Electronic Supplementary Information

Continuous photochemical benzylic bromination using *in situ* generated Br_2: Process intensification towards optimal PMI and throughput

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1. Contents

2. General Information

2.1. Materials and Methods

4-Fluorotoluene (97%) was purchased from Fluorochem. 2,4-Dichlorotoluene (>98%) and 2,6-dichlorotoluene (>99%) were purchased from TCI. Hydrobromic acid (48% aq. solution) was purchased from Sigma Aldrich. Sodium bromate (99.5%) was purchased from Alfa Aesar. Other reagents and solvents were obtained from standard commercial vendors (Sigma-Aldrich, VWR or TCI) and were used without further purification.

Note: the reaction was found to be very sensitive to impurities. For example, a batch of 2,6-dichlorotoluene from a different supplier (AKScientific) was found to perform poorly in this chemistry (10% vs >99% NMR assay yield), despite having a high purity (99.8% by GC). It is proposed that the problem may be caused by metal contamination, acting as a radical quencher.

NMR spectra: for reaction optimization, a 43 MHz benchtop NMR (Magritek Spinsolve Ultra) was used, for either ^{1}H or ^{19}F NMR. For verification of benchtop NMR results and product characterization, high resolution ^{1}H, ^{19}F and ^{13}C NMR spectra were recorded on a Bruker 300 MHz instrument at 300 MHz, 282 MHz and 75 MHz, respectively. Chemical shifts (δ) are expressed in ppm downfield from TMS as internal standard. The letters s, d, dd, t, q, and m are used to indicate singlet, doublet, doublet of doublets, triplet, quadruplet, and multiplet. The prefix br denotes a broad peak.

Infrared spectra: measured on a Bruker alpha p instrument, using attenuated total reflectance (ATR). Spectra were processed using OPUS v6.5 software.

Light source characterization: emission spectra were recorded using a fiber-coupled Avantes Starline AvaSpec-2048 spectrometer and were processed using Avasoft 8.7 software.

Flash column chromatography: automated flash column chromatography was performed on a Biotage Isolera system using columns packed with KP-SIL, 60 Å (32-63 µm particle size) silica.

Melting point: were measured using a Stuart SMP3 melting point apparatus. These were corrected to a sample of benzophenone, with a known melting point of 48.5 °C (3.4 °C correction).

2.2. Flow Reactor Setup

The reactions were conducted in a commercial continuous-flow reactor: Corning AdvancedFlow Lab Photo Reactor (Figure S1). Syrris Asia syringe pumps were used to deliver both streams for the bromine generator.

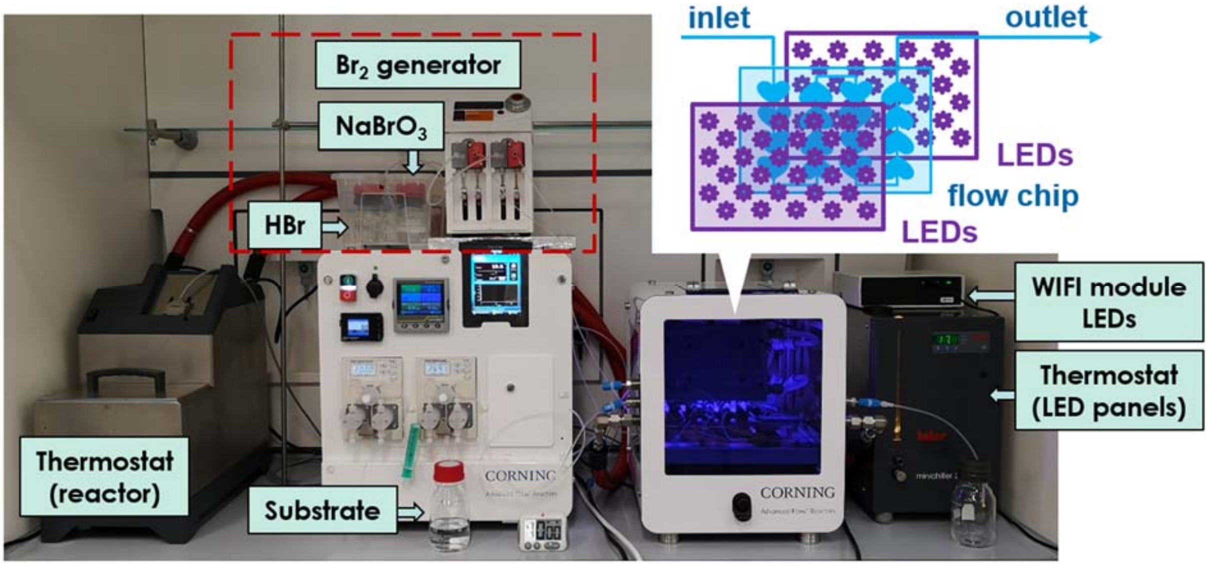


Figure S1. Photograph of commercial reactor setup, from left to right: **a)** thermostat for reaction plate; **b)** control module, containing pumps, mass flow controller, Huber controller and data logger; **c)** Syrris Asia pump for delivering Br_2 generator streams; **d)** fluidic module housing, with tinted plastic panels for light containment; **e)** thermostat for LED panels; **f)** wireless receiver for LED control.

Reactor module (G1LF fluidic module): The flow reactor used in this work consisted of a compact glass fluidic module (155 × 125 × 8 mm size, 0.4 mm channel depth, 2.77 mL internal volume), encased within a high capacity heat exchange channel (20 mL volume).

Light source: LED panels were mounted on both sides of the fluidic module (40 mm from the centre of the process stream). Each LED panel was equipped with 20 LEDs of 6 different wavelengths (120 LEDs in total) and a heat exchanger (T = 15 °C). The LED wavelength and intensity was controlled externally using a web-based interface, connected wirelessly to a router. This study utilized 405 nm LEDs; see details on LED power and emission spectra below, Table S1 and Figure S2.

Table S1. Power of LEDs of used in this study.

Peak wavelength [nm]	Radiant flux per LED [W]	Total radiant flux per reaction plate [W]	Photon flux [mmol/h][a]
405	1.42	56.8	690

[a]Photon flux is calculated based on the radiant flux specified in the respective LED data sheet.

