Supporting Information for:

On a seamlessly replicable circular photoreactor for lab-scale continuous flow applications

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1. Photoreactor construction manual

1.1 Overview of the system

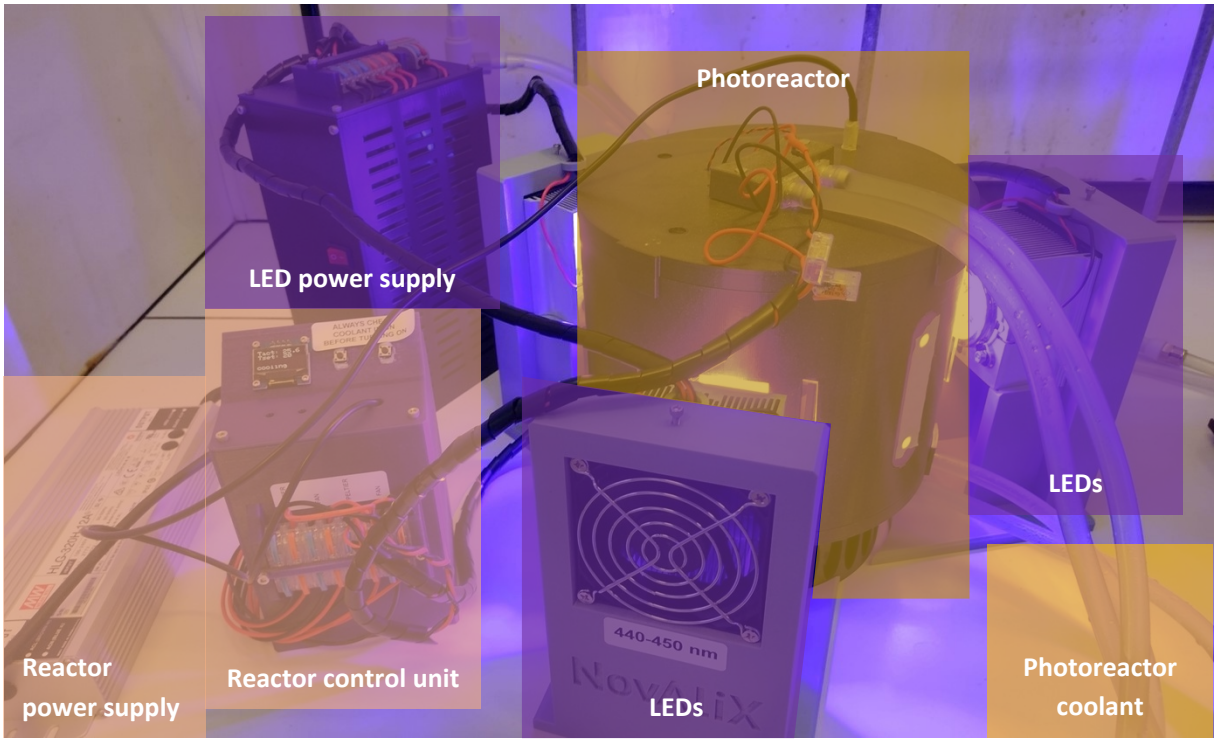


Figure S1. Overview of the home-made photoreactor system

The assembly of the photoreactor (3D-printed enclosure equipped with Peltier elements), reactor control unit (electronics enclosure for control of the Peltier elements), LED holders and LED power supply unit is described below.

1.2 3D printed parts

Parts for the valve module were designed with Autodesk Fusion 360, sliced with the Prusa slicer, and printed on a Prusa MK3S+ using PETG filament, using 0.20 mm layers and gyroid infill 20%. See below for relevant exploded views. If an FDM 3D printer suitable for PLA and PETG is not available, printing the parts can be outsourced to 3D printing capable FabLabs or commercial workshops.

1.2.1 List of 3D printed parts

Assembly	Part (file name)	Description
Photoreactor	Lid Bottom	Bottom of reactor enclosure – mounted on Foot and supporting both Frame and Reactor support
	Frame	Main part of the reactor enclosure – accommodates windows for light sources and inlets/outlets for flow reactor
	Clamp inside (4 x)	Clamps to hold the Peltier/heat exchange assembly in place (inside reactor)

	Foot	Foot allowing sufficient space for connection of wires and coolant to bottom lid
	Reactor support	Support for flow reactor (e.g. PFA tubing)
	Lid Top	Top of reactor enclosure
	Clamp outside (2 x)	Clamps to hold the Peltier/heat exchange assembly in place (outside reactor)
Control Unit	Frame	Frame housing the control unit (electronics)
	Back Panel	Back panel of the control unit
	Top	Top panel of the control unit
	Clamp	Clamp of the control unit (for wire connectors)
LED Holder	Plate (3 x)	Bottom part of the LED Holder, fitting the photoreactor's foot
	Foot (6 x)	Height adjuster
	Frame (3 x)	Frame supporting the LED/heatsink/fan assembly
LED Power Supply	Frame	Frame housing the power supply and distributing wires for the LEDs
	Back panel	Back panel of the power supply unit
	Top and Clamp	Top of the LEDs power supply unit including clamp for wire connectors

1.2.2 Photoreactor general exploded view

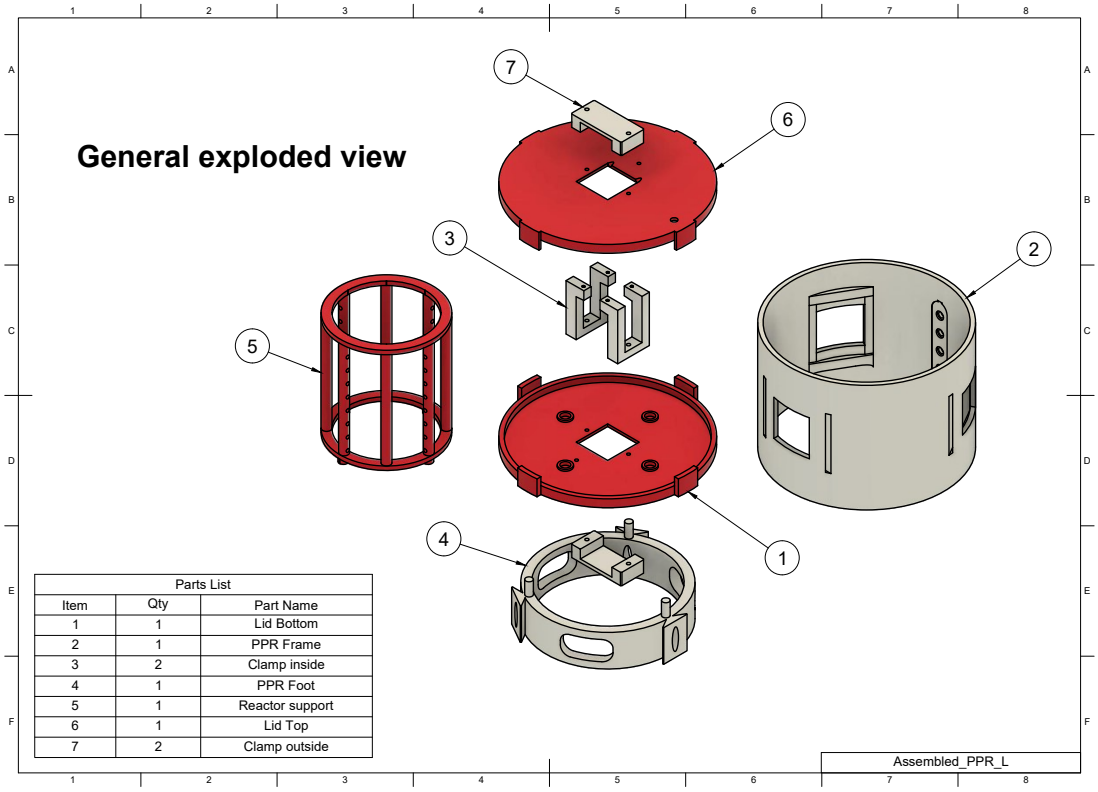


Figure S2. General exploded view of the photoreactor

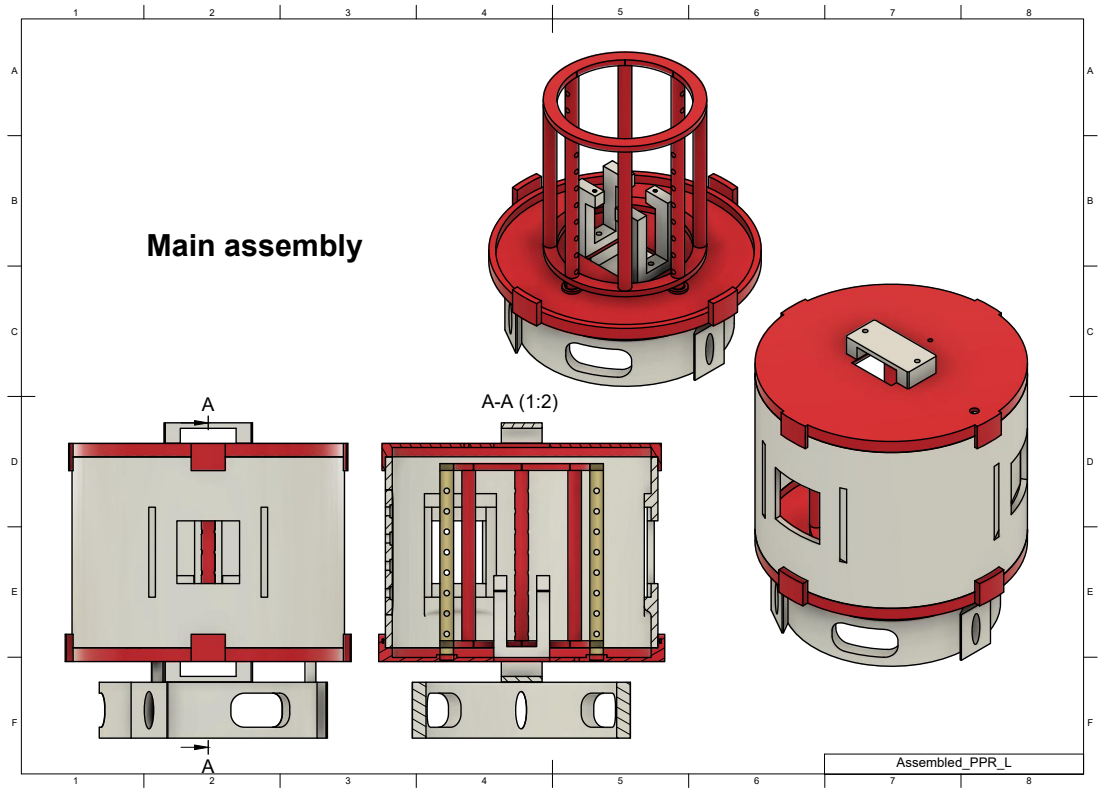


Figure S3. Assembled photoreactor

1.2.3 Control unit exploded view

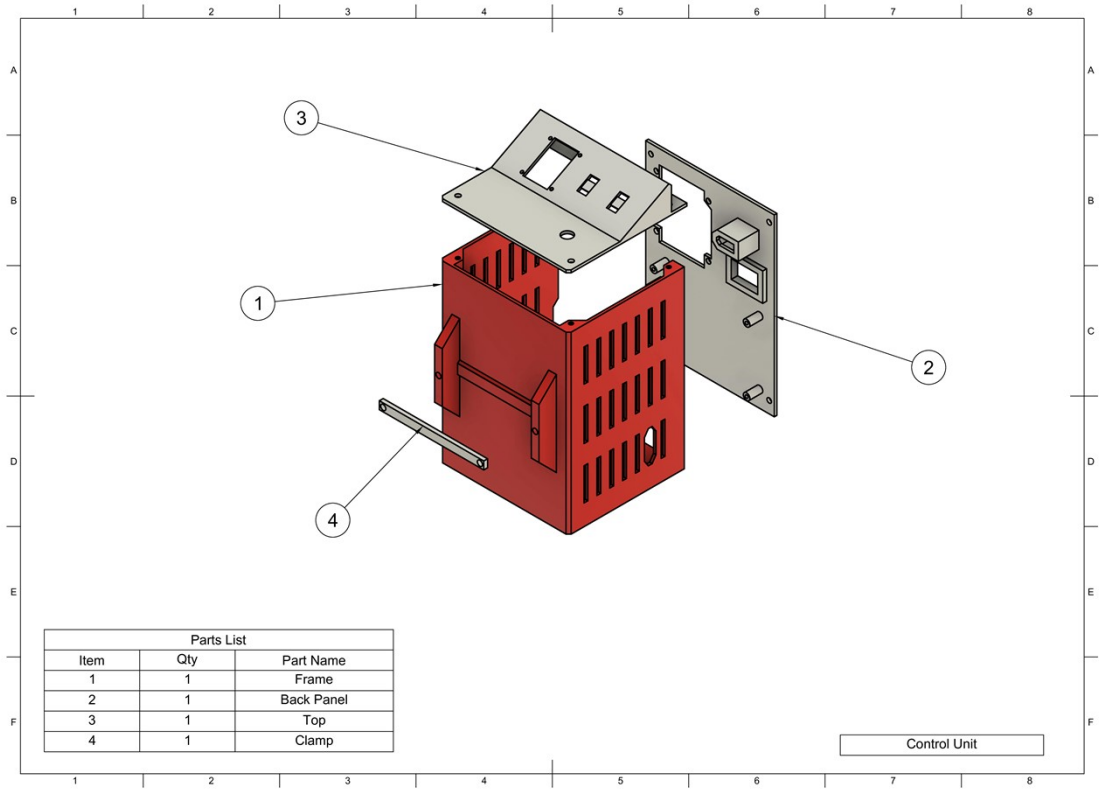


Figure S4. General exploded view of the control unit

1.2.4 LED holder exploded view

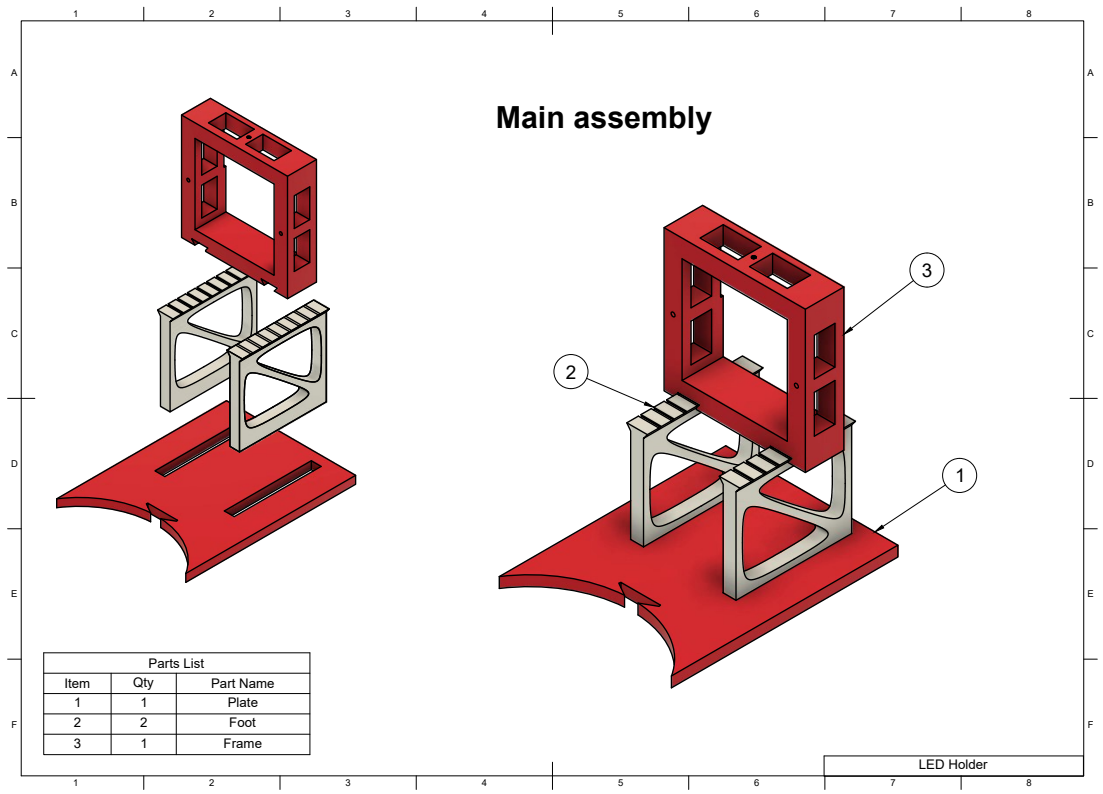


Figure S5. General exploded view of the LED holder

1.2.5 LED power supply exploded view

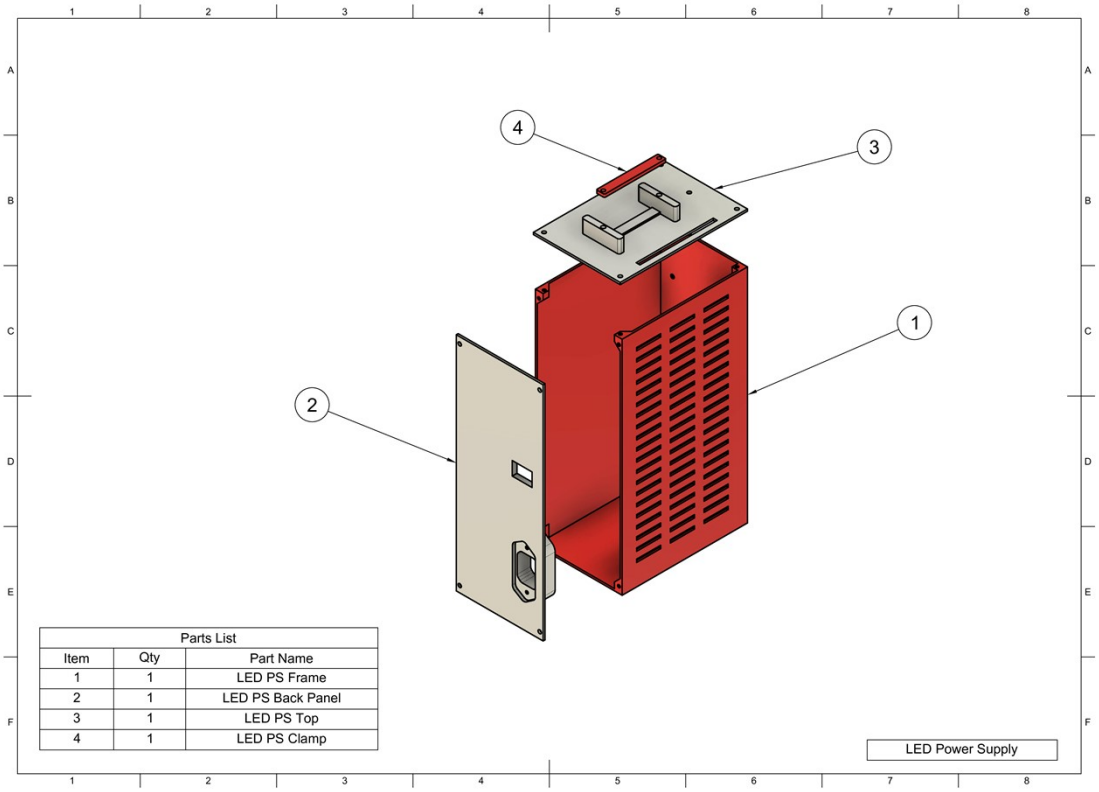


Figure S6. General exploded view of the LED power supply

1.2.6 General equipment for assembly

The following tools and equipment are required: Allen keys, flathead and Phillips screwdrivers, needle-nose pliers, soldering iron, wire stripper, multimeter, utility knife, soldering third hand (optional). Electronic and mechanical supplies common to several parts are listed below. During assembly, ensure proper care is taken to isolate elements, especially where high current wires are used, using heat shrink tubing and adequate use of the referenced connectors.

Part	Link
Wire 18 AWG (0.75 mm^2)	https://www.amazon.fr/dp/B09GKB582P/
Wire 14 AWG (2.0 mm^2), high current	https://www.amazon.fr/dp/B089KLXD6C/
Heat shrink tubing	https://befr.rs-online.com/web/p/heat-shrink-tubing/8214718
Jumper wire cables	https://www.amazon.fr/dp/B074P726ZR/
Pin headers for PCB (male and female)	https://www.amazon.fr/dp/B07CC4V9ZY/
Hot-melt adhesive	https://www.amazon.fr/dp/B09BQSQM7V/
Spiral wrap tube for wire management (optional)	https://www.amazon.fr/dp/B07YFVV9R8/
Screws M2, M2.5, M3, nuts	https://www.amazon.fr/dp/B0BQ7GGZ9M/

1.2.7 Photoreactor bill of materials

Part	Quant.	Link
Aluminium cooling block	2	https://www.amazon.fr/dp/B07NL2PDD6
Peltier module (15.5 V, 8.5 A, 72 W, 40 x 40 x 3.4 mm Quick-Cool High-Tech)	2	https://www.amazon.fr/dp/B079R1T7BZ/
Fan 12 V, 40 x 40 x 20 mm	2	https://www.amazon.fr/dp/B07B65FT8F/
Heatsink	2	https://befr.rs-online.com/web/p/heatsinks/6744835
Thermal paste > 5 W/(m*K)	4g	https://www.amazon.fr/dp/B07L9BDY3T
Reflecting foil		https://www.amazon.fr/dp/B0C45XQ28X/
Glass or acrylic, 3 mm thickness, 60 x 80 mm	3	https://www.amazon.fr/dp/B01MT24R3Z/
Nylon screws M3x30 with nuts	4	https://www.amazon.fr/dp/B0B53HCHG1/

Note: Peltier modules are sensitive elements and may become unusable if overheated. It is advisable to have spares available in case an emergency replacement is needed.

1.2.8 Control unit bill of materials

Part	Quant.	Link
Arduino Nano Every with headers	1	https://befr.rs-online.com/web/p/arduino/1927590
BTS7960B – H-bridge motor driver 42A high power	1	https://www.amazon.fr/dp/B07Y4TTK3Z
LM2596 adjustable step-down converter 3.2-40V to 1.25-35V	1	https://www.amazon.fr/dp/B08LVZL61S/
MeanWell HLG-320H-12A 12V 264W (power supply)	1	https://www.amazon.fr/dp/B0154DI5LS/
Power plug	1	https://www.amazon.fr/dp/B00A7MC996/
XT60 connectors	1	https://www.amazon.fr/dp/B07N1N2C94/
OLED display 128x64 px I2C 0.96 inch	1	https://www.amazon.fr/dp/B074N9VLZX
DS18B20 temperature sensor, 1-wire interface	1	https://www.amazon.fr/dp/B075FYYLLV/
On/off rocker switch	1	https://www.amazon.fr/dp/B07WYRNNTY/
Push button 2 pins	2	https://www.amazon.fr/dp/B07PMRS1SD/
Resistor 4.7 kΩ (¼ W)	1	https://www.amazon.fr/dp/B07KS2FXCF
Terminal set 1 to 1 (wire connector)	8	https://www.amazon.fr/dp/B087325PTL/
Screw terminal block 2 pin	6	https://www.amazon.fr/dp/B07RR7D267/
Screw terminal block 3 pin	1	
Jumper 2 pin (shunt)	2	https://www.amazon.fr/dp/B0B5LDXCX7/
Wire, screws, nuts		See general supplies
Photoreactor custom PCB (Printed Circuit Board)	1	Can be ordered from any PCB manufacturers (< 20€/board) – alternatively, a stripboard can be used, see below
Stripboard (to replace custom PCB if needed)	1	https://www.amazon.fr/dp/B08CXYTY5W/

Note: custom PCB can be ordered in min. from online manufacturers using the files provided in KiCAD format. Alternatively, the required circuit can be assembled on a plain stripboard. However, custom PCB provides a faster and more reliable assembly.

1.2.9 LEDs bill of materials

Part	Quant.	Link
Aluminium heatsink, fan and lens for LED chip	3	https://www.amazon.fr/dp/B01CW881TO/
LED COB (chip on board) 50W at desired wavelength	3	https://www.amazon.fr/dp/B09DQ2ZTZH/ https://fr.aliexpress.com/item/1005004638776709.html
Wire, screws, nuts		See general supplies

1.2.10 LED power supply unit bill of materials

Part	Quant.	Link
Power Supply Transformer AC 110V to DC 36V 10A 360W	1	https://www.amazon.fr/dp/B075L68NHB
LM2596 adjustable step-down converter 3.2-40V to 1.25-35V	1	https://www.amazon.fr/dp/B08LVZL61S/
LED dimmer DC (optional)	3	https://befr.rs-online.com/web/p/dimmer-switches/7693189
Terminal set 1 to 1 (wire connector)	6	https://www.amazon.fr/dp/B087325PTL/
Terminal set 2 to 6 (wire connector)	1	https://www.amazon.fr/dp/B08PCRXXJT/
C14 IEC panel mount connector male 10A 250V	1	https://befr.rs-online.com/web/p/iec-connectors/8117207
CEE 7/7 plug to IEC C13 socket	1	https://befr.rs-online.com/web/p/power-cords/2660615 (or alternative adapted to local power plug)
On/off rocker switch	1	https://www.amazon.fr/dp/B07WYRNNTY/
Wire, screws, nuts		See general supplies

1.2.11 Arduino software and computer control

The photoreactor is controlled by an Arduino Nano Every, programmed with Arduino. The code is adapted from the initial code published by Schiel *et al.*[1] The installation of the code on a Nano Every is described below:

1) Download and open the Arduino IDE (https://www.arduino.cc/en/software)
2) In the board manager, install Arduino megaAVR Boards (required for Nano Every)
3) In the library manager, install the following libraries
    a. Adafruit BusIO

b. Adafruit GFX
c. Adafruit SSD1306
d. OneWire
e. DallasTemperature
f. Vrekrer SCPI parser

4) Connect the Nano Every board to the computer with a microUSB cable
5) Upload the "PPR.ino" program to the board

The code allows both manual control of the photoreactor as a stand-alone unit (using the two push buttons as inputs and the LED panel as output) and computer control using serial communication (e.g., the Arduino's serial monitor). Automated control can be implemented using the following commands, using a baud rate of 9600 (other parameters are Arduino default: 8 data bits, no parity, one stop bit):

Command	**Outcome**
**IDN string*	Sets the Arduino board's identification string to *string*
**IDN?*	Returns the Arduino board's identification string
TEMP:ACT?	Returns the current temperature in Celsius degrees as *ACT:temp*
TEMP:SET temp	Sets the setting (target) temperature
TEMP:SET?	Returns the current setting (target) temperature as *SET:temp*
CLEAR	Clears errors
SUSPEND	Stops heating/cooling, resets device in "ready" (starting) state
STAT?	Returns the device's status as a string (heating, cooling, working, ready, error)

1.3 Assembly manual

1.3.1 Assembly of the photoreactor

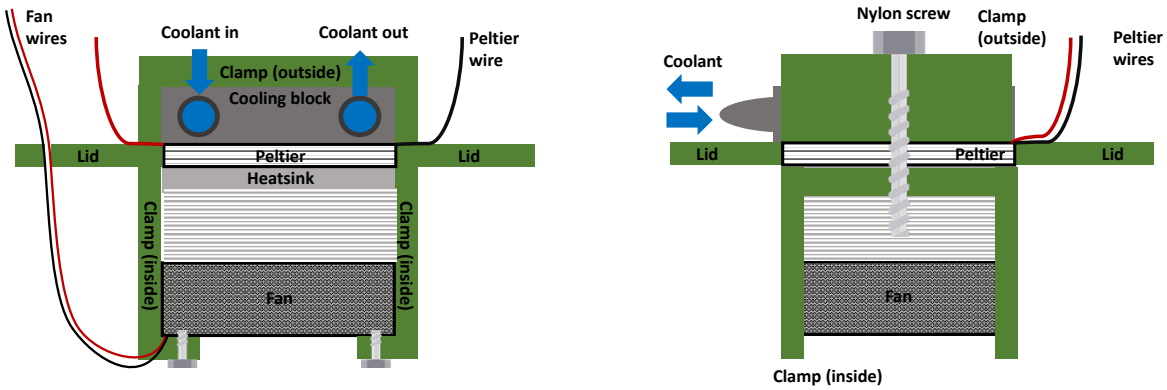
1) The Photoreactor foot is ready for use as printed; the holes can be used to let electric wires and coolant tubing in.
2) Assembly of the Lids (Bottom and Top have the same procedure):

a. Extend the fans and Peltier elements wires as needed for connection to the Control Unit later on (use high current, 14 AWG wires for the Peltier elements).
b. Identify the polarity of the Peltier elements. While this is not a major issue as the polarity can be switched by inverting the wires on the Control Unit if needed, it is advised to avoid ambiguity by placing the same "cooling side" facing inward the lids. For the Quick-Cool Peltier elements, the side branded "Quick-Cool" should cool when applying positive voltage from the red to the black wire.
c. Place the Peltier element in its slot (with wire fitting in the Lid's outside channels). Place the cooling block on the outside of the lid, covering the Peltier (the cooling element fluid inlet and outlet should be on the other side of the Peltier wires), after spreading conductive thermal paste on the Peltier's side. Place the Clamp (outside) on the cooling block and use 2 M3 Nylon screws to hold it in place. On the inside, place the heatsink to cover the Peltier, after spreading conductive thermal paste on the Peltier's side. Place the fan on top of the

heatsink (the fan's wires should be on the same side as the slot to let them out of the Photoreactor). Finally, place the Clamps (inside) and fix the assembly using M3 nylon nuts to tighten the nylon screws, and standard M2.5 screws to lightly compress the Clamp (inside) on the fan.

It is recommended to take extra care when putting thermal paste as it can stick to other parts easily.

d. Fit the fan's wires through the slot so they are accessible once the lid is in place.



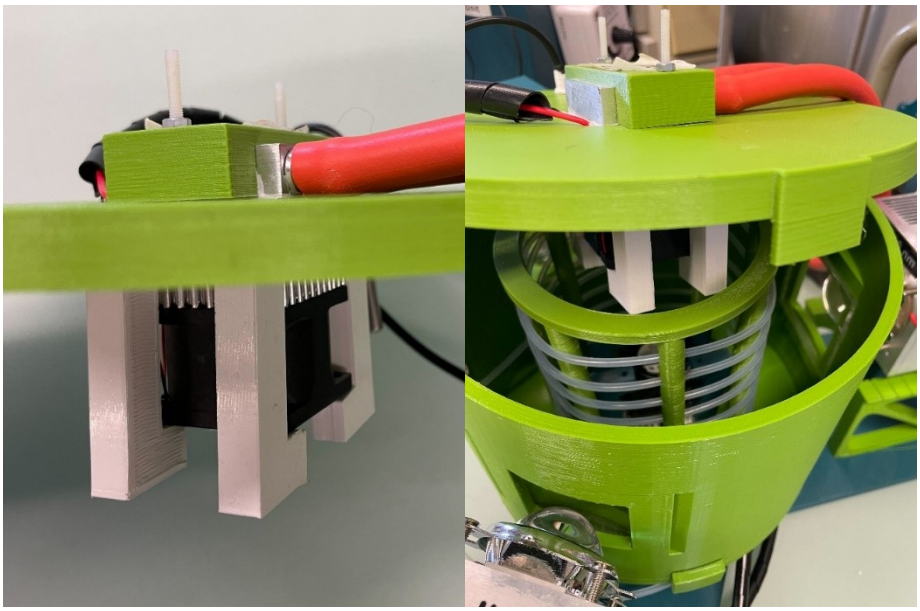


Figure S7. (Above) Representation of the cooling assembly (including cooling block, Peltier element, heatsink, fan and clamps). (Below) Picture of the assembled lid.

3) Assembly of the Frame:

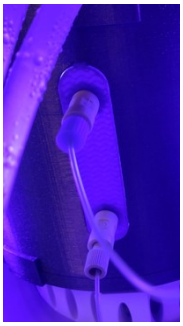
a. Prepare aluminum reflecting foil to fit inside the Photoreactor's wall (140 mm height x 600 mm circumference). Temporarily place the foil inside the Frame to mark the placement of the windows. Cut out the windows.

b. Stick the reflecting foil on the inside of the Frame, removing the adhesive protection slowly to ensure the foil has good contact with the surface.

c. If necessary, resize windows to the appropriate size (check they fit within the dedicated slots). Both glass and acrylic glass can be cut to desired dimensions, guides are available online depending on the choice of material.

d. Place the windows in their dedicated slots and fix them in place using hot-melt adhesive. Use adhesive generously to ensure there is no hole remaining between the inside and the outside of the frame, so that insulation is as efficient as possible.

4) Preparation of the flow reactor: fit the reactor coil in the Reactor Support and cap it with appropriate fittings. Include relevant mixers and precooling/preheating coil. The equipped Reactor Support can be inserted in the Photoreactor, using the corresponding slots in the Lid Bottom to fit snugly. The removable slot of the Photoreactor Frame can accommodate up to 4 standard 1/4-28 Flat Bottom Idex nuts, holding them in place using a Union on the outside of the Photoreactor to connect inlets and outlets to the relevant feeds. Alternative fitting types and numbers can be adapted, replacing only the removable slot.



5) Assembly of the various Photoreactor parts:

a. Assemble the Foot and the Bottom Lid.

b. Fit the Reactor Support (equipped with flow reactor) on the Bottom Lid using the slots to fit it.

c. Place the Frame on the Bottom Lid. Consider best placement of the flow inlets/outlets relative to the coolant tubing and electric wires.

d. Fit the Top Lid on top of the Frame, placing the electric wires on the same side as those of the Bottom Lid for convenience.

e. The parts are designed to fit together snuggly using appropriate slots, while remaining easily accessible (for instance for reactor coil change or if maintenance is required). This also means that parts may move relative to each other, for instance Lids could rotate relative to the frame. This is especially likely if tension is applied on the system, such as due to strained coolant tubing. Hence, attention should be paid before turning on the system that the installation is sufficiently stable.

