Supporting information

# Highly modular PDMS microwave-microfluidic chip reactor for MAOS applications

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## 1. General information

All chemicals and solvents were used as received without further purification, unless stated otherwise. Reagents and solvents were bought from Sigma Aldrich and TCI and if applicable, kept under argon atmosphere. Technical solvents were bought from VWR International and Biosolve, and are used as received. Product isolation was performed using silica (60, F254, Merck™), and TLC analysis was performed using Silica on aluminum foils TLC plates (F254, Supelco Sigma-Aldrich™) with visualization under ultraviolet light (254 nm and 365 nm) or appropriate TLC staining. $^{1}H$ (400MHz) and $^{13}C$ (100MHz) NMR spectra were recorded at ambient temperature using a Bruker-Avance 400 or Mercury 400. $^{1}H$ NMR spectra are reported in parts per million (ppm) downfield relative to $CDCl_3$ (7.26 ppm), $^{13}C$ NMR spectra are reported in ppm relative to $CDCl_3$ (77.2 ppm). NMR spectra uses the following abbreviations to describe the multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, h = hextet, hept = heptet, m = multiplet, dd = double doublet, td = triple doublet, br= broad. Known products were characterized by comparing to the corresponding $^{1}H$ NMR and $^{13}C$ NMR from literature. For chromatography, analytical TLC plates (F254, Supelco Sigma-Aldrich™) with visualization under ultraviolet light (254 nm and 365 nm) and 70-230 mesh silica gel were used. GC-MS analyses were performed on a GC-FID (Varian 430-GC) in combination with an auto sampler (Varian CP-8400) or LC-MS combination (Shimadzu GC-2010 Plus coupled to a Mass Spectrometer; Shimadzu GCMS-QP 2010 Ultra) with an auto sampler unit (AOC-20i, Shimadzu). High-resolution mass spectra were acquired on a quadrupole orthogonal acceleration time-of-flight mass spectrometer (Synapt G2 HDMS, Waters, Milford, MA). Spectrometer (Synapt G2 HDMS, Waters, Milford, MA). Samples were infused at 3μL/min and spectra were obtained in positive (or: negative) ionization mode with a resolution of 15000 (FWHM) using leucine enkephalin as lock mass. Melting points were determined with a Buchi B540 capillary melting point apparatus in open capillaries and are uncorrected.

## 2. General flow experimental information

For the flow-experiments, PFA Tubing (1/16" OD x .020" ID) and PEEK superflangeless fittings were purchased from HIDEX Health and Science technology. Reagents were pumped using Chemix4000 and Nexus 600 syringe pumps. Glass gas-tight syringe (1 mL) was purchased from SGE.

## 3. Chemicals

Solvents were purchased from Acros Organics and used as purchased. Deuterated solvents were used as purchased. All starting materials were purchased from Sigma Aldrich and TCI, if applicable and used as received without further purification.

## 4. General μW-μF-CR and setup information

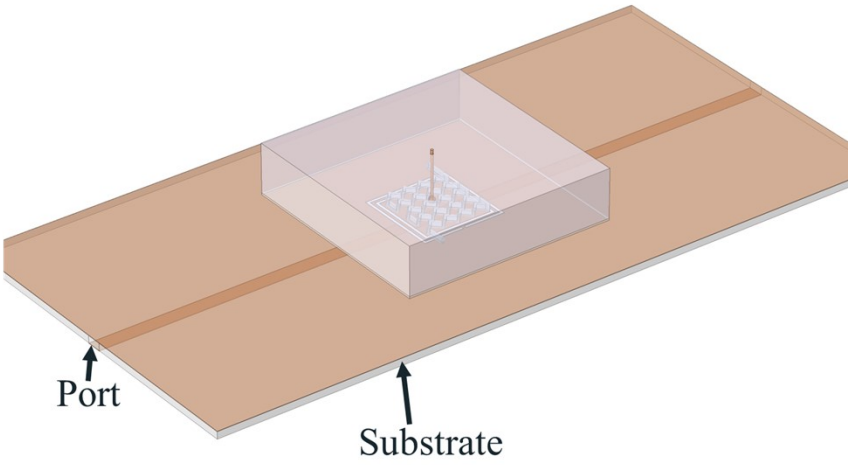
**Table S1.** Material used for CSRR fabrication and parameters for COMSOL simulations

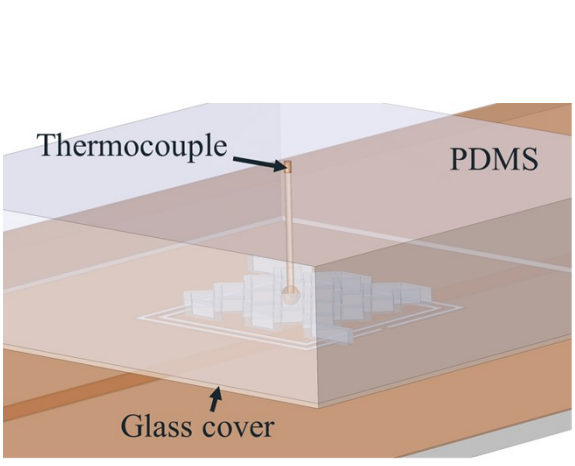
| | Material used | Heat capacity [J/(kg*K)] | Thermal conductivity [W/(m*K)] | Density [kg/m$^3$] | Permeability | Permittivity | Conductivity [S/m] |
|---|---|---|---|---|---|---|---|
| Traces and temperature sensor | Copper[a] | 385 | 400 | 8960 | ~ | ~ | 6e7 |
| Substrate | RO4003[b] | 960 | 0.71 | 1790 | 1 | ε'=3.55 tanδ=0.002 | ~ |
| Flow cell | PDMS[c] | 1460 | 0.16 | 965 | 1 | ε'=2.8 tanδ=0.054 | ~ |
| Flow cell cover | Borosilicate[d] | 800 | 1.4 | 2510 | 1 | ε'=6.4 tanδ=0.007 | ~ |
| Sample | Water[e] | 4190 @25°C | 0.6 @25°C | 990 @25°C | 1 | Temp dependent[f] | ~ |
| Sample | MeCN | 1700 | 0.2 | 783 | 1 | ε'=37.78 tanδ=0.084 | ~ |

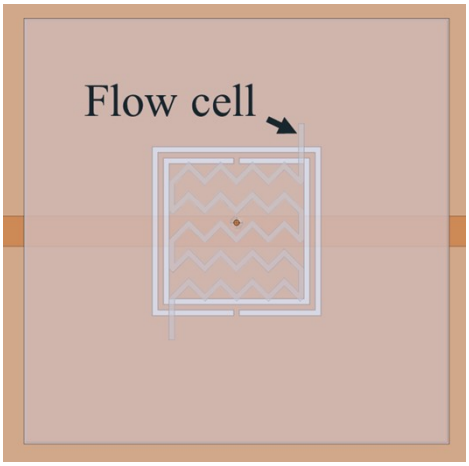
[a]https://pubchem.ncbi.nlm.nih.gov/compound/coppersection=springermaterials-properties.
[b]https://www.rogerscorp.com/advanced-electronics-solutions/ro4000-series-laminates/ro4003c-laminates
[c] 1 to 220 GHz Complex Permittivity Behavior of Flexible PDMS (Polydimethylsiloxane) Substrate
[d] https://www.schott.com/en-hr/products/d-263-p1000318/technical-details
[e] Crc handbook of chemistry and physics.
[f]Permittivity of pure water, at standard atmospheric pressure, over the frequency range 0–25 THz and the temperature range 0–100°C.
The width of a microstrip on the CSRR is 1.08 mm (both high and low frequency heaters).

*Simulations in COMSOL*:

The COMSOL simulations were conducted to determine temperature uniformity inside the flow cell. For that the 3D model shown below was used. The air domain that is enclosing the whole structure is left out for a better visualization. Lumped port in cable mode was used for MW excitation with 10 V peek-to-peek (1 W) input voltage. Scattering boundary conditions were used at the outer boundaries of air domain in order to represent the infinite simulations domain. Impedance boundary conditions were used at copper boundaries in order to include losses in copper due to finite conductivity. Finaly, the heat flux boundary conditions were used at all boundaries of the device to approximate the temperature dissipation due to air convection with convective heat flux value of 25 W/($m^2$K). The used dimensions are mentioned in main manuscript in Section 2.



*Fabrication of molds*:

The serpentine-channel pattern for the flow cells was designed with the measurements and volumes showed in Fig. S1. The height of the flow cells are 0.4 mm. The designed molds were then 3D-printed using a Phrozen mini8K printer.

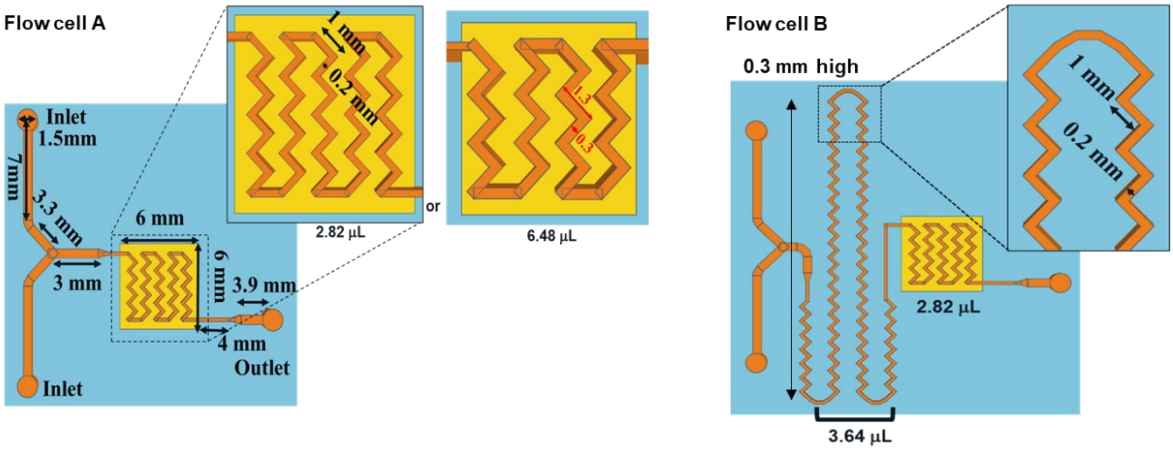



**Figure S1**: Measurements and volumes of designed flow cells.

*PDMS solution preparation and curing*

PDMS flow cells were manufactured using soft lithography, for that, a 3D-printed mold was used. A temperature sensor was precisely placed in the middle, followed by pouring PDMS into the mold. This way, the temperature sensor is embedded into the flow cell and remains in place. PDMS was mixed with the curing agent in a 10:1 ratio, as recommended in the datasheet. For the curing process, the PDMS flow cell was allowed to cool down at room temperature for 12 h to ensure that all bubbles disappear, and then heated at 120 °C for 6 h until fully solidified. Finally, the flow cell was removed from the mold, inlets and outlets were punched with a 1.5 mm diameter puncher for PFA tubing to fit. A borosilicate glass cover with 0.13 mm thickness was used to close the channels (Fig. S2).

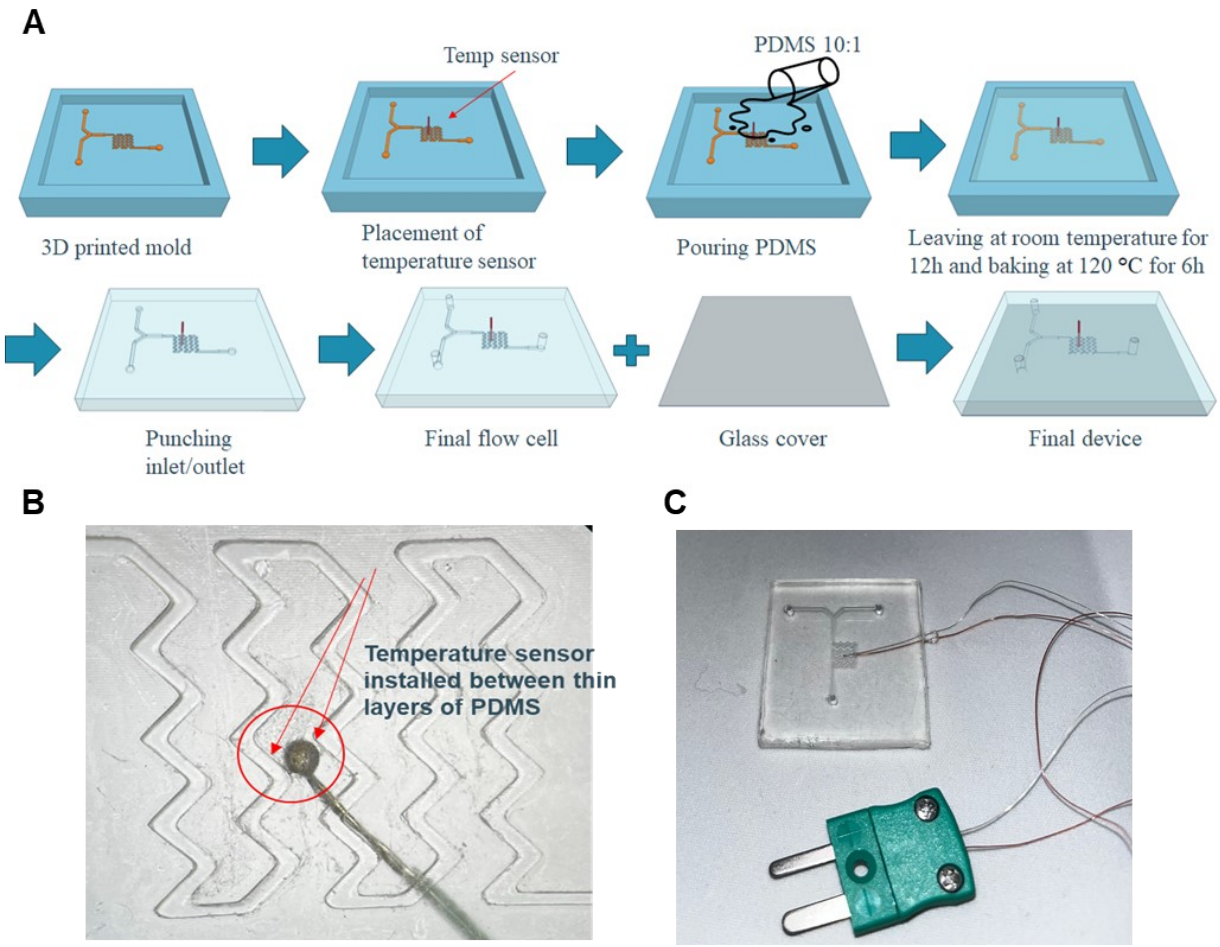



**Figure S2**: A) manufacturing process of flow cells; B) Picture of flow cell with temperature sensor between channels; C) Picture of flow final flow cell with temperature reader adapted.

*Microreactor assembly*

For assembly, a non-permanent bonding method was used, in which the PDMS flow cell with glass cover sits on top of the MW-heater, the two pieces are sandwiched together with applied pressure using a laser-cut polymethyl methacrylate (PMMA) cover, positioner and support. The setup is tightly secured with 4 bolts and nuts (Fig. S3).

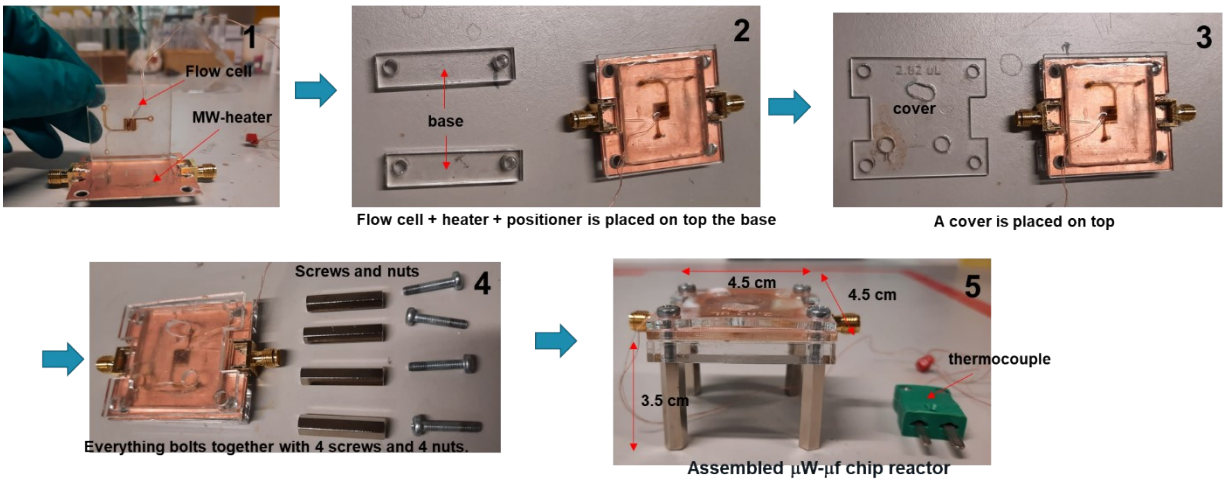



**Figure S3**: A) µW-µF-CR assembly process.

*Complete setup*

Before conducting reactions, the working frequency of the reactor loaded with reactants inside the flow cell is measured. The frequency is then entered into the signal generator to produce a MW signal for heating. Two setups are shown, with the first one working up to 2.5 GHz used in combination with the MW heater working at around 2 GHz and the second working between 6-12 GHz for experiments with the MW heater working at around 8 GHz. The setups are made to be similar with the possibility to change certain components to work at different frequencies. Both setups consist of a signal generator (ADF4355 or ADF4372, Analog Devices) connected to a step attenuator (HMC941ALP4E, Analog Devices) that is controlled with Arduino Nano to limit MW heating power and, with that, keeps the reaction temperature constant. A power amplifier (KU PA BB 233 BBA, Kuhne electronics or ZVA-183WA-S+, Minicircuits in combination with CMPA601C025F, Wolfspeed) is needed to increase the MW power to achieve the set temperature. Finally, the isolator (COI02040618G, Cernex or PE83CR1006, Pasternack) is connected to the reactor to prevent damaging the power amplifier. The whole setup is controlled using a PC with a proprietary application developed in MATLAB for easy temperature and frequency control (Fig. S6). The temperature was read using a temperature reader (TC01, National Instruments) connected to the temperature sensor. To supply the setup with electrical energy, two or four power supplies were used depending on the heating frequency (Fig. S4).

