Electronic Supporting Information

The α-Alkylation of Ketones in Flow

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1. General Methods

1.1 General Information

Solvent employed, THF, was dried prior to use, over flame dried 3 Å molecular sieves and stored in Young's flasks. All reagents were purchased from Sigma Aldrich, Fluorochem and Acros unless otherwise noted. All non-aqueous reactions were carried out under oxygen-free nitrogen using oven dried glassware. Wet flash column chromatography was carried out using Kieselgel silica gel 60, 0.040-0.063 mm (Merck). Thin layer chromatography (TLC) was carried out on pre-coated silica gel plates (Merck 60 PF254). Visualisation was achieved by UV. Infrared (IR) spectra were recorded on a Perkin-Elmer FT-IR Paragon 1000 spectrophotometer.

Low-resolution mass spectra were recorded on a Waters Quattro Micro triple quadrupole instrument in electrospray ionization (ESI) mode using 50% acetonitrile-water, containing 0.1% formic acid as the mobile phase. Samples were made up in acetonitrile at a concentration of *ca.* 1 mg mL^{-1}. High-resolution mass spectra were recorded on a Waters LCT Premier TOF LC-MS instrument in electrospray ionization (ESI) mode using 50% acetonitrile-water, containing 0.1% formic acid as the mobile phase. Samples were made up in acetonitrile at a concentration of ca. 1 mg mL^{-1}. NMR spectra were run in $CDCl_3$ using tetramethylsilane (TMS) as the internal standard at 20 °C. ^{1}H NMR spectra were recorded at 300 MHz in proton decoupled mode on a Bruker Avance 300 spectrometer or at 400 MHz in proton decoupled mode on a Bruker Avance 400 spectrometer. ^{13}C NMR spectra were recorded at 75 MHz on a Bruker Avance 300 instrument in proton decoupled mode or at 101 MHz on a Bruker Avance 400 instrument in proton decoupled mode. All spectra were recorded at University College Cork. Chemical shifts δ^{H} and δ^{C} are expressed as parts per million (ppm), positive shift being downfield from TMS; coupling constants (*J*) are expressed in hertz (Hz). Splitting patterns in ^{1}H NMR spectra are designated as s (singlet), d (doublet), dd (doublet of doublets), dt (doublet of triplets), t (triplet), q (quartet) and m (multiplet). For ^{13}C NMR spectra, the number of attached protons for each signal was determined using the DEPT pulse sequence run in the DEPT-90 and DEPT-135 modes. COSY, HSQC, and HMBC experiments were performed to aid the NMR assignment of novel chemical structures.

1.2 Synthetic Procedure for the α-Alkylation of Ketones in Batch

To a Schlenk tube under N_2 atmosphere containing anhydrous THF (5 mL $mmol^{-1}$) was added diisopropylamine (1.2 equiv.) at −78 °C and allowed to stir for 15 min. *n*-BuLi (1.1 equiv.) was added slowly, dropwise and held at this temperature stirring for 30 min. Ketone (1.0 equiv.) was added slowly, dropwise and the mixture was held at this temperature stirring for 1 h. Electrophile (1.2 equiv.) was added slowly, dropwise and the mixture was allowed warm to room temperature overnight (18 h). The reaction mixture was quenched with H_2O (0.5 mL).

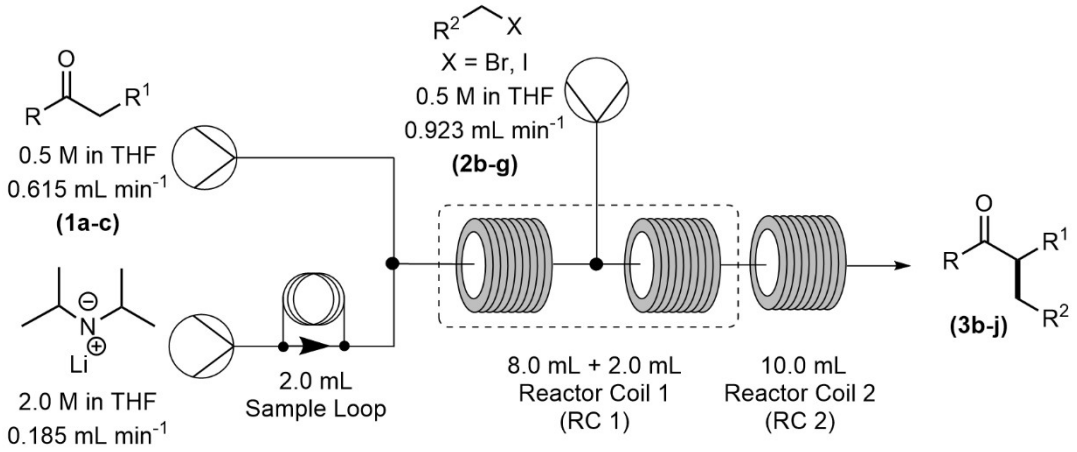
NH_4Cl (10 mL) was added, and the mixture was extracted with Et_2O (3 × 20 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude α-alkylated ketone was purified by column chromatography on silica gel to give the pure α-alkylated ketone.

1.3 Synthetic Procedure for the α-Alkylation of Ketones in Flow

Solutions were prepared using dry THF and dry glassware, while continuously remaining under N_2, this was performed in batch, externally to flow apparatus.

Continuous flow system was configured as outlined in scheme 1. All pre-prepared solutions and solvents were placed under N_2 atmosphere. Solvent and reagent lines A, B and D were primed with dry methanol and dry THF consecutively. *Via* a three-way injector valve, commercially available LDA (2 mL, 2 M) was loaded into a 2 mL sample loop, connected to line B.

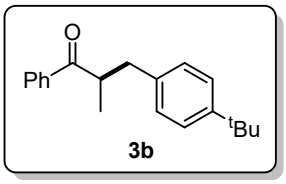
Ketone solution (0.615 mL min^{-1}, 0.5 M) linked up to line A and commercially available LDA (0.185 mL min^{-1}, 2 M) linked up to line B were pumped into reactor coil 1 *via* HPLC/piston pumps, where deprotonation occurred at room temperature. Electrophile solution (0.923 mL min^{-1}, 0.5 M) linked up to line D was pumped into reactor coil 2 *via* a peristaltic pump, where alkylation of the previously formed enolate occurred at room temperature and further at 75 °C. A second peristaltic pump, line C, was enabled as a back pressure regulator set to 7 bar. Once the system reached steady state conditions the reaction mixture was collected for 5.4 min. The overall reaction time was 30 min. The collected reaction mixture was quenched with NH_4Cl (5 mL) and extracted with Et_2O (3 × 10 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude α-alkylated ketone was purified by column chromatography on silica gel to give the pure α-alkylated ketone.



Scheme 1. Continuous flow set-up for substrate scope.

2. Analytical Data

3-(4-(tert-butyl)phenyl)-2-methyl-1-phenylpropan1-one, 3b



3b

Compound **3b** was prepared according to the general procedure **1.2.** using **propiophenone (1a)** and ***p-tert*-butylbenzyl bromide (2b)**. The crude compound was purified by silica gel column chromatography (1:1, hexane:DCM) to give the title compound **3b** as a pale yellow oil (374 mg, 81%).

