Supporting Information

Optimization of a decatungstate-catalyzed C(sp^3)–H alkylation using a continuous oscillatory milli-structured photoreactor

Zhenghui Wen[1], Apoorva Maheshwari[1], Carlo Sambiagio[1], Yuchao Deng[1,2,3], Gabriele Laudadio[1], Koen Van Aken[4,5], Yuhan Sun[2,3], Hannes P. L. Gemoets[4], Timothy Noël[1]*

[1]Department of Chemical Engineering and Chemistry, Micro Flow Chemistry & Synthetic Methodology, Eindhoven University of Technology, Den Dolech 2, 5612 AZ Eindhoven, The Netherlands.

[2]School of Physical Science and Technology, ShanghaiTech University, Shanghai, 201210, P.R. China.

[3]Shanghai Advanced Research Institute, Chinese Academy of Science, Shanghai, 201210, P.R. China.

[4]Creaflow BV, Industrielaan 12, 9800 Deinze, Belgium.

[5]Ecosynth NV, Industrielaan 12, 9800 Deinze, Belgium

E-mail: t.noel@tue.nl

Website : www.NoelResearchGroup.com

Table of Contents

Experimental setup – Homemade capillary reactor

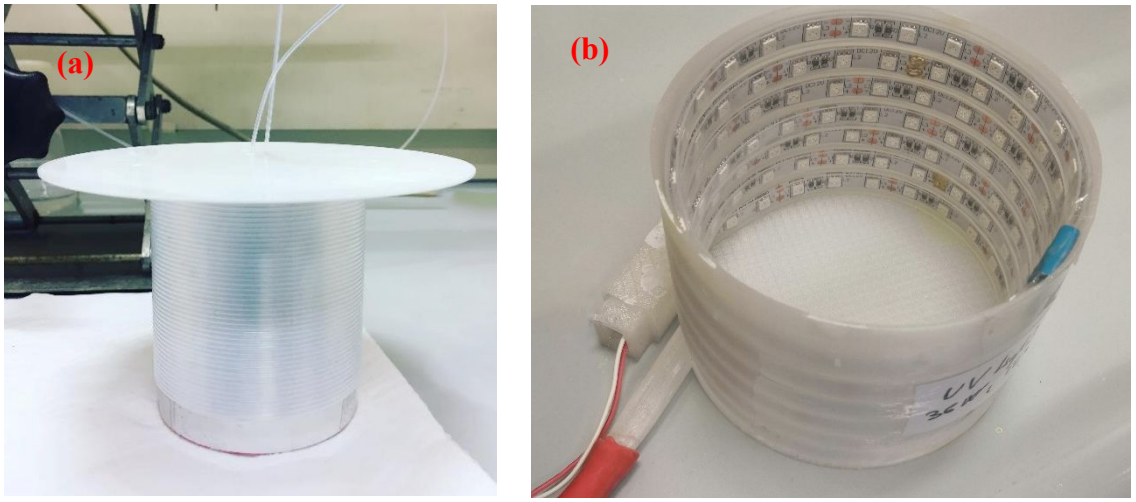


Figure S1. Pictures of our homemade photochemical flow reactor. (a) 5 mL flow reactor; (b) Flow setup with 3D-printed shell.

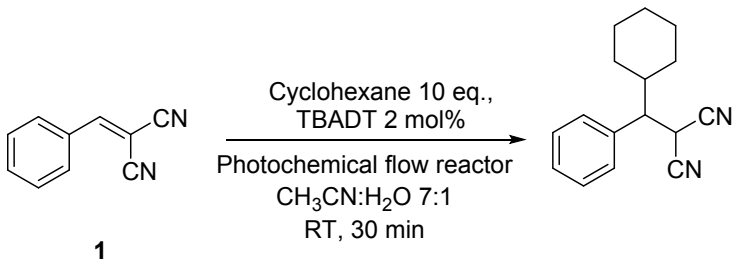
Our homemade photochemical flow reactor (5 mL) includes two parts:

1) PFA tubing (0.750 mm I.D.) coiled around 3D-printed reactor lid with cylinder (material: polylactic acid, PLA). The cylinder was covered with reflective tape to increase the efficiency of the set-up. Dimensions of the cylinder: length 9 cm, diameter 7.5 cm. Dimensions of the lid: diameter 14.5 cm.

