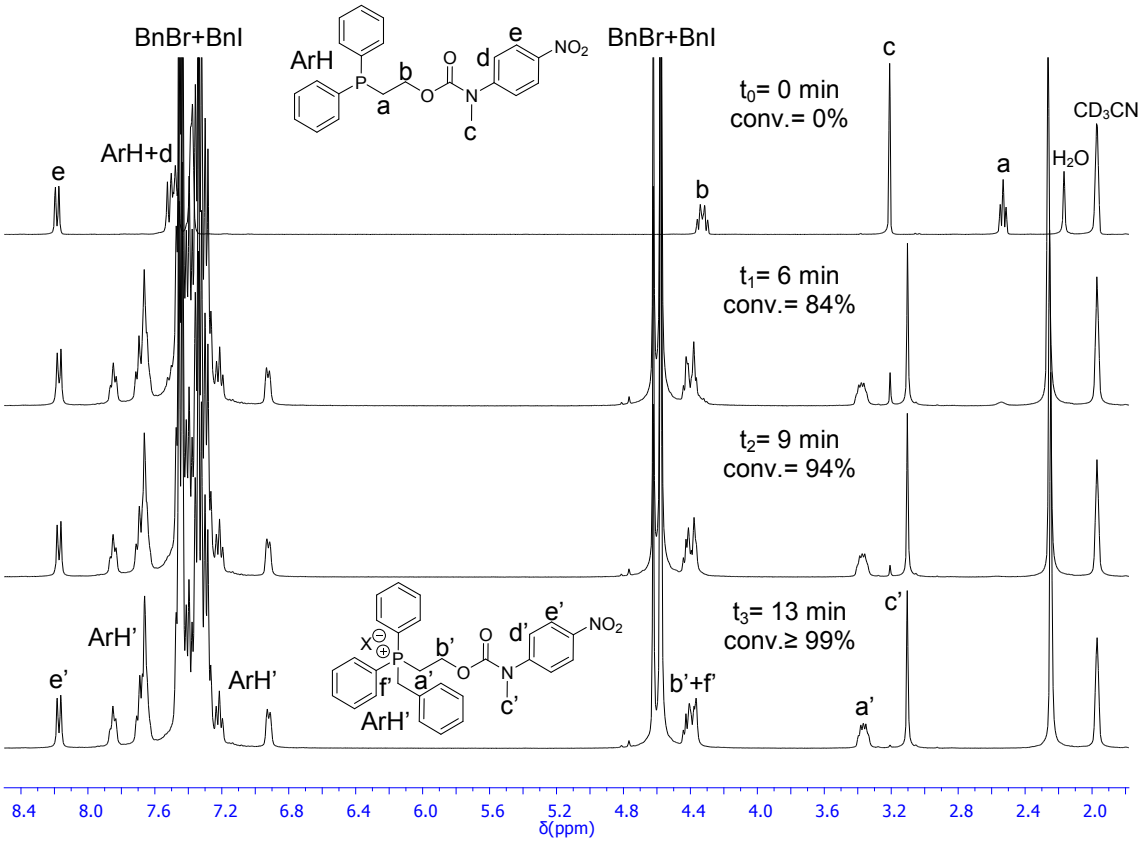


Fig. S51 ^{1}H NMR spectrum recorded overtime following the addition of 10 equivalents of BnBr and 10 equivalents of NaI to a solution of **3** in MeCN-d_3

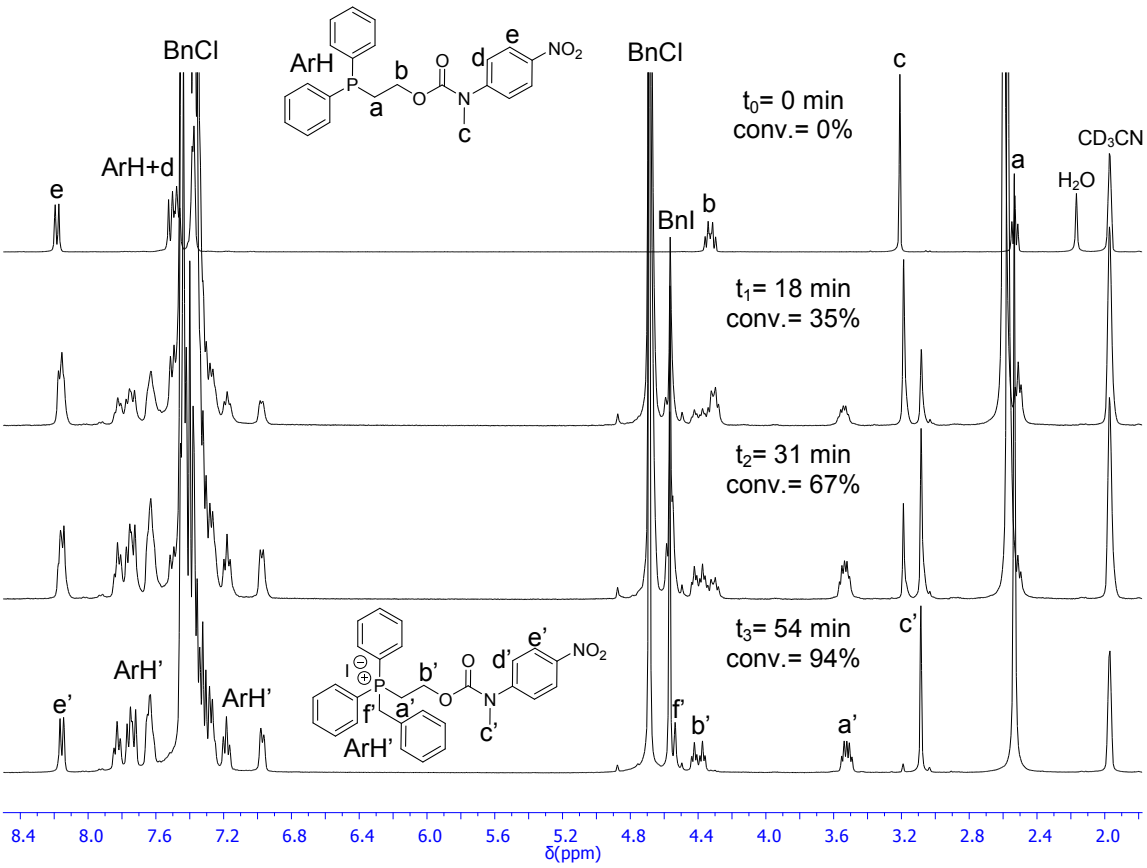


Fig. S52 ^{1}H NMR spectrum recorded overtime following the addition of 10 equivalents of BnCl and 10 equivalents of NaI to a solution of **3** in MeCN-d_3