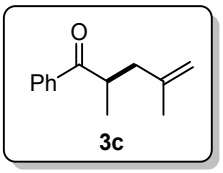
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 – 7.83 (m, 2H), 7.54 – 7.44 (m, 1H), 7.44 – 7.34 (m, 2H), 7.31 – 7.22 (m, 2H), 7.12 (d, *J* = 8.4 Hz, 2H), 3.81 – 3.63 (m, 1H), 3.13 (dd, *J* = 13.7, 6.2 Hz, 1H), 2.66 (dd, *J* = 13.8, 7.8 Hz, 1H), 1.27 (s, 9H), 1.19 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 203.8, 149.0, 136.9, 136.6, 132.9, 128.8, 128.7, 128.4, 125.3, 42.8, 39.0, 34.4, 31.5, 17.5.

IR (NaCl) vmax: 2963.98, 1683.43 cm^{-1}.

HRMS (ESI) calcd for $C_{20}H_{25}O$ $[M+H]^+$ m/z: 281.1905; found 281.1900.

2,4-dimethyl-1-phenylpent-4-en-1-one, 3c



3c

Compound **3c** was prepared according to the general procedure **1.2.** using **propiophenone (1a)** and **3-bromo-2-methylpropene (2c)**. The crude compound was purified by silica gel column chromatography (10:1, hexane:Et_2O) to give the title compound **3c** as a colourless oil (219 mg, 70%).

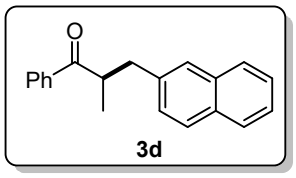
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 – 7.90 (m, 2H), 7.62 – 7.41 (m, 3H), 4.73 (d, *J* = 19.9 Hz, 2H), 3.76 – 3.58 (m, 1H), 2.56 (dd, *J* = 14.4, 6.3 Hz, 1H), 2.12 (dd, *J* = 14.5, 7.8 Hz, 1H), 1.75 (s, 3H), 1.19 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 203.8, 143.1, 136.5, 132.9, 128.7, 128.2, 112.2, 41.4, 38.7, 22.6, 17.2.

IR (NaCl) vmax: 2970.80, 2933.91, 1683.27 cm^{-1}.

HRMS (ESI) calcd for $C_{13}H_{17}O$ $[M+H]^+$ m/z: 189.1285; found 189.1274.

2-methyl-3-(naphthalen-2-yl)-1-phenylpropan-1-one, 3d



Compound **3d** was prepared according to the general procedure **1.2.** using **propiophenone (1a)** and **2-(bromomethyl)naphthalene (2d)**. The crude compound was purified by silica gel column chromatography (1:1, hexane:DCM) to give the title compound **3d** as a white solid (326 mg, 72%).

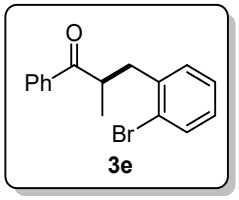
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 – 7.88 (m, 2H), 7.83 – 7.69 (m, 3H), 7.63 (s, 1H), 7.57 – 7.29 (m, 6H), 3.93 – 3.76 (m, 1H), 3.34 (dd, J = 13.7, 6.2 Hz, 1H), 2.85 (dd, J = 13.7, 7.9 Hz, 1H), 1.23 (d, J = 6.9 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 203.7, 137.5, 136.5, 133.5, 133.0, 132.2, 128.7, 128.3, 128.0, 127.6, 127.6, 127.5, 126.0, 125.4, 42.8, 39.5, 17.5.

IR (NaCl) vmax: 3054.97, 2969.56, 2939.19, 1681.55 cm^{-1}.

HRMS (ESI) calcd for $C_{20}H_{19}O$ $[M+H]^+$ m/z: 275.1437, found 275.1430.

3-(2-bromophenyl)-2-methyl-1-phenylpropan-1-one, 3e



Compound **3e** was prepared according to the general procedure **1.2.** using **propiophenone (1a)** and **1-bromo-2-(bromomethyl)benzene (2e)**. The crude compound was purified by silica gel column chromatography (1:1, hexane:DCM) to give the title compound **3e** as a pale yellow oil (357 mg, 71%).

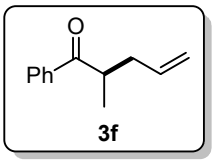
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 – 7.86 (m, 2H), 7.55 – 7.45 (m, 2H), 7.45 – 7.35 (m, 2H), 7.23 – 7.09 (m, 2H), 7.05 – 6.96 (m, 1H), 4.04 – 3.85 (m, 1H), 3.25 (dd, *J* = 13.5, 6.9 Hz, 1H), 2.86 (dd, *J* = 13.6, 7.4 Hz, 1H), 1.20 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 203.7, 139.2, 136.5, 133.0, 132.9, 132.0, 128.6, 128.3, 128.1, 127.3, 124.6, 40.4, 39.6, 17.7.

IR (NaCl) vmax: 2970.91, 2931.67, 1681.23, 664.26 cm^{-1}.

HRMS (ESI) calcd for $C_{16}H_{16}BrO$ $[M+H]^+$ m/z: 303.0383, found 303.0379.

2-methyl-1-phenylpent-4-en-1-one, 3f



3f

Compound **3f** from **allyl iodide:** Compound **3f** was prepared according to the general procedure **1.2.** using **propiophenone (1a)** and **allyl iodide (2f)**. The crude compound was purified by silica gel column chromatography (10:1, hexane:Et_2O) to give the title compound **3f** as a colourless oil (217 mg, 75%).

Compound **3f** from **allyl bromide:** Compound **3f** was prepared according to the general procedure **1.2.** using **propiophenone (1a)** and **allyl bromide (2g)**. The crude compound was purified by silica gel column chromatography (10:1, hexane: Et_2O) to give the title compound **3f** as a colourless oil (206 mg, 71%).

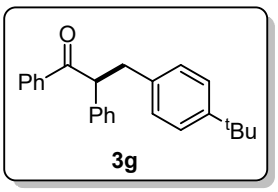
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 – 7.90 (m, 2H), 7.60 – 7.52 (m, 1H), 7.51 – 7.43 (m, 2H), 5.87 – 5.70 (m, 1H), 5.10 – 4.97 (m, 2H), 3.61 – 3.47 (m, 1H), 2.63 – 2.58 (m, 1H), 2.26 – 2.14 (m, 1H), 1.21 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 203.6, 136.5, 135.8, 132.9, 128.6, 128.3, 116.7, 40.5, 37.6, 17.0.

IR (NaCl) vmax: 2975.77, 2933.08, 1682.79 cm^{-1}.

HRMS (ESI) calcd for $C_{12}H_{14}NaO$ $[M+Na]^+$ m/z: 197.0946, found 197.0937.

3-(4-(tert-butyl)phenyl)-1,2-diphenylpropan-1-one, 3g



3g

Compound **3g** was prepared according to the general procedure **1.2.** using **2-phenylacetophenone (1b)** and ***p-tert*-butylbenzyl bromide (2b)**. The crude compound was purified by silica gel column chromatography (9:1, hexane:Et_2O) to give the title compound **3g** as a white solid (483 mg, 85%).

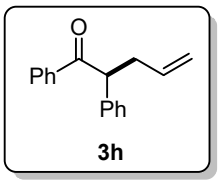
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, *J* = 7.3 Hz, 2H), 7.38 (t, *J* = 7.3 Hz, 1H), 7.33 – 7.12 (m, 9H), 7.04 (d, *J* = 8.2 Hz, 2H), 4.83 (t, *J* = 7.8 Hz, 1H), 3.58 (dd, *J* = 13.8, 8.0 Hz, 1H), 3.02 (dd, *J* = 13.8, 6.3 Hz, 1H), 1.25 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 199.4, 149.0, 139.5, 136.9, 136.9, 132.8, 129.0, 128.8, 128.8, 128.5, 128.4, 127.2, 125.2, 55.9, 39.7, 34.4, 31.4.

