Electronic Supplementary Information (ESI)

for

Continuous-flow synthesis of fluorine-containing fine chemicals with integrated benchtop NMR analysis

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1. Lab plant flow chart with liquid control system

**Scheme S1** Flow chart of THTMD-XL lab plant with integrated liquid control system and benchtop NMR analysis.

**Pumps**
Supplier: Knauer GmbH

- **P-01** Knauer Smartline P100 with 10 mL pump head
  - Flow rate: max. 10 mL/min
  - Pressure: max. 400 bar

- **P-purge** Knauer Smartline K-501 with 10 mL pump head
  - Flow rate: max. 10 mL/min
  - Pressure: max. 400 bar

**Heating cartridge in THTMD**
Supplier: Hotrod®
Typ HHP 20 mm
- Diameter: 20 mm, length: 200 mm, maximum power: 2500 W, voltage supply: 230 V
- Integrated thermocouple: **TIC-001 NiCr-Ni Typ K**
Connection cable: 1500 mm

**Control unit for heating cartridge in THTMD**
Supplier: Fraunhofer ICT-IMM
Voltage supply: 230 V
Integrated controller: JUMO iTRON B70.2040

**Cartridges**
Supplier: Fraunhofer ICT-IMM
*CART1* length 5 cm, ¼“ stainless steel pipe (1.4435), V = 0.8 mL
*CART2* length 18 cm, 3/8“ stainless steel pipe (1.4435), V = 7 mL
*CART3* length 15 cm, ¼“ stainless steel pipe (1.4435), V = 2.4 mL
Frits für ¼“ tubes: pore size 10 µm, thickness: 1 mm, stainless steel (1.4401)
Connectors: Swagelok® 1/16” connection nut with clamp ring

**3-Way valves**
Supplier: Swagelok®
Type: SS-41GX1
1/16” connectors, stainless steel body (1.4401), Packung aus modifiziertem PTFE, working pressure: 172 bar (2500 psig), maximum temperature: +148 °C

**Dosing valves**
Supplier: Swagelok®
Type: SS-SS2-KZ-VH
1/8” connectors, stainless steel body 1.4401, working pressure: 137 bar, maximum temperature: +148 °C, material O-ring: Kalrez (FFKM), complete blocking not possible, dosing with micrometer screw

**Flipper magnetic valves**
Supplier: Bürkert
Type: 6650
3/2-Way universal passage, seal: FFKM, construction material: PEEK, voltage: 24 V, maximum pressure: 1 bar
Additional components: cable head Typ 2504 with integrated booster- and power reduction electronic, 24 V/DC, connection plate material: PEEK with UNF1/4-28-F connectors

**Gas-liquid separator**
Supplier: Fraunhofer ICT-IMM
Liquid feed capillary: 1/16” OD, 127 µm ID, stainless steel
Gas feed capillary: 1/8“stainless steel
Gas withdrawing capillary: ¼“stainless steel
Separator body: FEP tubing, 14 mm OD, 12 mm ID, length 100 mm
Screw connection material for separator body: Teflon

**Nitrogen mass flow controller for g/l-splitter**
Supplier: Bronkhorst®
Type: F-201C-FAC-22-P, S.N. M2207388B, 5 ls/min, maximum pressure: 4 bar (a), working temperature: 20 °C, signal out 0-5 V, signal in 0-5 V with control box for 5 V mass flow controller

**Sensors and regulation units**

a) **Temperature detection (single unit)**
Supplier: TC direct
*TI-001* Typ K, diameter: 0.5 mm, length: 150 mm, material: stainless steel (1.4541), connection cable: 2000 mm with PFA isolation

b) **Pressure detection**
Supplier: Landefeld
*PI-001/PI-002* MIDAS Type 1001, pressure range: 0-100 bar, material of contacting elements for measurement: stainless steel 1.4571 and 1.4542, temperature range of measuring medium: -20°C to +125 °C, voltage feed: 10-30 V DC, output signal: 4 to 20 mA
Figure S1 Detailed description of lab plant.

Figure S2 Detailed description of liquid control system.
2. Tube Heat Transfer Micro Device XL (THTMD-XL)

Figure S3 Microstructured inner tube in full length (left) and close-up of microstructure (right) of THTMD-XL.