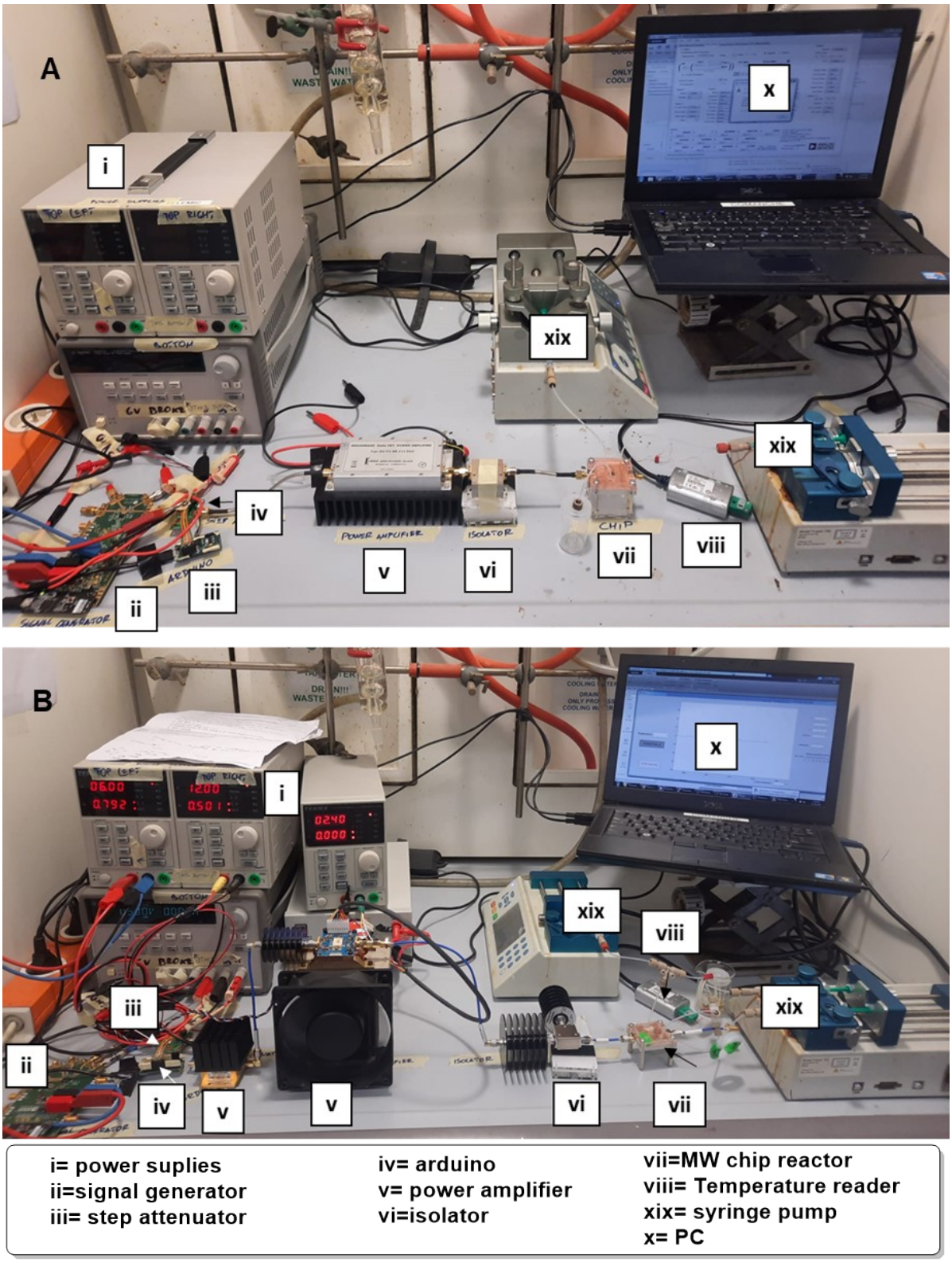



**Figure S4**: A) Complete setup working up to 2.5 GHz. B) Complete setup working between 6-12 GHz.

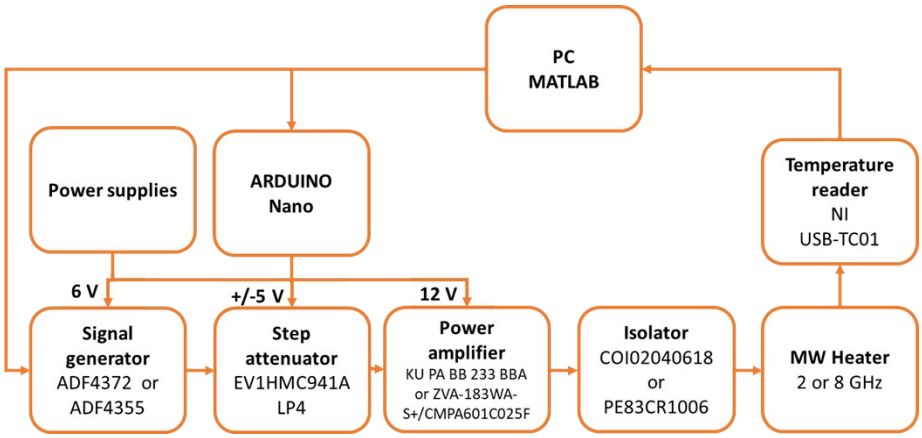



**Figure S5**: Flowchart of setups

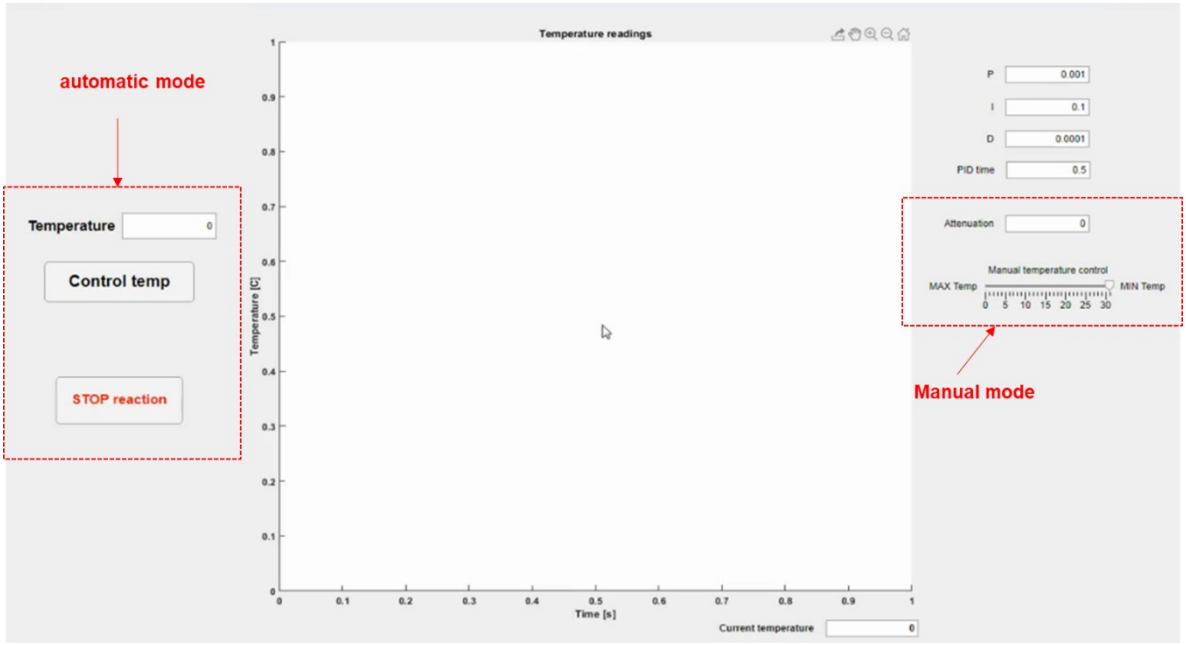



**Figure S6**: Developed application for temperature control.

*Frequency response of final device VS simulation*

The frequency response of the complete device of measurements and simulations is shown below. The difference in curves can be attributed to small deviation in position of temperature sensor, applied pressure on a flow cell, and manufacturing error in both CSRR and microfluidic device. Nevertheless, the deviation is not significant and the same resonant mode was assumed resulting in almost the same temperature uniformity when comparing simulations and experimental measurements as shown in section below.

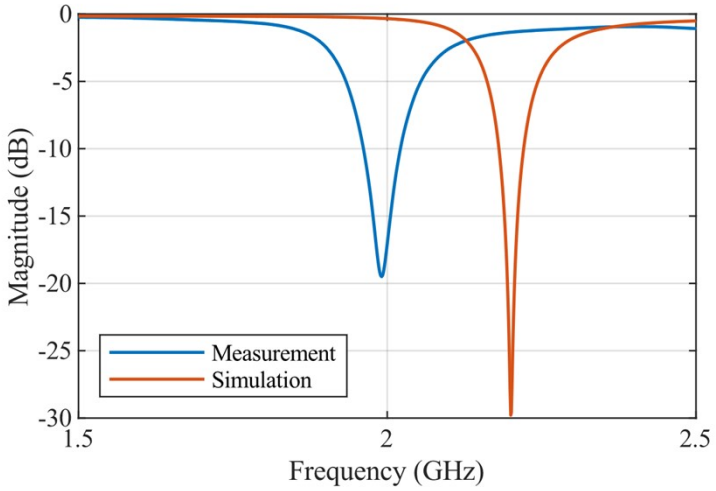



**Figure S7**: Experimental frequency response of reactor VS simulation

*Temperature uniformity assessment*

The temperature dependent fluorescent die Rhodamine B was used to assess the temperature uniformity inside the microfluidic channel. The measurement setup has been previously described by Tomislav *et al.*[1] with fluorescent intensity corelated with temperature according to Gest *et al.*[2] The solution was prepared by dissolving Rhodamine B in deionized water with 1 mmol/l concentration according to Ren *et al.,*[3] and temperature distribution was calculated according to Gest *et al.*[2] For that, an Olympus IX73 microscope, Hamamatsu OrcaFlash4.0LT+ digital camera, and a CoolLED pe-4000 light source, together with the CSRR1 working at around 2 GHz, were used. The light source was set to emit at 550 nm, and the intensity change at around 625 nm was recorded as a function of temperature. The solution was inserted in a reactor, and a signal generator (AnaPico, APSIN6000, 9 kHz - 6.5 GHz) connected to a power amplifier (Kuhne electronic, KU PA 200270-10 B) were used to supply the device with MW heating power of 2.1 W at 2.145 GHz. The camera was set to

record every 100 ms with a thermocouple recording the temperature every second. As we are interested in a steady state, the MW heating was conducted for 1.5 minutes.

Due to the low flow rate used in chemical reactions of around 10 µl/min and a small temperature variation with a flow rate,[1] the measurements were conducted on stationary sample inside the microfluidic channels. This allowed for direct comparison of measurements with COMSOL simulation results. The MW reactor used here is the same as the one used for chemical reactions with slightly different permittivity of a substrate of 3.55 instead of 3.66, influencing only heating frequency without affecting the temperature distribution. The steady state temperature distribution after 1.5 minutes inside the microfluidic channel using a 2 GHz CSRR while heating at 2.14 GHz with 2.1 W is shown below:

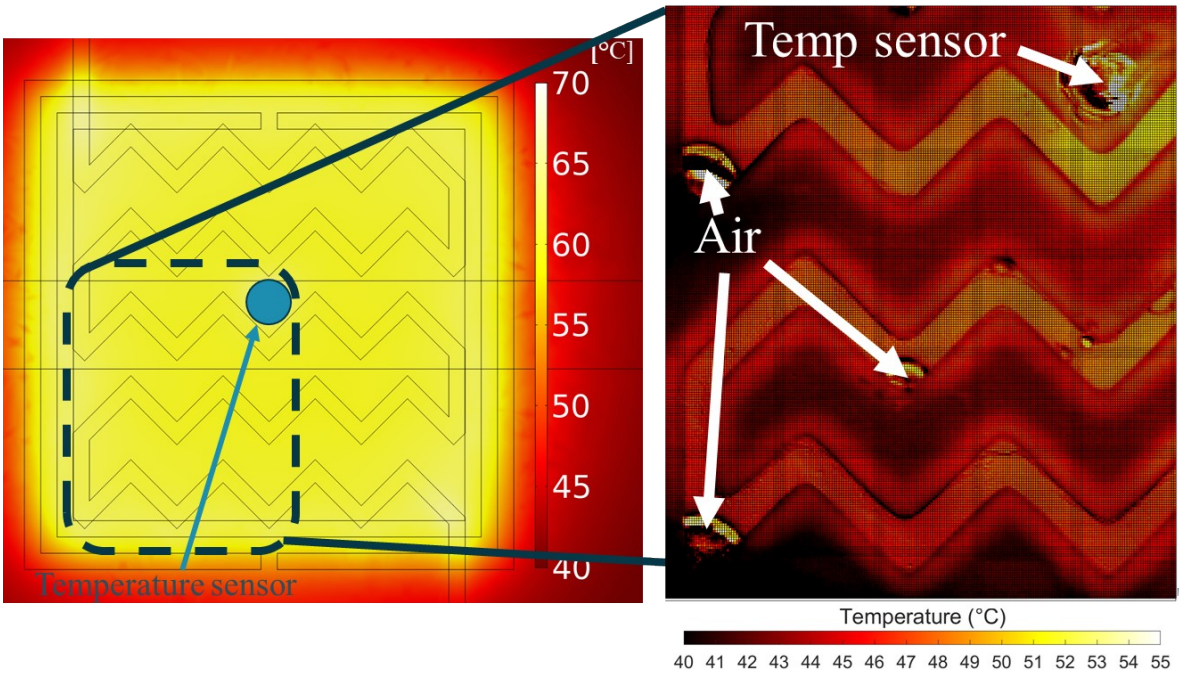



**Figure S8**: Temperature uniformity assessment

The temperature inside the channels is raging between 46 and 50°C with temperature sensor measuring 48°C indicating great agreement between the two. The temperature inside the channel next to the sensor is slightly elevated due its influence on E-field distribution which is in accordance with COMSOL simulations. Due to the great agreement between the measurement results and simulations with COSMOL for 2 GHz heater, it is considered that that precise temperature measurements are achievable using only one thermocouple and

COMSOL simulations are sufficient to assess the temperature distribution for a second heater working at 8 GHz.

*Power dissipation simulations*

According to COMSOL simulations, 11% (0.11 W) of input power is dissipated inside the working fluid (water) and 41% (0.41) inside the PDMS flow cell. The rest is dissipated in the copper traces or substrate. Due to the narrow channels that were used to promote mixing, the liquid is not positioned in the place where E-field is the strongest sacrificing the heating efficiency. This design was preferred as it offers better temperature uniformity inside the reactor. To investigate the temperature increase inside the sample only due to MW irradiation, the COMSOL simulation was conducted where PDMS and borosilicate do not have MW losses (no temperature increase with MW irradiation), and borosilicate has no thermal conductivity (preventing conducive heating from copper below). The applied power was adjusted to achieve the same power dissipation of 0.11 W inside the sample. The resulting temperature profile is shown below where it is visible that we do indeed have temperature increase due to only MW irradiation. Investigation of different solvents and improvement of MW heating efficiency is subject to further work. When comparing to other commercially available reactors, the CEM uses 750 W compared to our setup where power needed for set chemical reactions is around 2 W showing 375-fold improvement while using lower volume.

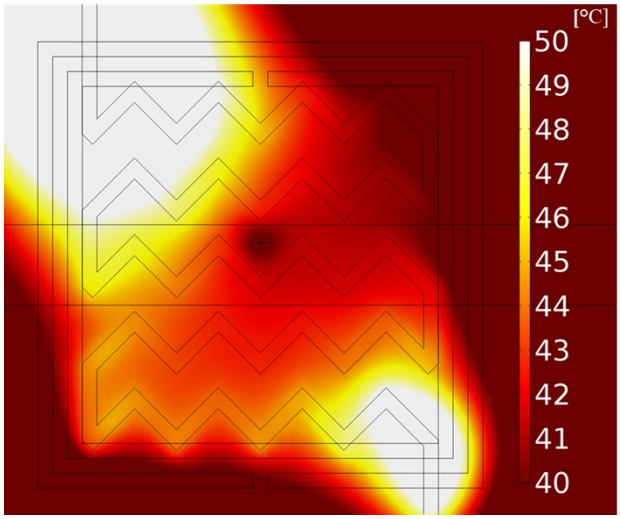



**Figure S9**: Power dissipation simulations

*Reactor's temperature profile*

The temperature profile of the Ugi reaction is shown below. The reaction temperature was set to 70°C. The spike observed around 10 seconds can be attributed to the solvent entering the flow cell. This sudden influx altered the temperature within the system, prompting a delay as the temperature controller adjusted to counteract this shift. However, it is worth noting that the temperature stabilizes shortly afterwards.

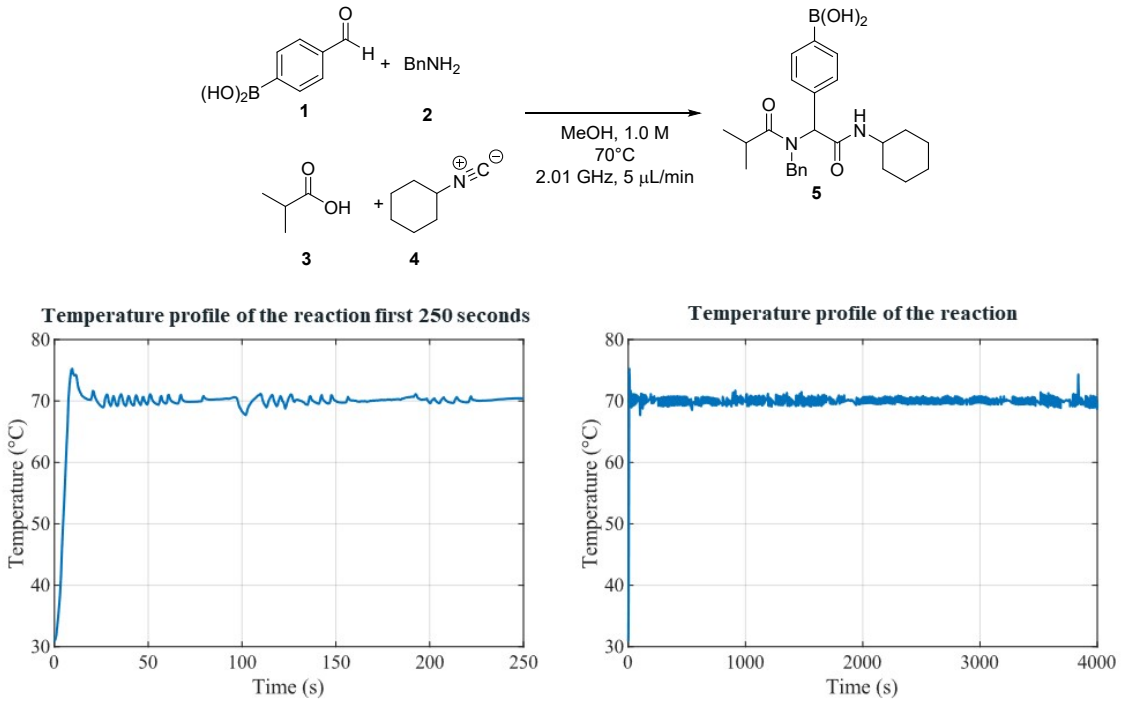



**Figure S10**: Experimental temperature profiles

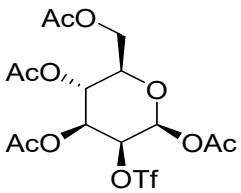
*Cleaning and multiple use of the flow cells and reactor*

The PDMS flow cells showed good performance and durability. Nevertheless PDMS compatibility with solvents and chemicals should be taken into account before running a reaction.[4] After completion of an experiment, the reactor is washed through by the flow of pure isopropanol and can be reused multiple times.