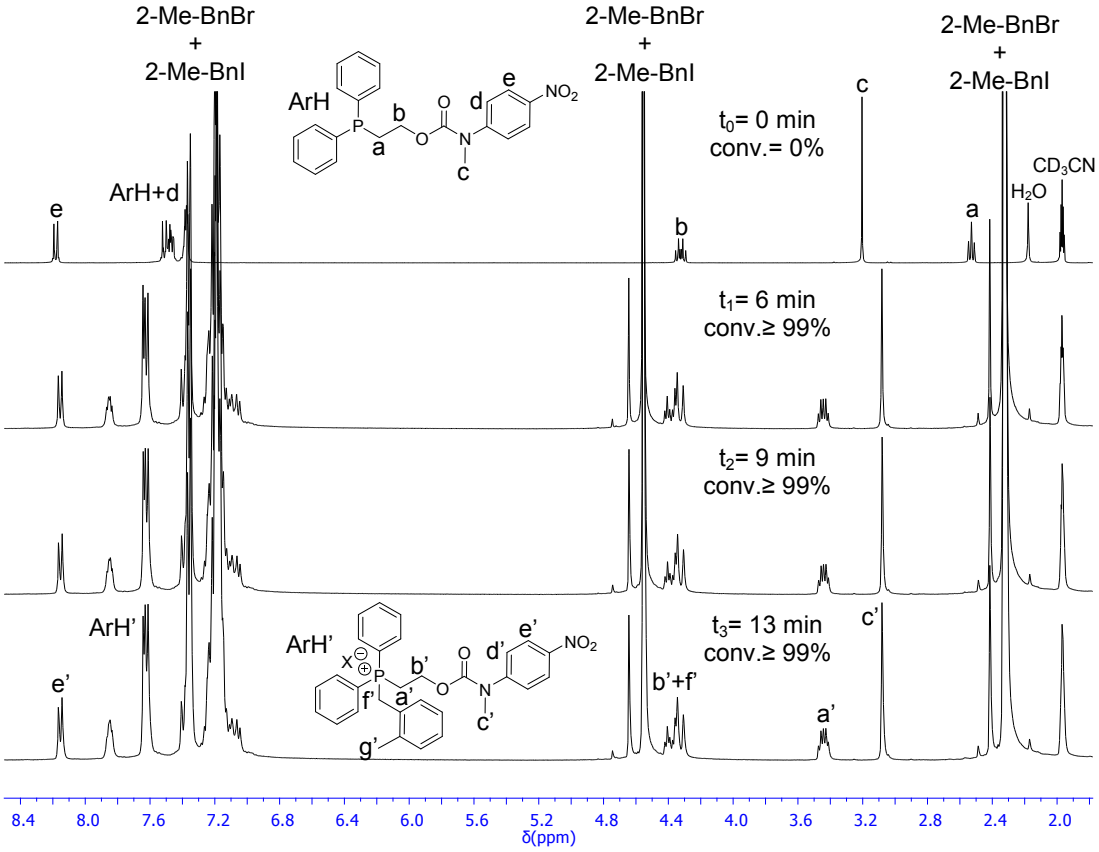


Fig. S53 ^{1}H NMR spectrum recorded overtime following the addition of 10 equivalents of 2-Me-BnBr and 10 equivalents of NaI to a solution of **3** in MeCN-d_3

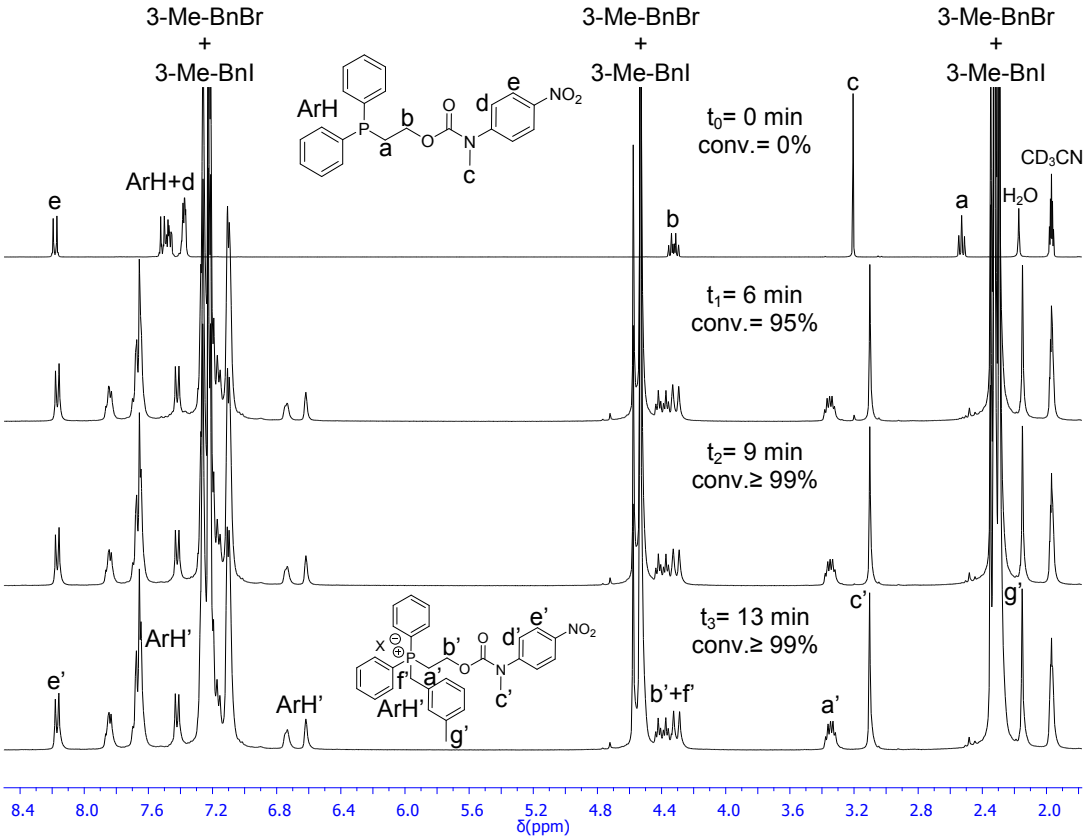


Fig. S54 ^{1}H NMR spectrum recorded overtime following the addition of 10 equivalents of 3-Me-BnBr and 10 equivalents of NaI to a solution of **3** in MeCN-d_3

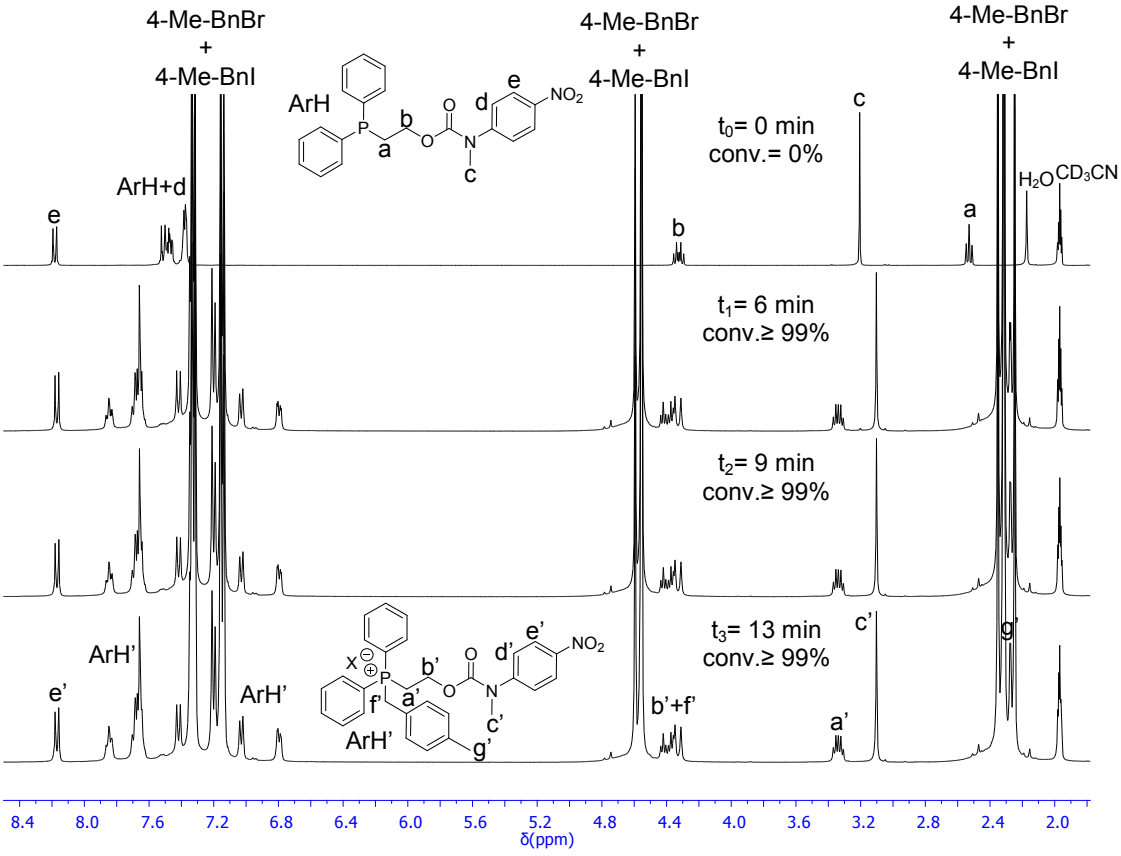


Fig. S55 ^{1}H NMR spectrum recorded overtime following the addition of 10 equivalents of 4-Me-BnBr and 10 equivalents of NaI to a solution of **3** in MeCN-d_3

