In situ sulfidation of Pd/C: A straightforward method for chemoselective conjugate reduction by continuous hydrogenation

Jonathan C. Moore, Rowena A. Howie, Samuel L. Bourne, Gareth Jenkins, Peter Licence, Martyn Poliakoff and Michael W. George*

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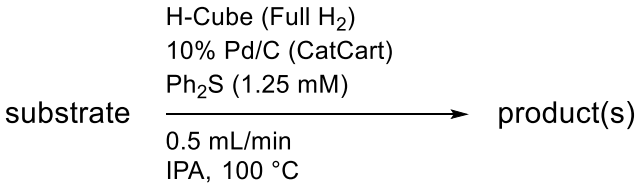
Materials and Methods

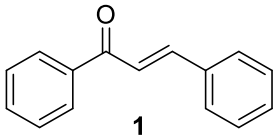
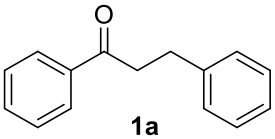
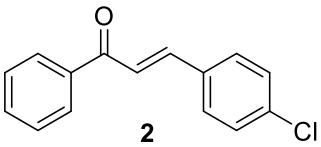
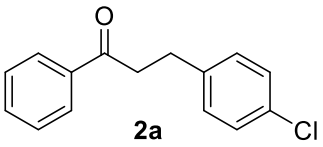
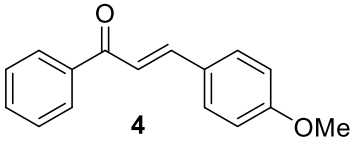
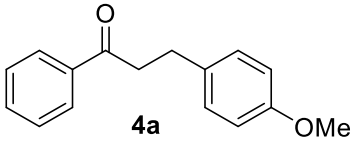
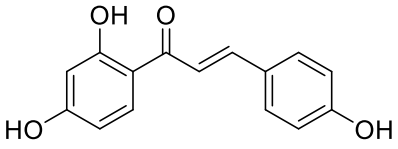
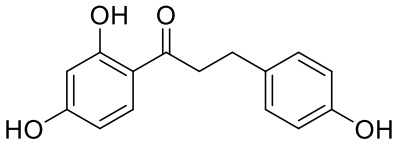
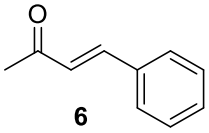
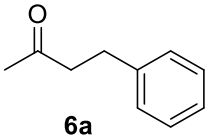
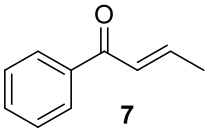
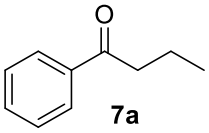
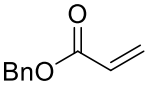
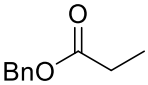
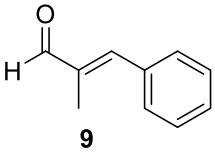
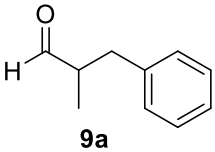
All reagents were purchased from a chemical supplier and used without further purification. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at ambient temperature using a Bruker AV3400HD (400 MHz), spectrometer. Data are expressed as chemical shifts in parts per million (ppm) relative to residual solvent signals ($CHCl_3$, ^{1}H NMR 7.26), ($CDCl_3$, ^{13}C NMR 77.16) as the internal standard on the δ scale. Infra-red spectra were recorded using a Bruker Tensor 27 FT-IR spectrophotometer using an ATR attachment and their peaks are quoted as υ_{max} in cm^{-1}. HRMS analyses were performed on a Bruker micrOTOFII mass spectrometer (Bruker Daltonik, Bremen, Germany), interfaced to an Agilent 1200 HPLC (Agilent Technologies, Santa Clara, USA). Samples were presented in solution for analysis by Flow Injection, 1µL of solution being injected into the ion source of the instrument along with a flow of 0.2 mL min^{-1} of 70% methanol/water eluent. The mass spectrometer was operated in electrospray ionisation (ESI) mode at a typical resolving power of 8000. Control of the analysis was performed through Bruker's Compass Open Access QC automated data acquisition and reporting software (v1.3; Bruker Daltonik, Bremen, Germany). Data could be further processed, if required, using DataAnalysis software (v3, B110, 64bit; Bruker Daltonik, Bremen, Germany).

General Procedure for Continuous Hydrogenation



The catalyst cartridge was equilibrated with IPA at 3 mL min^{-1} for 1 min. The flow rate was then reduced to 0.5 mL min^{-1} and H_2 generation was initiated in "Full H_2" mode (30 mL H_2 min^{-1}) at 100 °C. Once the temperature had been reached, the inlet tube was switched to a solution of diphenyl sulfide in IPA (1.25 mM). After 20 mins, the inlet tube was switched to IPA for 3 mins and then to a solution of substrate (0.5 mmol) in IPA (5 mL). Once the substrate solution was almost empty, the inlet was switched back to IPA for a further 20 mins. The crude material was obtained by removal of the solvent under reduced pressure.