## 5. Synthesis and characterization of starting materials

**(2*S*,3*S*,4*S*,5*R*,6*R*)-6-(acetoxymethyl)-3-(((trifluoromethyl)sulfonyl)oxy)tetrahydro-2H-pyran-2,4,5-triyl triacetate (9)**[5]

The compounds **9** was prepared according to the procedure described by Teodorović *et al*., and obtained as a white solid (2.37 g, 5.00 mmol, quant.).




**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 5.91 (d, *J* = 3.6, 1H), 5.33 – 5.25 (m, 1H), 5.19 (dd, *J* = 10.0, 3.0 Hz, 1H), 5.14 (d, *J* = 2.9 Hz, 1H), 4.24 (dd, *J* = 12.5, 5.2 Hz, 1H), 4.17 (dd, *J* = 12.5, 2.2 Hz, 1H), 3.83 (ddd, *J* = 9.9, 5.1, 2.5 Hz, 1H), 2.16 (s, 3H), 2.11 (s, 3H), 2.09 (s, 3H), 2.06 (s, 3H).

**$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 170.7, 169.9, 169.3, 168.1, 118.3 (q, *J* = 320 Hz, $CF_3$), 89.2, 81.4, 73.7, 69.7, 64.7, 61.8, 20.8, 20.7, 20.6, 20.6.

Spectroscopic data were consistent with literature values.[6]

**Synthesis of starting propargylamines**

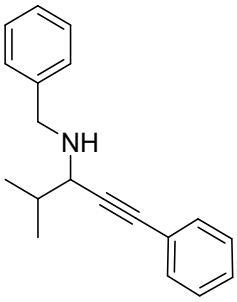
**General procedure 1 (GP1)**

The compounds **15a-d, g** were prepared according to procedure described by Van der Eycken *et al*.[7] To a microwave vial equipped with a magnetic stir bar were added amine (1.5 mmol), aldehyde (1.0 mmol), acetylene (3.0 mmol), copper bromide (0.2 mmol) and toluene (1.0 mL). The mixture was degassed and backfilled with argon. The reaction vessel was sealed and irradiated in the cavity of CEM-Discover microwave reactor at a ceiling temperature of 100 °C and a maximum power of 80 W for 25 min. The resulting reaction mixture was cooled to the ambient temperature and subjected to the column chromatography to afford the desired propargylamine.

**General procedure 2 (GP2)**

The compounds **15e-15f** were prepared according to the modified procedure described by Van der Eycken *et al*.[8] In a 5 mL sealed screw cap vial equipped with a magnetic stir bar were added amine (0.75 mmol), aldehyde (0.5 mmol), copper (I) bromide (0.2 mmol), acetylene (1.5 mmol), and toluene (1.5 mL). The mixture was degassed, backfilled with nitrogen and then stirred under nitrogen at 100°C overnight. The resulting reaction mixture was cooled to the ambient temperature and subjected to the column chromatography to afford the desired propargylamine.

***N*-benzyl-4-methyl-1-phenylpent-1-yn-3-amine 15a**



Compound **15a** was prepared according to the general procedure 1 (**GP1**) and isolated as an orange oil (231.5 mg, 88% yield).

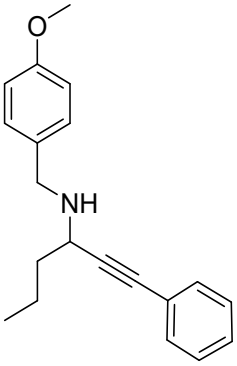
**Column Chromatography**: Silica, gradient 3-10% EtOAc/Heptane.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.46–7.43 (m, 2H), 7.41–7.35 (m, 3H), 7.33–7.29 (m, 5H), 4.10 (d, *J* = 12.99 Hz, 1H), 3.89 (d, *J* = 12.99 Hz, 1H), 3.40 (d, *J* = 5.46 Hz, 1H), 2.00 – 1.89 (m, 1H), 1.06 (d, *J* = 6.78 Hz, 6H).

**$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 140.3, 131.8, 128.5, 128.5, 128.4, 128.0, 127.1, 123.7, 89.9, 84.8, 56.4, 51.9, 33.1, 20.0, 18.2.

Spectroscopic data were consistent with literature values.[7]

***N*-(4-methoxybenzyl)-1-phenylhex-1-yn-3-amine 15b**



Compound **15b** was prepared according to the general procedure 1 (**GP1**) and isolated as an dark red oil (175.90 mg, 60% yield).

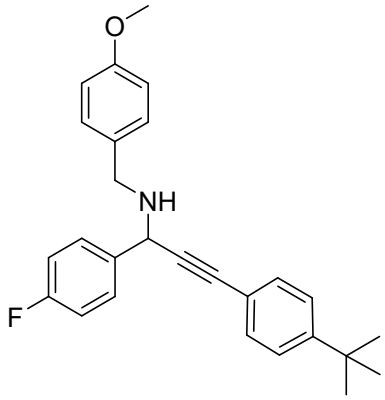
**Column Chromatography**: Silica, gradient 3-10% EtOAc/Heptane.

**$^1$H NMR** δ (400 MHz, $CDCl_3$) 7.49-7.43 (m, 2H), 7.36-7.28 (m, 5H), 6.88 (d, *J* = 8.6 Hz, 2H), 4.03 (d, *J* = 12.6 Hz, 1H), 3.84 (d, *J* = 12.6 Hz, 1H), 3.81 (s, 3H), 3.59 (dd, *J* = 7.4, 6.3 Hz, 1H), 1.75-1.66 (m, 2H), 1.63-1.48 (m, 2H), 0.96 (t, *J* = 7.3 Hz, 3H).

**$^{13}$C NMR** δ (101 MHz, $CDCl_3$) 158.8, 132.3, 131.8, 129.7, 128.4, 128.0, 123.6, 113.9, 91.3, 84.0, 55.4, 51.0, 49.8, 38.4, 19.6, 14.1.

Spectroscopic data were consistent with literature values.[9]

**3-(4-(tert-butyl)phenyl)-1-(4-fluorophenyl)-*N*-(4-methoxybenzyl)prop-2-yn-1-amine 15c**




Compound **15c** was prepared according to the general procedure 1 (**GP1**) and isolated as an brown oil (341.02 mg, 85% yield).

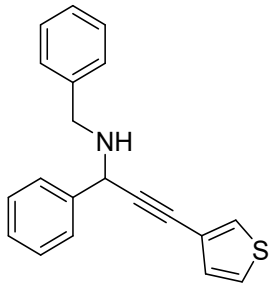
**Column Chromatography**: Silica, gradient 3-10% EtOAc/Heptane.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.59-7.55 (m, 2H), 7.44-7.30 (m, 6H), 7.03 (t, *J* = 9.1 Hz, 2H), 6.87 (d, *J* = 8.2 Hz, 2H), 4.74 (s, 1H), 3.91 (s, 2H), 3.80 (s, 3H), 1.32 (s, 9H).

**$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 163.6, 161.2, 158.9, 151.7, 136.4, 131.9, 131.6, 129.8, 129.5, 129.4, 125.5, 120.1, 115.4, 115.2, 114.0, 88.4, 86.2, 55.4, 52.9, 50.6, 34.9, 31.3.

Spectroscopic data were consistent with literature values.[7]

***N*-benzyl-1-phenyl-3-(thiophen-3-yl)prop-2-yn-1-amine 15d**




Compound **15d** was prepared according to the general procedure 1 (**GP1**) and isolated as a dark red oil (127.3 mg, 42% yield).

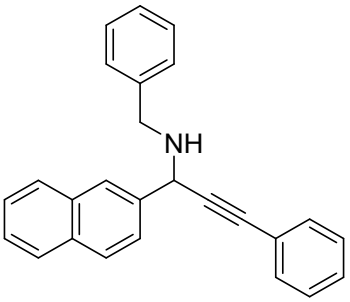
**Column Chromatography**: Silica, gradient 3-10% EtOAc/Heptane.

**$^1$H NMR** δ (400 MHz, $CDCl_3$) 7.58 (d, *J* = 7.53 Hz, 2H), 7.44–7.24 (m, 10H), 7.13 (d, *J* = 4.89 Hz, 1H), 4.77 (s, 1H), 3.96 (s, 2H), 1.88 (br, 1H)

**$^{13}$C NMR** δ (101 MHz, $CDCl_3$) 140.4, 139.9, 130.2, 128.7, 128.6, 128.6, 128.5, 127.9, 127.8, 127.2, 125.4, 122.2, 88.9, 80.9, 53.8, 51.3.

Spectroscopic data were consistent with literature values.[7]

***N*-benzyl-1-(naphthalen-2-yl)-3-phenylprop-2-yn-1-amine 15e**




Compound **15e** was prepared according to the general procedure 2 (**GP2**) and isolated as an orange oil (97.2 mg, 56% yield).

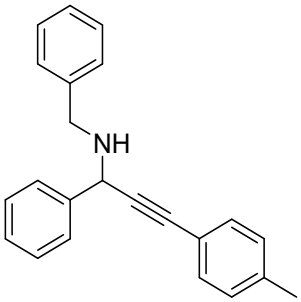
**Column Chromatography**: Silica, gradient 3-10% EtOAc/Heptane.

**$^1$H NMR** δ (400 MHz, $CDCl_3$) δ 8.08 (s, 1 H), 7.89 (d, *J* = 7.8 Hz, 2 H), 7.86 (d, *J* = 8.4 Hz, 1 H), 7.77 (d, *J* = 7.8 Hz, 1 H), 7.58- 7.50 (m, 2 H), 7.50-7.44 (m, 4 H), 7.39-7.35 (m, 5 H), 7.31-7.28 (m, 1 H), 5.01 (s, 1 H), 4.05 (s, 2 H), 1.87 (br, 1 H)

**$^{13}$C NMR** δ (101 MHz, $CDCl_3$) δ 139.8, 137.7, 133.3, 133.1, 131.9, 128.5, 128.4, 128.4, 128.3, 128.1, 127.7, 127.2, 126.4, 126.2, 126.1, 125.9, 123.2, 89.2, 86.1, 53.8, 51.2.

Spectroscopic data were consistent with literature values.[10]

***N*-benzyl-1-phenyl-3-(*p*-tolyl)prop-2-yn-1-amine 15f**




Compound **15g** was prepared according to the general procedure 1 (**GP1**) and isolated as an orange oil (140 mg, 45% yield).

**Column Chromatography**: Silica, gradient 3-10% EtOAc/Heptane.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.66 (d, J = 7.3 Hz, 2H), 7.48–7.41 (m, 5H), 7.40–7.35 (m, 3H), 7.35–7.26 (m, 2H), 7.17 (d, *J* = 7.9 Hz, 2H), 4.84 (s, 1H), 4.08–3.98 (m, 2H), 2.40 (s, 3H), 1.91 (br, 1H).

**$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 140.5, 139.9, 138.4, 131.8, 129.2, 128.61 (2C), 128.56, 127.9, 127.8, 127.2, 120.2, 88.5, 86.0, 53.8, 51.2, 21.6.

Spectroscopic data were consistent with literature values[7]

## 6. Synthesis using developed μw-μf-CR

### 6.1 Ugi reaction

**(4-(1-(*N*-benzylisobutyramido)-2-(cyclohexylamino)-2-oxoethyl)phenyl)boronic acid 5**

Two solutions were prepared: solution #1, 4-formylphenylboronic acid **1** (75 mg, 0.5 mmol) and benzylamine **2** (54 μL, 0.5 mmol) in methanol (250 μL), the solution was premixed and stirred at room temperature for 5 min. Solution #2, isobutyric acid **3** (50 μL, 0.55 mmol) and cyclohexylisocyanide **4** (70 μL, 0.55 mmol). Solution #1 and Solution #2 were dosed into the reactor by a dual syringe pump at a rate of 2.5 μL/min by a syringe pump (combined flow rate = 5 μL/min, $t_R$ = 78 s). The temperature of the reactor was set at 70 °C and the working frequency at 2.01 GHz. Solution streams were combined inside the μw-μf-CR using flow cell A (6.48 μL). The exit line was connected to a flask containing 1M HCl(aq) (3 mL) and EtOAc (3 ml) and equipped with a magnetic stirrer. After completion, the organic phase was separated, dried over $Na_2SO_4$ and evaporated under reduced pressure. Compound **5** was obtained as a white solid (163 mg, yield 75%).

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 8.09 (br, OH), 7.97 (br, OH), 7.61 (br, OH), 7.44 (br, OH), 7.26–7.05 (m, 7H), 6.94 – 6.86 (m, 2H), 6.11 (s, 0.82H), 5.78 (s, 0.18H), 4.83–4.55 (m, 2H), 3.69– 3.64 (m, 1H), 2.76– 2.70 (m, 1H), 1.84–1.59 (m, 6H), 1.37–0.98 (m, 12H).

**$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 175.80, 168.96, 137.85, 136.74, 134.45, 132.24, 128.22, 126.69, 126.05, 83.87, 62.83, 49.88, 48.51, 32.73, 27.30, 25.49, 24.90, 9.38.

Spectroscopic data were consistent with literature values.[11]

### 6.2 Ritter reaction

***N*-(tert-butyl)benzamide 8**

Two solutions were prepared: solution #1, $H_2SO_4$ (96 %: 48 μL) diluted with acetic acid to 200 μL. Solution #2, benzonitrile **6** (0.5 mmol, 51 μL) and tert-butyl acetate **7** (1.0 mmol, 134 μL) were diluted with acetic acid to 200 μL. Solution #1 and Solution #2 were dosed into the reactor by a dual syringe pump at a rate of 4 μL/min by a syringe pump (combined flow rate = 8 μL/min, $t_R$ = 21 s). Solution streams were combined inside the μw-μf-CR using flow cell B. The exit line was connected to a flask containing 2 M NaOH (3 mL) in an ice

bath, and equipped with a magnetic stirrer. After completion, the solution was diluted with EtOAc and transferred in a separatory funnel containing a saturated $CH_3CO_2Na$ solution. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over $Na_2SO_4$. The solvent was removed in vacuum and the product was isolated through column chromatography. Compound **8** was obtained as a white solid (70.8 mg, yield 80%).

Note: The residence time was calculated without considering the mixing elements of the flow cell but only the volume of the reactor zone (2.82 μL).

**$^1$H NMR** δ (400 MHz, $CDCl_3$) 7.71 – 7.69 ppm (m, 2H), 7.45 – 7.42 (m, 1H), 7.39 – 7.35 (m, 2H), 6.1 (br, 1H), 1.45 (s, 9H).

**$^{13}$C NMR** δ (101 MHz, $CDCl_3$) 167.0, 136.0, 131.1, 128.5, 126.8, 77.2, 51.6, 28.9.

Spectroscopic data were consistent with literature values.[12]

## 6.3 Fluorination reaction

**1,3,4,6-Tetra-O-Acetyl-2-deoxy-2-fluoro-2-deoxy-D-glucose 10**

A solution of reagents was prepared: 1.3.4.6-tetra-O-acetyl-2-O-trifluoromethanesulfonyl-*β*-D-mannopyranose (48 mg; 0.1 mmol), cryptand Kryptofix 222 (38 mg, 0.1 mmol), KF (4.1 mg, 0.07mmol) and $K_2CO_3$ (2.5mg, 0.015mmol) were dissolved in 1 ml of dry acetonitrile. The solution was dosed at a rate of 5 μL/min by a syringe pump ($t_R$ = 34 s). The temperature of the reactor was set at 90 °C and the working frequency at 2.0 GHz. Solution streams were combined inside the μw-μf-CR using flow cell A (2.82 μL). The exit line was connected to a flask containing 1N HCl solution (1 ml) and EtOAc (3 ml) and equipped with a magnetic stirrer. After completion, the solution was transferred in a separatory funnel containing a saturated $NaHCO_3$ solution. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over $Na_2SO_4$. The solvent was removed in vacuum and the reaction crude was analysed by GC-MS.

Compound **10** was obtained as a white solid (10.8 mg, yield 61%).

Spectroscopic data were consistent with literature values.[13]

## 6.4 Two-step amidation reaction

***N*-phenethylcinnamamide 14**

Three solutions were prepared: solution #1, cinnamic acid (0.1 mmol, 14.8 mg) and methyl propiolate (0.11 mmol, 10.6 μL) in acetonitrile (300 μL). Solution #2, triethylamine (0.22 mmol, 30.7 μL) in acetonitrile (300 μL). Solution #3 phenethylamine in acetonitrile (3mL, 0.3 M). Solution #1 and Solution #2 were dosed into the first reactor unit by a dual syringe pump at combined flow rate = 5 μL/min, ($t_R$ = 39 s). Solution streams were combined inside the μw-μf-CR using flow cell A (6.48 μL). The temperature of the μw-μf-CR was set at 70 °C and the working frequency at 2.04 GHz. Solution #3 was dosed into the second reactor unit (tubular PFA reactor 200 μL) by a syringe pump at a rate of 25 μL/min.

The exit line was connected to a flask containing water (3 ml) and EtOAc (3 ml) and equipped with a magnetic stirrer. After completion, the solution was transferred in a separatory funnel containing a 1N HCl solution (1 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over $Na_2SO_4$. The solvent was removed in vacuum and the product was isolated through column chromatography.