2) 3D-printed outer shell was made out of PLA. Inside of the shell LED strips (2.5 m, 36W, 300SMD5050 LEDs, LedLightingHut, λ=365 nm) are mounted. An inlet for pressurized air is incorporated in the shell, a constant airflow during operation prevents overheating of the LEDs.

Experiment procedure:

In 10 mL 7:1 CH_3CN:water, 0.1 M of **1** and 2 mol% of TBADT were dissolved and mixed with 10 eq. of cyclohexane. The solution was pumped into the reactor at a flow rate of 0.167 mL/min. In this case 74% conversion was obtained after 30 minutes residence time at atmospheric pressure.



1

Experimental setup – HANU reactor

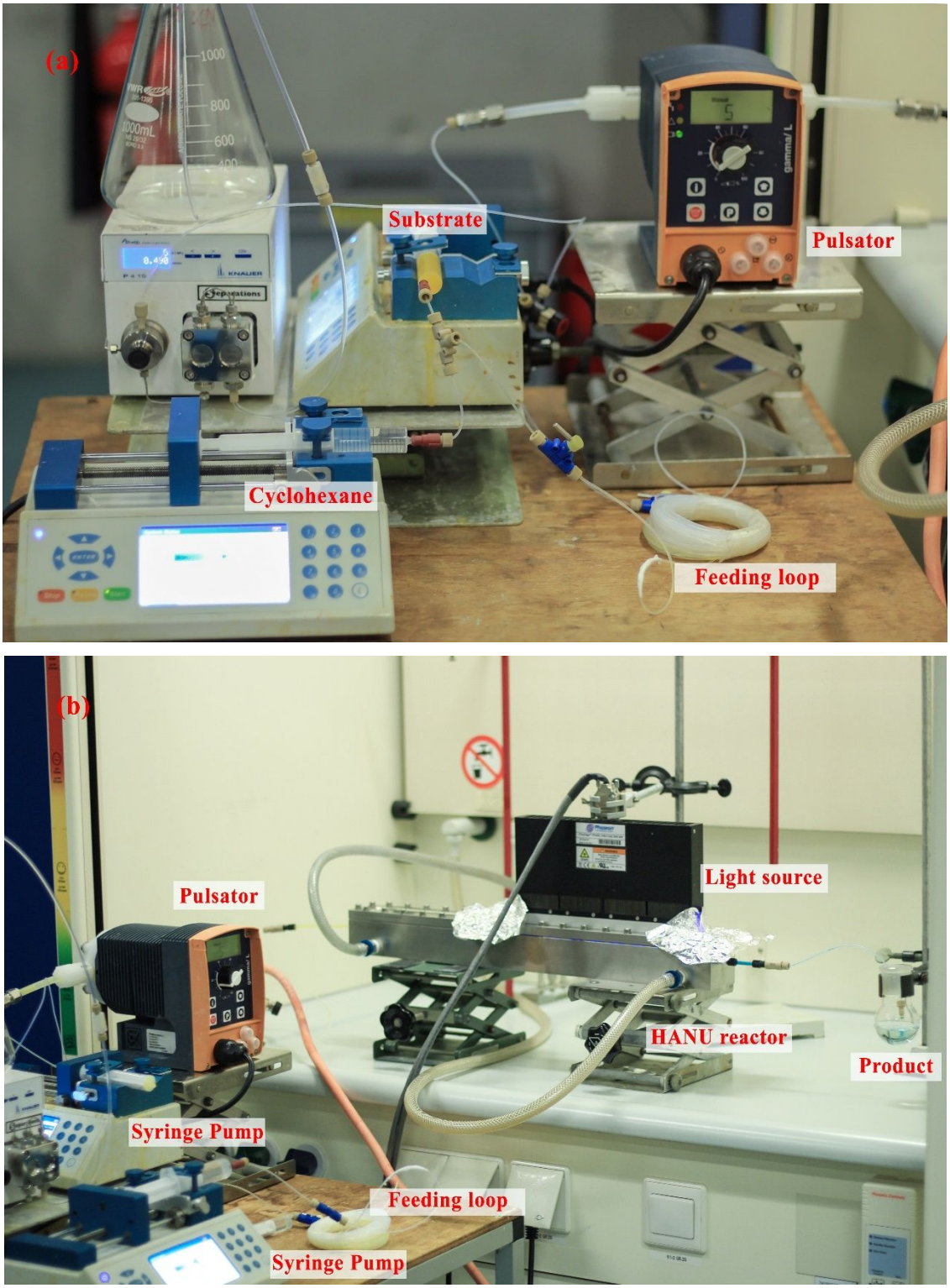


Figure S2. Photographs of the HANU reactor setup.

