Supplementary Information

Investigations on the Continuous Flow Generation of 2,6-Dichloro-*N*-fluoropyridinium Tetrafluoroborate using F_2 Gas

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1. General Methods

All materials were purchased from commercial suppliers and used without further purification. Extra dry MeCN (99.9% over molecular sieve, AcroSeal) from Acros was used.

For reaction optimization, ^{19}F NMR spectra of neat reaction mixtures were recorded on a 43 MHz benchtop NMR (Magritek Spinsolve Ultra). For product characterization, high resolution ^{1}H spectra were recorded on a Bruker 300 MHz instrument. ^{19}F NMR spectra were recorded either on the same instrument at 282 MHz or on a 500 MHz instrument at 470 MHz. ^{13}C NMR spectra were recorded on a 500 MHz instrument at 125 MHz. Chemical shifts (δ) are expressed in ppm, and the residual solvent peak of CD_3CN was used as reference for ^{1}H NMR. For ^{19}F NMR, α,α,α-trifluorotoluene (TFT) and trichlorofluoromethane ($CFCl_3$) were used as references and external standards. The letters s, d, t and m are used to indicate singlet, duplet, triplet and multiplet.

HPLC analysis was carried out on a Shimadzu instrument using a C18 reversed-phase analytical column (150 × 4.6 mm, particle size 5 µm) at 37 °C by using mobile phases A (water/acetonitrile 90:10 (v/v) +0.1% TFA) and B (acetonitrile + 0.1% TFA) at a flow rate of 1.5 mL/min. The following gradient was applied: linear increase from 30% solution B to 100% B in 10 min, going back to 30% B and holding for 3.5 min. All samples were prepared in HPLC grade acetonitrile and analyzed at 254 nm. For quantification, biphenyl was used as external standard (ETSD).

LC-MS analysis was carried out on a Shimadzu instrument using a C18 reversed-phase (RP) analytical column (150 mm × 4.6 mm, particle size 5 µm using mobile phases A (H_2O/MeCN 90:10 (v/v) + 0.1% HCOOH) and B (MeCN + 0.1% HCOOH) at a flow rate of 0.6 mL/min. The following gradient was applied: hold at 5% B for 2 min, increase to 20% solvent B over 6 min, increase to 100% solvent B over 10 min and hold at 100% B for 6 min. Low resolution mass spectra were obtained on a Shimadzu LCMS-QP2020 instrument using electrospray ionization (ESI) in positive or negative mode.

GC-MS analysis was performed on a Shimadzu GCMS-QP2010 SE coupled with a DSQ II (EI, 70 eV). A fused silica capillary column Rtx-5MS column (5% diphenyl, 95% dimethylpolysiloxane, 30 m × 0.25 mm × 0.25 µm) was used. The injector temperature was set at 280 °C. After 1 min at 50 °C, the oven temperature was in-creased by 25 °C/min to 300 °C and maintained at 300 °C for 3 min. As a carrier gas, helium at 40 cm s−1 linear velocity was used. MS conditions were ionization voltage of 70 eV and the acquisition mass range of 50−450 m/z. Mass spectral libraries (Wiley Registry of Mass Spectral Data 11th Edition, NIST/EPA/NIH Mass Spectral Library 14) were searched with NIST MS Search software.

GC-FID analysis was performed on a Shimadzu GCFID 2030 instrument equipped with a flame ionization detector, using an RTX-5MS column (30 m × 0.25 mm ID × 0.25 µm) and helium as carrier gas (40 cm/s linear velocity). The injector temperature was set to 280 °C. After 1 min at 50 °C, the temperature was increased by 25 °C min^{-1} to reach 300 °C and then kept constant at 300 °C for 3 min. The detector gases used for flame ionization were hydrogen and synthetic air (5.0 purity).

CAUTION: F_2 gas is very toxic and corrosive, therefore, extreme care should be taken in handling this material. F_2 gas should only be handled using a dedicated F_2 gas facility. A double glove principle (inner glove: LLDPE laminated film gloves; outer glove: neoprene/nitrile glove) is recommended as PPE. Exposure to F_2 should be treated in the same way as for HF. Thus, the operator must be familiar with the proper first aid treatment. All wetted parts of the equipment employed should be checked on their compatibility. For detailed information on the handling of F_2 gas in continuous flow, see [S1].

2. Equipment

10% F_2 in N_2 gas delivery: A central gas supply system to transport 10% F_2 in N_2 in a safe and controlled manner from a cylinder to the point of use was employed [S1]. The facility was designed and constructed by AirLiquide and is intended for the conduction of lab-scale synthetic operations.

Mass flow controller (MFC): A lowΔp MFC from Bronkhorst, which was calibrated for 10% F_2 in N_2, was used. Inlet pressure: 7 bar, outlet pressure: 0.5 bar, max flow: 100 mLn/min

Pumps: The feed solutions were pumped using Syrris Asia syringe pumps.

Check valves (CVs): IDEX CVs (CV-3321) were attached at the outlet of the pumps as well as on each inlet to the NaOH quench solution. A FITOK CV (CVS series) was attached at the outlet of the MFC.

Sample loop: An IDEX 6-port injection valve was used (V-450, 69 bar, IDEX). A 4 mL sample loop (PFA tubing: 1/16" OD, 0.8 mm ID) was installed.

Switching valve: An IDEX 4-way valve (V-100L) was used for sampling.

Pressure relief valves: Adjustable spring type Chemtrix BPRs set to 5 bar were used.

Tubing: PFA or PTFE tubing with either 1/16" OD and 0.8 mm ID or 1/8" OD and 1/16" ID were used as feedlines, connector tubings and coil reactors. Connectors and nuts made of PEEK or ETFE with ferrules made of ETFE and SS were used.

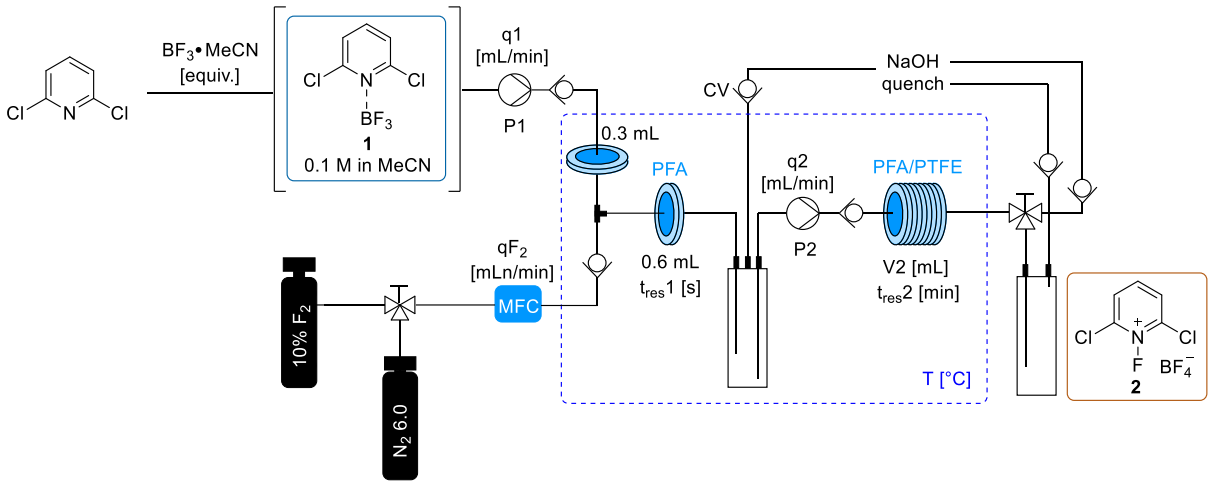
Gas/liquid separator: A self-made gas/liquid separator consisting of a 20 mL borosilicate vial (IKA electrochemistry vial) and an Omnifit Q series bottle cap (GL32, PTFE inner body) with 3 fitting connections was used (see Figure S2).

Silicon carbide (SiC) reactor: The Protrix flow reactor contains 3M™ SiC modules that can be flexibly configured (in terms of number and type) to deliver the required number of reagent inputs, reaction volume and temperature zones. Each SiC module is fabricated from 3M™ SiC grade C and contains the process channel and an integrated heat exchange layer. The SiC layers are diffusion bonded to give a gas-tight, metal-free flow path with high chemical compatibility (Figure S8). The flow path proceeds in series between the modules and the heat exchange layers are arranged in parallel. Depending on the residence times, either an MRPX module alone or in combination with MRPA residence time modules was employed. The SiC modules are connected in the holder using FFKM O-rings. The standard FFKM O-rings were replaced with Chemraz Type 585 for the process channels. Standard PTFE interconnector plates were used.
Thermal control was achieved using a thermostat (CC304B, Huber) filled with EtOH as cooling fluid.

Wetted materials: PEEK, ETFE, FFKM, SS316L, PCTFE, Silicon nitride, SiC, PTFE, PFA, Chemraz Type 585 (O-rings)

3. Generation of 2,6-Dichloro-*N*-fluoropyridinium Tetrafluoroborate (**2**)

Table S1. Optimization for the In-situ Generation of **2** in Continuous Flow[a]



Entry	BF_3 [equiv.]	q1/q2 [mL/min]	F_2 [equiv.]	qF_2 [mLn/min]	$t_{res}1$ [s][b]	V2 [mL]	$t_{res}2$ [min]	T [°C]	Yield 2 [%][c]
1	2	1	1.5	33.6	1.0	9.1	9.1	−10	53
2	3	1	1.5	33.6	1.0	9.1	9.1	−10	69
3	4	1	1.5	33.6	1.0	9.1	9.1	−10	63
4	3	1	1	22.4	1.5	9.1	9.1	−10	46
5	3	1	2	44.8	0.8	9.1	9.1	−10	66
6	3	0.75	1	16.8	2.1	9.1	12.1	−10	39
7	3	1	1.5	33.6	1.0	9.1	9.1	−20	60
8	3	1	1.5	33.6	1.0	9.1	9.1	0	61
9	3	1	1.5	33.6	1.0	9.1	9.1	10	66
10	3	1	1.5	33.6	1.0	9.1	9.1	20	73
11	3	1	1.5	33.6	1.0	9.1	9.1	30	61
12	3	1	1.5	33.6	1.0	4.6	4.6	20	72
13	3	1	1.5	33.6	1.0	3.4	3.4	20	69
14	3	1	1.5	33.6	1.0	2.3	2.3	20	68
15	3	1	1.5	33.6	1.0	-	-	20	67
16	3	1	1.5	33.6	1.0	4.6	4.6	−10	67
17	3	1	1.5	33.6	1.0	-	-	−10	57

a…CV: check valve; MFC: mass flow controller; PFA/PTFE coils: 1.6 mm OD, 0.8 mm ID.
b…The residence time reflects the calculated residence time.
c…Determined by ^{19}F NMR (43 MHz) integration against trifluorotoluene as external standard. Given values reflect averages of steady state fractions.

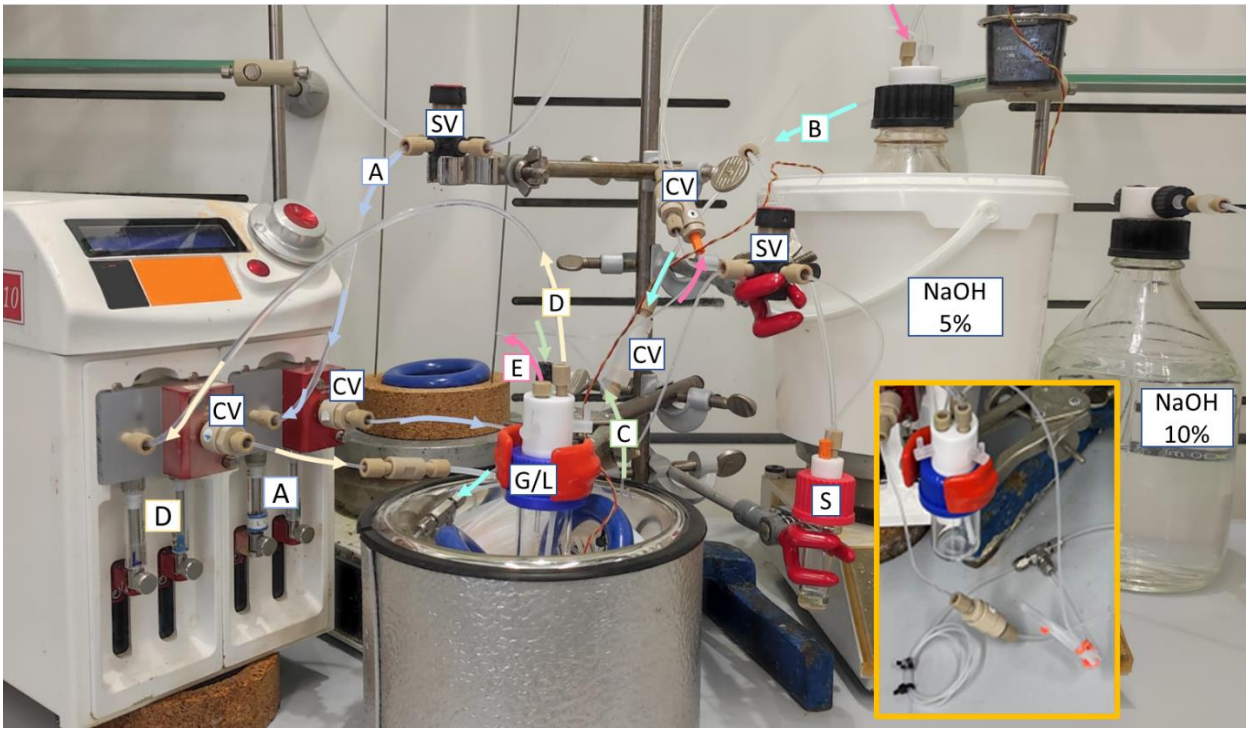


Figure S1. Image of the continuous flow set-up for the diClNFPy **2** generation step. CV: **C**heck **V**alve; SV: **S**witching **V**alve, S: Sampling, A: DCP-BF_3 complex **1** feed (0.1 M), B: 10% F_2/N_2 feed, C: reaction mixture into g/l separator, D: liquid reaction feed out of g/l separator and into sampling vial, E: excess gas out of g/l separator and into the 5% NaOH quench. All residence time coils, mixers and the g/l separator (shown in the insert) are placed inside a Dewar for cooling to the respective temperature (see Table S1).