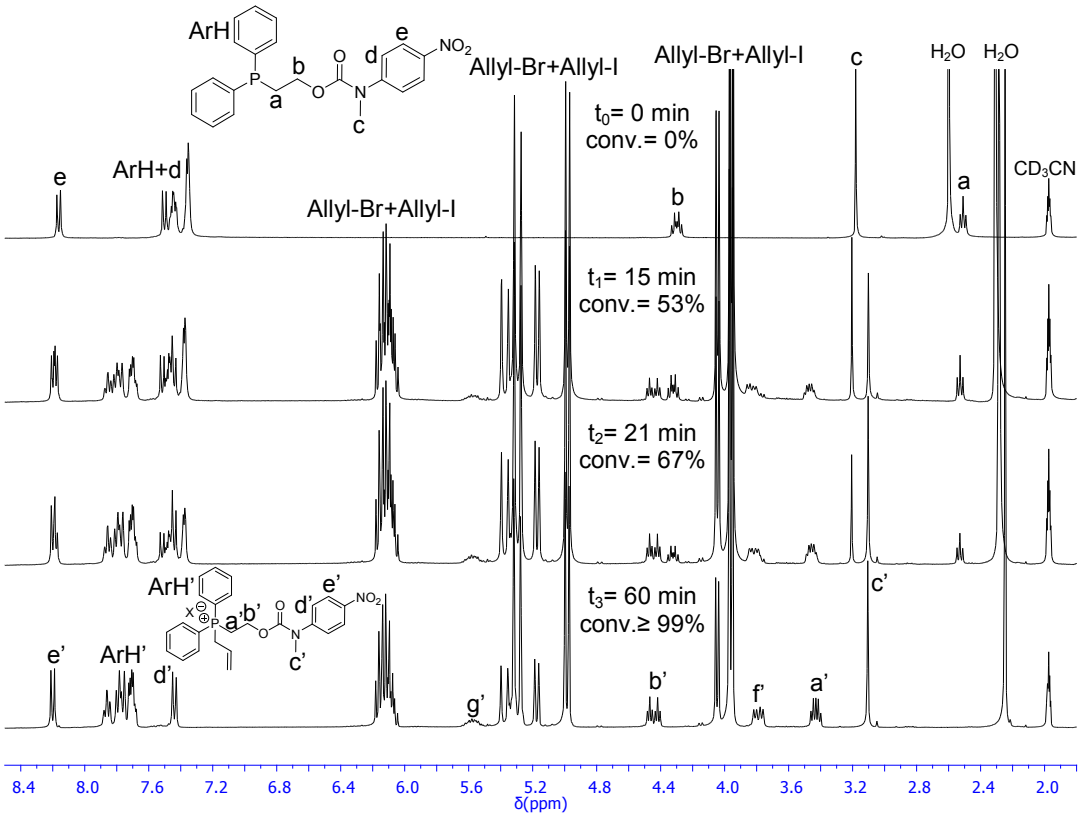


Fig. S56 ^{1}H NMR spectrum recorded overtime following the addition of 10 equivalents of Allyl-Br and 10 equivalents of NaI to a solution of **3** in MeCN-d_3

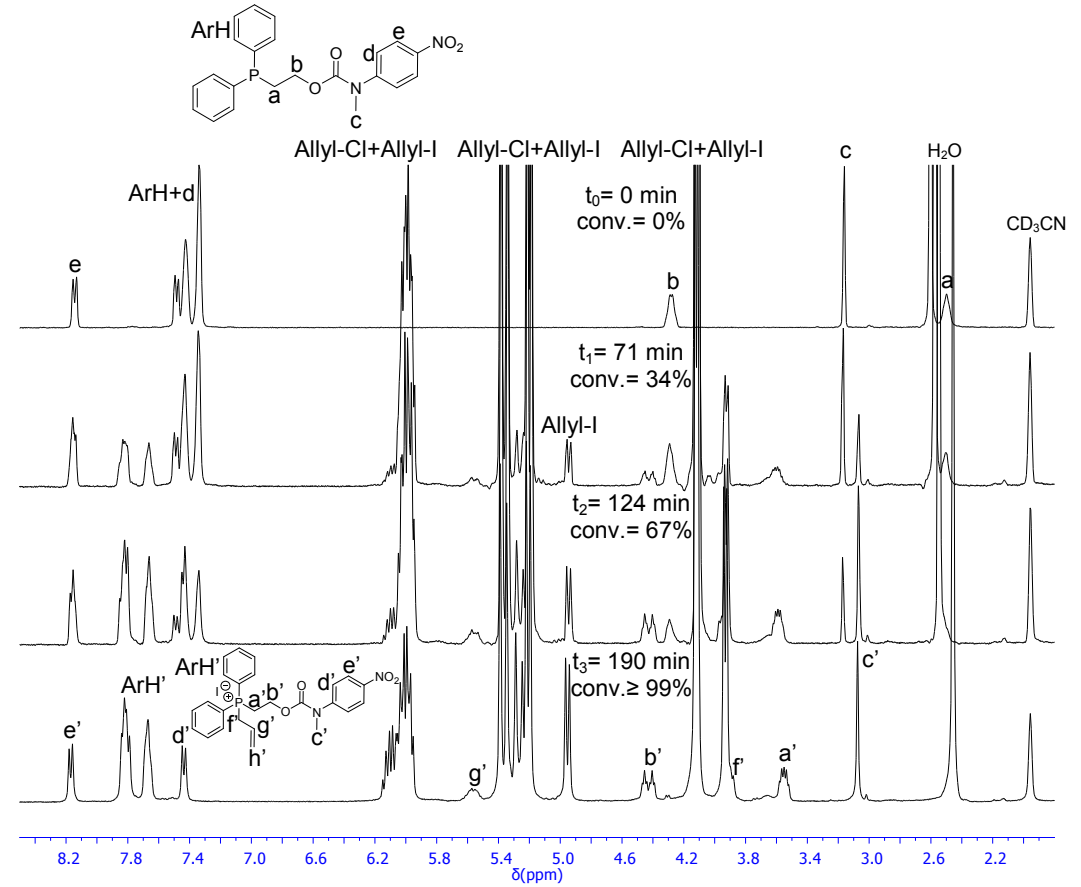


Fig. S57 ^{1}H NMR spectrum recorded overtime following the addition of 10 equivalents of Allyl-Cl and 10 equivalents of NaI to a solution of **3** in MeCN-d_3