List of Substrates and Products

Entry	Substrate	Ref.	Product	Ref.
1	 **1**	S[1]	 **1a**	S[2]
2	 **2**	S[3]	 **2a**	S[4]
3	 **4**	S[5]	 **4a**	S[4]
4	 isoliquiritigenin (**5**)	S[6]	 davidigenin (**5a**)	S[7]
5	 **6**	S[8]	 **6a**	S[2]
6	 **7**	S[9]	 **7a**	S[10]
7	 **8**	S[11]	 **8a**	S[12]
8	 **9**	S[13]	 **9a**	S[14]

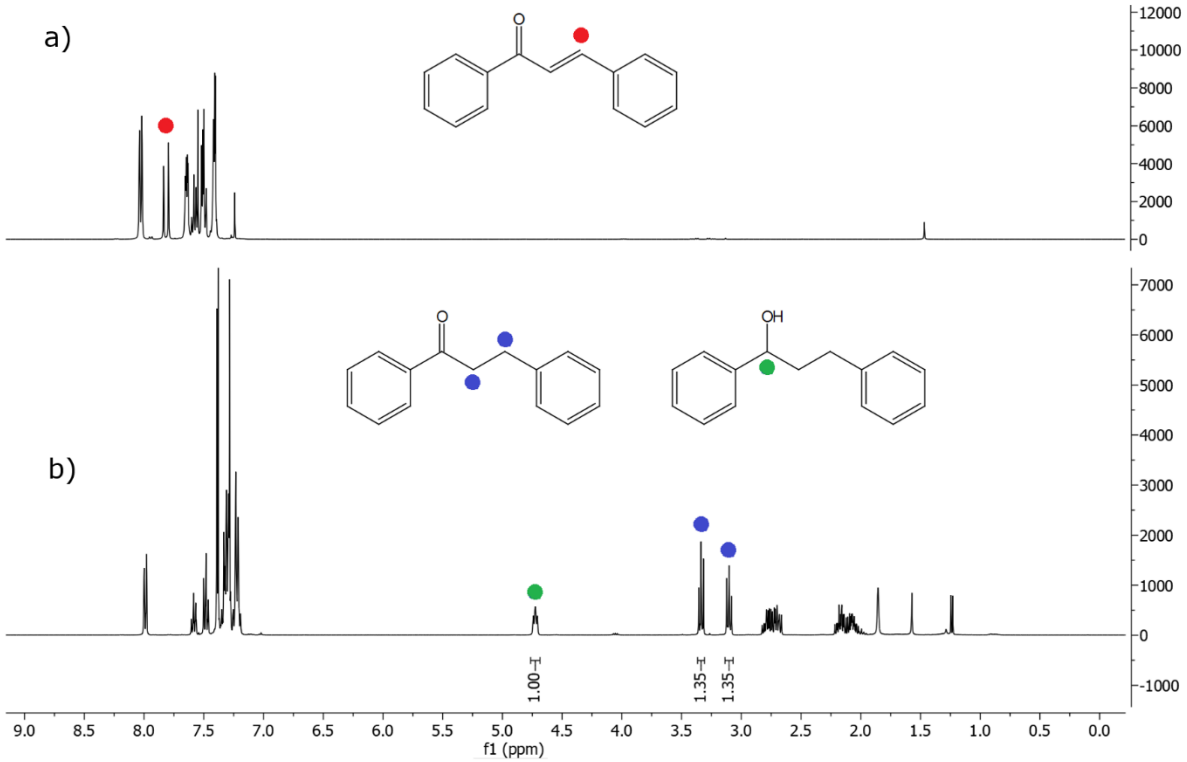
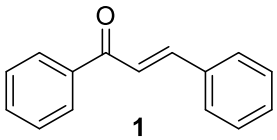


Fig. S1 – Example of determination of product distributions by ^{1}H NMR a) ^{1}H NMR spectrum of chalcone (**1**); b) ^{1}H NMR spectrum of a crude mixture showing >95% conversion and 40% selectivity for the targeted dihydrochalcone **1a** over the corresponding alcohol **1b** (0.675:1 molar ratio).

Compound Characterisation

(*E*)-Chalcone (1)

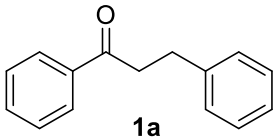


1

(*E*)-Chalcone (**1**) was obtained commercially and used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.06 – 7.99 (2H, m), 7.82 (1H, d, *J* = 15.7 Hz), 7.69 – 7.62 (2H, m), 7.62 – 7.57 (1H, m), 7.57 – 7.48 (3H, m), 7.47 – 7.39 (3H, m); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 190.7, 145.0, 138.4, 135.0, 132.9, 130.7, 129.1, 128.8, 128.6, 128.6, 122.2.

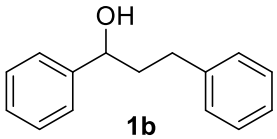
1,3-Diphenylpropan-1-one (1a)



1a

FTIR (ATR) ν_{max} /cm^{-1}: 2951, 1680, 1494, 1447, 1364, 1291, 1204; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.99 – 7.94 (2H, m), 7.59 – 7.53 (1H, m), 7.49 – 7.42 (2H, m), 7.34 – 7.24 (2H, m), 7.24 – 7.18 (1H, m), 3.34 – 3.28 (2H, m) 3.11 – 3.05 (2H, m); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 199.4, 141.4, 137.0, 133.2, 128.8, 128.7, 128.6, 128.2, 126.3, 40.6, 30.3.; **HRMS** (ESI) m/z calculated for $C_{15}H_{14}NaO$ $[M+Na]^+$ 233.0937, obtained 233.0949.

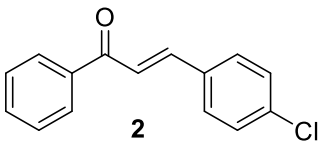
1,3-Diphenylpropan-1-ol (1b)



1b

FTIR (ATR) ν_{max} /cm^{-1}: 3360, 1494, 1453, 1056, 1028; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.40 – 7.33 (4H, m), 7.33 – 7.25 (3H, m), 7.23 – 7.16 (3H, m), 4.74 – 4.66 (1H, m), 2.81 – 2.63 (2H, m), 2.20 -1.98 (2H, m); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 144.7, 141.9, 128.7, 128.6, 128.5, 127.8, 126.1, 126.0, 74.0, 40.6, 32.2.; **HRMS** (ESI) m/z calculated for $C_{15}H_{16}NaO$ $[M+Na]^+$ 235.1099, obtained 235.1099.