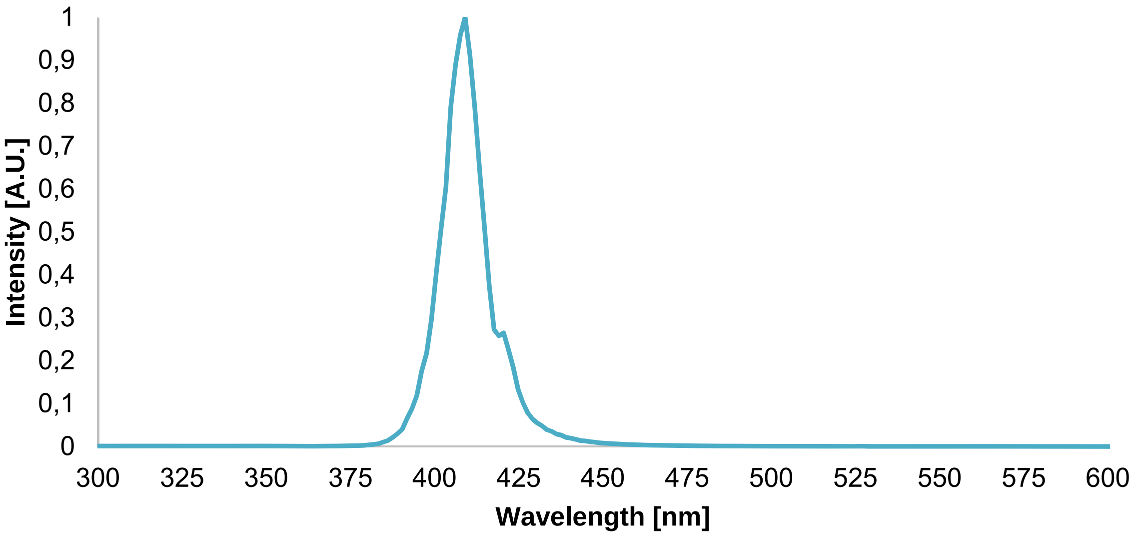


Figure S2. Emission spectrum of LEDs used in this study.

Temperature control: Thermal regulation of the LED panels was carried out using a Huber Minichiller 280 filled with 30% ethylene glycol in water. Thermal regulation of the glass fluidic module was carried out using a Huber Ministat 230 filled with silicon oil (–20 °C to 195 °C).

Pumps: The substrate solution was delivered to the photoreactor using a FLOM UI 22-110DC HPLC pump (0.01-10 mL/min; wetted parts: PTFE, PCTFE, FFKM and ruby).

The Br_2 generator solutions were delivered using a Syrris Asia reciprocating syringe pump, equipped with “red” syringes (2.5 mL / 5 mL volume; 0.05-10 mL/min flow rate; wetted parts: PTFE and glass).

General connections: Connection between the pumps, fluidic module input and output was achieved using 1/8” (external diameter) PFA tubing (Swagelok), using metal-free connectors (Swagelok MS-GC-2 swaging system). Other connections used 1/16” (external diameter) PFA tubing, with 1/4” PTFE finger tight fittings. **Note: Br_2 is incompatible with PEEK material, so PTFE connectors and fittings should be used wherever possible.**

Sample loop: Optimization experiments were conducted using an Upchurch 6-way switching valve to inject the reaction mixture (part # V-450, https://www.idex-hs.com/store/injection-valve-2-postion-6-port-040-black.html), with a 5 mL sample loop (made from 1/16” outer diameter, 0.8 mm inner diameter PFA tubing) installed.

2.3. General procedure for optimization experiments in flow

The bromination of substrate **1** was optimized using a sample loop to inject the substrate, whereas substrates **4** and **6** were pumped directly through the reactor.

The substrate solution was prepared by dissolving the toluene-derived substrate in chlorobenzene in a volumetric flask to give a 0.5-4 M solution. In some cases, the substrate was used without dilution (neat reactions). The NaBr/$NaBrO_3$ solution (1st generation Br_2 generator) was prepared by dissolving NaBr (34.4 g, 334 mmol) and $NaBrO_3$ (9.96 g, 66 mmol) in deionized water, in a 100 mL volumetric flask. The 2.2 M $NaBrO_3$ solution (2nd/3rd generation Br_2 generator) was prepared by dissolving $NaBrO_3$ (83.0 g, 550 mmol) in deionized water, in a 250 mL volumetric flask. The HBr (48%) was either used directly, or diluted to give a 4 M solution (i.e. 67.4 g HBr diluted to 100 mL total volume with water).

A collection flask (waste) was charged with a saturated solution of sodium thiosulfate and was stirred with a magnetic stirrer. The reactor was turned on (LEDs, pump and thermostats) the system was given ~10 min to equilibrate. The 5 mL sample loop was charged with the substrate solution and injected into the reactor. To account for any dilution effects at the edges of the injected sample, only the central fraction (~1 mL) was collected into a vial containing 2 mL of saturated sodium thiosulfate solution. After adding ~2 mL DCM and mixing the biphasic system until all the bromine was quenched, the organic phase was analyzed by benchtop NMR (^{19}F for substrate **1** or ^{1}H for substrates **4** and **6**).

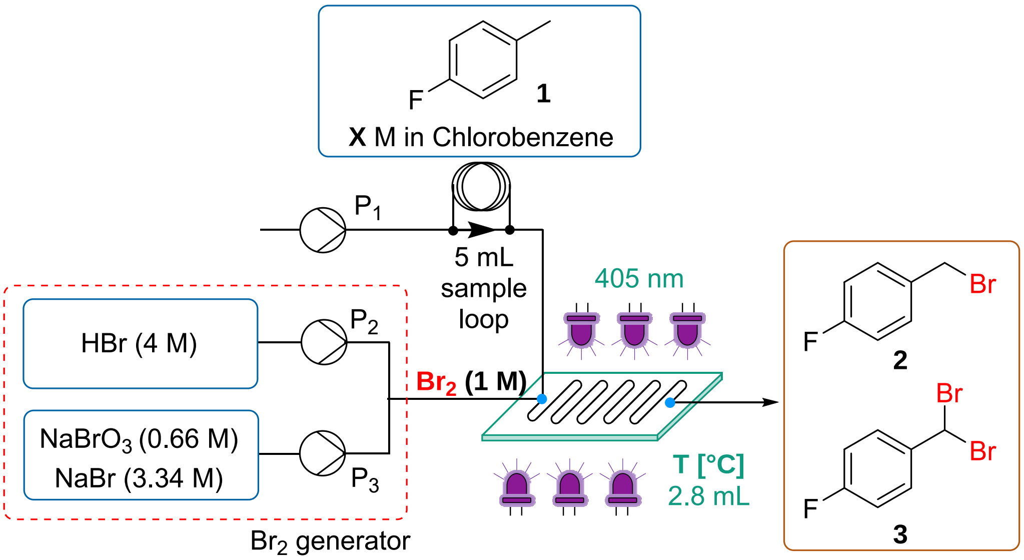
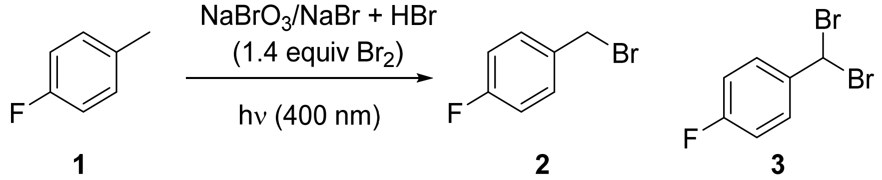