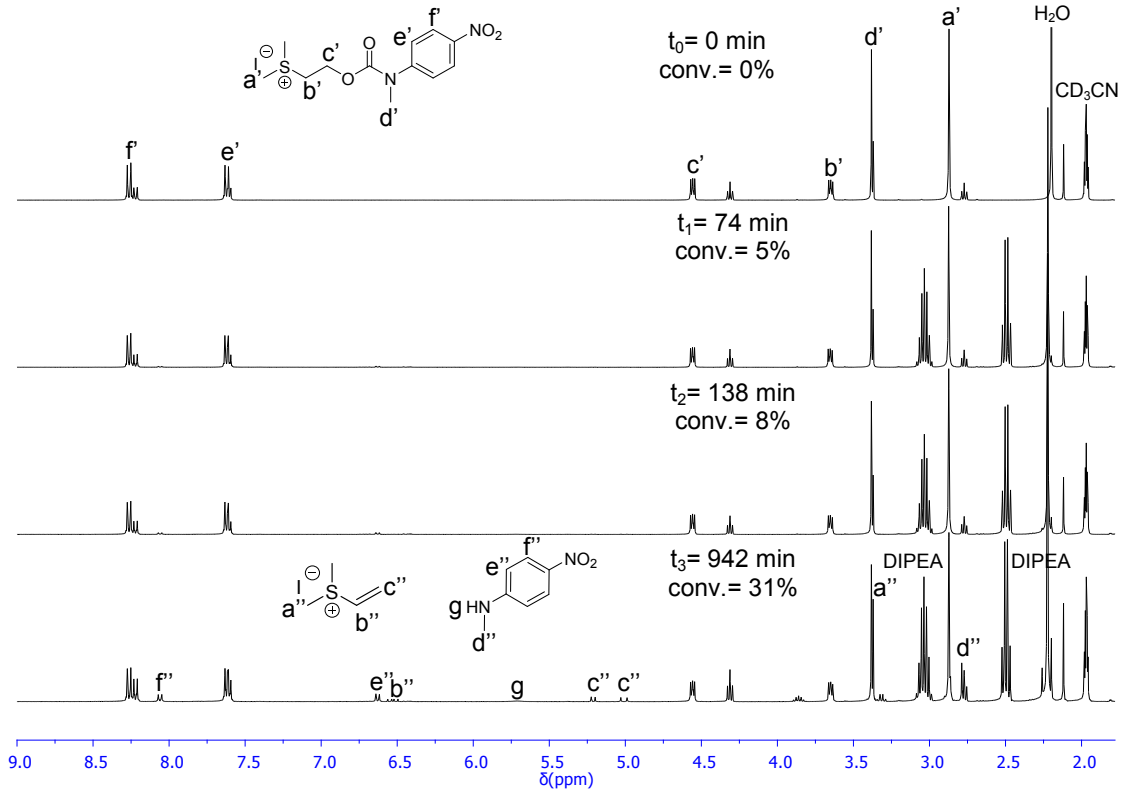


Fig. S58 ^{1}H NMR spectrum recorded overtime following the addition of DIPEA to a solution of alkylated **1** in MeCN-d_3

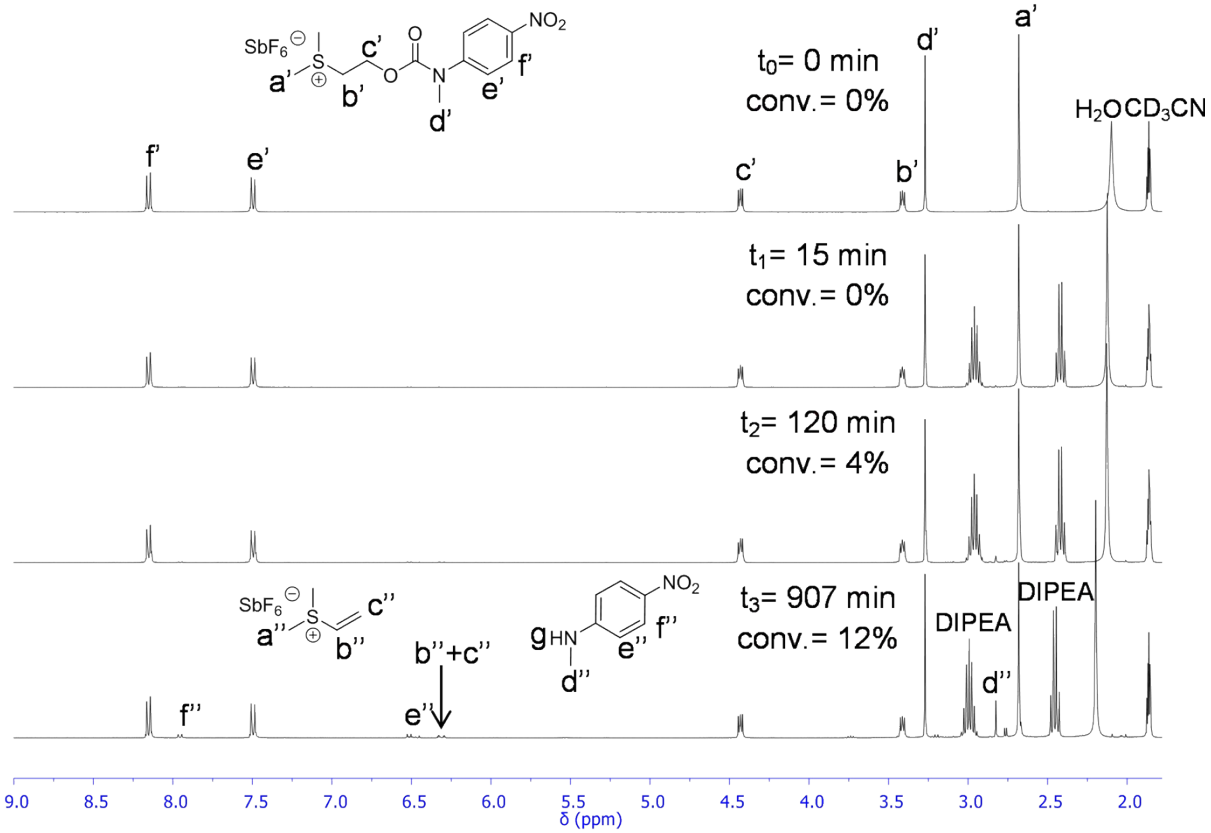


Fig. S59 ^{1}H NMR spectrum recorded overtime following the addition of DIPEA to a solution of alkylated **1** in presence of $AgSbF_6$ in MeCN-d_3