(*E*)-3-(4-Chlorophenyl)-1-phenylprop-2-en-1-one (2)



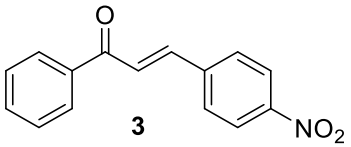
2

To a room temperature solution of acetophenone (500 mg, 4.16 mmol) in EtOH (8 mL) was added an aqueous solution of NaOH (3M, 4.2 mL) and then 4-chlorobenzaldehyde (585 mg, 4.16 mmol). The reaction mixture was stirred at room temperature for two hours and the resulting precipitate was collected by filtration and washed

with H_2O (3 x 10 mL). The crude material was purified by re-crystallisation from hot methanol to yield the title compound (505 mg, 2.08 mmol, 50%) as an off-white crystalline solid.

FTIR (ATR) ν_{max}/cm^{-1}: 1655, 1603, 1590, 1489, 1216, 983; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.04 - 8.00 (2H, m), 7.76 (1H, d, *J* = 15.7 Hz), 7.63 – 7.56 (3H, m), 7.54 – 7.47 (3H, m), 7.43 – 7.37 (2H, m); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 190.4, 143.5, 138.2, 136.6, 133.5, 133.1, 129.7, 129.4, 128.8, 128.7, 122.6; **HRMS** (ESI) m/z calculated for $C_{15}H_{11}ClNaO$ $[M+Na]^+$ 265.0391, obtained 265.0392.

(*E*)-3-(4-Nitrophenyl)-1-phenylprop-2-en-1-one (3)