Figure S3. A schematic representation of the flow setup used in these experiments, using the example of the bromination of **1**, using Br_2 generator v1.

3. Additional optimization data

3.1. Solvent selection experiments in batch

Table S2. Initial scoping experiments in batch, to determine solvent performance using *in situ* generated Br_2.



Entry	Solvent	Reaction time [min][a]	1 [%][b]	2 [%][b]	3 [%][b]
1	MeCN	60	100	0	0
2	EtOAc	45	86	14	0
3	DCM	6	0	58	42
4	iPrOAc	60	62	38	0
5	MTBE	70	73	27	0
6	Me-THF	7	100	0	0
7	cyclohexane	7	5	65	30
8	PhCl	3	0	64	36
9	AcOH	60	100	0	0
10	propylene carbonate	60	100	0	0

[a] Reaction was analyzed once the red bromine color was entirely consumed, or after ~60 min.
[b] Reaction composition was measured using benchtop (43 MHz) ^{19}F NMR.

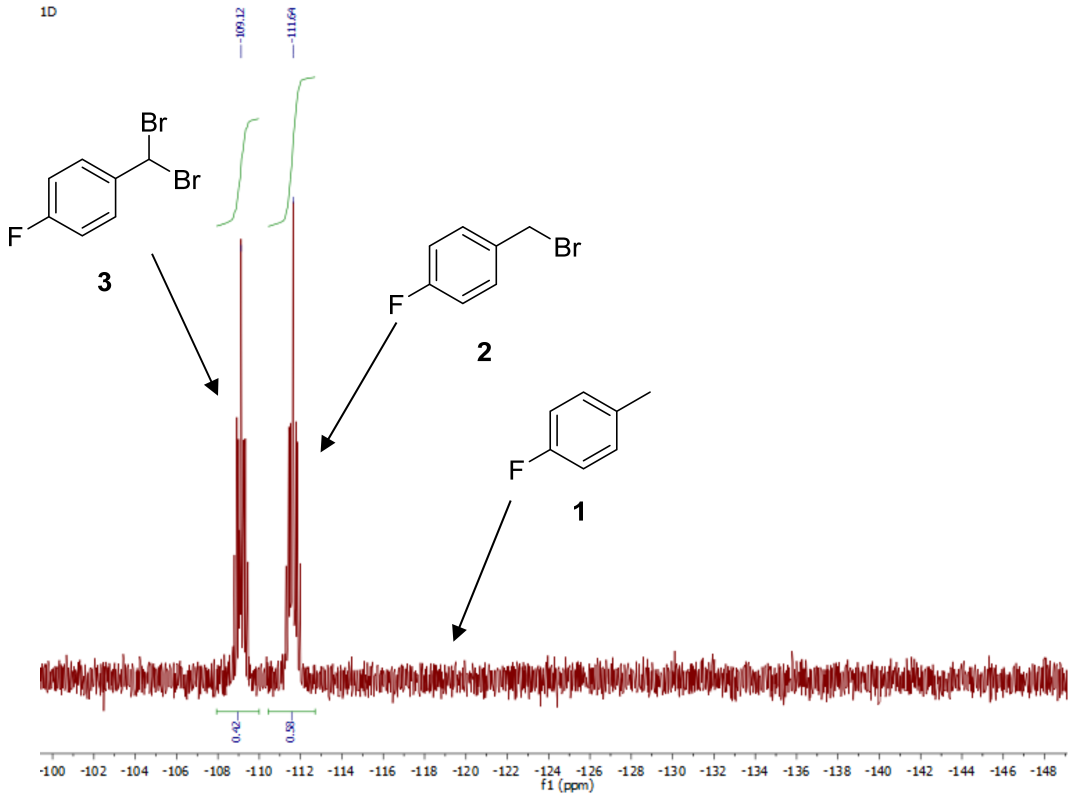


Fig. S1. Representative 43 MHz ^{19}F NMR, showing final reaction mixture composition.

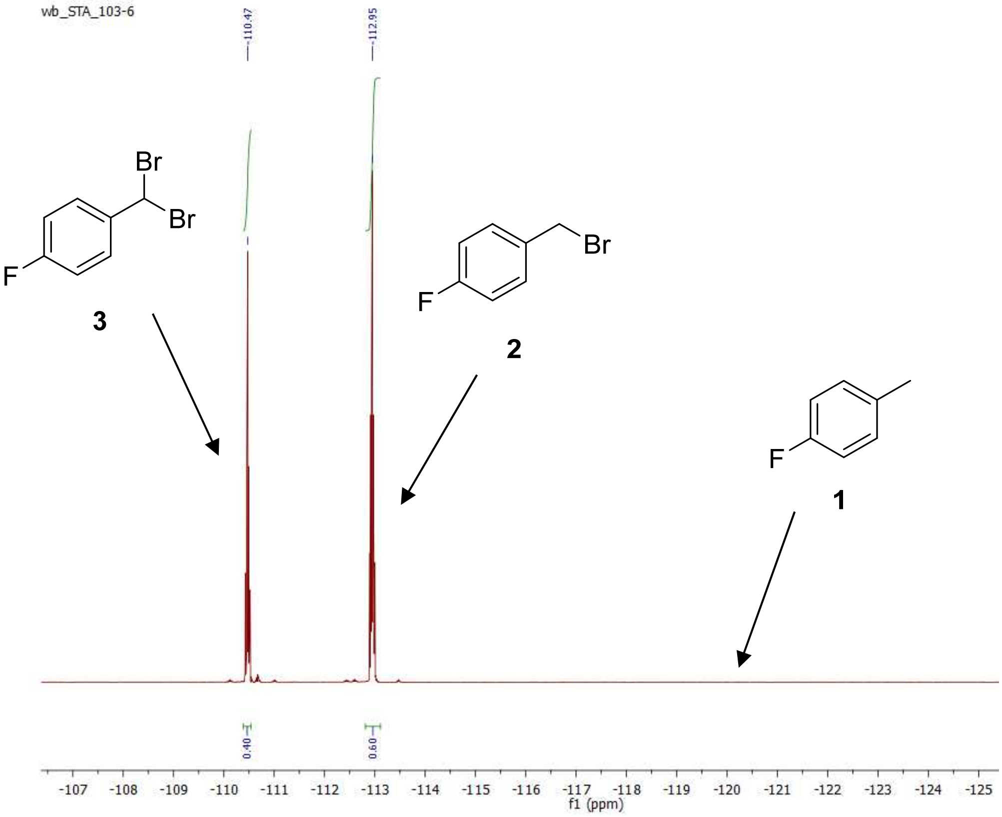
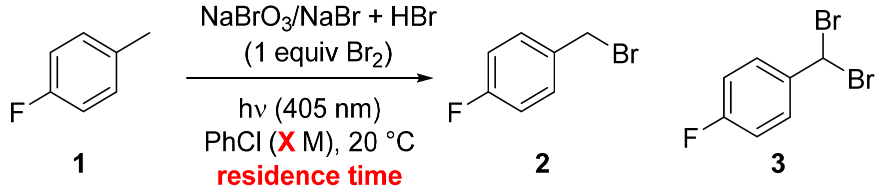