IR (NaCl) vmax: 2958.80, 1674.00 cm^{-1}.

HRMS (ESI) calcd for $C_{25}H_{26}NaO$ $[M+Na]^+$ m/z: 365.1877, found 365.1876.

1,2-diphenylpent-4-en-1-one, 3h



3h

Compound **3h** was prepared according to the general procedure **1.2.** using **2-phenylacetophenone (2b)** and **allyl iodide (2f)**. The crude compound was purified by silica gel column chromatography (10:1, hexane:Et_2O) to give the title compound **3h** as a pale yellow oil (313 mg, 80%).

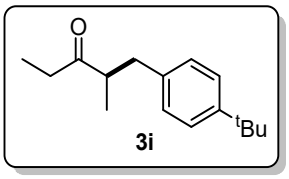
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 – 7.89 (m, 2H), 7.50 – 7.43 (m, 1H), 7.37 (t, *J* = 7.6 Hz, 2H), 7.33 – 7.24 (m, 4H), 7.23 – 7.15 (m, 1H), 5.84 – 5.64 (m, 1H), 5.10 – 4.90 (m, 2H), 4.62 (t, *J* = 7.3 Hz, 1H), 3.02 – 2.88 (m, 1H), 2.64 – 2.50 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 199.2, 139.1, 136.8, 136.0, 132.9, 129.0, 128.7, 128.6, 128.3, 127.2, 116.7, 53.7, 38.2.

IR (NaCl) vmax: 2917.30, 1681.71 cm^{-1}.

HRMS (ESI) calcd for $C_{17}H_{17}O$ $[M+H]^+$ m/z: 237.1273, found 237.1274.

1-(4-(tert-butyl)phenyl)-2-methylpentan-3-one, 3i



3i

Compound **3i** was prepared according to the general procedure **1.2.** using **3-pentanone (1c)** and ***p-tert*-butylbenzyl bromide (2b)**. The crude compound was purified by silica gel column chromatography (10:1, hexane:Et_2O) to give the title compound **3i** as a colourless oil (203 mg, 53%).

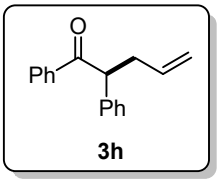
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 – 7.26 (m, 2H), 7.11 – 7.01 (m, 2H), 2.95 (dd, *J* = 13.3, 6.9 Hz, 1H), 2.89 – 2.76 (m, 1H), 2.58 – 2.21 (m, 3H), 1.30 (s, 9H), 1.08 (d, *J* = 6.8 Hz, 3H), 0.98 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 214.9, 149.0, 136.7, 128.6, 125.3, 47.9, 38.7, 35.0, 34.4, 31.4, 16.6, 7.6.

IR (NaCl) vmax: 2965.18, 1714.64 cm^{-1}.

HRMS (ESI) calcd for $C_{16}H_{25}O$ $[M+H]^+$ m/z: 233.1905, found 233.1900.

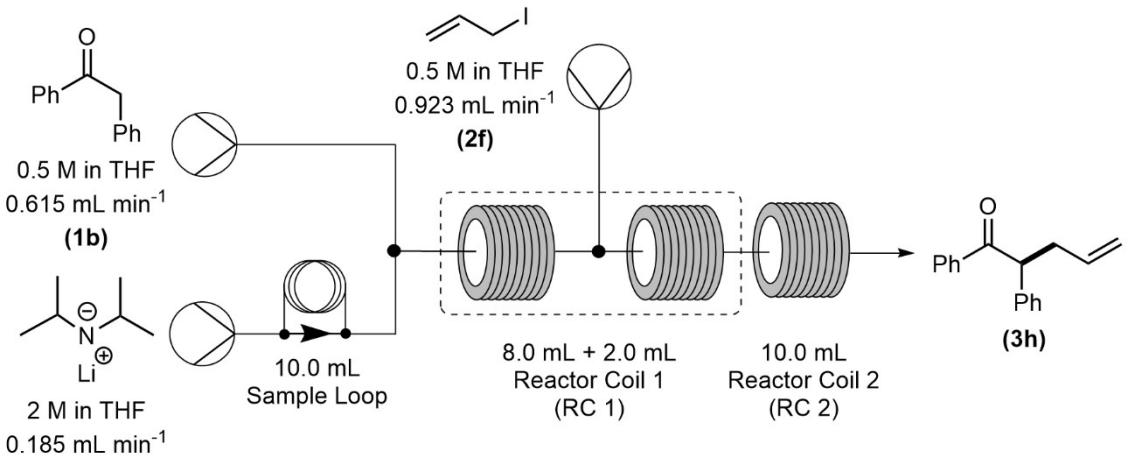
3. Procedure for the scaled-out synthesis of 1,2-diphenylpent-4-en-1-one, 3h



0.5 M solutions of 2-phenylacetopheone and allyl iodide were prepared using dry THF and dry glassware, while continuously remaining under N_2 atmosphere, this was performed in batch, externally to flow apparatus.

Continuous flow system was configured as outlined in Scheme 2. All pre-prepared solutions and solvents were placed under N_2 atmosphere. Solvent and reagent lines A, B and D were primed with dry methanol and dry THF consecutively. *Via* a three-way injector valve, commercially available LDA (10 mL, 2 M) was loaded into a 10 mL sample loop, connected to line B.

2-phenylacetophenone **(1b)** solution (0.615 mL min^{-1}, 0.5 M) linked up to line A and commercially available LDA (0.185 mL min^{-1}, 2 M) linked up to line B were pumped into reactor coil 1 *via* HPLC/piston pumps where deprotonation occurred at room temperature. Allyl iodide **(2f)** solution (0.923 mL min^{-1}, 0.5 M) linked up to line D was pumped into reactor coil 2 *via* a peristaltic pump where alkylation of the enolate occurred at room temperature and further at 75 °C. A second peristaltic pump, line C, was enabled as a back pressure regulator set to 7 bar. Once the system reached steady state conditions the reaction mixture was collected for 45 min. The collected reaction mixture was quenched with NH_4Cl (40 mL) and extracted with Et_2O (3 × 80 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude α-alkylated ketone was sufficiently pure (see following spectrum, 96% steady state yield) but could be further purified by column chromatography on silica gel to give the pure α-alkylated ketone in 82%.



Scheme 2. Continuous flow set up for a scaled-out reaction.

The crude compound was purified by silica gel column chromatography (10:1, hexane:Et_2O) to give the title compound **3h** as a pale yellow oil (2681 mg, 82 %).

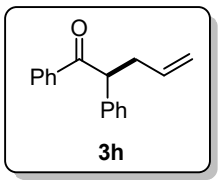
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 – 7.88 (m, 2H), 7.46 (t, *J* = 7.3 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 2H), 7.33 – 7.24 (m, 4H), 7.22 – 7.15 (m, 1H), 5.81 – 5.64 (m, 1H), 5.10 – 4.90 (m, 2H), 4.62 (t, *J* = 7.3 Hz, 1H), 3.01 – 2.89 (m, 1H), 2.63 – 2.50 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 199.2, 139.1, 136.8, 136.0, 132.9, 128.9, 128.7, 128.5, 128.3, 127.1, 116.7, 53.7, 38.2.

IR (NaCl) vmax: 2917.49, 1681.37 cm^{-1}.

HRMS (ESI) calcd for $C_{17}H_{17}O$ $[M+H]^+$ m/z: 237.1278, found 237.1274.