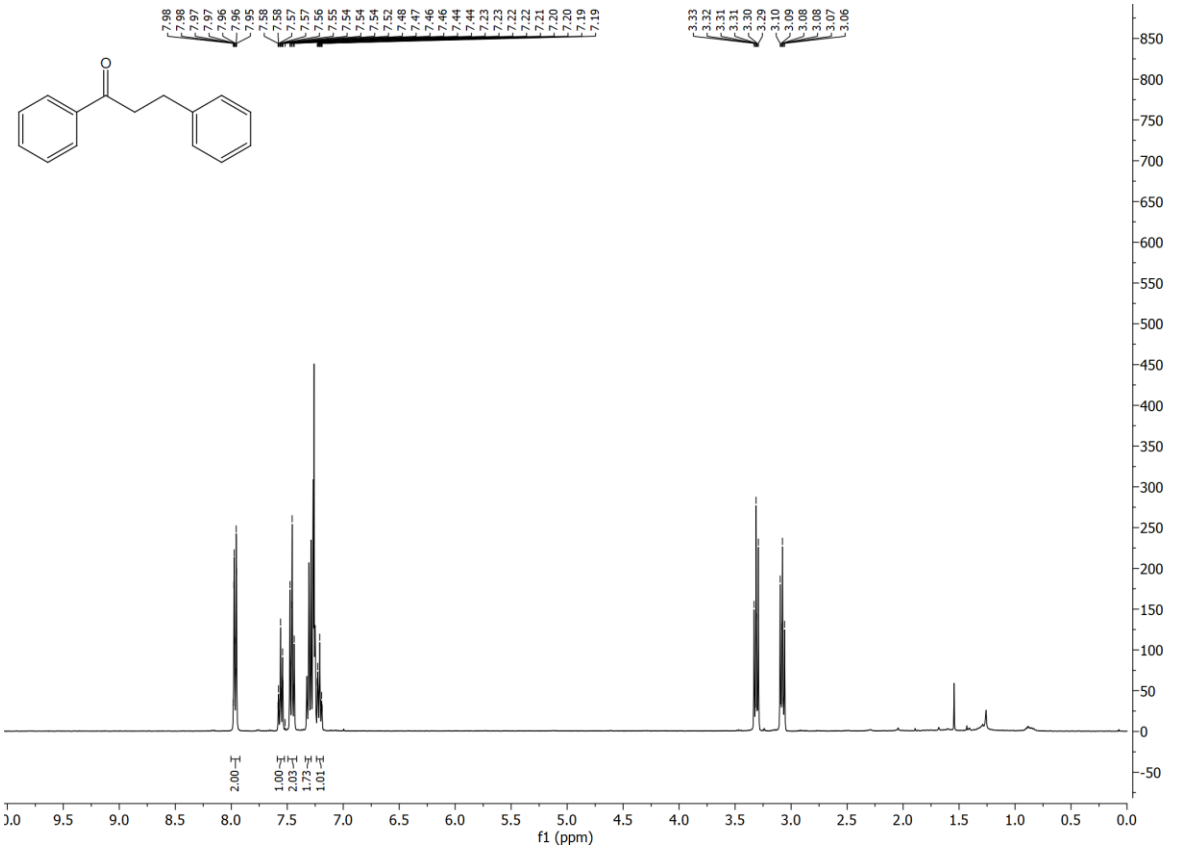


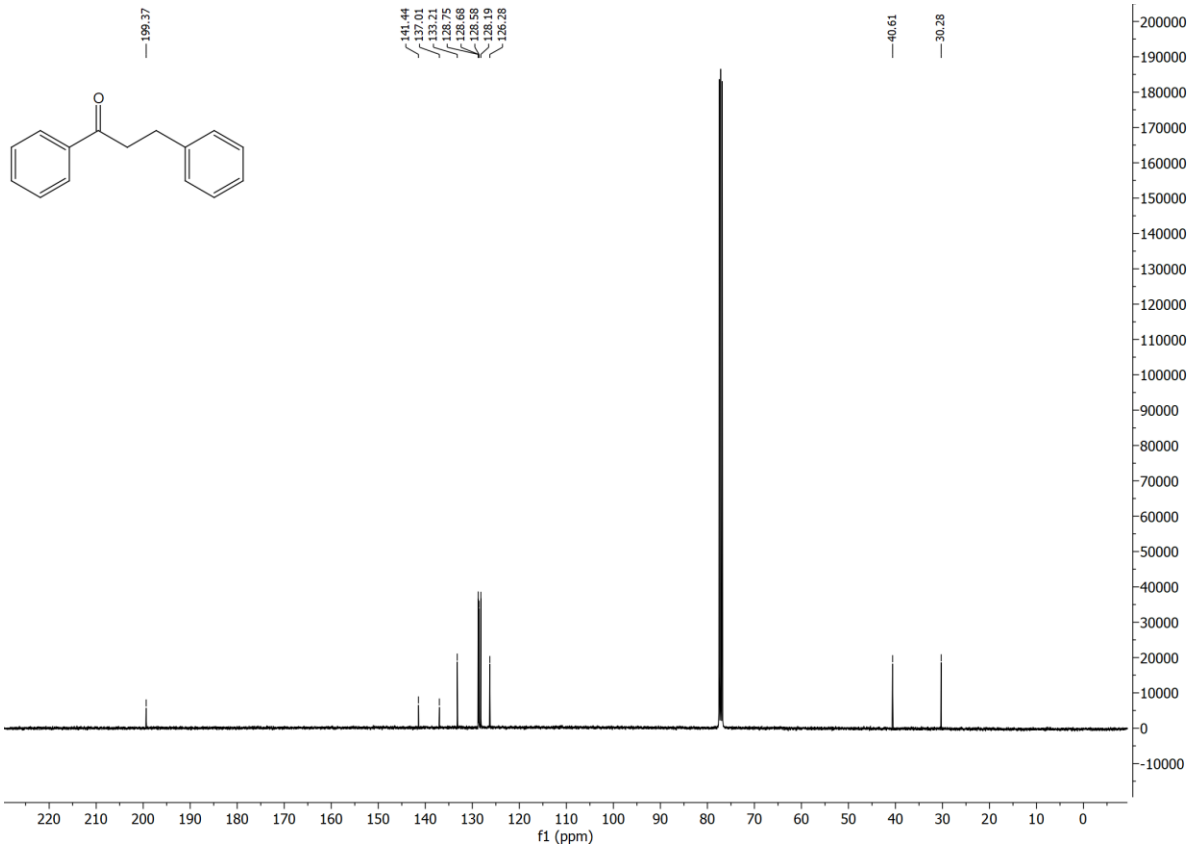
3

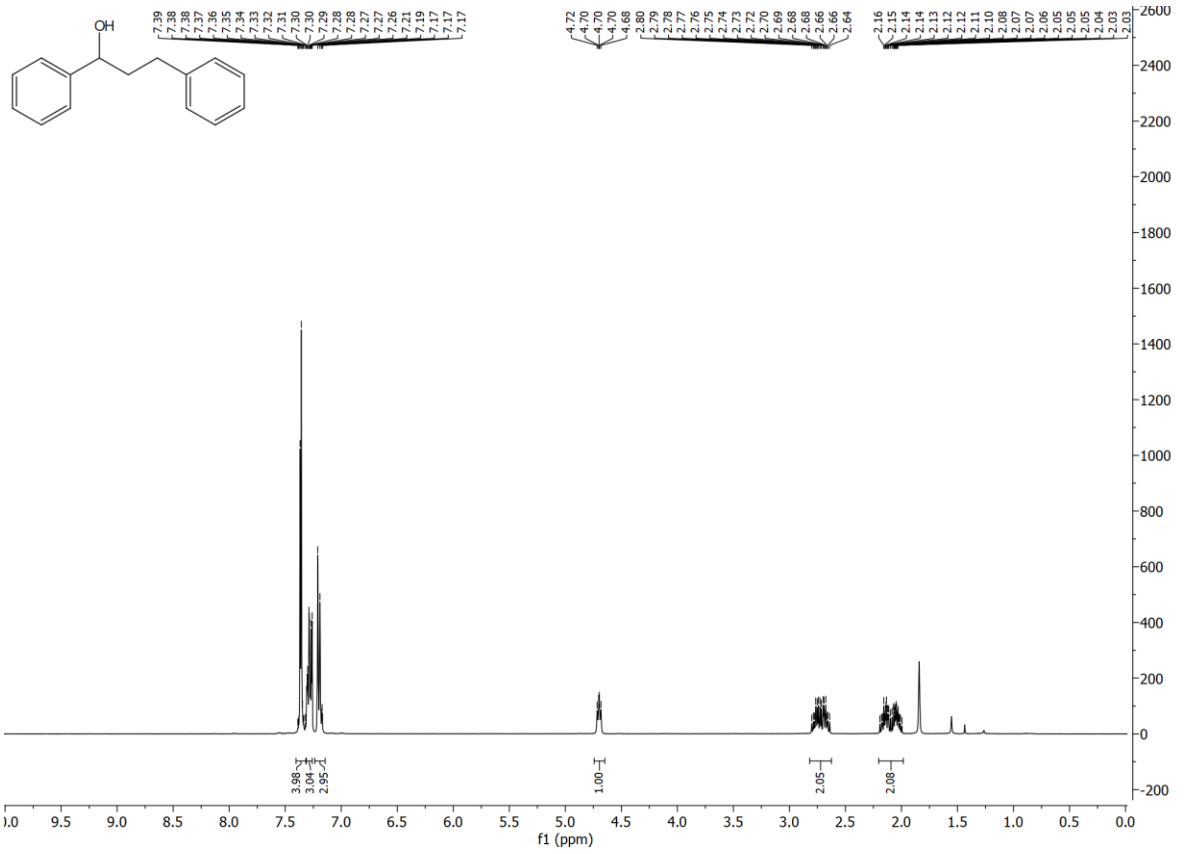
To a room temperature solution of acetophenone (500 mg, 4.16 mmol) in EtOH (8 mL) was added an aqueous solution of NaOH (3M, 4.2 mL) and then 4-nitrobenzaldehyde (629 mg, 4.16 mmol). The reaction mixture was stirred at room temperature for two hours and the resulting precipitate was collected by filtration and washed with H_2O (3 x 10 mL). The crude material was purified by re-crystalisation from hot methanol to yield the title compound (421 mg, 1.66 mmol, 40%) as an orange crystalline solid.