Fig. S2. Representative 282 MHz ^{19}F NMR, showing final reaction composition.

3.2. Initial optimization in flow (Br_2 generator v1)

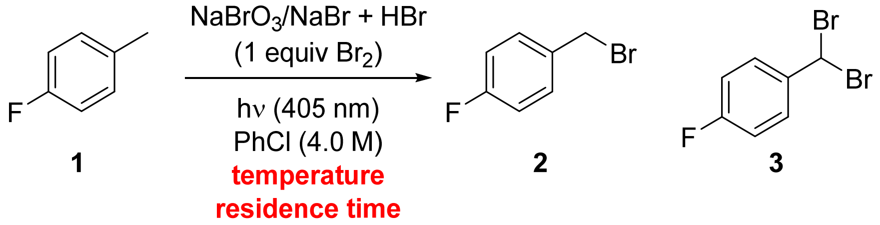
Table S3. Initial scoping experiments in flow, using the Br_2 generator v1.



Entry	Concentration [M]	Residence time [s]	1 [%][a]	2 [%][a]	3 [%][a]
1	0.5	15	19	74	7
2	0.5	30	14	78	8
3	0.5	60	18	77	6
4	1.0	10	38	59	3
5	**1.0**	**15**	**20**	**73**	**8**
6	1.5	15	63	37	0
7	1.5	20	18	75	7
8	1.5	30	17	75	8
9	**2.0**	**15**	**57**	**42**	**1**
10	2.0	30	16	76	8
11	**4.0**	**15**	**93**	**7**	**0**
12	**4.0**	**30**	**69**	**31**	**0**
13	4.0	40	32	64	4
14	4.0	50	24	71	5
15	**4.0**	**60**	**20**	**74**	**6**
16	9.1	15	99	1	0
17	9.1	45	92	8	0
18	9.1	60	81	19	0

[a] Reaction composition was measured using benchtop (43 MHz) ^{19}F NMR. Highlighted entries are present in main manuscript.

Table S4. Initial screen of temperature in flow, using the Br_2 generator v1.



Entry	Temperature [°C]	Residence time [s]	1 [%][a]	2 [%][a]	3 [%][a]
1	20	30	64	35	1
2	30	30	37	59	3
3	40	30	26	69	5
4	**50**	**30**	**23**	**70**	**7**
5	20	60	20	74	6
6	**5**	**60**	**47**	**52**	**1**

[a] Reaction composition was measured using benchtop (43 MHz) ^{19}F NMR. Highlighted entries are present in main manuscript.

PMI calculation:

Reagent	**kg consumed per kg product**
HBr (4 M aqueous solution)	5.71
$NaBrO_3$ (0.66 M) / NaBr (3.34 M) aqueous solution	5.02
Substrate	0.84
Chlorobenzene (solvent)	1.28
$Na_2S_2O_3$ (2.64 M aqueous solution)	0.69
Total (PMI)	**13.55**

This calculation takes into account the mass of all starting materials and quench solution (including water), based on a 69% yield of the desired product **2**.

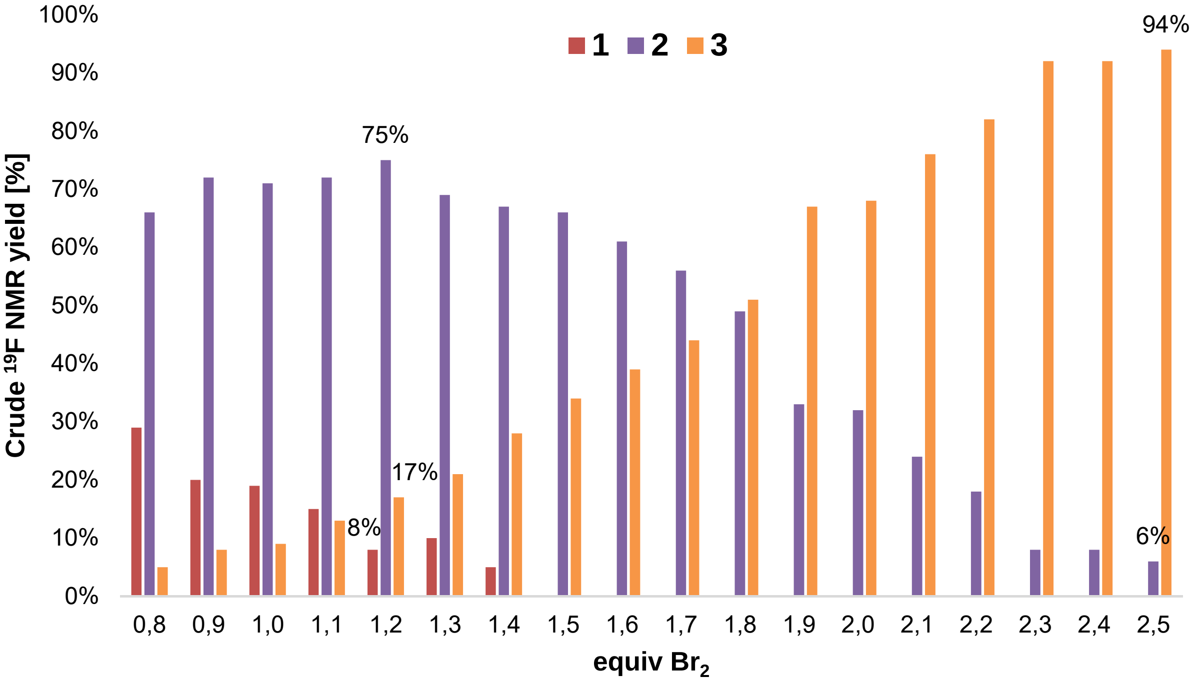
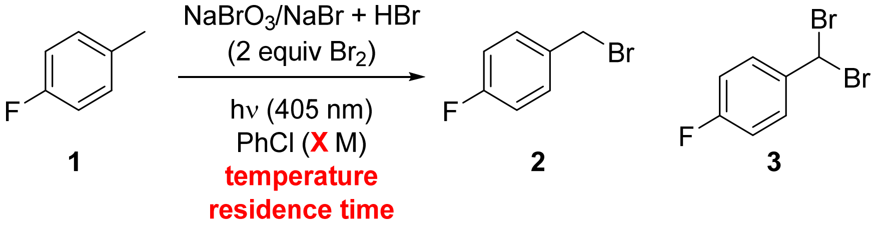