'Crude' material:

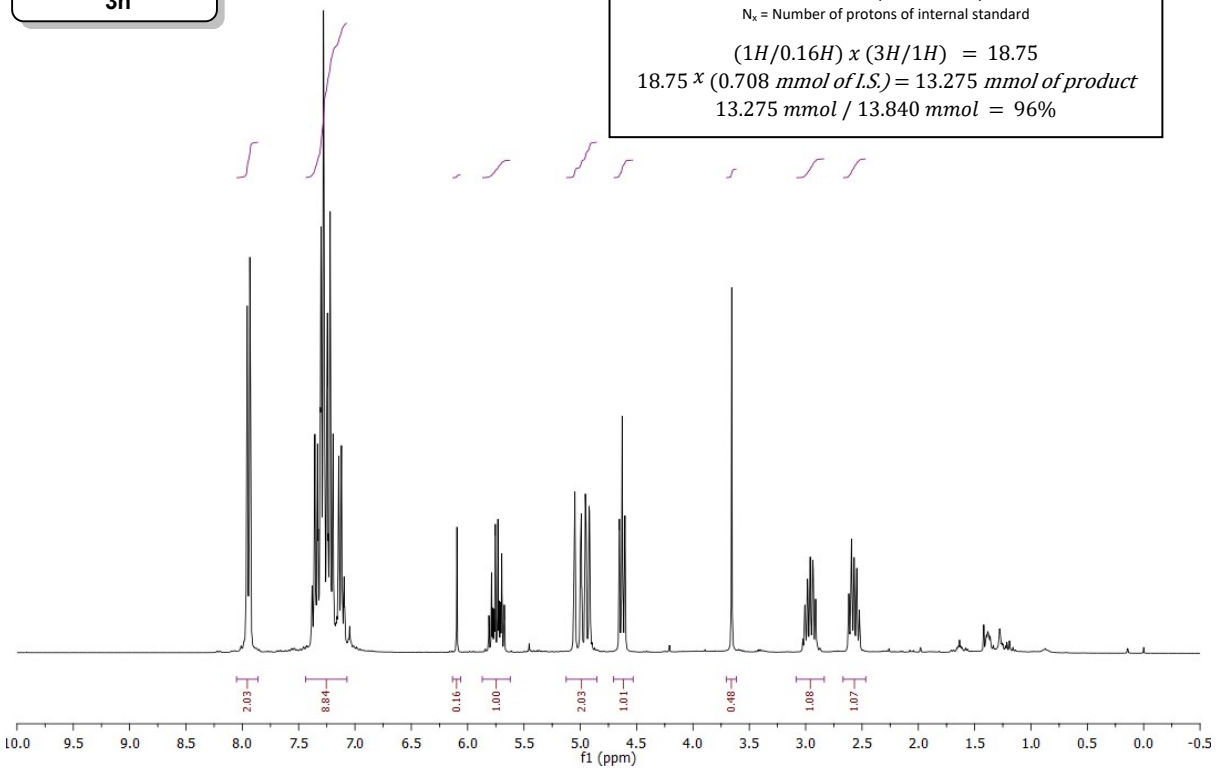


3h

$$Mx\ /\ My\ =\ (Ix\ /\ Iy)\ x\ (Ny/Nx)$$

M_x = mmol analyte
M_y = mmol internal standard
I_x = integration of analyte
I_y = integration of internal standard
N_x = Number of protons of analyte
N_x = Number of protons of internal standard

$$(1H/0.16H)\ x\ (3H/1H)\ =\ 18.75$$
$$18.75\ x\ (0.708\ mmol\ of\ I.S.) = 13.275\ mmol\ of\ product$$
$$13.275\ mmol\ /\ 13.840\ mmol\ =\ 96\%$$