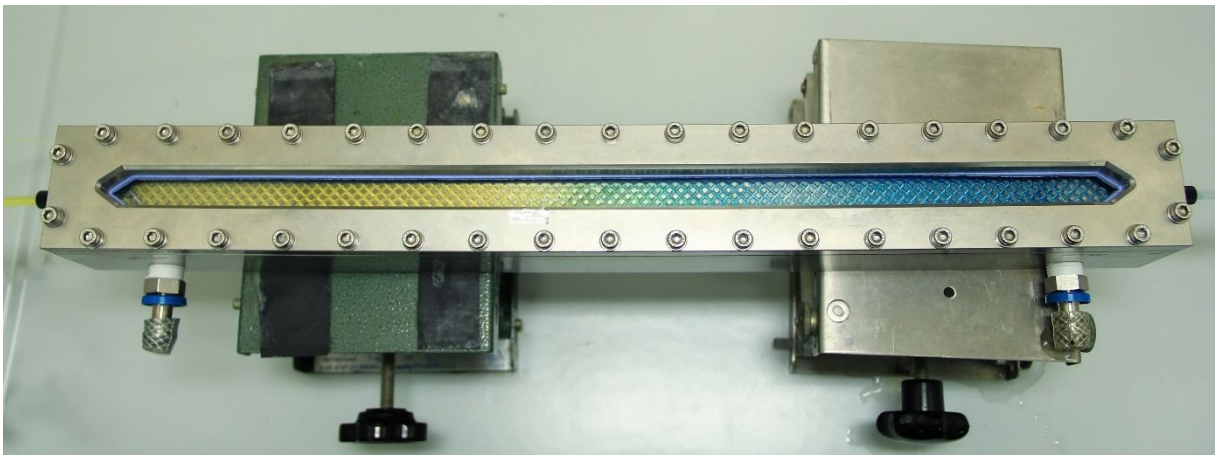


Figure S3. Photograph of the HANU reactor. The orange part (left) was the reactant mixture without light irradiation; the blue part (right) was the reaction mixture with light irradiation.

Detailed information about the equipment used in the experiments are listed below:

Photoreactor (HANU^{TM} HX 15-316L-CUB): A stainless-steel milli-structured flow reactor (Size: 540 × 60 × 60 mm; channel dimensions: 480 × 20 × 2 mm) with a series of cubic static mixing elements (2 × 2 × 2 mm) along the channel. The volume of the channel is 15 mL, but only half of the reactor was irradiated (see Figure S2b), therefore the volume considered was 7.5 mL.

Light source (FireEdge FE400 240×10AC 365-4W, Phoseon): Air-cooled high-performance LED array with a emitting window sizes being 240 × 10 mm and peak irradiance of 4 W/cm^2·(Input power: 240 W; optical output: 96 W 365 nm). The light source was put on the top of the reaction plate. It is noteworthy that the light source only covered half of the reactor (Figure S2).

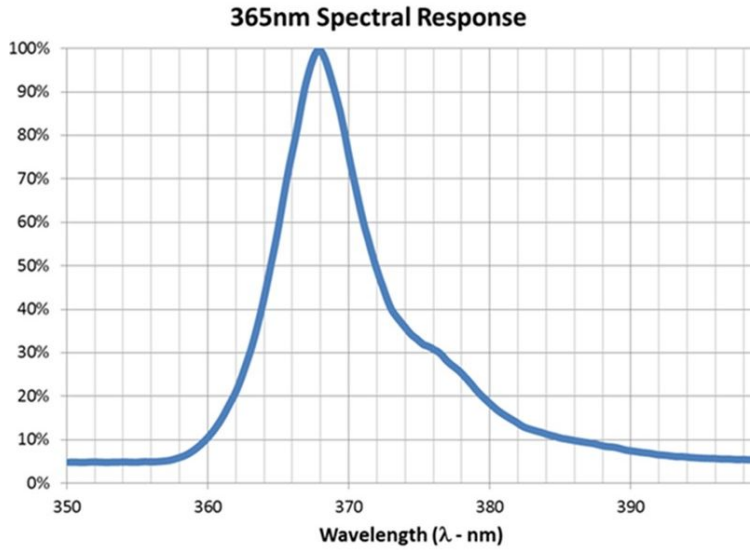


Figure S4. Emission spectra of the light source (365 nm) used in this study. (Provided by Phoseon)