Fig. S3. Graph showing the change in product distribution, with variation of Br_2 loading. Concentration = **0.05 M**, temperature = 20 °C, residence time = 60 s. Reaction composition was measured using benchtop (43 MHz) ^{19}F NMR.

Table S5. Initial optimization towards dibromination, using the Br_2 generator v1.



Entry	Temperature [°C]	Concentration [M]	Residence time [s]	1 [%][a]	2 [%][a]	3 [%][a]
1	20	1.0	30	0	64	36
2	20	1.0	60	0	20	80
3	50	4.0	30	16	75	9
4	**50**	**4.0**	**60**	**0**	**25**	**75**

[a] Reaction composition was measured using benchtop (43 MHz) ^{19}F NMR. Highlighted entries are present in main manuscript.

3.3. Bromine generator optimization

Balanced equation:

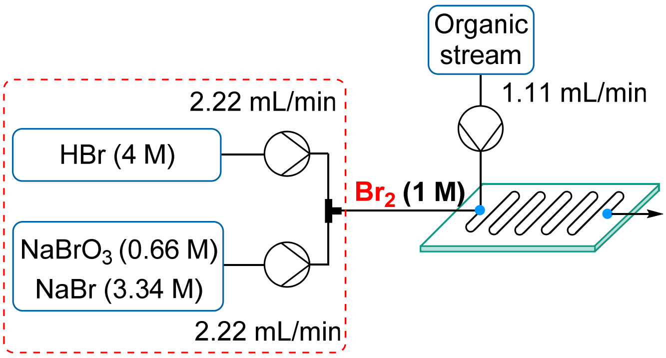
$$5NaBr + NaBrO_3 + 6HBr \longrightarrow 3Br_2 + 6\,NaBr + 3H_2O$$

Half equations:

$$5Br^- \longrightarrow {}^5/_2Br_2 + 5e^-$$

$$BrO_3^- + 6\,H^+ + 5e^- \longrightarrow {}^1/_2Br_2 + 3H_2O$$

3.3.1. Br₂ generator v1



Generator v1
1 mmol Br_2 per mL aq.
35 g/h product **2** at optimal conditions

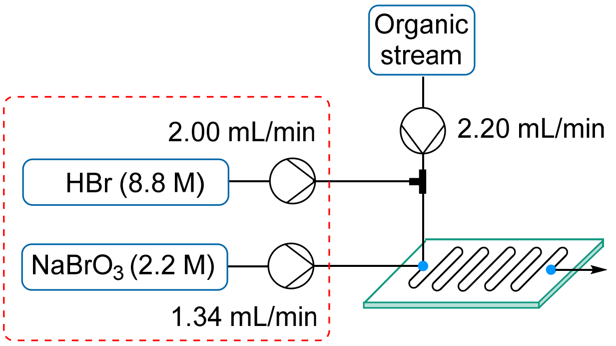
- Br_2 dissolved in aqueous phase
- Concentration of Br_2 only 1M
- Significant quantity of aqueous salt waste, lower productivity

Fig. S4. Photo of Br_2 generator v1: Br_2 is fully dissolved in aqueous solution.

PMI calculation for generation of Br_2:

Reagent	Theoretical kg consumed per kg Br_2 generated
HBr (4 M aqueous solution)	3.82
$NaBrO_3$/NaBr (0.66 M/3.34 M aqueous solution)	4.10
Total (PMI)	**7.92**

3.3.2. Br_2 generator v2



Generator v2
2.6 mmol Br_2 per mL aq.
74 g/h product **2** at optimal conditions

- Removed NaBr
- Reconfigured mixing – HBr and organic stream mix prior to reaction plate. Br_2 is now formed in the reactor so cannot accumulate in tubing joints.
- Increased concentration of HBr and $NaBrO_3$ streams

PMI calculation for product **2** using Br_2 generator v2:

Reagent	kg consumed per kg product
HBr (8.8 M aqueous solution)	2.60
$NaBrO_3$ (2.2 M aqueous solution)	1.52
Substrate	0.84
Chlorobenzene (solvent)	1.28
$Na_2S_2O_3$ (2.64 M aqueous solution)	0.69
Total (PMI)	**6.93**

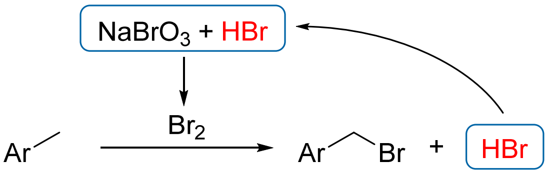
This calculation takes into account the mass of all starting materials, quench mixture (including water). The reaction workup is not included.