Compound **14** was obtained as a white solid (21.8 mg, yield 87%).

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 15.6 Hz, 1H), 7.51 – 7.44 (m, 2H), 7.39–7.28 (m, 5H), 7.24 (dd, *J* = 6.5, 5.0 Hz, 3H), 6.53 (dd, *J* = 15.6, 2.1 Hz, 1H), 5.64 (s, 1H), 3.67 (q, 2H), 2.93 (t, *J* = 7.1 Hz, 2H).

**$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 165.97, 141.22, 139.01, 134.94, 129.80, 128.95, 128.94, 128.84, 127.92, 126.71, 120.71, 40.94, 35.81.

Spectroscopic data were consistent with literature values.[14]

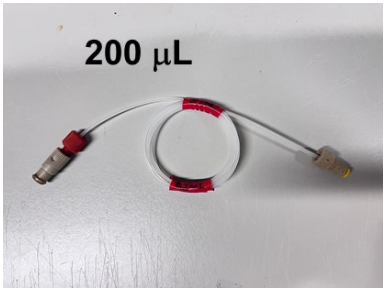



**Figure S7**: tubular PFA reactor

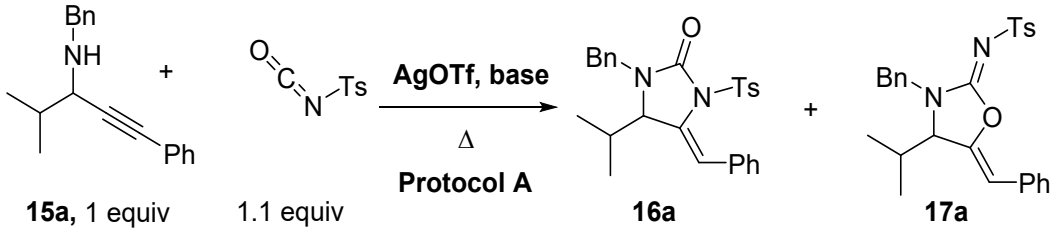
## 6.5 AgOTf-catalyzed protocols A and B

### 6.5.1 Optimization of the AgOTf-catalyzed protocols A and B conditions under continuous flow

An oven-dried microwave vial equipped with a magnetic stirring bar was charged with propargylamine **15a** (0.1 mmol) dissolved in dry solvent, followed by the addition of tosyl isocyanate (21.7 mg, 0.11 mmol). The mixture was stirred at rt for 5 min, and then catalyst and an additive were added (base or acid). The reaction vessel was sealed and irradiated in the cavity of CEM-Discover microwave reactor at maximum power of 50 W. The progress of the reaction was monitored by TLC. The solvent was removed in vacuum and the product was isolated through column chromatography (5-20% EtOAc/heptane).

Note: All starting propargylamines were used freshly prepared. The use of stored propargylamines can lead to reduced combined yield of cycloizomerized products.

**Table S2.** Optimization of AgOTf-catalyzed protocol **A** (basic conditions)



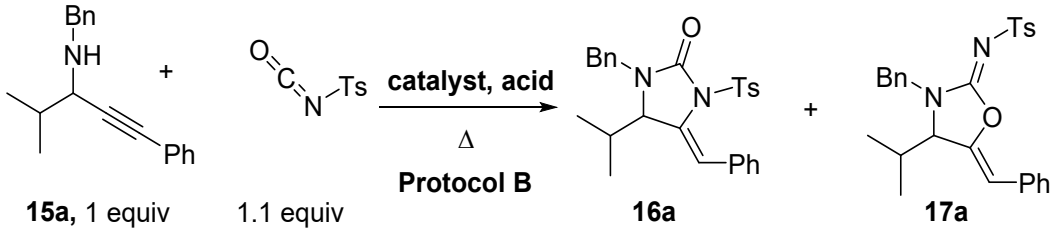

**15a,** 1 equiv 1.1 equiv **16a** **17a**

| entry | solvent | catalyst | base | T(°C) | reactor | time | 16a[a] (%) | 17a[a] (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | toluene | 20 mol% | | 60 | CEM | 10 min | 87(84) | 12 |
| 2 | toluene/MeCN | 20 mol% | | 70 | CEM | 10 min x 3 | 52 | 17 |
| 3 | toluene/MeCN | 20 mol% | 10 mol% $Et_3N$ | 70 | CEM | 5 min | 74 | 5 |
| 4 | toluene/MeCN | no catalyst | 10 mol% $Et_3N$ | 70 | CEM | 10 min x 3 | nr | nr |
| 5 | toluene/MeCN | 20 mol% | 10 mol% DBU | rt | - | 10 min | 60 | 25 |
| 6 | toluene/MeCN | 20 mol% | 10 mol% DABCO | 70 | CEM | 10 min | 70 | 9 |
| 7 | toluene/MeCN | 20 mol% | 10 mol% DMAP | 70 | CEM | 10 min | 57 | 13 |
| 8 | toluene/MeCN | 20 mol% | 10 mol% TMG | 70 | CEM | 10 min | 57 | 11 |
| 9 | toluene/MeCN | 10 mol% | 10 mol% $Et_3N$ | 70 | CEM | 10 min | 72 | 4 |
| 10 | toluene/MeCN | 5 mol% | 10 mol% $Et_3N$ | 70 | CEM | 10 min | 61 | 10 |
| 11 | toluene/MeCN | 5 mol% | 20 mol% $Et_3N$ | 70 | CEM | 10 min | 75(74) | 4 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 13 | toluene/MeCN | 5 mol% | 20 mol% $Et_3N$ | 70 | oil bath | 2 h | 73(70) | 5 |

Unless otherwise stated all reactions were carried out on a 0.1 mmol scale in a mixture of solvents toluene/MeCN (1:1) using a CEM discover reactor at 50 W (2.45 GHz). [a]Yields were determined by $^1$H NMR using 3,4,5-trimethoxybenzaldehyde as internal standard. Isolated yields are indicated in brackets.
Note: It was necessary to work with mixtures of polar and non-polar solvents in order to avoid swelling of PDMS.[4]

**Table S3.** Optimization of AgOTf-catalyzed protocol **B** (acidic conditions)




**15a,** 1 equiv 1.1 equiv **16a** **17a**

| entry | solvent | catalyst | base | T (°C) | reactor | time | 16a[a] (%) | 17a[a] (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | toluene | 20 mol% | - | 60 | CEM | 10 min | 87(84) | 12 |
| 2 | toluene | 20 mol% | 25 mol% TsOH | 70 | CEM | 20 min | trace | trace |
| 3 | MeCN | 20 mol% | 25 mol% TsOH | 70 | CEM | 20 min | nr | nr |
| 4 | MeCN | 20 mol% | 25 mol% MsOH | 70 | CEM | 20 min | nr | nr |
| 5 | MeCN | 20 mol% | 25 mol% BzOH | 70 | CEM | 10 min | 25 | 75 |
| 6 | toluene/MeCN | 20 mol% | 40 mol% BzOH | 70 | CEM | 20 min | 12 | 86 |
| 8 | toluene/MeCN | 20 mol% | 40 mol% AcOH | 70 | CEM | 1 h | 16 | 50 |
| 9 | toluene/MeCN | 20 mol% | 1 equiv AcOH | 70 | CEM | 10 min | 12 | 82(80) |
| | toluene/MeCN | 10 mol% | 1 equiv AcOH | 70 | CEM | 10 min | 10 | 60 |
| 10 | AcOH | 20 mol% | -- | 70 | CEM | 10 min | 8 | 48 |
| 11 | toluene/MeCN | 20 mol% | 1 equiv AcOH | 80 | CEM | 10 min | 17 | 75 |
| 12 | toluene/MeCN | No catalyst | 1 equiv AcOH | 70 | CEM | 10 min | nr | nr |
| 13 | toluene/MeCN | 20 mol% | 1 equiv AcOH | 70 | oil bath | 2 h | 8 | 80 |

Unless otherwise stated all reactions were carried out on a 0.1 mmol scale in a mixture of solvents toluene/MeCN (1:1) using a CEM discover reactor at 50 W (2.45 GHz). [a]Yields were determined by $^1$H NMR using 3,4,5-trimethoxybenzaldehyde as internal standard. Isolated yields are indicated in brackets.

### 6.5.1 Optimization of the AgOTf-catalyzed protocols A and B conditions under continuous flow

Two solutions were prepared: solution #1 by mixing propargylamine **15a** (0.1 mmol, 26.3 mg) and tosyl isocyanate (21.7 mg, 0.11 mmol) in toluene/MeCN (1:1, 200 μL), the solution was stirred at room temperature for 5 min followed by the addition of an additive (base or acid). Solution #2, catalyst in toluene/MeCN (1:1, 200 μL). Solution #1 and Solution #2 were dosed into the reactor unit by a dual syringe pump. Solution streams were combined using a T-mixer. The reaction was performed using a μw-μf-CR with flow cell A (2.82 μL). The working frequency was set at 2.04 GHz. The exit line was connected to a flask containing water (3 ml) and EtOAc (3 ml) and equipped with a magnetic stirrer. After completion, the solution was diluted and transferred into a separatory funnel. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over $Na_2SO_4$. The solvent was removed in vacuum and the product was isolated through column chromatography.

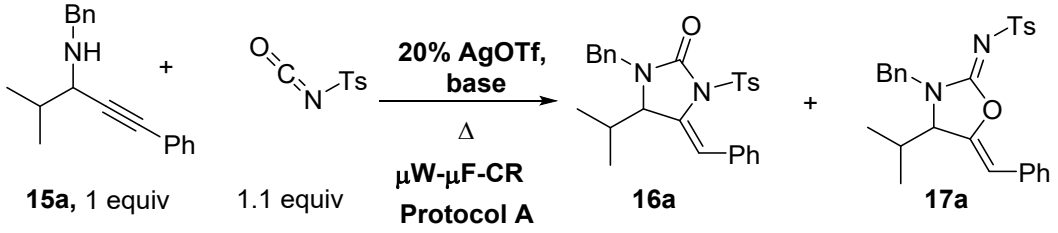
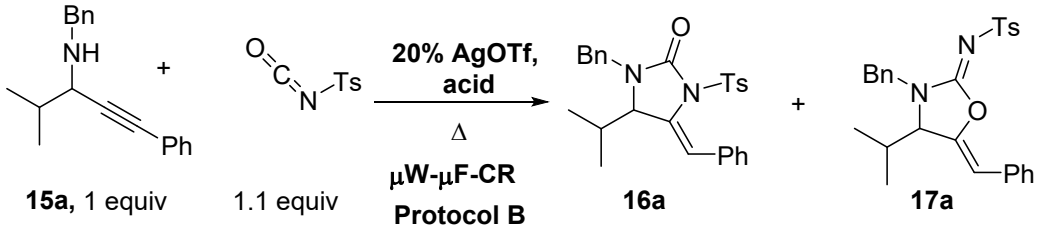



**Table S4.** Optimization of AgOTf-catalyzed protocol **A** (basic conditions) under continuous-flow.

| Entry | M | Additive | T °C | Reactor | Flow rate (μL/min) | $t_R$ (s) | 16a[a] (%) | 17a[a] (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | 0.25 | 5% mol $Et_3N$ | 70 | CR | 5 | 34 | 17 | 50 |
| 2 | 0.25 | 5% mol $Et_3N$ | 80 | CR | 5 | 34 | 17 | 59 |
| 3 | 0.25 | 20% mol $Et_3N$ | 80 | CR | 5 | 34 | 5 | 70 |
| 4 | 0.25 | 25% mol $Et_3N$ | 80 | CR | 5 | 34 | 6 | 83(80) |
| 5 | 0.25 | 25% mol $Et_3N$ | 80 | CR | 8 | 21 | 6 | 68 |

Unless otherwise stated all reactions were carried out on a 0.1 mmol scale in a mixture of solvents toluene/MeCN (1:1) using μW-μF-CR, maximum available power 4.4 W, 2.04 GHz. [a]Yields were determined by $^1H$ NMR using 3,4,5-trimethoxybenzaldehyde as internal standard. Isolated yields are indicated in brackets.

**Table S5.** Optimization of AgOTf-catalyzed protocol **B** (acidic conditions) under continuous-flow.




**15a,** 1 equiv 1.1 equiv **16a** **17a**

| Entry | M | Additive | T °C | Reactor | flow rate (μL/min) | $t_R$ (s) | 16a[a] (%) | 17a[a] (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | 0.25 | 1 equiv. AcOH | 70 | CR | 5 | 34 | 8 | 60 |
| 2 | 0.25 | 1 equiv. AcOH | 70 | CR | 2.5 | 68 | 8 | 84 |
| 3 | 0.25 | 1 equiv. AcOH | 90 | CR | 5 | 34 | 8 | 67 |
| 4 | 0.25 | AcOH as cosolvent (100mL) | 90 | CR | 5 | 34 | 10 | 52 |
| 5 | 0.25 | 2 equiv. AcOH | 90 | CR | 5 | 34 | 8 | 72 |
| 6 | 0.25 | 2 equiv. AcOH | 100 | CR | 5 | 34 | 10 | 77 |
| 7 | 0.5 | 2 equiv. AcOH | 100 | CR | 5 | 34 | 7 | 84 |
| 8 | 0.5 | 2 equiv. AcOH | 100 | CR | 7 | 24 | 10 | 82(81) |

Unless otherwise stated all reactions were carried out on a 0.1 mmol scale in a mixture of solvents toluene/MeCN (1:1) using μW-μF-CR, maximum available power 4.4 W, 2.04 GHz. [a]Yields were determined by $^1$H NMR using 3,4,5-trimethoxybenzaldehyde as internal standard. Isolated yields are indicated in brackets.

### 6.5.2 High frequency experiments

Two solutions were prepared: solution #1 by mixing propargylamine **15a** (0.1 mmol, 26.3 mg) and tosyl isocyanate (21.7 mg, 0.11 mmol) in toluene/MeCN (1:1, 200 μL for protocol A or 100 μL for protocol B), the solution was stirred at room temperature for 5 min followed by the addition of an additive (3.5 μL of $Et_3N$ for protocol A or 12 μL of AcOH for protocol B). Solution #2, AgOTf (1.28 mg for protocol A or 5 mg for protocol B) in toluene/MeCN (1:1, 200 μL for protocol A or or 100 μL for protocol B). Solution #1 and Solution #2 were dosed into the reactor unit by a dual syringe pump at a combined rate of 5 μL/min for protocol A or 7 μL/min for protocol B. Solution streams were combined using a T-mixer. The reaction was performed in setup **S4B** using a μw-μf-CR with flow cell A (2.82 μL). The working frequency was set at 7.69 GHz. The temperature was set at 80°C for protocol A or 100°C for protocol B. The exit line was connected to a flask containing water (3 ml) and EtOAc (3 ml)

and equipped with a magnetic stirrer. After completion, the solution was diluted and transferred into a separatory funnel. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over $Na_2SO_4$. The solvent was removed in vacuum and the product was isolated through column chromatography.

Compound **16a** as a colourless oil (34 mg, 76% yield).

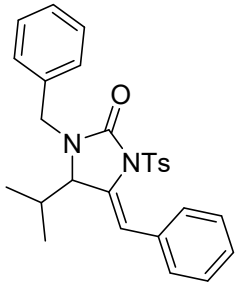
Compound **17a** was obtained as as a colourless oil (35 mg, 77% yield).

### 6.5.3 General procedure for AgOTf-catalyzed cyclization protocols A and B in μW-μF-CR

Two solutions were prepared: solution #1 by mixing propargylamine **15a-g** (0.1 mmol) and tosyl isocyanate (21.7 mg, 0.11 mmol) in toluene/MeCN (1:1, 200 μL for protocol A or 100 μL for protocol B), the solution was stirred at room temperature for 5 min followed by the addition of an additive (3.5 μL of $Et_3N$ for protocol A or 12 μL of AcOH for protocol B). Solution #2, AgOTf (1.28 mg for protocol A or 5 mg for protocol B) in toluene/MeCN (1:1, 200 μL for protocol A or or 100 μL for protocol B). Solution #1 and Solution #2 were dosed into the reactor unit by a dual syringe pump at a combined rate of 5 μL/min for protocol A or 8 μL/min for protocol B. Solution streams were combined using a T-mixer. The reaction was performed using a μw-μf-CR with flow cell A (2.82 μL). The temperature was set at 80°C for protocol A or 100°C for protocol B. The working frequency was set at 2.04 GHz. The exit line was connected to a flask containing water (3 ml) and EtOAc (3 ml) and equipped with a magnetic stirrer. After completion, the solution was diluted and transferred into a separatory funnel. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over $Na_2SO_4$. The solvent was removed in vacuum and the product was isolated through column chromatography.

## 7. Product characterization

### *N*-((*Z*)-3-benzyl-5-((*Z*)-benzylidene)-4-isopropyloxazolidin-2-ylidene)-4-methylbenzenesulfonamide 16a




Compound **16a** was prepared according to the general protocol **A** and isolated as a colourless oil (36.8 mg, 80% yield).

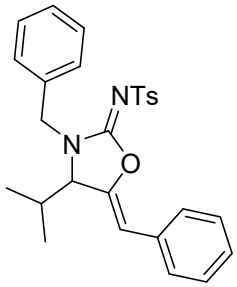
**Column Chromatography**: Silica, gradient 5-20% EtOAc/heptane

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.0 Hz, 2H), 7.39 – 7.32 (m, 4H), 7.28 – 7.26 (m, 2H), 7.24 – 7.19 (m, 3H), 7.19 – 7.14 (m, 3H), 5.97 (s, 1H), 5.06 (d, *J* = 16.0 Hz, 1H), 4.15 (d, *J* = 16.0 Hz, 1H), 3.88 (dd, *J* = 4.0, 1.0 Hz, 1H), 2.46 (s, 3H), 2.16 – 2.08 (m, 1H), 1.15 (d, *J* = 8.0 Hz, 3H), 1.06 (d, *J* = 8 Hz, 3H).

**$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 155.3, 144.4, 136.7, 136.1, 135.8, 129.9, 129.0, 129.0, 128.7, 128.6, 128.4, 128.1, 128.1, 126.9, 117.4, 77.2, 64.8, 45.8, 30.3, 21.8, 18.6, 16.2.

**HRMS** Calculated for $C_{27}H_{29}N_2O_3S$ $[M+H]^+$ 461.1893, found 461.1900

**(*Z*)-1-benzyl-4-benzylidene-5-isopropyl-3-tosylimidazolidin-2-one 17a**




Compound **17a** was prepared according to the general protocol **B** and isolated as a colourless oil (37.3 mg, 81% yield).