1.3.2 Assembly of the control unit

The Control Unit is adapted from the one published by Schiel *et al.*[1] to allow a more modular design adaptable to different enclosures. An Arduino board controls the power supplied to the Peltier cooling unit to reach the target temperature set by the user.

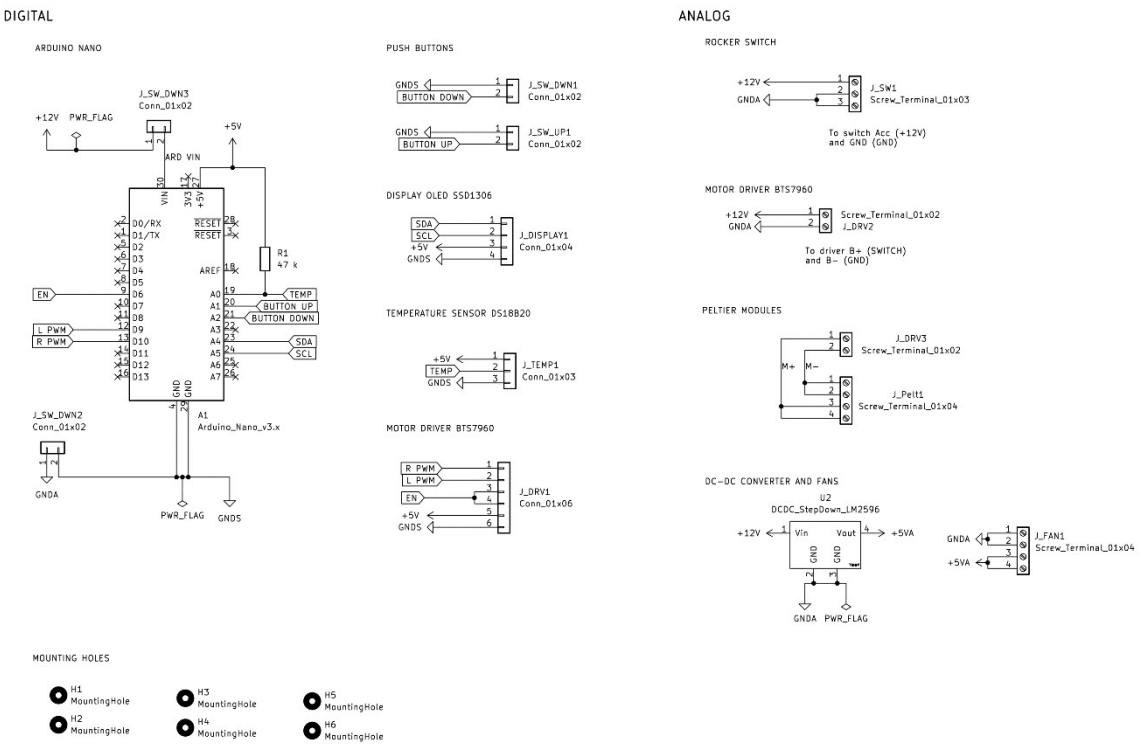


Figure S8. Schematic (KiCAD) of the custom PCB linking the Arduino control unit with other components

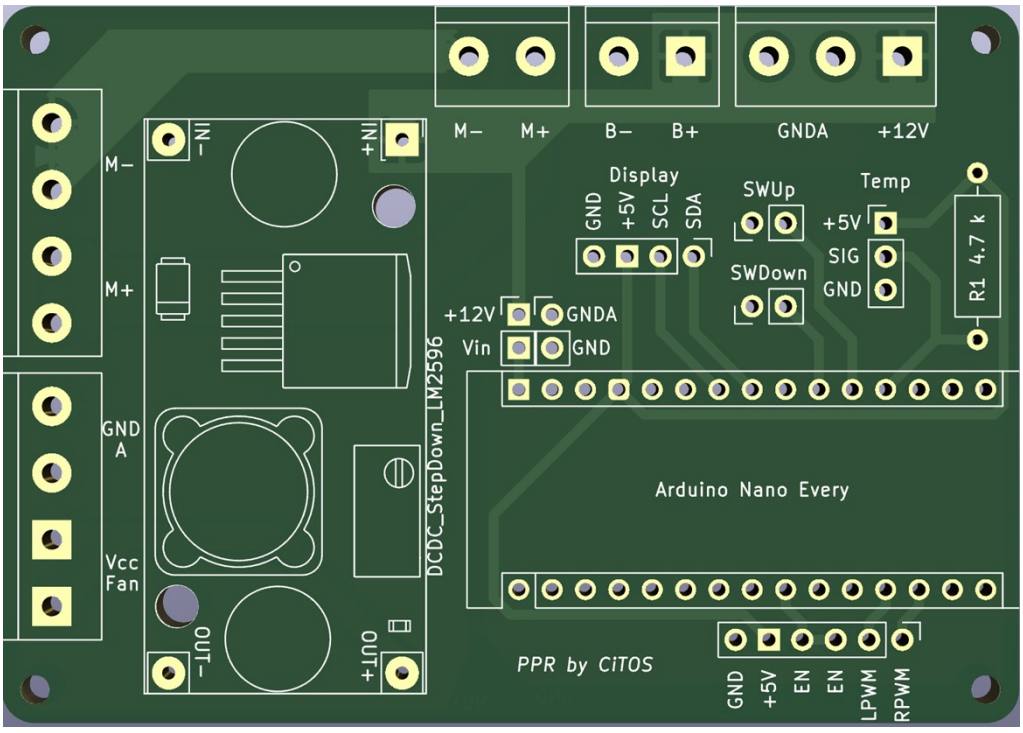


Figure S9. Custom PCB (top face) showing the various components

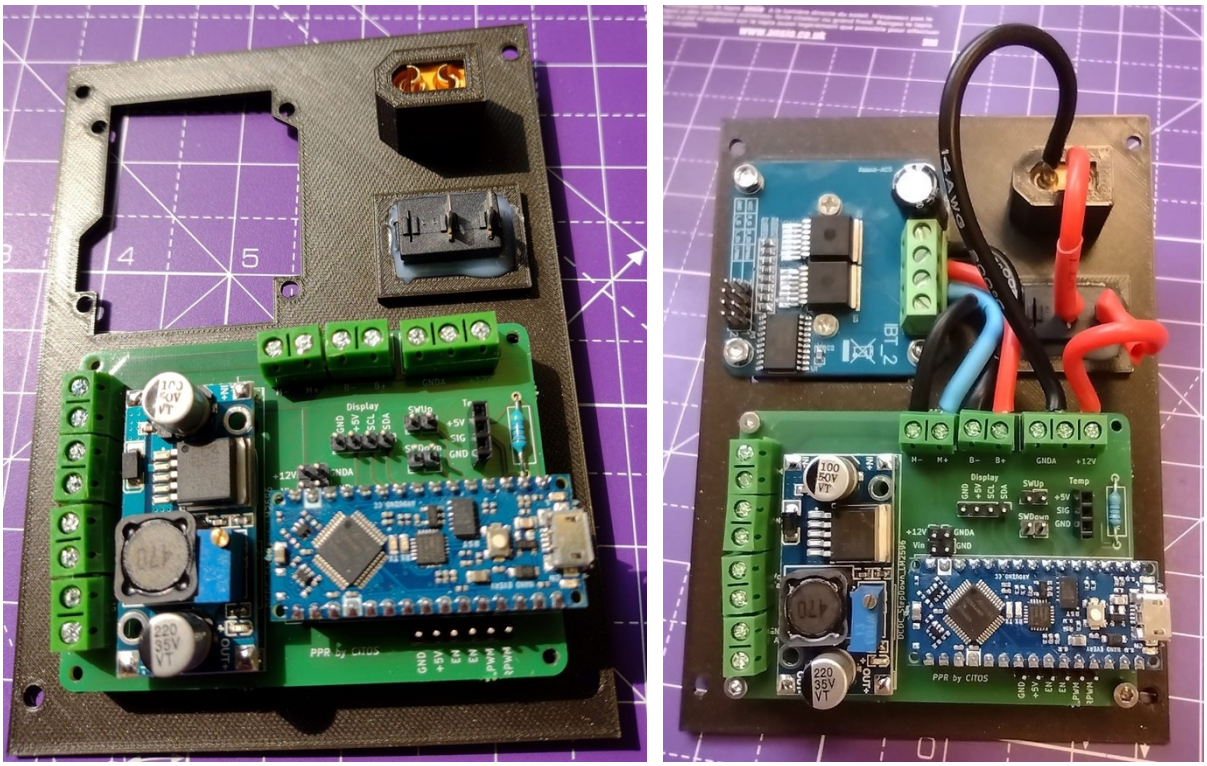


Figure S10. Control unit Back Panel at various stages of assembly

The steps below mention pin headers and jumper wires to connect most electronic components to the custom PCB. It is also possible to solder the components directly on the PCB. Soldering provides greater reliability of the assembly but leads to more difficult maintenance if components need to be changed or for troubleshooting tests.

1) Connect the power supply (MeanWell HLG-320H) input to the power plug using a screwdriver.
2) Solder the output of the power supply to the XT60 male connector. The output cable can be extended if required, using high current wire (14 AWG). Isolate the cables with heat shrink tubing.
3) Solder the required components on the custom PCB (if using a stripboard instead, refer to the instructions from the supporting information published by Schiel *et al.*[1]):

a. 3 female pin headers for the temperature sensor (+5V, SIG, GND)
b. 2 x 15 female pin headers for the Arduino board
c. 4 male pin headers for the push buttons (SWUp, SWDown)
d. 4 male pin headers for the OLED Display (GND, +5V, SCL, SDA)
e. 6 male pin headers for the motor driver (GND, +5V, EN, EN, LPWM, RPWM)
f. 4 male pin headers analog/digital linkers (+12V, Vin, GNDA, GND)
g. Screw terminal blocks on the +12V/GNDA, B-/B+, M-/M+ (2 pins at top and 4 pins at left-hand side of PCB) and GNDA/Vcc fan markings

4) Solder the resistor
5) Solder the LM22596 step-down converter as indicated (using male pin headers or short bare wire to mount it on the PCB)

6) Mount the Arduino board on its headers. Mount 2 jumpers to link the +12V and Vin pins on the one hand, and the GNDA/GND pins on the other hand.

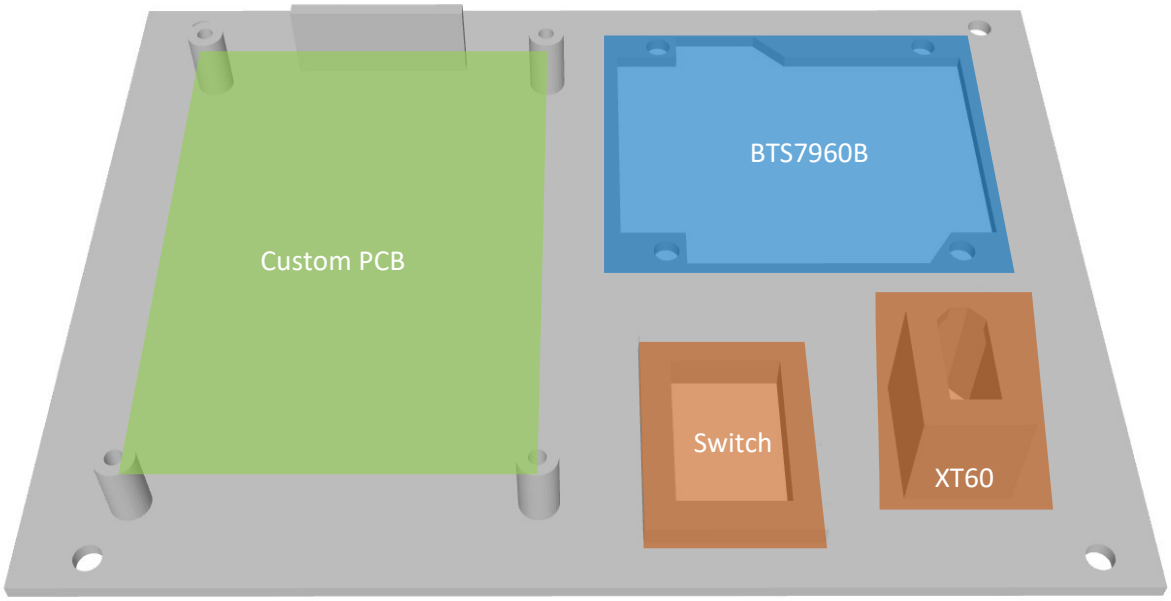


Figure S11. Locations of components on Back Panel

7) Fit the XT60 female connector in its dedicated slot on the Back Panel. Solder high current (14 AWG) wires (5-10 cm for +12V, 10-15 cm for GND) on the connector and isolate it with heat shrink tubing.
8) Fit the on/off rocker switch in its slot on the Back Panel, using hot-melt adhesive to fix in place. Solder the +12V wire from the XT60 on the switch (making sure to insert heat shrink tubing before soldering for isolation after). Solder another high current wire (5 cm) on the switch and isolate it.
9) Mount the custom PCB on the Back Panel using M2 (10 mm) screws.
10) Connect the wires from the switch and XT60 to the +12V/GNDA terminal blocks of the custom PCB (tighten screws to hold in place).
11) Connect 4 high current wires (5-10 cm) to the top M-/M+/B-/B+ terminal blocks of the custom PCB.

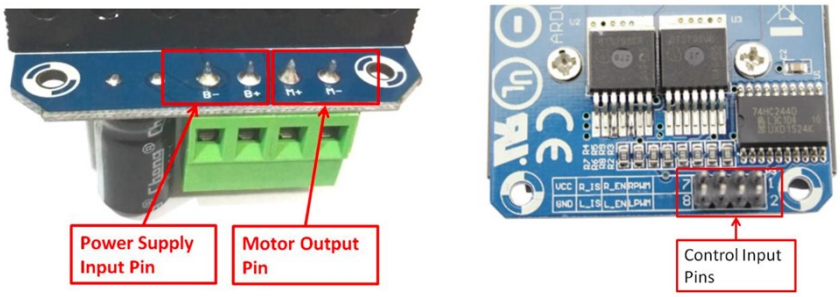


Figure S12. BTS7960B close-up of relevant connections. Reproduced from *https://www.handsontec.com/dataspecs/module/BTS7960%20Motor%20Driver.pdf*

12) Connect the other end of the M-/M+/B-/B+ wires to the relevant terminal blocks on the BTS7960B motor driver. Mount the BTS7960B on the Back Panel using M3 (10 mm) screws and M3 nuts.
13) Use a set of 6 jumper wires (female to female) to connect the motor driver control pins from the custom PCB to the BTS7970B (GND, +5V, EN, EN, LPWM, RPWM). Tape can be used to hold the jumper wire in place more tightly.

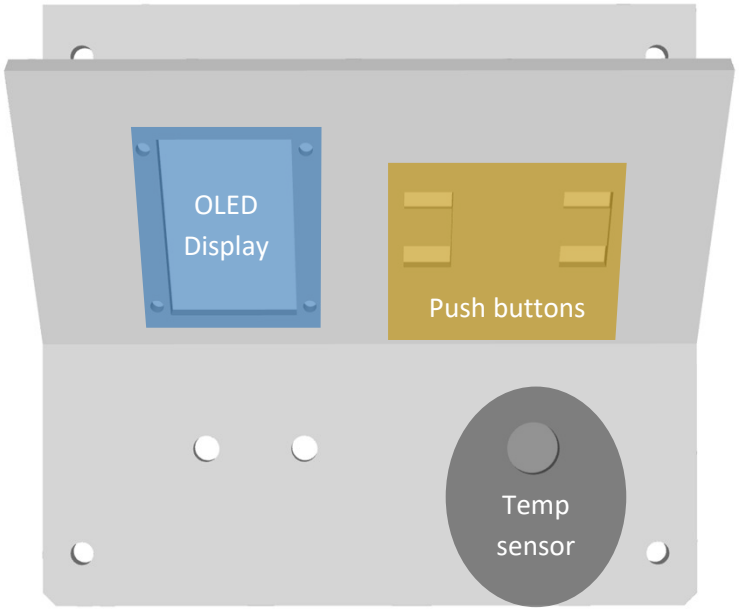


Figure S13. Locations of components on Top of Control Unit

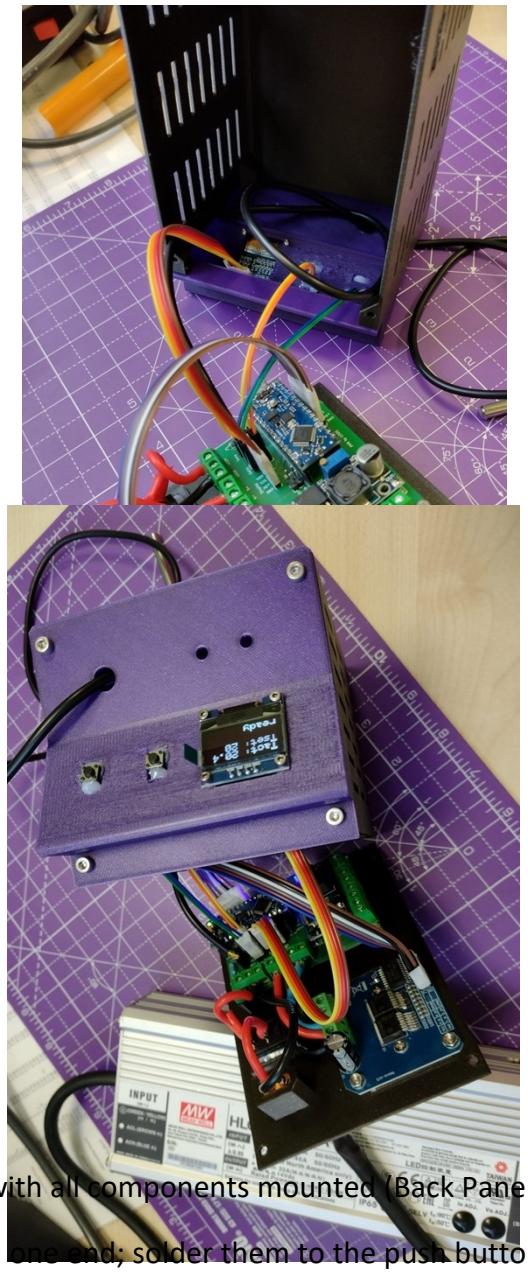


Figure S14. Control Unit with all components mounted (Back Panel open for demonstration)

1) Strip 4 jumper wires on one end; solder them to the push buttons (one wire for each pin). Isolate with heat shrink tubing. Mount the push buttons in their dedicated slot on the Top panel and use hot-melt adhesive to fix them in place
2) Mount the OLED Display on the Top panel using M2 (10 mm) screws and connect 4 jumper wires on its pins
3) Insert the temperature sensor cabling in the dedicated slot
4) Connect the OLED Display, push buttons and temperature sensor to corresponding header pins on the custom PCB. Tape can be used to hold the temperature sensor connectors in place.
5) Mount the Top on the Frame using M3 (6 mm) screws.

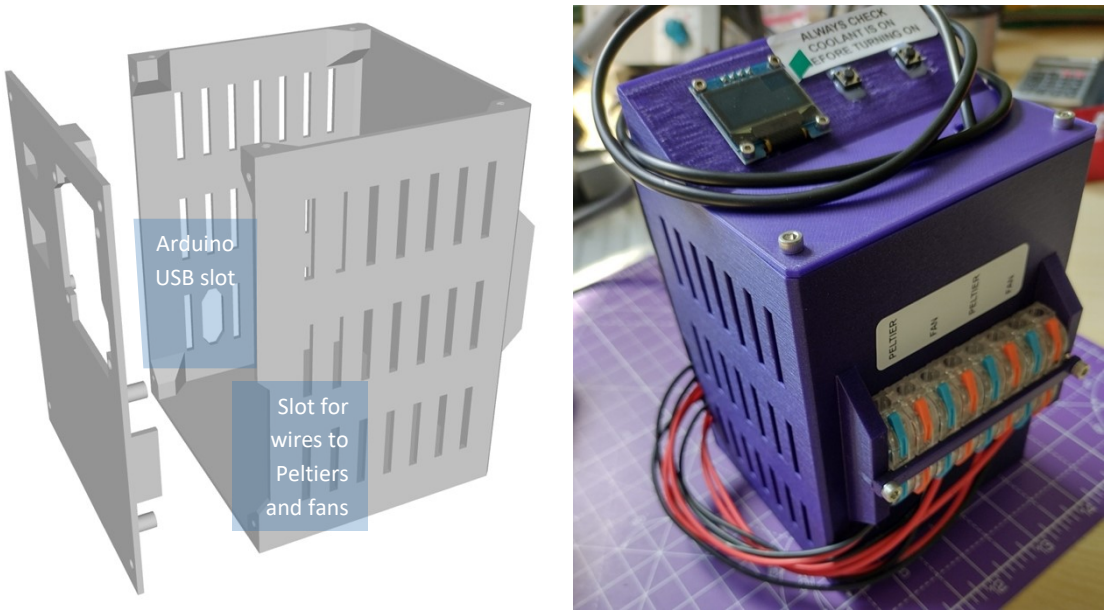
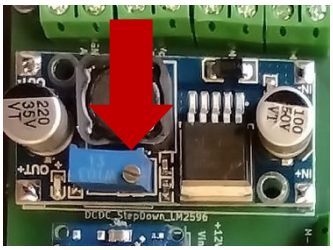


Figure S15. Control unit side and front views

6) Mount the 8 terminal blocks (1 to 1 wire connectors) on the front of the Frame, using the Clamp and M3 (6 mm) screws. Use 8 high power wires (15-20 cm) to connect the terminal blocks to the screw terminal blocks on the custom PCB (M-/M+/GNDA/Vcc fans on the left of the PCB).
   It is advisable to use a sensible color code (for wires and terminal blocks) and labelling for easier identification when connecting to the photoreactor. Ultimately, each Peltier will need to be connected to one M+ and one M- terminal, and each fan will need to be connected to one Vcc fan and one GNDA terminal, through the 1 to 1 wire connectors. The wire connectors allow easier assembly and disassembly of the Control Unit with the Photoreactor.
7) Before closing the Back Panel, adjust the step-down converter to 7 V. This can be done by measuring the output voltage with a multimeter with the system turned on and adjusting the flathead screw until reaching the desired value. This can be set to higher voltage to increase the fans' speed (for instance if they have trouble starting when powering up the system) and may vary if other fans are used.



8) Mount the Back panel using M3 screws.

1.3.3 Assembly of the LEDs

Caution: the LED COB used here should never be directly exposed to eyesight; adequate protective equipment should be used whenever they are powered on, e.g. filtering safety specs and filtering screens.

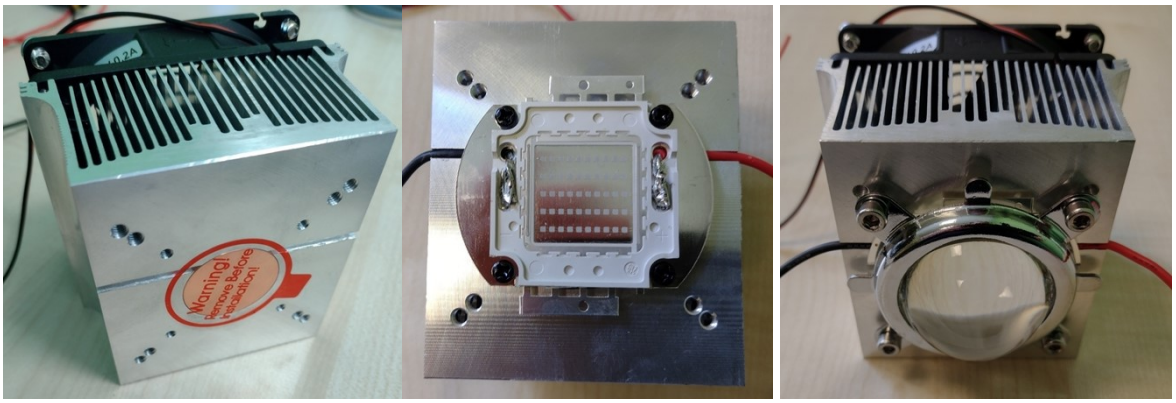


Figure S16. Various stages of assembly of the LEDs

1) Disassemble the lens from the heatsink. Remove the protecting label from the heatsink. Place the heatsink lying on the fan, so that the heatsink is at the top.

2) Place the LED COB on the heatsink and insert high current (14 AWG) wires between them, using the channels to fit the wires. The wires need to have a stripped length covering the COB interface (see central picture in Figure S16). The wires should also be sufficiently long to be connected to the LED Power Supply when in use (variable but >20-30 cm). Consider using appropriate colors for the polarity of the COB.

3) Solder the wires to the COB interface, ensuring good contact across the area (using a flat soldering tip is recommended).

4) Mount the COB to the heatsink using appropriate screws.

5) Fit the lens on the COB and mount it using appropriate screws.

6) Mount the assembled COB/heatsink/fan in the 3D printed Holder Frame using M3 screws.

1.3.4 Assembly of the LED Power Supply

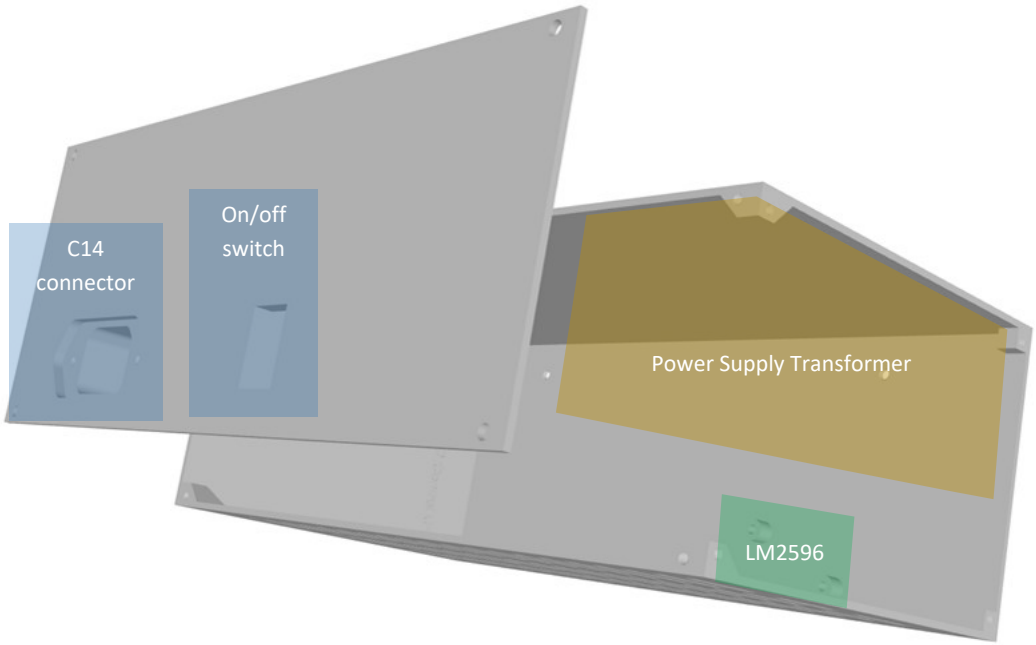


Figure S17. Location of components on the LED Power Supply Frame and Back Panel

1) Check the Power Supply Transformer is configured for the correct voltage based on local AC input (the transformer can be switched between 110V and 220V). Mount the Power Supply Transformer using M4 screws.
2) Fit the C14 IEC connector in its dedicated slot on the Back Panel, using hot-melt adhesive to fix in place.
3) Fit the on/off rocker switch in its slot on the Back Panel, using hot-melt adhesive to fix in place.
4) Prepare high current wires (14 AWG) to connect the C14 connector pins to the Power Supply Transformer AC input slots (L, N and ground), via the on/off switch (wire length 5 to 20 cm). Solder the wires on the C14 and switch and isolate with heat shrink tubing; fix with a screwdriver on the transformer.
5) Connect high current wires to Power Supply Transformer DC output slots to terminal sets (3 wires for V+, 3 wires for V-, 5-10 sm). The other end will be connected to terminal sets on the Top panel, and from there to the LEDs.
6) Solder wires (5-10 cm) on the LM2596 inputs, to connect IN+ and IN- to the one of the Power Supply Transformer DC output V+ and V- (resp.).
7) Solder wires (10-15 cm) on the LM2596 outputs, to connect OUT+ and OUT- to a terminal set on the Top panel, and from there to the fans.
8) Mount the LM2596 using M3 (8 mm) screws and connect the input wires to the Power Supply Transformer.

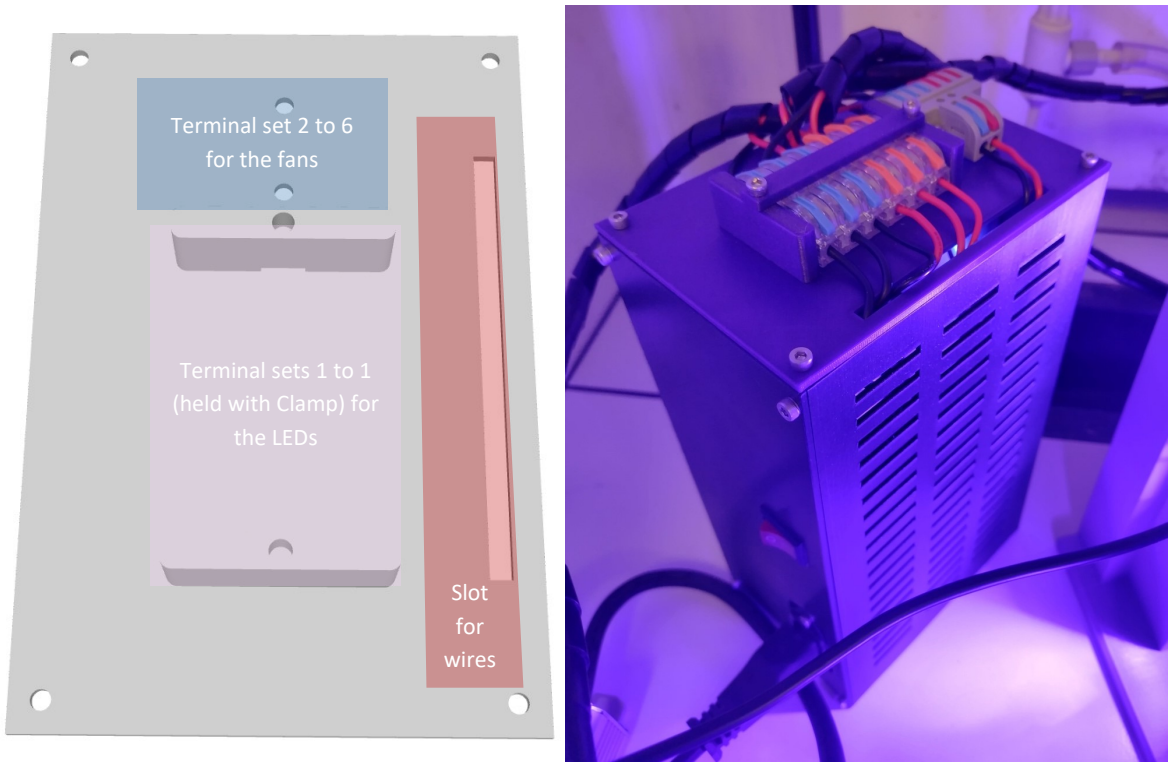


Figure S18. Location of components on the LED Power Supply Top (left) and assembled LED Power Supply (right)

9) Mount the 6 terminal blocks (1 to 1 wire connectors) on the Top panel, using the Clamp and M3 (6 mm) screws. Mount the 2 to 6 wire connector terminal block using M3 screws.

10) Connect the 6 high current wires to the 1 to 1 wire connectors (having them go through the Top panel wires slot). Connect the 2 LM2596 output wires to the 2 to 6 wire connector (having them go through the Top panel wires slot). Mount the Top panel to the Frame using M3 screws.

11) Before closing the Back Panel, adjust the step-down converter to 7 V.

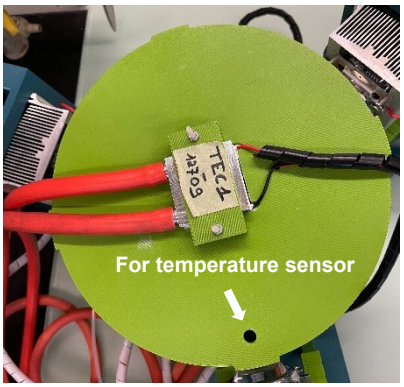
12) Mount the Back Panel using M3 screws.

13) If modulation of the LED output is desired, the LED dimmer can be used (between the Power Supply and the LED). This will allow adjustment of the voltage delivered to the LEDs.

1.3.5 Final assembly

1) To connect the Photoreactor to the Control Unit, plug in the 4 Peltier and the 4 fans wires to the corresponding terminal connectors on the front of the Control Unit (proper labelling ensuring the Peltier are connected to the M+/M- outputs of the custom PCB and the fans to the Vcc/GNDA outputs).

Place the temperature sensor inside the Photoreactor using its dedicated slot on the Top Lid. PTFE tape can be used to fix the position and seal the hole. ***Important!*** Place it at a height close to the light beam entry point to enhance temperature modulation.



2) To connect the LEDs to their Power Supply, plug in the 6 LED wires to the corresponding terminal connectors (1 to 1) on the top of the Supply Unit, and the 6 fan wires to the corresponding terminal connector (2 to 6).

3) Ensure the Photoreactor cooling blocks are properly connected to a circulating coolant (e.g. tap water).

4) Plug in the Control Unit and the LED Power Supply.

5) Place the LEDs around the photoreactor (see next section for remarks), taking appropriate precautions for eye protection (e.g. filtering screen).