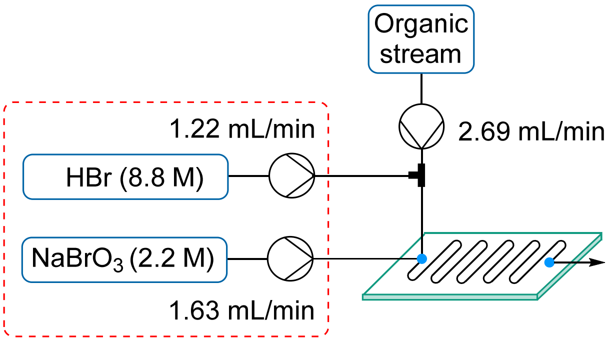
Fig. S5. Photo of Br_2 generator v2 (without organic phase): Br_2 is now immiscible with the aqueous phase, forming dark brown slugs.

PMI calculation for generation of Br_2:

Reagent	Theoretical kg consumed per kg Br_2 generated
HBr (8.8 M aqueous solution)	2.12
$NaBrO_3$ (2.2 M aqueous solution)	1.18
Total (PMI)	**3.29**

3.3.3. Br_2 generator v3





Generator v3
3.8 mmol Br_2 per mL aq.
228 g/h product **2** at optimal conditions

- Decreased equivalents of HBr, to make use of HBr generated during benzylic bromination reaction.

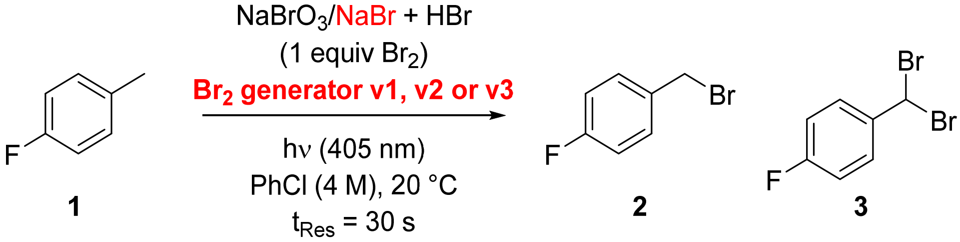
Fig. S6. Photo of Br_2 generator v3 (with organic phase): Br_2 is transferred effectively into the organic phase.

PMI calculation for generation of Br_2:

Reagent	Theoretical kg consumed per kg Br_2 generated
HBr (8.8 M aqueous solution)	1.06
$NaBrO_3$ (2.2 M aqueous solution)	1.18
Total (PMI)	**2.24**

3.3.4. Comparison of Br_2 generator versions

To demonstrate the difference in reaction rates between the three generator versions, a standard comparison was performed:



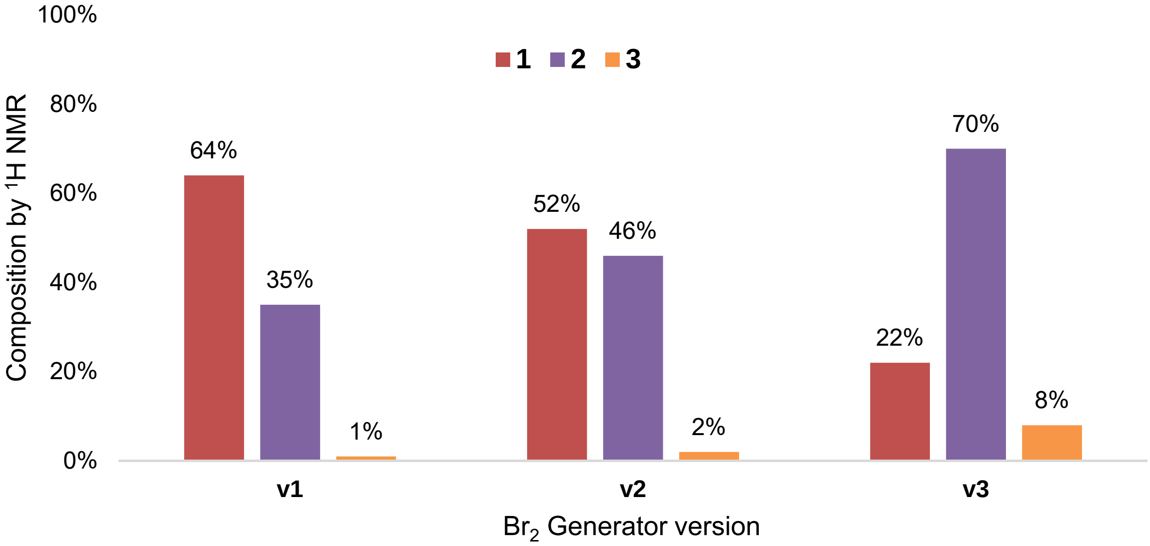


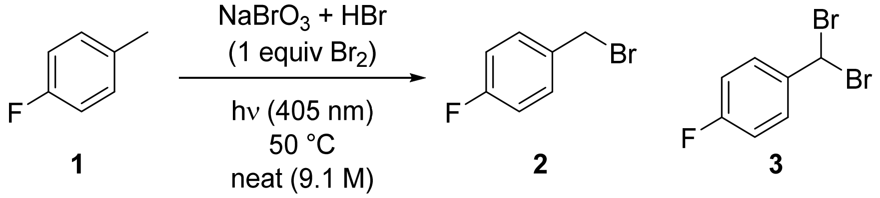
Fig. S7. Comparison of three generations of Br_2 generator, using the standard reaction, monobromination of **1**.

Using Br_2 generator v3, the reaction was found to be significantly faster, so additional optimization was carried out, in order to further improve productivity and PMI.

3.4. Further optimization using Br_2 generator v3

3.4.1. Reaction intensification

Table S6. Further reaction intensification using Br_2 generator v3.



Entry	Residence time [s]	1 [%][a]	2 [%][a]	3 [%][a]
1[b]	**15**	**20**	**68**	**12**
2	20	18	69	14

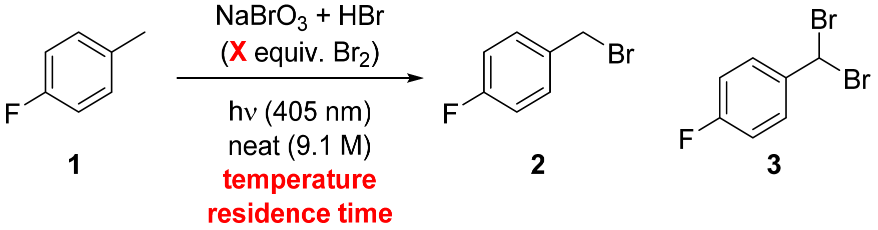
[a]Reaction composition was measured using benchtop (43 MHz) ^{19}F NMR. Highlighted entries are present in main manuscript. [b]Productivity of 228 g/h calculated based on these conditions (taking into account the ^{1}H NMR yield of the desired product **2**).