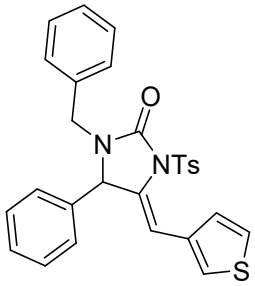
**Column Chromatography**: Silica, gradient 10-30% EtOAc/heptane

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.0 Hz, 2H), 7.59 (d, *J* = 7.4 Hz, 2H), 7.41 – 7.37 (m, 2H), 7.33 (dd, *J* = 5.0, 1.8 Hz, 3H), 7.29 (d, *J* = 7.4 Hz, 1H), 7.23 (dd, *J* = 6.7, 2.7 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 2H), 5.52 (d, *J* = 1.4 Hz, 1H), 5.16 (d, *J* = 15.2 Hz, 1H), 4.12 (dd, *J* = 2.6, 1.7 Hz, 1H), 4.08 (d, *J* = 15.2 Hz, 1H), 2.35 (s, 3H), 2.20 – 2.09 (m, 1H), 0.98 (d, *J* = 7.0 Hz, 3H), 0.78 (d, *J* = 7.0 Hz, 3H).

**$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 155.5, 144.8, 142.5, 140.0, 133.9, 132.4, 129.2, 129.2, 129.0, 128.7, 128.6, 128.3, 127.8, 126.8, 77.2, 63.5, 46.4, 29.8, 21.6, 17.3, 15.1.

**HRMS** Calculated for $C_{27}H_{29}N_2O_3S$ $[M+H]^+$ 461.1893, found 461.1901

**(*Z*)-1-benzyl-5-phenyl-4-(thiophen-3-ylmethylene)-3-tosylimidazolidin-2-one 16d**




Compound **16d** was prepared according to the general protocol **A** and isolated as a light-yellow oil (38.5 mg, 77% yield).

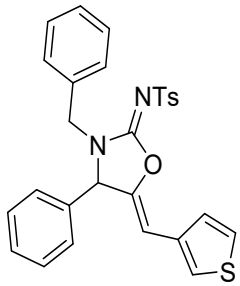
**Column Chromatography**: Silica, gradient 5-20% EtOAc/heptane

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.0 Hz, 2H), 7.53 (d, *J* = 2.0 Hz, 1H), 7.43 (dd, *J* = 4.9, 2.0 Hz, 3H), 7.35 (dd, *J* = 5.0, 1.2 Hz, 1H), 7.31 – 7.27 (m, 6H), 7.19 (dd, *J* = 6.0, 3.0 Hz, 2H), 7.10 (dd, *J* = 7.0, 2.0 Hz, 2H), 5.42 (d, *J* = 2.0 Hz, 1H), 5.15 (d, *J* = 2.0 Hz, 1H), 5.02 (d, *J* = 14.9 Hz, 1H), 3.68 (d, *J* = 14.9 Hz, 1H), 2.41 (s, 3H).

**$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 154.9, 147.1, 142.8, 140.2, 135.5, 133.7, 133.0, 130.0, 129.6, 129.4, 129.1, 128.8, 128.6, 128.3, 128.2, 126.8, 125.7, 124.6, 101.9, 77.2, 62.8, 46.3, 21.6.

**HRMS** Calculated for $C_{28}H_{25}N_2O_3S_2$ $[M+H]^+$ 501.1301, found 501.1313

***N*-((2*Z*,5*Z*)-3-benzyl-4-phenyl-5-(thiophen-3-ylmethylene)oxazolidin-2-ylidene)-4-methylbenzenesulfonamide 17d**




Compound **17d** was prepared according to the general protocol **B** and isolated as a light-yellow oil (42.5 mg, 85% yield).

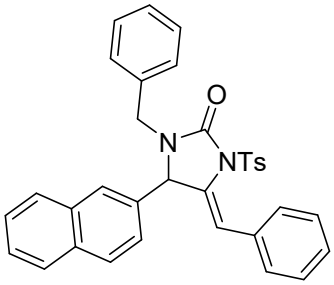
**Column Chromatography**: Silica, gradient 10-30% EtOAc/heptane

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.0 Hz, 2H), 7.52 (d, *J* = 4.0 Hz, 1H), 7.43 – 7.32 (m, 3H), 7.35 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.32 – 7.24 (m, 7H), 7.19 (dd, *J* = 6.7, 2.2 Hz, 3H), 7.09 (dd, *J* = 7.0, 2.0 Hz, 2H), 5.42 (d, *J* = 2.0 Hz, 1H), 5.15 (d, *J* = 2.0 Hz, 1H), 5.04 (s, 1H), 5.0 (s, 1H) 3.68 (d, *J* = 15.0 Hz, 1H), 2.41 (s, 3H).

**$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 154.9, 147.1, 142.8, 140.2, 135.5, 133.7, 133.0, 125.7, 124.7, 101.9, 77.2, 62.8, 46.3, 21.7.

**HRMS** Calculated for $C_{28}H_{25}N_2O_3S_2$ $[M+H]^+$ 501.1301, found 501.1313

**(*Z*)-1-benzyl-4-benzylidene-5-(naphthalen-2-yl)-3-tosylimidazolidin-2-one 16e**




Compound **16e** was prepared according to the general protocol **A** and isolated as a light-yellow oil (46.2 mg, 85% yield).

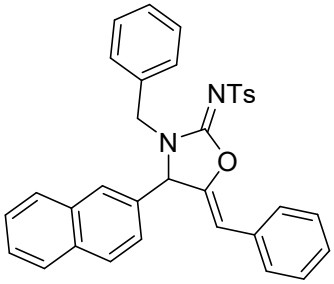
**Column Chromatography**: Silica, gradient 5-20% EtOAc/heptane

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.89 – 7.86 (m, *2*H), 7.82 – 7.79 (m, 3H), 7.55 (dd, *J* = 5.6, 3.9 Hz, 3H), 7.41 – 7.27 (m, 5H), 7.25 – 7.10 (m, 6H), 6.72 (d, *J* = 7.2 Hz, 2H), 5.73 (d, *J* = 2.0 Hz, 1H), 5.10 (d, *J* = 2.1 Hz, 1H), 4.95 (d, *J* = 14.9 Hz, 1H), 3.48 (d, *J* = 14.9 Hz, 1H), 2.51 (s, 3H).

**$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 155.3, 145.0, 135.9, 135.8, 134.8, 133.8, 133.8, 133.2, 133.0, 129.8, 129.6, 129.0, 128.7, 128.7, 128.6, 128.5, 128.3, 128.1, 128.0, 128.0, 127.5, 127.1, 126.9, 124.7, 119.9, 77.2, 64.4, 45.1, 22.0.

**HRMS** Calculated for $C_{34}H_{29}N_2O_3S$ $[M+H]^+$ 545.1893, found 545.1886

***N*-((*Z*)-3-benzyl-5-((*Z*)-benzylidene)-4-(naphthalen-2-yl)oxazolidin-2-ylidene)-4-methylbenzenesulfonamide 17e**




Compound **17e** was prepared according to the general protocol **B** and isolated as a colorless oil (48 mg, 88% yield).

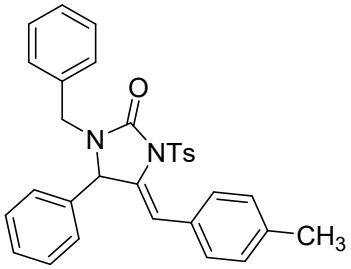
**Column Chromatography**: Silica, gradient 10-30% EtOAc/heptane

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.3 Hz, 2H), 7.96 – 7.86 (m, 3H), 7.69 (d, *J* = 1.4 Hz, 1H), 7.61 (dd, *J* = 6.3, 3.2 Hz, 2H), 7.57 – 7.52 (m, 2H), 7.43 – 7.27 (m, 9H), 7.15 (dd, *J* = 7.4, 1.9 Hz, 2H), 5.37 (d, *J* = 2.1 Hz, 1H), 5.34 (d, *J* = 2.1 Hz, 1H), 5.11 (d, *J* = 14.9 Hz, 1H), 3.73 (d, *J* = 14.9 Hz, 1H), 2.43 (s, 3H).

**$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 155.1, 147.8, 142.8, 140.1, 133.9, 133.7, 133.2, 132.7, 132.3, 130.2, 129.4, 129.1, 128.9, 128.8, 128.7, 128.1, 128.1, 127.9, 127.4, 127.2, 127.0, 124.3, 107.5, 77.2, 63.5, 46.4, 21.7.

**HRMS** Calculated for $C_{34}H_{29}N_2O_3S$ $[M+H]^+$ 545.1893, found 545.1898

**(*Z*)-1-benzyl-4-(4-methylbenzylidene)-5-phenyl-3-tosylimidazolidin-2-one 16f**




Compound **16g** was prepared according to the protocol **A** and isolated as a colorless oil (35.3 mg, 70% yield).

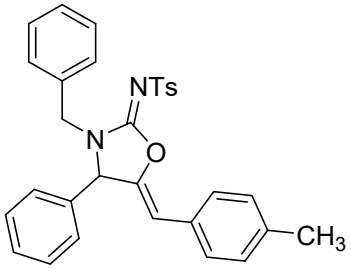
**Column Chromatography**: Silica, gradient 5-20% EtOAc/heptane.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.2 Hz, 2H), 7.42 (dd, *J* = 6.7, 2.3 Hz, 5H), 7.34 – 7.24 (m, 5H), 7.21 – 7.14 (m, 4H), 7.11 (dd, *J* = 6.4, 2.7 Hz, 2H), 5.25 (d, *J* = 2.0 Hz, 1H), 5.14 (d, *J* = 1.8 Hz, 1H), 5.05 (d, *J* = 14.8 Hz, 1H), 3.68 (d, *J* = 14.9 Hz, 1H), 2.39 (s, 3H), 2.34 (s, 3H).

**$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 155.1, 147.2, 142.7, 140.1, 137.8, 135.7, 133.7, 129.9, 129.6, 129.5, 129.4, 129.4, 129.1, 128.9, 128.8, 128.6, 128.3, 126.9, 107.2, 77.2, 63.2, 46.3, 21.6, 21.4.

**HRMS** Calculated for $C_{31}H_{29}N_2O_3S$ $[M+H]^+$ 509.1821, found 509.1900

***N*-((*Z*)-3-benzyl-5-((*Z*)-4-methylbenzylidene)-4-phenyloxazolidin-2-ylidene)-4-methylbenzenesulfonamide 17f**




Compound **17g** was prepared according to the protocol **B** and isolated as a white solid (40 mg, 79% yield)

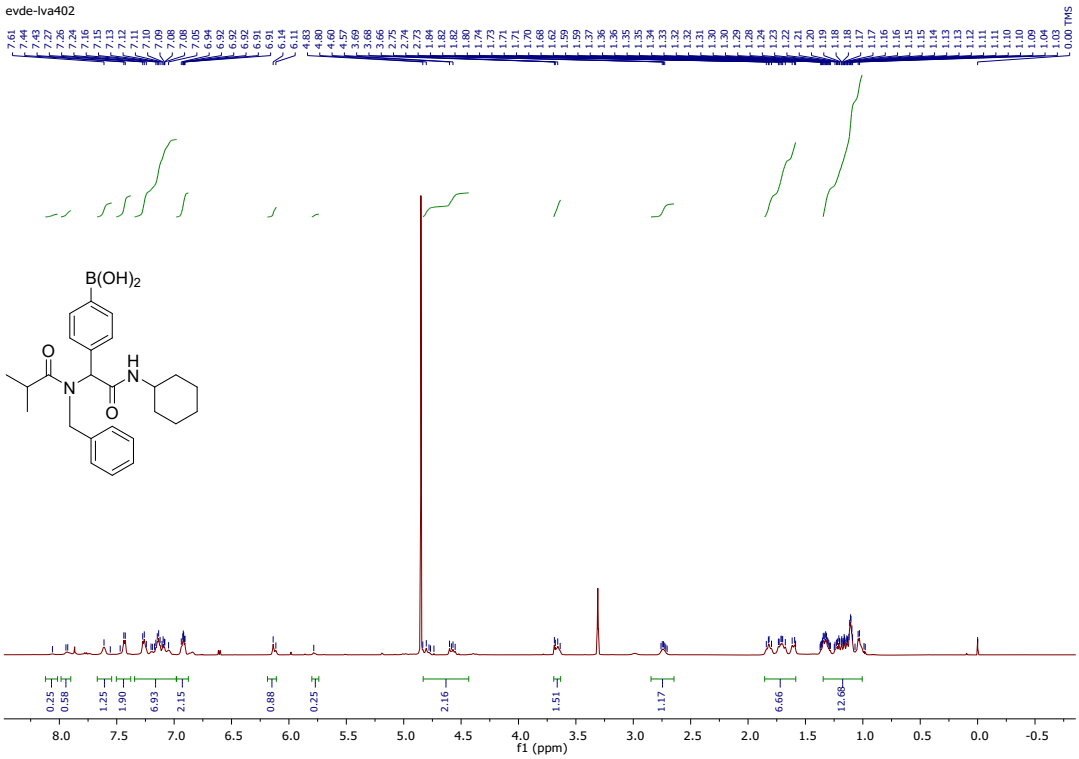
**Column Chromatography**: Silica, gradient 10-30% EtOAc/heptane

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.3 Hz, 2H), 7.42 (dd, *J* = 6.4, 2.2 Hz, 5H), 7.32 – 7.24 (m, 5H), 7.21 – 7.14 (m, 4H), 7.11 (dd, *J* = 6.5, 2.9 Hz, 2H), 5.25 (d, *J* = 2.1 Hz, 1H), 5.14 (d, *J* = 2.0 Hz, 1H), 5.05 (d, *J* = 14.8 Hz, 1H), 3.68 (d, *J* = 14.8 Hz, 1H), 2.39 (s, 3H), 2.34 (s, 3H).

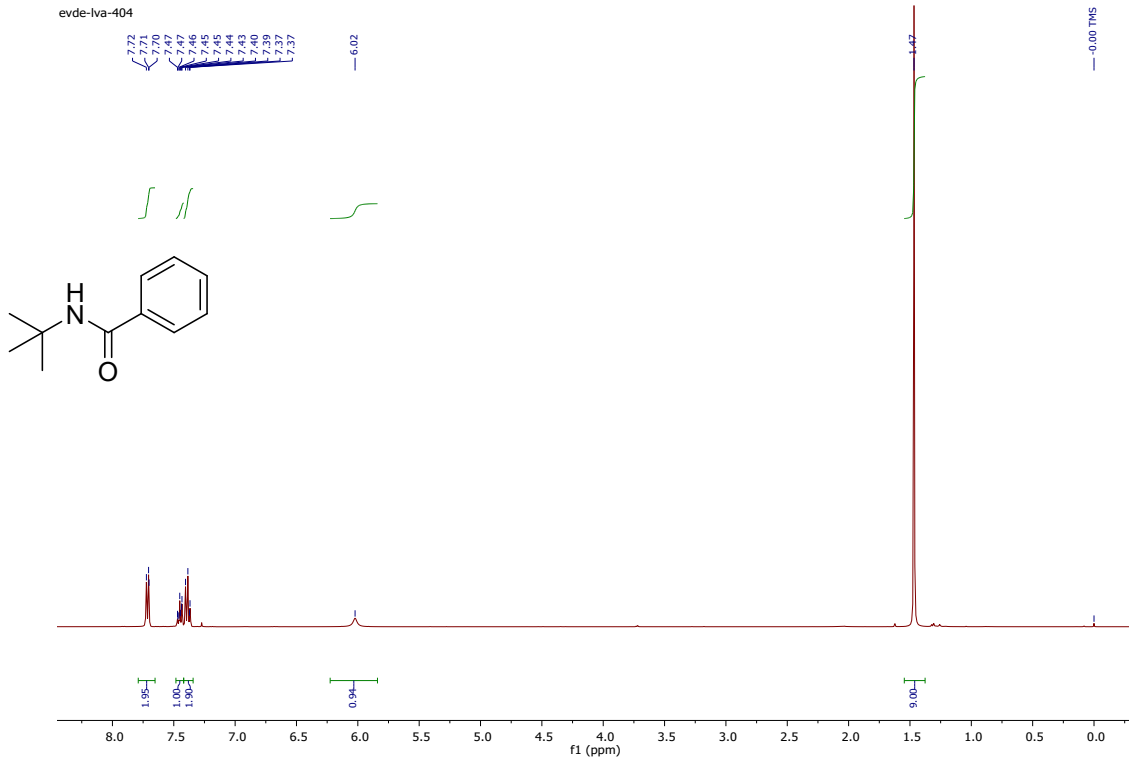
**$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 155.1, 147.2, 142.7, 140.1, 137.8, 135.7, 133.7, 129.9, 129.6, 129.5, 129.4, 129.3, 129.0, 128.8, 128.7, 128.6, 128.3, 126.9, 107.2, 77.2, 63.2, 46.5, 21.6, 21.4.