Figure S2. Self-made gravity-based gas/liquid separator.

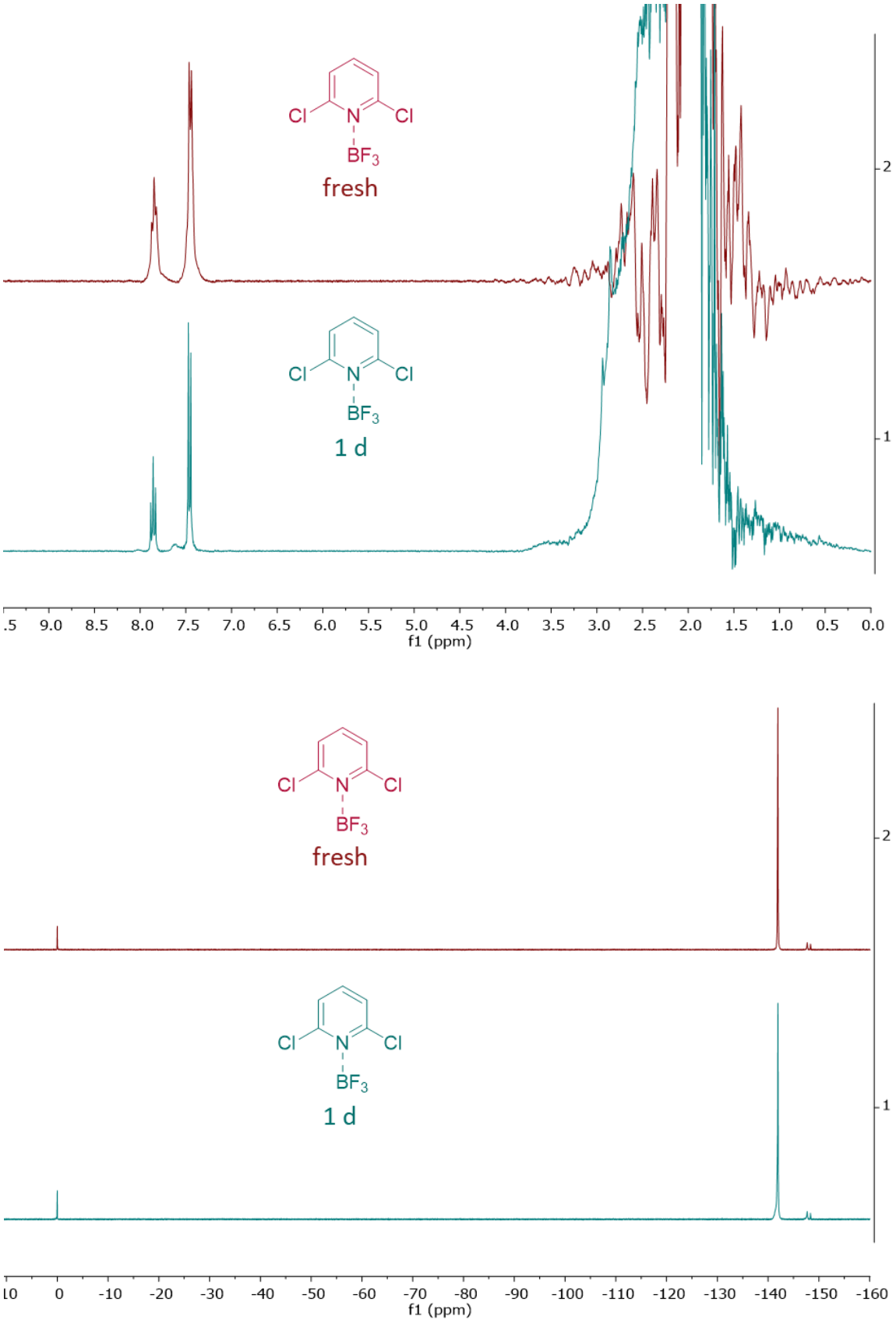


Figure S3. Stability of the 0.1 M solution of DCP-BF_3 complex **1** (3 equiv. BF_3). ^{1}H NMR (300 MHz) and ^{19}F NMR (282 MHz) in CD_3CN were measured at −10 °C for the freshly prepared solution and at room temperature for the solution after standing for 1 d at room temperature, respectively.

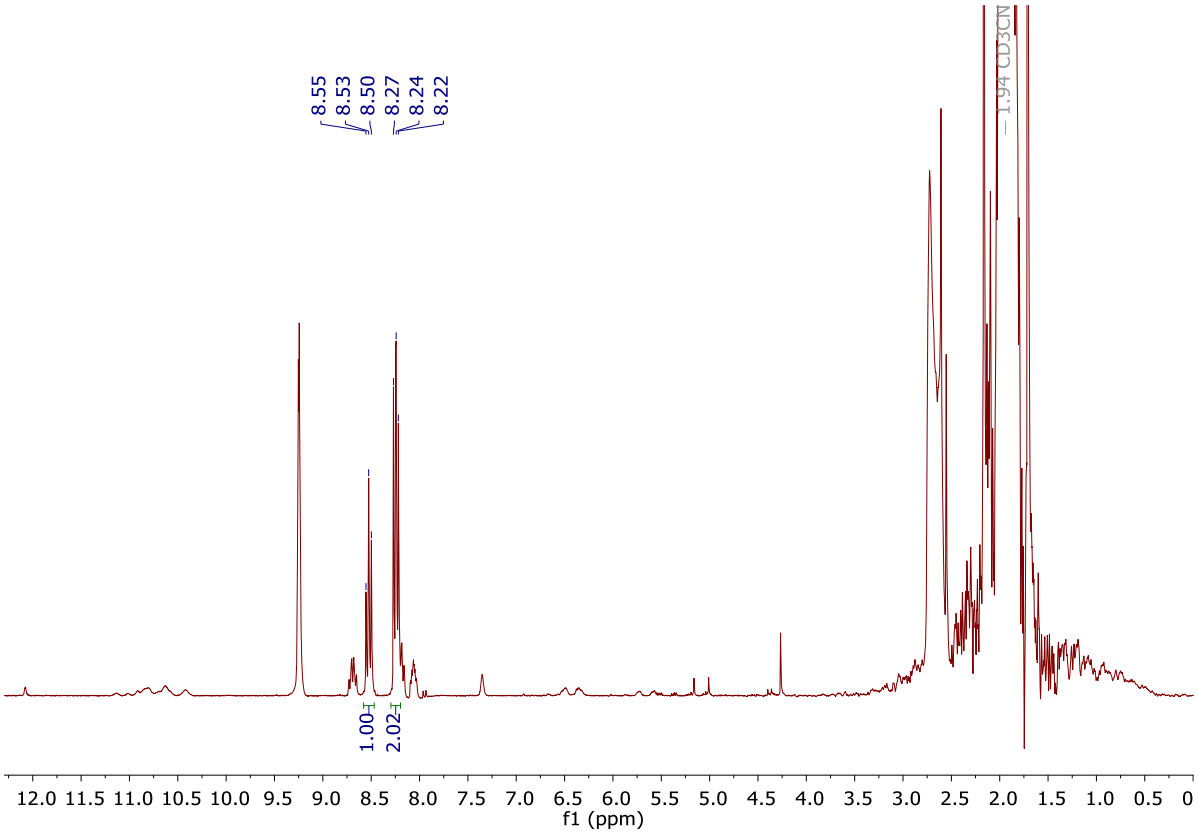


Figure S4. ^{1}H NMR (300 MHz, CD_3CN) of the outlet feed solution of in-situ generated diClNFPy **2** measured at −10 °C.

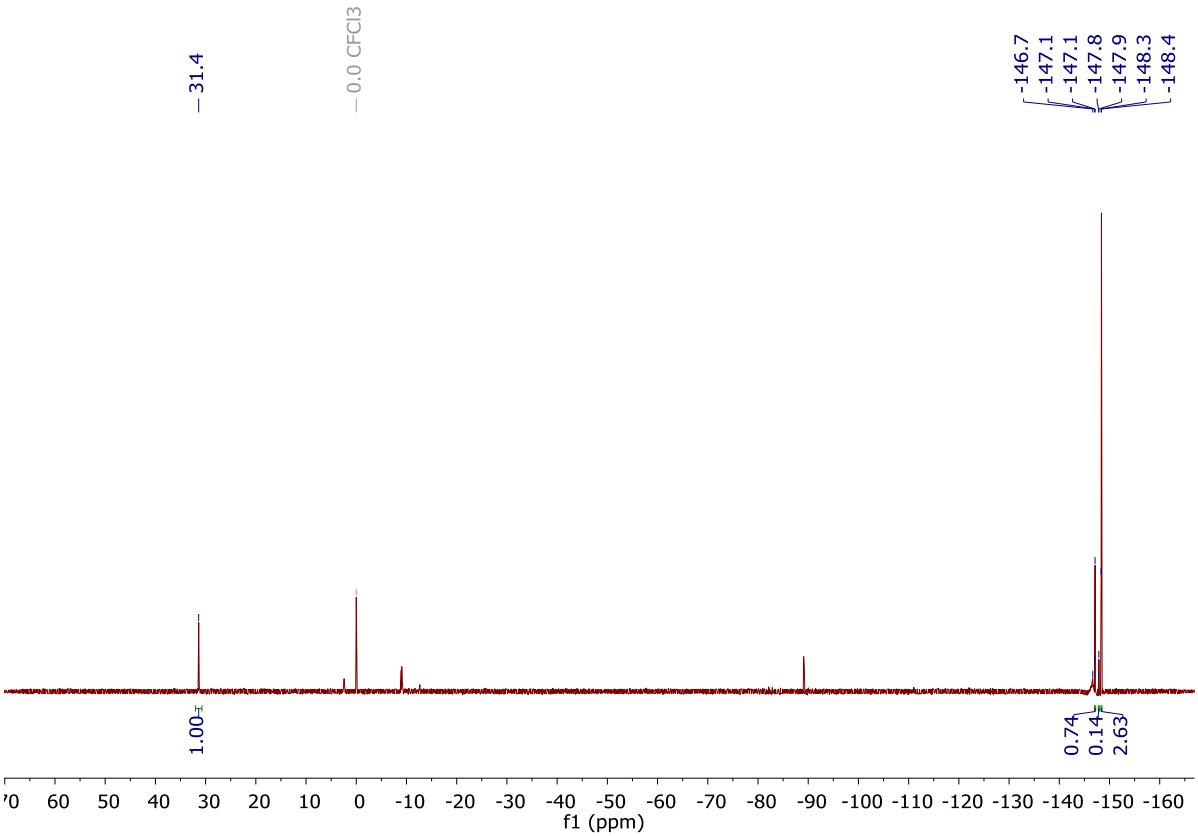


Figure S5. ^{19}F NMR (282 MHz, CD_3CN) of the outlet feed solution of in-situ generated diClNFPy **2** measured at −10 °C.

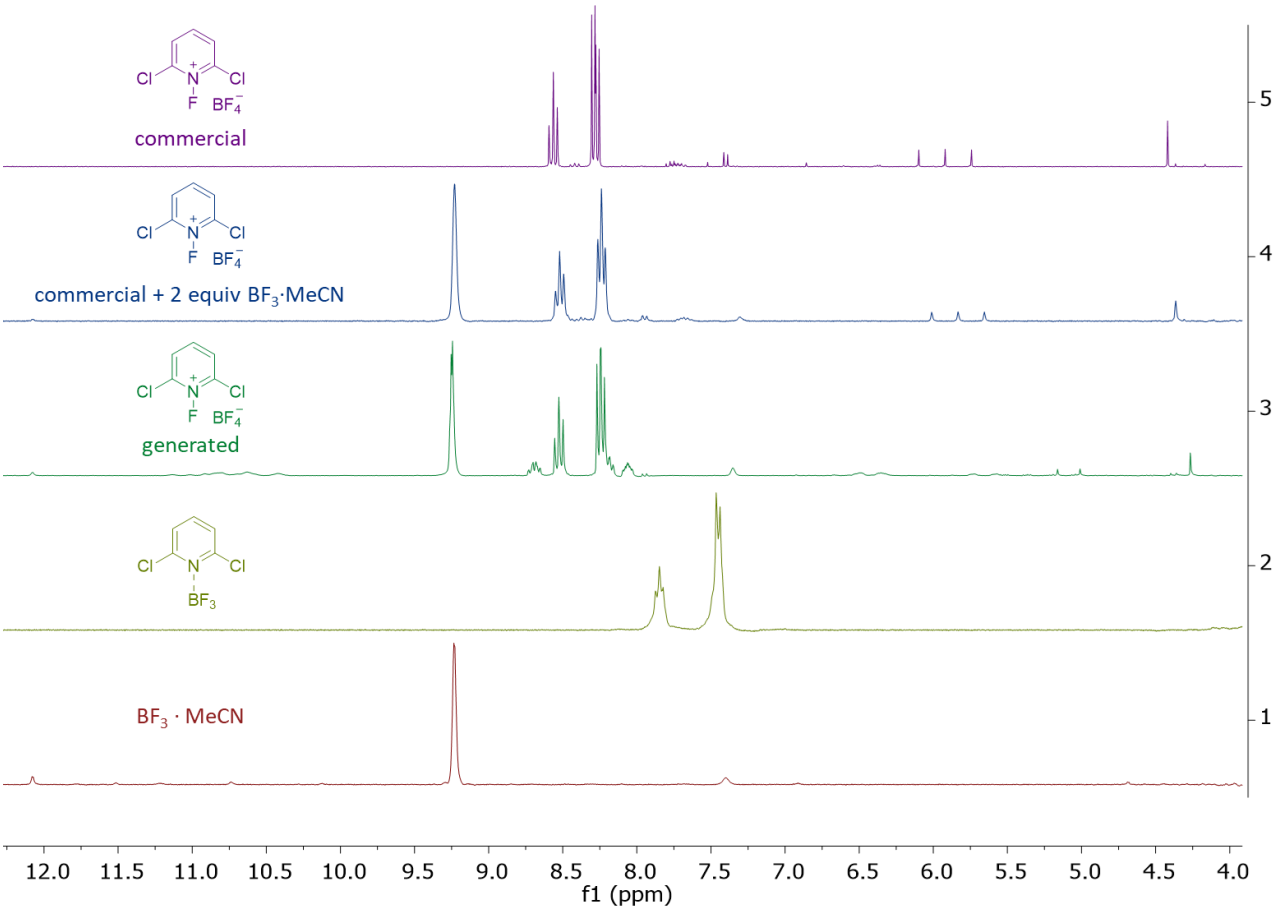


Figure S6. ^{1}H NMR (300 MHz, CD_3CN) comparison of commercial vs. in-situ generated diClNFPy **2**. ^{1}H NMRs 1, 3 and 4 were measured at −10 °C. Full conversion of the pre-formed DCP-BF_3 (3 equiv. BF_3) complex was obtained. The signal at 9.25 ppm is also present in the pure BF_3·MeCN complex.