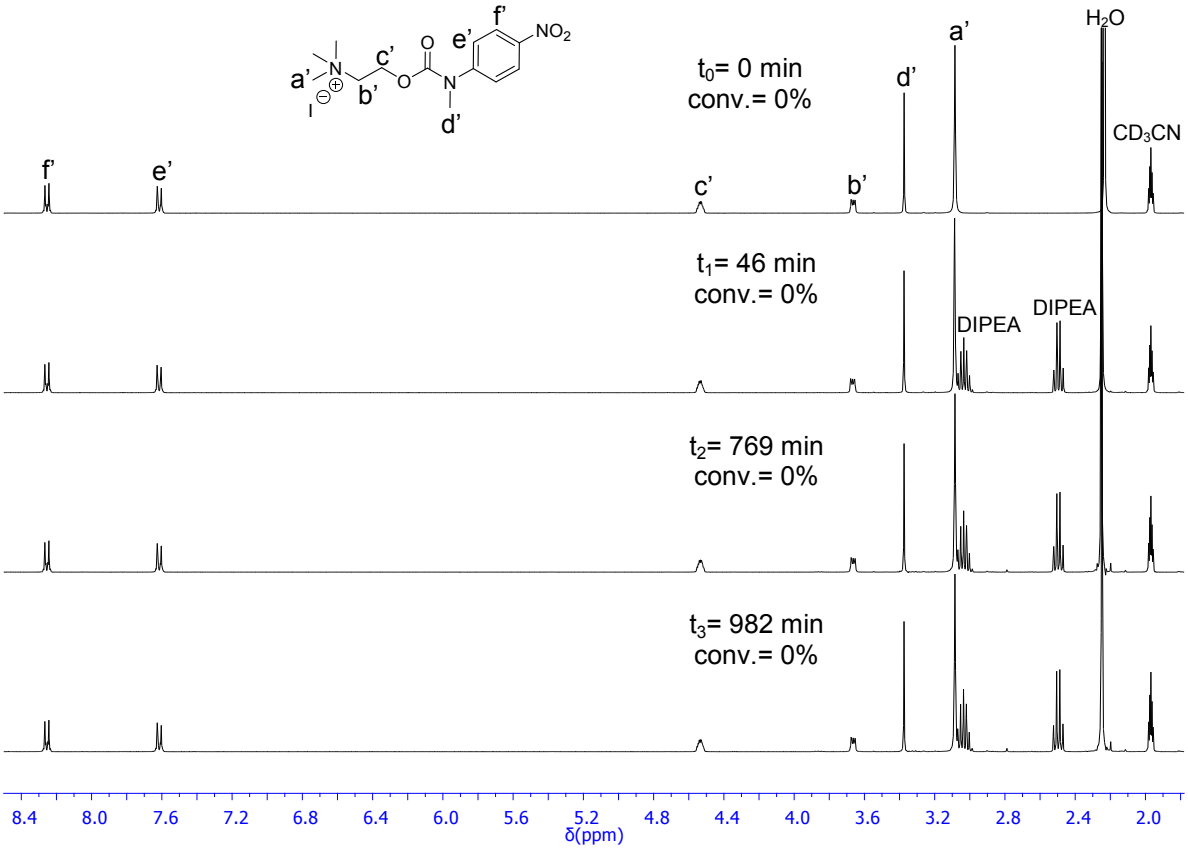


Fig. S60 ^{1}H NMR spectrum recorded overtime following the addition of DIPEA to a solution of alkylated **2** in MeCN-d_3

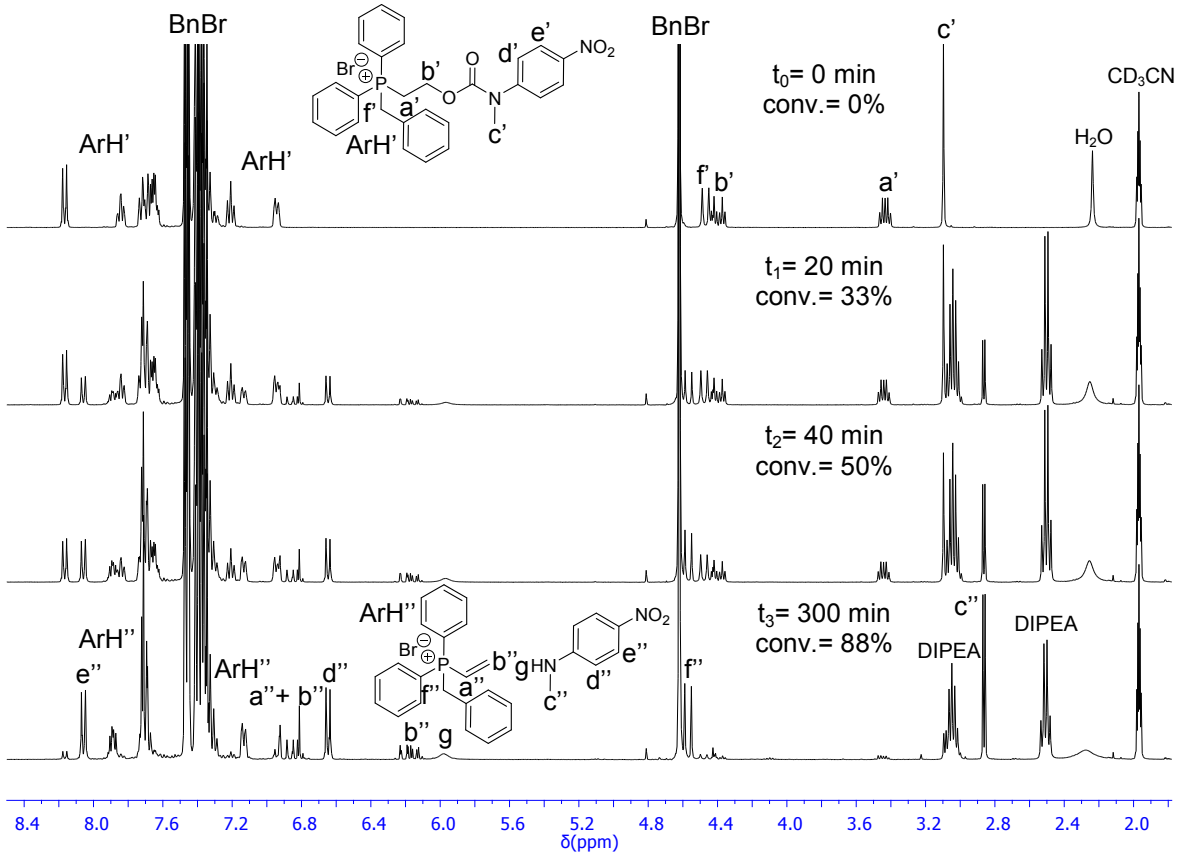


Fig. S61 ^{1}H NMR spectrum recorded overtime following the addition of DIPEA to a solution of alkylated **3** (BnBr) in MeCN-d_3

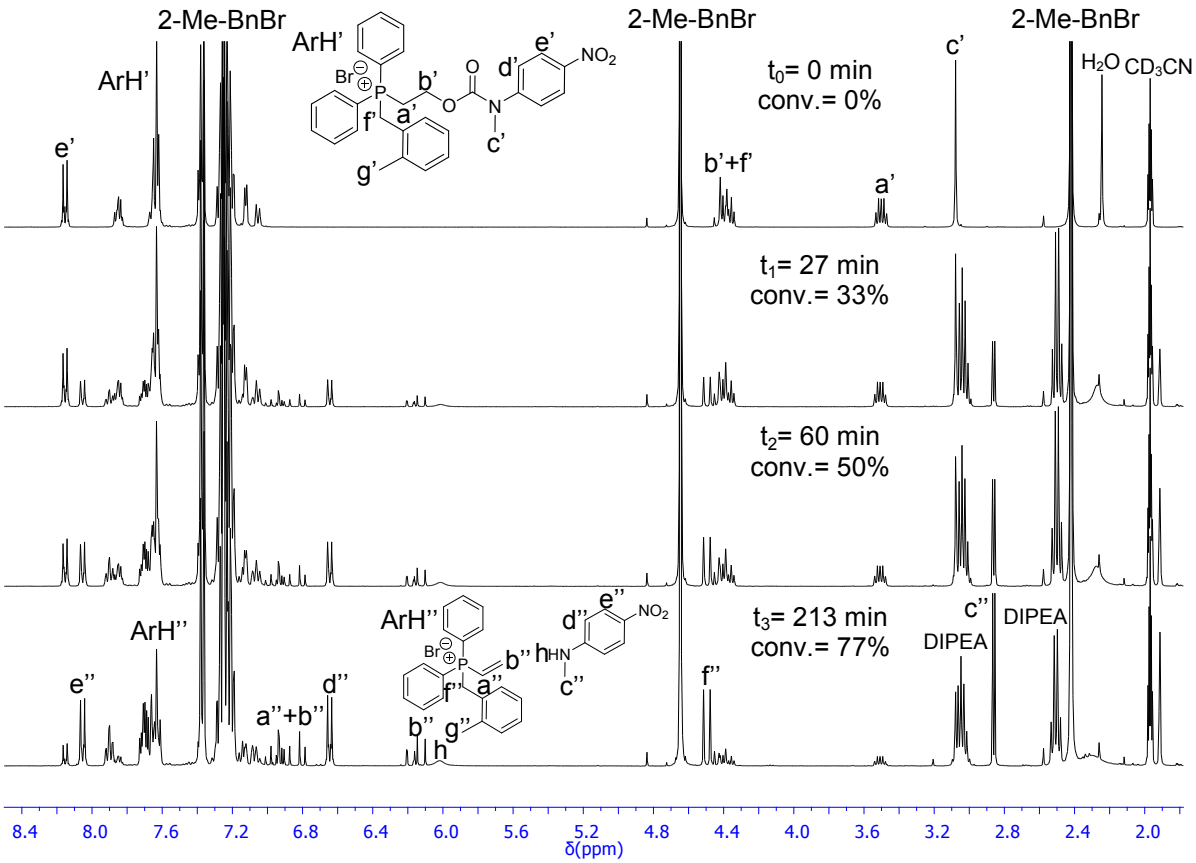


Fig. S62 ^{1}H NMR spectrum recorded overtime following the addition of DIPEA to a solution of alkylated **3** (2-Me-BnBr) in MeCN-d_3