**HRMS** Calculated for $C_{31}H_{29}N_2O_3S$ $[M+H]^+$ 509.1821, found 509.1894

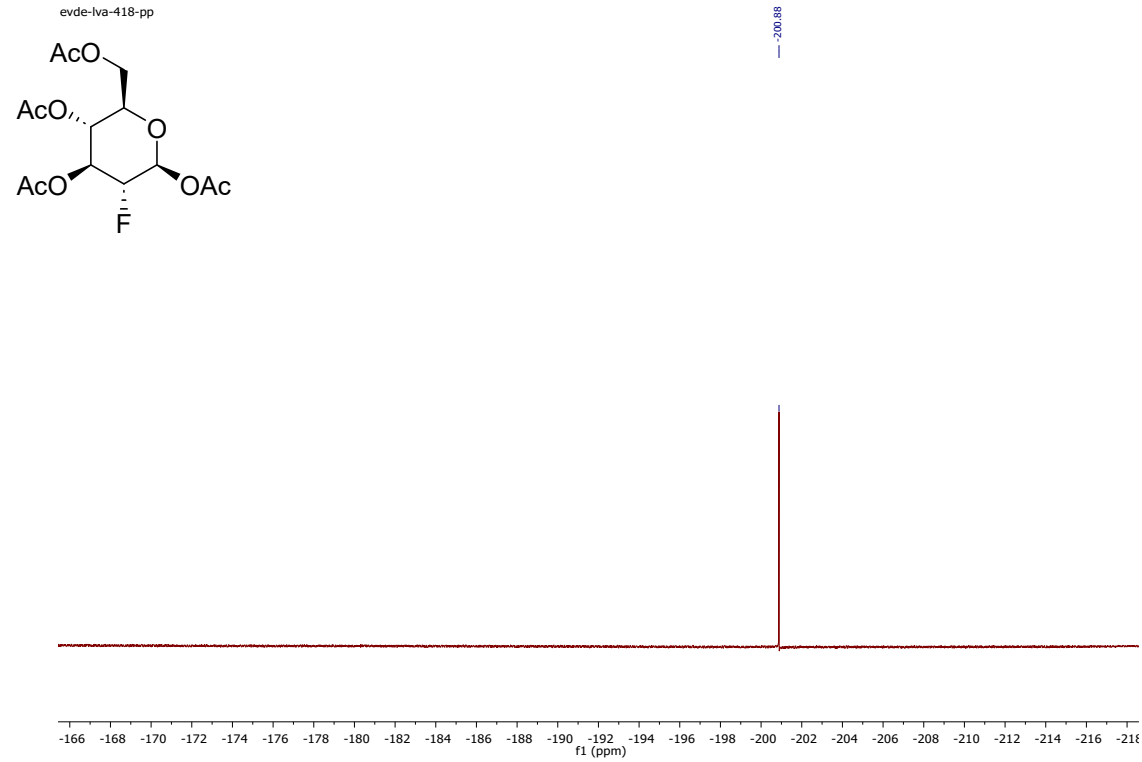
**m.p.:** 181-183°C



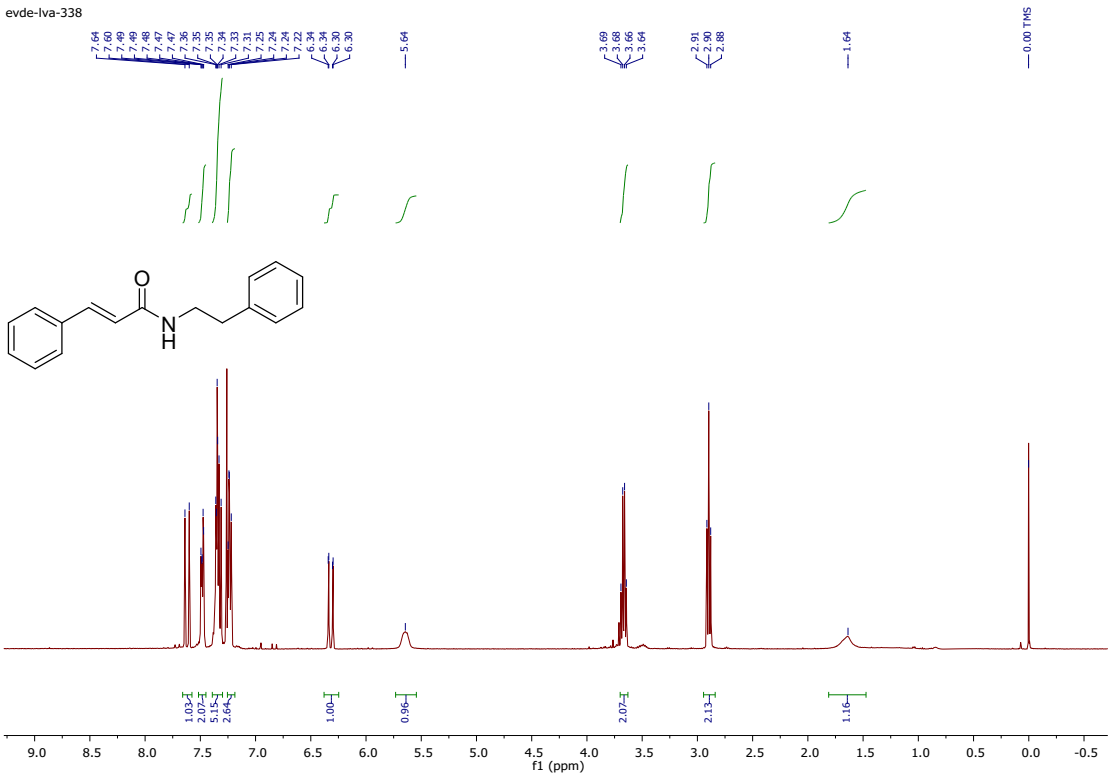

$^1$H NMR (400 MHz, $CDCl_3$) of compound **5**



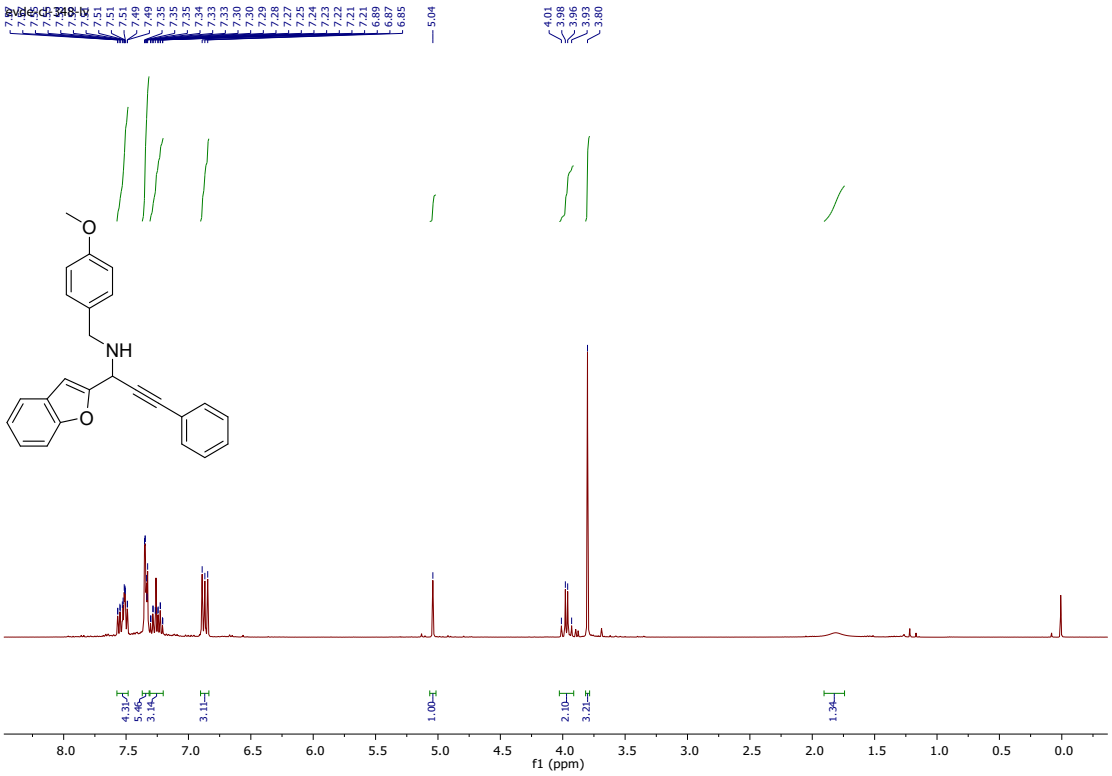

$^1$H NMR (400 MHz, $CDCl_3$) of compound **8**



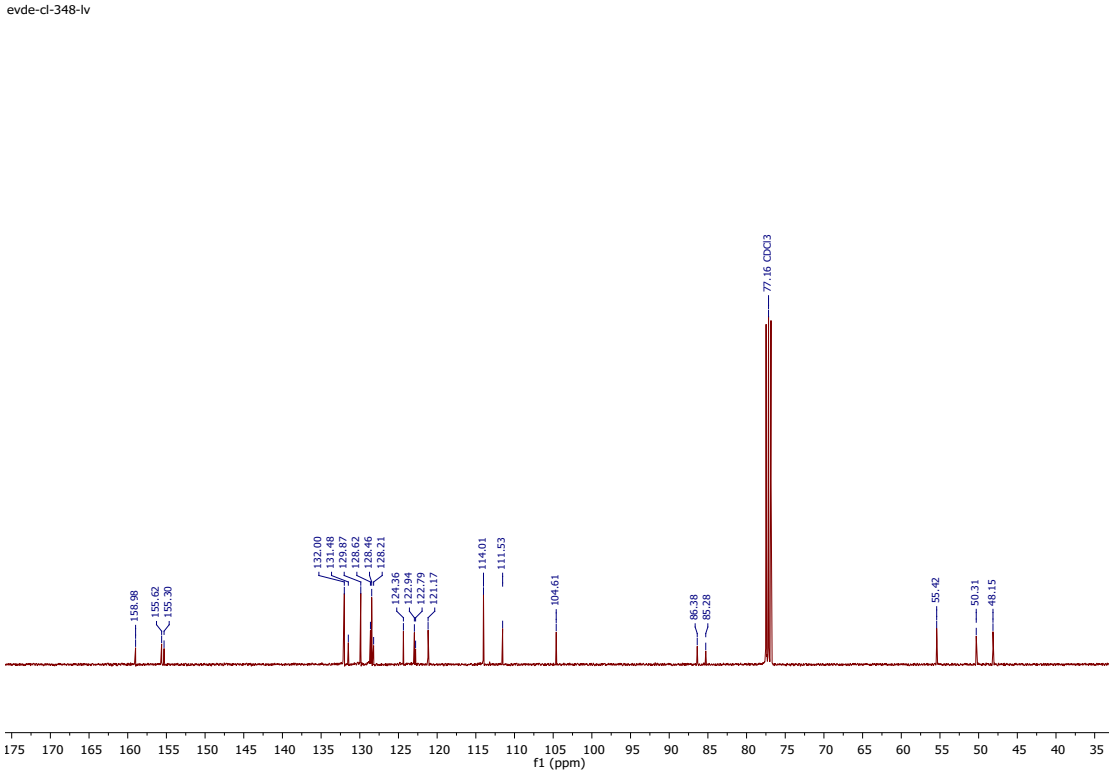

$^{19}F$ NMR (376 MHz, $CDCl_3$) of compound **10**



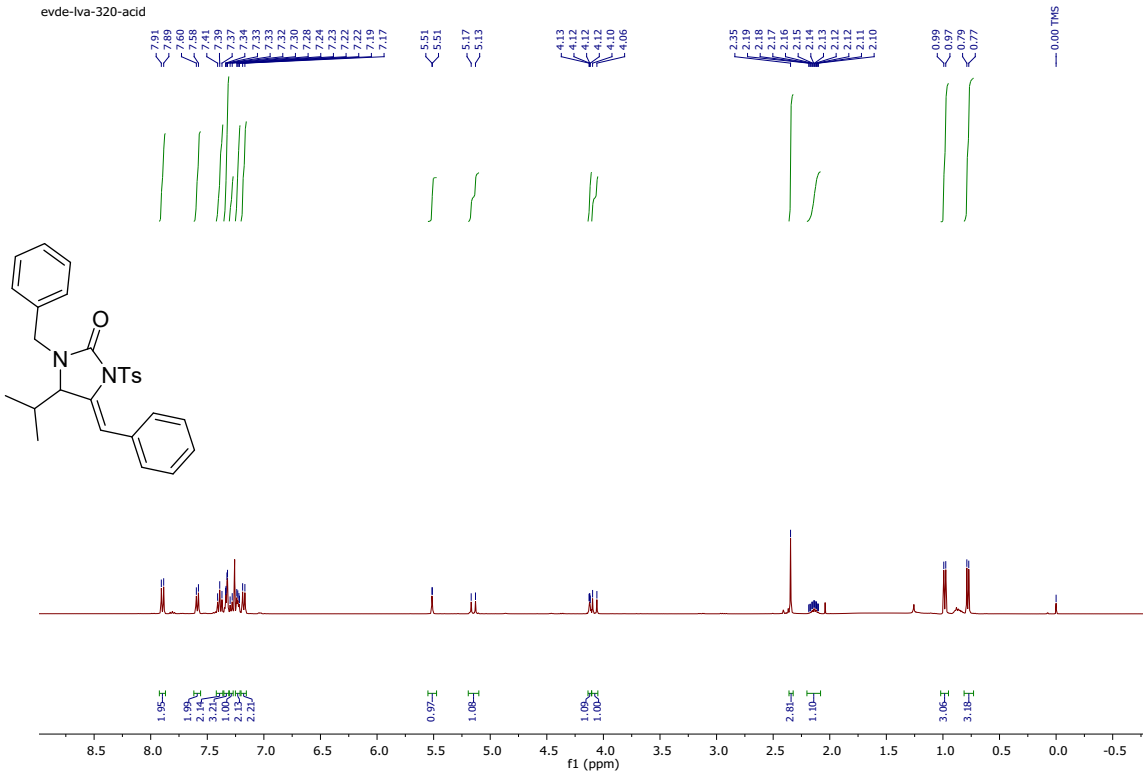

$^{1}H$ NMR (400 MHz, $CDCl_3$) of compound **14**



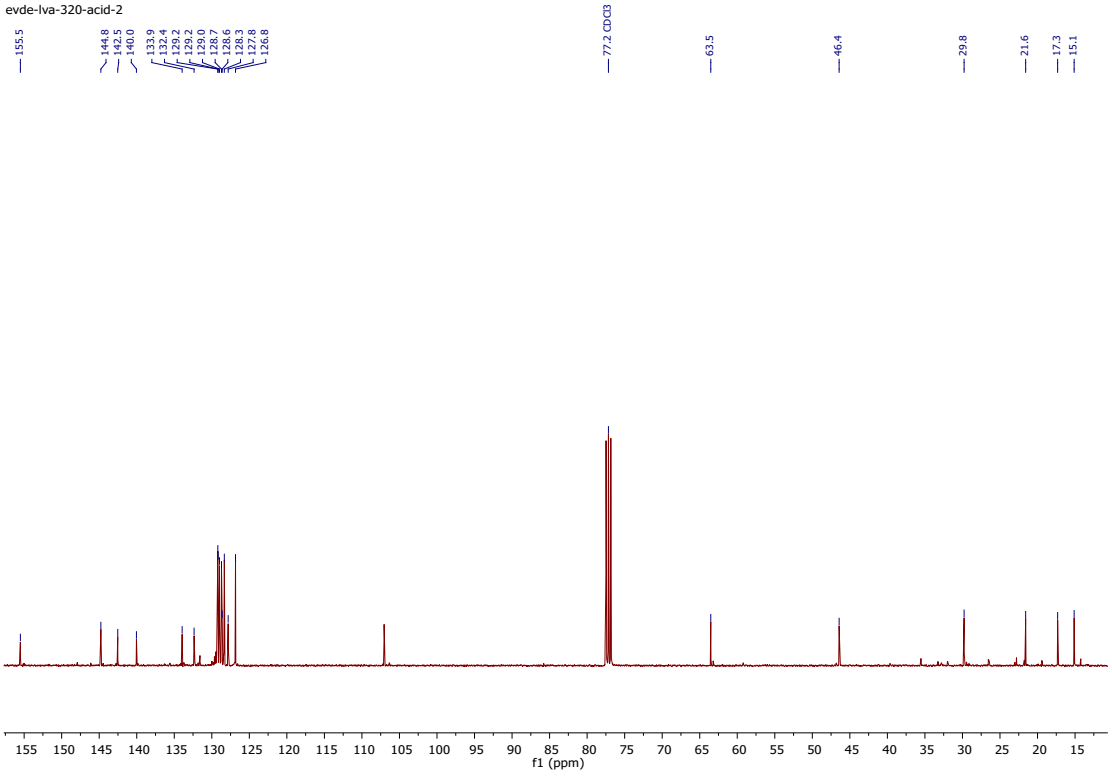

$^{1}$H NMR (400 MHz, $CDCl_3$) of compound **15f**



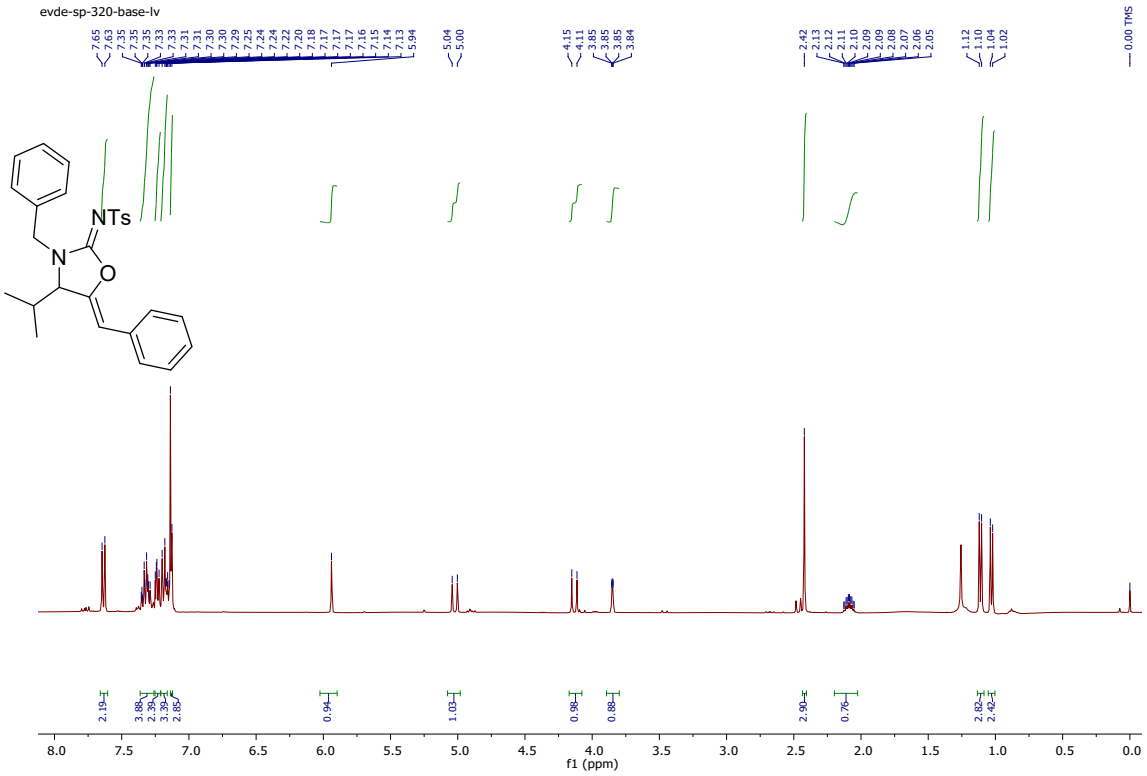

$^{13}$C NMR (101 MHz, $CDCl_3$) of compound **15f**