1.4 Operation and general considerations

- The Control Unit follows a similar control protocol as the one reported by Schiel *et al.*[1]
- Before use, make sure the temperature sensor is fitted inside the photoreactor (preferably, close to the light source entry point) and the reactor is fitted as sealed as possible (making sure cable or tubing tension does not cause parts to move out of alignment). Using tape can help to improve fitting. Make sure the lights sources are places properly – the LEDs produce significant heat that could melt PETG if in contact.
- Always check the coolant (e.g. chilled or tap water) is running; visual reminders are advisable as overheating can damage the Peltier unit and require replacing them. It is advisable to ensure fittings are tight at all points of the setup and to check for leaks after reconfiguring the system in any way.
- On power-up, the photoreactor is in ready mode. After pressing a push button or sending instruction via serial, the photoreactor enters heating or cooling mode and starts alimenting the Peltier elements to heat or cool as required.
- The photoreactor will enter error mode under certain conditions:
  - Actual temperature outside of limits, for instance due to overheating (default -10 to 60 °C)
  - Set (target) temperature not reached quickly enough (default 10 min. for heating, 60 min. for cooling)

    Additionally, the photoreactor only starts heating if above a certain temperature (default 0 °C).

These parameters can be changed (see “Temperature configuration and limits” in the Arduino code).

- Remote control of the photoreactor needs to be considered properly, especially the handling of errors, which will often require manual intervention (though not always, for instance when testing highest or lowest reachable temperatures).
- Lower temperatures can be reached by using lower temperature coolant and improving insulation. More extensive work using stronger power supply and Peltier modules could also be considered if required.
- Care should be taken when running reactions that no leaks occur inside the photoreactor, as this could lead to damage of the 3D printed parts (PETG is not resistance to most solvents), especially if a leak is not discovered and mitigated quickly. Hence, attention should be paid to the selection of flow elements appropriate to the working conditions (pressure, temperature) and to monitoring of the system stability when in use.

1.5 Troubleshooting

- If fans don’t start properly, increasing the step-down converter voltage in the Control Unit can help.
- If a wrong temperature is displayed, push buttons do not appear to work, or the OLED display stops working properly, check jumper wire connections.
- While rare, electronic components such as the Arduino Nano Every or the motor driver may fail and need replacement.
- Unexpected behavior of the Peltier elements (i.e. heating when cooling was expected) may happen if a Peltier is connected to the reversed poles.
- For general troubleshooting, checking connections with a multimeter often helps finding problems’ origin.

1.6 Temperature control

Additional test was performed with type-K thermocouples, which were strategically positioned at the top, middle, and bottom levels of the reactor support, ensuring direct contact with the PFA coil. Despite the three LEDs (3*50 W, 400 nm) operating at maximum intensity, the heatsinks and their fans facilitated efficient heat transfer, resulting in a minimal temperature gradient within the reactor (≤ 0.5 °C), for the range of temperatures used in this work (20-40 °C). It is important to keep the temperature sensor from the reactor at the height of light beam and close to the window (near hottest point) to have a better control of the temperature (see Figure S19 for comparison).

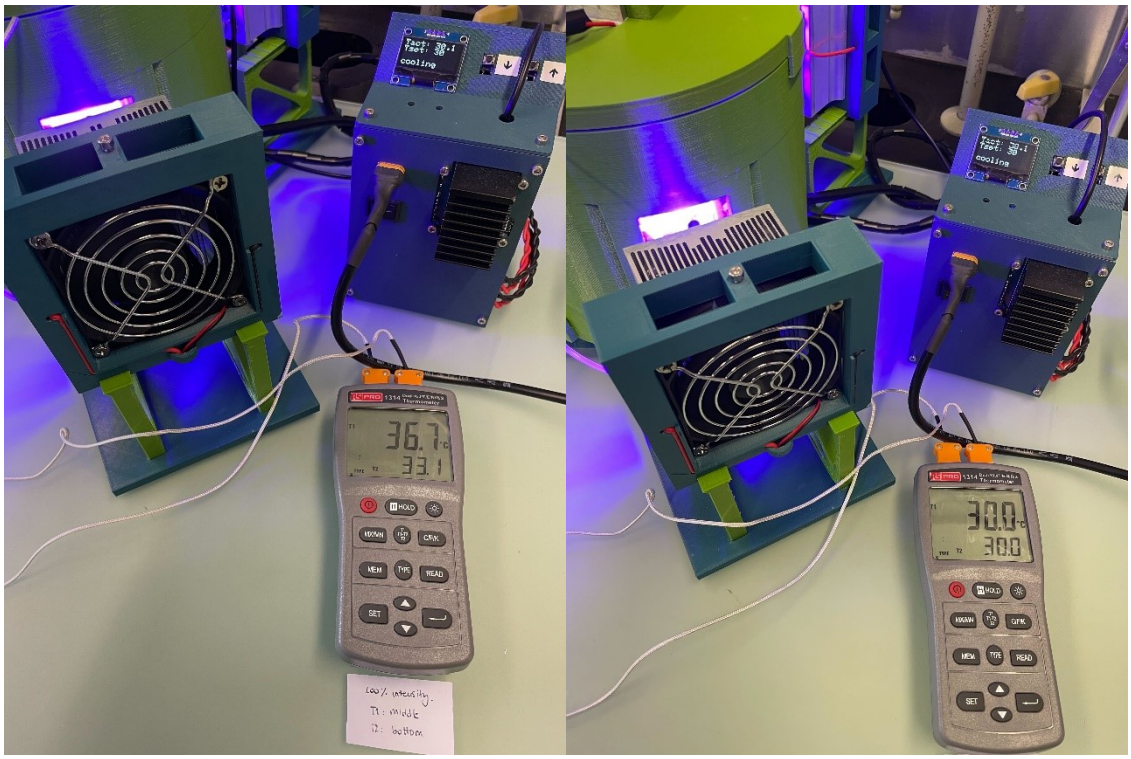


Figure S19. Temperature measurement. Thermocouple T1 was placed at the middle level of the reactor support in the light entry point, and T2, at the bottom. (Right) temperature sensor of the photoreactor in the top level of the reactor support. (Left) temperature sensor of the photoreactor in the middle level of the reactor support, near the beam of the LED.

2. Continuous flow setups

2.1 In-house photoreactor setup

The in-house photoreactor was integrated in a flow setup and assembled using commercially available parts (details in Section 2.2). General list of equipment and elements are described in this section. The details about the set up used for each reaction will be described later in their individual section.

2.1.1 Pump

The pumps used to handle the liquid feeds were: 1) Syrris Asia syringe pumps equipped with “red” (2.5-5.0 mL), “blue” (500-1000 µL) or “green” (250-500 µL) glass syringes, 2) SF-10 pump (Vapourtec) or 3) Azura P4.1S pump (Knauer).

2.1.2 Connectors, ferrules and mixers

Coned polyetheretherketone (PEEK) nuts, arrow-headed mixer, super Flangeless PEEK nuts, ETFE ferrules and SS rings were used. Connectors, ferrules and unions were purchased from IDEX/Upchurch Scientific (see Section 2.2).

2.1.3 Check-valves

A check-valve purchased from IDEX/Upchurch Scientific and embedded in a PEEK check-valve holder was inserted between the pump and the reactor and another one between the Mass Flow Controller and the pump.

2.1.4 Back-pressure regulator

Dome-type BPRs were purchased from Zaiput Flow Technologies (BPR-10). The BPR was connected to a compressed gas cylinder provided with a pressure regulator to set the working pressure.

2.1.5 PFA tubing and coils

Coil reactors, connecting and collection lines were constructed from perfluoroalkoxy (PFA) tubing (1/16”, 1.58 mm outer diameter, 750 µm internal diameter; 1/8” O.D, 1/8”, 3.17 mm outer diameter, 2.40 mm internal diameter and 1/8" OD x 1/16" ID, 3.17 mm outer diameter, 1.55 mm internal diameter).

Note: Alternatively, FEP tubes can be used, which also work for photochemical reactions and are more cost-effective.

2.1.6 Mass Flow Controller

Calibrated Bronkhorst® Mass Flow Controller (MFC) designed for H_2 (Measuring range: 0-20 mLs/min) was used. A conversion factor was applied to set the correct flow rate corresponding to O_2 (according to gas conversion factor calculations provided by www.fluidat.com).

2.2 Part numbers & vendors

Standard fluidic elements and connectors were purchased from IDEX/Upchurch Scientific, from Valco Instruments Co. Inc or from Swagelok.

Item	Details	Vendor	Reference
Connectors	One-Piece Fingertight 10-32 Coned, for 1/16" OD Natural	IDEX/ Upchurch Scientific	F-120
	Super Flangeless™ Nut PEEK 1/4-28 Flat-Bottom, for 1/16" & 1/32" OD Natural	IDEX/ Upchurch Scientific	P-255
	Super Flangeless™ Ferrule w/SST Ring, Tefzel™ (ETFE), 1/4-28 Flat-Bottom, for 1/16" OD Yellow	IDEX/ Upchurch Scientific	P-259
	Super Flangeless™ Nut, PEEK 1/4-28 Flat Bottom for 1/8" OD Natural	IDEX/ Upchurch Scientific	P-331
	Super Flangeless™ Ferrule w/SST Ring, Tefzel™ (ETFE), 1/4-28 Flat Bottom, for 1/8" OD Yellow	IDEX/ Upchurch Scientific	P-359
	316 Stainless Steel Nut for 1/8 in. Swagelok Tube Fitting	Swagelok	SS-202-1

	Flangeless Nut Short, PEEK 1/4-28 Flat-Bottom, for 1/8" OD Natural	IDEX/ Upchurch Scientific	P-335X
	Super Flangeless™ Ferrule PEEK w/SST Ring, 1/4-28 Flat-Bottom, for 1/8" OD Natural	IDEX/ Upchurch Scientific	P-350X
	316 Stainless Steel Front Ferrule for 1/8 in. Swagelok Tube Fitting	Swagelok	SS-203-1
	316 Stainless Steel Back Ferrule for 1/8 in. Swagelok Tube Fitting	Swagelok	SS-204-1
Mixer	High Pressure Static Mixing Tee	IDEX/ Upchurch Scientific	U-466
	PEEK Low Pressure Tee Body 1/8" PEEK .050 thru hole	IDEX/ Upchurch Scientific	P-714-01
Check-valve	Check-valve inline cartridge 1.5 psi	IDEX/ Upchurch Scientific	CV-3001
Dome-type BPR	Dome-type BPR, metal-free, with adjustable set point	Zaiput Flow Techn.	BPR-10
Cartridge holder	BPR Holder Assembly	IDEX/ Upchurch Scientific	P-465
Tubing	High-purity PFA tubing (1.58 mm outer diameter, 750 µm internal diameter)	VICI (Valco Ins. Co. Inc.)	JR-T-4002-M25
	PFA Tubing, (3.17 mm outer diameter, 2.40 mm internal diameter)	Swagelok	PFA-T2-030-100
	PFA+ Tubing Natural 1/16" OD x .030" ID x 50ft	IDEX/ Upchurch Scientific	1912L

	PFA Tubing Natural 1/8" OD x 1/16" ID x 50ft	IDEX/ Upchurch Scientific	1641L

3. Additional experimental details

3.1 Chemicals

Chemicals, purities, CAS numbers and suppliers are provided in the following table. All reagents and solvents were used directly as purchased or purified according to standard procedures. Methyl Vinyl Ketone was distilled under reduced pressure prior to use. Photocatalysts (3DPA2FBN and 4CzIPN)[2] and catalyst (NiBr2(dtbbpy))[3] were synthesized following methods previously reported.

Solvents	Purity (%)	CAS number	Supplier
DI Water			
Acetonitrile	≥99.9	75-05-8	Fisher
Gas	**Purity (%)**	**CAS number**	**Supplier**
ALPHAGAZ™ 1 oxygen	≥ 99.995 mol	7782-44-7	Air Liquide
Chemicals	**Purity (%)**	**CAS number**	**Supplier**
(L)-Methionine	≥99.9	63-68-3	UCB
Rose Bengal	-	632-69-9	TCI
Methyl vinyl ketone	95.3	78-94-4	Thermo Scientific
Tris(2,2'-bipyridyl)ruthenium(II) Chloride Hexahydrate	>98.0	50525-27-4	TCI
Trifluoroacetic acid	≥99.9	76-05-1	Merck
N,N-Dibutylbutan-1-amine	≥99.0	102-82-9	Merck
4-Bromobenzoic Acid Methyl Ester	> 98	619-42-1	TCI
4-bromobenzotrifluoride	99	402-43-7	Merck
5-bromopyridine-2-carbonitrile	97	97483-77-7	Merck
3-bromothiophene	97	872-31-1	Merck
5-bromopyrimidine	97	4595-59-9	Merck
tert-Butyl 4-iodopiperidine-1-carboxylate	98	301673-14-3	AmBeed
Tert-butyl 3-iodoazetidine-1-carboxylate	98	254454-54-1	Combi-blocks
3-Methylindole	> 98	83-34-1	TCI
tert-butyl N-[2-(1H-indol-3-yl)ethyl]carbamate	95	103549-24-2	AmBeed
ethyl bromodifluoroacetate	98	667-27-6	Merck
Benzylamine	≥99.5	100-46-9	Merck
2,2-dimethoxyethylamine	99	22483-09-6	Merck

3.2 Analytical methods

^{1}H, ^{13}C and ^{19}F NMR spectra were recorded with a Bruker Avance III spectrometer at 400 MHz. The chemical shifts are reported in ppm relative to TMS as internal standard or to solvent residual peak.

Reactions were monitored by analytical TLCs on silica gel aluminium plates RP-18W and revealed by UV light (254 nm) and/or by chemical stains (e.g. KMnO4 or phosphomolybdic acid (PMA) solutions), and with a LCMS Ultimate 3000 (Thermo Fischer) equipped with Agilent Poroshell 100 EC-18 column, Ultimate 3000 DAD UV detector and HCT ultra (Brucker) MS detector. Purifications of the products were performed on Puriflash Silica HP or Puriflash C18 STD Flash column (Interchim) using an automated BiotageTM Puriflash chromatography coupled with UV detector at 220 and 254 nm. HPLC analysis were performed on 1100 serie (Agilent).

3.3 Experimental procedures

3.3.1 Photocatalytic oxidation of methionine

3.3.1.1 Procedure

A solution of (L)-methionine (0.3 M) and Rose Bengal (0.1 mol%) in deionized water was pumped and conveyed with a stream of oxygen fed by a Mass Flow Controller (Figure S20). Flow rates were modified as specified in the manuscript to explore different residence times while maintaining constant the excess of oxygen (1.1 equiv). Mixing and irradiation (3 blue LEDs, 400 nm, 50 W each) occurred along the entire reaction channel (2.6 mL internal volume) under a specific back pressure (2.8 or 4 bars). After stabilizing the system during 5 residence times, three samples were collected for each condition. Solvent was evaporated under reduced pressure and the reaction mixture was redissolved in deuterated water to then be analyzed by ^{1}H NMR. An average conversion of the three samples was reported.

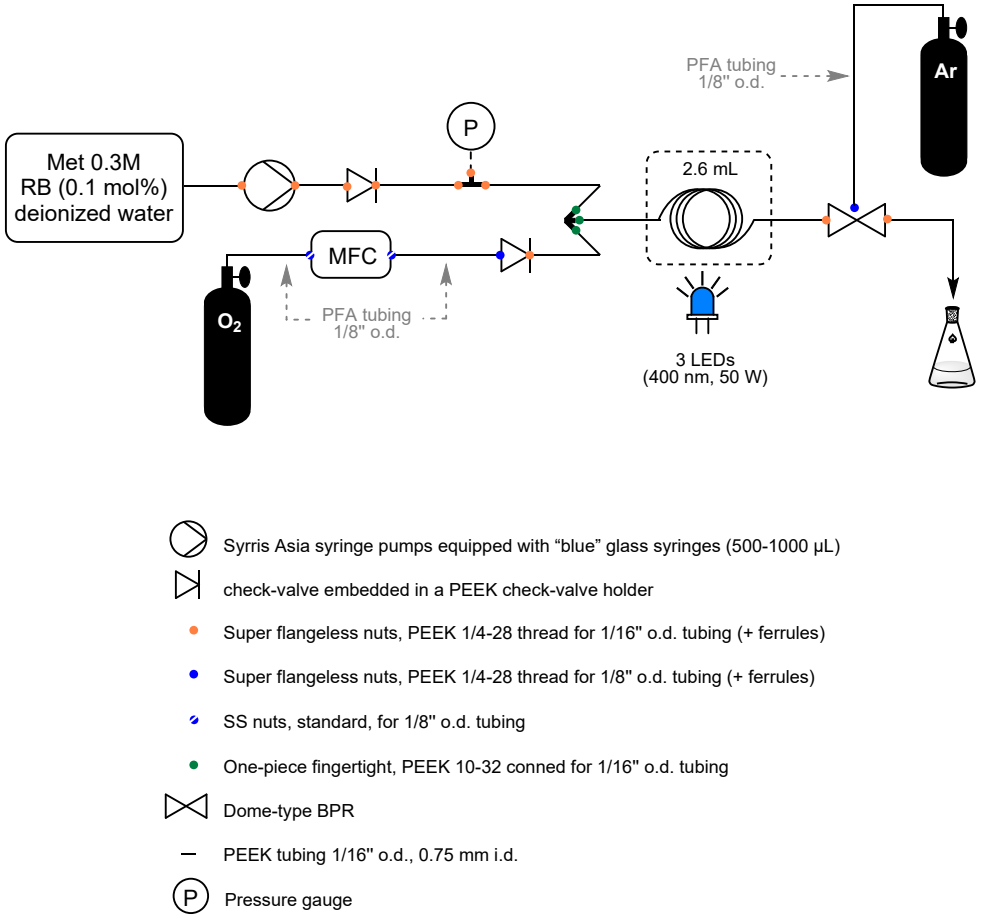


Figure S20. Detailed flow setup diagram for the photooxidation of methionine

3.3.1.2 Residence time calculation and oxygen equivalents calculation

By definition, the residence time is calculated according to Equation S1:

$$\text{Residence time (min)} = \frac{\text{Internal volume (mL)}}{\text{Flow rate (mL} \cdot \text{min - 1)}} \quad \textbf{(Equation S1)}$$

In this case, the total flow rate is the sum of the liquid flow rate and the gas flow rate fed into the reactor. The actual gas flow rate is calculated from the flow rate measured by the MFC, using Equations S2 and S3, where T_{real} and P_{real} correspond to the actual temperature and pressure settings in the system. The equivalents of oxygen are reported considering standard pressure (1 atm) and temperature (273.15 K) conditions.

$$nO2 = \frac{PN\,(atm) \cdot VN\,(L)}{R\,(L \cdot atm \cdot mol - 1 \cdot K - 1) \cdot TN\,(K)} \quad \textbf{(Equation S2)}$$

$$Vreal = \frac{nO2 \cdot R \cdot Treal}{Preal} \quad \textbf{(Equation S3)}$$

3.3.1.3 Determination of methionine conversion

The quantification of methionine oxidation was computed using Equation S4 by integrating selected peaks in the ^{1}H NMR spectrum (Figure S21) of the crude corresponding to the initial compound (2.05 ppm, triplet, 2H) and the oxidized product (2.75 ppm, singlet, 3H).

$$\text{Conversion} = 100 * \frac{\frac{I\,(2.75\ ppm)}{3}}{\frac{I\,(2.75\ ppm)}{3} + \frac{I\,(2.55\ ppm)}{2}} \quad \textbf{(Equation S4)}$$

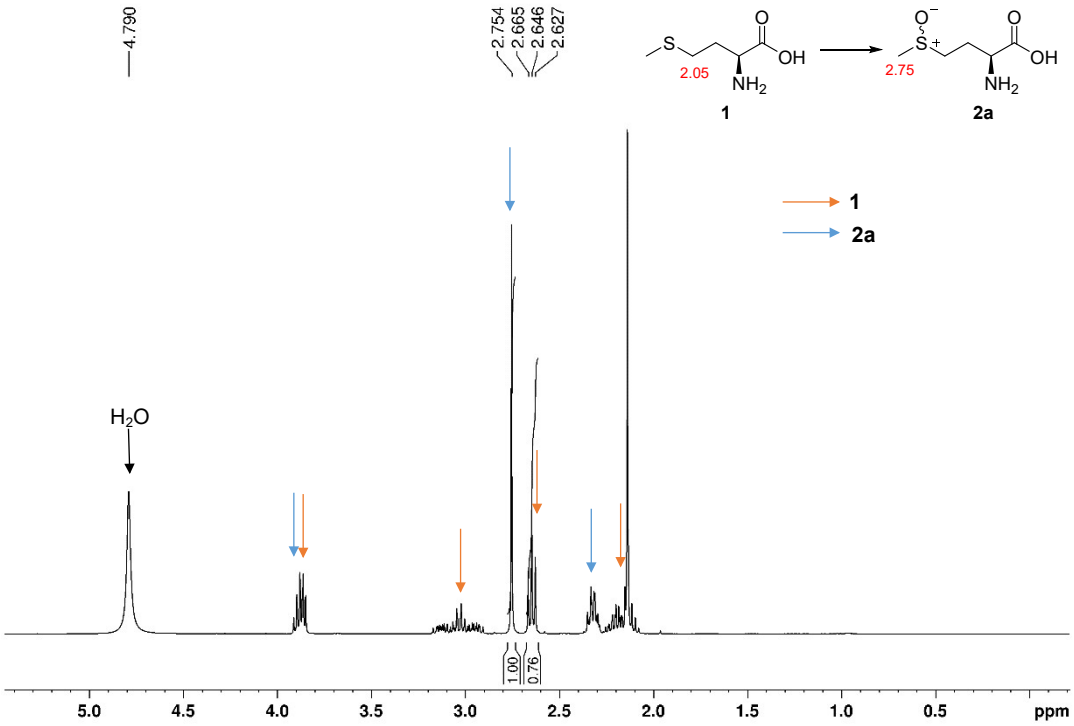


Figure S21. ^{1}H NMR spectrum (400 MHz, D_2O) of the crude mixture for photooxidation of methionine

3.3.2 Photocatalyzed α-alkylation of amines

3.3.2.1 Procedure

The synthesis of the starting material, 2-phenyl-1,2,3,4-tetrahydroisoquinoline, was conducted following established protocols, and the obtained NMR data aligned with the information provided in the literature. [4]

Under inert atmosphere, a solution of 2-phenyl-1,2,3,4-tetrahydroisoquinoline (0.25 M), methyl vinyl ketone (2.0 equiv), $Ru(bpy)_3Cl_2{\cdot}6H_2O$ (0.02 equiv) and TFA (1 equiv) was prepared in acetonitrile. The solvent had been previously degassed by bubbling with N_2 and sonicating

during 30 min. The solution was pumped into the photoreactor (Figure S22) with the flow rates and temperature as specified in the manuscript. The mixture was irradiated with 3 blue LEDs (400 nm, 50 W each) all along the coil reactor (2.6 mL internal volume). After stabilizing the system during 1.5 residence times, two samples were collected for each condition. Following the collected amount, K_2CO_3 (2 equiv) was introduced to neutralize the mixture. Subsequently, it was filtered through a silica plug employing Et_2O as the eluent. The mixture was concentrated *in vacuo* and the conversion was analyzed by ^1H NMR, using deuterated chloroform as solvent. The average conversion of the two samples was reported.

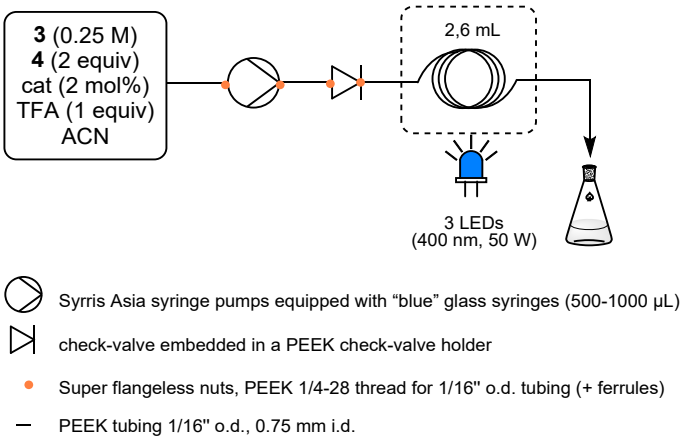


Figure S22. Detailed flow setup diagram for the α-functionalization of amines

3.3.2.2 Determination of 2-phenyl-1,2,3,4-tetrahydroisoquinoline conversion

The quantification of 2-phenyl-1,2,3,4-tetrahydroisoquinoline functionalization was carried out using Equation S5, by integrating specific peaks in the ^1H NMR spectrum (Figure S23) of the crude corresponding to the initial compound (4.40 ppm, singlet, 2H) and the alkylated product (4.72 ppm, double of doublets, 1H).

$$\text{Conversion} = 100 * \frac{\frac{I\,(4.72\ ppm)}{1}}{\frac{I\,(4.72\ ppm)}{1} + \frac{I\,(4.40\ ppm)}{2}} \quad \textbf{(Equation S5)}$$

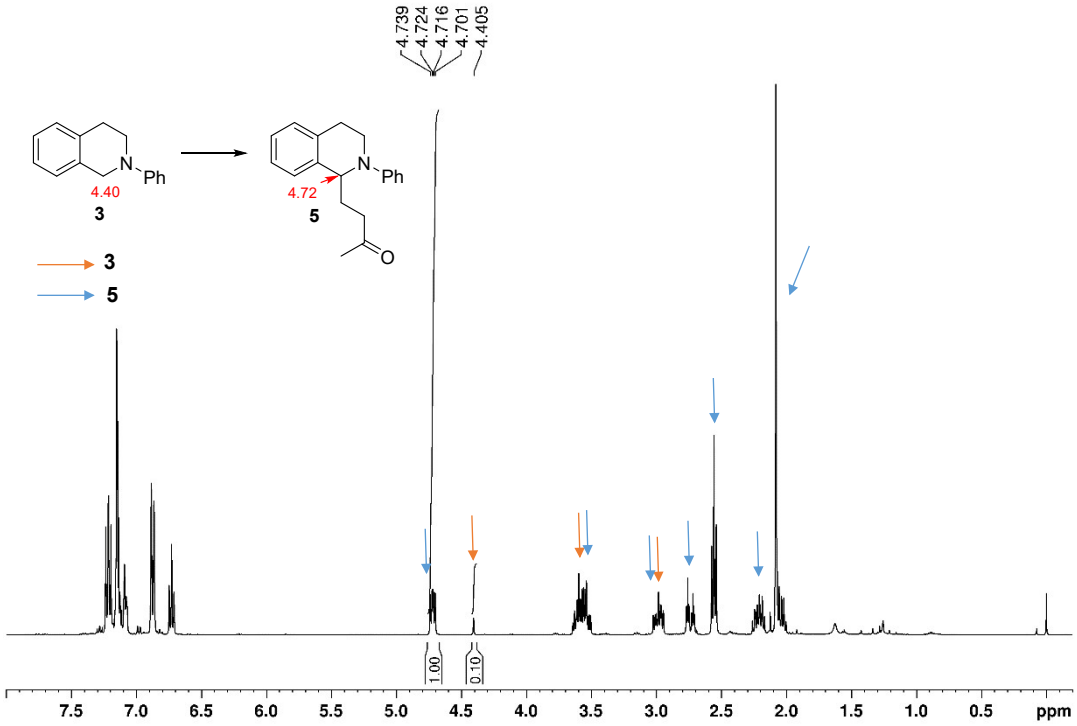


Figure S23. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of the crude mixture for α-alkylation of 2-phenyl-1,2,3,4-tetrahydroisoquinoline

3.3.3 Photocatalyzed cross-electrophile coupling via XAT

3.3.3.1 Determination of yield by quantitative NMR

Compound **8a** yield was calculated according to equation S6, taking into account the purity of the sample determined by quantitative ^{19}F NMR with α,α,α-trifluorotoluene as internal standard.

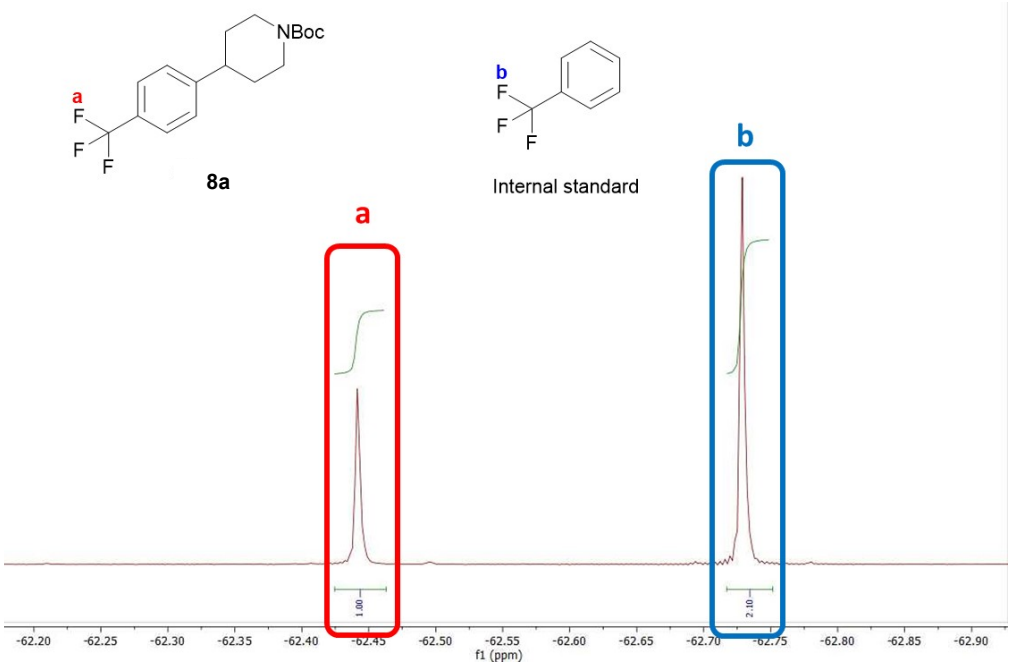


Figure S24. ^{9}F NMR spectrum (376 MHz, $CDCl_3$) of compound **8a** with α,α,α-Trifluorotoluene as internal standard

$$\text{Yield} = \frac{\text{NMR purity} * \text{crude mass}}{\text{expected mass}}$$ **(Equation S6)**

Compound **8b** yield was calculated according to equation S6, taking into account the purity of the sample determined by quantitative ^{1}H NMR with styrene as internal standard.

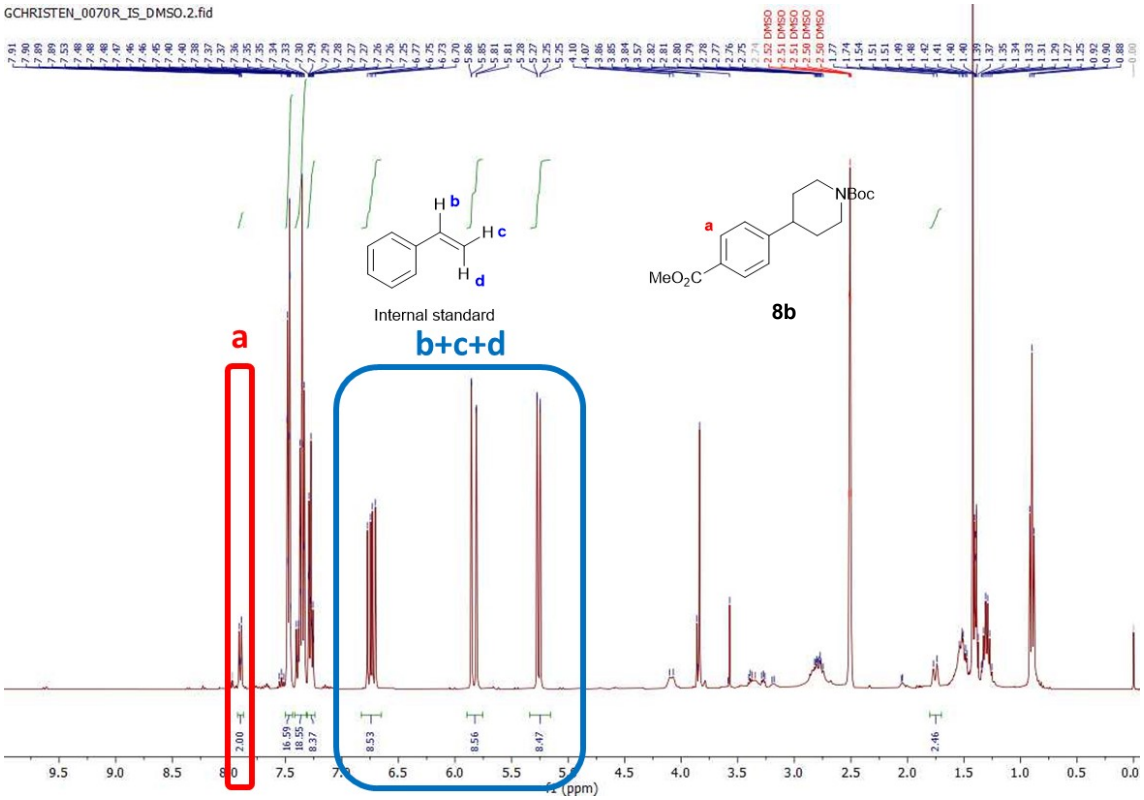


Figure S25. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **8b** with styrene as internal standard

3.3.3.2 Determination of yield by quantitative HPLC

Column: Agilent Poroshell EC-C18 4.6x100mm 4µm

Temperature: RT

Injection volume: 1 µL

Flow-Rate: 1 mL/min

Mobile Phase A: Water with 0.1% Formic Acid (V/V)

Mobile Phase B: Acetonitrile

Detection: UV at 220 nm

Run-Time: 18 min

HPLC Method:

Time (min)	%A	%B
0.0	98	2
0.9	98	2
1.0	35	65
11.1	20	80
11.7	0	100
13.5	0	100
13.6	98	2
18.0	98	2

- Linearity has been evaluated and confirmed for the range 0.1 to 2 mg/mL.
- The reaction mixtures are diluted to match this range.
- The calibration standards are stored in the fridge before the analysis.
- A QC (at 1mg/mL) is injected after the samples to validate the sequence (deviation below 5% accepted) .