3. Capillary photoreactor

Figure S4 1st Generation of the capillary photoreactor with blue, green and red LED.
**Light Emitting Diodes**
Supplier: Cree, Inc.
Type: XP-E series
XPEROY-L1-0000-00A01 (royal blue, 445 nm)
XPEGRN-L1-0000-00C01 (green, 520 nm)
XPERED-L1-0000-00501 (red, 630 nm)

**Central Heat Exchanger and LED carrier**
Supplier of CAD design: Fraunhofer ICT-IMM
External company for 3D printing (selective laser melting): FIT prototyping GmbH

**Power Supply for LEDs**
Supplier: Basetech GmbH
Type: BT-305

**Cryostat for LED cooling**
Supplier: Julabo
Type: F10 with HC E07 (control unit)
4. SNR measurement of $^{19}$F NMR experiments with CF$_3$ signal

Figure S5  $^{19}$F NMR spectra of 4-(trifluoromethyl) benzyl alcohol in DMSO with $c = 0.6$ mol L$^{-1}$ with $f_i = 0.5$ mL min$^{-1}$; scan numbers from bottom to top: 4, 8, 16, 64.
Figure S6 $^{19}\text{F}$ NMR spectra of 4-(trifluoromethyl)benzyl alcohol in DMSO with $c = 0.3 \text{ mol L}^{-1}$ with $f = 0.5 \text{ mL min}^{-1}$; scan numbers from bottom to top: 4, 8, 16, 64.
Figure S7 $^{19}$F NMR spectra of 4-(trifluoromethyl)benzyl alcohol in DMSO with $c = 0.15 \text{ mol L}^{-1}$ with $f = 0.5 \text{ mL min}^{-1}$; scan numbers from bottom to top: 4, 8, 16, 64.
Figure S8 $^{19}$F NMR spectra of 4-(trifluoromethyl)benzyl alcohol in DMSO with $c = 0.6 \text{ mol L}^{-1}$ with $f = 2 \text{ mL min}^{-1}$; scan numbers from bottom to top: 4, 8, 16, 64.
Figure S9 $^{19}$F NMR spectra of 4-(trifluoromethyl)benzyl alcohol in DMSO with $c = 0.3$ mol L$^{-1}$ with $f_l = 2$ mL min$^{-1}$; scan numbers from bottom to top: 4, 8, 16, 64.
**Figure S10** $^{19}$F NMR spectra of 4-(trifluoromethyl)benzyl alcohol in DMSO with $c = 0.15 \text{ mol L}^{-1}$ with $f = 2 \text{ mL min}^{-1}$; scan numbers from bottom to top: 4, 8, 16, 64.
Figure S11 $^{19}$F NMR spectra of 4-(trifluoromethyl)benzyl alcohol in DMSO with $c = 0.6 \text{ mol L}^{-1}$ with $f_i = 4 \text{ mL min}^{-1}$; scan numbers from bottom to top: 4, 8, 16, 64.
Figure S12: $^{19}$F NMR spectra of 4-(trifluoromethyl)benzyl alcohol in DMSO with $c = 0.3 \text{ mol L}^{-1}$ with $f = 4 \text{ mL min}^{-1}$; scan numbers from bottom to top: 4, 8, 16, 64.
Figure S13 $^{19}$F NMR spectra of 4-(trifluoromethyl)benzyl alcohol in DMSO with $c = 0.15 \text{ mol L}^{-1}$ with $f = 4 \text{ mL min}^{-1}$; scan numbers from bottom to top: 4, 8, 16, 64.
5. **Software interface**

![Diagram of software interface](image)

- **Status of magnetic valves in LCS**
- **Status of connectivity**
- **Method of measurement**
- **Parameters for purging**
- **Status NMR spectrometer**

**Figure S14** Front end of the LabView-based software interface for LCS and NMR spectrometer control.
a. Electronic communication with NMR spectrometer via LabView
b. Electronic communication with HPLC pump and magnetic valves via LabView
6. Experimental

Online- and offline-NMR spectroscopy

$^1$H and $^{19}$F NMR spectra were recorded with a NMReady-60e benchtop NMR spectrometer (Nanalysis Corp.) with Larmor frequencies of 58.63 MHz for $^1$H and 55.17 MHz for $^{19}$F. High-resolution $^1$H and $^{13}$C spectra were recorded with an Avance III HD 300 NMR spectrometer (Bruker BioSpin GmbH) with Larmor frequencies of 300.13 MHz for $^1$H and 75.48 MHz for $^{13}$C.

Glassware from Norell Inc. was used for standard NMR tubes and for the manufacturing of the flow cell. Deuterated solvents were purchased from Deutero GmbH. NMR spectra were processed with ACD/NMR Processor software (academic edition) from ACD/Labs. Chemical shifts are reported relative to SiMe$_4$ ($^1$H: $\delta$ = 0.00 ppm) and CFCl$_3$ ($^{19}$F: $\delta$ = 0.00 ppm). As internal standards the residual DMSO-d$_6$ solvent proton signal (2.50 ppm) was used.