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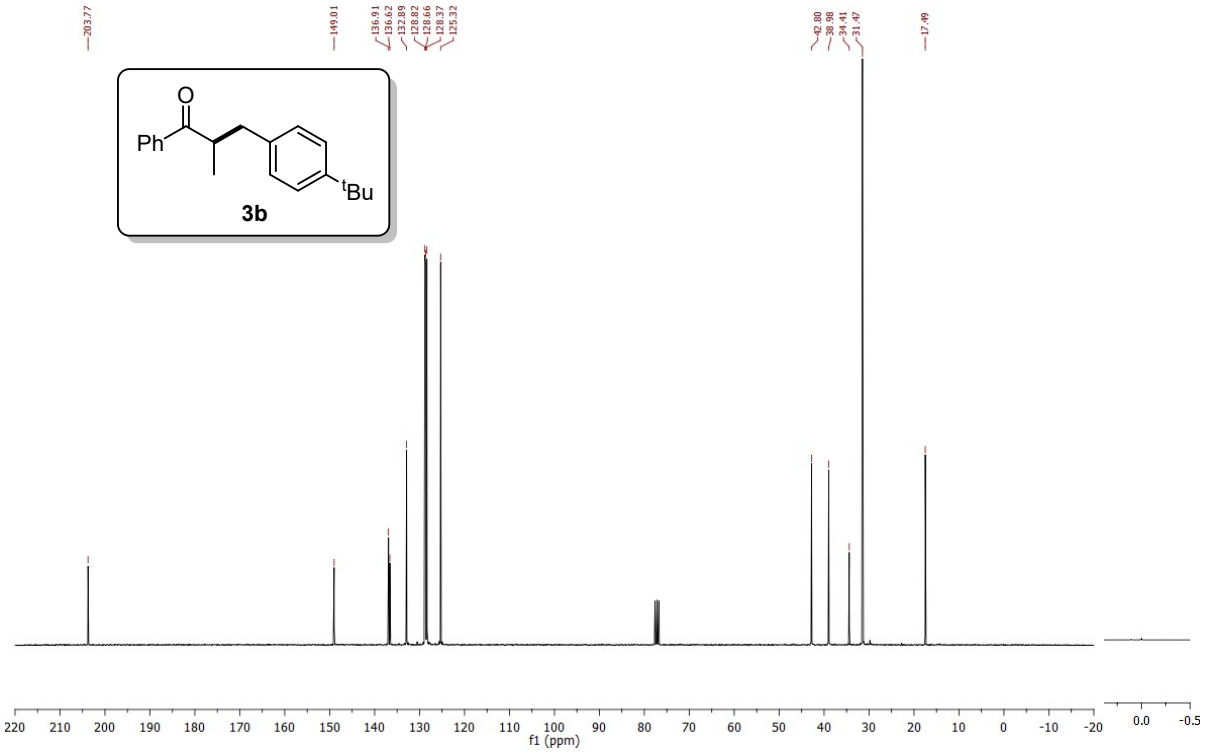
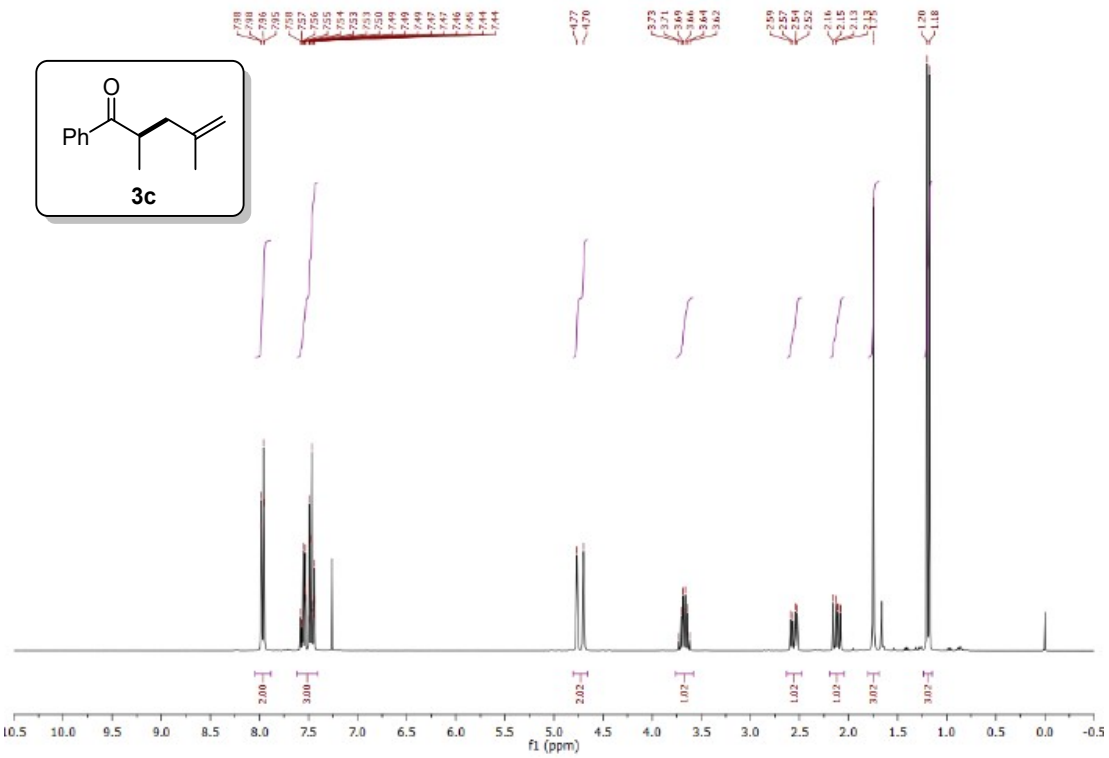
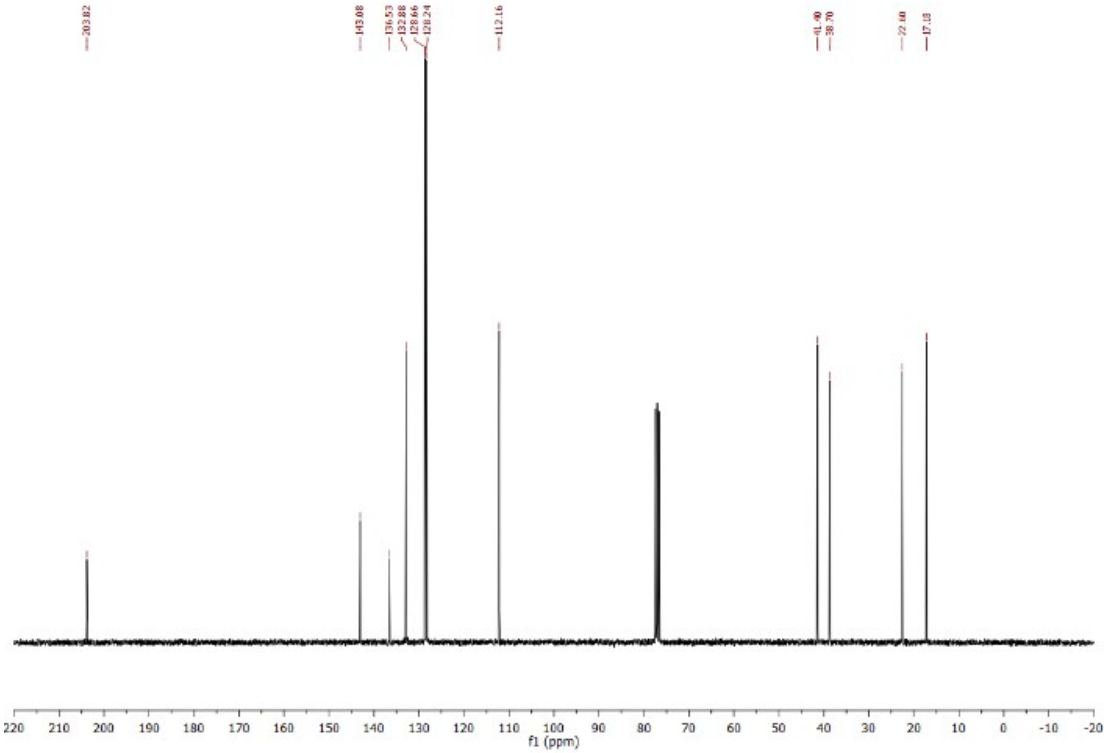
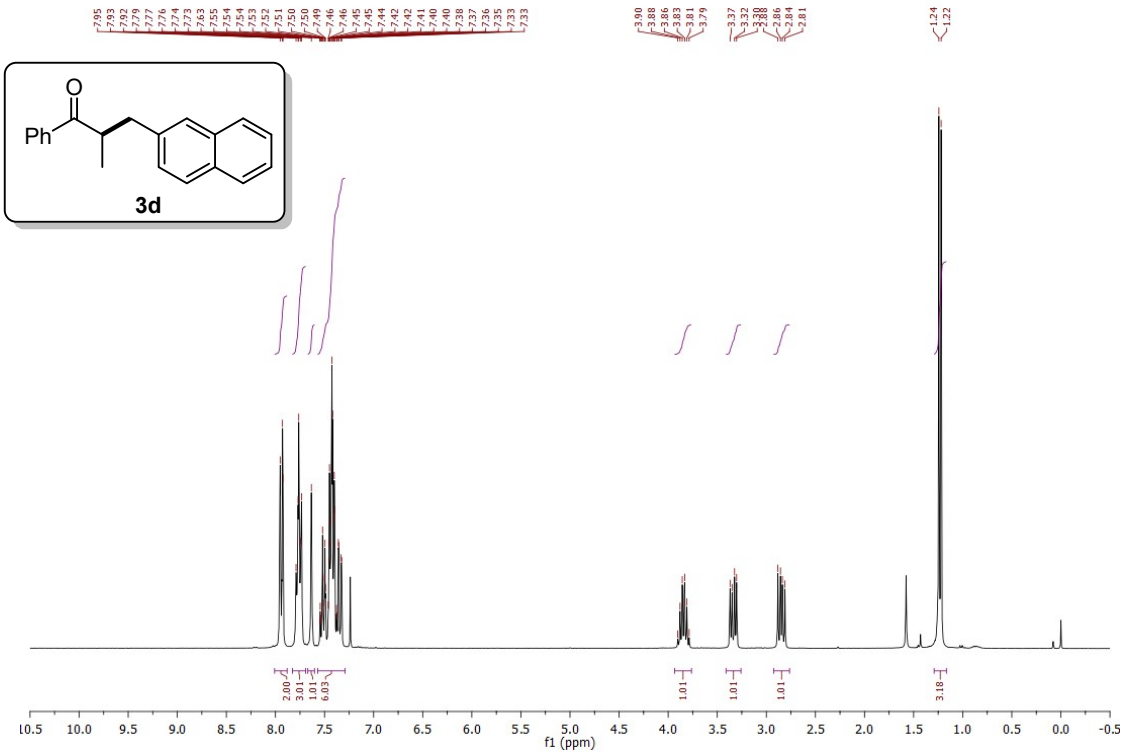
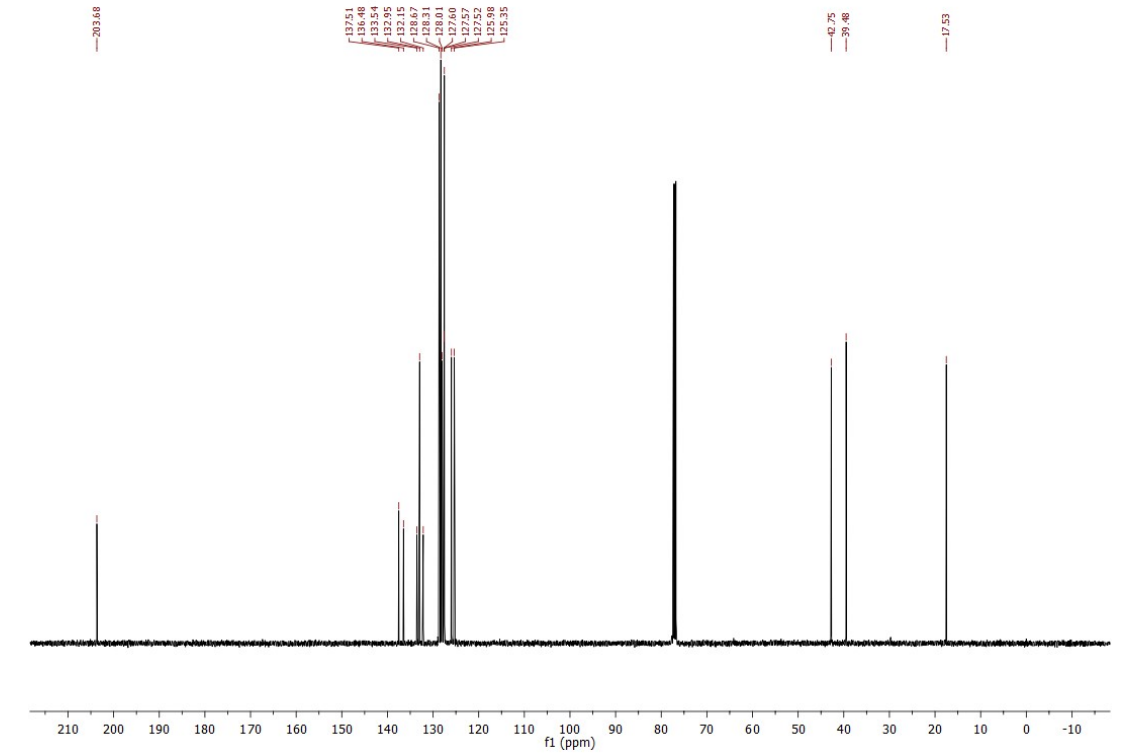
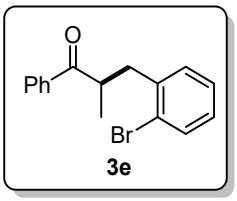