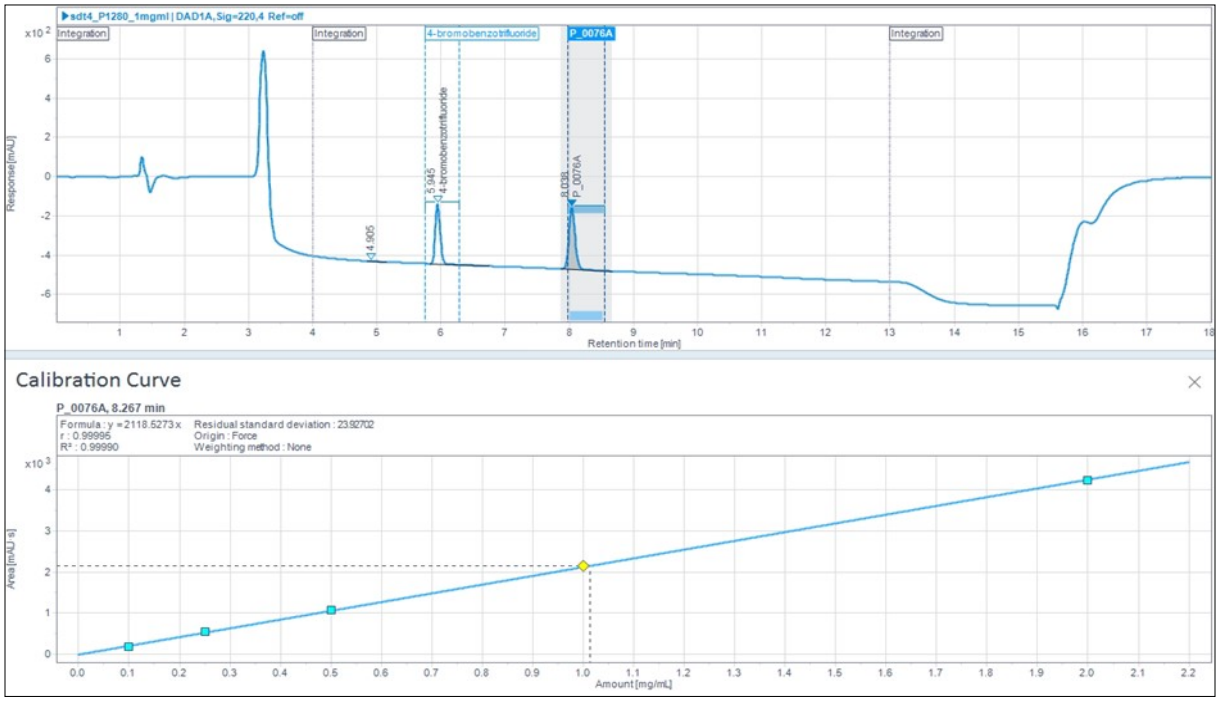


Figure S26. Chromatogram and calibration curve example for compound **8a** (yield)

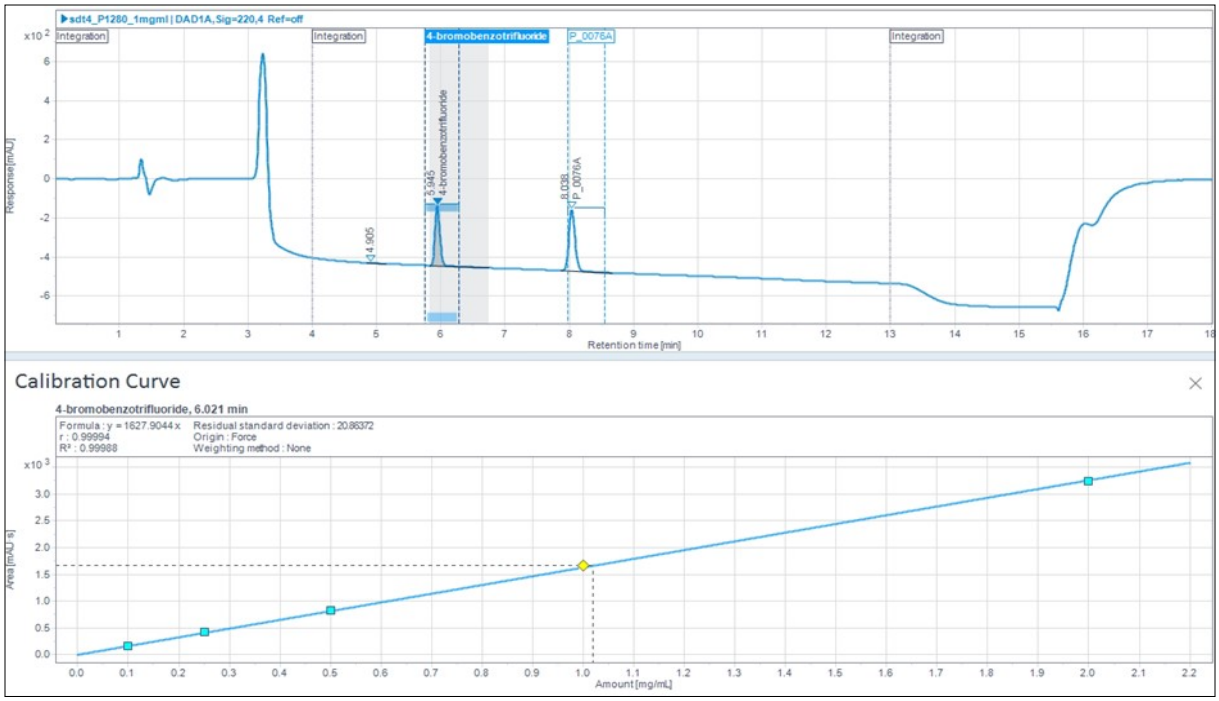


Figure S27. Chromatogram and calibration curve example for compound **6a** (conversion)

3.3.3.3 Batch screening: photocatalyst

To an oven-dried microwave vial with a stir bar are added tert-butyl 4-iodopiperidine-1-carboxylate 6b (1.24 equiv., 196.4 mg, 0.63 mmol), methyl 4-bromobenzoate (1 equiv., 109.2 mg, 0.508 mmol), photocatalyst (0.02 equiv.) and NiBr2(dtbbpy) (0.1 equiv., 24.9 mg, 0.051 mmol). The vial is sealed and flushed with argon. Then tri-n-butylamine (2.89 equiv., 272 mg, 0.35 mL, 1.47 mmol) and dioxane (5 mL) are added to the vial. The reaction mixture is stirred until dissolution and the solution is degassed with argon for 5 min. The vial is then irradiated at 450 nm with a blue LED lamp (hepatochem device, fan ON). After 95 h, the reaction mixture is diluted with water (5 mL) then extracted with EtOAc (3x10 mL). The organic layers are combined, washed with brine (3x15 mL), dried on Na_2SO_4, filtered, and concentrated under reduced pressure. If present, compound **8b** is quantified in the crude by ^{1}H NMR with styrene as internal standard.

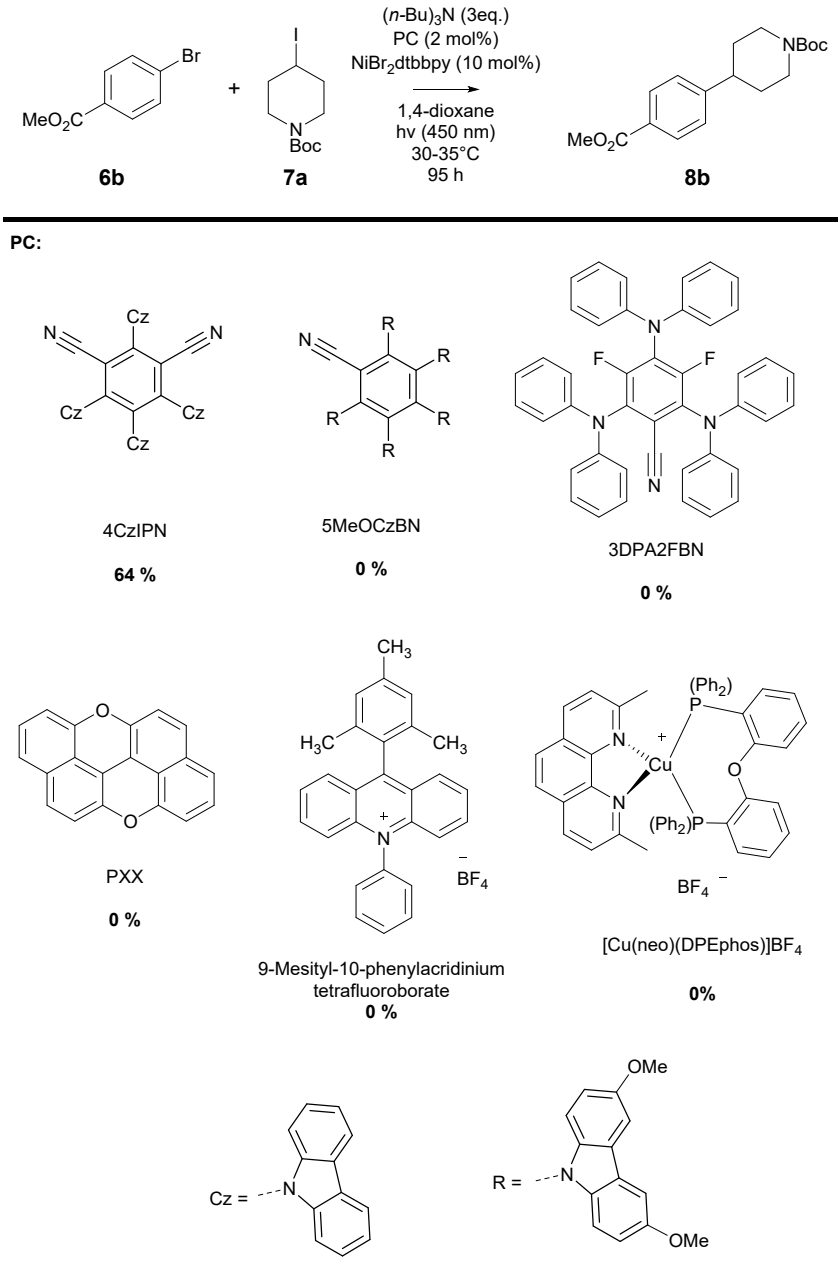
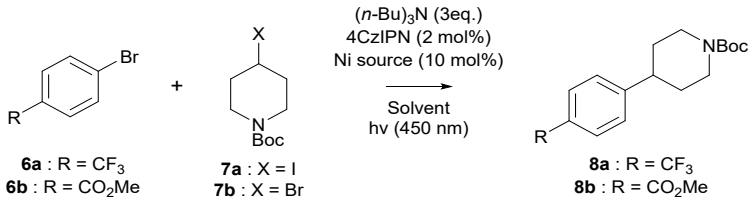


Figure S28. Photocatalyst screening with the corresponding **8b** yield, quantified by ^{1}H NMR with styrene as internal standard.

3.3.3.4 Batch screening: Ni source/solvent

To an oven-dried microwave vial with a stir bar are added alkyl halide **7a** or **7b** (1.24 equiv.), aryl halide (1 equiv.), 4CzIPN (0.02 equiv., 8.2 mg, 0.01 mmol) and nickel source (0.1 equiv.). The vial is sealed and flushed with argon. Then tri-*n*-butylamine (2.89 equiv., 272 mg, 0.35 mL, 1.47 mmol) and solvent (5 mL) are added to the vial. The reaction mixture is stirred until dissolution and the solution is degassed with argon for 5 min. The vial is then irradiated at 450 nm with a blue LED lamp (hepatochem device, fan ON). After 95 h, the reaction mixture is diluted with water (5 mL) then extracted with EtOAc (3x10 mL). The organic layers are combined, washed with brine (3x15 mL), dried on Na_2SO_4, filtered, and concentrated under reduced pressure. If present, compound **8a** is quantified by quantitative ^{19}F NMR with α,α,α-Trifluorotoluene as internal standard and compound **8b** is quantified in the crude by quantitative ^{1}H NMR with styrene as internal standard.



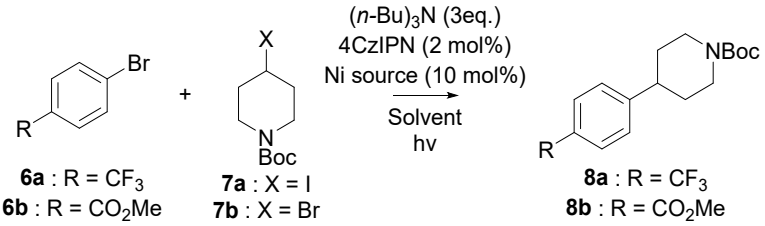
6a : R = CF_3
6b : R = CO_2Me

7a : X = I
7b : X = Br

8a : R = CF_3
8b : R = CO_2Me

Entry	Solvent	Alkyl	Aryl	Ni source	t (h)	[1a-d] (M)	Yield (%)
1	1,4-dioxane	**7a**	**6b**	$NiBr_2$.glyme + dtbbpy	30	0.1	21
2	1,4-dioxane				72		64
8	1,4-dioxane			$NiBr_2$(dtbbpy)	72		84
9	1,4-dioxane		**6a**	$NiBr_2$.glyme + dtbbpy	48		36
10	1,4-dioxane				48	0.5	13
11	1,4-dioxane			$NiBr_2$(dtbbpy)	72	0.1	87
12	DMSO				72		6
13	DMF				72		2
14	1,4-dioxane	**7b**		$NiBr_2$.glyme + dtbbpy	45		12
15	1,4-dioxane			$NiBr_2$(dtbbpy)	45		3

3.3.3.5 Preliminary flow screening: residence time and wavelength



To a volumetric flask are added alkyl halide **7a** or **7b** (1.24 equiv.), aryl halide **6a** or **6b** (1 equiv.), 4CzIPN (0.0203 equiv., 1.5 mL, 0.0031 mmol) and nickel source (0.1 equiv.). The flask is sealed and flushed with argon. Then N,N-Dibutyl-1-butanamine (2.97 equiv., 1.5 mL, 0.45 mmol) and dioxane (1.5 mL) are added to the flask. The reaction mixture is sonicated until dissolution and the solution is degassed with argon for 5 min. The prepared solution is then transferred to a syringe and pumped through the flow set-up (2 mL hepatochem reactor, 450 nm blue LED, fan ON) at the required flow rate for 1.5 residence time for equilibration. The feed is then collected.

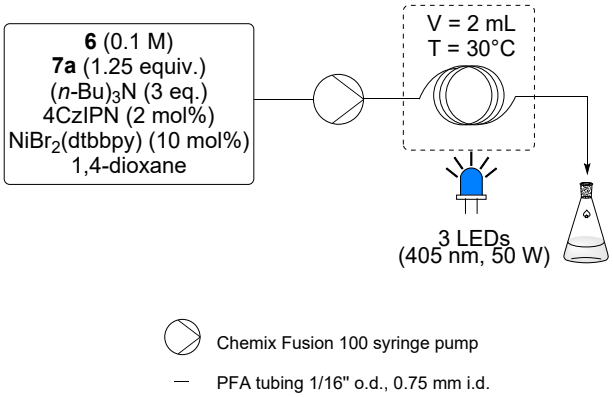


Figure S29. Flow setup diagram for the photocatalyzed cross-electrophile coupling

Entry	Aryl	Ni source	t_R (min)	Flow rate (mL min^{-1})	λ (nm)	Yield (%)
1	**6b**	$NiBr_2$.glyme + dtbbpy	40	0.025	450	0
2			20	0.05		0
3	**6a**	$NiBr_2$(dtbbpy)	60	0.033		19
4					405	25
5					380	16

3.3.3.6 Flow optimization: screening DoE

In a 5 mL volumetric flask, compound **6a** (1 equiv., 0.25 mL, 0.11 mmol), 4CzIPN (0.049 equiv., 0.25 mL, 0.0055 mmol) and $NiBr_2$(dtbbpy) (0.098 equiv., 0.25 mL, 0.011 mmol) are added. The flask is sealed with a septum and flushed with argon. Then N,N-Dibutyl-1-butanamine (5.022 equiv., 0.25 mL, 0.56 mmol), 4-bromobenzotrifluoride (3.004 equiv., 0.25 mL, 0.34 mmol) are added and then dioxane (0.25 mL) to complete the flask. The reaction mixture is stirred until dissolution and the solution is degassed with argon for 5 min (solution A). The flow set-up is washed with dioxane, then solution is pumped through the flow set-up under irradiation at 400-405 nm with blue LED lamps (temperature set at 60°C), at 0.025 mL min^{-1} for 160 min (equilibration). The feed is then collected for 10 min. Yield is determined by quantitative HPLC.

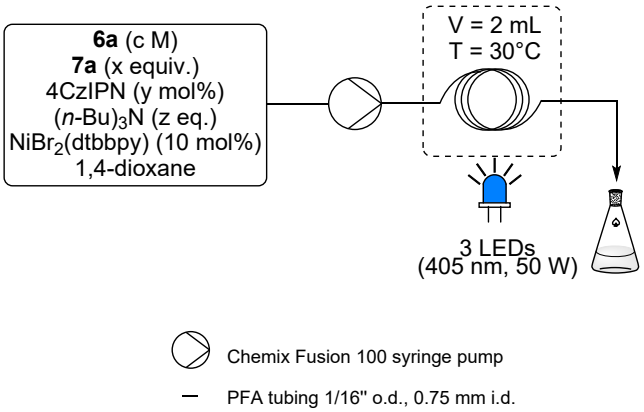


Figure S30. Flow setup diagram for the DoE photocatalyzed cross-electrophile coupling

Parameters:

- [c]=0.05 M-0.45 M in 1,4-dioxane
- [pCF3PhBr] stoichiometry: 1 – 3 equiv.
- $(n\text{-}Bu)_3$ stoichiometry: 1 –5 equiv.
- 4CzIPN loading: 1 – 5 mol%
- Temperature: 25-55 °C
- Residence time: 20-80 min.

Responses:

- Yield (%)
- Space-Time-Yield (mg mL^{-1} h^{-1})

Strategy:

- Factorial design 2^{6-2}
- 2 central points

Entry	[7a] (M)	n(6a) (equiv.)	n((*n*-Bu_3)N) (equiv.)	4CzIPN (mol%)	t_R (min)	T (°C)	Yield (%)	STY (mg mL^{-1} h^{-1})
1	0.45	3	5	5	20	25	17	38.25
2	0.25	2	3	3	20	40	41	20.28
3	0.45	3	5	5	80	55	28	15.6
4	0.05	3	5	5	80	25	85	21
5	0.25	2	3	3	50	40	44	21.9
6	0.45	3	5	1	20	55	28	63.15
7	0.45	3	1	1	80	25	22	12.38
8	0.05	1	1	5	80	25	41	2.51
9	0.05	3	5	1	20	25	36	8.85
10	0.45	1	5	1	80	25	21	11.74
11	0.45	1	5	5	20	25	12	26.1
12	0.05	1	5	5	20	55	22	5.4
13	0.05	3	1	5	20	55	17	4.35
14	0.05	1	5	1	80	55	40	2.44
15	0.45	1	1	1	20	55	4	9.15
16	0.05	1	1	1	20	25	11	2.7
17	0.45	1	1	5	80	55	10	5.36
18	0.05	3	1	1	80	55	23	1.43

Yield

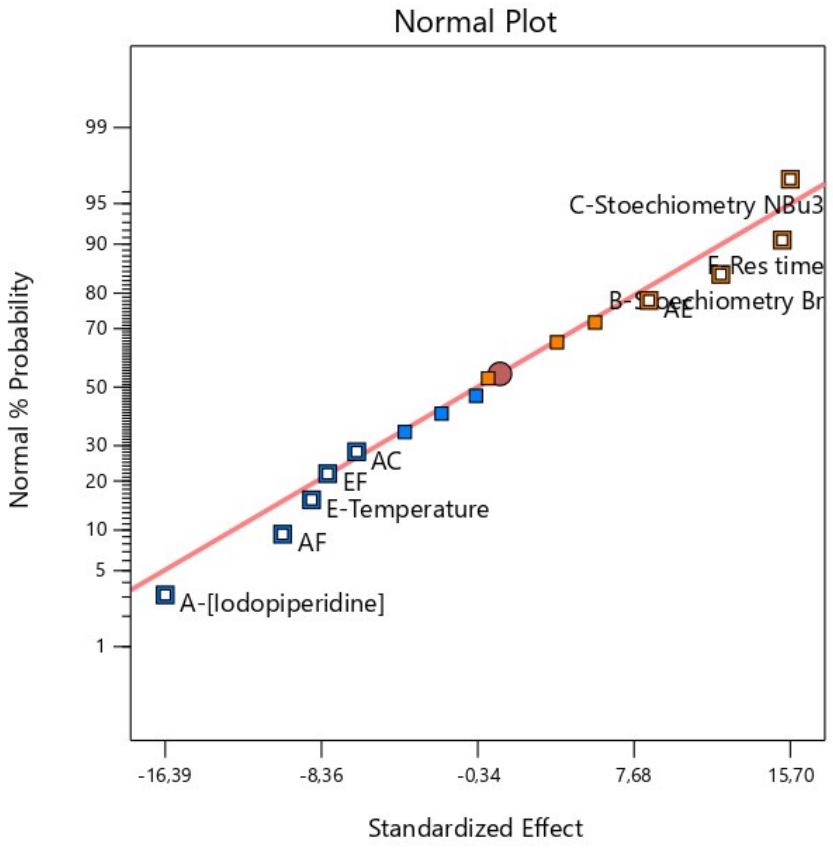
Warning! Pure error terms not shown

Shapiro-Wilk test

W-value = 0,962
p-value = 0,831

A: [Iodopiperidine]
B: Stoechiometry Br
C: Stoechiometry NBu3
D: 4CzIPN loading
E: Temperature
F: Res time

Positive Effects
Negative Effects



Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	5044,07	9	560,45	14,15	0,0010	significant
A-[Iodopiperidine]	1074,04	1	1074,04	27,12	0,0012	
B-Stoechiometry Br	589,15	1	589,15	14,88	0,0062	
C-Stoechiometry NBu3	986,12	1	986,12	24,90	0,0016	
E-Temperature	314,80	1	314,80	7,95	0,0258	
F-Res time	934,98	1	934,98	23,61	0,0018	
AC	171,81	1	171,81	4,34	0,0758	
AE	285,53	1	285,53	7,21	0,0313	
AF	429,01	1	429,01	10,83	0,0133	
EF	258,65	1	258,65	6,53	0,0378	
Curvature	503,44	1	503,44	12,71	0,0092	
Residual	277,20	7	39,60			
Lack of Fit	271,69	6	45,28	8,22	0,2609	not significant
Pure Error	5,51	1	5,51			
Cor Total	5824,71	17				

Std. Dev.	6,29	**R^2**	0,9479
Mean	27,90	**Adjusted R^2**	0,8809
C.V. %	22,55	**Predicted R^2**	0,6328
		Adeq Precision	14,5330

STY

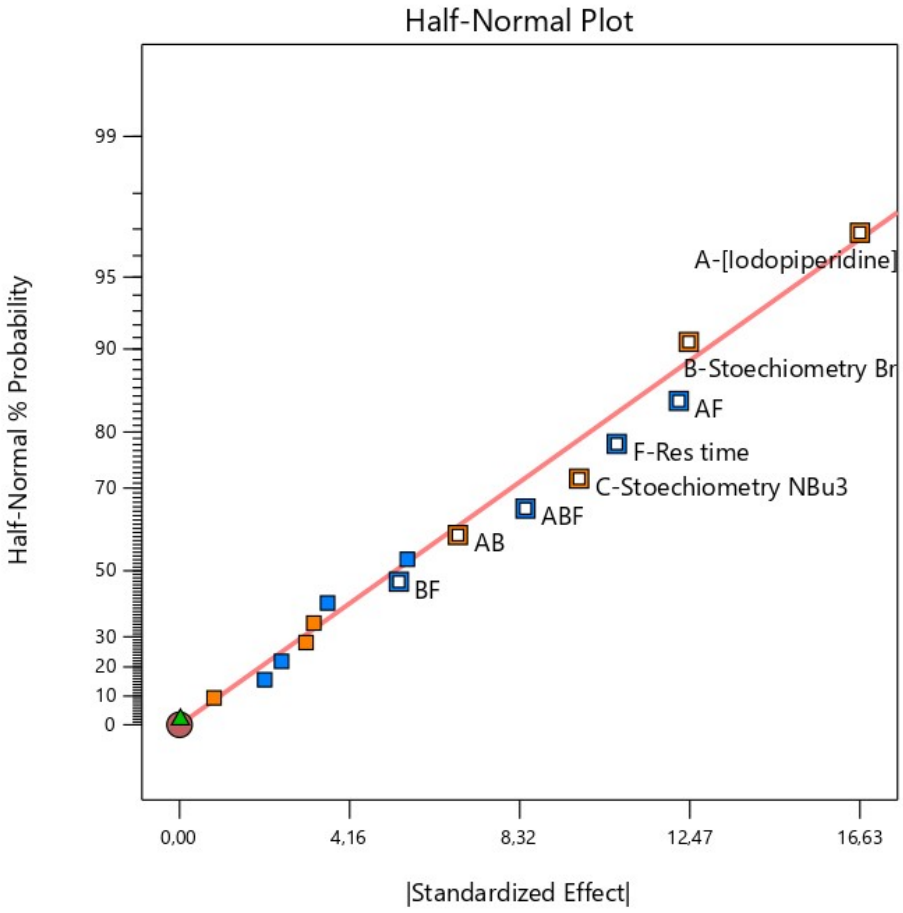
Error estimates

Shapiro-Wilk test

W-value = 0,924
p-value = 0,503

A: [Iodopiperidine]
B: Stoechiometry Br
C: Stoechiometry NBu3
D: 4CzIPN loading
E: Temperature
F: Res time

Positive Effects
Negative Effects



Response 3: STY

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	3747,34	8	468,42	10,99	0,0008	significant
A-[Iodopiperidine]	1106,39	1	1106,39	25,95	0,0007	
B-Stoechiometry Br	620,01	1	620,01	14,54	0,0041	
C-Stoechiometry NBu3	381,71	1	381,71	8,95	0,0151	
F-Res time	456,89	1	456,89	10,72	0,0096	
AB	185,30	1	185,30	4,35	0,0667	
AF	595,97	1	595,97	13,98	0,0046	
BF	115,03	1	115,03	2,70	0,1349	
ABF	286,03	1	286,03	6,71	0,0292	
Residual	383,70	9	42,63			
Lack of Fit	382,39	8	47,80	36,43	0,1275	not significant
Pure Error	1,31	1	1,31			
Cor Total	4131,04	17				

Std. Dev.	6,53		**R^2**	0,9071
Mean	15,14		**Adjusted R^2**	0,8246
C.V. %	43,12		**Predicted R^2**	0,5985
			Adeq Precision	12,5608

Factor	Effect on yield[a]	Effect on STY[a]
[**7a**] mol/L	--	++
[**6a**] stoichiometry	+	+
(*n*-Bu)$_3$N stoichiometry	++	+
4CzIPN loading	0	0
T (°C)	-	0
Res. Time	++	-

[a]--: large negative impact; -: moderate negative impact; 0: no impact; +: moderate positive impact; ++: large positive impact

3.3.3.7 General procedure for the synthesis of compounds 8

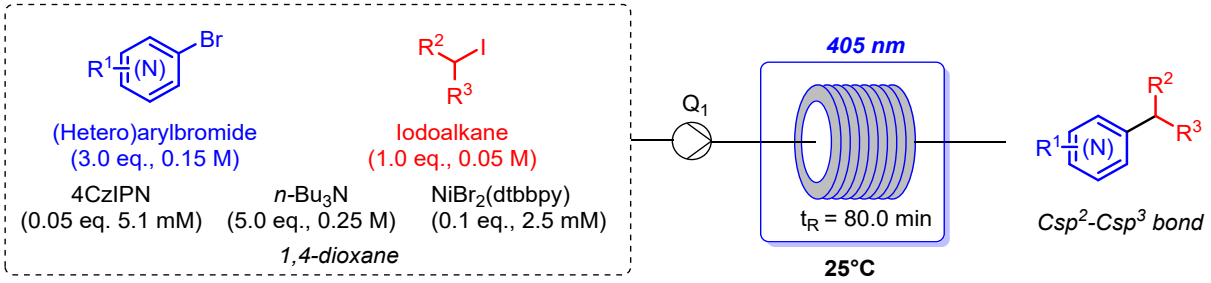


Figure S31. Diagram for the synthesis of compounds **8**

A solution of arylbromide **6** (3.0 equiv., 0.15 M), iodoalkane **7** (1.0 equiv., 0.05 M), n-Bu_3N (5.0 equiv., 0.25 M), 4CzIPN (0.05 equiv., 5.1 mM) and $NiBr_2$(dtbbpy) (0.1 equiv., 2.5mM) in 1,4-dioxane was pumped through the photoreactor at 0.025 mL.min^{-1}, irradiated at 405 nm, for 160 min for equilibration and collected for 210 min into an Erlenmeyer flask. The collected fraction was diluted with water (10 mL) and extracted with EtOAc (3x15 mL). The combined organic layers were washed with brine (3x30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude reaction mixtures were purified by flash chromatography to afford the coupling products **8**.

Tert-butyl 4-[4-(trifluoromethyl)phenyl]piperidine-1-carboxylate (8a; CAS: 732275-91-1)
Tert-butyl 4-iodopiperidine-1-carboxylate **7a** and 4-bromobenzotrifluoride **6a** were used. **8a** was purified by flash chromatography on SiO_2 (Cyclohexane/CH_2Cl_2 100: 0 to 0: 100).
Isolated as a yellow oil in 66% yield.
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (d, J = 8.3 Hz), 7.31 (d, J = 8.3 Hz), 4.42-4.07 (m, 2H), 2.91-2.76 (m, 2H), 2.72 (tdt, J = 12.0, 3.3 Hz), 1.89-1.76 (m, 2H), 1.71-1.55 (m, 2H), 1.48 (s, 9H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 154.9, 149.9, 128.8 (q, J = 32.6 Hz), 125.6 (q, *J* = 3.9 Hz), 124.4 (q, *J* = 271.9 Hz), 79.7, 42.8, 33.1, 28.6 ppm.
^{19}F (376 MHz, $CDCl_3$): δ -62.4 ppm.

Tert-butyl 3-[4-(trifluoromethyl)phenyl]azetidine-1-carboxylate (8c; CAS: 1638255-66-9)
Tert-butyl 3-iodoazetidine-1-carboxylate **7d** and 4-bromobenzotrifluoride **6a** were used. **8c** was purified by flash chromatography on SiO_2 (Cyclohexane/CH_2Cl_2 100: 0 to 0: 100).
Isolated as a colorless oil in 73% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, *J* = 8.0 Hz, 2H), 7.43 (d, *J* = 8.0 Hz, 2H), 4.36 (t, *J* = 8.8 Hz, 2H), 3.97 (dd, *J* = 8.2, 5.6 Hz, 2H), 3.83-3.73 (m, 1H), 1.47 (s, 9H) ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ 156.5, 146.5, 129.5 (q, *J* = 32.6 Hz), 127.3, 124.2 (q, *J* = 272.3 Hz), 125.8 (q, *J* = 3.8 Hz), 80.0, 33.5, 28.5 ppm.
^{19}F NMR (376 MHz, $CDCl_3$): δ -62.49 ppm.

Tert-butyl 3-{[4-(trifluoromethyl)phenyl]methyl}azetidine-1-carboxylate (8d, CAS: 2385359-31-7)
Tert-butyl 3-(iodomethyl)azetidine-1-carboxylate **7c** and 4-bromobenzotrifluoride **6a** were used. **8d** was purified by flash chromatography on SiO_2 (Cyclohexane/CH_2Cl_2 100: 0 to 0: 100).
Isolated as white solid in 36% yield.
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 ppm (d, *J* = 8.1 H, 2H), 7.26 (d, *J* = 7.2 Hz, 2H), 4.00 (t, *J* = 8.3 Hz, 2H), 3.72-3.59 (m, 2H), 3.00-2.89 (m, 2H), 2.89-2.73 (m, 1H), 1.43 (s, 9H) ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ 193.6, 180.5, 162.8, 166.2, 165.9, 162.7 (q, J = 4.0 Hz), 116.6, 77.2, 66.7, 65.5, 45.8 ppm.
^{19}F (376 MHz, $CDCl_3$): δ -62.4s ppm.
HRMS: expected: 316.1524 [M+H]+ found: 260.0898 [M-*t*Bu+H]+

Tert-butyl 3-(6-cyanopyridin-3-yl)azetidine-1-carboxylate (8e)
Tert-butyl 3-iodoazetidine-1-carboxylate **7d** and 5-bromopyridine-2-carbonitrile **6c** were used. **8e** was purified by flash chromatography on SiO_2 (Cyclohexane/EtOAc 100: 0 to 50: 50) and by chromatography on C18 (H_2O/MeCN 99:1 to 0:100).
Isolated as a white solid in 21% yield.
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.97 (s, 1H), 7.87 (dd, *J* = 8.2, 2.3 Hz, 1H), 7.72 (d, *J* = 7.8 Hz, 1H), 4.41 (t, J = 8.8 Hz, 2H), 3.95 (dd, J = 8.8, 5.5 Hz, 2H), 3.81 (m, 1H), 1.47 (s, 9H) ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ 156.3, 150.4, 142.1, 135.6, 135.1, 132.7, 128.8, 128.7, 117.2, 80.4, 31.32, 28.5 ppm.
HRMS: expected: 260.1399 [M+H]+ found: 212.0743 [M-*t*Bu+H]+

Tert-butyl 4-(thiophen-3-yl)piperidine-1-carboxylate (8f; CAS: 690261-78-0)
Tert-butyl 4-iodopiperidine-1-carboxylate **7a** and 3-bromothiophene **6d** were used. **8f** was purified by flash chromatography on SiO_2 (Cyclohexane/CH_2Cl_2 100: 0 to 0: 100).
Isolated as brown oil in 63% yield.
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (s, 1H), 7.01-6.92 (m, 2H), 4.41-4.04 (m, 2H), 2.95-2.68 (m, 3H), 2.01-1.83 (m, 2H), 1.68-1.50 (m, 2H), 1.47 (s, 9H) ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ 155.0, 146.9, 126.8, 125.6, 119.1, 79.6, 37.9, 33.1, 28.6 ppm.