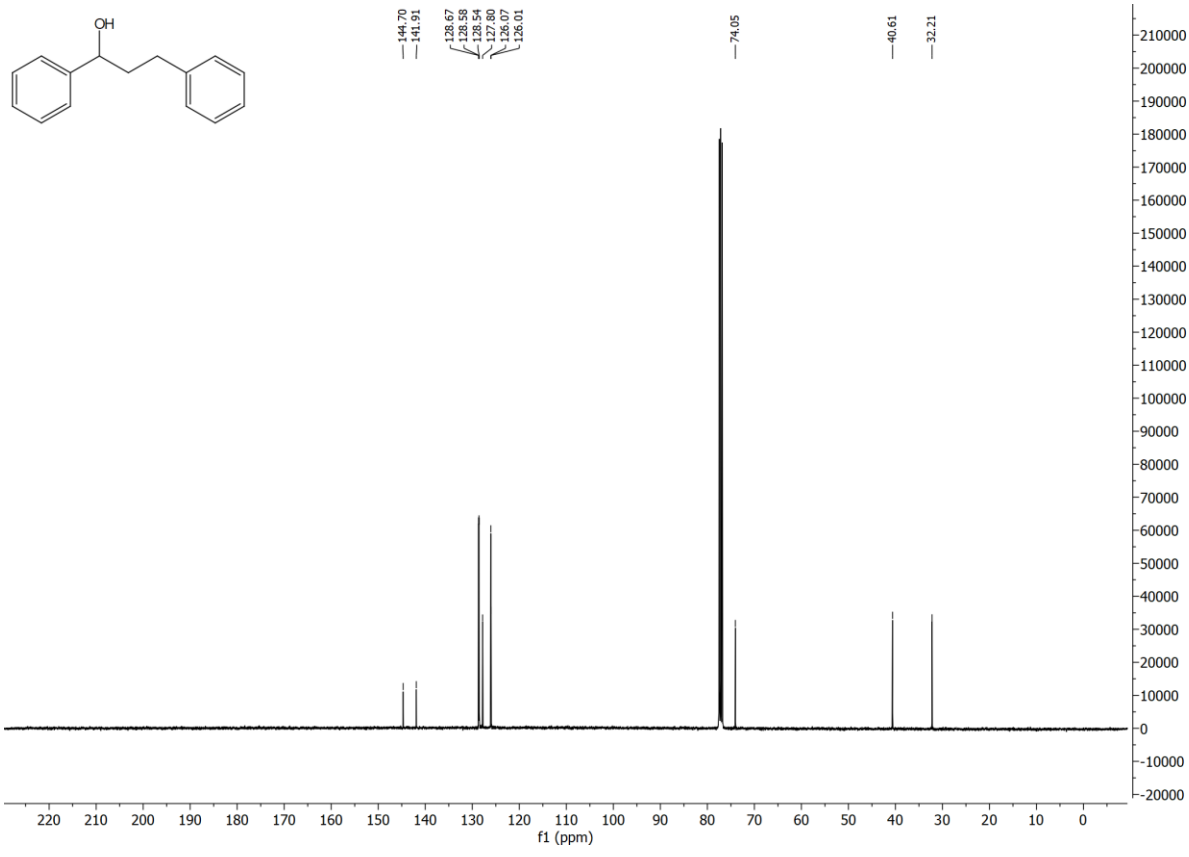
FTIR (ATR) ν_{max}/cm^{-1}: 1656, 1594, 1512, 1330, 1216, 1104; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.31 – 8.26 (2H, m), 8.07 – 8.01 (2H, m), 7.86 - 7.77 (3H, m), 7.68 -7.60 (2H, m), 7.57 -7.51 (2H, m); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 189.8, 148.7, 141.7, 141.2, 137.7, 133.5, 129.1, 129.0, 128.8, 125.9, 124.4; **HRMS** (ESI) m/z calculated for $C_{15}H_{11}NNaO_3$ $[M+Na]^+$ 276.0631, obtained 276.0640.

^{1}H and ^{13}C NMR Spectra






OH
7.39 7.38 7.38 7.37 7.36 7.35 7.34 7.33 7.32 7.31 7.30 7.30 7.29 7.28 7.28 7.27 7.27 7.26 7.21 7.19 7.17 7.17 7.17 7.17
4.72 4.70 4.70 4.70 4.68
2.80 2.79 2.78 2.77 2.76 2.75 2.74 2.73 2.72 2.70 2.69 2.68 2.68 2.66 2.66 2.64
2.16 2.15 2.14 2.14 2.13 2.12 2.11 2.10 2.08 2.07 2.07 2.06 2.05 2.05 2.04 2.03 2.03
3.98
3.04
2.95
1.00
2.05
2.08
f1 (ppm)