Syringe Pumps (Fusion 2000 Touch, Chemyx Inc.): The cyclohexane and substrate solution were delivered to the feeding loop. The flow rate of substrate solution was set to 1 mL/min, while the flow rate of cyclohexane was adjusted according to the equivalent of cyclohexane and concentration of the substrate.

Feeding loop: PFA tubing (0.750 mm I.D.) was employed. The volume of feeding loop was 10 mL.

Pulsator (gamma/ L diaphragm metering pump, ProMinent): Placed between the feeding loop and the photoreactor, the pulsator was used to pulse the reactants solution. This had a tunable pulsation intensity (0-100%, corresponding approximately to 0-0.44 mL per stroke) and a constant frequency (3 Hz).

Experimental procedure:

Two syringe pumps were used to inject the two feeds. Feed 1: substrate solution (0.1-0.8 M) + biphenyl (0.1 M) + TBADT (2-7 mol%), flow rate = 1 mL/min; Feed 2: cyclohexane (5-15 equiv.), flow rate = 0.11-0.86 mL/min according to the equivalents of cyclohexane. The two feeds were mixed in a T-Mixer and pumped into a feeding loop. Once the reaction mixture was loaded into the loop (slug flow between the two different phases), the resulting mixture was pushed through the HANU reactor with acetonitrile via a 6-way valve. Experimental parameters, such as flow rate, pulsation, and light intensity were adjusted according to the different conditions. At the reactor outlet, the samples were collected in GC vials, diluted with acetonitrile, and analyzed by GC-FID.

Product isolation was performed following the following procedure:

Representative conditions: 0.1 M substrate, 2 mol% TBADT, 10 equiv. cyclohexane, without pulsation, residence time 15 min. At the end of the reaction, the reaction crude (acetonitrile/cyclohexane solution) was collected, and the solvents were removed in vacuo. The dry crude product was purified via flash chromatography (eluent: cyclohexane/EtOAc 95:5), giving the product in 83% yield (0.4936 g) as a colorless oil. GC yield under these conditions was 88% (see Figure S5a below).

Effect of pulsation

The effect of 5% pulsation at different residence times is shown in Figure S5. While higher yields and conversion were observed for residence times ⩽ 5 min, the effect of pulsation seems negligible at residence times > 5 min.

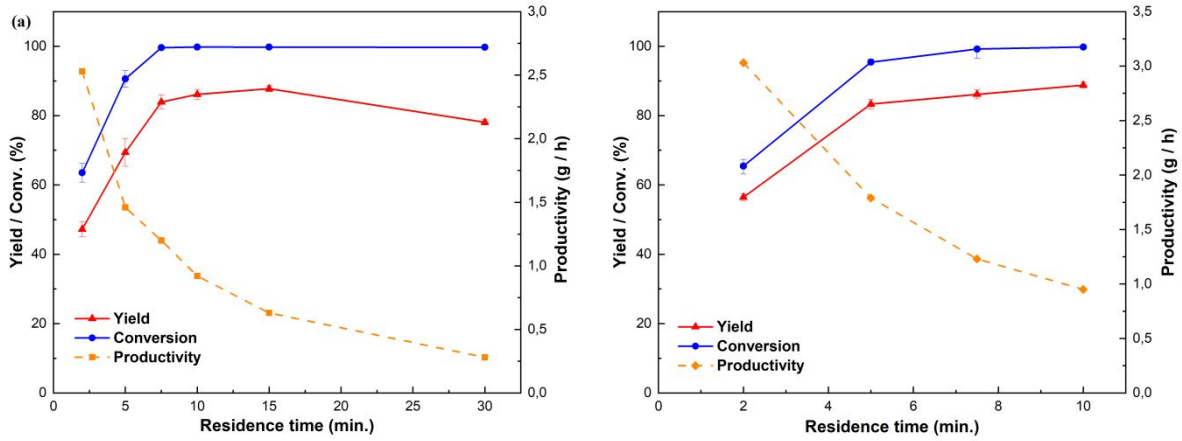


Figure S5. Effect of residence time on conversion, yield and productivity without pulsation (a) and with 5% pulsation (b). Reaction conditions: 0.1 M alkene substrate, 2 mol% TBADT, 10 equiv. cyclohexane, 96 W 365 nm light.