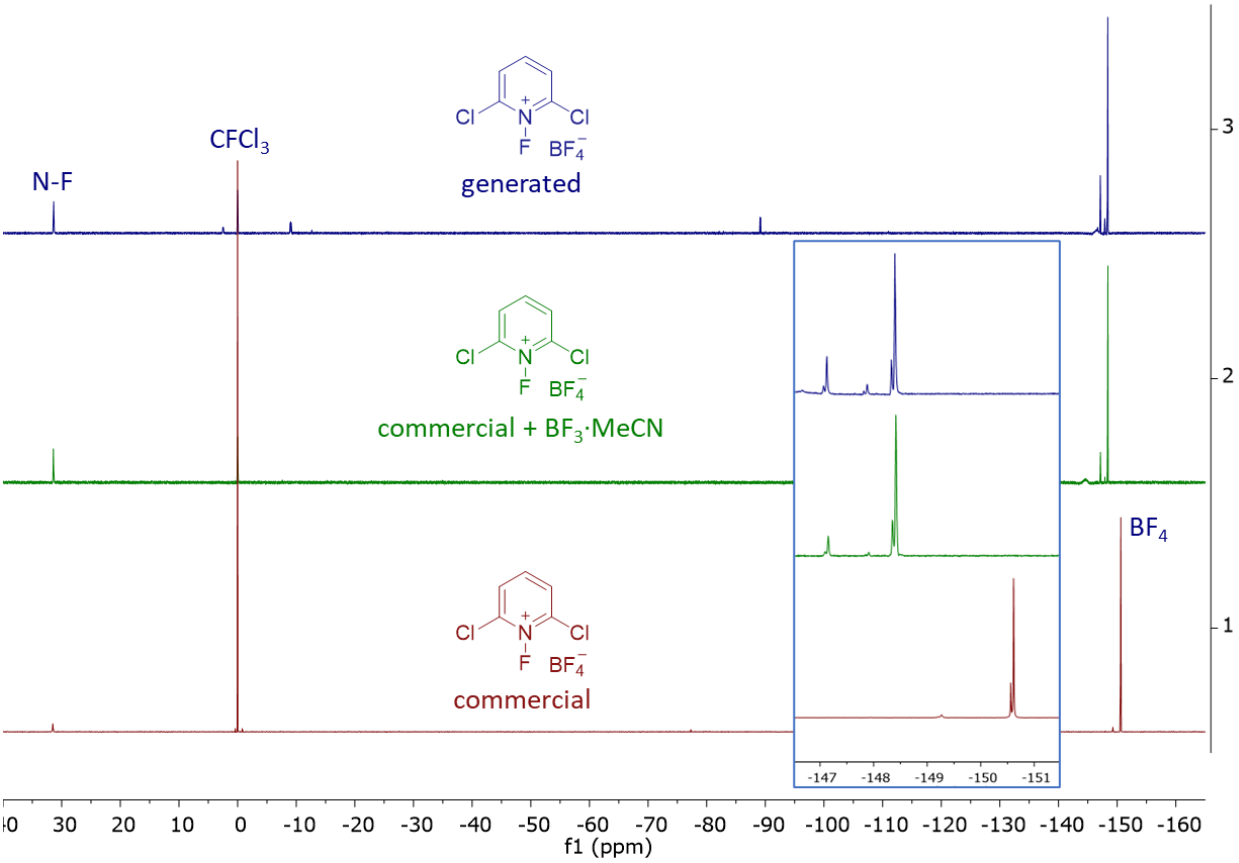
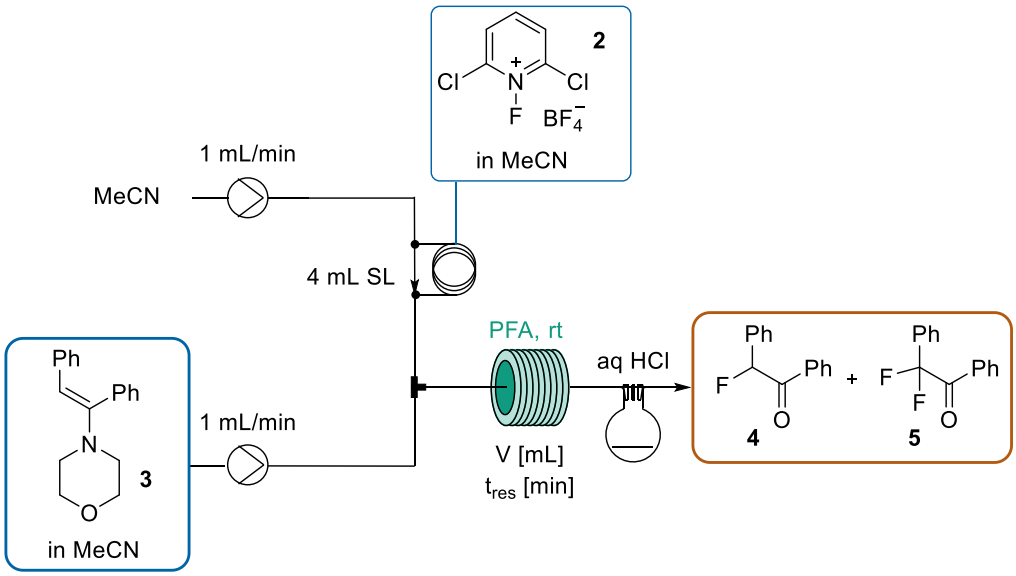


Figure S7. Influence of the BF_3·MeCN complex on the signals in ^{19}F NMR (282 MHz, CD_3CN). The ^{19}F NMRs of the outlet feed solution after diClNFPy generation and the commercial diClNFPy + 2 equiv. of BF_3·MeCN were measured at −10 °C. The BF_4 signal shows a downfield shift from −150.6 ppm to −148.6 ppm when BF_3·MeCN is used in excess.

4. Fluorination of Enamine 3 with Commercial diClNFPy 2 in Flow

Table S2. Pre-Experiments with Commercial diClNFPy **2** in Continuous Flow[a]

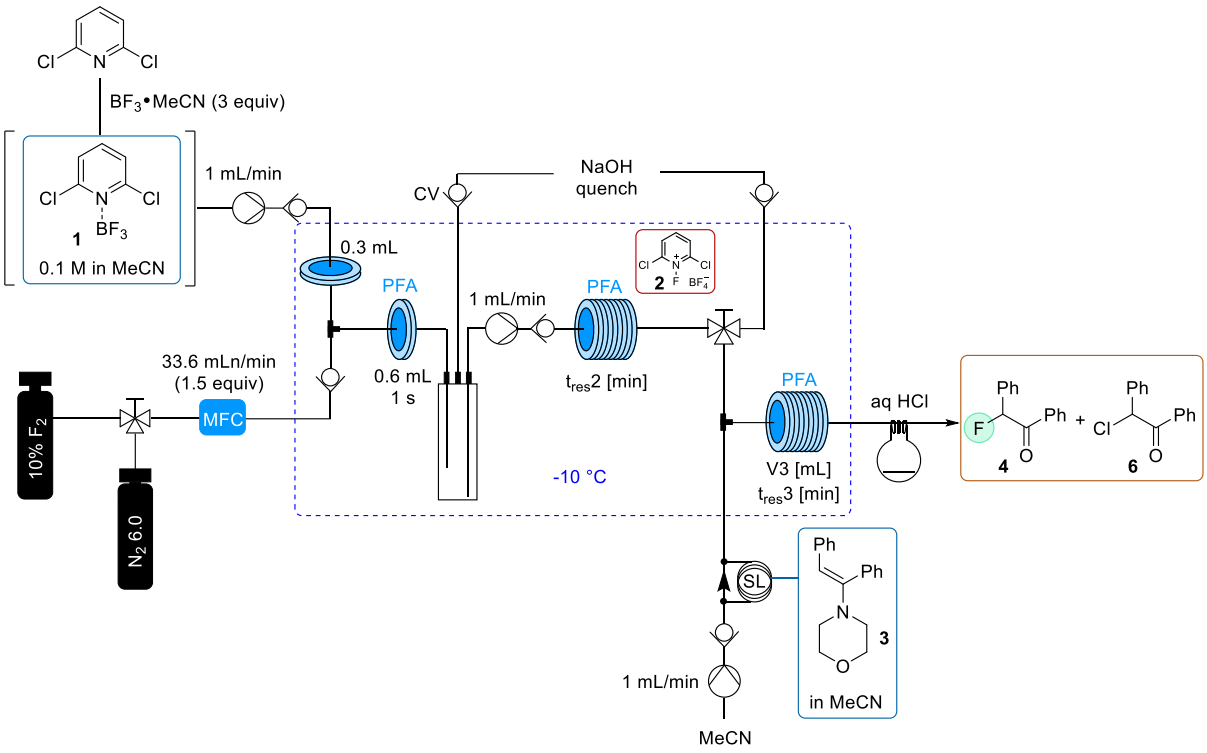


Entry	Conc in V [M]	Equiv. 2	V [mL]	t_{res} [min]	4 [%][b]	5 [%][b]	3 [%][b]
1	0.027	1.05	4	2	90	3	7
2	0.05	1.05	4	2	90	3	7
3	0.05	1.05	5	2.5	91	4	5
4	0.05	1.05	8	4	90	6	4
5	0.05	0.5	4	2.5	42	–	58

a…SL: sample loop, PFA coil: 1.6 mm OD, 0.8 mm ID.

b…HPLC peak area integration at 254 nm.

5. Telescoped N-F Generation + Fluorination of Enamine 3 in a Coil Reactor



Scheme S1. Schematic set-up for the telescoped N-F generation/enamine fluorination in a coil reactor. CV: check valve; MFC: mass flow controller; SL: 4 mL sample loop; PFA coils: 1.6 mm OD, 0.8 mm ID

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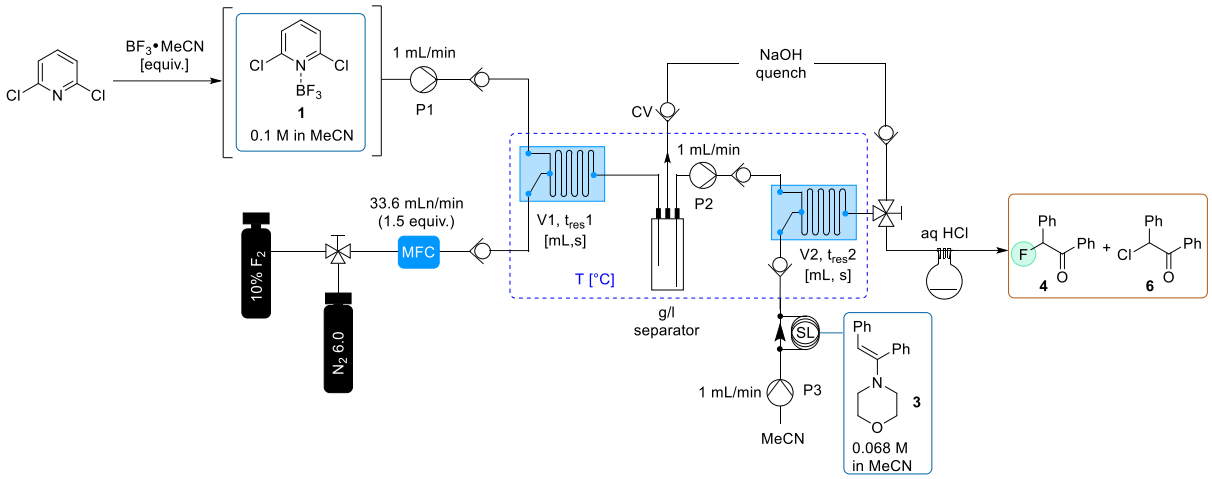
6. Telescoped N-F Generation + Fluorination of Enamine 3 in a SiC Reactor

Table S3. Optimizations for the telescoped N-F generation/enamine fluorination in a SiC reactor[a]



Entry	BF_3 equiv.	N-F 2 equiv.	Conc 3 [M]	V1 [mL]	$t_{res}1$ [s][b]	V2 [mL]	$t_{res}2$ [s]	T [°C]	Yield 4 [%][c]	Conv. 3 [%][d]	Select. 4 [%][e]
1	3	1.01	0.068	0.96	1.7	2.76	83	0	40	58	83
2	3	1.38	0.05	0.96	1.7	2.76	83	0	25	47	77
3	3	2.03	0.034	0.96	1.7	2.76	83	0	23	43	72
4	3	0.69	0.1	0.96	1.7	2.76	83	0	23	36	91
5	3	1.01	0.068	0.96	1.7	2.76	83	-10	58	86	72
6	3	1.38	0.05	0.96	1.7	2.76	83	-10	51	82	70
7[f]	3	1.01	0.068	0.96	1.7	2.76	4.7	-10	51	86	67
8[f]	3	1.01	0.068	2.76	4.8	0.96	1.6	-10	52	87	62
9[f]	3	1.01	0.068	4.57	7.9	3.94	6.6	-10	64	94	69
10[f]	3	1.01	0.068	8.18	14.2	5.12	8.6	-10	57	90	66
11[f]	2	1.01	0.068	4.57	7.9	3.94	6.6	-10	52	82	68
12[f]	1	1.01	0.068	4.57	7.9	3.94	6.6	-10	25	61	63
13[g]	3	1.01	0.068	4.57	7.9	3.94	6.6	-10	57	86	68

a…CV: check valve; MFC: mass flow controller; SL: 4 mL sample loop; Channel sizes Protrix: 1.0 x 1.0 mm – 1.4 x 1.4 mm

b…The residence time reflects the calculated residence time.

c…Determined by HPLC integration at 254 nm against biphenyl as ETSD. Given values reflect averages of steady state fractions.

d…Conversion of **3** by HPLC peak area integration at 254 nm.

e…Selectivity for **4** vs. chlorinated product **6** by HPLC peak area integration at 254 nm.

f…No g/l separator (see Scheme S2 for the schematic set-up). The residence time $t_{res}2$ also reflects the calculated residence time.

g…No g/l separator. **3** was pumped directly for 45 min.