OH
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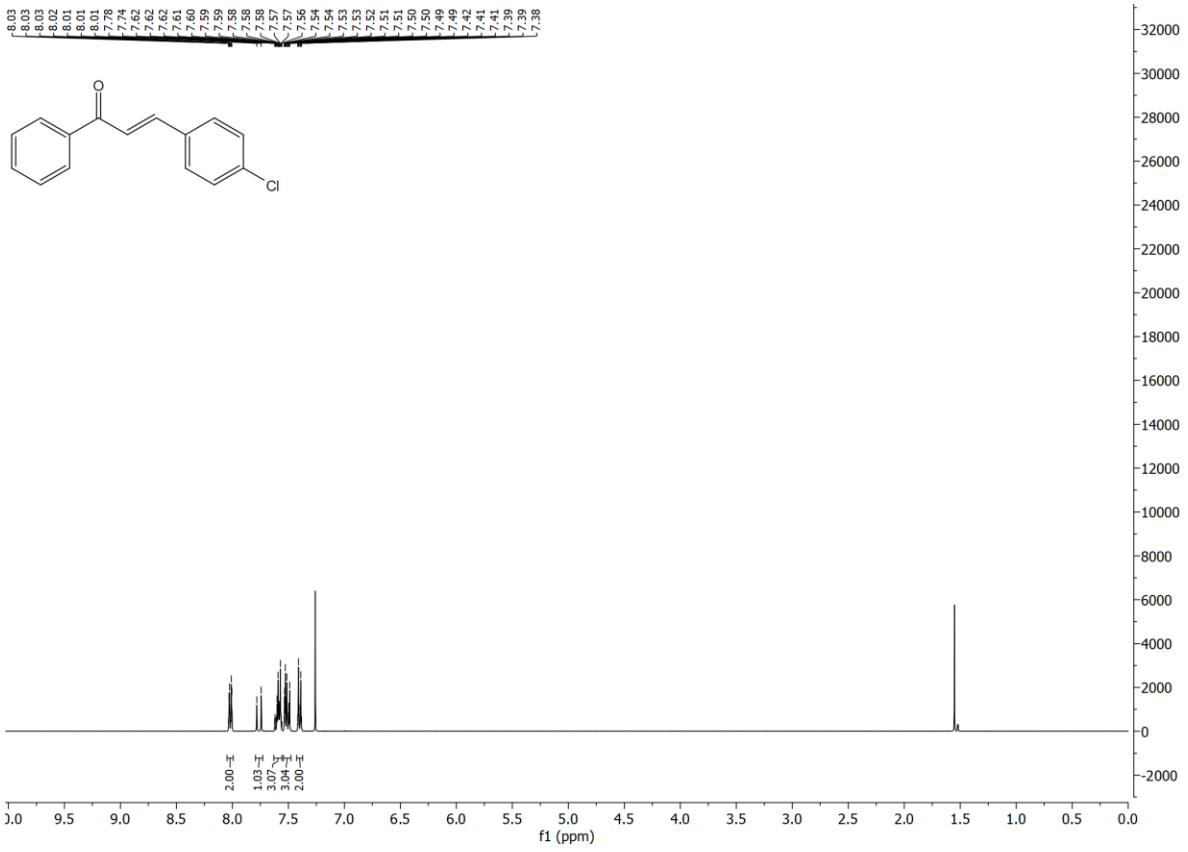
141.91
128.67
128.58
128.54
127.80
126.07
126.01
74.05
40.61
32.21
f1 (ppm)


8.03
8.03
8.03
8.02
8.01
8.01
8.01
7.78
7.74
7.62
7.62
7.62
7.61
7.60
7.59
7.59
7.58
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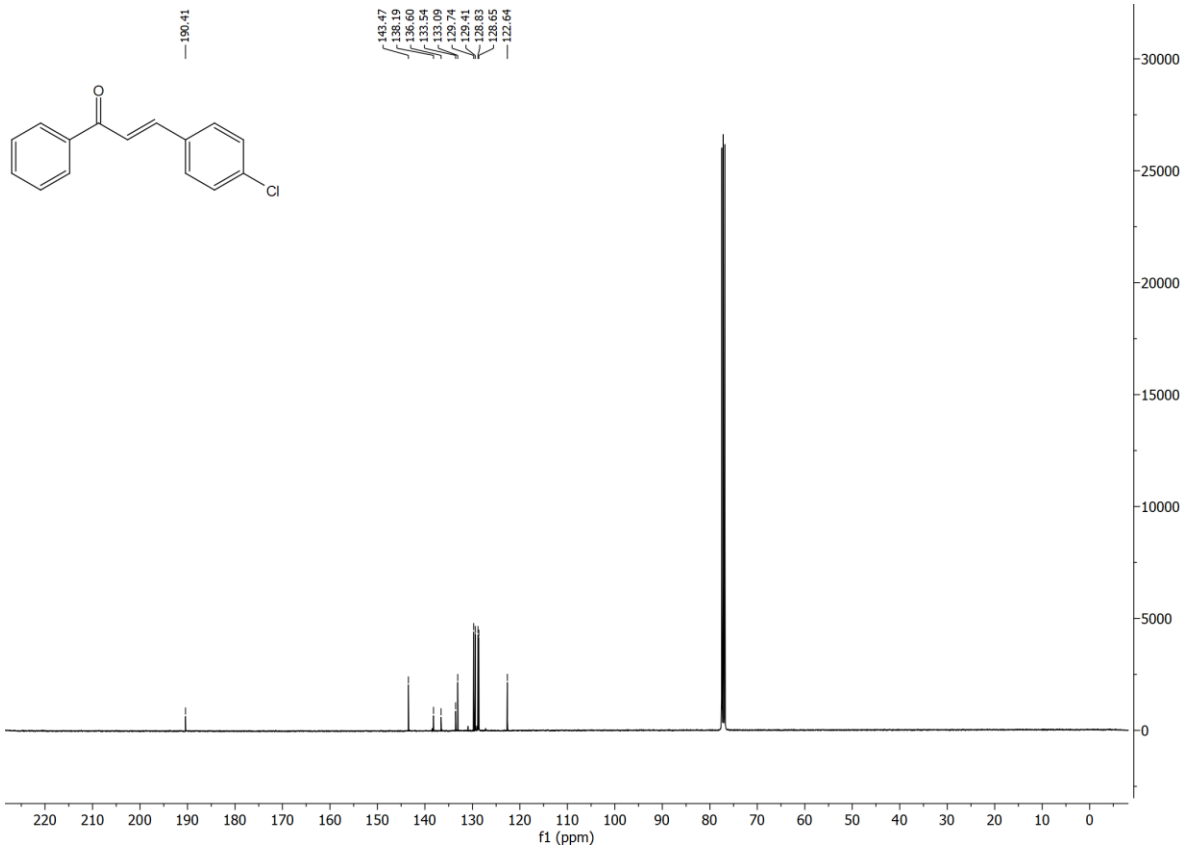
7.53
7.52
7.51
7.51
7.50
7.50
7.49
7.49
7.42
7.41
7.41
7.39
7.39
7.38
O
Cl
2.00
1.03
3.07
3.04
2.00
f1 (ppm)