GC-FID

All samples were analyzed with a Shimadzu GC2010 Plus gas chromatograph with flame ionization detector (FID) using a Rtx-1 column (30 m × 0.32 mm × 0.25 μm) and helium as carrier gas. After 1.5 min, the temperature was increased from 80 °C to 250 °C at a rate of 20 °C·min^{-1} and kept constant at 250 °C for 10 min. The hydrogen flow rate was 40 mL·min^{-1}, helium flow rate was 60 mL·min^{-1}, the front inlet temperature was 250 °C, and the detection temperature was 300 °C.

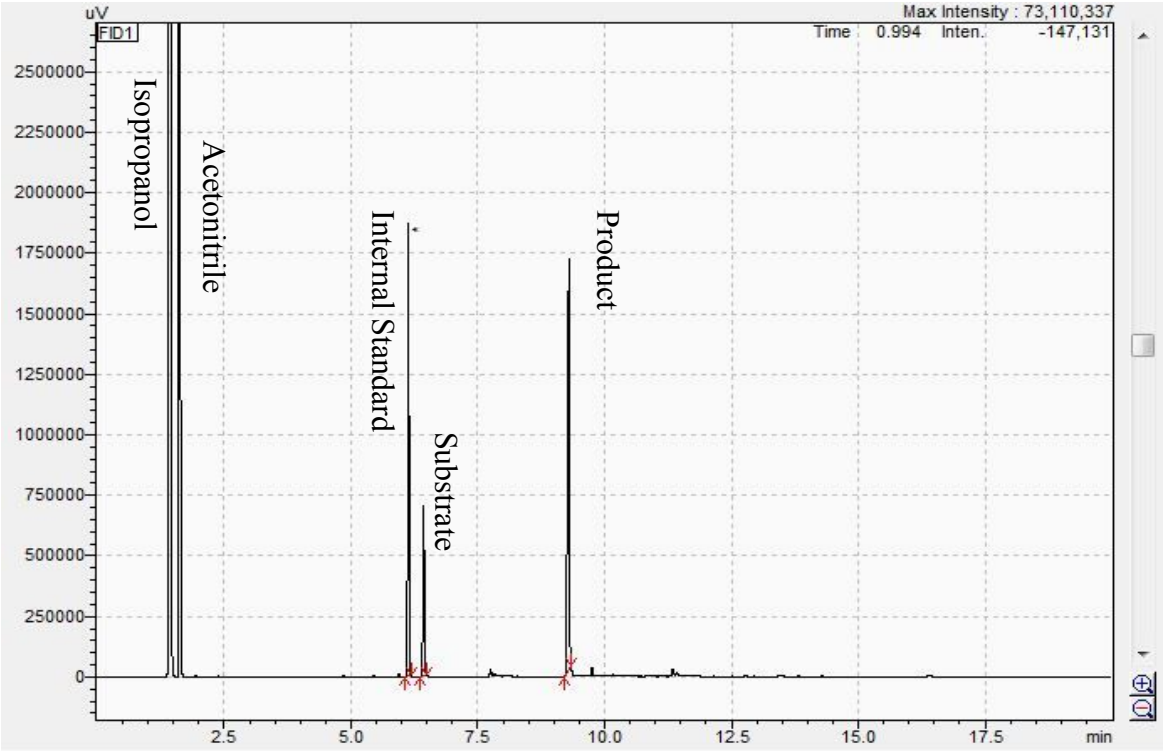
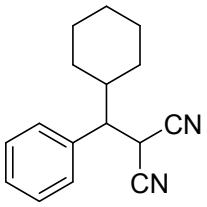