Tert-butyl 3-(thiophen-3-yl)azetidine-1-carboxylate (8g; CAS: 2453192-08-8)
Tert-butyl 3-iodoazetidine-1-carboxylate **7d** and 3-bromothiophene **6d** were used. **8g** was purified by flash chromatography on SiO_2 (Cyclohexane/EtOAc 100: 0 to 50: 50).

Isolated as a light brown oil in 48% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.29 (m, 1H), 7.11-7.05 (m, 2H), 4.28 (t, J = 8.3 Hz, 2H), 3.99-3.91 (m, 2H), 3.85-3.75 (m, 1H), 1.46 (s, 9H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 156.6, 143.2, 126.7, 126.4, 120.7, 79.7, 29.4, 28.6 ppm.

Tert-butyl 4-(pyrimidin-5-yl)piperidine-1-carboxylate (8h; CAS: 1019206-22-4)

Tert-butyl 4-iodopiperidine-1-carboxylate **7a** and 5-bromopyrimidine **6e** were used. **8h** was purified by flash chromatography on SiO_2 (Cyclohexane/CH_2Cl_2 100: 0 to 0: 100).

Isolated as brown oil in 76% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.10 (s, 1H), 8.60 ppm (s, 2H), 4.45-4.15 (m, 2H), 2.97-2.75 (m, 2H), 2.75-2.60 (m, 1H), 1.93-1.80 (m, 2H), 1.80-1.61 (m, 2H), 1.48 (s, 9H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 157.4, 155.7, 154.8, 138.4, 80.0, 38.4, 32.6, 28.6 ppm.

3.3.4. Photocatalyzed difluoroamidation of indoles

3.3.4.1. Conversion determined by ^{1}H NMR

The conversion of 3-methylindole **9a** into compound **11a** is determined based on the integration of the proton at 7.58 ppm and 7.69 ppm:

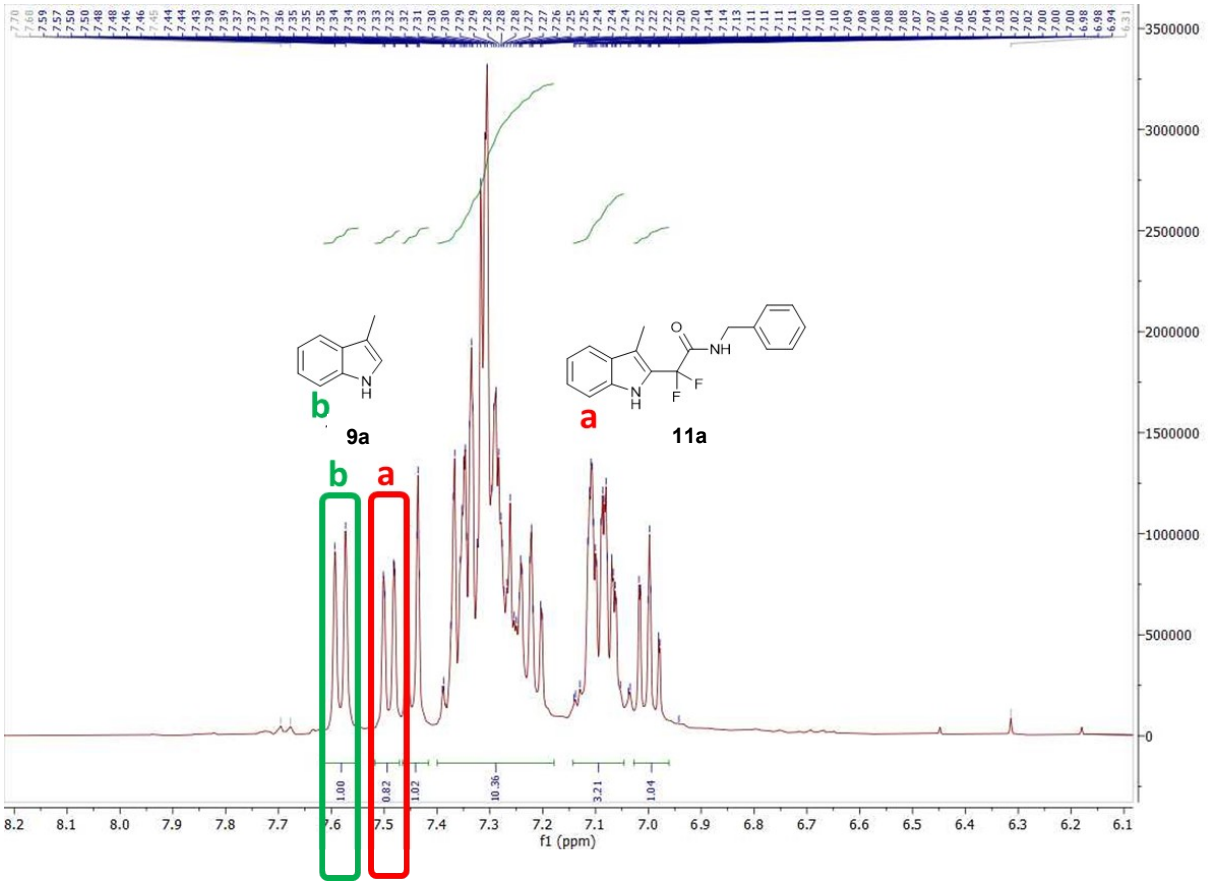


Figure S32. ^{1}H NMR spectrum (400 MHz, DMSO-d6) of the crude mixture for the conversion of **9a** into **11a**

$$\text{Conversion} = \frac{1 - Ia}{Ia + Ib} * 100 \quad \textbf{(Equation 7)}$$

3.3.4.2. Yield and conversion determination by quantitative ^{19}F NMR

For the determination of the yield and the conversion, calibration curves for **10a** and **11a** were constructed with ^{19}F NMR using α,α,α-Trifluorotoluene as internal standard (IS). Equations 8 and 9 were used for the calculation.

Calibration curve for **11a**

m (IS)	I (IS)	m (**10a**)	I (**10a**)	I(**10a**)/I(SI)	m(**10a**)/m(SI)
				0	0
11.16	1	19.43	1.02	1.02	1.74E+00
11.62	1	9.62	0.47	0.47	8.28E-01
14.15	1	1.01	0.04	0.04	7.14E-02

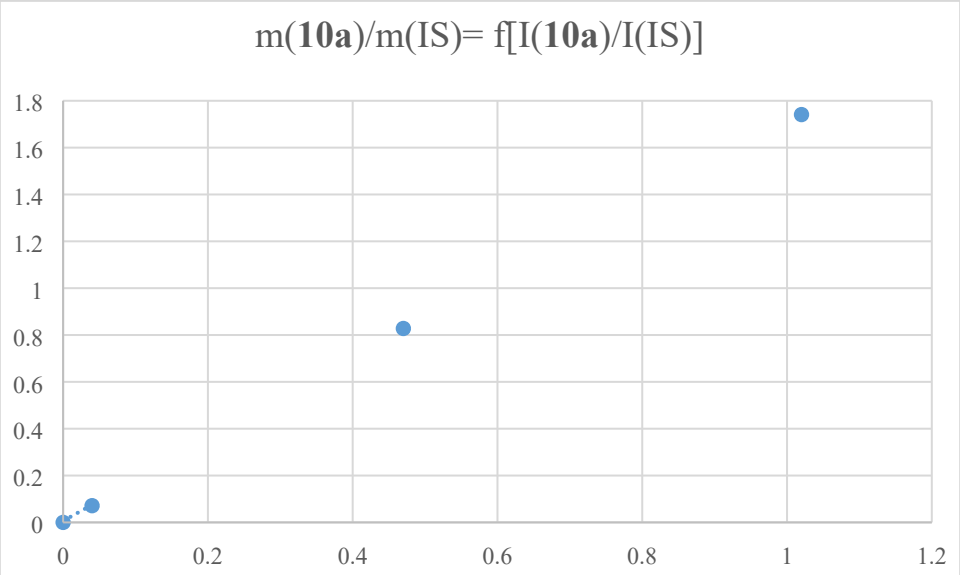


Figure S33. Calibration curve with internal standard for compound **10a**

Calibration curve for **11a**

m (IS)	I (IS)	m (**11a**)	I(**11a**)	I(**11a**)/I(SI)	m(**11a**)/m(SI)
				0	0
11.16	1	1.02	0.05	0.05	9.14E-02
11.62	1	10.12	0.42	0.42	8.71E-01
14.15	1	19.76	0.67	0.67	1.40E+00

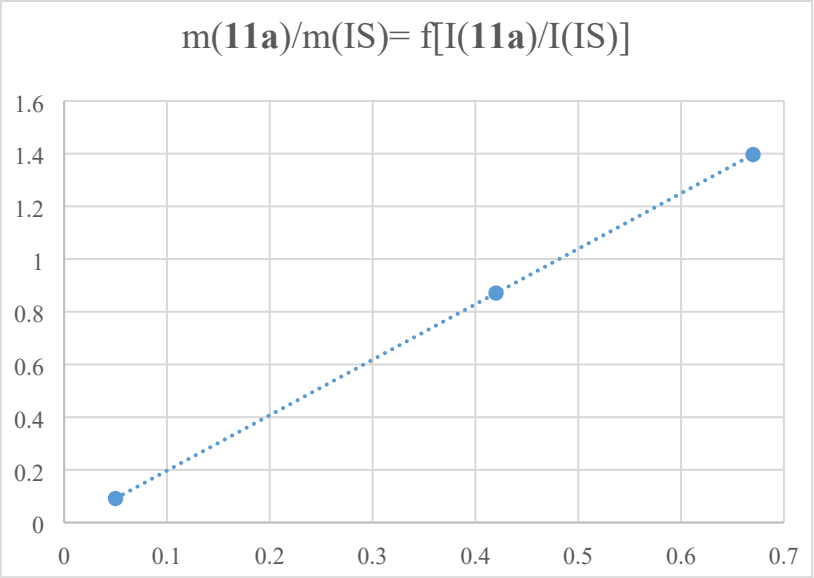


Figure S34. Calibration curve with internal standard for compound **11a**

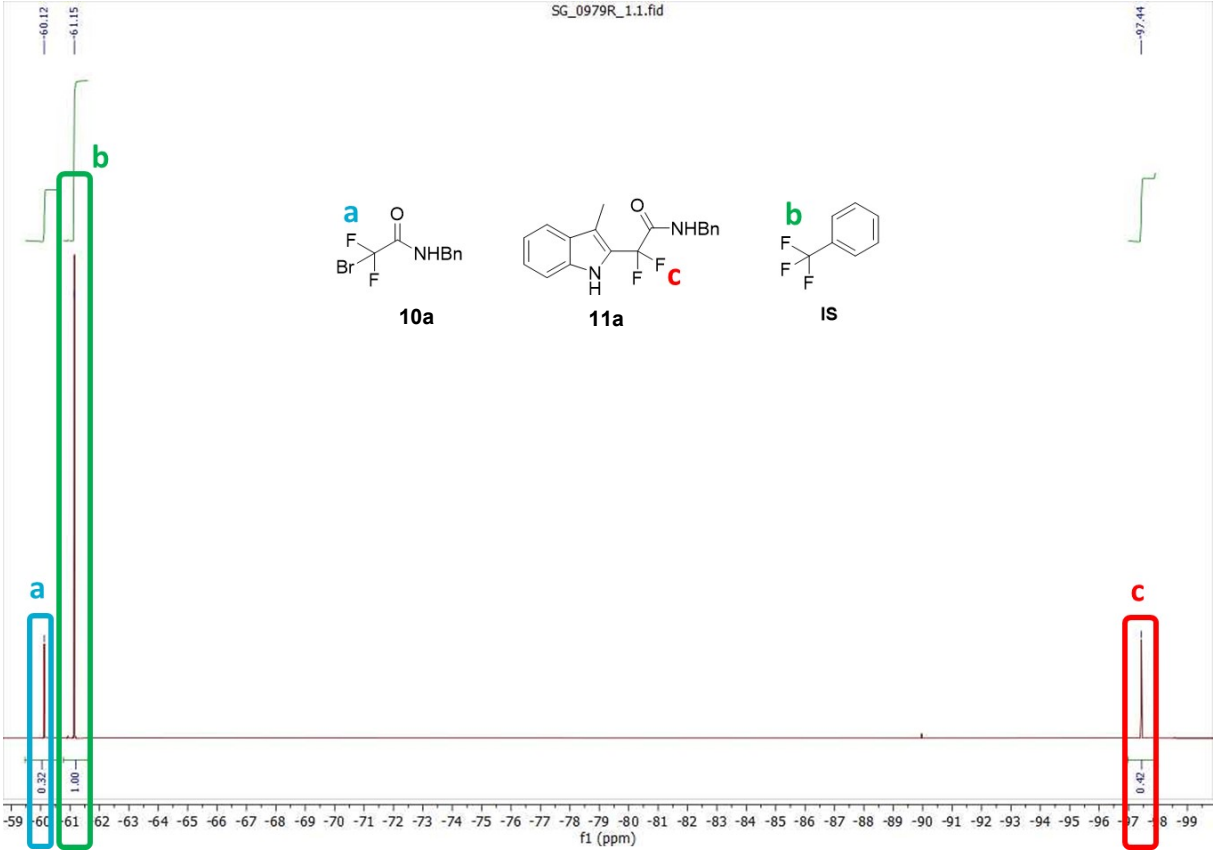
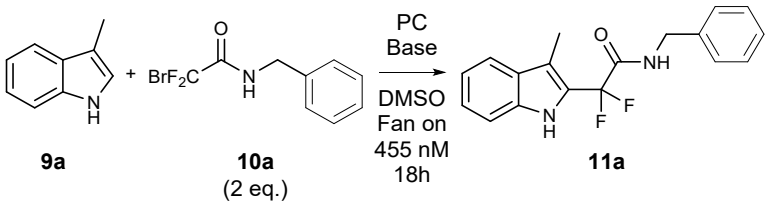


Figure S35. ^{9}F NMR spectrum (376 MHz, DMSO-d6) of the reaction mixture with α,α,α-Trifluorotoluene as internal standard

$$\text{Yield} = \frac{\text{m}\,(\mathbf{11a})\text{real}}{\text{m}\,(\mathbf{11a})\text{theoretical}} = \frac{2.1501 * \text{m(IS)} * \dfrac{\text{I}\,(\mathbf{11a})}{\text{I}\,(\text{IS})} + 0.014 * \text{m(IS)}}{\text{m}\,(\mathbf{11a})\text{theoretical}} * 100\% \qquad \textbf{(Equation 8)}$$

$$\text{Conversion} = \text{m}\,(\mathbf{10a})0 - \frac{1.7086 * \text{m(IS)} * \frac{\text{I}\,(\mathbf{10a})}{\text{I}\,(\text{IS})} + 0.0065}{\text{m}\,(\mathbf{10a})0}$$ **(Equation 9)**

3.3.4.3 Batch optimization: screening of photocatalyst and base



To an oven dried microwave tube, photocatalyst (0.005 mmol, 0.02 equiv.) and 3-Methylindole **9a** (39.8 mg, 0.25 mmol, 1 equiv.) were dissolved in DMSO (1 mL). Base (0.50 mmol, 2 equiv.) and N-benzyl-2-bromo-2,2-difluoroacetamide **10a** (132 mg, 0.5 mmol, 2 equiv.) were then added. Argon was bubbled through the solution for 20 min. and the tube was sealed. Then, the reaction medium was irradiated with blue LEDs (hepatochem 465 nm) overnight (~18 h). Water was then added and the solution was extracted 3 times with EtOAc. The combined organic phase was washed with NH_4Cl aq., water and brine, dried and evaporated under reduced pressure to afford the crude product.

Entry	Conditions		Results (NMR)	
	PC (2mol%)	Base (2 equiv.)	Conv. (^{1}H)	Yield (^{19}F)
1	4CzIPN	*p*-Me-C_6H_4-N(Me)$_2$	100%	33%
2	5MeOCzBN		50%	20%
3	Ru(Phen)$_3$.Cl$_2$xH$_2$O		50%	15%
4	5CzBn		100%	25%
5	3DPA2FBN		100%	80%
6		Et_3N	100%	48%
7		DIPEA	100%	45%
8		2,6-lutidine	90%	72%
9		Ph_3N	ND (Not homogeneous)	
10		DBU	50%	20%

3.3.4.4 Preliminary flow optimization: stoichiometry and wavelength

In a 5 mL volumetric flask 3-Methylindole **9a** (164 mg, 1.25 mmol), N-benzyl-2-bromo-2,2-difluoroacetamide **10a** (amount according to Table) and 2 mL of DMSO are added. 3DPA2FBN, N,N-dimethyl-p-toluidine (2 equiv.) and α,α,α-Trifluorotoluene (internal standard, 1.3 equiv.) are then added and the flask completed to 5 mL with DMSO. Argon is bubbled through the solution for 20 min. The solution is taken with a syringe and pumped through hepatochem PhotoRedoxBox Duo and irradiated with blue light at the required flow rate. After 1.5 residence time of equilibration, the stream is collected for 10 min in a flask protected from light and the solution analyzed by ^{19}F NMR.

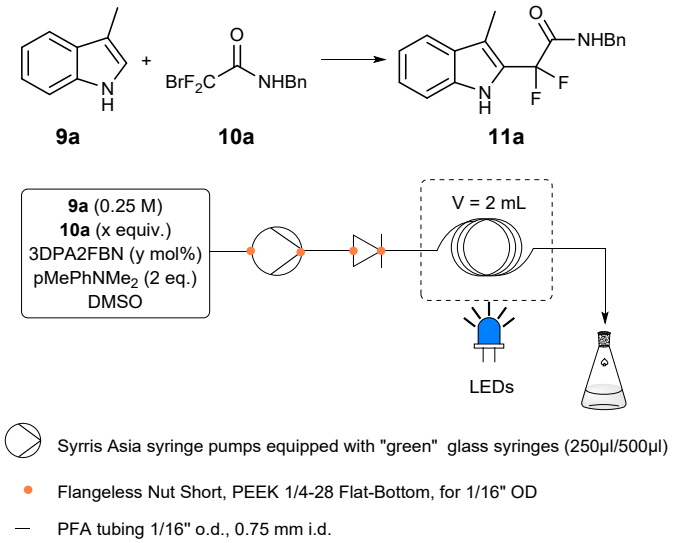


Figure S36. Diagram for the photocalyzed difluoroamidation of indoles

Entry	Stoichiometry			t_R (min)	Fan	λ (nm)	Conv 9a	Yield
	9a	10a	3DPA2FBN					
1	1.00	1.50	2 mol%	30	Off	450	39%	45%
2				60			42%	49%
3	1.25	1.00	1 mol%	20	On		31%	26%
4				40			47%	41%
5				20		405	55%	45%
6				40			80%	66%
7				40	Off		79%	64%

3.3.4.5 General experimental procedure for the DoE

In a 5 mL volumetric flask are added 3-Methylindole **9a**, N-benzyl-2-bromo-2,2-difluoroacetamide **10a** and 2 mL of DMSO. 3DPA2FBN, N,N-dimethyl-p-toluidine and α,α,α-Trifluorotoluene (internal standard, 1.3 equiv.) are then added and the flask completed to 5 mL with DMSO. Argon bubbled through the solution for 20 min. The solution is taken in a syringe and pumped through photoreactor and irradiated with blue light at the required flow rate. After 1.5 residence time of equilibration, the stream is collected for 10 min. in a flask protected from light and the solution analyzed by ^{19}F NMR.

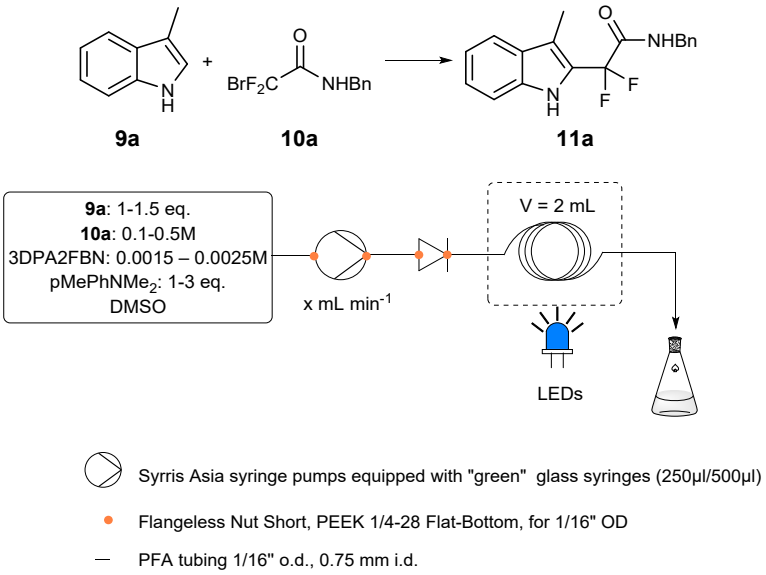


Figure S37. Diagram for the DoE of photocalyzed difluoroamidation of indoles

3.3.4.6 Screening DoE

Parameters:

- [PC]=[3DPA2FBN]= 0.0015 M – 0.0025 M
- [**10a**]: 0.1 – 0.5 M
- **9a** stoichiometry: 1.0 – 1.5 equiv.
- *p*-Me-C_6H_4-$N(Me)_2$ base stoichiometry: 1.0 – 3.0 equiv.
- Residence time: 20-40 min.

The feed solutions were prepared in DMSO as solvent and the reactor was set at 30 °C for all the experiments.

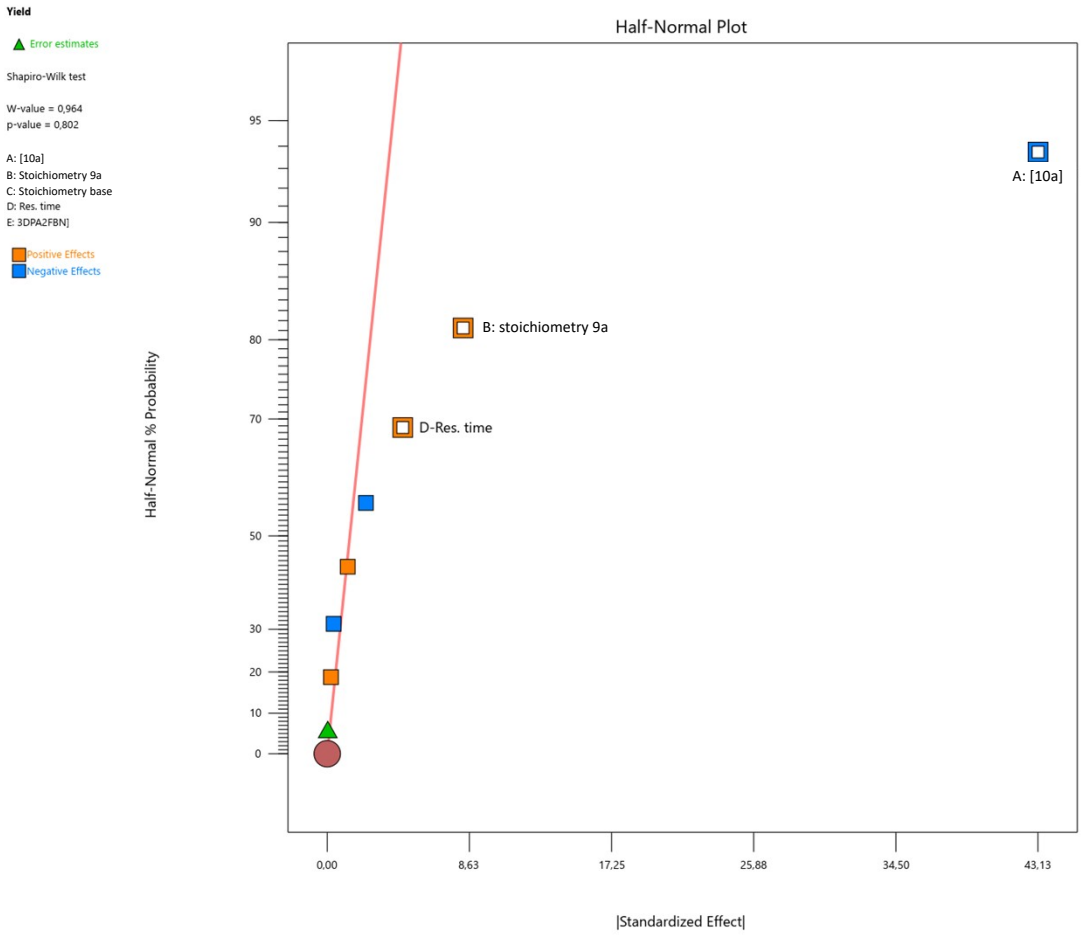
Responses:

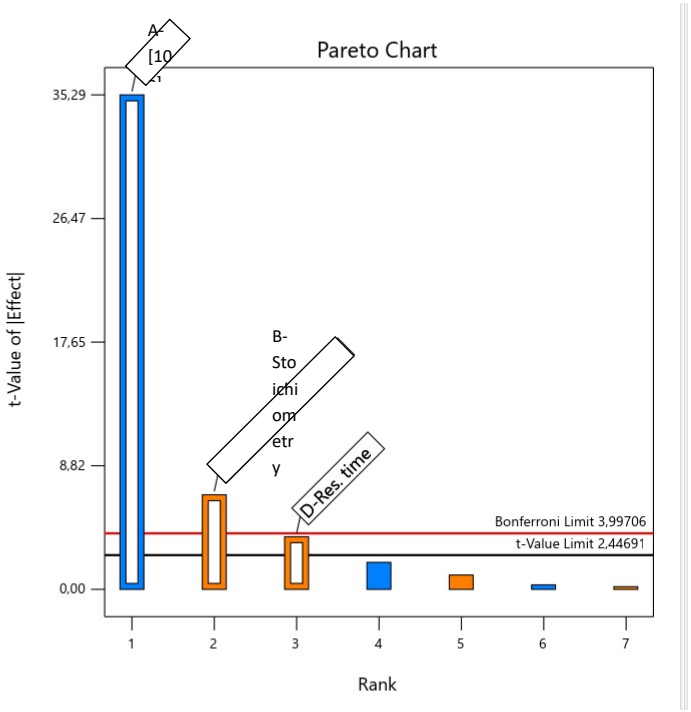
- Yield (%)
- Space-Time-Yield (mg mL^{-1} h^{-1})

Strategy:

- Fractional Factorial design 2^{5-2}
- 2 central points

[10a] (mol L^{-1})	9a (eq)	Base (eq)	t_R (min.)	[PC] (mol L^{-1})	Yield (%)	STY (mg mL^{-1} h^{-1})	Conv. (%)
0.1	1	3	40	0.001	67.7	31.95	100
0.5	1	1	20	0.001	23.59	111.525	56.65
0.1	1.5	1	20	0.003	73.32	69.15	100
0.3	1.25	2	30	0.002	46.33	87.825	90.43
0.5	1.5	1	40	0.001	34.94	82.425	83.55
0.1	1	1	40	0.003	70.68	33.375	100
0.5	1.5	3	40	0.003	33.68	79.425	81.68
0.5	1	3	20	0.003	19.37	91.35	54.51
0.1	1.5	3	20	0.001	72.38	68.25	99.11
0.3	1.25	2	30	0.002	47.17	89.4	89.36





ANOVA for selected factorial model

Response 1: Yield

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	3897,54	3	1299,18	292,37	< 0.0001	significant
A-[10a]	3719,53	1	3719,53	837,05	< 0.0001	
B-Stoichiometry 9a	135,96	1	135,96	30,60	0,0015	
D-Res. time	42,04	1	42,04	9,46	0,0218	
Residual	26,66	6	4,44			
Lack of Fit	26,31	5	5,26	14,91	0,1940	not significant
Pure Error	0,3528	1	0,3528			
Cor Total	3924,20	9				

Fit Statistics

Std. Dev.	2,11	**R^2**	0,9932
Mean	48,92	**Adjusted R^2**	0,9898
C.V. %	4,31	**Predicted R^2**	0,9813
		Adeq Precision	38,5311

STY

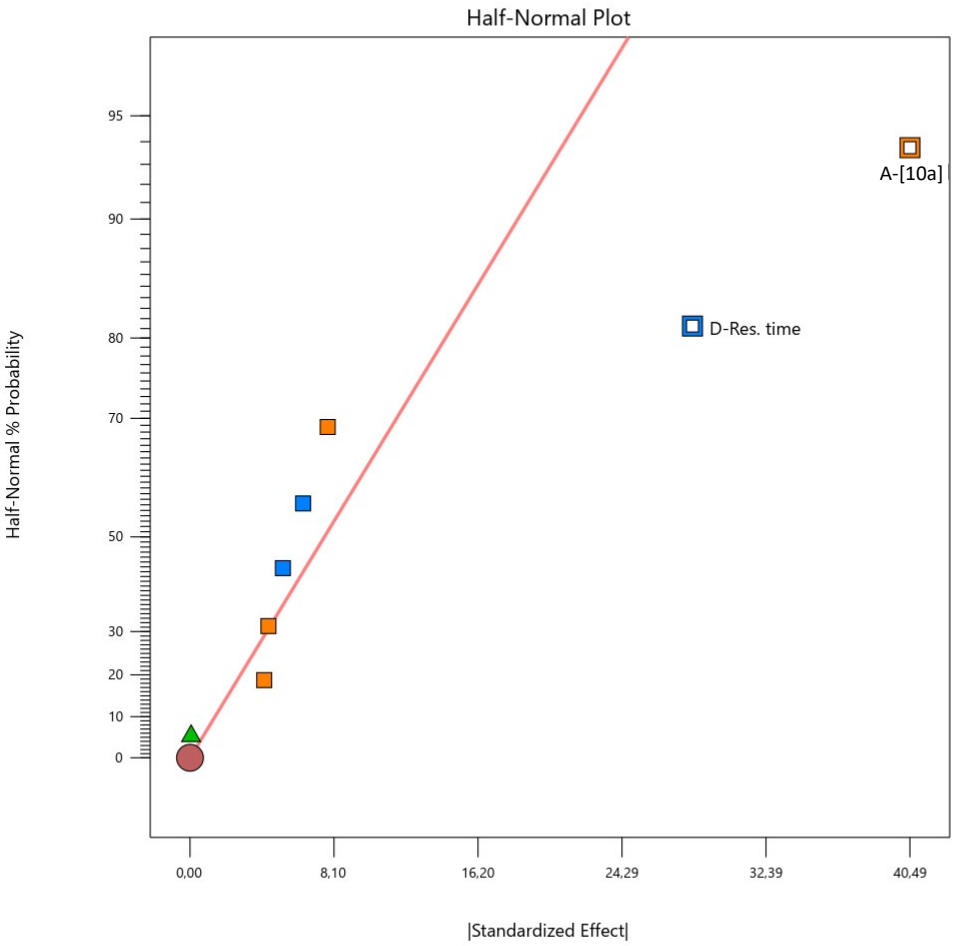
Error estimates

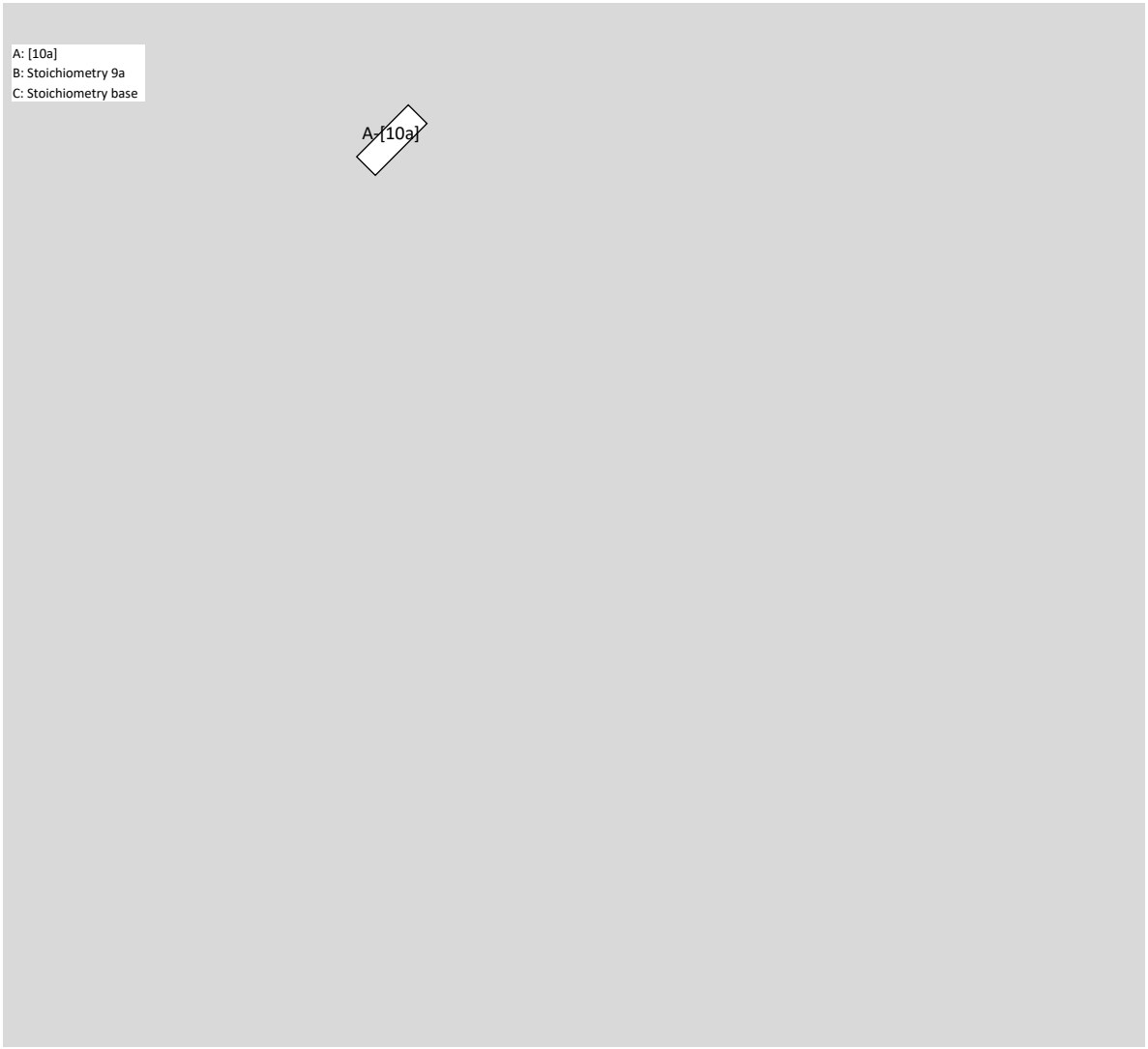
Shapiro-Wilk test

W-value = 0,855
p-value = 0,211

A: [10a]
B: Stoichiometry 9a
C: Stoichiometry base
D: Res. time
E: 3DPA2FBN]

Positive Effects
Negative Effects





ANOVA for selected factorial model

Response 2: STY

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	4876,36	2	2438,18	44,23	0,0003	significant
A-[10a]	3278,68	1	3278,68	59,47	0,0002	
D-Res. time	1597,68	1	1597,68	28,98	0,0017	
Curvature	499,96	1	499,96	9,07	0,0237	
Residual	330,79	6	55,13			
Lack of Fit	329,55	5	65,91	53,48	0,1034	not significant
Pure Error	1,23	1	1,23			
Cor Total	5707,10	9				

Fit Statistics

Std. Dev.	7,43	**R^2**	0,9365
Mean	74,47	**Adjusted R^2**	0,9153
C.V. %	9,97	**Predicted R^2**	0,8370
		Adeq Precision	14,6407

3.3.4.7 Response surface model

Parameters:

- [**10a**]: 0.1 – 0.4 M
- Residence time: 10-30 min.