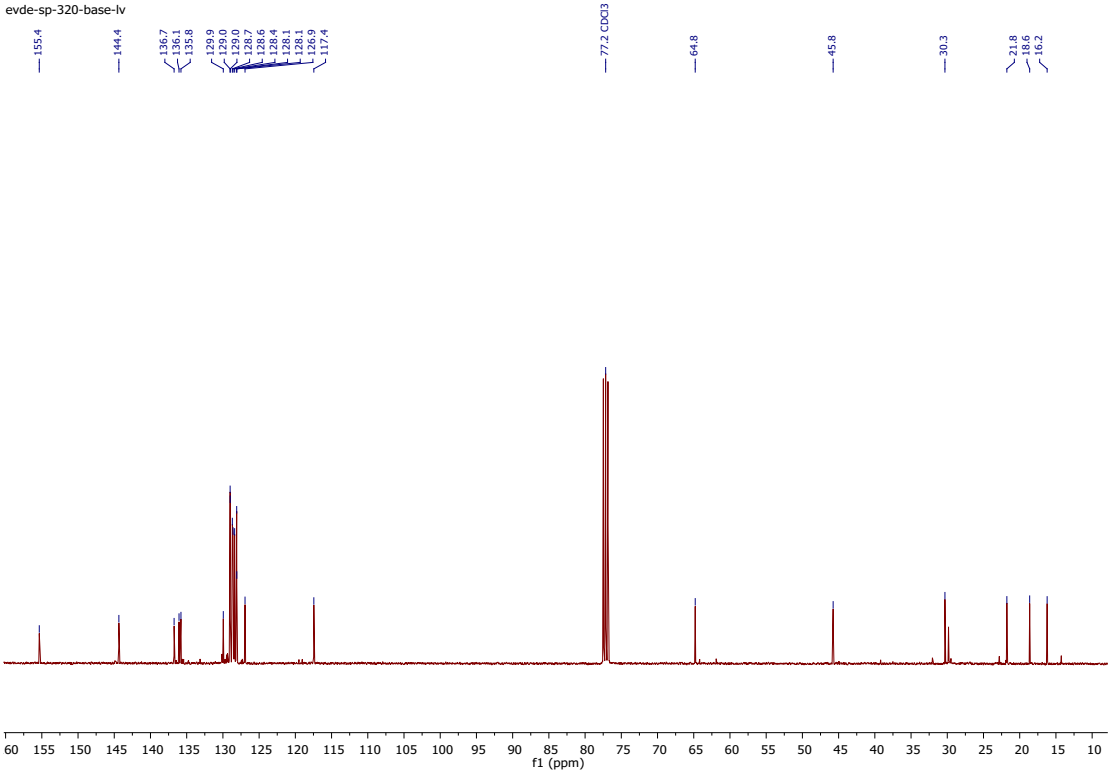

$^{1}$H NMR (400 MHz, $CDCl_3$) of compound **16a**



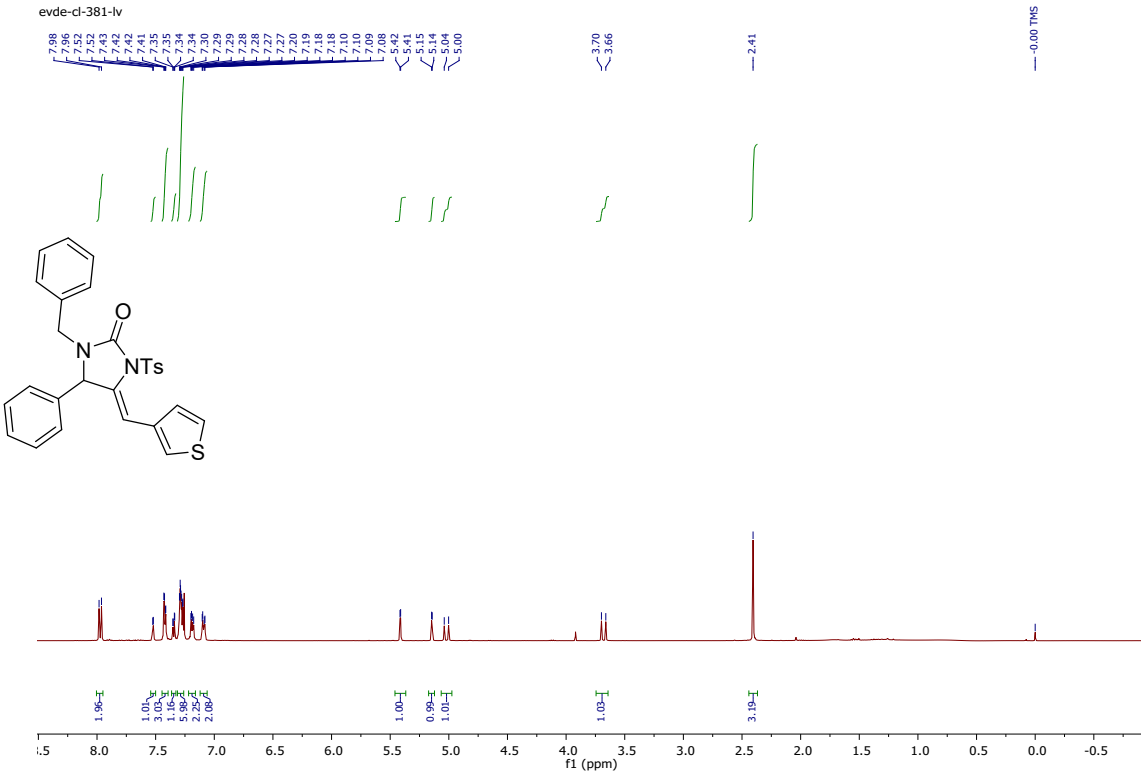

$^{13}$C NMR (101 MHz, $CDCl_3$) of compound **16a**



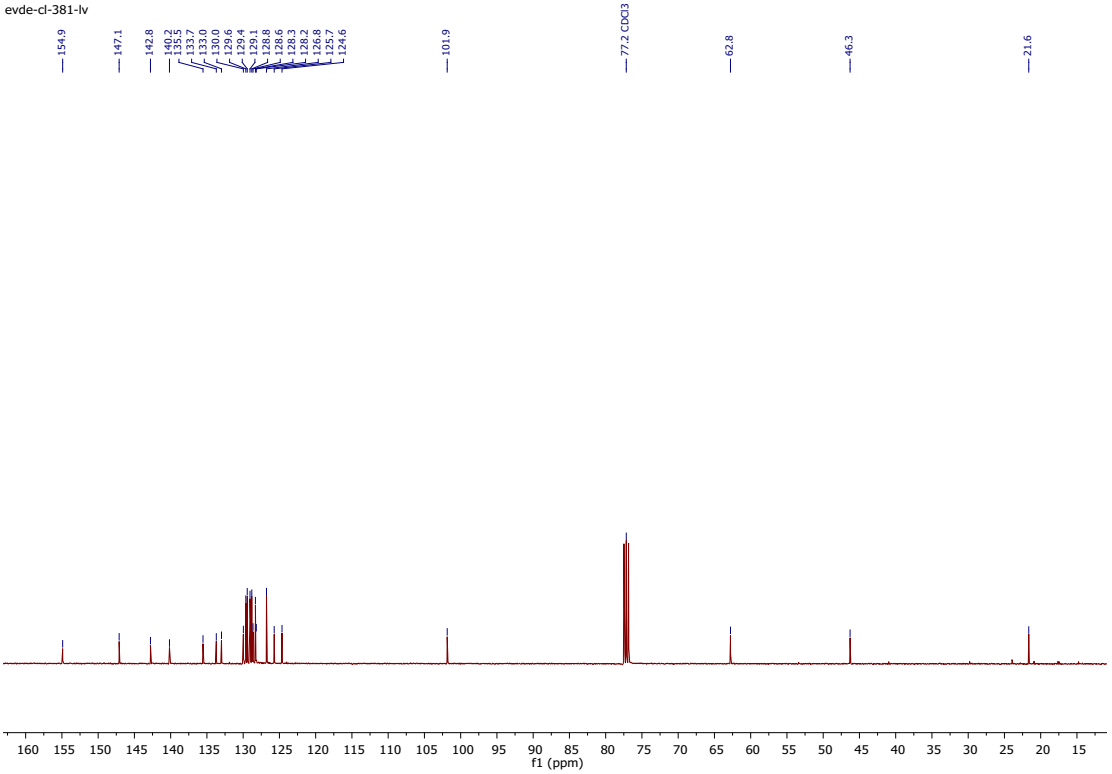

$^{1}$H NMR (400 MHz, $CDCl_3$) of compound **17a**



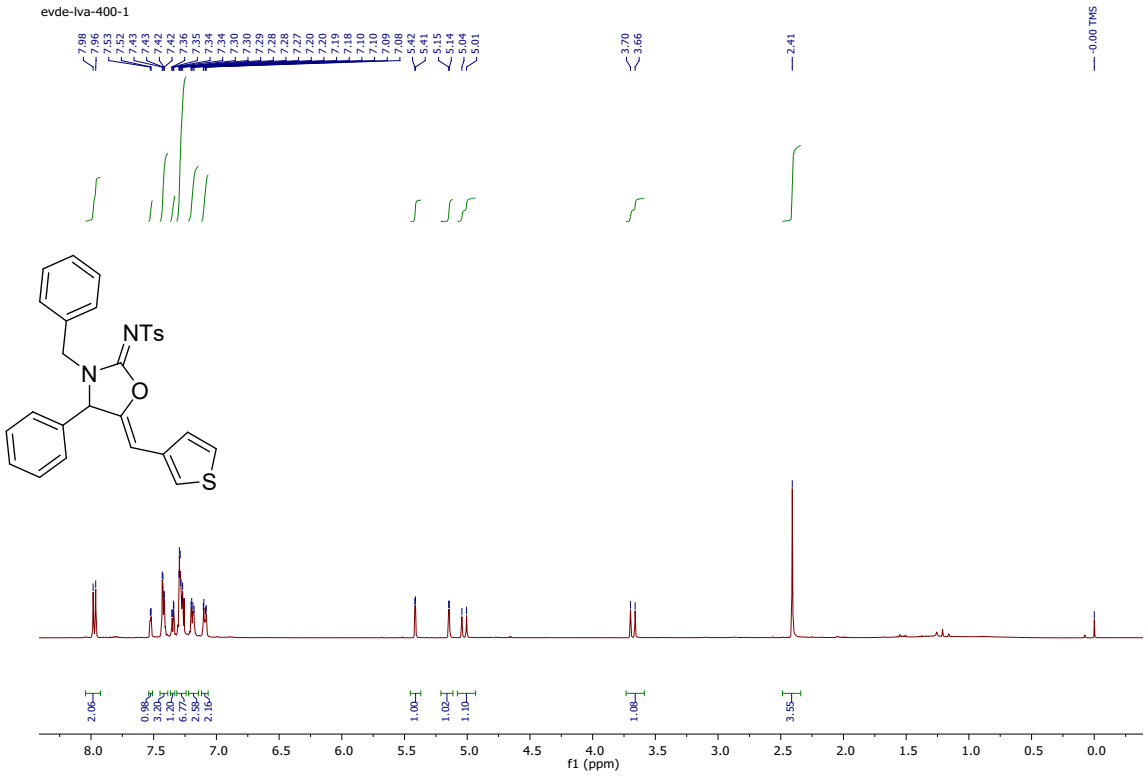

$^{13}$C NMR (101 MHz, $CDCl_3$) of compound **17a**



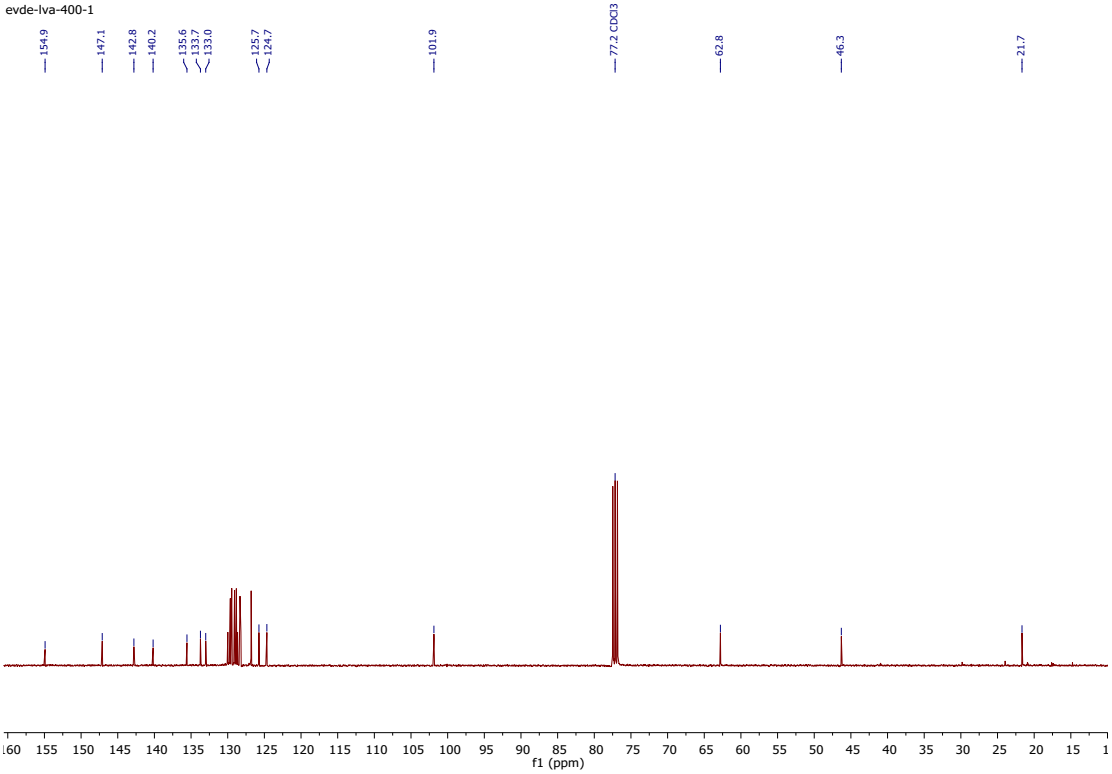

$^{1}$H NMR (400 MHz, $CDCl_3$) of compound **16d**



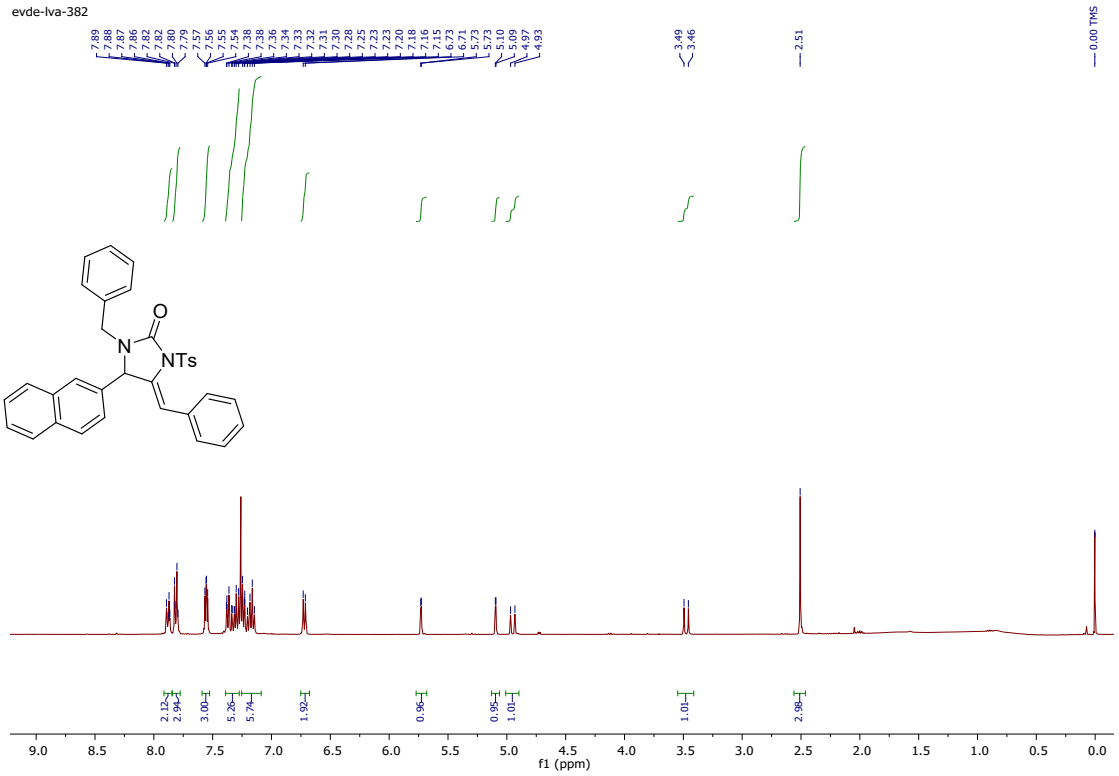

$^{13}$C NMR (101 MHz, $CDCl_3$) of compound **16d**



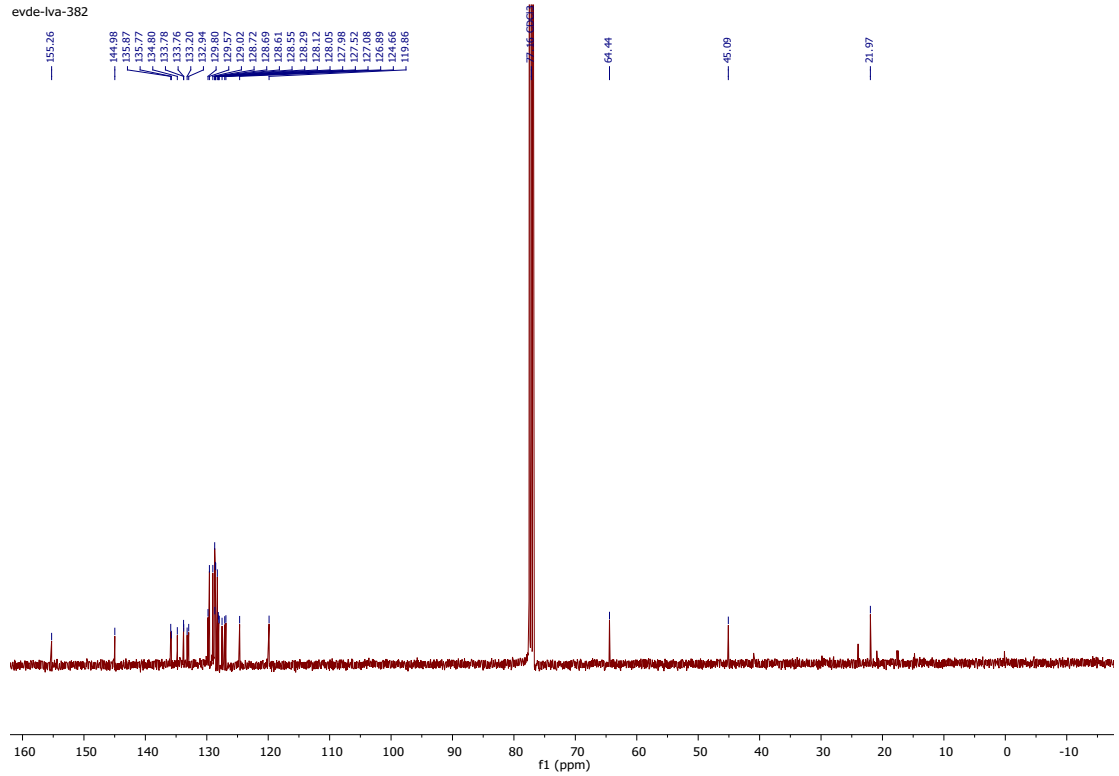

$^{1}$H NMR (400 MHz, $CDCl_3$) of compound **17d**



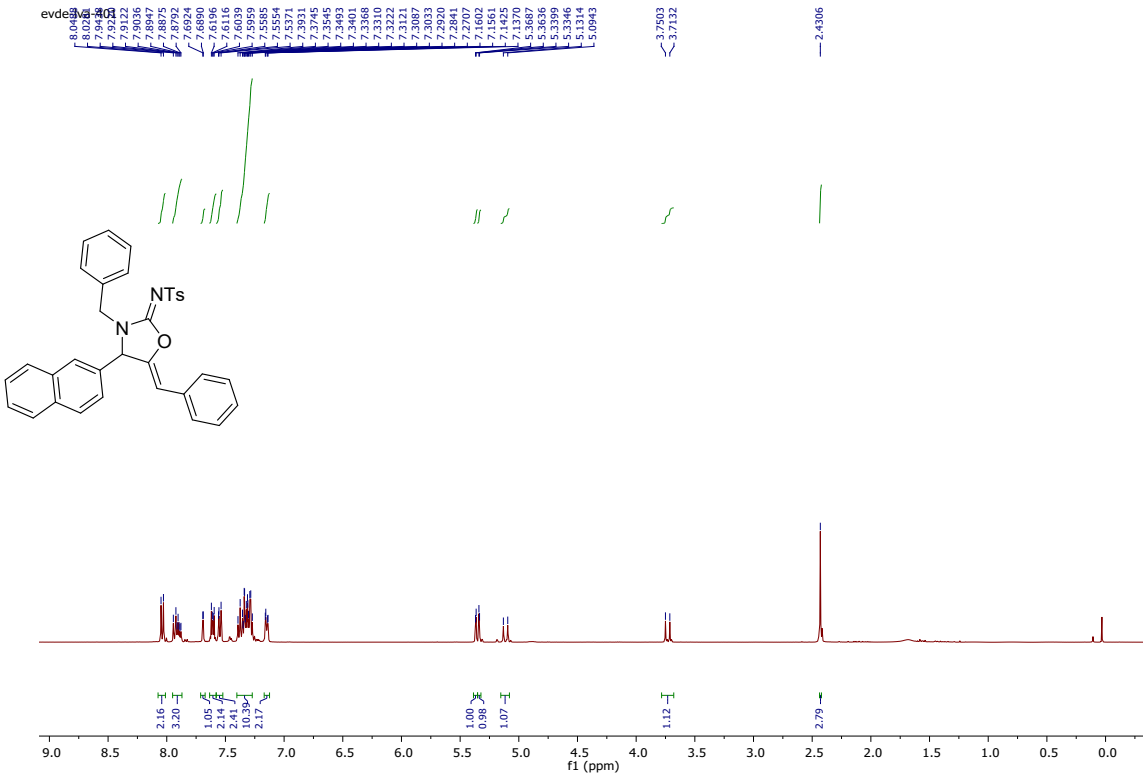