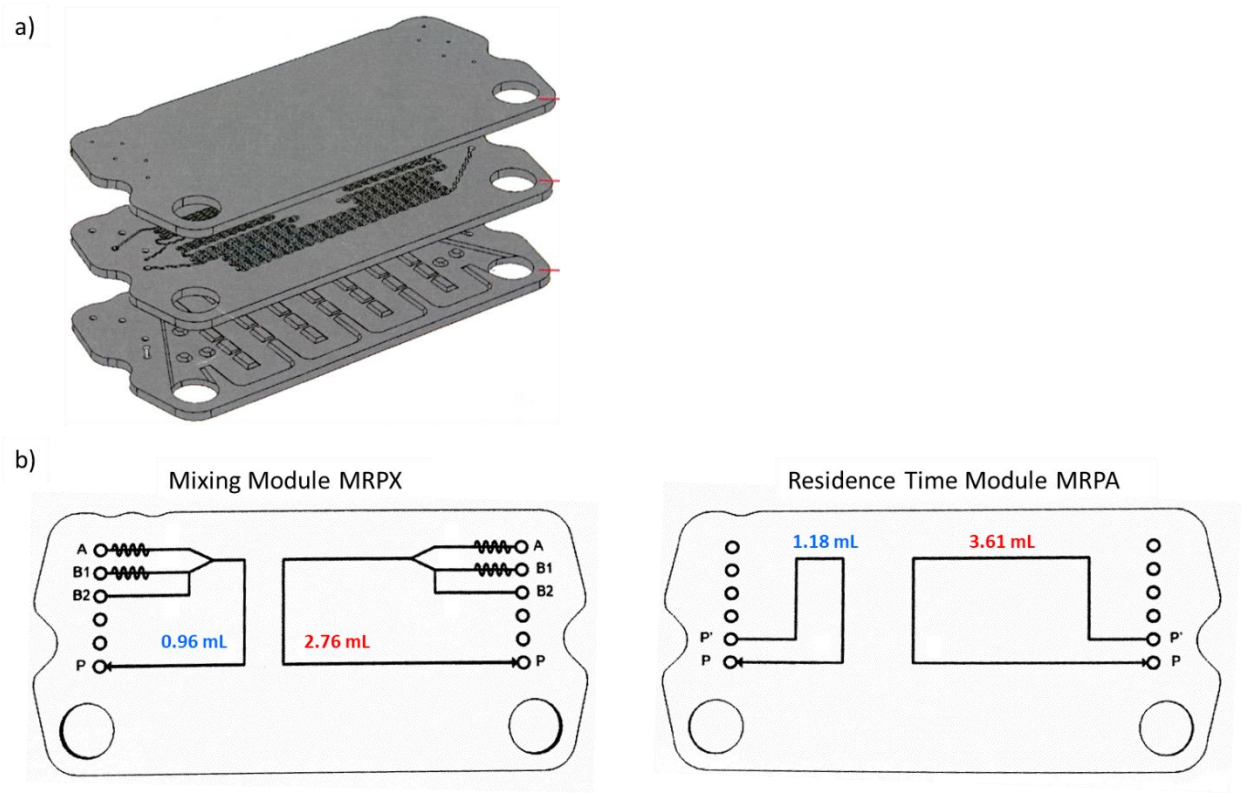
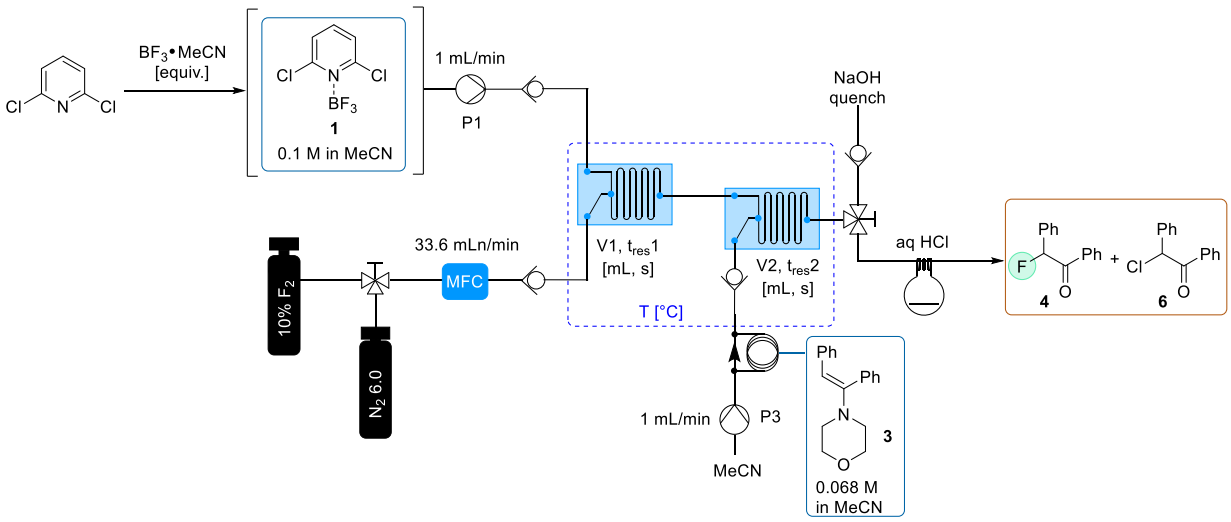


Figure S8. Protrix SiC modules. a) Exploded view of a 3M^{TM} SiC Protrix module – showing process and service channel arrangement. NOTE: SiC reactor modules are diffusion bonded and cannot be opened. b) Schematic of the zig-zag meso-channel layouts for the process fluid. Channel dimensions: 1 x 1 mm (pre-heat and mixer zone), 1.4 x 1.4 mm (residence channel); two independent reaction volumes are present per module.

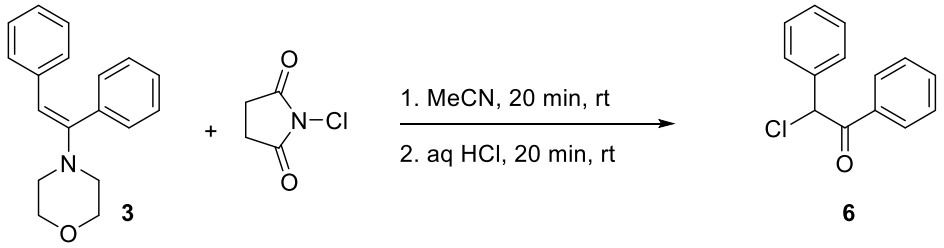


Scheme S2. Schematic set-up for the telescoped N-F generation/enamine fluorination in a SiC reactor without the g/l separator.

Figure S9. Image of the continuous flow set-up for the telescoped diClNFPy **2** generation and fluorination of enamine **3**. CV: **C**heck **V**alve; SV: **S**witching **V**alve; S: Sampling; PS: **P**ressure **S**ensor; PRV: **P**ressure **R**elief **V**alve; IV: **I**njection **V**alve; SL: **S**ample **L**oop; TC: **T**emperature **C**ontrol for the Huber thermostat (not shown); A: DCP-BF_3 complex **1** feed (0.1 M), B: 10% F_2/N_2 feed, C: diClNFPy **2** outlet connected to second reactor volume for the enamine fluorination, D: enamine **3** feed, E: reaction mixture outlet. R: Protrix SiC reactor using 2 modules; 1: Reactor volume 1 for diClNFPy **2** generation; 2: Reactor volume 2 for the fluorination of enamine **3** with in-situ generated diClNFPy **2**.

7. Side Product Identification

For the identification of the side product with an HPLC retention time at 7.0 min, the crude isolated product (after hydrolysis and extraction) of the telescoped fluorination of **3** with in-situ generated diClNFPy **2** was further purified by flash column chromatography. Thereby a mixture enriched with this side product was obtained, which still contained the monofluorinated product **4** and hydrolyzed substrate. GC-MS revealed that the chlorinated 1,2-diphenylethan-1-one was generated as side product. To further corroborate this suggested structure, 2-chloro-1,2-diphenylethan-1-one **6** was synthesized by reaction of substrate **3** with NCS (see Experimental Section and Scheme S3). Comparisons by GC-MS, HPLC, ^{1}H and ^{13}C NMR (Figures S10–S13) confirmed that the side product was chlorinated 1,2-diphenylethan-1-one **6**.



Scheme S3. Synthesis of chlorinated product **6**.

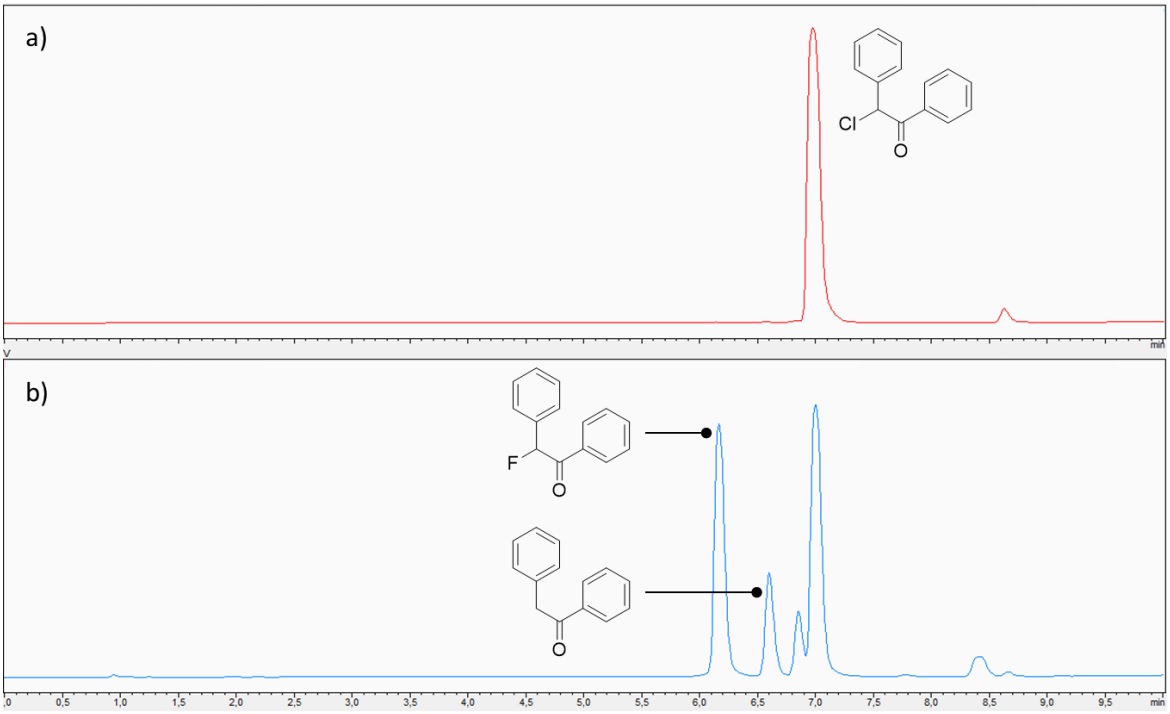


Figure S10. HPLC comparison of synthesized 2-chloro-1,2-diphenylethan-1-one **6** (a) and product obtained after column chromatography of the continuous flow fluorination of enamine **3** (b).

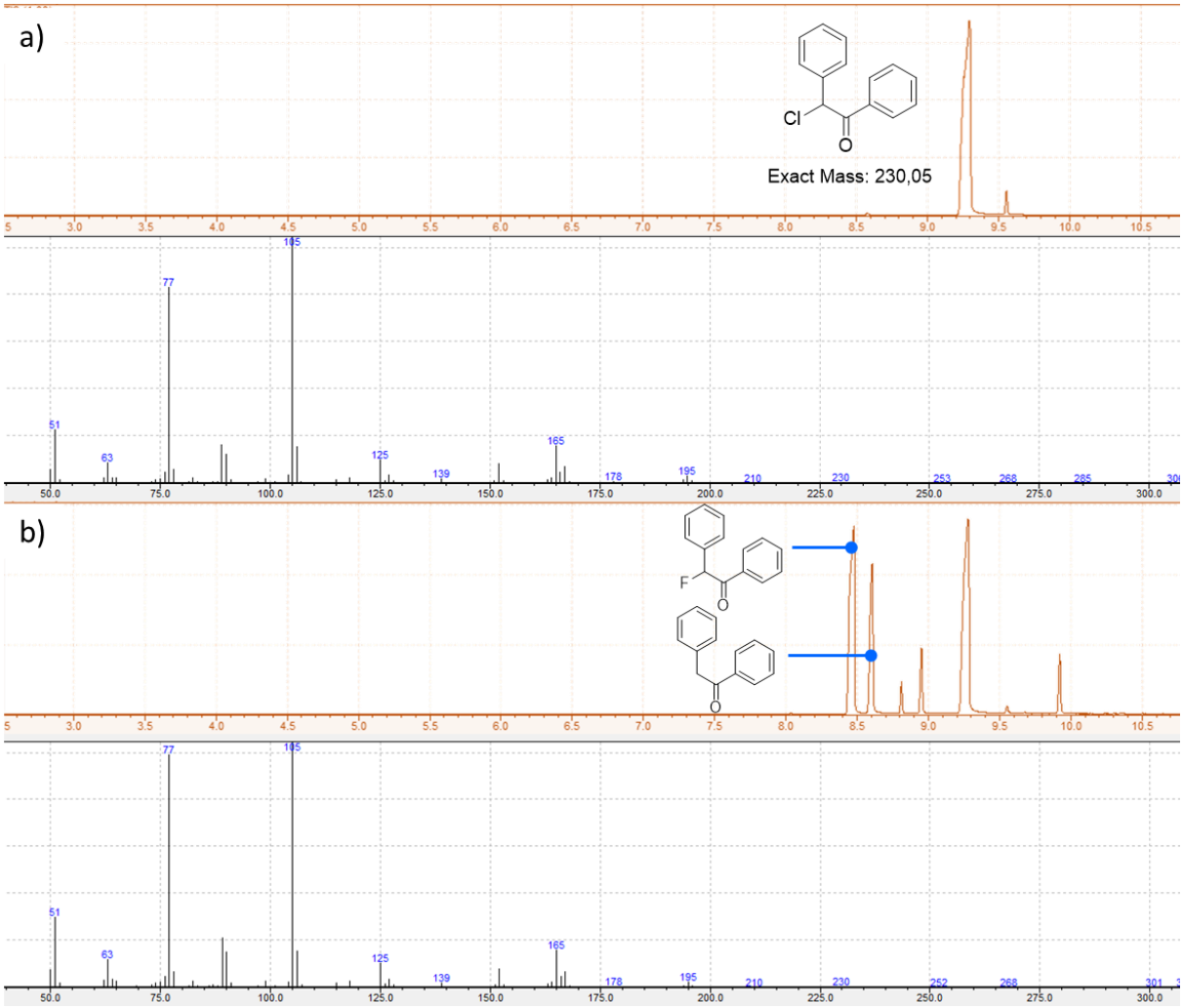


Figure S11. GC-MS comparison of synthesized 2-chloro-1,2-diphenylethan-1-one **6** (a) and product obtained after column chromatography of the continuous flow fluorination of enamine **3** (b).