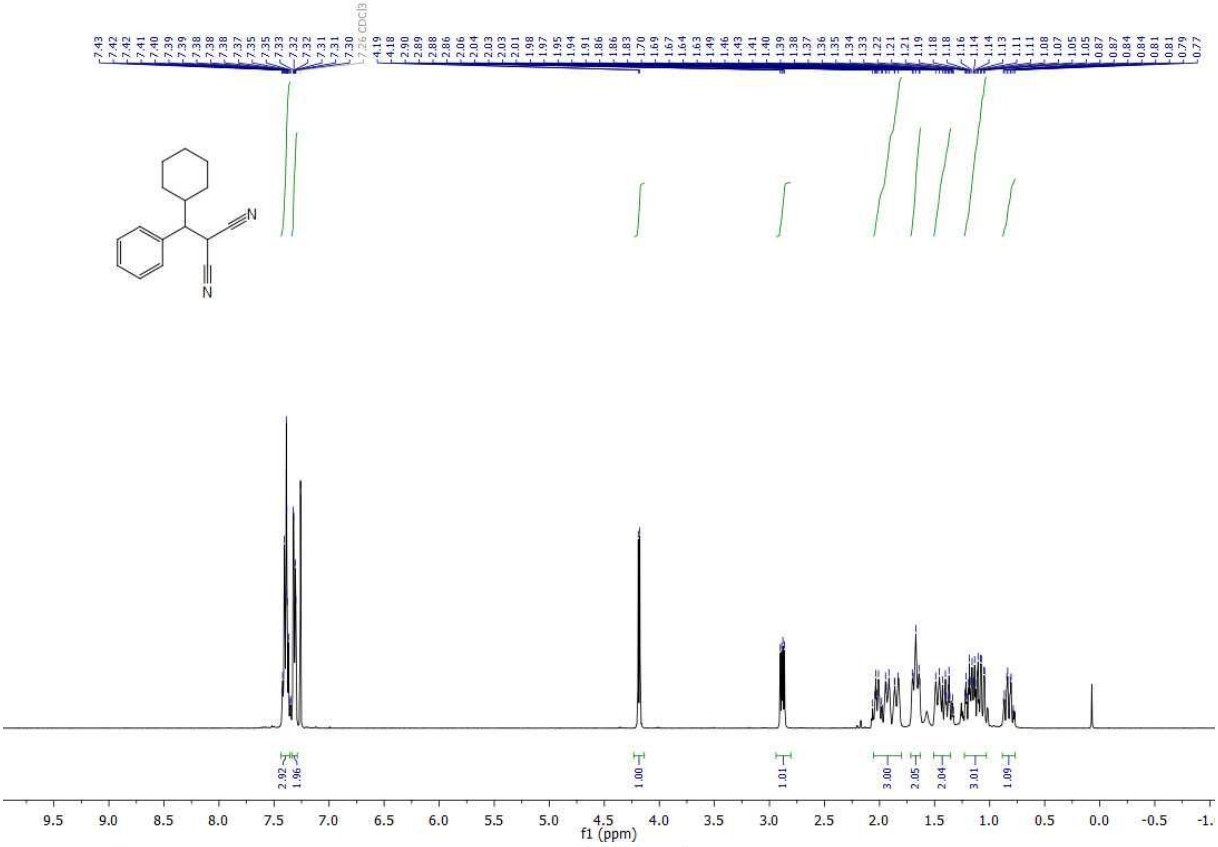
Figure S6. Example of GC-FID file.