*The feed solutions were prepared in DMSO as solvent and the reactor was set at 30 °C for all the experiments. The concentration of **9a** was kept at 1.25 equiv with respect to **10a**, the 3DPA2FBN loading at 1 mol% and the amount of base at 1.5 equiv.*

Responses:

- Yield (%)
- Space-Time-Yield (mg mL^{-1} h^{-1})

Strategy:

- Central composite (face centered)

Run	[10a] (M)	t_R (min)	Conv (NMR) (%)	Yield (%)	STY (mg mL^{-1} h^{-1})
1	0.4	30	30.97%	26.98%	67.85
2	0.25	20	35.84%	30.82%	72.65
3	0.1	30	89.81%	71.95%	45.23
4	0.25	10	21.23%	17.19%	81.06
5	0.1	20	73.24%	68.76%	64.85
6	0.1	10	52.78%	44.25%	83.46
7	0.4	20	22.08%	19.10%	72.05
8	0.25	30	47.54%	39.16%	61.54
9	0.25	20	35.28%	30.75%	72.50
10	0.4	10	13.77%	11.02%	83.16

ANOVA for Quadratic model

Response 1: Yield

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	0,3801	5	0,0760	73,09	0,0005	significant
A-[10a]	0,2725	1	0,2725	261,94	< 0.0001	
B-Res. time	0,0718	1	0,0718	69,00	0,0011	
AB	0,0034	1	0,0034	3,31	0,1429	
A^2	0,0312	1	0,0312	30,00	0,0054	
B^2	0,0041	1	0,0041	3,95	0,1179	
Residual	0,0042	4	0,0010			
Lack of Fit	0,0042	3	0,0014	6841,90	0,0089	significant
Pure Error	2,027E-07	1	2,027E-07			
Cor Total	0,3843	9				

Fit Statistics

Std. Dev.	0,0323	**R^2**	0,9892
Mean	0,3600	**Adjusted R^2**	0,9756
C.V. %	8,96	**Predicted R^2**	0,8851
		Adeq Precision	25,8157

ANOVA for 2FI model

Response 2: STY

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	1165,94	3	388,65	55,04	< 0.0001	significant
A-[10a]	145,24	1	145,24	20,57	0,0040	
B-Res. time	889,41	1	889,41	125,95	< 0.0001	
AB	131,29	1	131,29	18,59	0,0050	
Residual	42,37	6	7,06			
Lack of Fit	42,36	5	8,47	751,97	0,0277	significant
Pure Error	0,0113	1	0,0113			
Cor Total	1208,31	9				

Fit Statistics

Std. Dev.	2,66	**R^2**	0,9649
Mean	70,43	**Adjusted R^2**	0,9474
C.V. %	3,77	**Predicted R^2**	0,8816
		Adeq Precision	21,3063

3.3.4.8 Difluoroamide 10a formation in flow

In a 10 mL volumetric flask, ethyl bromodifluoroacetate and α,α,α-trifluorotoluene (internal standard, 1.3 equiv.) are added. The flask is completed with DMSO to afford solution A.
In a 10 mL volumetric flask, benzylamine is added and the flask is completed with DMSO to afford solution B.

Solutions A and B are taken up in syringes and pumped through the flow setup at the required flow rate. After 1.5 residence time of equilibration, the stream is collected for 10 min. and the solution analyzed by ^{19}F NMR.

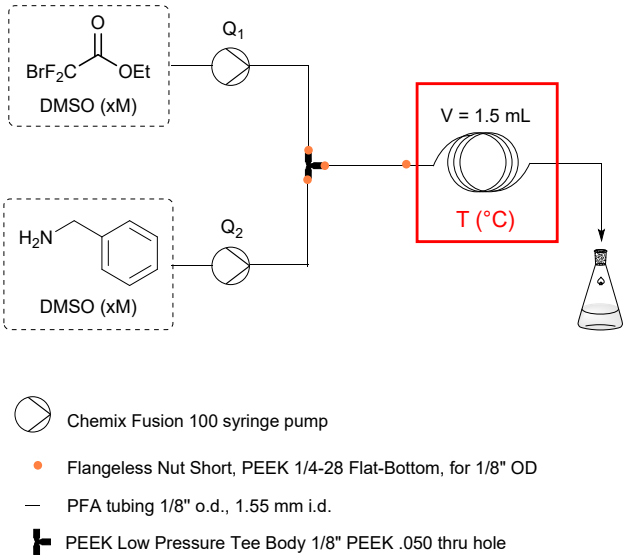


Figure S38. Diagram for the formation of Difluoroamide **10a** in flow

Entry	T (°C)	Residence time (min)	x (mol L^{-1})	Yield (%)
1	60	30	0.5	100
2		10		95
3		15		100
4	100		1	100
5			2	100
6	120	5	1	90
7		10		90

3.3.4.9 Large scale synthesis of 11a

In a 500 mL volumetric flask, 3-Methylindole **9a** (10.25 g, 78.1 mmol, 1.25 equiv.), N-benzyl-2-bromo-2,2-difluoroacetamide **10a** (16.5 g, 62.5 mmol, 1 equiv.), and 200 mL of DMSO are added. 3DPA2FBN (801 mg, 1.25 mmol, 0.02 equiv.), N,N-dimethyl-p-toluidine (13.6 mL, 93.8 mmol, 1.5 equiv.) and α,α,α-trifluorotoluene (internal standard, 10 mL, 81.2 mmol, 1.3 equiv.) are then added and the flask completed with DMSO. Argon is bubbled through the solution for 40 min. The solution mixture is pumped through the mid-scale flow reactor and irradiated with blue light (405 nm, T = 30 °C) at 1 mL min^{-1} with Asia syringe pump. After 30 min. equilibration, the stream was collected for 6 hours in a flask protected from light.

The reaction was monitored every hour by collecting the stream for 15 s, diluting in DMSO-d_6 and recording ^{19}F NMR.

Water (300 mL) was added to the collection flask and the aqueous layer was extracted with iPrOAc (3x300 mL). The organic layers were combined, washed with water (900 mL), HCl 1N (900 mL), brine (900 mL), dried over sodium sulfate, filtered and evaporated to dryness. The crude was purified by chromatography (SiO_2, AcOEt/cHexane 90/10 to 75/25 in 40 min.) to afford compound **11a** (6.48 g, 20.6 mmol, yield = 46%) as a white oil.

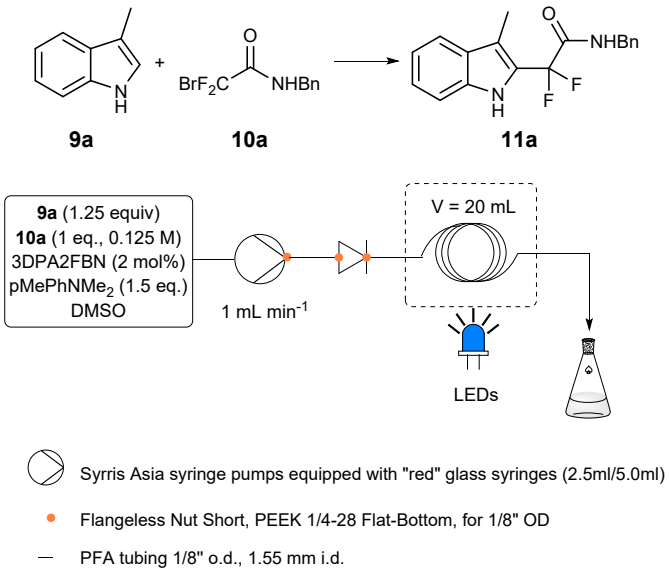


Figure S39. Diagram for the large formation of **11a** in flow

3.3.4.10 General procedure for the synthesis of compounds 11

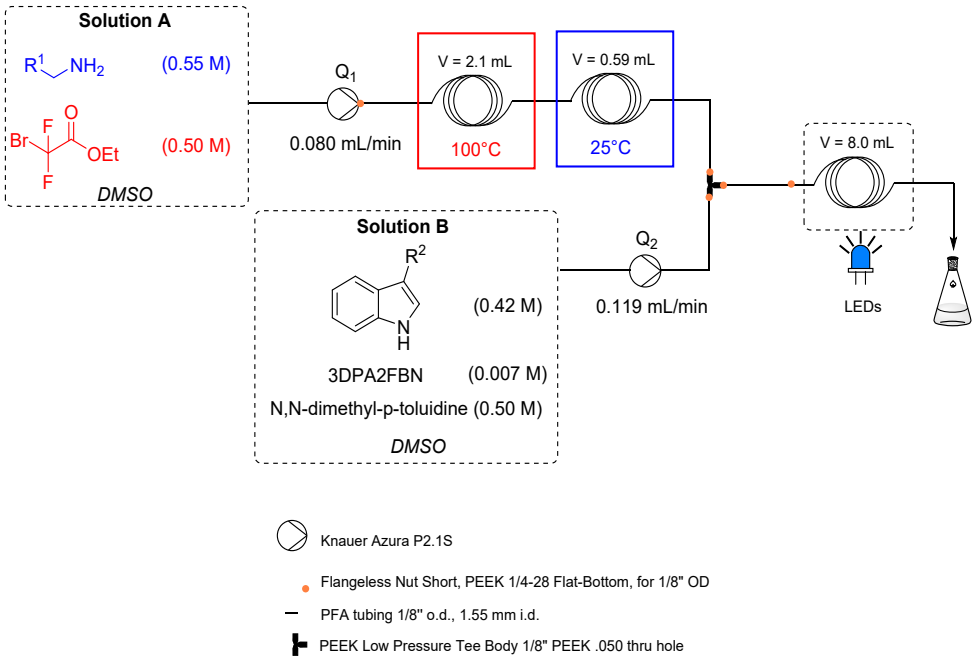


Figure S40. Diagram for the synthesis of compounds **11**

A solution of amine (1.1 equiv., 0.55 M) and ethyl 2-bromo-2,2-difluoroacetate (1.0 equiv., 0.50 M) in DMSO was pumped at 0.080 mL min^{-1} in a reactor heated at 100 °C. The exit feed was cooled down with a cooling loop plunged in a water bath at room temperature. A solution of indole (1.25 equiv. 0.42 M), 3DPA2FBN (2 mol%, 0.007 M) and N,N-dimethyl-p-toluidine (1.5 equiv., 0.50 M) in DMSO was pumped at 0.119 mL min^{-1} and mixed with the exit feed from the first step. The resulting solution was pumped through the photoreactor irradiated at 405 nm. The setup was equilibrated for 110 min and collected for 10 min into a vial at room temperature. The collected fraction was diluted with water (5 mL) and the layers separated. The aqueous layer was extracted with *i*-PrOAc (3x3 mL). The combined organic layers were washed with brine (3x5 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography to afford compound **11**.

N-(2-{2-[(benzylcarbamoyl)difluoromethyl)-2-(3-methyl-1H-indol-2-yl)acetamide (11a)
Benzylamine (**13a**) and 3-methylindole (**9a**) were used. **11a** was purified by flash chromatography on SiO_2 (Cyclohexane/EtOAc 100:0 to 0:100).
Isolated as a white oil in 30% yield.
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.87 (s_{br}, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.41-7.31 (m, 4H), 7.28 (m, 3H), 7.16 (t, *J* = 7.5 Hz, 1H), 6.84 (s_{br}, 1H), 4.55 (d, *J* = 5.8 Hz, 2H), 2.43 (t, *J* = 2.8 Hz, 3H) ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 163.9 (t, *J* = 31.05 Hz), 136.5, 135.9, 129.1, 128.4, 128.3, 128.1, 124.3, 123.5 (*J* = 29.7 Hz), 120.1, 119.8, 113.6, 112.6 (t, *J* = 250.7 Hz), 111.7, 43.9, 8.9 ppm.

N-(2,2-dimethoxyethyl)-2,2-difluoro-2-(3-methyl-1H-indol-2-yl)acetamide (11b)
2,2-dimethoxyethylamine (**13b**) and 3-methylindole (**9a**) were used. **11b** was purified by flash chromatography on SiO_2 (Cyclohexane/EtOAc 100:0 to 0:100).
Isolated as a yellow solid in 30% yield.
^{1}H NMR (400 MHz, DMSO-d6): δ 11.34 (s, 1H), 9.01 (s_{br}, 1H), 7.57 (d, *J* = 7.4 Hz, 1H), 7.40 (d, *J* = 8.3 Hz, 1H), 7.19 (t, *J* = 7.4 Hz, 1H), 7.05 (t, *J* = 8.3 Hz, 1H), 4.49 (t, J = 5.5 Hz, 1H), 3.32-3.21 (m, 8H), 2.32-2.26 (m, 3H) ppm.
^{13}C NMR (100 MHz, DMSO-d6): δ 162.8 (t, *J* = 31.5 Hz), 135.5, 127.8, 124.7, 123.2, 119.2, 119.1, 115.5, 113.0, 111.9, 110.6, 101.2, 53.4, 40.8, 40.0 (t, *J* = 22.1 Hz), 8.2 ppm.
^{19}F NMR (376 MHz, DMSO-d6): δ -47.43 ppm.
HRMS: expected: 311.1207 [M-H]- found: 311.1205 [M-H]-

Tert-butyl N-(2-{2-[(benzylcarbamoyl)difluoromethyl]-1H-indol-3-yl}ethyl)carbamate (11c)
Benzylamine (**13a**) and tert-butyl N-[2-(1H-indol-3-yl)ethyl]carbamate (**9b**) were used. **11c** was purified by flash chromatography on C18 (H_2O/MeCN 99:1 to 0:100).
Isolated as an orange oil in 35% yield.

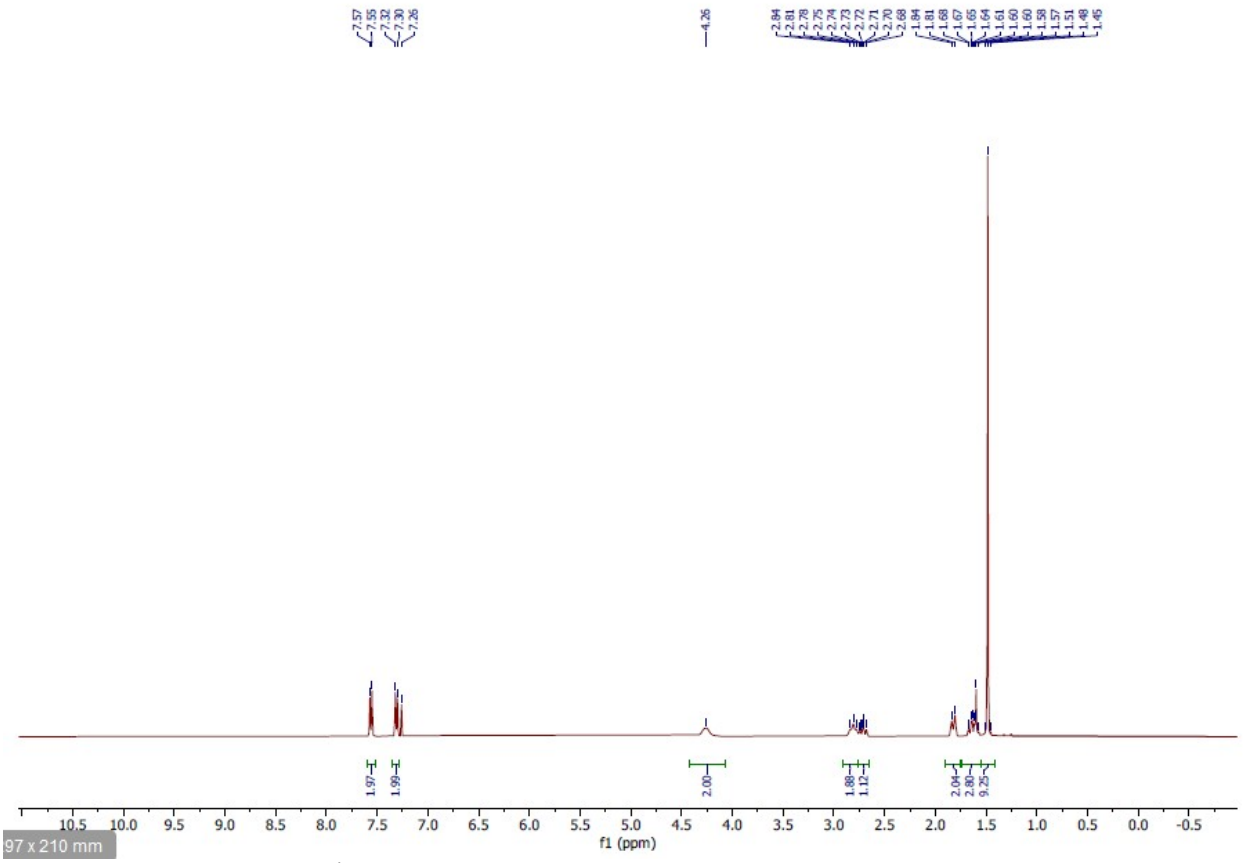
^{1}H NMR (400 MHz, DMSO-d6): δ 11.42 (s, 1H), 9.44 (s_{br}, 1H), 7.64 (d, J = 7.5 Hz, 1H), 7.41 (d, J = 8.1 Hz, 1H), 7.37-7.15 (m, 6H), 7.07 (t, J = 7.6 Hz, 1H), 6.91-6.82 (m, 1H), 4.39 (d, *J* = 6.3 Hz, 2H), 3.14-3.03 (m, 2H), 2.96-2.86 (m, 2H), 1.41-1.30 (m, 9H) ppm.
^{13}C NMR (100 MHz, DMSO-d6): δ 163.2 (t, *J* = 30.3 Hz), 156.1, 138.7, 136.2, 128.8, 128.6, 128.0, 127.7, 127.3, 124.1, 123.7, 119.9, 119.8, 113.6, 112.5, 78.0, 45.7, 43.0, 41.7, 40.4 (t, *J* = 23.8 Hz), 28.7, 24.7 ppm.
^{19}F NMR (376 MHz, DMSO-d6): δ -97.17 ppm.
HRMS: expected: 440.1997 [M-H]- found: 440.2000 [M-H]-

Tert-butyl N-[2-(2-{[(2,2-dimethoxyethyl)carbamoyl]difluoromethyl}-1H-indol-3-yl)ethyl] carbamate (11d)

2,2-dimethoxyethylamine (**13b**) and tert-butyl N-[2-(1H-indol-3-yl)ethyl]carbamate (**9b**) were used. **11d** was purified by flash chromatography on SiO_2 (Cyclohexane/EtOAc 100:0 to 0:100). Isolated as an orange solid in 20% yield.
^{1}H NMR (400 MHz, DMSO-d6): δ 11.40 (s, 1H), 8.94 (s_{br}, 1H), 7.64 (d, *J* = 7.8 Hz, 1H), 7.41 (d, *J* = 8.1 Hz, 1H), 7.20 (t, *J* = 7.3 Hz, 1H), 7.07 (t, *J* = 7.2 Hz), 6.93-6.82 (m, 1H), 4.50 (t, *J* = 6.2 Hz, 1H), 3.37-3.21 (m, 8H), 3.16-3.04 (m, 2H), 2.97-2.86 (m, 2H), 1.42-1.29 (m, 9H) ppm.
^{13}C NMR (100 MHz, DMSO-d6): δ 163.3 (t, *J* = 30.3 Hz), 156.1, 136.1, 128.0, 125.4 (t, *J* = 28.5 Hz), 123.7, 119.9, 119.8, 115.9, 113.6, 112.5, 101.7, 78.0, 53.7, 41.7, 41.3, 40.5 (t, *J* = 20.9 Hz), 28.7, 24.7 ppm.
^{19}F NMR (376 MHz, DMSO-d6): δ -97.12 ppm.
HRMS: expected: 442.2099 [M-H]- found: 440.1943 [M-H]-

4. NMR Spectra for isolated compounds

Tert-butyl 4-[4-(trifluoromethyl)phenyl]piperidine-1-carboxylate (8a)



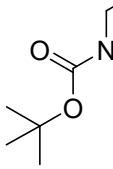


Figure S41. ^{1}H NMR spectrum in $CDCl_3$, 400 MHz, of compound **8a**

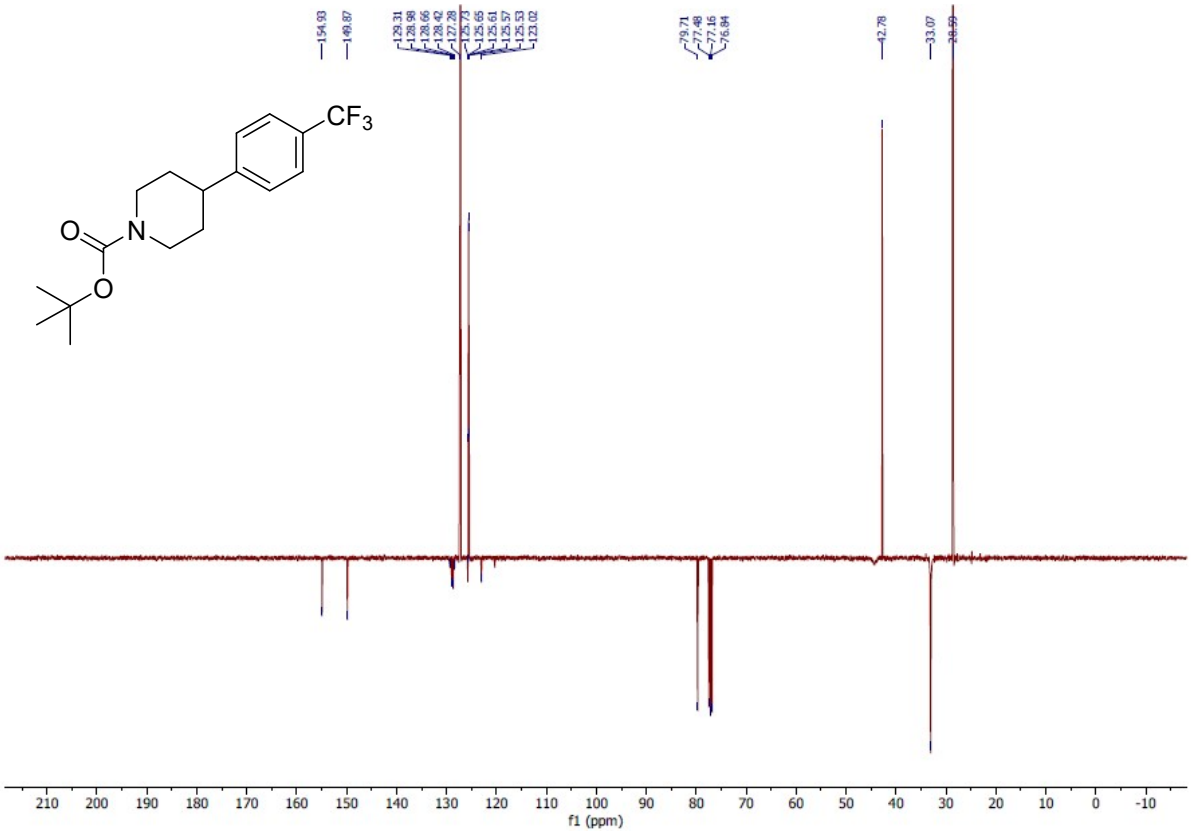


Figure S42. ^{13}C NMR DEPT135 spectrum in $CDCl_3$, 100 MHz, of compound **8a**

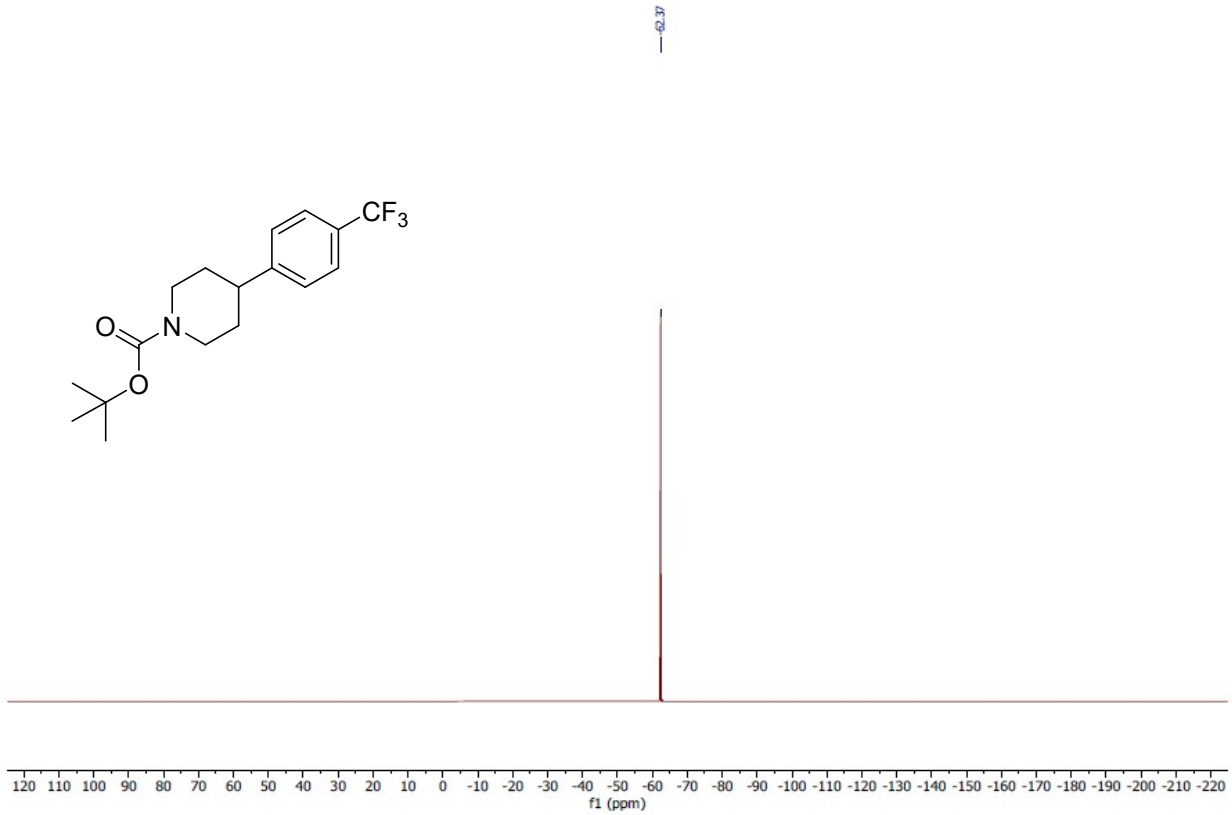


Figure S43. ^{19}F NMR spectrum in $CDCl_3$, 376 MHz, of compound **8a**

Tert-butyl 3-[4-(trifluoromethyl)phenyl]azetidine-1-carboxylate (8c)