Table S7. Flow rates using highlighted conditions in Table S5 (above)

Reagent stream	Flow rate [mL/min]
HBr (8.8 M aqueous solution)	3.35
$NaBrO_3$ (2.2 M aqueous solution)	4.48
Substrate	3.25
Total	**11.08**

3.4.2. Optimization towards full conversion

Table S8. Optimization towards complete conversion of starting material **1**, using Br_2 generator v3.



Entry	Residence time [s]	Br_2 loading [equiv.]	Temperature [°C]	1 [%][a]	2 [%][a]	3 [%][a]
1	15	1	50	20	68	12
2	20	1	50	18	69	14
3	20	1.1	50	14	72	14
4	15	1.3	50	18	69	14
5	20	1.3	50	6	70	24
6	20	1.35	50	6	69	24
7	20	1.35	55	8	67	25
8	20	1.4	55	5	68	27
9	**18**	**1.4**	**55**	**3**	**67**	**30**

[a] Reaction composition was measured using benchtop (43 MHz) ^{19}F NMR. Highlighted entries are present in main manuscript.

Table S9. Flow rates using highlighted conditions in Table S7 (above)

Reagent stream	Flow rate [mL/min]
HBr (8.8 M aqueous solution)	3.04
$NaBrO_3$ (2.2 M aqueous solution)	4.08
Substrate	2.11
Total	**9.23**

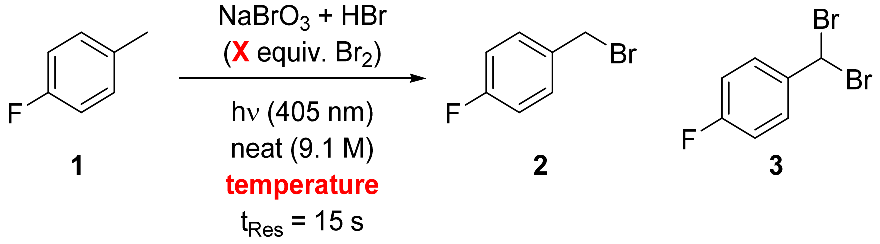
PMI calculation:

Reagent	kg consumed per kg product
HBr (8.8 M aqueous solution)	1.87
$NaBrO_3$ (2.2 M aqueous solution)	2.08
Substrate **1**	0.87
$Na_2S_2O_3$ (2.64 M aqueous solution)	0.69
Total (PMI)	**5.51**

This calculation takes into account the mass of all starting materials, quench mixture (including water). Diethylphosphite reduction of the dibrominated product **3** is not considered.

3.4.3. *Optimization towards full selectivity*

Table S10. Optimization towards complete selectivity for product **2**, using Br_2 generator v3.



Entry	Br_2 loading [equiv.]	Temperature [°C]	1 [%][a]	2 [%][a]	3 [%][a]
1	0.8	50	34	60	6
2	0.7	50	41	55	4
3	0.7	40	40	56	5
4	0.6	40	46	50	4
5	**0.6**	**30**	**47**	**50**	**3**

[a] Reaction composition was measured using benchtop (43 MHz) ^{19}F NMR. Highlighted entries are present in main manuscript.

Table S11. Flow rates using highlighted conditions in Table S9 (above)

Reagent stream	Flow rate [mL/min]
HBr (8.8 M aqueous solution)	2.80
$NaBrO_3$ (2.2 M aqueous solution)	3.75
Substrate	4.53
Total	**11.08**

PMI calculation:

Reagent	kg consumed per kg product
HBr (8.8 M aqueous solution)	1.07
$NaBrO_3$ (2.2 M aqueous solution)	1.20
Substrate **1**	1.17
$Na_2S_2O_3$ (2.64 M aqueous solution)	0.69
Total (PMI)	**4.12**

This calculation takes into account the mass of all starting materials, quench mixture (including water). Recycling of the staring material **1** is not considered.

3.4.4. *Quench with morpholine and isolation*

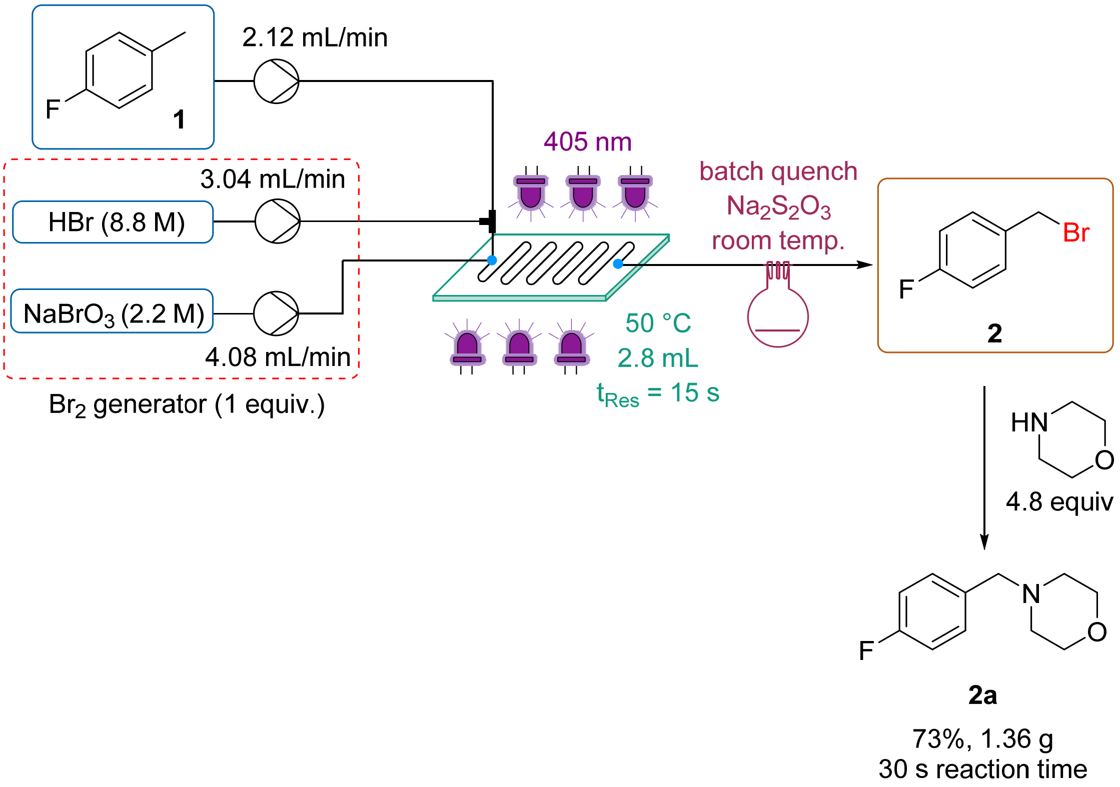


Fig. S8. Schematic view of reaction setup used for isolation of **2** as its morpholine adduct **2a**.