190.41
143.47
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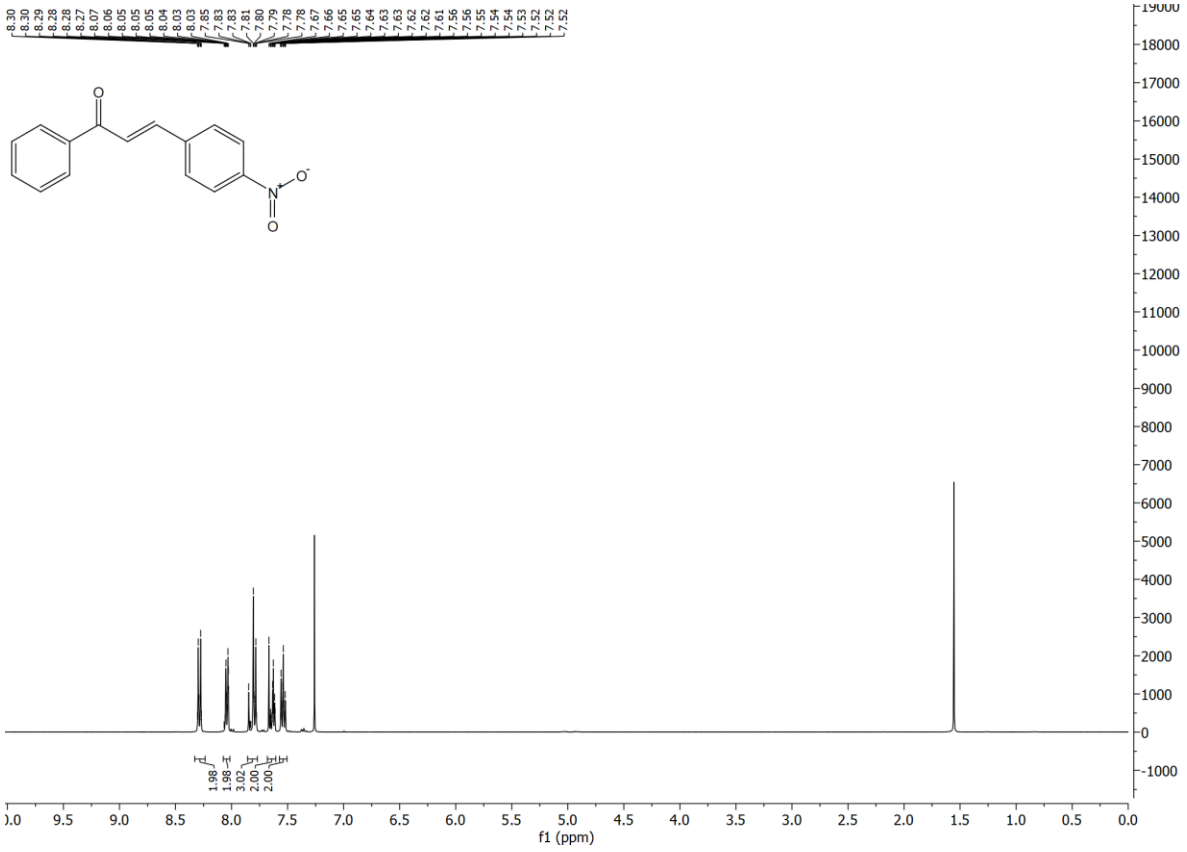
133.54
133.09
129.74
129.41
128.83
128.65
122.64
O
Cl
f1 (ppm)