O
Ph
3c
f1 (ppm)


f1 (ppm)

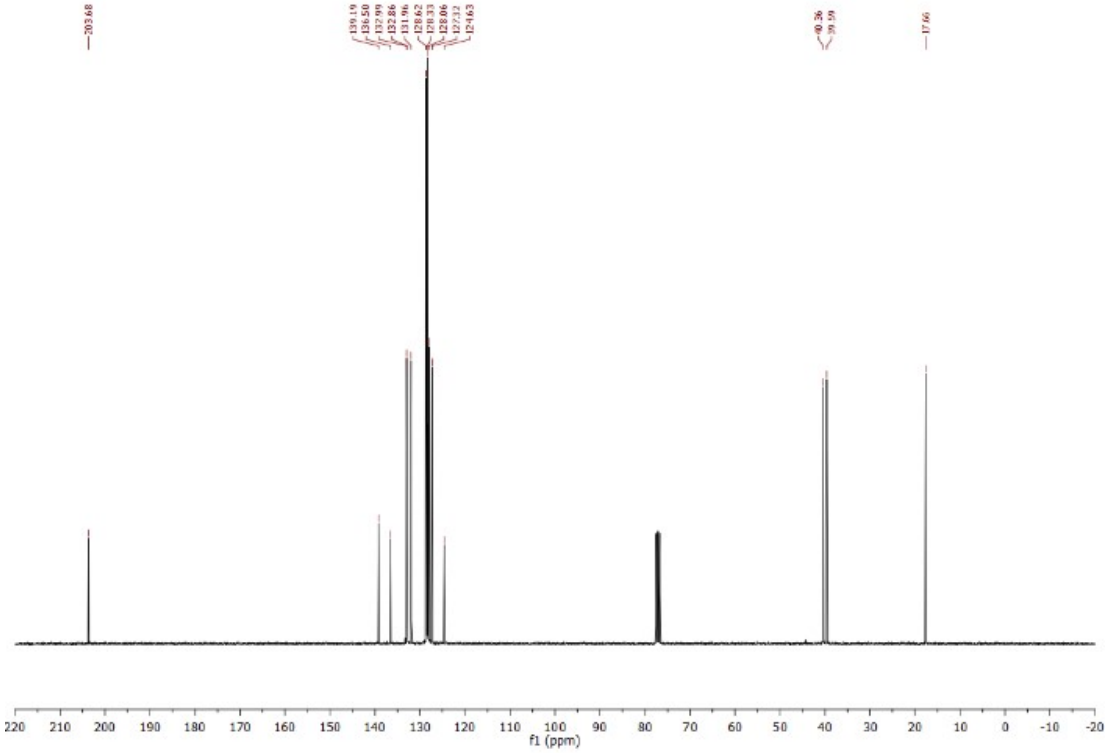

Ph
O
3d
f1 (ppm)

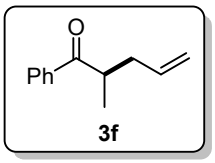

f1 (ppm)


O
Ph
Br

3e

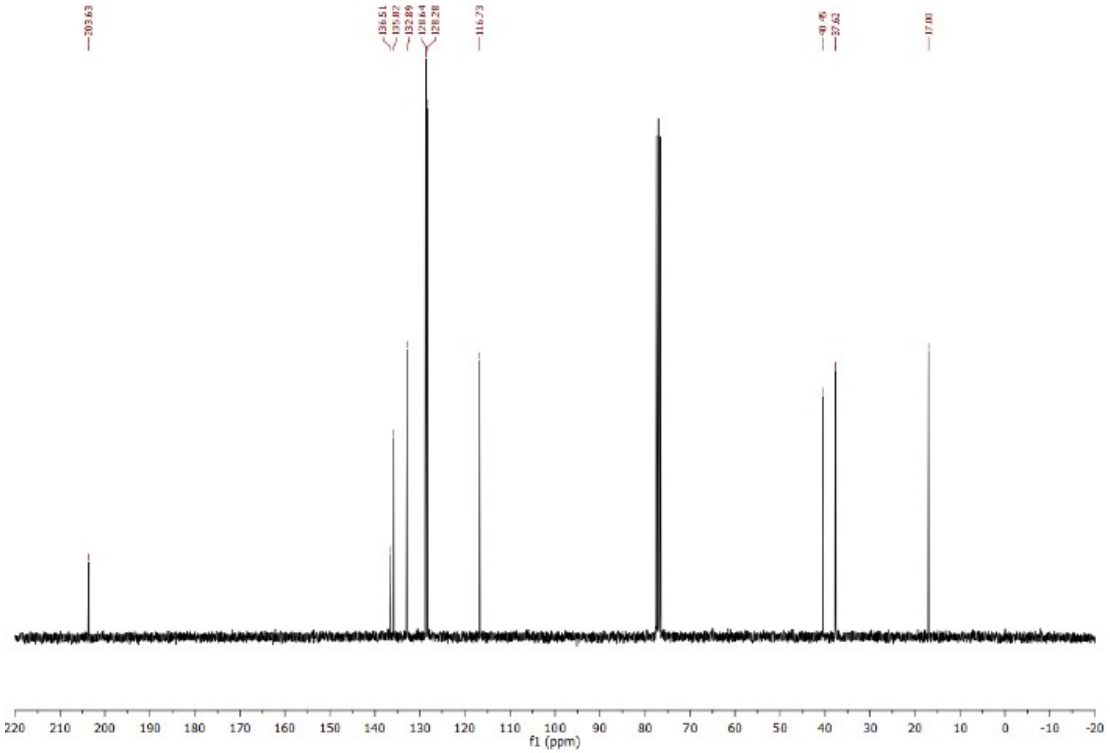
2.00
2.01
2.02
2.06
1.00
1.02
1.01
1.01
3.01
f1 (ppm)