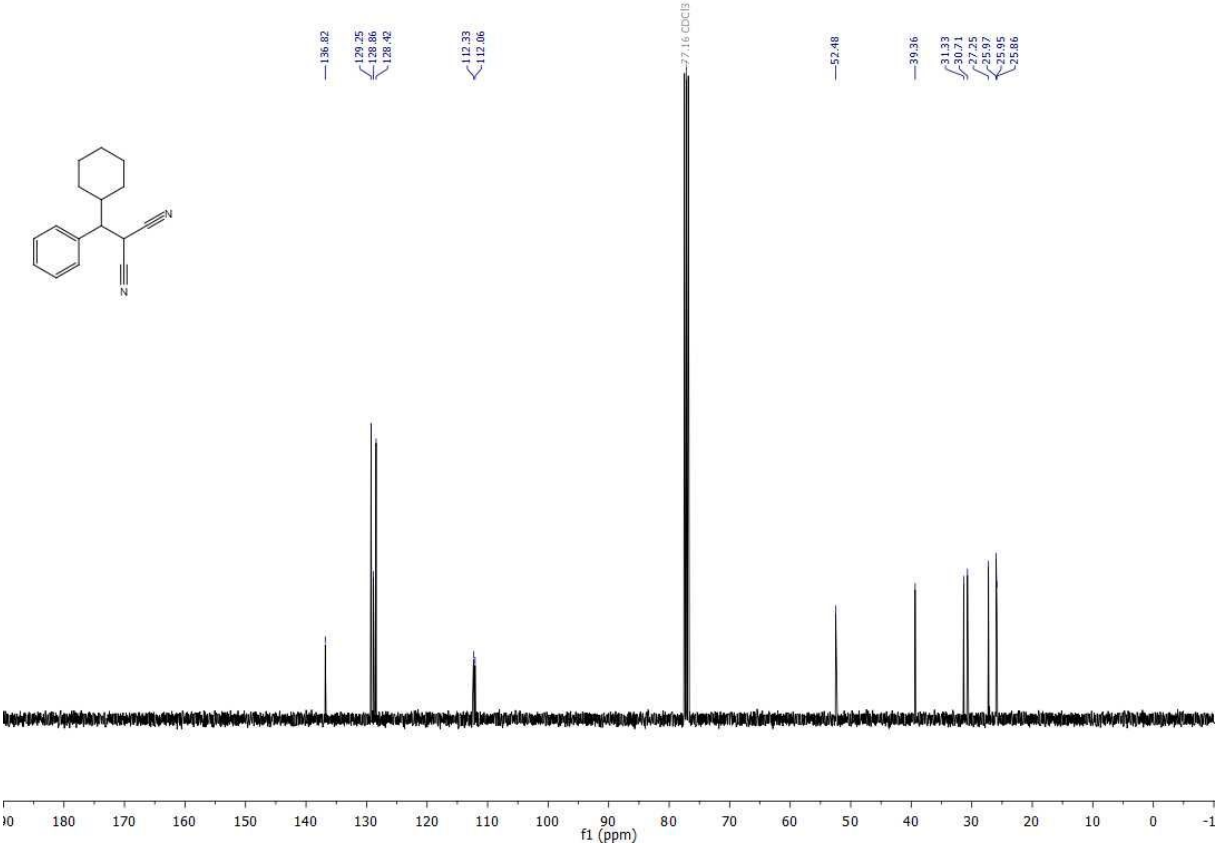
Characterization data



2-(cyclohexyl(phenyl)methyl)malononitrile: The product was prepared following the procedure described above. Following collecion, the solvent was evaporated and the crude product was purified by the flash chromatography (eluent: cyclohexane/EtOAc: 95/5). The product was obtained as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 – 7.36 (m, 3H), 7.34 – 7.29 (m, 2H), 4.18 (d, *J* = 5.5 Hz, 1H), 2.88 (dd, *J* = 9.8, 5.5 Hz, 1H), 2.05 – 1.80 (m, 3H), 1.72 – 1.63 (m, 2H), 1.51 – 1.35 (m, 2H), 1.23 – 1.03 (m, 3H), 0.88 – 0.77 (m, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 136.8, 129.3, 128.9, 128.4, 112.3, 112.1, 52.5, 39.4, 31.3, 30.7, 27.3, 26.0, 26.0, 25.9.

NMR spectra


7.43
7.42
7.42
7.41
7.40
7.39
7.39
7.38
7.38
7.38
7.37
7.35
7.33
7.32
7.32
7.31
7.31
7.30
7.26 CDCl3
4.19
4.18
2.90
2.89
2.88
2.86
2.06
2.04
2.03
2.03
2.01
1.98
1.97
1.95
1.94
1.91
1.86
1.86
1.83
1.70
1.69
1.67
1.64
1.63
1.49
1.46
1.45
1.41
1.40
1.39
1.38
1.37
1.36
1.35
1.34
1.33
1.22
1.21
1.21
1.19
1.18
1.16
1.14
1.14
1.13
1.11
1.08
1.07
1.05
1.05
0.87
0.87
0.84
0.84
0.81
0.81
0.79
0.77
N
N
2.92
1.96
1.00
1.01
3.00
2.05
2.04
3.01
1.09
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


136.82
129.25
128.86
128.42
112.33
112.06
77.16 CDCl3
52.48
39.36
31.33
30.71
27.25
25.97
25.95
25.86
N
N
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)