Krapcho decarboxylation

10.8 g (0.04 mol, 1 eq) Ethyl (3,5-dichloropyridin-2-yl)(difluoro)acetate (1) was dissolved in a DMSO-water mixture (97/3, v/v; 100 mL) and lithium chloride (3.39 g, 0.08 mol, 2 eq) was added. The suspension was stirred at room temperature until all LiCl has dissolved resulting in a clear and colourless solution.

The substrate solution was pumped with various flow rates and at various temperatures through the THTMD, the gas-liquid splitter and into the flow cell for online NMR analysis. The dark brown reaction solution was collected in one vessel and stirred into cold water (200 mL). The resulting suspension was extracted with ethyl acetate (3 x 80 mL). The organic phases were combined, washed with water (2x 50 mL) and dried with Na$_2$SO$_4$. The solvent was evaporated at 40 °C under reduced pressure and subjected to flash chromatography with cyclohexane as eluent. The purified product was used for $^1$H NMR analysis in standard NMR tubes with DMSO-d$_6$ as solvent.

$^{1}$H-NMR (300 MHz; DMSO-d$_6$): $\delta$ 8.75 (d, $J$ = 2.2 Hz, 1H), 8.46 (d, $J$ = 1.8 Hz, 1H), 7.19 (t, $J$ = 53.2 Hz, 1H); $^{13}$C NMR (75 MHz; DMSO-d$_6$): $\delta$ 146.7 (CH), 146.1 (t, $J$ = 23.1, C), 138.4 (CH), 133.7 (C), 130.3 (C), 111.8 (t, $J$ = 239.9 Hz, CH).
Ruppert-Prakash reaction with TMS-CF₃
Benzaldehyde (1.77 g, 0.017 mol, 1 eq) and TMS-CF₃ (2.84 g, 0.02 mol, 1.2 eq) were mixed with 100 mL DMSO resulting in a clear and colourless solution.

The substrate solution was pumped at various temperatures through the THTMD and analysed online with the benchtop NMR spectrometer. The slightly yellow reaction solution was collected in one vessel and stirred into cold water (200 mL). The resulting suspension was extracted with dichloromethane (3 x 80 mL). The organic phases were combined, washed with water (2x 50 mL) and dried with Na₂SO₄. The solvent was evaporated at 40 °C under reduced pressure and subjected to flash chromatography with cyclohexane as eluent. The purified product was used for ¹H NMR analysis in standard NMR tubes with DMSO-d₆ as solvent.

Ruppert-Prakash reaction with TMS-C₂F₅

Method 1:
Benzaldehyde (1.77 g, 0.017 mol, 1 eq) and TMS-C₂F₅ (3.84 g, 0.02 mol, 1.2 eq) were mixed with 100 mL DMSO resulting in a clear and colourless solution. Vigorous stirring was necessary in this case for breaking the binary phase system between DMSO and TMS-C₂F₅. The substrate solution was used as described above for the Ruppert-Prakash reaction with TMS-CF₃.

Method 2:
Benzaldehyde (1.77 g, 0.017 mol, 1 eq) and TMS-C₂F₅ (3.84 g, 0.02 mol, 1.2 eq) were each mixed with 50 mL DMSO resulting in clear and colourless solution. Vigorous stirring was necessary for the DMSO / TMS-C₂F₅ mixture for breaking the binary phase system between the two liquids.
Both solutions were pumped separately with two HPLC pumps into a static T-piece mixer and via the cartridge – reactor – cartridge cascade of the lab plant into the flow cells for NMR analysis. The flow rates of both HPLC pumps were kept equal so that a constant substrate concentration of 0.2 M was given throughout the complete runtime. During the runtime various temperatures were applied at the THTMD.

Dye-sensitized C-H arylation of furan with a trifluoromethylated diazonium salt

3-(Trifluoromethyl)phenyl diazonium tetrafluoroborate (5.2 g, 0.02 mol, 1 eq) was dissolved in DMSO (50 mL). Eosin Y (138.4 mg, 0.2 mmol, 0.01 eq) was dissolved in a solvent mixture of DMSO and furan (35.5/14.5, v/v).