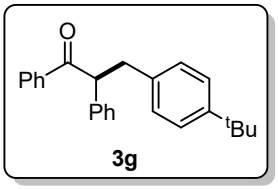

203.68
139.19
136.50
132.99
132.86
131.96
128.62
128.33
128.06
127.32
124.63
40.36
39.59
17.66
f1 (ppm)


O
Ph

3f

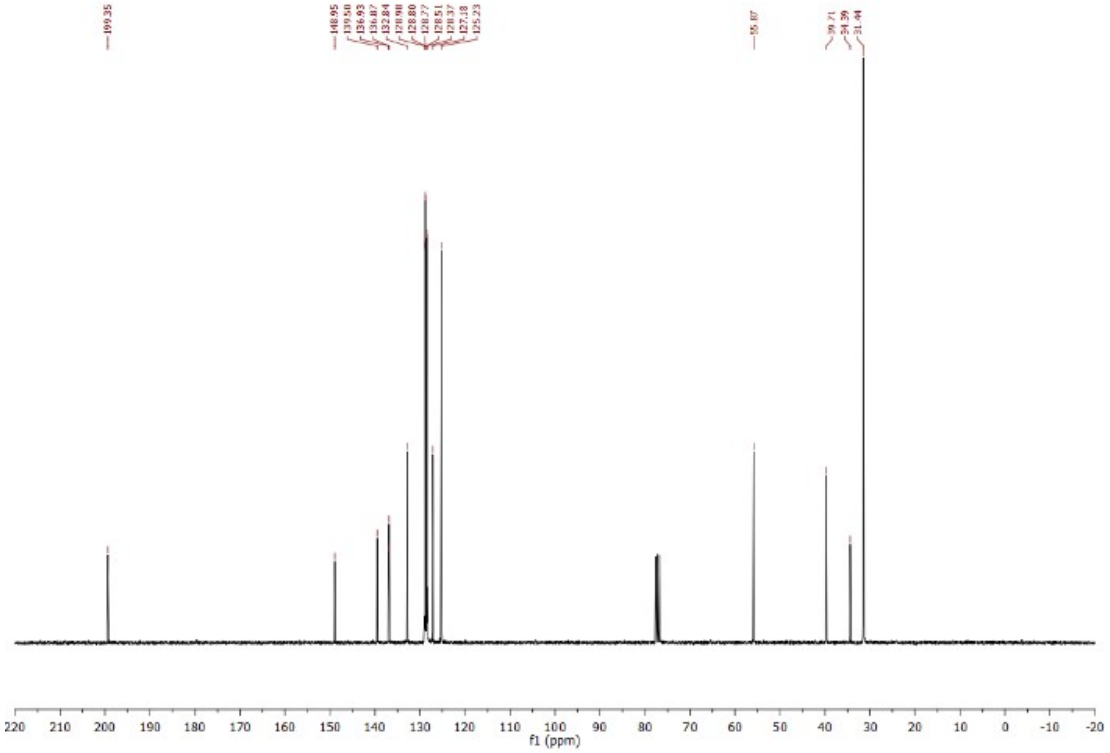
2.00
1.01
2.01
1.01
2.03
1.02
1.04
1.03
3.03
f1 (ppm)

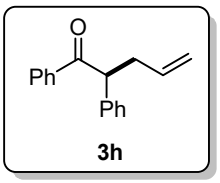

203.63
136.51
135.82
132.89
128.64
128.28
116.73
40.45
37.62
17.00
f1 (ppm)


O
Ph
Ph
tBu

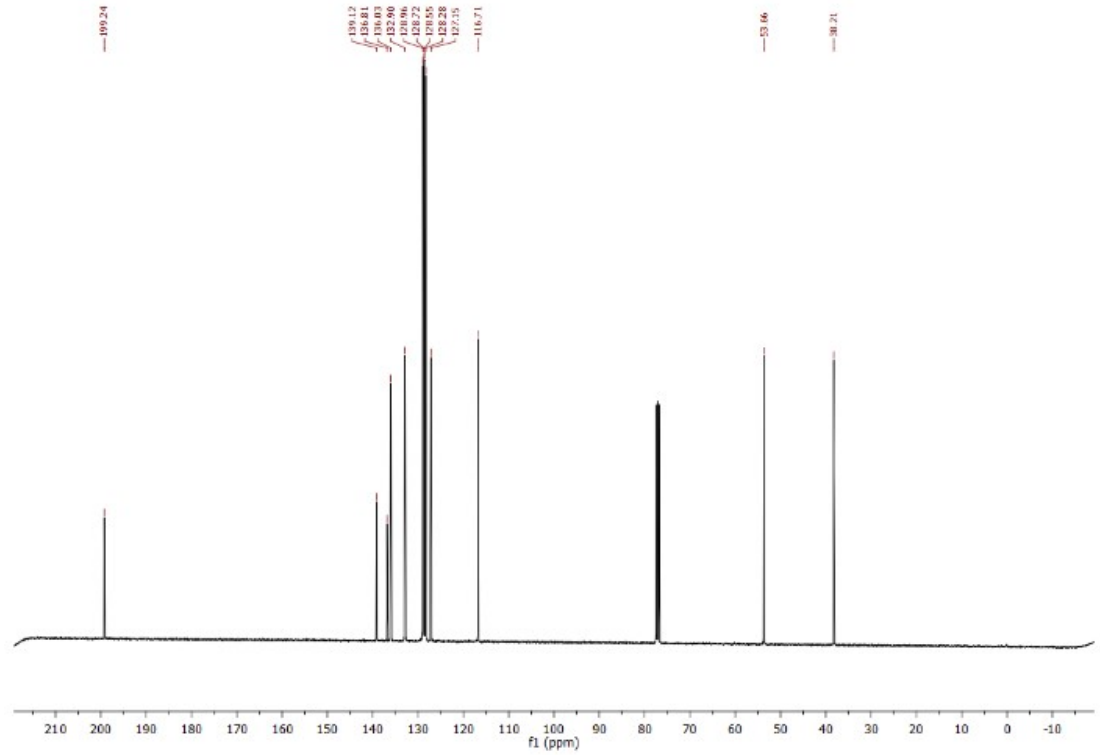
3g

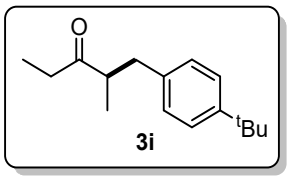
7.90
7.88
7.41
7.38
7.36
7.31
7.28
7.26
7.23
7.22
7.21
7.19
7.05
7.02
4.86
4.84
4.81
3.62
3.59
3.57
3.55
3.05
3.03
3.01
2.99
1.25
2.02
1.10
9.02
2.02
1.00
1.00
1.00
9.00
f1 (ppm)


199.35
148.95
139.50
136.93
136.87
132.84
128.98
128.80
128.77
128.51
128.37
127.18
125.23
55.87
39.71
34.39
31.44
f1 (ppm)