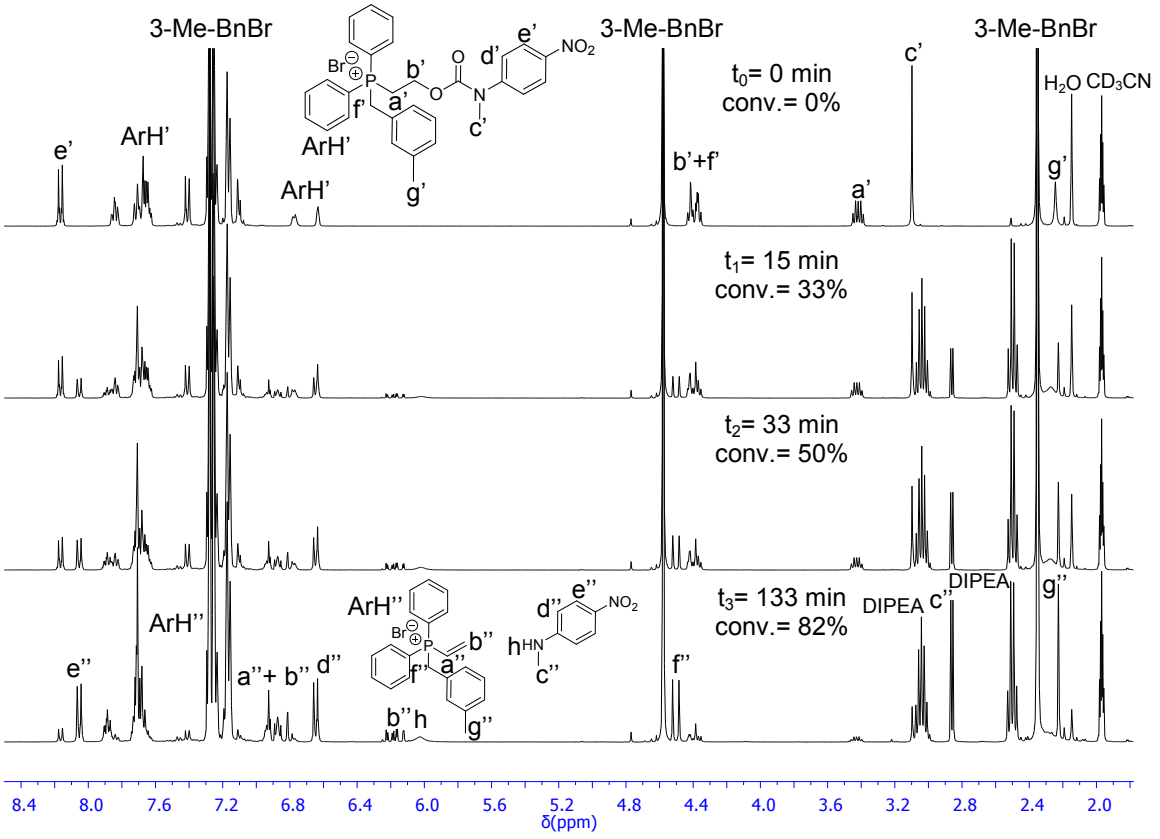


Fig. S63 ^{1}H NMR spectrum recorded overtime following the addition of DIPEA to a solution of alkylated **3** (3-Me-BnBr) in MeCN-d_3

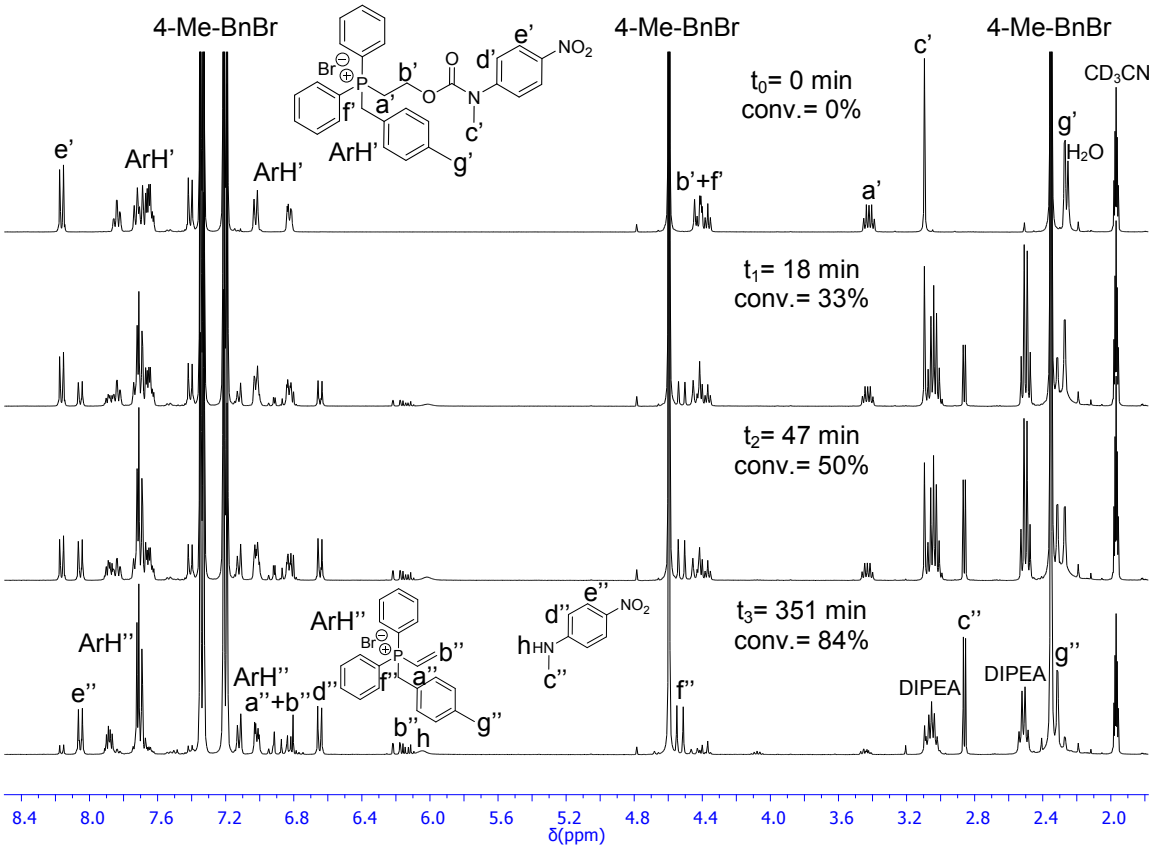


Fig. S64 ^{1}H NMR spectrum recorded overtime following the addition of DIPEA to a solution of alkylated **3** (4-Me-BnBr) in MeCN-d_3