Both reaction solutions were pumped separately with two HPLC pumps into a static T-piece mixer and via the capillary microreactor and the gas-liquid splitter into the flow cells for online NMR analysis. The flow rates of both HPLC pumps were kept equal so that a constant substrate concentration of 0.2 M was given throughout the complete runtime. The dark yellow reaction solution was collected in one vessel and stirred into cold water (200 mL). The resulting suspension was extracted with ethyl acetate (3 x 80 mL). The organic phases were combined, washed with water (2x 50 mL) and dried with Na₂SO₄. The solvent was evaporated at 40 °C under reduced pressure and subjected to flash chromatography with cyclohexane as eluent. The purified product was used for ¹H NMR analysis in standard NMR tubes with DMSO-d₆ as solvent.

¹H-NMR (300 MHz; DMSO-d₆): δ 7.52-7.49 (m, 2H), 7.43-7.38 (m, 3H), 5.40 (dd, J = 19.7 Hz, 5.2 Hz, 1H), 0.01 (s, 9H); ¹³C NMR (75 MHz; DMSO-d₆): δ 134.6 (C), 129.2 (CH), 128.2 (CH), 128.1 (CH), 119.0 (qt, J = 288.3 Hz, 36.3 Hz C), 113.0 (tq, J = 261.9 Hz, 35.2 Hz), 71.0 (dd, J = 30.1 Hz, 21.5 Hz, CH), 0.52 (CH₃).³,⁴

¹H-NMR (300 MHz; CDCl₃): δ 7.94 (br.s, 1H), 7.86-7.82 (m, 1H), 7.55-7.50 (m, 3H), 6.75 (dd, J = 3.44 Hz, 0.69 Hz, 1H), 6.52 (dd, J = 3.44 Hz, 1.83 Hz, 1H); ¹³C NMR (75 MHz; CDCl₃): δ 152.4 (C), 142.8 (CH), 131.1 (q, J = 31.9 Hz, C), 129.1 (CH), 126.7 (CH), 124.1 (q, J = 272.9 Hz, C), 123.7 (q, J = 3.3 Hz, CH), 120.5 (q, J = 3.3 Hz, CH), 111.9 (CH), 106.3 (CH).⁵
$^1$H-NMR (300 MHz; DMSO-$d_6$): $\delta$ 7.96-7.93 (m, 2H), 7.77 (dd, $J = 1.83$ Hz, 0.73 Hz, 1H), 7.63-7.55 (m, 2H), 7.13 (dd, $J = 3.3$ Hz, 0.73 Hz, 1H), 6.61 (dd, $J = 3.3$ Hz, 1.83 Hz, 1H); $^{13}$C NMR (75 MHz; DMSO-$d_6$): $\delta$ 151.9 (C), 144.1 (C), 131.7 (C), 130.4 (C), 130.3 (q, $J = 31.9$ Hz, C), 127.4 (C), 124.5 (q, $J = 271.8$ Hz, C), 124.0 (q, $J = 3.3$ Hz, CH), 120.0 (q, $J = 3.3$ Hz, CH), 112.7 (CH), 108.0 (CH).
Figure S 15 Top: Static T-mixer with incoming orange Eosin Y solution and colourless substrate solution resulting in deep pink solution; Bottom: colour change of the substrate solution from deep pink (bottom part of the reactor) to dark yellow upon irradiation with green light. Formation of gas slugs due to the expulsion of molecular nitrogen during the reaction. Internal light source is switched off for taking the picture.
7. $^{19}$F NMR spectra of Krapcho decarboxylation in continuous-flow
8. High-resolution $^1$H / $^{13}$C NMR spectrum of purified 2 (DMSO-d$_6$)
9. $^1$H NMR spectrum of partly hydrolysed TMS-CF$_3$ in DMSO-d$_6$
10. $^{19}\text{F}$ NMR spectra of Ruppert-Prakash reaction with TMS-CF$_3$ in continuous-flow (non-dried DMSO)
11. High-resolution $^1$H / $^{13}$C NMR spectra of purified 4 (DMSO-d$_6$)
12. $^1$H NMR spectrum of partly hydrolysed TMS-C$_2$F$_5$ in DMSO-d$_6$
13. $^{19}$F NMR spectra of Ruppert-Prakash reaction with TMS-$C_2F_5$ in continuous-flow (non-dried DMSO)
14. $^{19}$F NMR spectra of Ruppert-Prakash reaction with TMS-$C_2F_5$ in continuous-flow (dry DMSO)
15. High-resolution $^1$H / $^{13}$C NMR spectra of purified 5 (DMSO-d$_6$)
16. $^{19}$F NMR spectra of dye-sensitized C-H arylation in continuous-flow
17. High-resolution $^1$H / $^{13}$C NMR spectrum of purified 7 (DMSO-d$_6$)
18. High-resolution $^1$H NMR spectrum of purified 7 (300 MHz, CDCl$_3$)
19. References