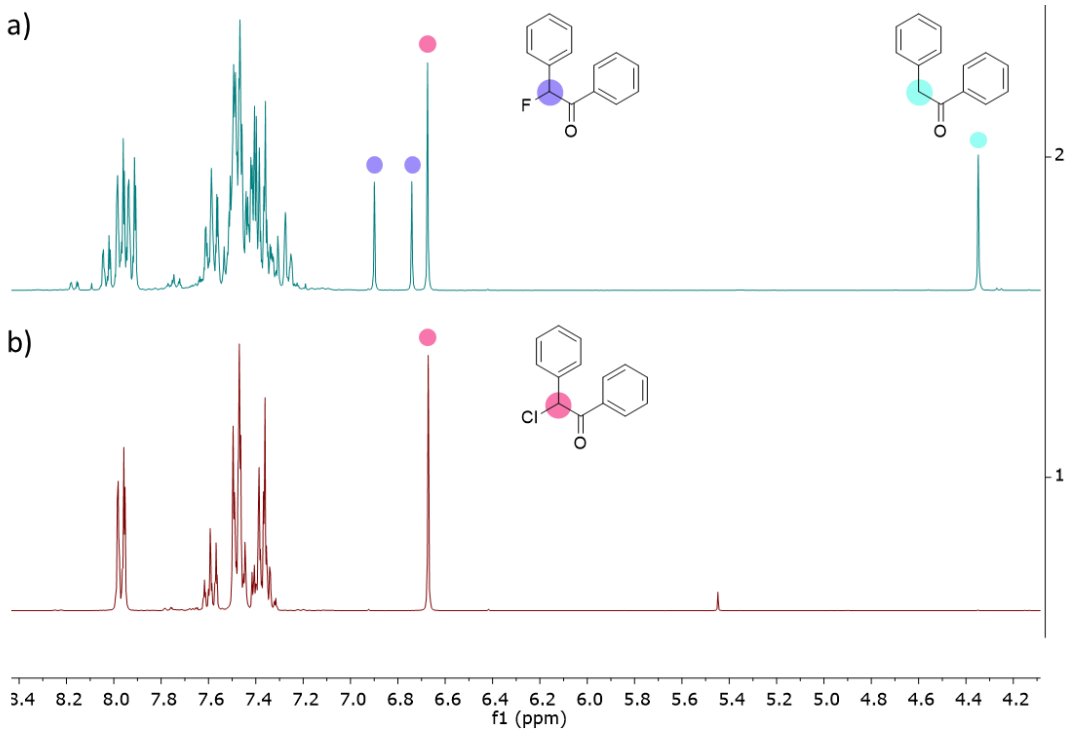


Figure S12. ^{1}H NMR (300 MHz, CD_3CN) comparison of product obtained after column chromatography of the continuous flow fluorination of enamine **3** (a) and synthesized 2-chloro-1,2-diphenylethan-1-one **6** (b).

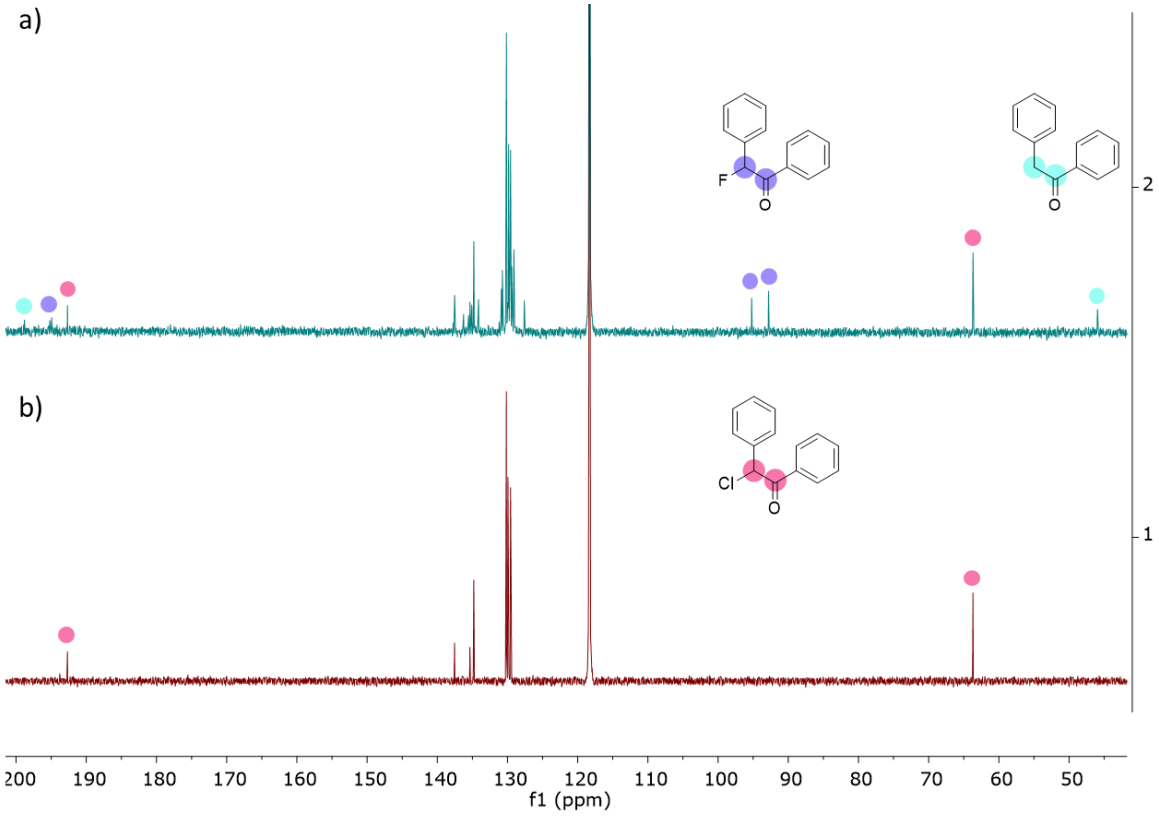
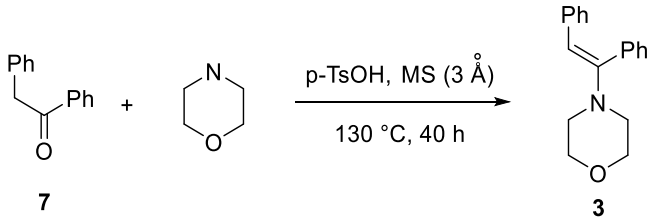


Figure S13. ^{13}C NMR (300 MHz, CD_3CN) comparison of product obtained after column chromatography of the continuous flow fluorination of enamine **3** (a) and synthesized 2-chloro-1,2-diphenylethan-1-one **6** (b).

8. Experimental Procedures

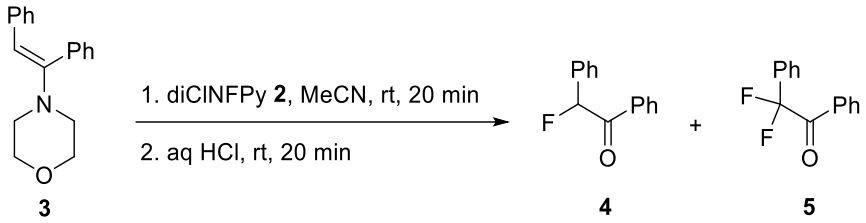
8.1 Synthesis of (*E*)-4-(1,2-Diphenylvinyl)morpholine (**3**)



Deoxybenzoin (15 g, 76.4 mmol), morpholine (100 mL, 1.15 mol, 15 equiv.), *p*-TsOH (0.3 g, 1.6 mmol, 2 mol%) and 10 g of molecular sieves (3 Å) were placed in a 250 mL round bottom flask. The mixture was heated to 130 °C for 40 h. Reaction progress was checked using GC-FID. 100 mL of toluene were added, and the mixture was filtered by suction. The mother liquor was washed with H_2O (3 x 100 mL). The organic phases were then dried over $MgSO_4$. The solvent was evaporated yielding a yellowish-dark brown liquid of high viscosity. The product crystallized from the liquid after standing overnight in the fridge. After recrystallization from MeOH, **3** was obtained as slightly yellow crystals in 54% yield (10.9 g) in >95% purity (^{1}H NMR). The NMR data were in agreement with previously published values [S2].

^{1}H NMR (300 MHz, CD_3CN): δ 7.34–7.25 (m, 5H), 7.02–6.88 (m, 3H), 6.78–6.75 (m, 2H), 5.67 (s, 1H), 3.68–3.65 (m, 4H), 2.85–2.82 (m, 4H). ^{13}C NMR (75 MHz, CD_3CN): δ 152.3, 139.9, 138.1, 131.3, 129.5, 129.3, 129.2, 128.6, 125.1, 106.3, 67.5, 50.3.

8.2 Synthesis of 2-Fluoro-1,2-diphenylethanone (**4**) with Commercial diClNFPy **2** in Batch



50 mL of a 0.07 M solution of 1,2-diphenylvinylmorpholine (**3**) (950.0 mg, 3.58 mmol) and 50 mL of a 0.075 M solution of diClNFPy **2** (954.0 mg, 3.76 mmol, 1.05 equiv.), each in anhydrous MeCN, were combined in a round bottom flask that was prior flushed with Argon. The yellow reaction mixture was stirred for 20 min under Ar atmosphere, then 150 mL of a 2 M aqueous HCl solution were added. The reaction mixture was stirred for 20 min, in which the color faded, and extracted with DCM (3 x 50 mL). The organic phases were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure. Since this product still contained dichloropyridine, the dry product was dissolved in a MeCN/H_2O mixture (1:1) which was evaporated immediately. This step removed remaining dichloropyridine. The residue was dried in a vacuum oven at 50 °C overnight. **4** was obtained in 80% yield (613 mg) in 85% purity by ^{1}H NMR and ^{19}F NMR. Isolated product also contained 6% of difluoro-byproduct **5** and 9% of substrate **7**. The NMR data were in agreement with previously published values [S3].

^{1}H NMR (300 MHz, CD_3CN): δ 7.93–7.90 (m, 2H), 7.62–7.56 (m, 1 H), 7.51–7.46 (m, 4H), 7.44–7.40 (m, 3H), 6.81 (d, J = 48.0 Hz, 1H). ^{19}F NMR (282 MHz, CD_3CN): δ −174.1 (d, J = 47.9 Hz).

8.3 Synthesis of 2-Fluoro-1,2-diphenylethanone (4) with Commercial diClNFPy 2 in Flow

A 4 mL sample loop was charged with a solution of diClNFPy **2** in anhydrous MeCN. The N-F reagent was combined with a solution of enamine **3** in anhydrous MeCN in a T-mixer. Both feeds were pumped with a flow rate of 1 mL/min through a coil reactor (1/16" OD, 0.8 mm ID) at room temperature. For concentrations, equivalents and residence times, see Table S2. Aliquots of the collected fractions were taken for HPLC analysis (254 nm).

8.4 Synthesis of DCP-BF_3 complex 1

A 100 mL volumetric flask was flushed with Argon and charged with 2,6-dichloropyridine (1.51 g, 10 mmol) and BF_3·MeCN (16%) (14.61 mL, 30 mmol, 3 equiv.). The flask was filled with anhydrous MeCN, a magnetic stir bar was added, a septum and an argon balloon were attached. The mixture was stirred for ≥ 10 min at room temperature before use.

8.5 Flow Procedure for the Generation of diClNFPy 2 (Table S1)

The set-up was first flushed and tested for leaks with N_2 6.0, which was fed via a MFC. While still delivering N_2, anhydrous MeCN was pumped by syringe pump P1 at a flow rate of 1 mL/min through a precooling unit (0.3 mL) and the 0.6 mL residence time coil into the g/l-separator. After 1.5 min collection time inside the g/l separator, withdrawal of the separator with a flow rate of 1 mL/min by syringe pump P2 was switched on. The liquid stream of the g/l separator was fed into a second residence time coil (V2). All coils and the g/l separator were placed inside a Dewar, which was cooled to the respective temperature. The set-up was purged with N_2/MeCN for 10 min, then the MeCN feed was switched to the 0.1 M DCP-BF_3 complex **1** feed solution, and after 2 min the N_2 feed was switched to 10% F_2/N_2. Four fractions of 5 mL each were collected, 1 mL was sampled, and 10 µL of TFT were added as reference and external standard for ^{19}F NMR (43 MHz Benchtop) analysis and quantification. Fractions that could not be measured instantly were placed in an ice/salt bath.