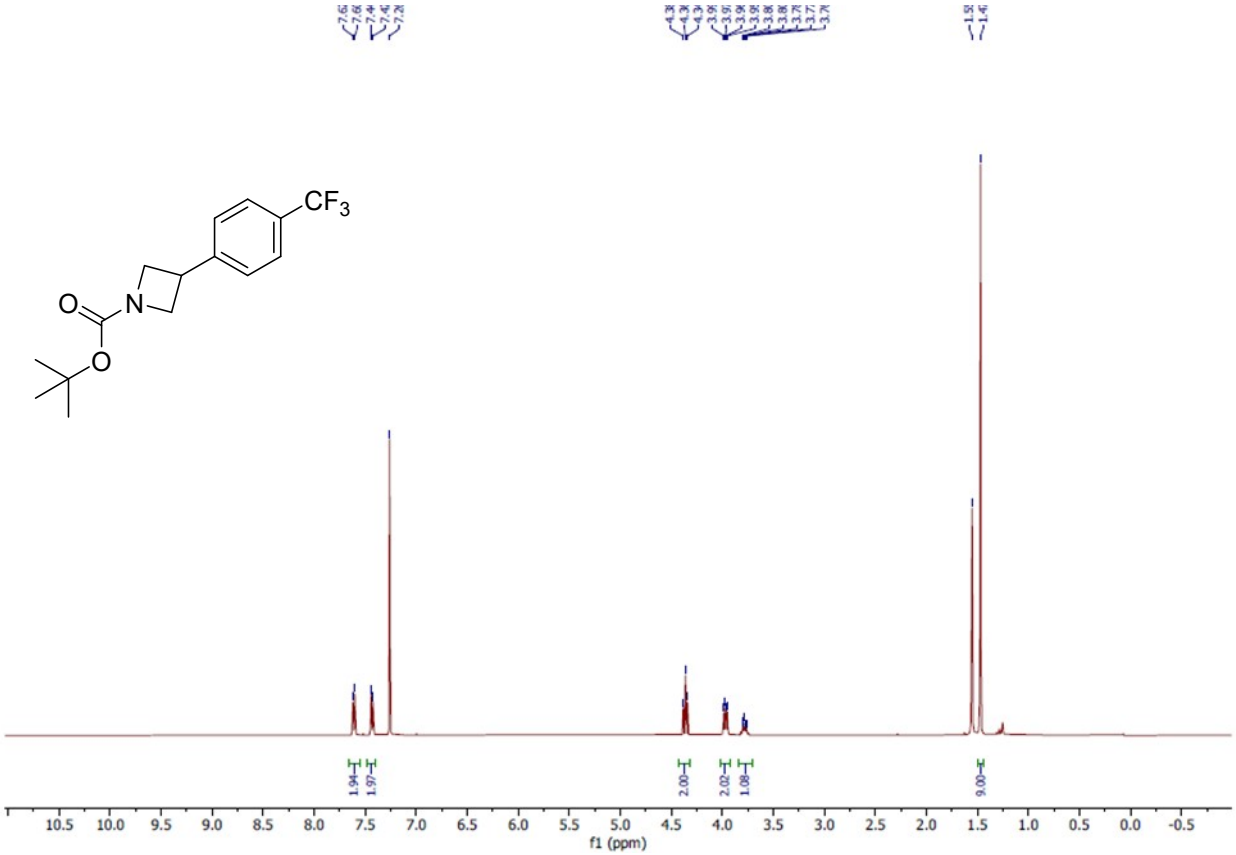


Figure S44. ^{1}H NMR spectrum in $CDCl_3$, 400 MHz, of compound **8c**

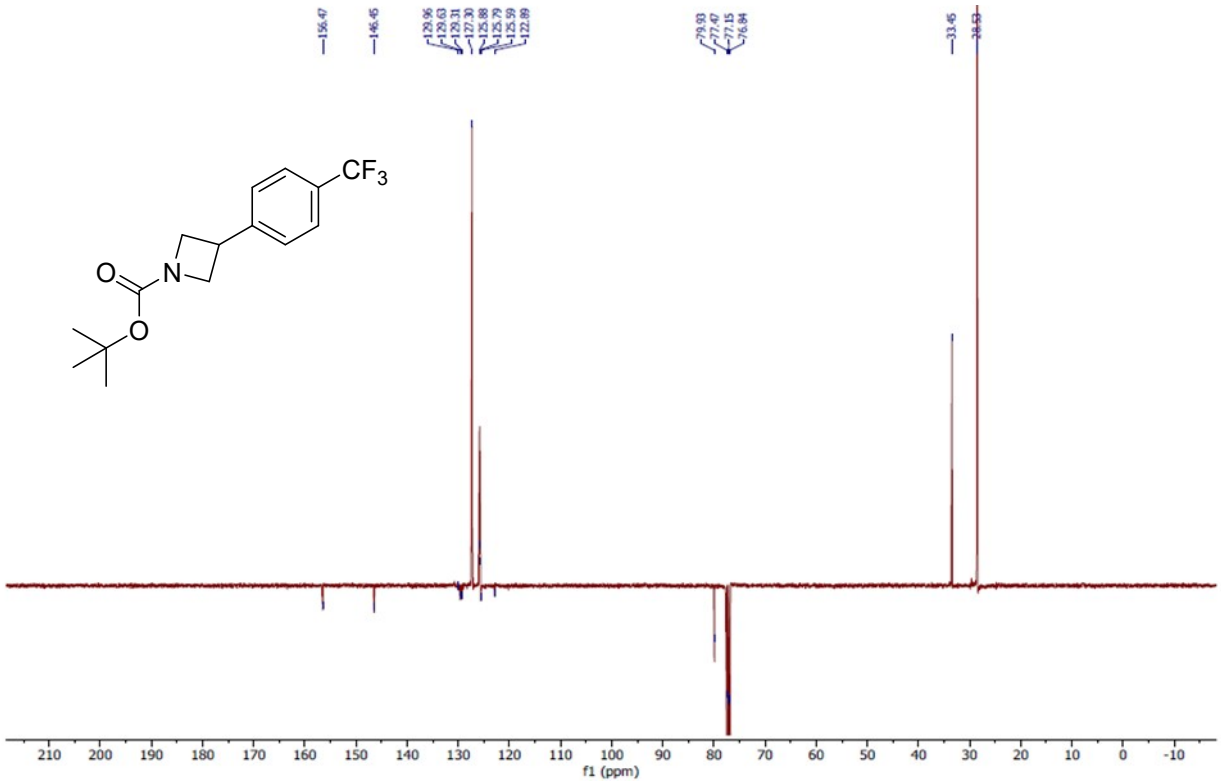


Figure S45. ^{13}C NMR DEPT135 spectrum in $CDCl_3$, 100 MHz, of compound **8c**

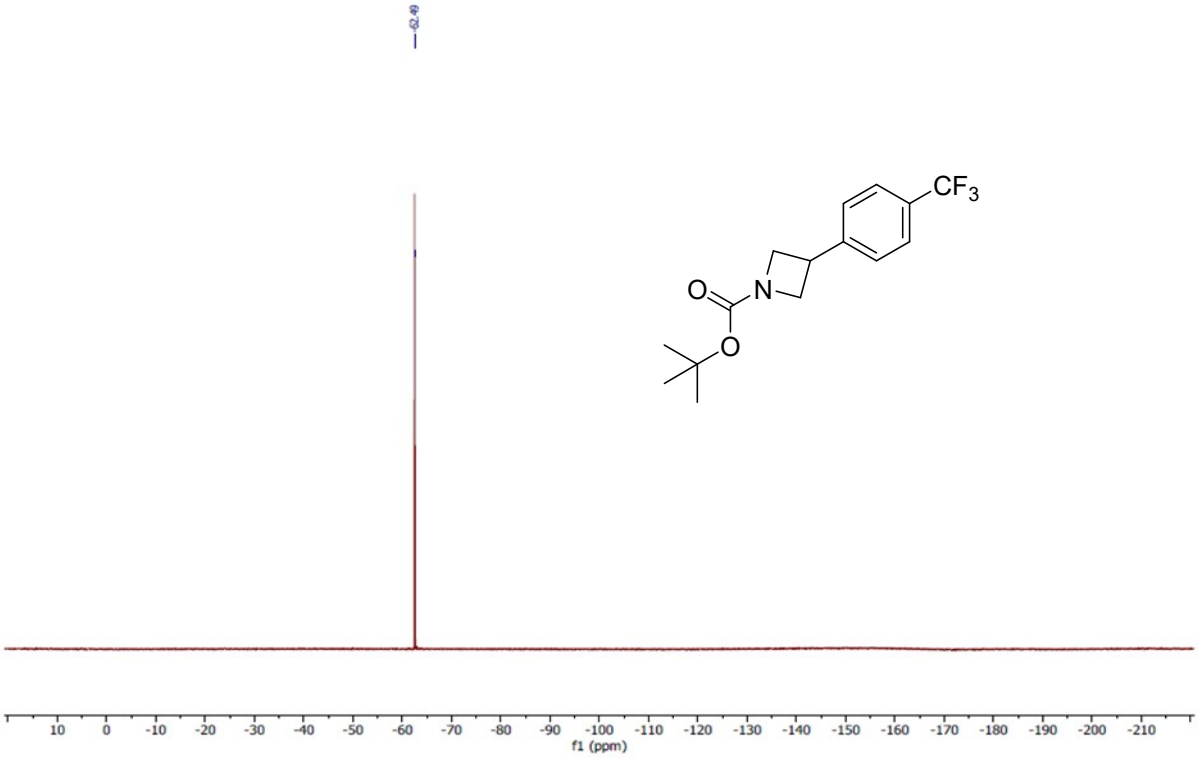


Figure S46. ^{19}F NMR spectrum in $CDCl_3$, 376 MHz, of compound **8c**

Tert-butyl 3-{[4-(trifluoromethyl)phenyl]methyl}azetidine-1-carboxylate (8d)

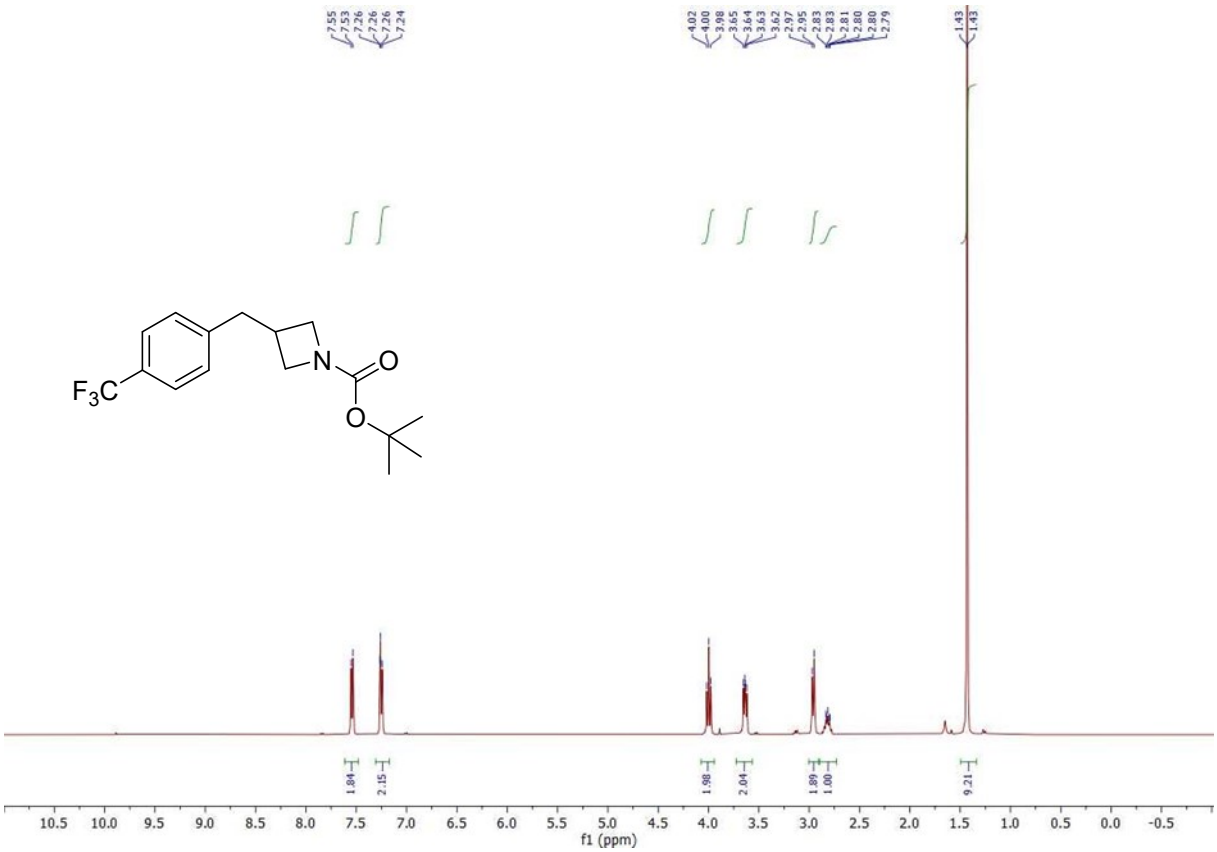


Figure S47. ^{1}H NMR spectrum in $CDCl_3$, 400 MHz, of compound **8d**

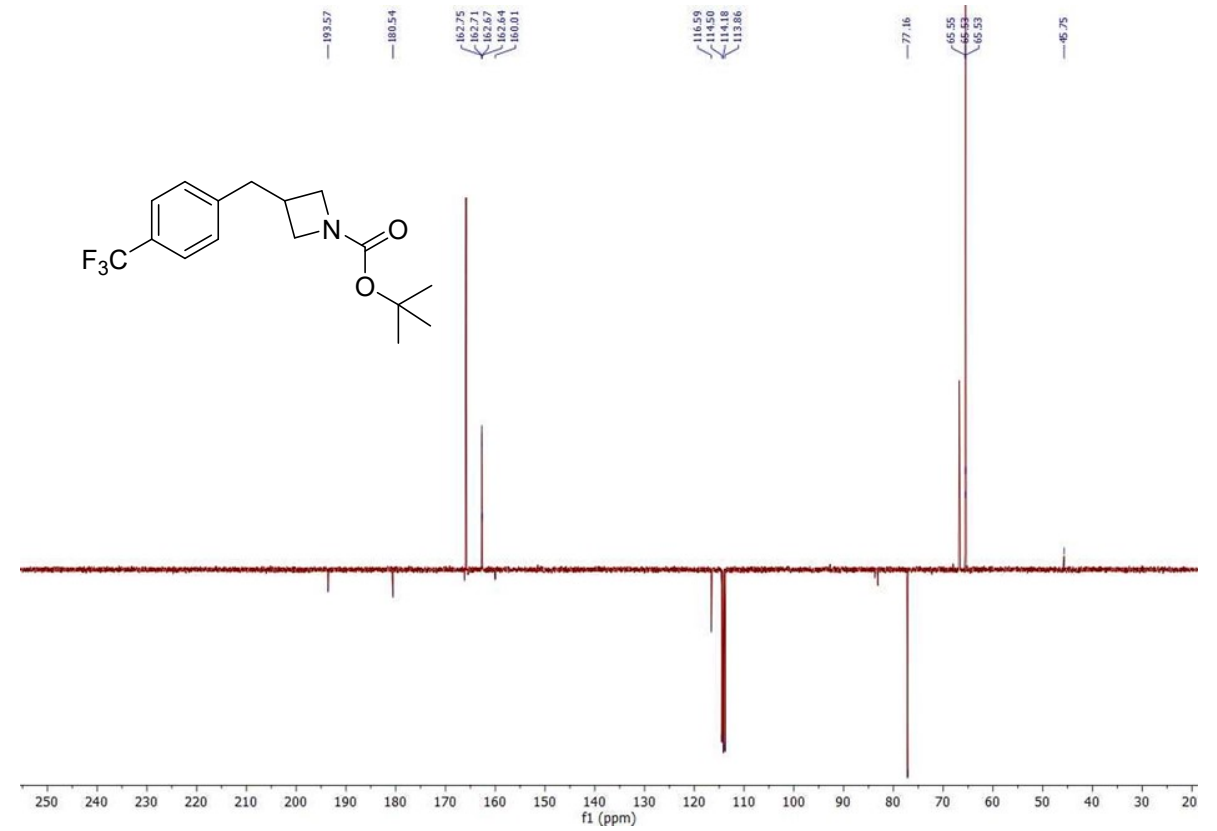


Figure S48. ^{13}C NMR DEPT135 spectrum in $CDCl_3$, 100 MHz, of compound **8d**

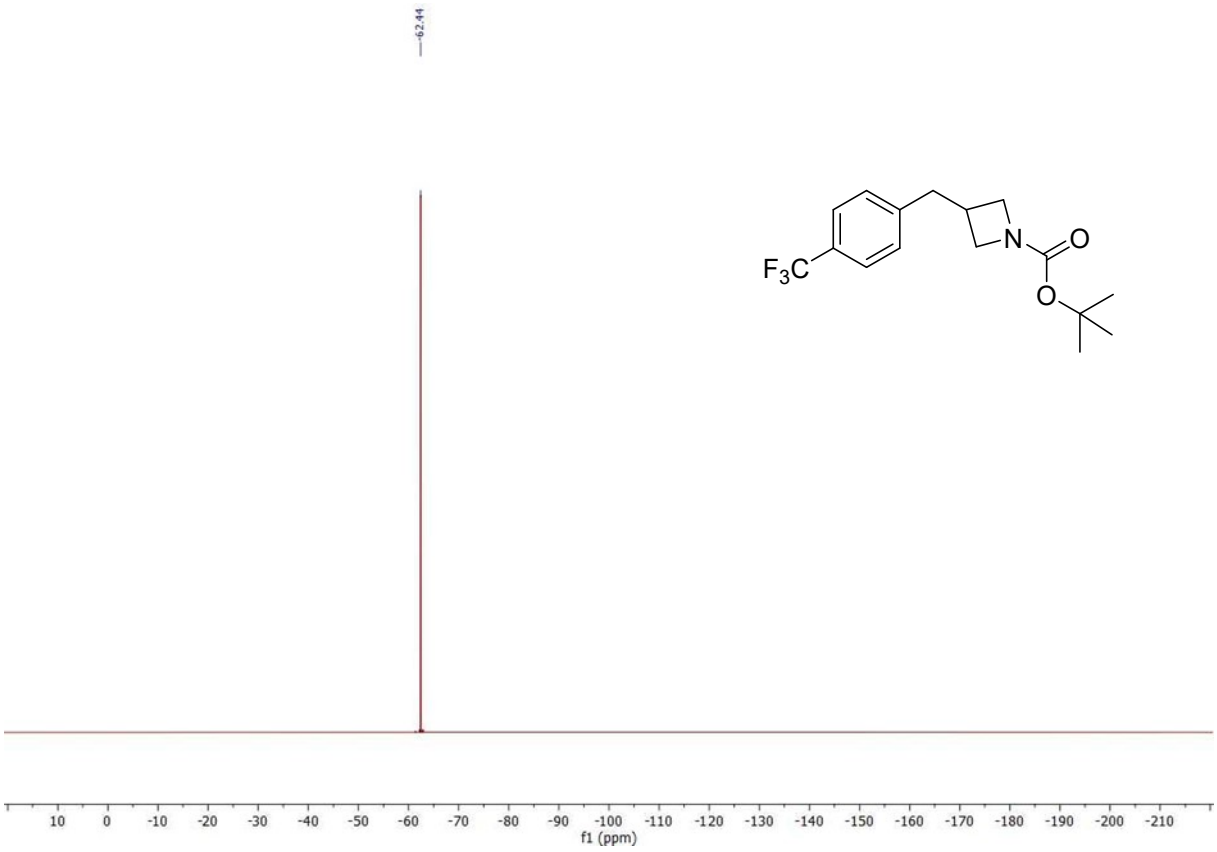


Figure S49. ^{19}F NMR spectrum in $CDCl_3$, 376 MHz, of compound **8d**

Tert-butyl 3-(6-cyanopyridin-3-yl)azetidine-1-carboxylate (8e)

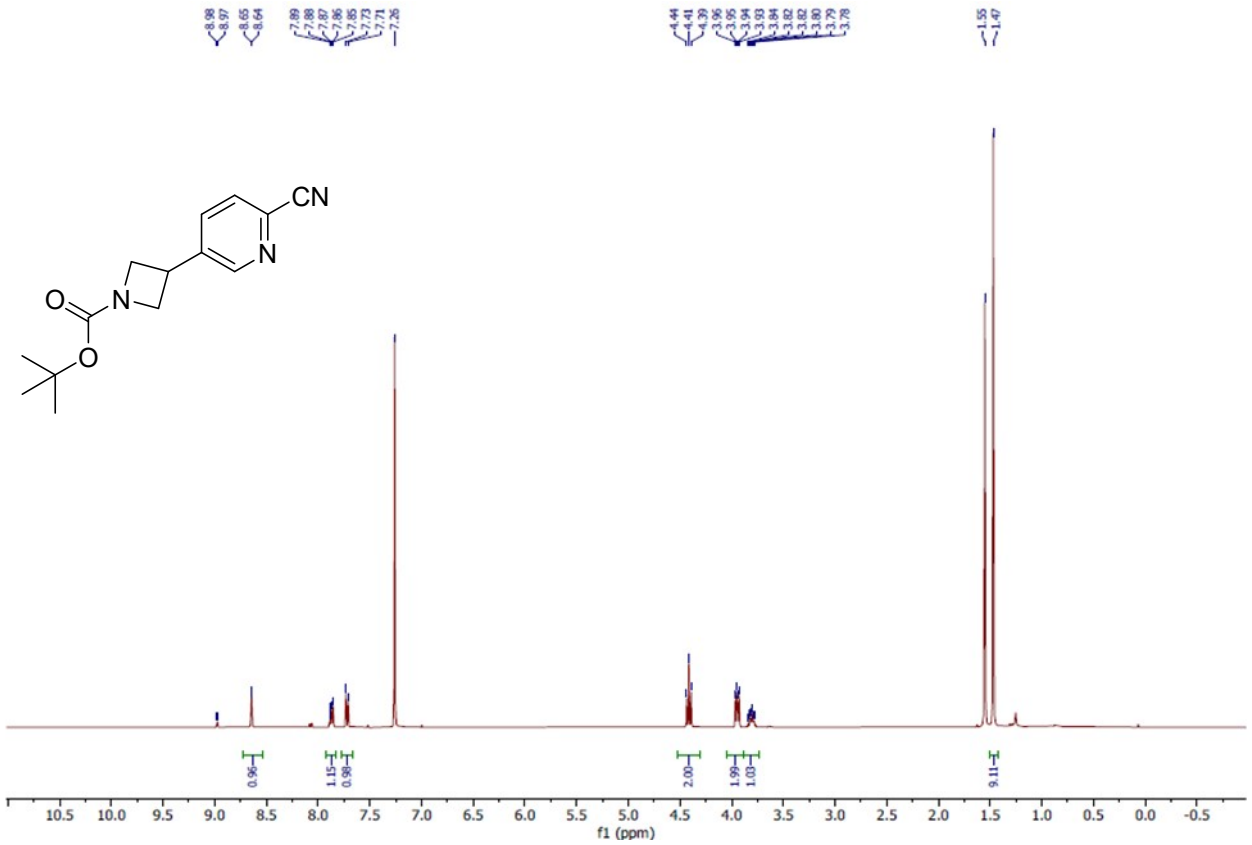


Figure S50. ^{1}H NMR spectrum in $CDCl_3$, 400 MHz, of compound **8e**

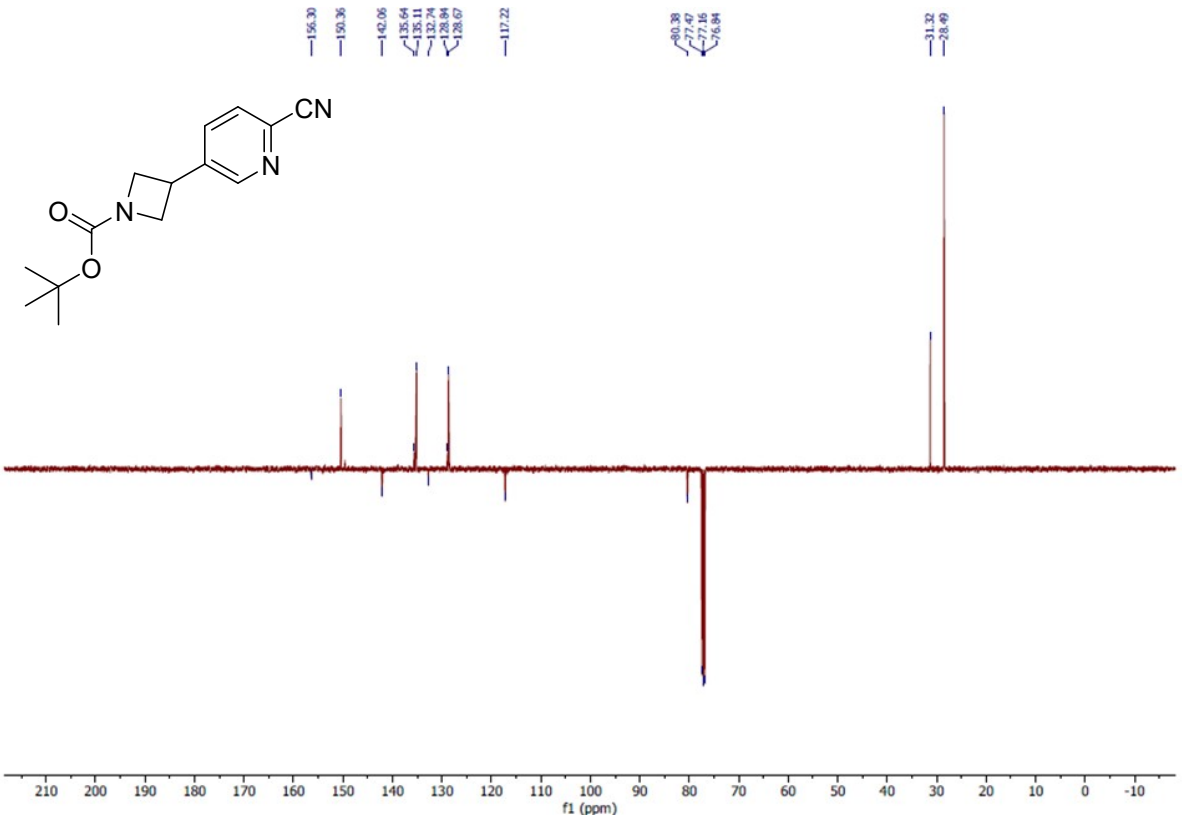


Figure S51. ^{13}C NMR DEPT135 spectrum in $CDCl_3$, 100 MHz, of compound **8e**

Tert-butyl 4-(thiophen-3-yl)piperidine-1-carboxylate (8f)

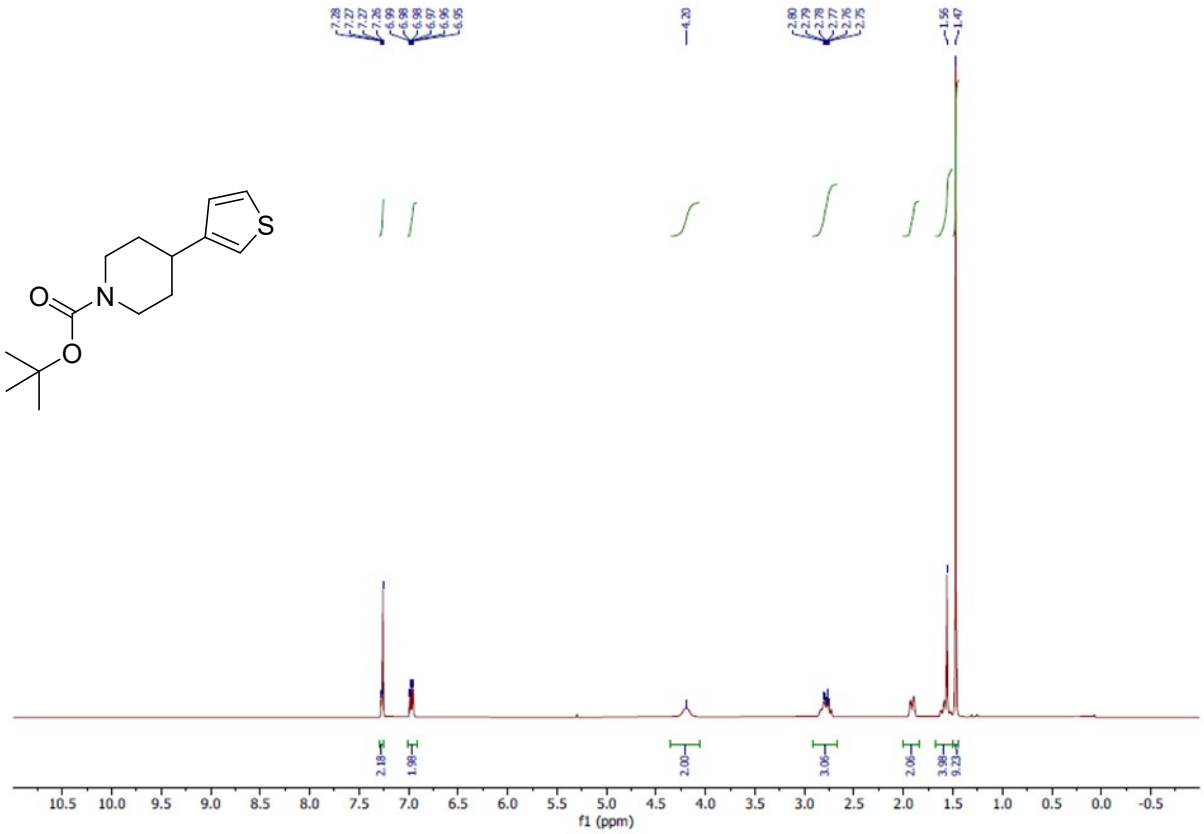


Figure S52. ^{1}H NMR spectrum in $CDCl_3$, 400 MHz, of compound **8f**

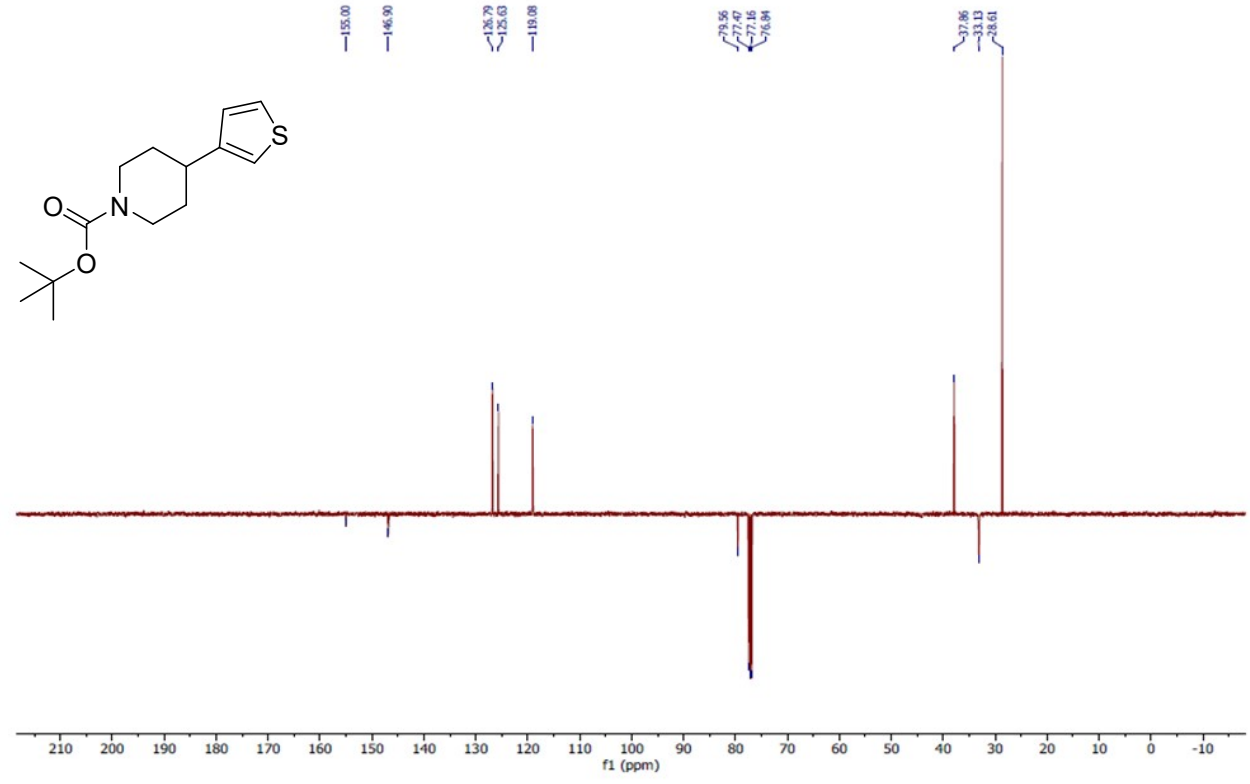


Figure S53. ^{13}C NMR DEPT135 spectrum in $CDCl_3$, 100 MHz, of compound **8f**

Tert-butyl 3-(thiophen-3-yl)azetidine-1-carboxylate (8g)

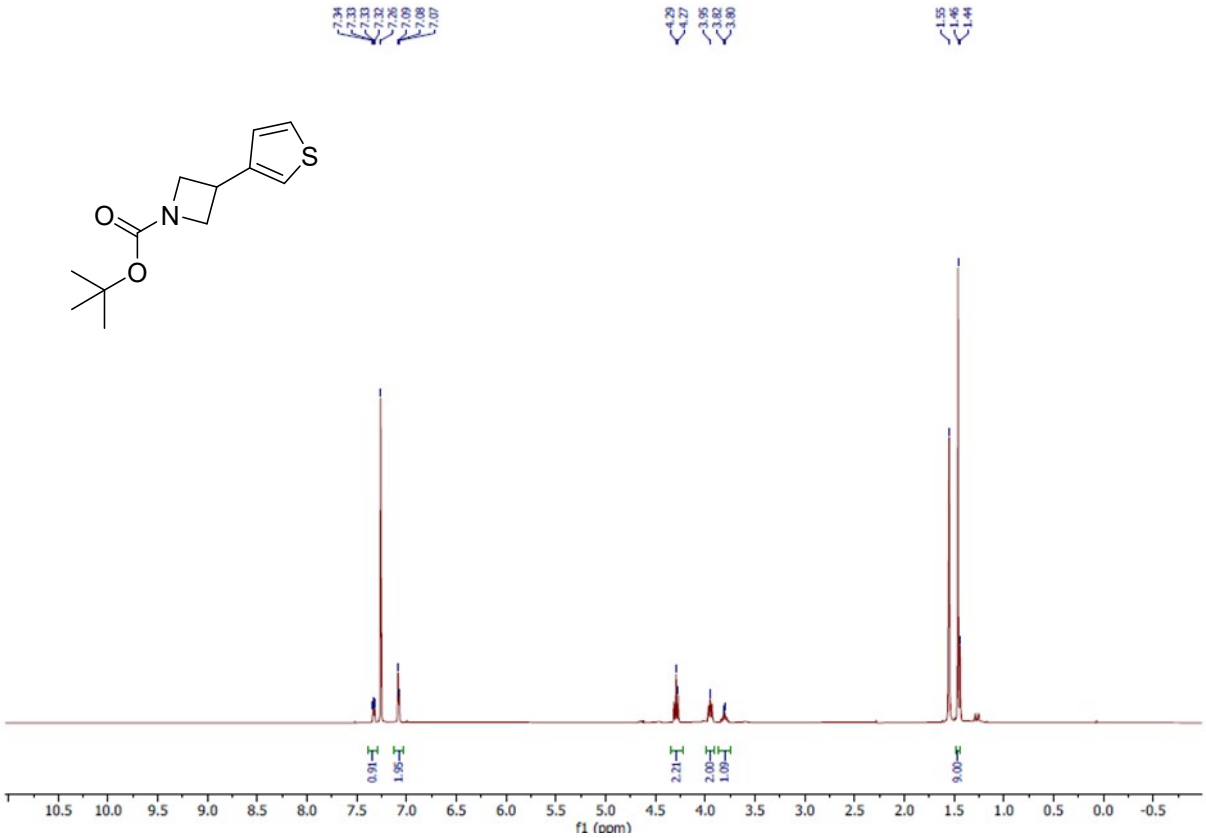


Figure S54. ^{1}H NMR spectrum in $CDCl_3$, 400 MHz, of compound **8g**

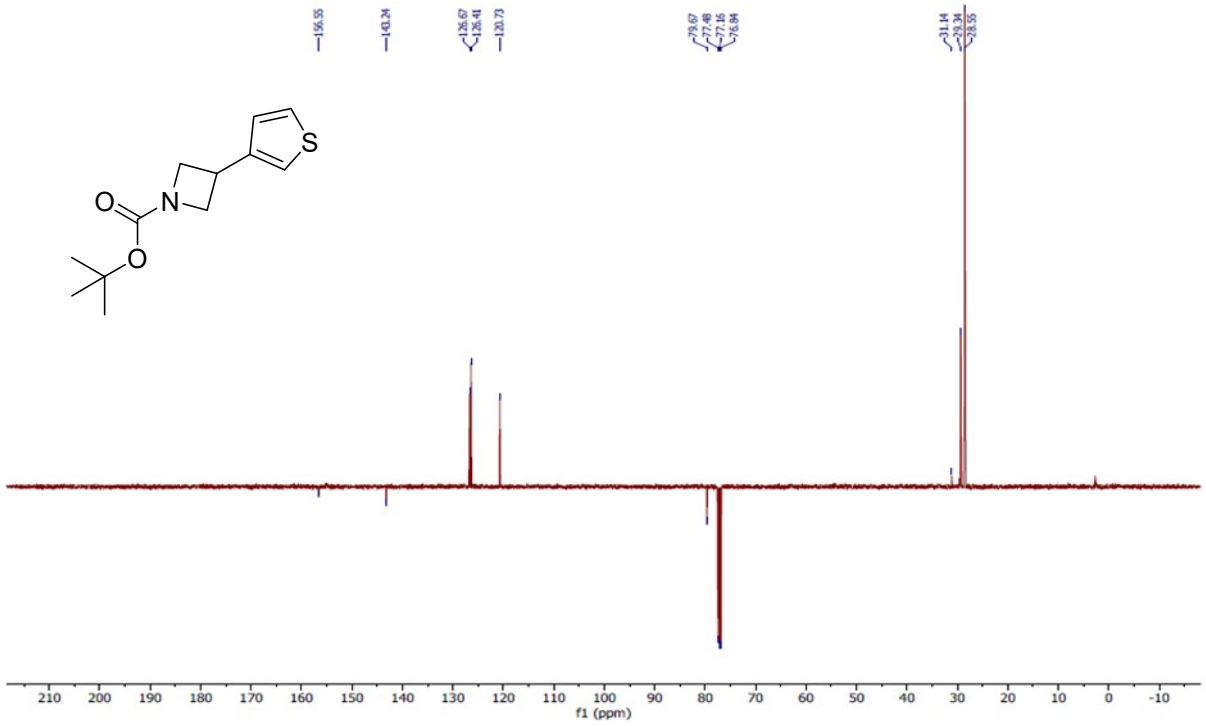


Figure S55. ^{13}C NMR DEPT135 spectrum in $CDCl_3$, 100 MHz, of compound **8g**

Tert-butyl 4-(pyrimidin-5-yl)piperidine-1-carboxylate (8h)