$^{13}$C NMR (101 MHz, $CDCl_3$) of compound **17d**



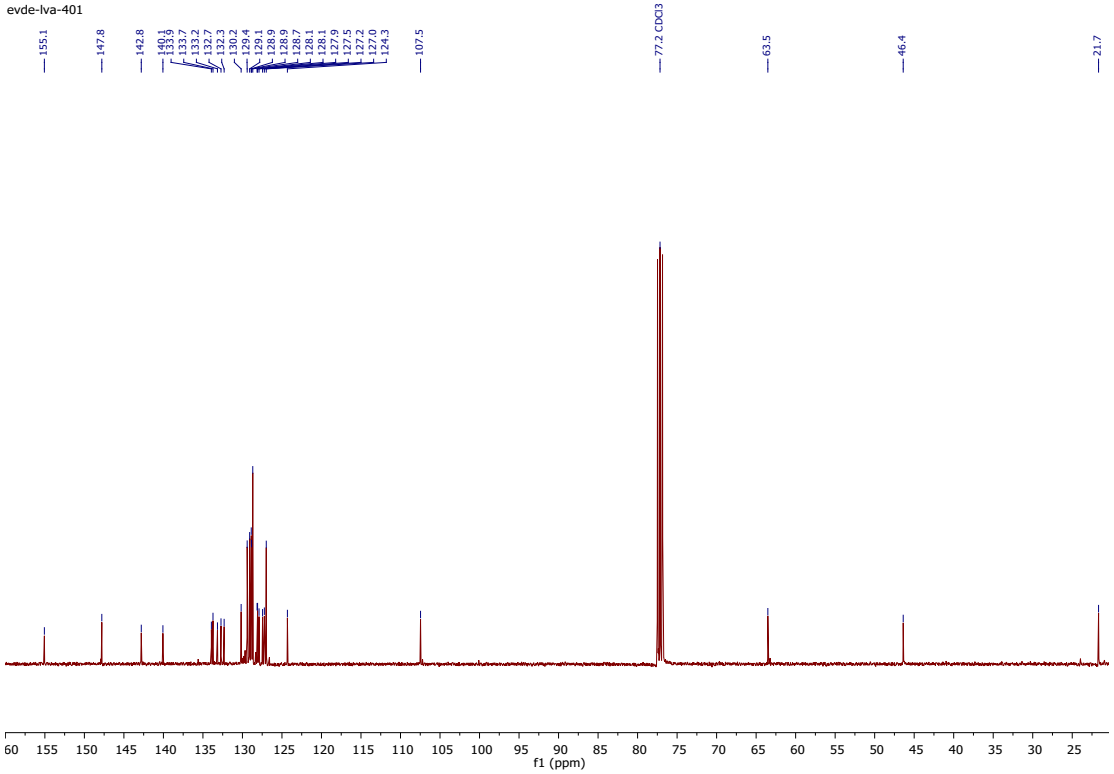

$^{1}$H NMR (400 MHz, $CDCl_3$) of compound **16e**



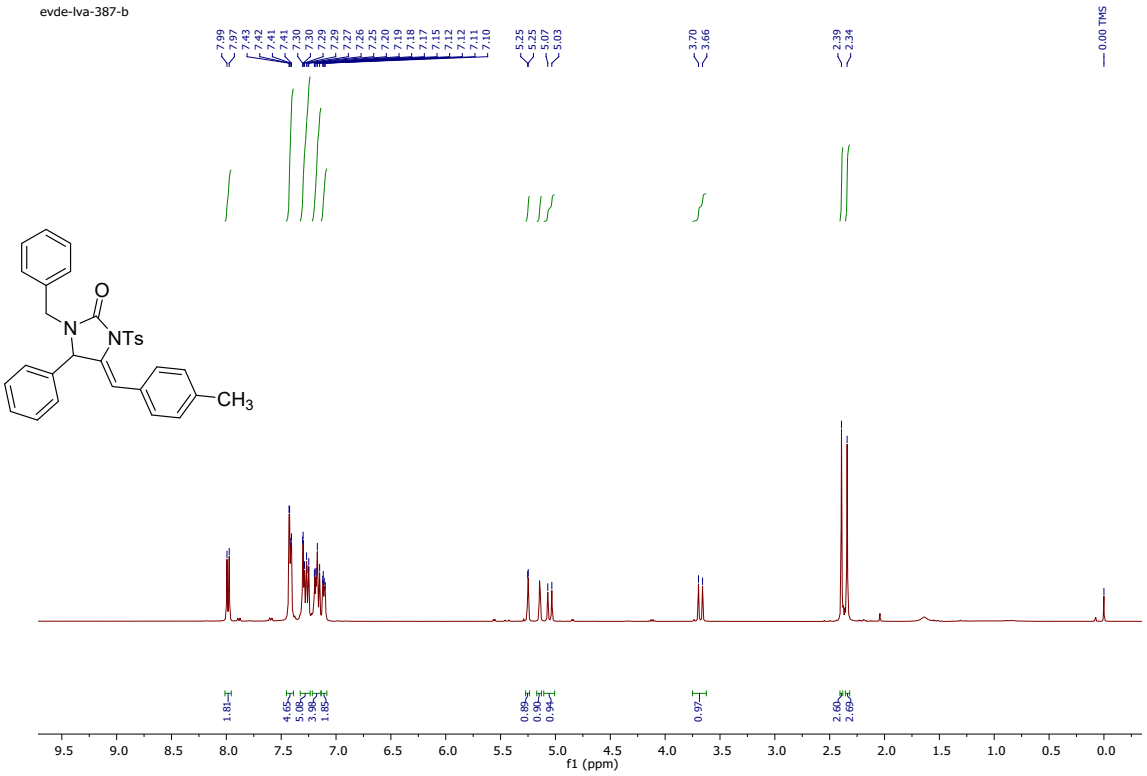

$^{13}$C NMR (101 MHz, $CDCl_3$) of compound **16e**



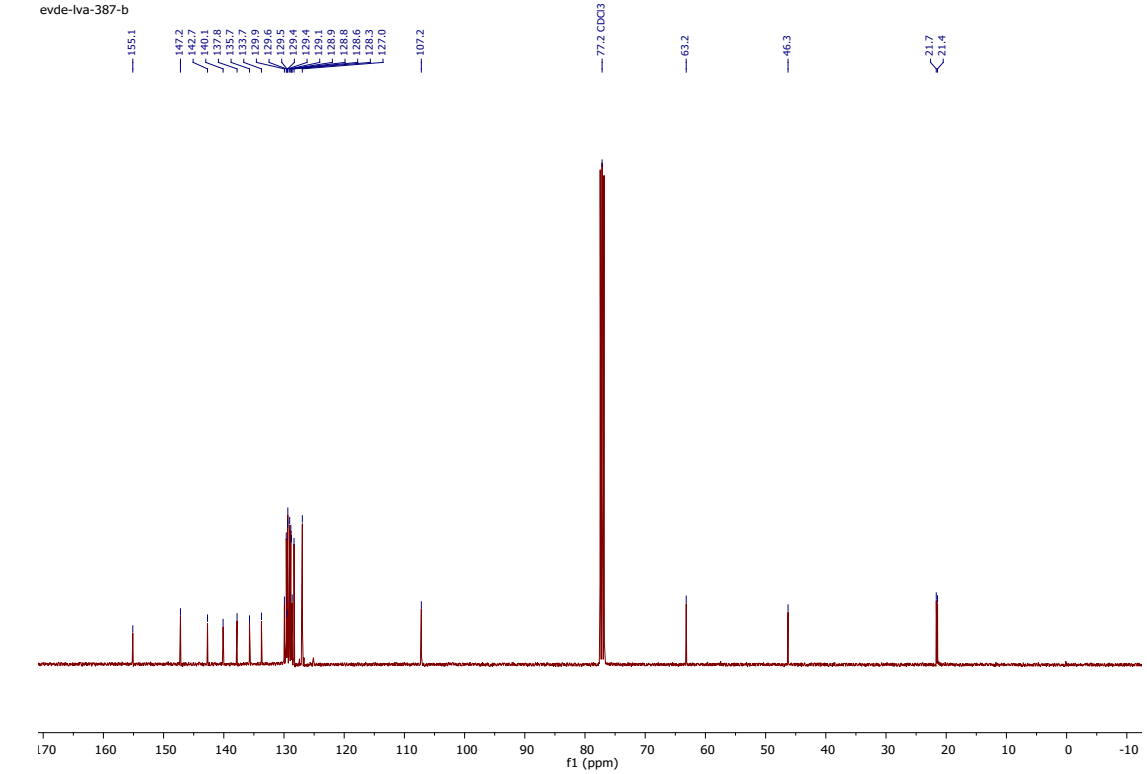

$^{1}$H NMR (400 MHz, $CDCl_3$) of compound **17e**



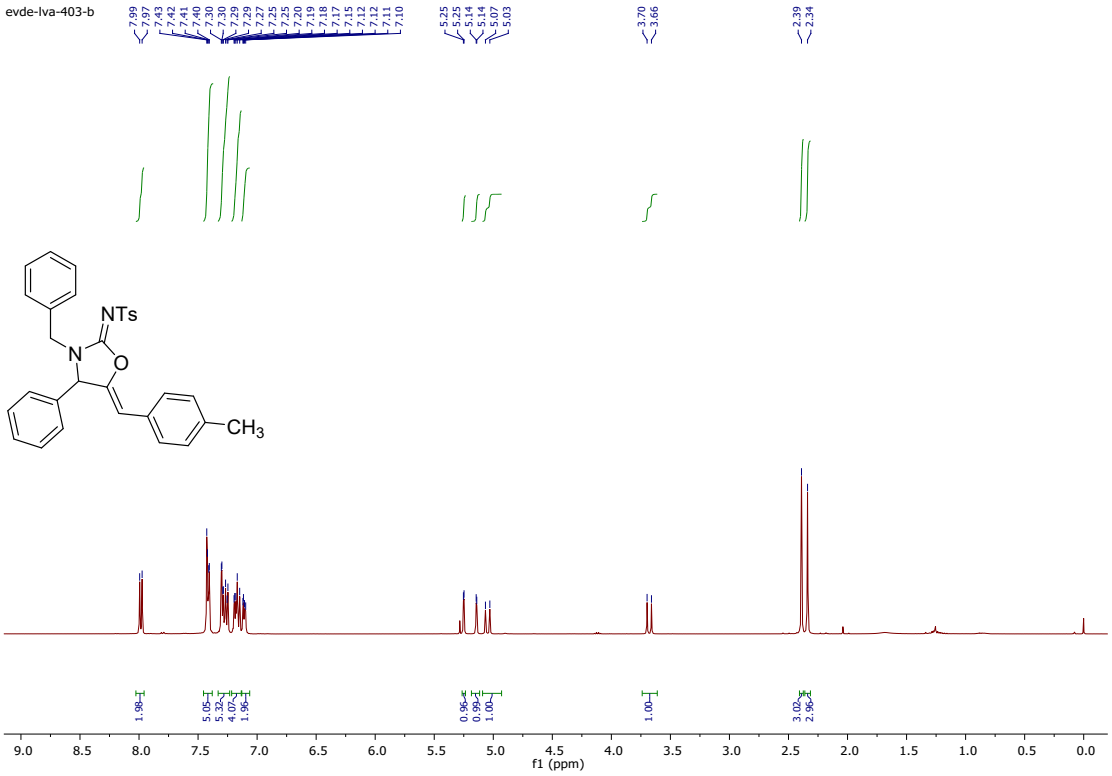

$^{13}$C NMR (101 MHz, $CDCl_3$) of compound **17e**



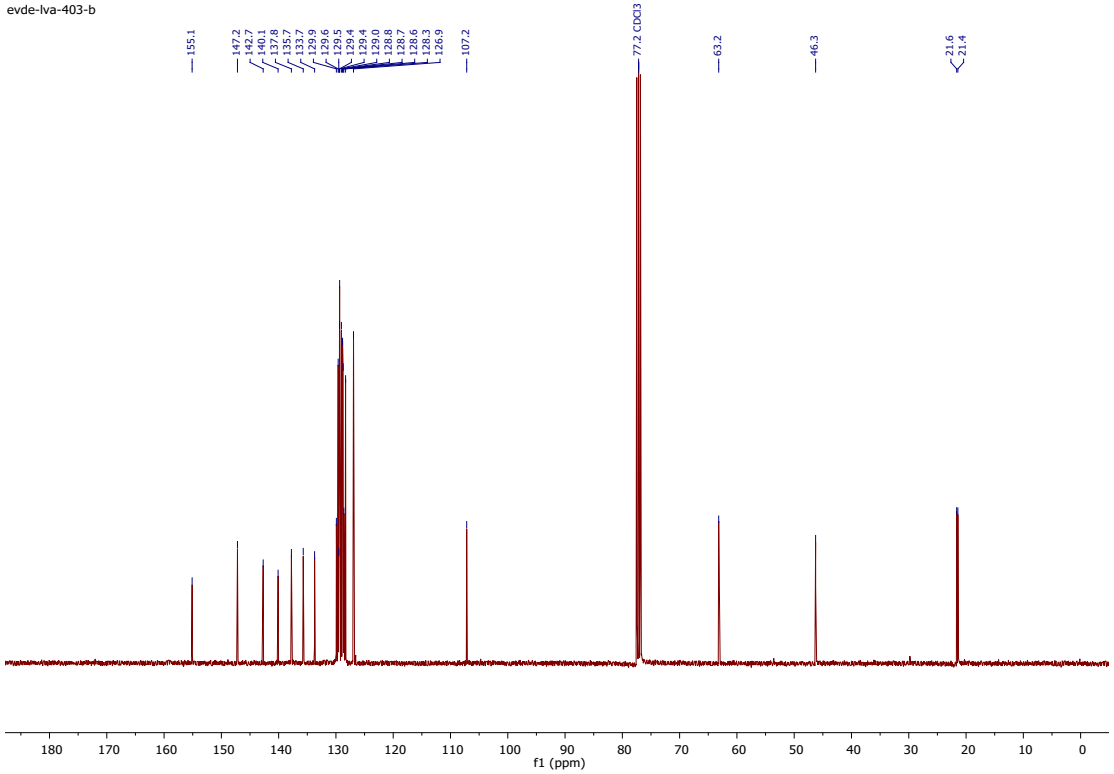

$^{1}$H NMR (400 MHz, $CDCl_3$) of compound **16f**




$^{13}$C NMR (101 MHz, $CDCl_3$) of compound **16f**




$^{1}$H NMR (400 MHz, $CDCl_3$) of compound **17f**




$^{13}$C NMR (101 MHz, $CDCl_3$) of compound **17f**

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