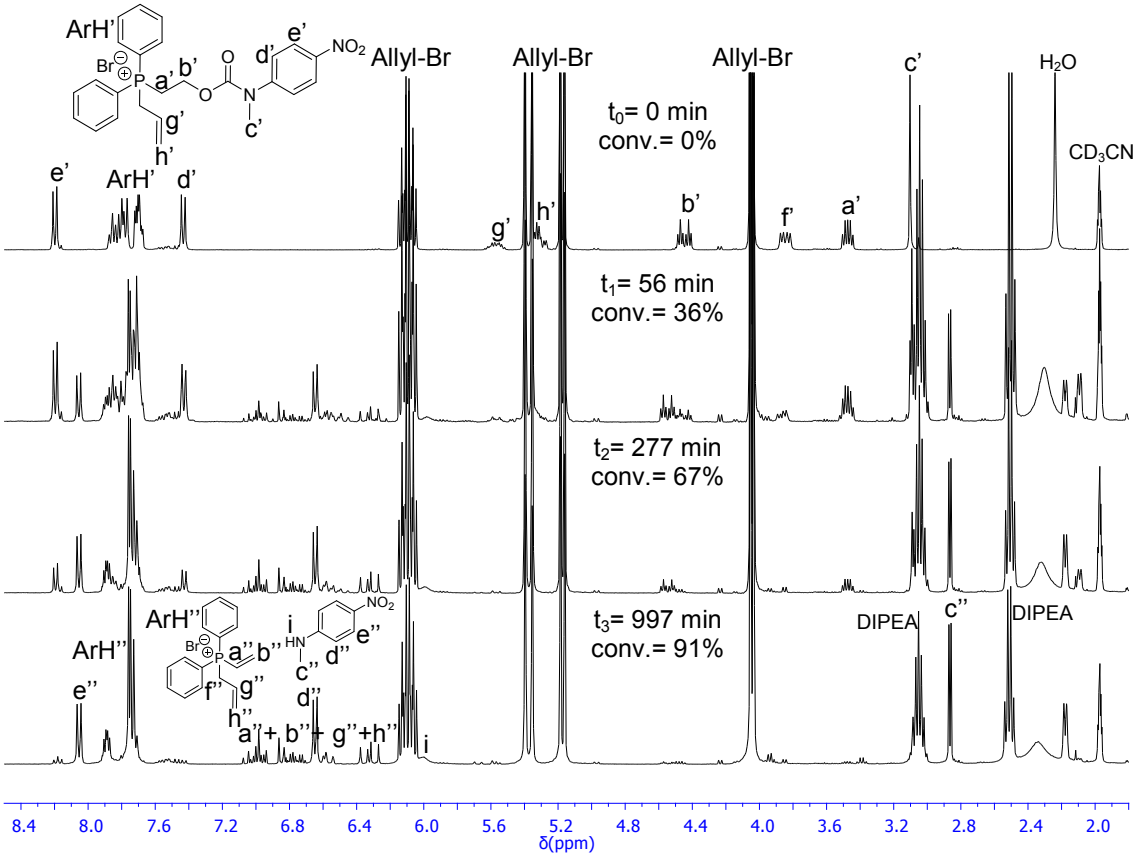


Fig. S65 ^{1}H NMR spectrum recorded overtime following the addition of DIPEA to a solution of alkylated **3** (Allyl-Br) in MeCN-d_3

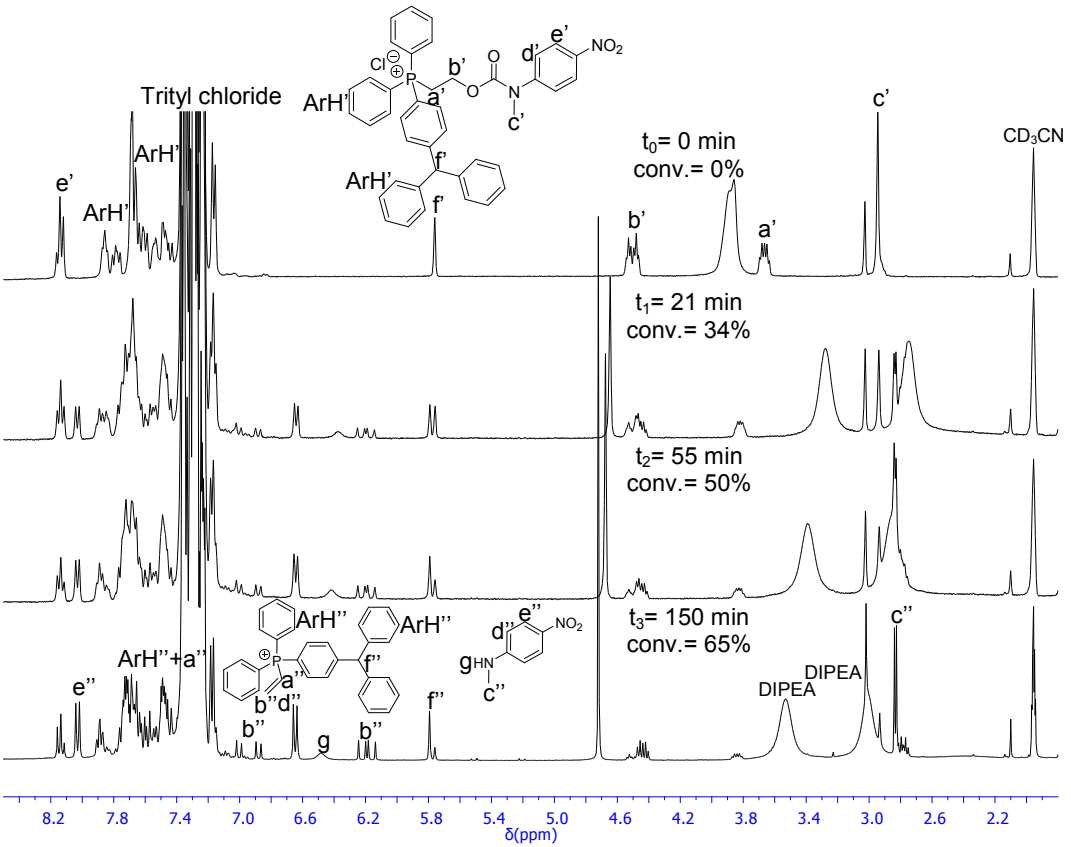


Fig. S66 ^{1}H NMR spectrum recorded overtime following the addition of DIPEA to a solution of alkylated **3** (Trityl chloride) in MeCN-d_3