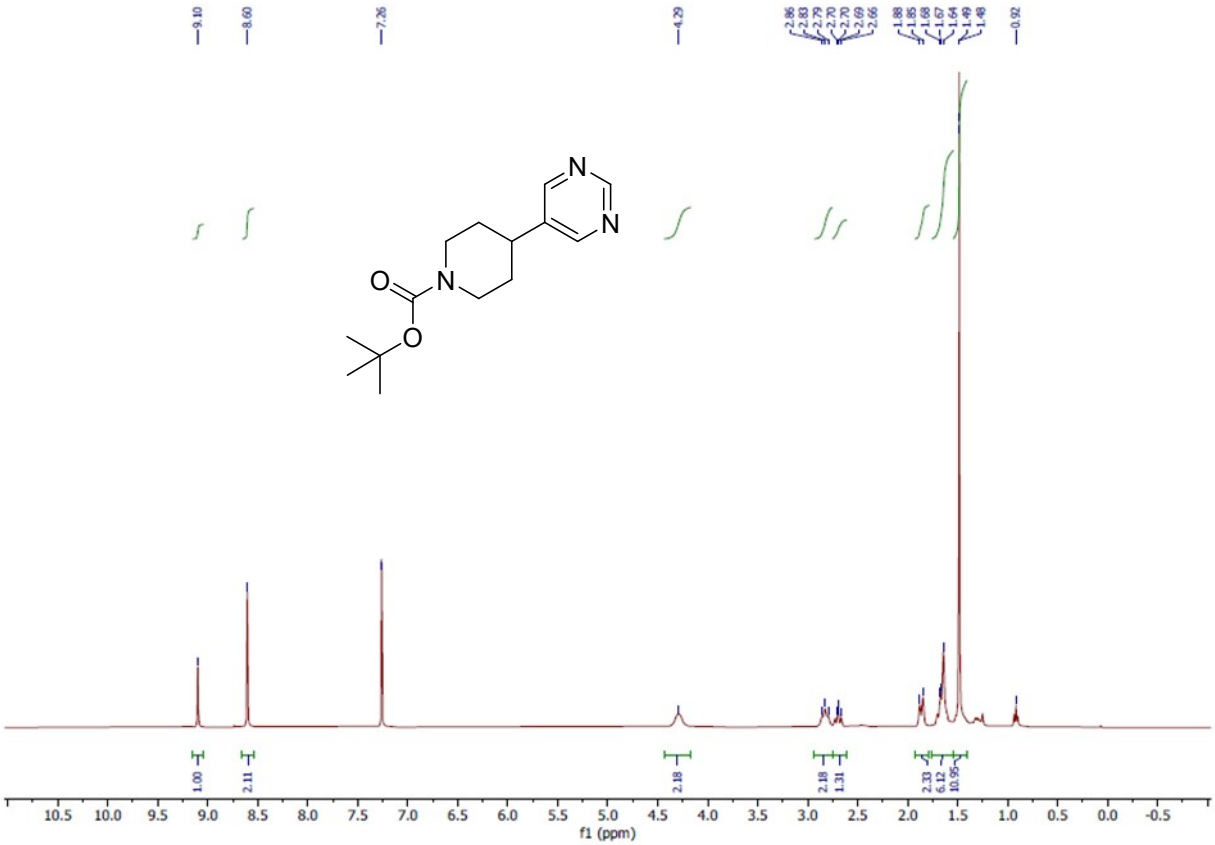


Figure S56. ^{1}H NMR spectrum in $CDCl_3$, 400 MHz, of compound **8h**

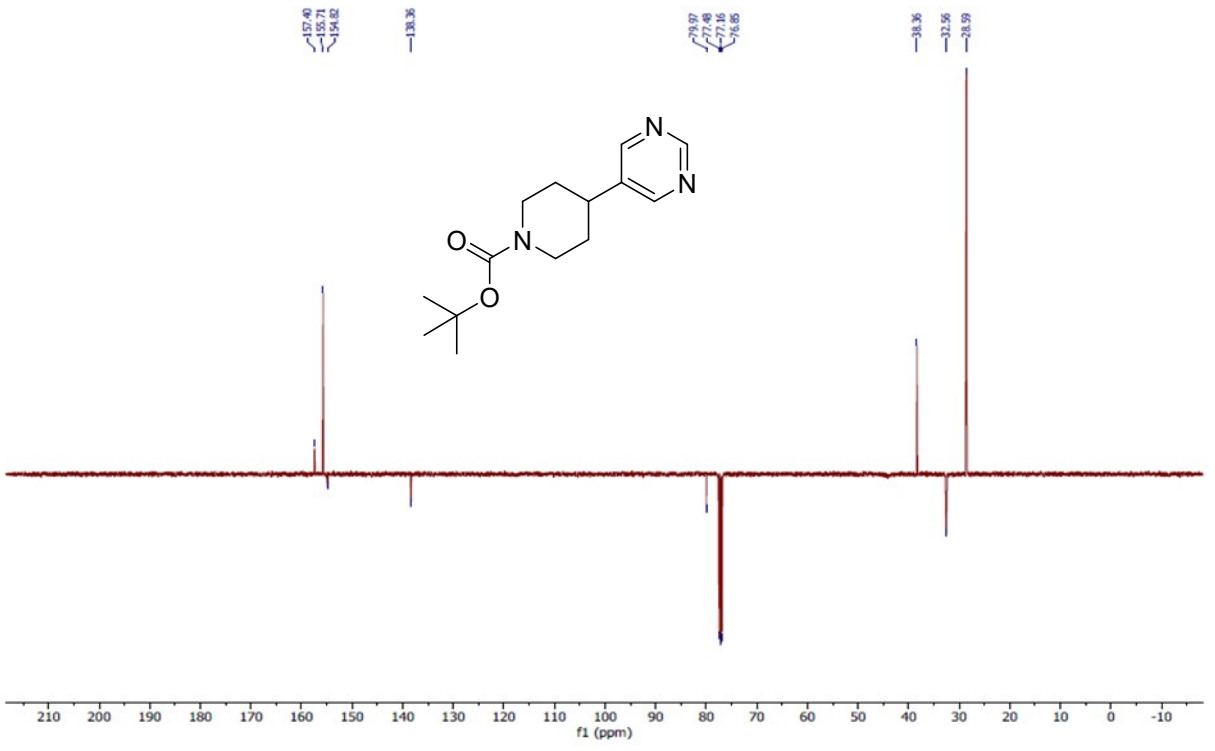


Figure S57. ^{13}C NMR DEPT135 spectrum in $CDCl_3$, 100 MHz, of compound **8h**

N-(2-{2-[(benzylcarbamoyl)difluoromethyl)-2-(3-methyl-1H-indol-2-yl)acetamide (11a)

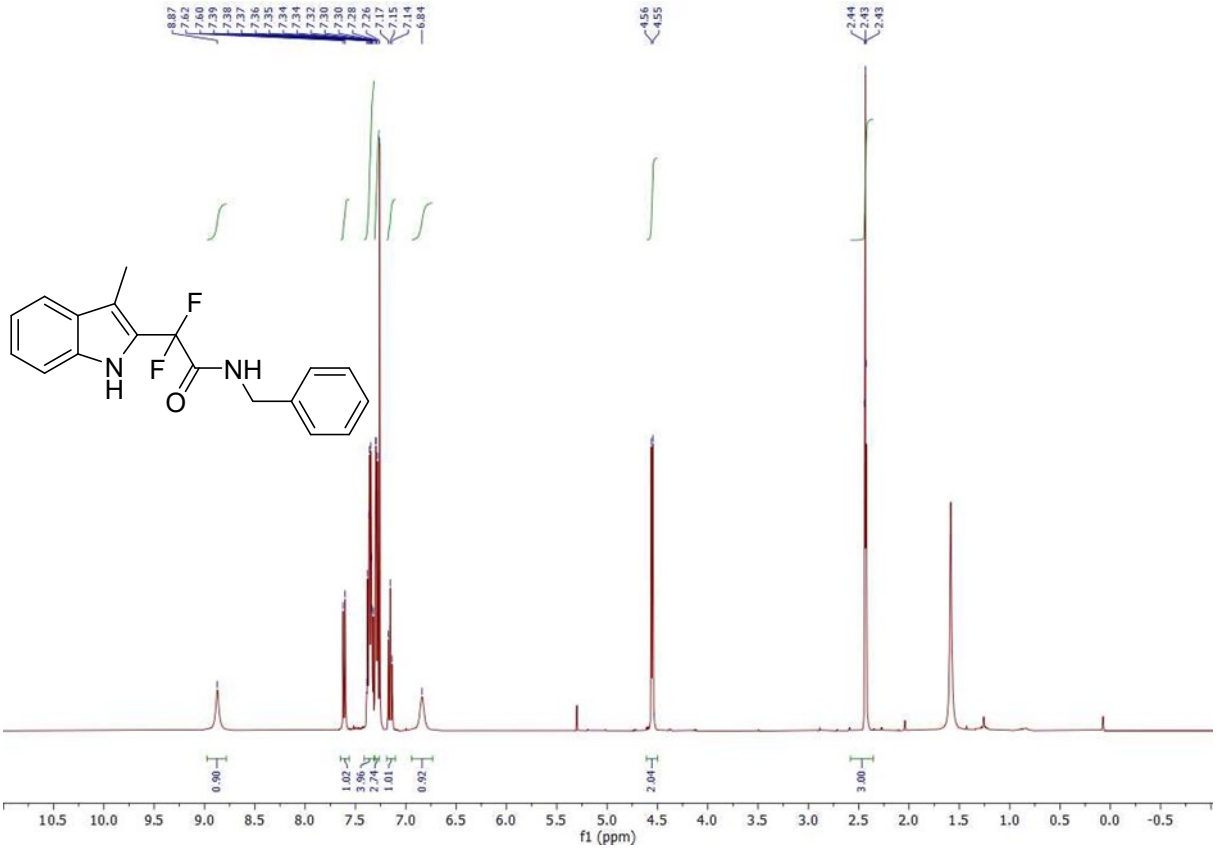


Figure S58. ^{1}H NMR spectrum in $CDCl_3$, 400 MHz, of compound **11a**

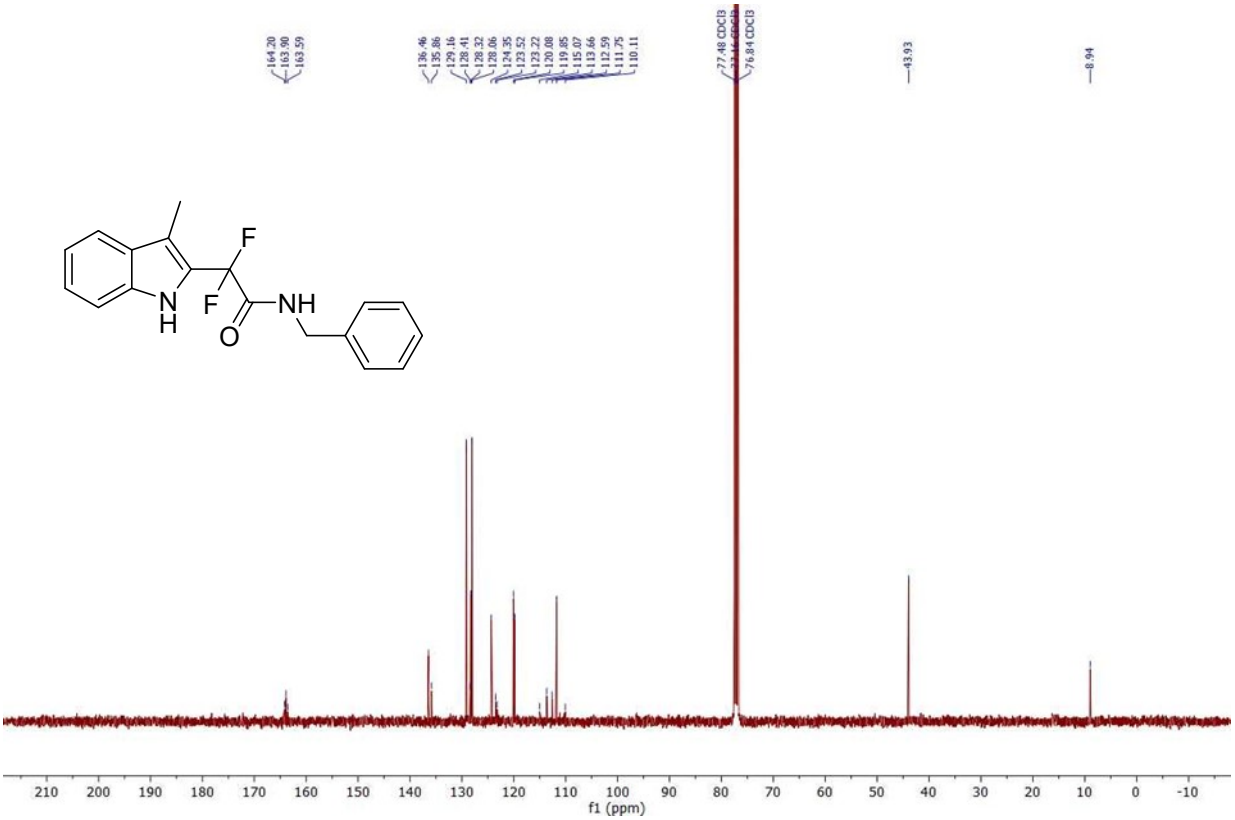


Figure S59. ^{13}C NMR APT spectrum in DMSO-d6, 400 MHz, of compound **11a**

N-(2,2-dimethoxyethyl)-2,2-difluoro-2-(3-methyl-1H-indol-2-yl)acetamide (11b)

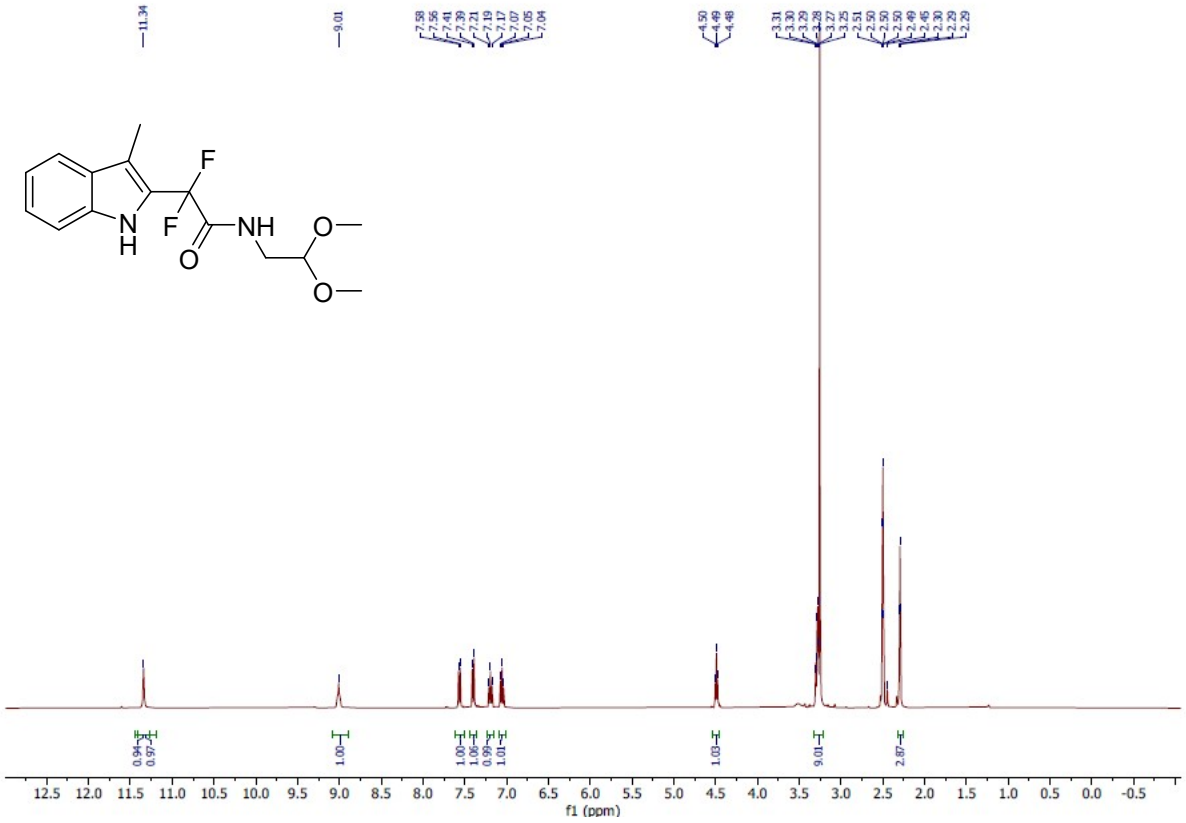
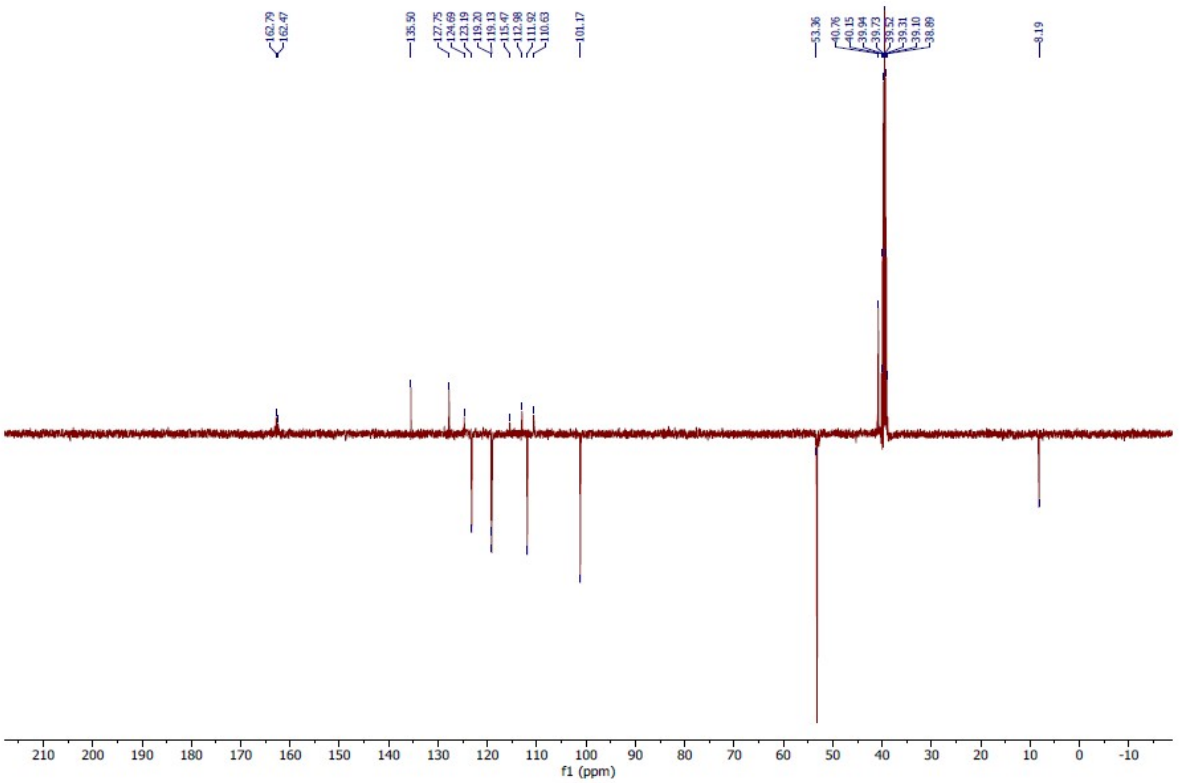


Figure S60. ^{1}H NMR spectrum in DMSO-d6, 400 MHz, of compound **11b**



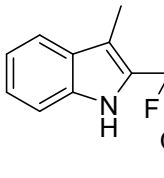


Figure S61. ^{13}C NMR DEPT135 spectrum in DMSO-d6, 100 MHz, of compound **11b**

Tert-butyl N-(2-{2-[(benzylcarbamoyl)difluoromethyl]-1H-indol-3-yl}ethyl)carbamate (11c)

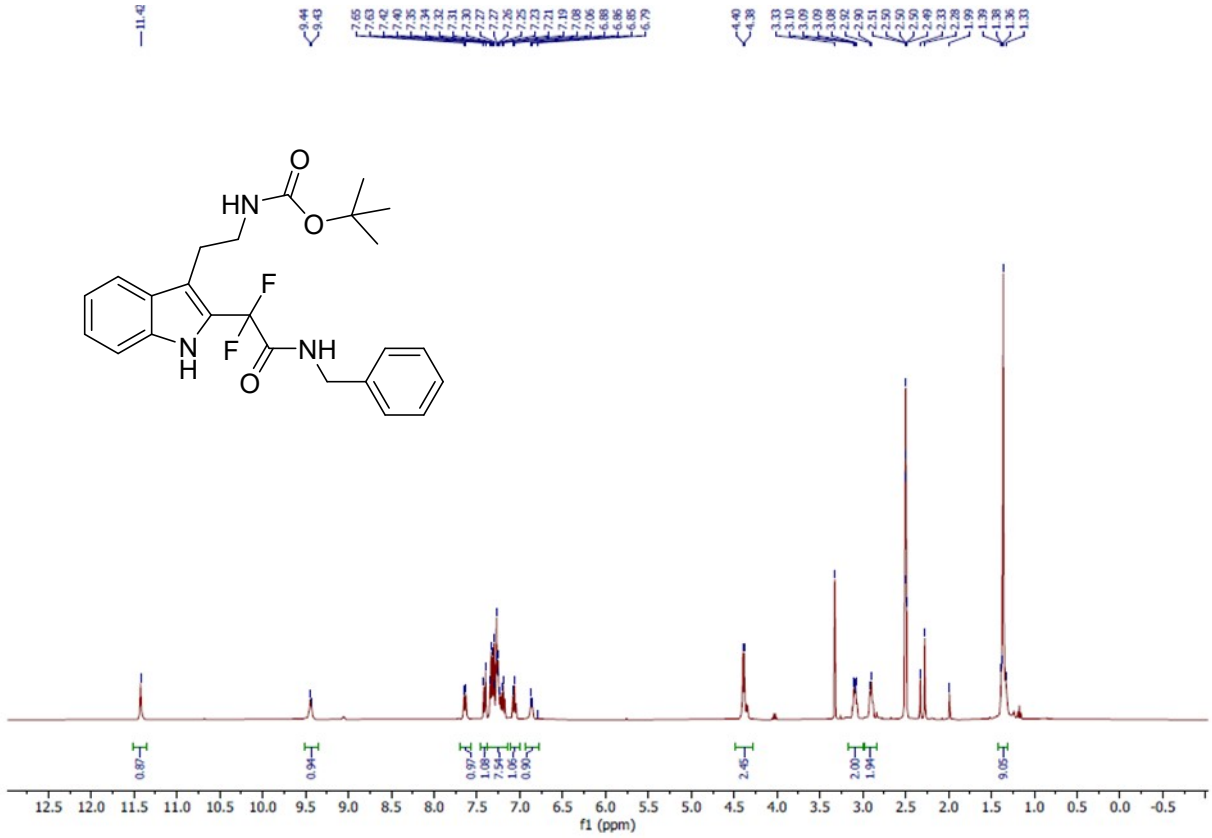


Figure S62. ^{1}H NMR spectrum in DMSO-d6, 400 MHz, of compound **11c**

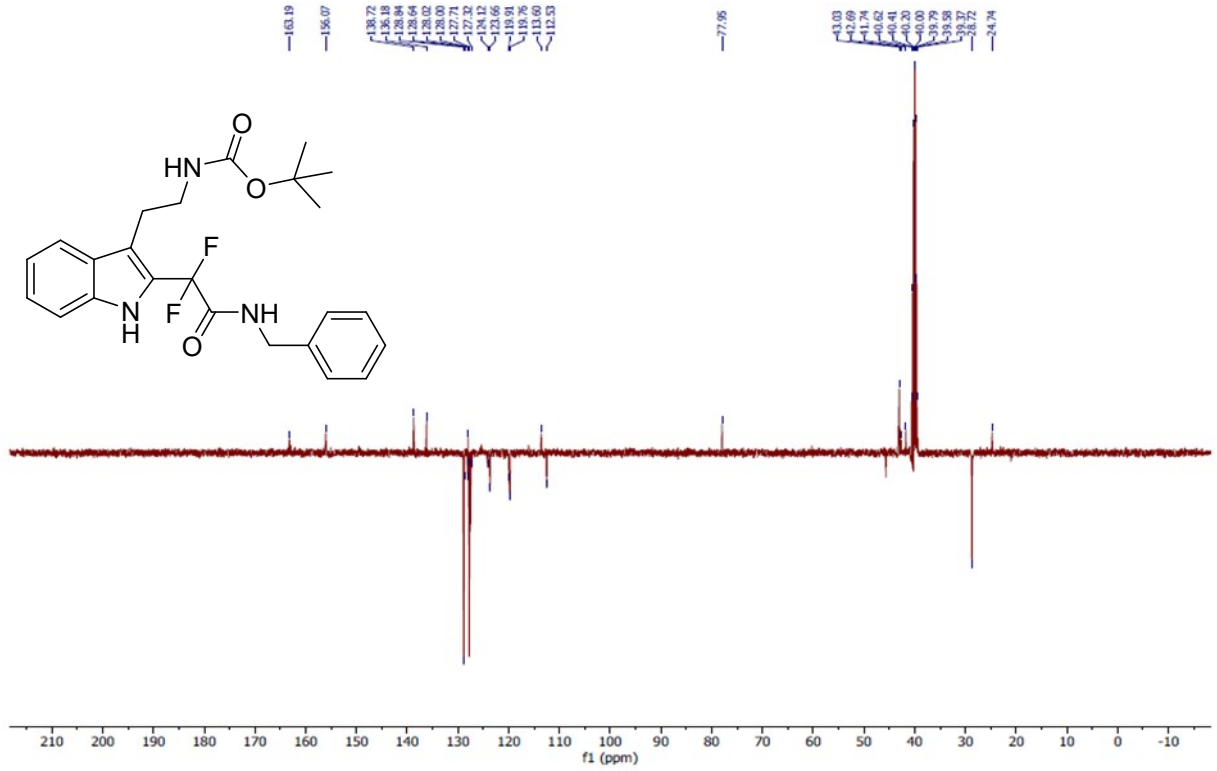


Figure S63. ^{13}C NMR DEPT135 spectrum in DMSO-d6, 100 MHz, of compound **11c**

Tert-butyl N-[2-(2-{[(2,2-dimethoxyethyl)carbamoyl]difluoromethyl}-1H-indol-3-yl)ethyl] carbamate (11d)

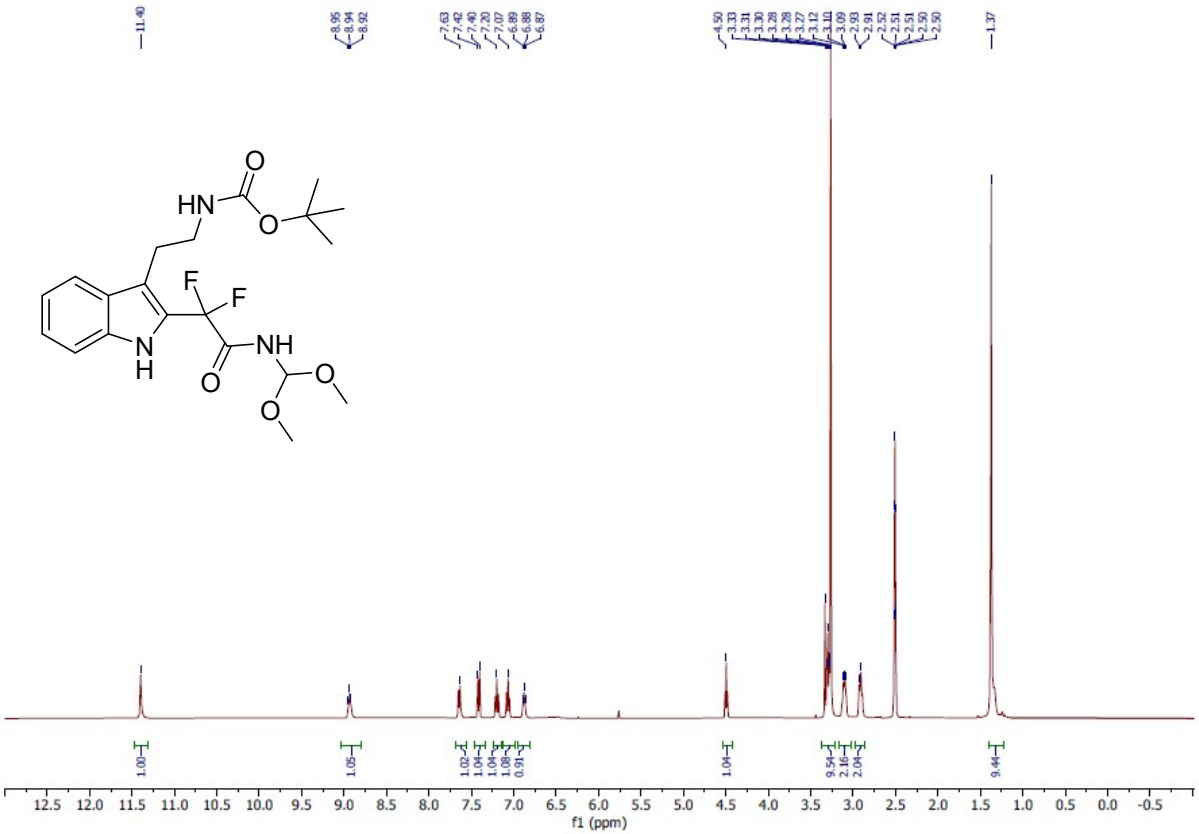


Figure S64. ^{1}H NMR spectrum in DMSO-d6, 400 MHz, of compound **11d**

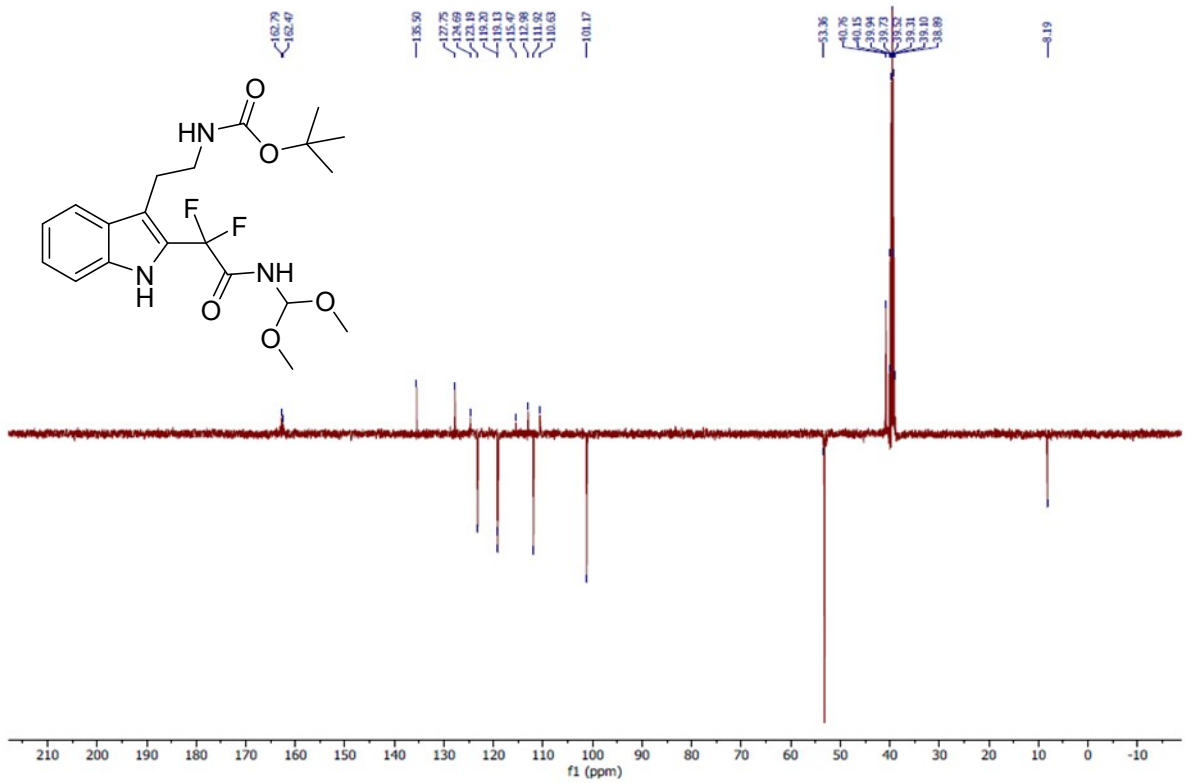


Figure S65. ^{13}C NMR DEPT135 spectrum in DMSO-d6, 100 MHz, of compound **11d**

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