The head spaces of the g/l separator and the sampling vessel were connected to a stirred quench solution of 5% aqueous NaOH, which also served as waste quench for not sampled product stream. The headspace of the 5% aqueous NaOH was connected to a 10% aqueous NaOH solution, which served as gas scrubber.

8.6 Telescoped Flow Procedure for the Synthesis of 4 in a Coil Reactor

The set-up was first flushed and tested for leaks with N_2 6.0, which was fed at 33.6 mLn/min via a MFC. While still delivering N_2, anhydrous MeCN was pumped by syringe pump P1 at a flow rate of 1 mL/min through a precooling unit (0.3 mL) and the 0.6 mL residence time coil into the g/l-separator. After 1.5 min collection time inside the g/l separator, withdrawal of the separator with a flow rate of 1 mL/min by syringe pump P2 was switched on. The liquid stream of the g/l separator was fed into a second residence time coil (V2), which was connected to the residence time coil V3 for the fluorination of enamine **3** via a T-mixer. For equilibration, anhydrous MeCN was pumped at 1 mL/min with syringe pump P3. All coils and the g/l separator were placed inside a Dewar, which was cooled to the respective temperature. The set-up was purged with N_2/MeCN for 10 min, then the MeCN feed was switched to the 0.1 M DCP-BF_3 complex **1** feed solution, and after 2 min the N_2 feed was switched to 10% F_2/N_2. After 5 min, enamine **3** was injected via the sample loop and mixed with the outlet stream of generated DiClNFPy **2**. For concentrations, residence times and temperatures, see main manuscript. Four fractions of 1 mL each were collected and for quantitative HPLC analysis (254 nm), 500 µL were added into 1 mL of ETSD stock solution (biphenyl, 0.02 M).

8.7 Telescoped Flow Procedure for the Synthesis of **4** in a Protrix SiC Reactor (Table S3)

The temperature of the SiC reactor was set utilizing a thermostat (Huber) with EtOH as thermofluid. The set-up was first flushed and tested for leaks with N_2 6.0, which was fed at 33.6 mLn/min via a MFC into inlet B1. While still delivering N_2, anhydrous MeCN was fed by syringe pump P1 at a flow rate of 1 mL/min into inlet A. The outlet P was directed into the gravity-based g/l separator. After 1.5 min collection time inside the g/l separator, withdrawal of the separator with a flow rate of 1 mL/min by syringe pump P2 was switched on. The liquid stream of the g/l separator was fed into inlet B1 of the second independent reactor volume (V2) of the modules, where it was mixed with the enamine **3** feed, which was pumped at 1 mL/min with syringe pump P3 into inlet A. For equilibration, anhydrous MeCN was pumped with P3. The set-up was purged with N_2/MeCN for 10 min, then the MeCN feed was switched to the 0.1 M DCP-BF_3 complex **1** feed solution, and after 2 min the N_2 feed was switched to 10% F_2/N_2. After 5 min, enamine **3**was injected via the sample loop and mixed with the outlet stream of generated DiClNFPy **2**. For concentrations, residence times and temperatures, see Table S4. Four fractions of 1 mL each were collected and for quantitative HPLC analysis (254 nm), 500 µL were added into 1 mL of ETSD stock solution (biphenyl, 0.02 M).

For experiments without g/l separator, the outlet stream of generated diClNFPy **2** was directly attached to inlet B1 at the second independent reactor volume (V2) of the modules.

For product isolation, the reaction at the conditions of entry 13 (Table S4) was run continuously for 45 min, with the enamine feed pumped directly, omitting the sample loop. The steady state fractions were combined and worked up as described in Section 8.2. **4** was obtained in 75% yield (573 mg) as orange-brown solid. Isolated product also contained 25% of chlorinated byproduct **6** and 16% of substrate **7**.

^{1}H NMR (300 MHz, CD_3CN): δ 7.93–7.90 (m, 2H), 7.59–7.57 (m, 1 H), 7.50–7.46 (m, 4H), 7.44–7.40 (m, 3H), 6.81 (d, *J* = 48.0 Hz, 1H)i. ^{13}C NMR (75 MHz, CD_3CN): δ 195.1 (d, *J* = 21.0 Hz), 135.3, 135.1, 134.8, 130.9 (d, *J* = 3.0 Hz), 130.2, 129.8, 129.6 (d, *J* = 2.3 Hz), 129.1 (d, *J* = 5.3 Hz), 94.0 (d, *J* = 180 Hz). ^{19}F NMR (282 MHz, CD_3CN): δ −174.1 (d, *J* = 45.1 Hz).

8.8 Synthesis of 2-Chloro-1,2-diphenylethan-1-one (6)

5 mL of a 0.07 M solution of 1,2-diphenylvinylmorpholine (**3**) (95.0 mg, 0.36 mmol) and 5 mL of a 0.075 M solution of *N*-chloro-succinimide (50.2 mg, 0.38 mmol, 1.05 equiv.), each in anhydrous MeCN, were combined in a round bottom flask that was prior flushed with Argon. The greenish reaction mixture was stirred for 20 min under Ar atmosphere, then 15 mL of a 2 M aqueous HCl solution were added. The reaction mixture was stirred for 20 min, in which the color faded, and extracted with DCM (3 x 10 mL). The organic phases were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the product was dried within a vacuum oven at 50 °C overnight. **6** was obtained as off-white solid in 71% yield (85 mg). The NMR data were in agreement with the previously published values [S4].

^{1}H NMR (300 MHz, CD_3CN) δ 7.99–7.95 (m, 2H), 7.62–7.56 (m, 1H), 7.50–7.44 (m, 4H), 7.42–7.34 (m, 3H), 6.67 (s, 1H). ^{13}C NMR (75 MHz, CD_3CN) δ 192.7, 137.5, 135.4, 134.8, 130.2, 129.9, 129.8, 129.6, 63.7.

9. NMR Spectra of Isolated Compounds

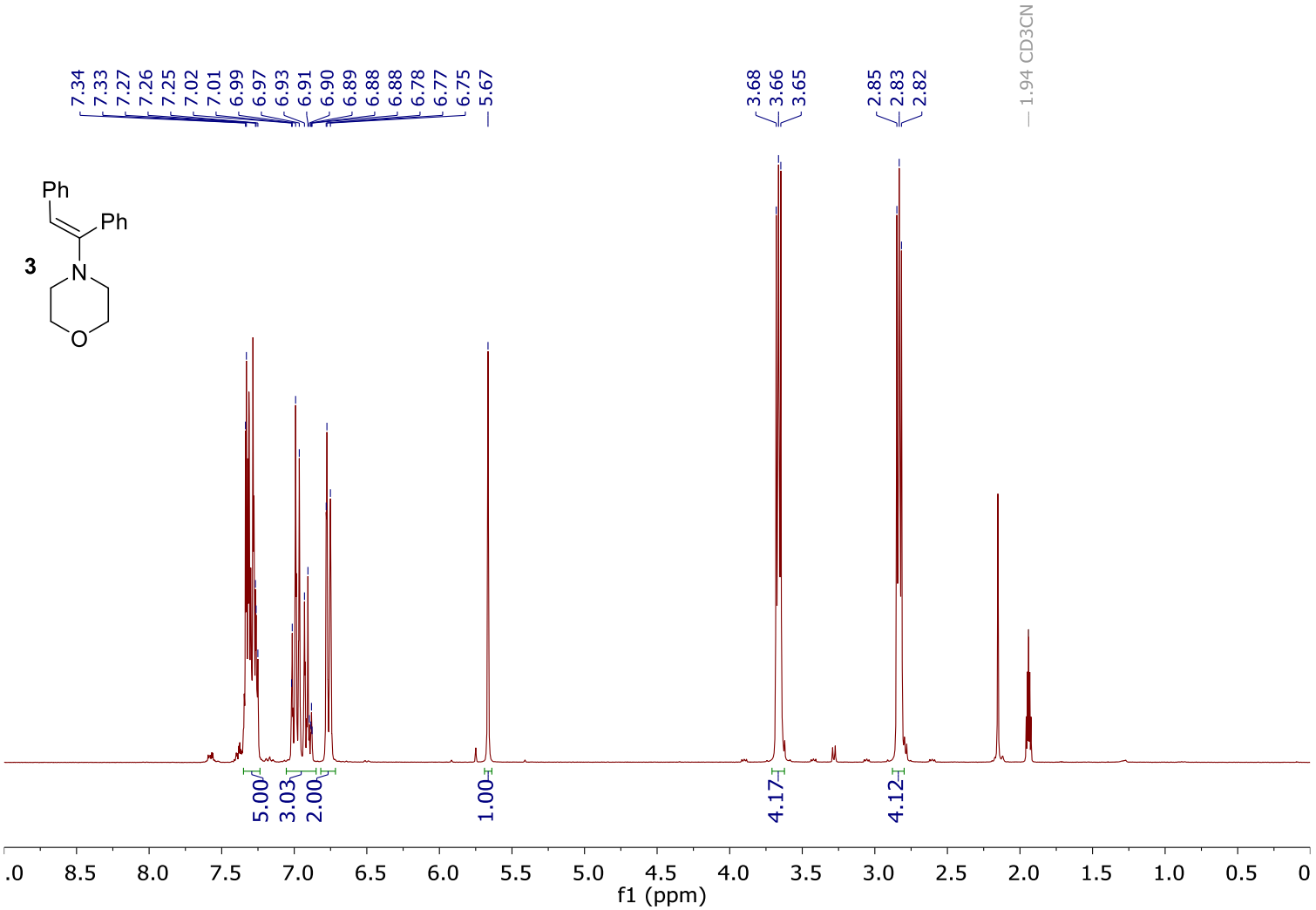


Figure S14. ^{1}H NMR (300 MHz, CD_3CN) of diphenylvinylmorpholine **3**.

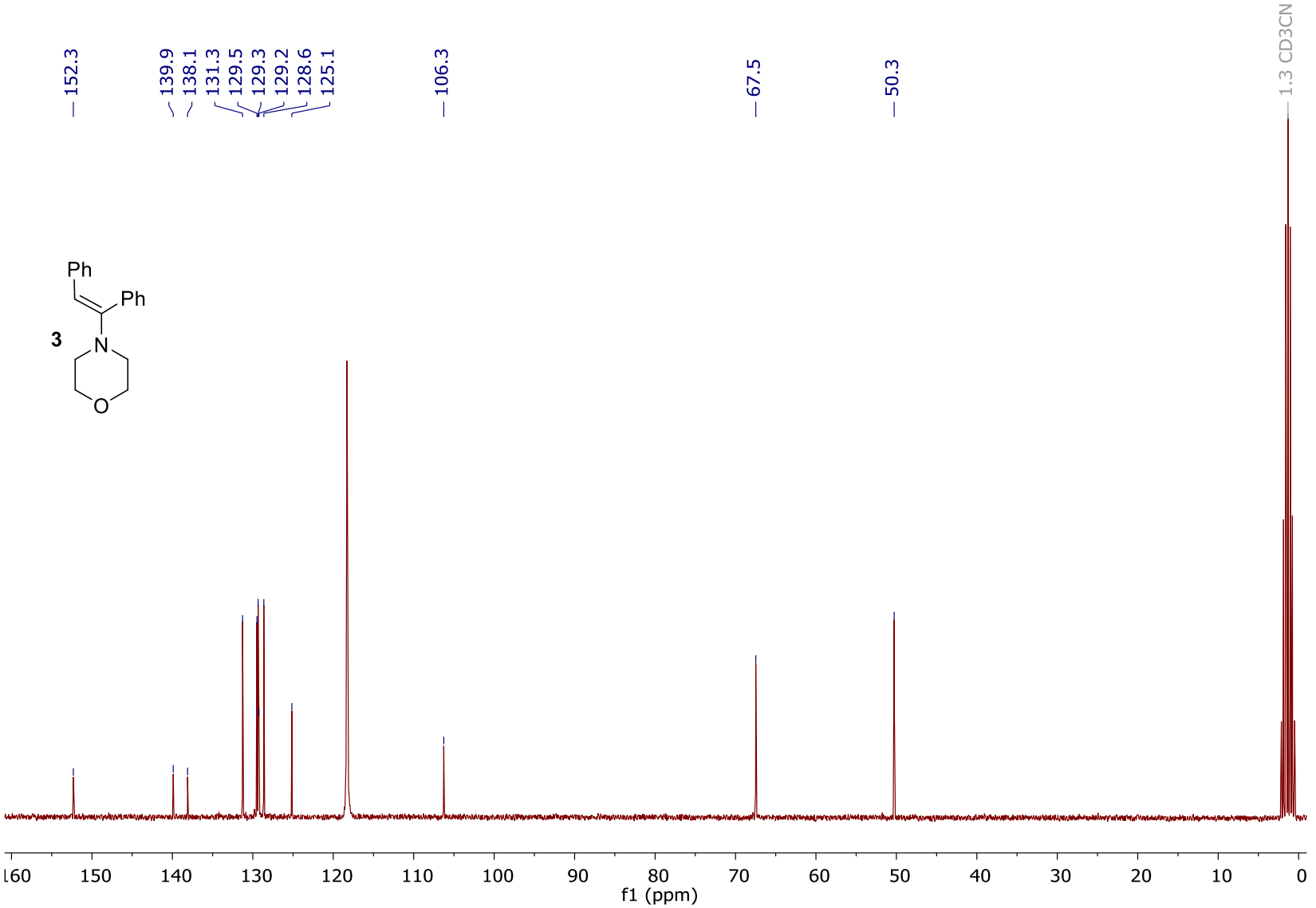


Figure S15. ^{13}C NMR (75 MHz, CD_3CN) of diphenylvinylmorpholine **3**.