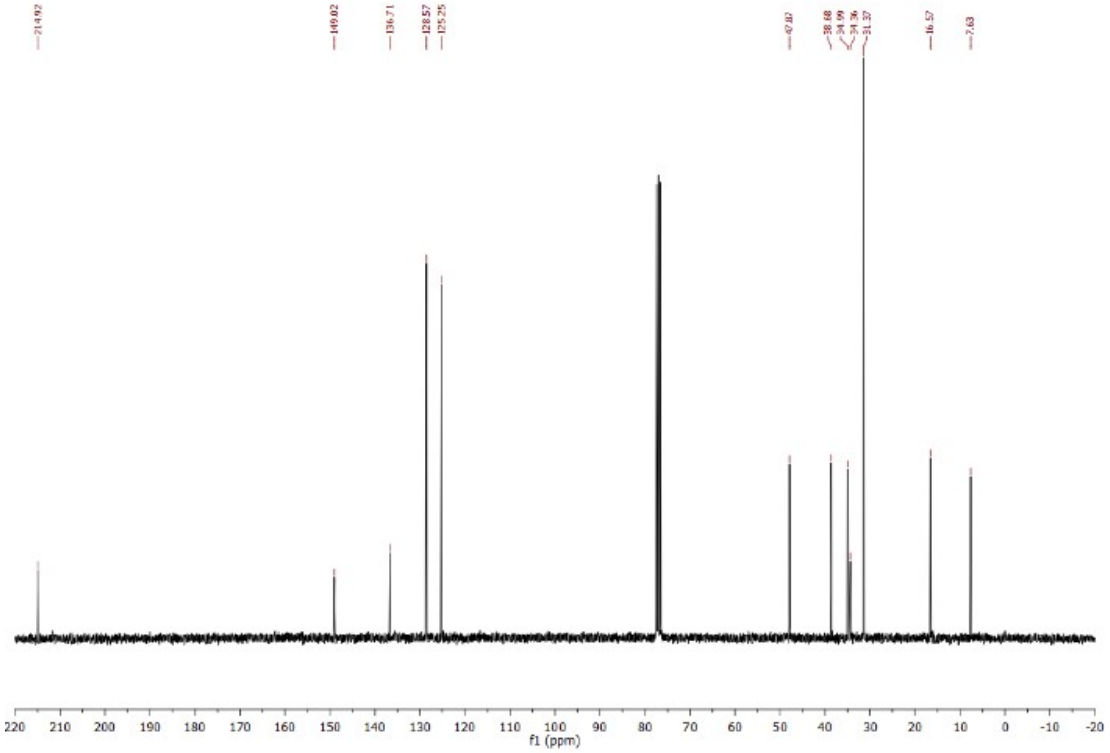


3h

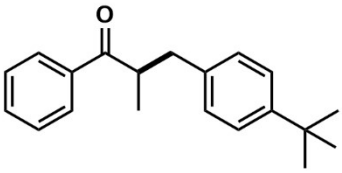
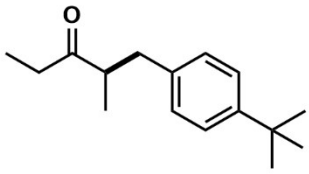
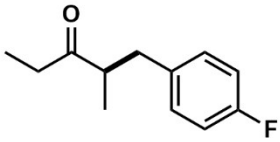
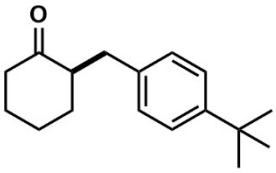




3i



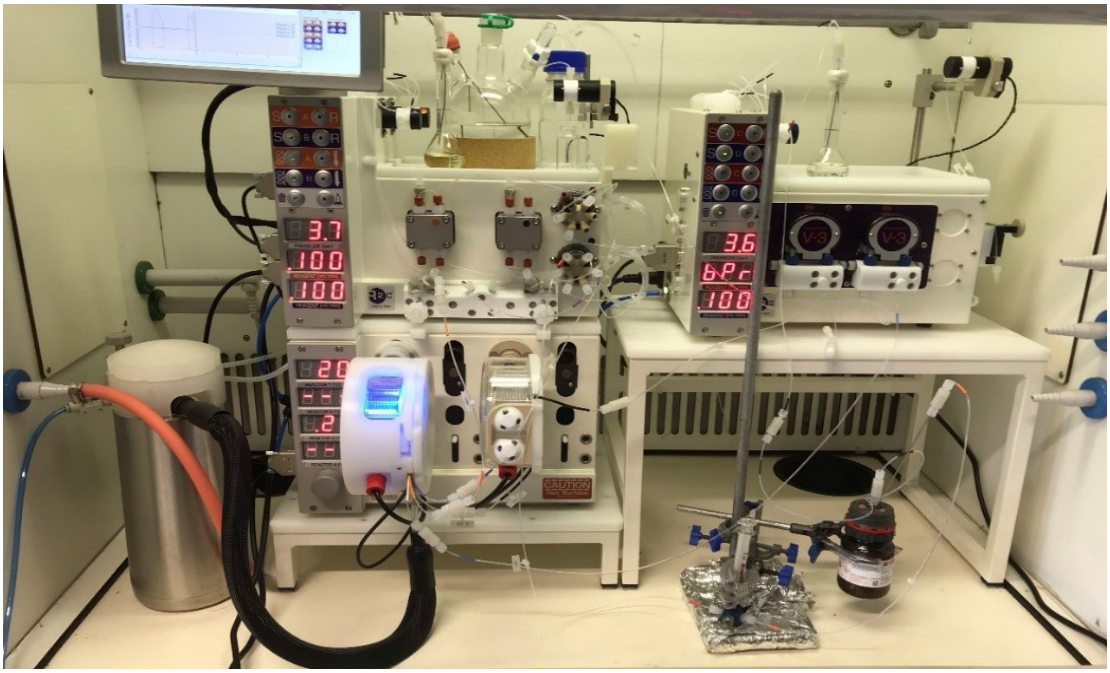
5. Some early comparative examples of Batch & Flow

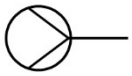
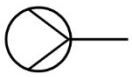
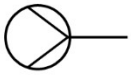
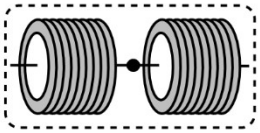
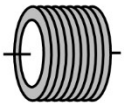
Product	Batch Results Isolated (Yield %)[b]	Flow Results	
		Steady State (Yield %)[a]	Isolated (Yield %)[b]
	44	90	81
	-	55	54
	26	73	-
	49	34	-

[a]Determined by use of ^{1}H NMR spectra with 1,3,5-trimethoxybenzene as internal standard.

[b]Isolated yield after purification by column chromatography on SiO_2.

6. Continuous Flow Apparatus Set-up



Symbol	Component	Apparatus
	Pump/Line A	Vapourtec R2C+ acid resistant HPLC/piston pump
	Pump/Line B	Vapourtec R2C+ acid resistant HPLC/piston pump
	Pump/Line D	Vapourtec R2S slurry and suspension V3 peristaltic pump
	Sample Loop	Vapourtec sample injection loop (2 or 10 mL)
	Reactor Coil 1 (RC 1)	Vapourtec 10 mL cooled dual tube reactor (2 and 8 mL)
	Reactor Coil 2 (RC 2)	Vapourtec standard 10 mL coiled tubular reactor
	Pump/Line C	Vapourtec R2S slurry and suspension V3 peristaltic pump (Back pressure regulator)