8.30
8.30
8.29
8.28
8.28
8.27
8.07
8.06
8.05
8.05
8.05
8.04
8.03
7.85
7.83
7.83
7.81
7.80
7.79
7.78
7.78
7.67
7.66
7.65
7.65
7.64
7.63
7.63
7.62
7.62
7.61
7.56
7.56
7.55
7.54
7.54
7.53
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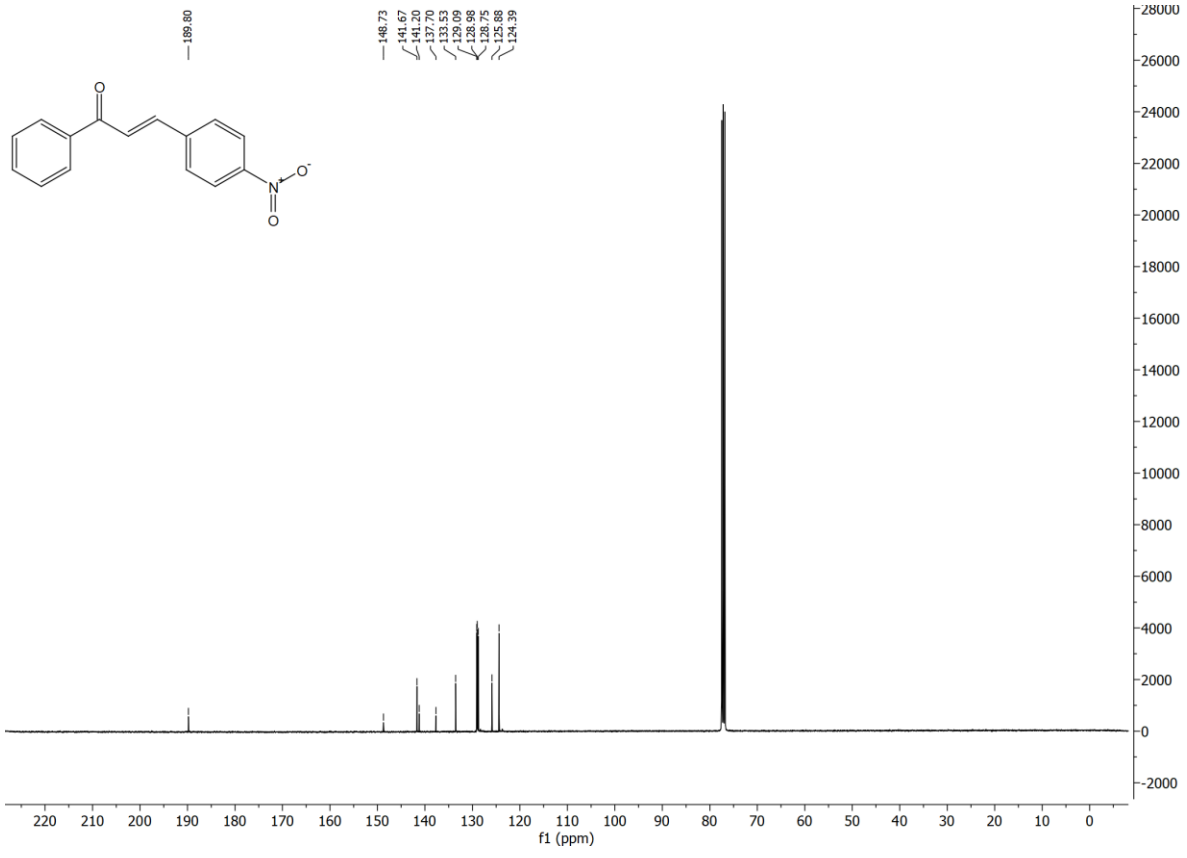
1.98
1.98
3.02
2.00
2.00
f1 (ppm)


189.80
148.73
141.67
141.20
137.70
133.53
129.09
128.98
128.75
125.68
124.39
O
N
O
O
f1 (ppm)

GreenMotion™ Analysis

The selected answers are highlighted in bold:

1) Raw materials origin:
   a) Natural raw material
   b) Raw material obtained by hemisynthesis
   c) **Raw material obtained from chemical synthesis**

2) Renewable carbon percentage: **0%**

3) GHS pictograms of the final product:

   a) Explosive
   b) Toxic
   c) Corrosive
   d) Dangerous for Environment
   e) Flammable
   f) Nocive (Exclamation point)
   g) Dangerous for health (CMR) Cat. 1
   h) Dangerous for health (CMR) Cat. 2
   i) Combustive
   j) Compressed gas

4) Is this process step natural? **No**

5) Tick GHS pictograms visible on the reagents and solvents labels:

   a) Explosive
   b) Toxic
   c) Corrosive
   d) Dangerous for Environment
   e) Flammable
   f) Nocive (Exclamation point)
   g) Dangerous for health (CMR) Cat. 1
   h) Dangerous for health (CMR) Cat. 2
   i) Combustive
   j) Compressed gas

6) Tick the solvents used during this step:

   a) No solvent
   b) Water
   c) Supercritical CO_2
   d) Supercritical tetrafluoroethane
   e) Supercritical water
   f) Ethanol
   g) Vegetable oil
   h) Another renewable solvent
   i) Hexane
   j) Cyclohexane, methylcyclohexane
   k) Toluene
   l) MTBE
   m) MEK
   n) THF
   o) Acetone
   p) Isopropyl acetate
   q) Ethyl acetate
   r) Another petrochemical solvent
   s) Methanol
   t) Methylene chloride

7) Step yield: **84%**

8) Number of solvents used: **1**

9) Atom economy: **1**
The atom economy calculation was simplified by the calculation of the carbon economy.
A Chain reduction leading to the loss of carbon atoms will be penalized unlike in case of a rearrangement or addition step in which the total carbon atoms of reactants engaged will be kept.
Carbon economy definition : Number of carbons of the product at the end of the step / Total number of carbons in the main reagents involved

10) Is it a protection or a deprotection step: **No**

11) Is it a:

a) microbiological transformation step? **No**
b) steam distillation step? **No**

12) Step duration (hours): 0.1666 (5 mL of substrate solution at 0.5 mL min^{-1}

13) Reaction step under pressure?

a) Process at atmospheric pressure
b) Process under pressure

14) Ways of heating:

a) No heating
b) Steam 1 bar
c) Steam up to 3 bars
d) Steam up to 6 bars
e) Steam up to 15 bars
f) Oil
g) Electrical resistance
h) Gas

15) Ways of cooling:

a) No cooling
b) Water
c) Glycol water
d) Brine

16) Distillation conditions:

a) No distillation
b) Distillation at atmospheric pressure
c) Distillation under vacuum

17) Does the step belong to the following list? **No.** If yes, tick its name.

a) Sulfonylation
b) Nitrification
c) Chlorination
d) Silylation
e) Polyoxyethylenation with ethylene oxide
f) Process using isocyanate, short alkyl halide or alkyl sulfate
g) Process using phosphorous oxychloride
h) Crystallization
i) Ozonolysis
j) Liquid-liquid extraction
k) Other energy intensive process

18) E-factor: **1.34**

Definition of E-Factor: mass of waste (kg) / mass of desired product (kg).
*s*EF (Simple E-factor) was used, which discounts solvent waste. This has been highlighted as the most appropriate way to calculate E-factors for new process development research.[15]
101 mg CatCart waste + 17 mg waste from chalcone (104 mg substrate – 88 mg product = 17 mg) = 118 mg waste; 88 mg prod; 118 / 88 = 1.34.

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