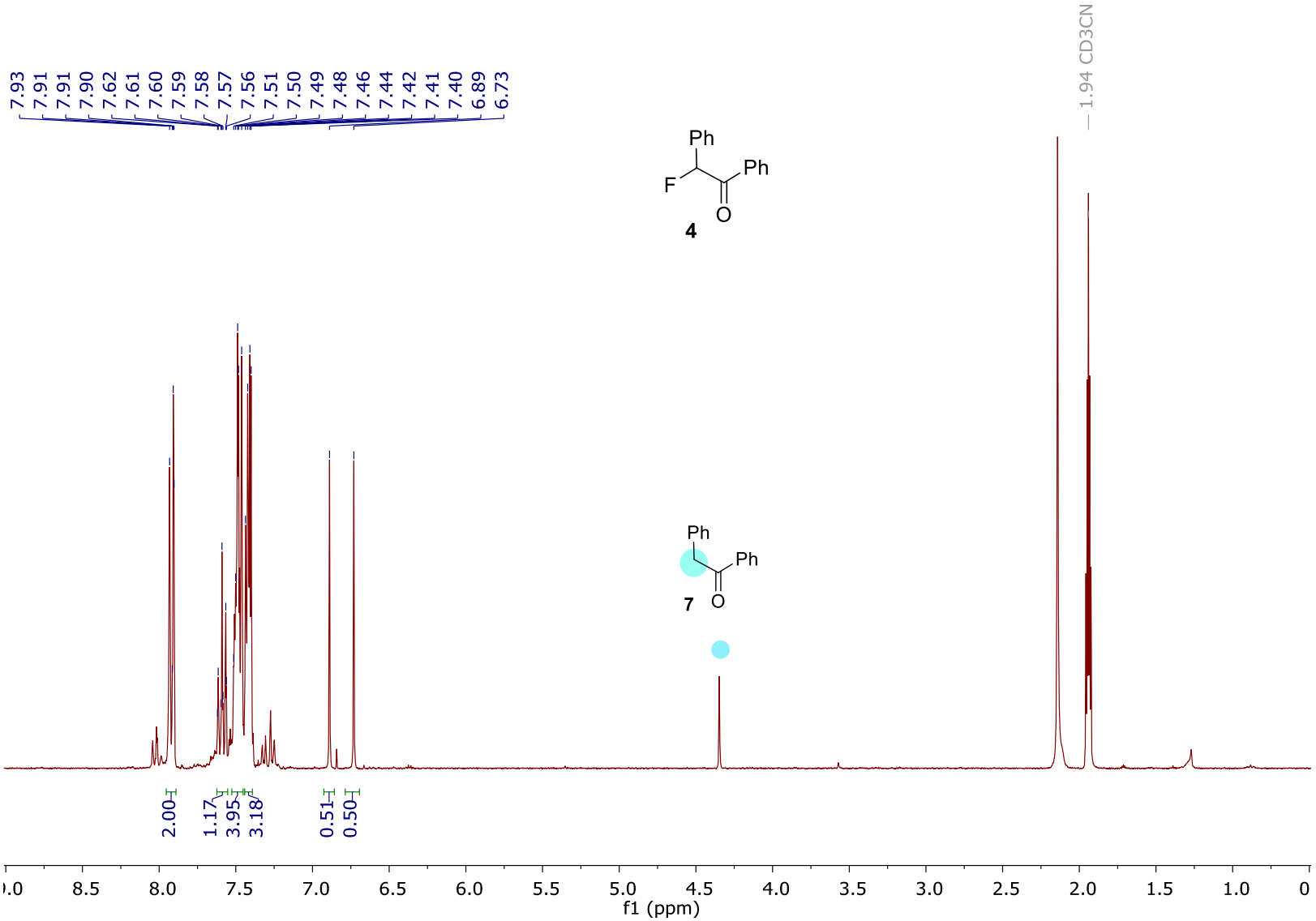


Figure S16. ^{1}H NMR (300 MHz, CD_3CN) of crude isolated (after extraction) 2-fluoro-1,2-diphenylethan-1-one (**4**), synthesized with commercial **2** in batch.

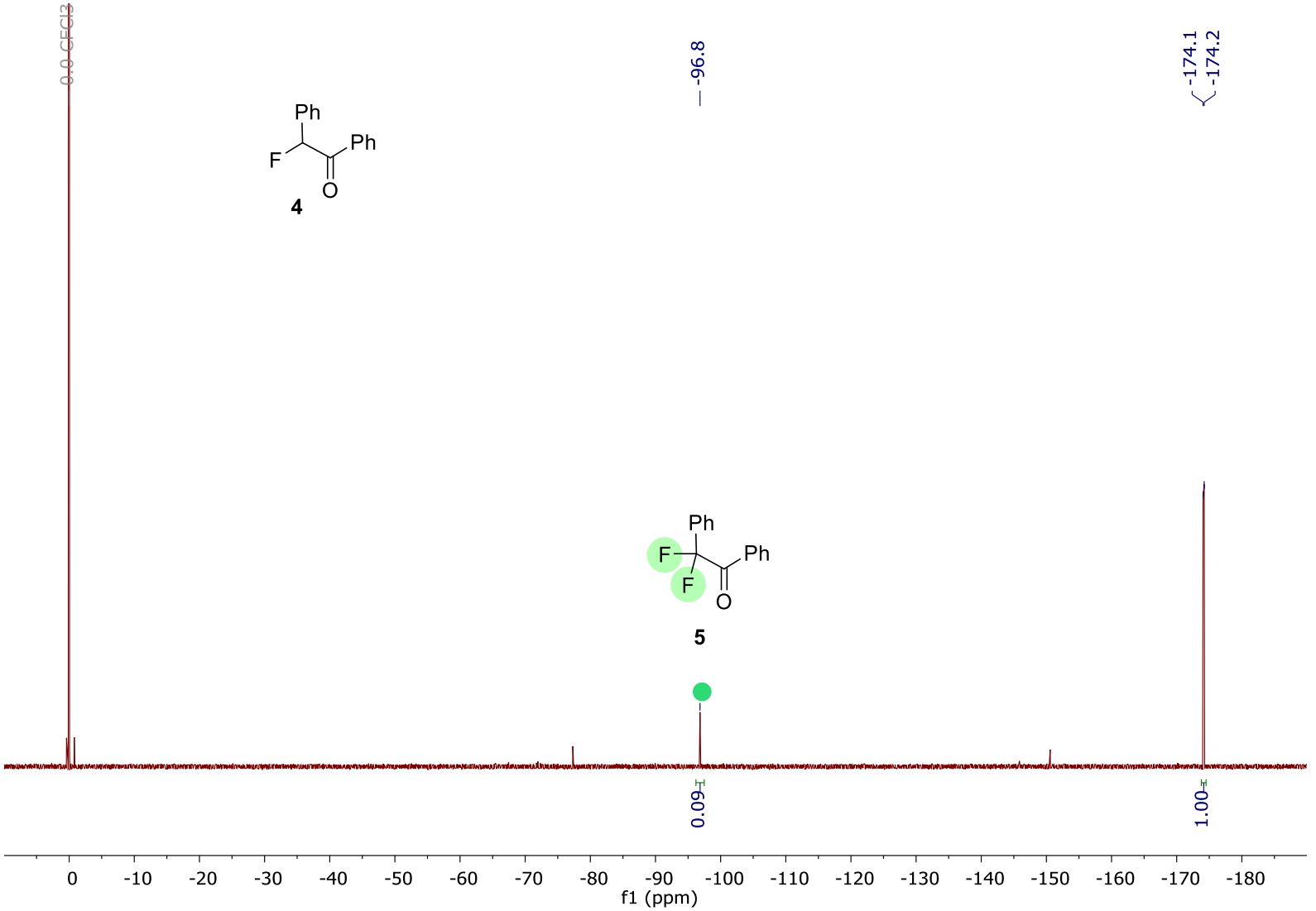


Figure S17. ^{19}F NMR (282 MHz, CD_3CN) of crude isolated (after extraction) 2-fluoro-1,2-diphenylethan-1-one (**4**), synthesized with commercial **2** in batch. The signal at −77.3 ppm originates from an impurity of CD_3CN.

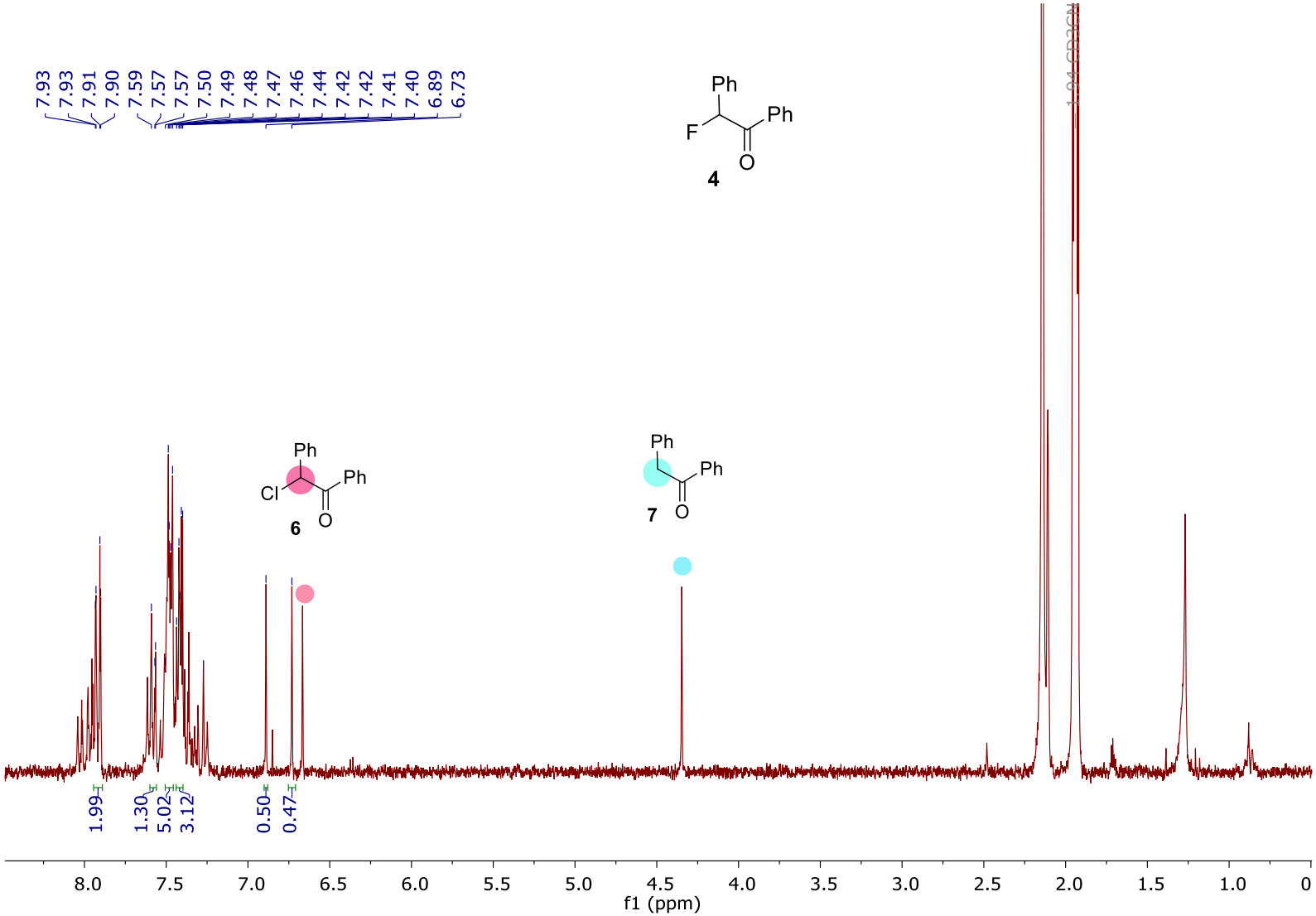


Figure S18. ^{1}H NMR (300 MHz, CD_3CN) of crude isolated (after extraction) 2-fluoro-1,2-diphenylethan-1-one (**4**), synthesized with in-situ generated **2** in continuous flow.

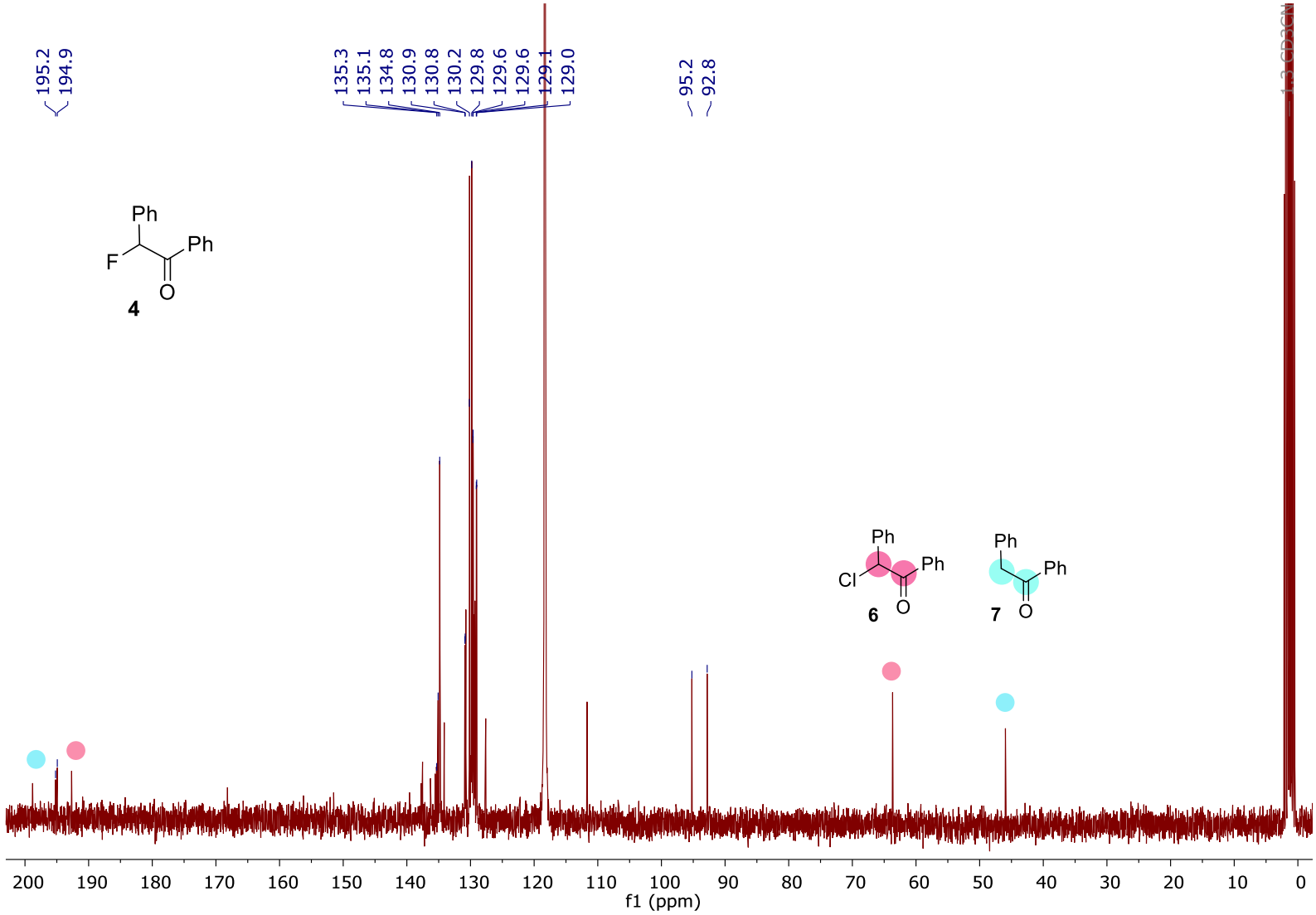


Figure S19. ^{13}C NMR (75 MHz, CD_3CN) of crude isolated (after extraction) 2-fluoro-1,2-diphenylethan-1-one (**4**), synthesized with in-situ generated **2** in continuous flow.