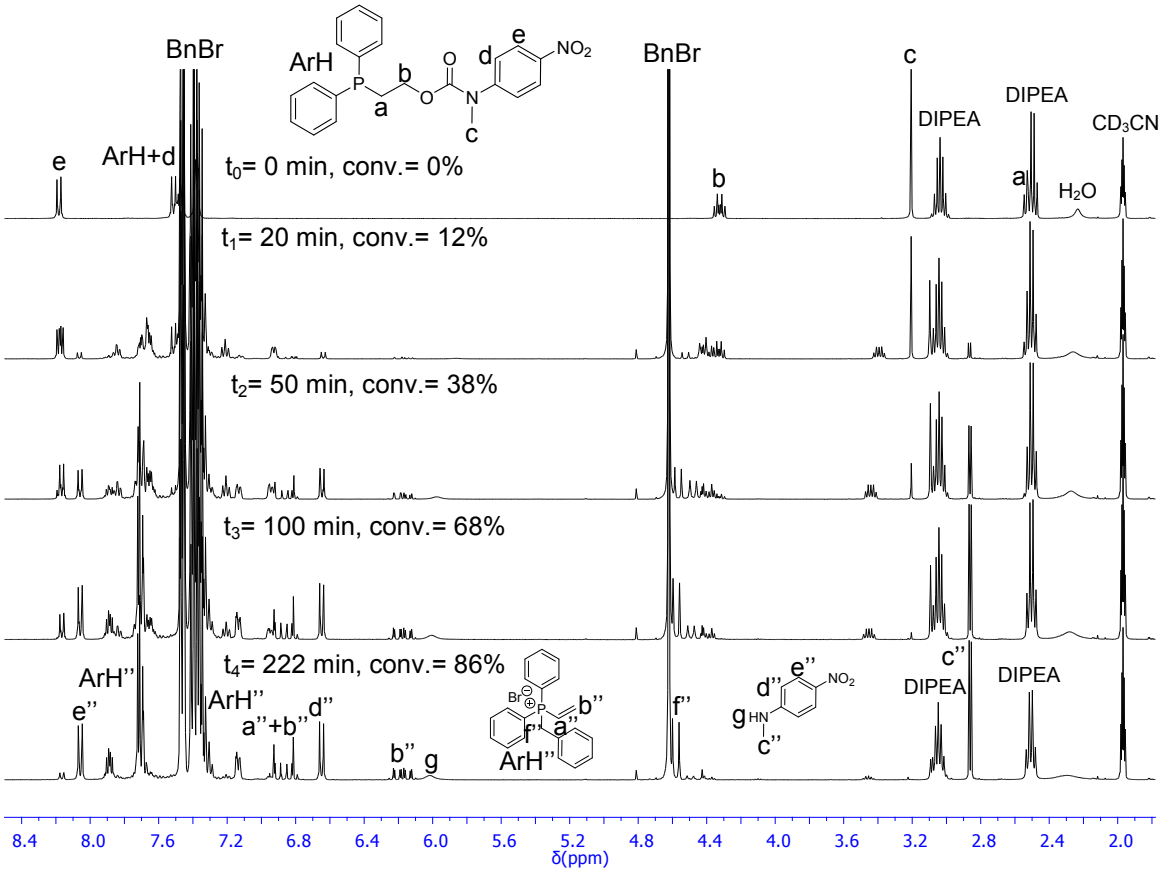


Fig. S67 ^{1}H NMR spectrum recorded overtime following the addition of 10 equivalents of BnBr to a solution of **3** and 2 equivalents of DIPEA in MeCN-d_3

Table. S2 Data obtained for the "*one pot*" reaction following the addition of 10 equivalents of BnBr to a solution of **3** and 2 equivalents of DIPEA in MeCN-d_3 at 20 °C calculated using ^{1}H NMR spectroscopy

t (min)	detector **3** (area/3H)	detector **3** (%)	alkylated detector **3** (area/3H)	alkylated detector **3** (%)	reporter group (area/3H)	reporter group (%)
0	0.75	100	0.00	0	0.00	0
6	0.57	76	0.15	20	0.02	2
7	0.54	72	0.18	24	0.02	2
9	0.51	68	0.21	28	0.03	4
10	0.48	64	0.23	30	0.03	4
12	0.45	60	0.24	32	0.03	4
13	0.43	57	0.26	34	0.05	6
15	0.41	55	0.29	38	0.05	6
16	0.39	52	0.30	40	0.06	8
17	0.37	49	0.30	40	0.08	10
19	0.35	47	0.32	42	0.08	10
20	0.33	44	0.33	44	0.09	12
22	0.31	41	0.33	44	0.09	12
23	0.29	39	0.35	46	0.09	12
24	0.28	37	0.35	46	0.11	14
26	0.26	35	0.35	46	0.11	14
27	0.25	33	0.36	48	0.12	16
29	0.24	32	0.36	48	0.14	18
30	0.22	29	0.36	48	0.14	18
31	0.21	28	0.36	48	0.15	20
33	0.2	27	0.36	48	0.17	22
34	0.19	25	0.36	48	0.18	24
36	0.18	24	0.36	48	0.20	26
37	0.17	23	0.36	48	0.21	28
38	0.16	21	0.36	48	0.21	28
40	0.15	20	0.36	48	0.23	30
41	0.14	19	0.36	48	0.23	30
43	0.13	17	0.36	48	0.24	32
44	0.13	17	0.36	48	0.24	32

45	0.12	16	0.35	46	0.26	34
47	0.11	15	0.35	46	0.26	34
48	0.11	15	0.35	46	0.27	36
50	0.1	13	0.35	46	0.29	38
51	0.1	13	0.35	46	0.29	38
52	0.09	12	0.33	44	0.30	40
54	0.09	12	0.33	44	0.32	42
55	0.08	11	0.33	44	0.32	42
57	0.08	11	0.32	42	0.33	44
58	0.07	9	0.32	42	0.33	44
60	0.07	9	0.32	42	0.35	46
61	0.06	8	0.32	42	0.35	46
62	0.06	8	0.30	40	0.36	48
64	0.06	8	0.30	40	0.38	50
65	0.06	8	0.30	40	0.38	50
67	0.05	7	0.30	40	0.38	50
68	0.05	7	0.30	40	0.38	50
69	0.05	7	0.30	40	0.38	50
71	0.05	7	0.29	38	0.41	54
72	0.05	7	0.29	38	0.41	54
74	0.04	5	0.27	36	0.42	56
75	0.04	5	0.27	36	0.42	56
76	0.03	4	0.27	36	0.42	56
78	0.03	4	0.27	36	0.44	58
79	0.03	4	0.26	34	0.44	58
81	0.03	4	0.26	34	0.44	58
82	0.03	4	0.26	34	0.44	58
83	0.03	4	0.26	34	0.45	60
85	0.02	3	0.24	32	0.45	60
86	0.02	3	0.24	32	0.47	62
88	0.02	3	0.24	32	0.47	62
89	0.02	3	0.24	32	0.48	64
90	0.02	3	0.24	32	0.48	64
92	0.02	3	0.23	30	0.48	64

93	0.02	3	0.23	30	0.48	64
95	0.02	3	0.23	30	0.50	66
96	0.02	3	0.23	30	0.50	66
97	0.02	3	0.23	30	0.50	66
99	0.01	1	0.21	28	0.50	66
100	0.01	1	0.21	28	0.51	68
102	0.01	1	0.21	28	0.51	68
103	0.01	1	0.21	28	0.51	68
105	0.01	1	0.21	28	0.51	68
106	0.01	1	0.20	26	0.53	70
107	0.01	1	0.20	26	0.53	70
109	0.01	1	0.20	26	0.53	70
110	0.01	1	0.20	26	0.53	70
112	0.01	1	0.20	26	0.53	70
121	0.01	1	0.18	24	0.54	72
122	0.01	1	0.18	24	0.54	72
123	0.01	1	0.17	22	0.56	74
125	0.01	1	0.17	22	0.56	74
135	0.01	1	0.15	20	0.56	74
145	0.01	1	0.14	18	0.57	76
156	0	0	0.14	18	0.57	76
166	0	0	0.12	16	0.59	78
175	0	0	0.12	16	0.59	78
185	0	0	0.11	14	0.62	82
195	0	0	0.11	14	0.62	82
205	0	0	0.09	12	0.63	84
215	0	0	0.09	12	0.65	86
222	0	0	0.08	10	0.65	86

References

1. T. Iwai, T. Fujihara, J. Terao, Y. Tsuji, *J. Am. Chem. Soc*., 2010, **132**, 9602.
2. N. Kanbayashi, K. Onitsuka, *Angew. Chemie Int. Ed*., 2011, **50**, 5197.
3. S. Vargas, M. Rubio, A. Suárez, D. del Río, E. Álvarez, A. Pizzano, *Organometallics,* 2006*,* **25***,* 961.