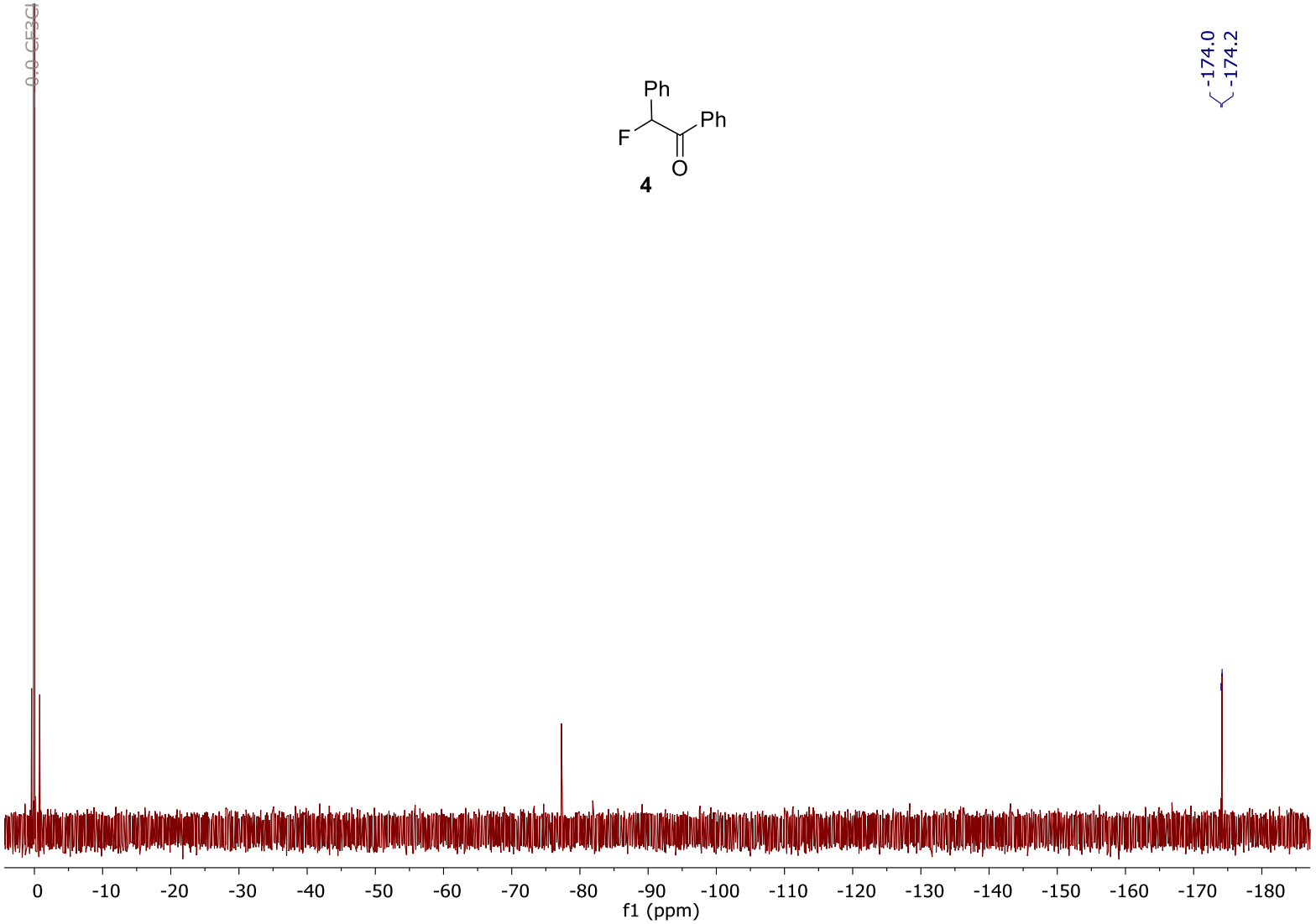


Figure S20. ^{19}F NMR (282 MHz, CD_3CN) of crude isolated (after extraction) 2-fluoro-1,2-diphenylethan-1-one (**4**), synthesized with in-situ generated **2** in continuous flow. The signal at −77.3 ppm originates from an impurity of CD_3CN.

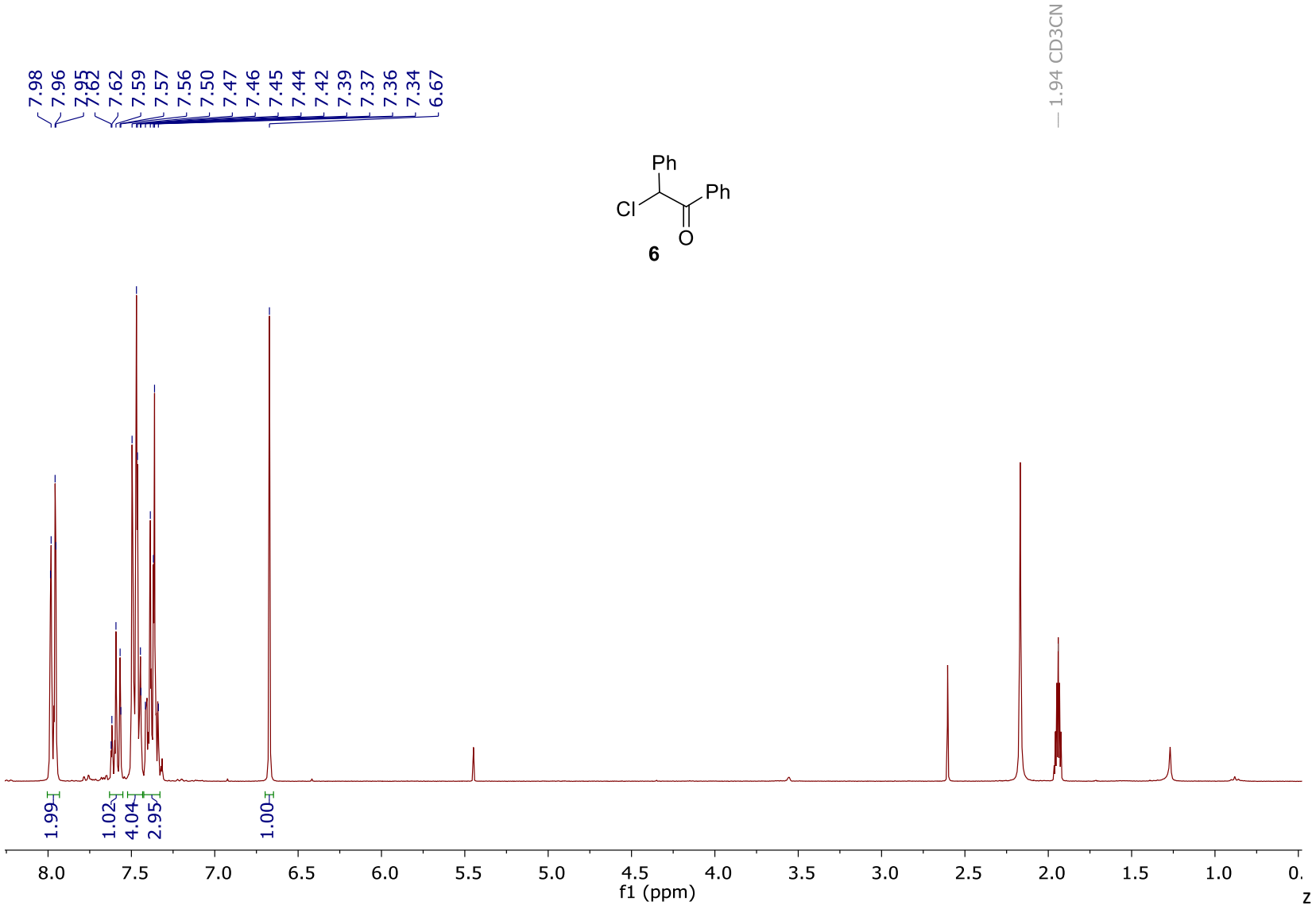


Figure S21. ^{1}H NMR (300 MHz, CD_3CN) of crude isolated (after extraction) 2-chloro-1,2-diphenylethan-1-one (**6**).

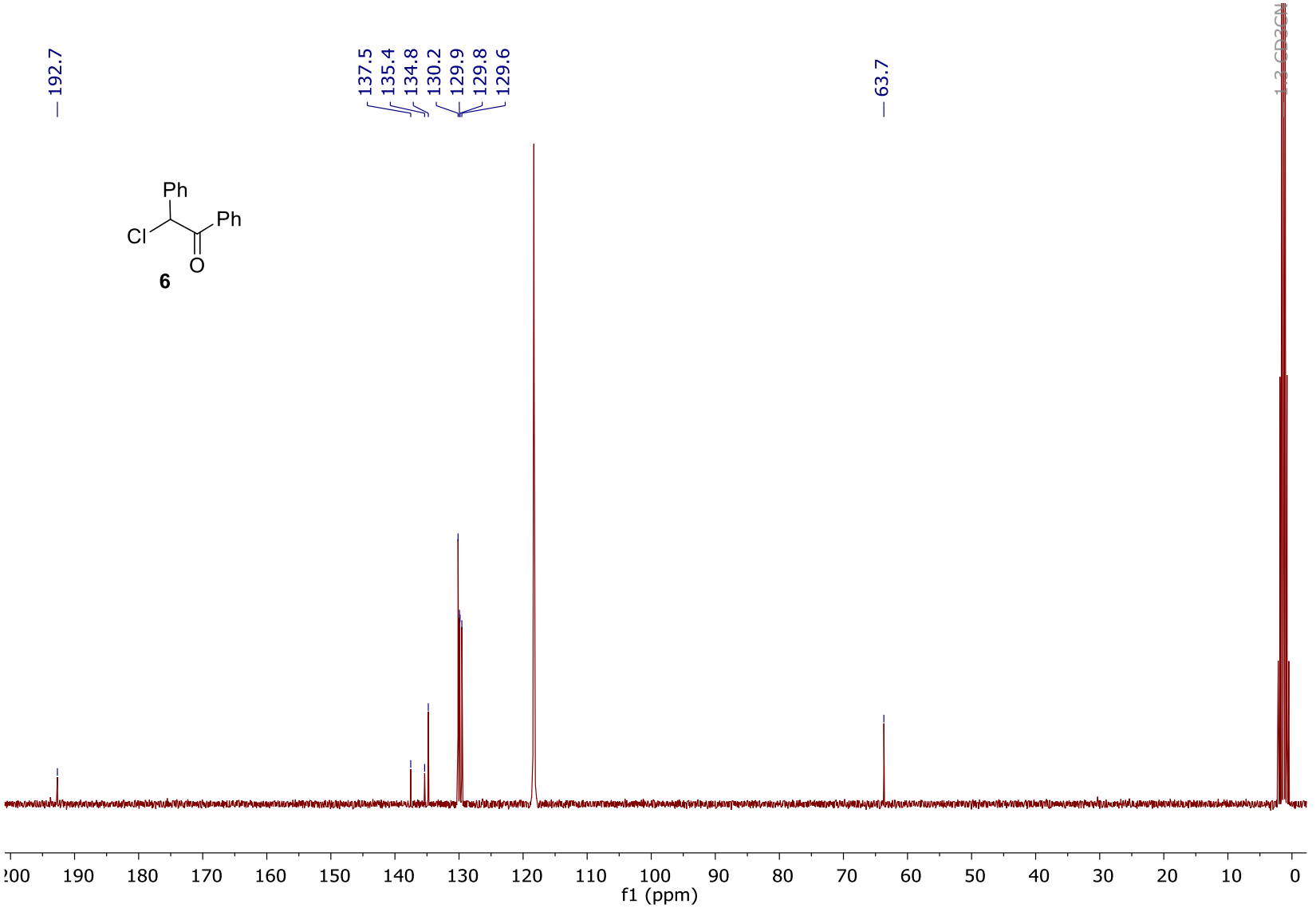


Figure S22. ^{13}C NMR (75 MHz, CD_3CN) of crude isolated (after extraction) 2-chloror-1,2-diphenylethan-1-one (**6**).

10.References

[S1] Znidar D, Dallinger D, Kappe CO (2022) Practical Guidelines for the Safe Use of Fluorine Gas Employing Continuous Flow Technology. ACS Chem Heal Saf 29:165–174.

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[S4] Jobin-Des Lauriers A, Legault CY (2015) Iodine(III)-Mediated Oxidative Hydrolysis of Haloalkenes: Access to α-Halo Ketones by a Release-and-Catch Mechanism. Org Lett 18:108–111.