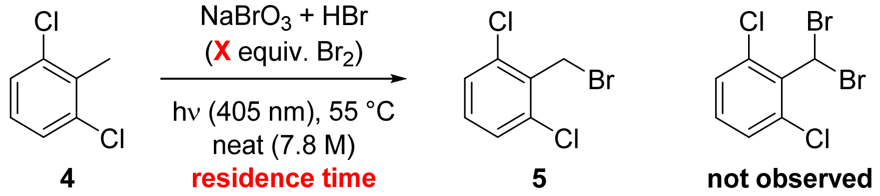
PMI calculation:

Reagent	kg consumed per kg product
HBr (8.8 M aqueous solution)	1.32
$NaBrO_3$ (2.2 M aqueous solution)	1.46
Substrate	0.86
$Na_2S_2O_3$ (2.64 M aqueous solution)	0.69
Total (PMI)	**4.33**

This calculation takes into account the mass of all starting materials, quench mixture (including water), in order to produce benzyl bromide **2**. The reaction workup and derivatization with morpholine are not included.

3.5. Monobromination of 2,6-dichlorotoluene

3.5.1. Optimization studies



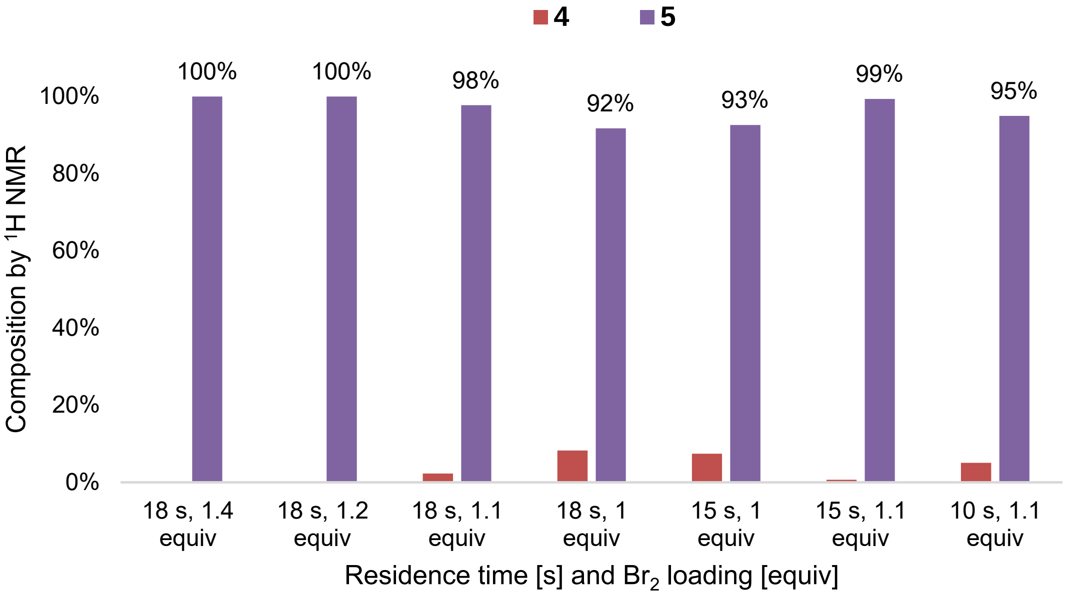


Fig. S9. Optimization of the residence time and Br_2 equivalents required for the monobromination of **4**.

Fig. S10. Photo of room temperature quench, showing product crystallization upon contact with the quench solution, leading to excess Br_2 entrapped within product crystals.

Fig. S11. Photo of heated quench, whereby the product remains a liquid, allowing effective quenching of the excess Br_2.

3.5.2. *In-line quench*

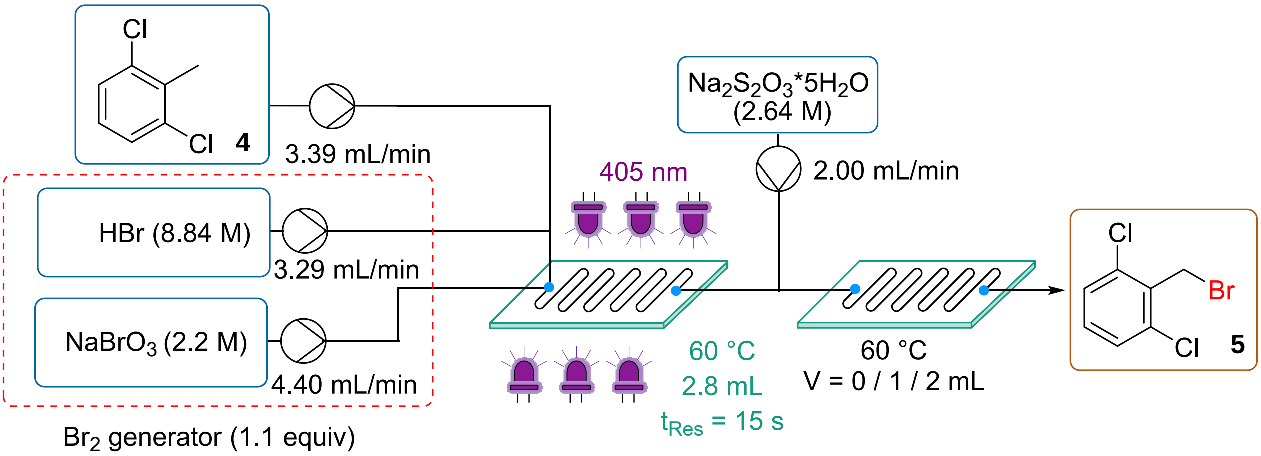


Fig. S12. Schematic showing the reaction setup for the use of an inline quench, using a Little Things Factory© mixing chip. **Note:** a 1 mL chip was insufficient for complete mixing prior to collection (by visual inspection of output color), but 2 mL showed complete discoloration of excess Br_2.

3.5.3. *Scale-out run*

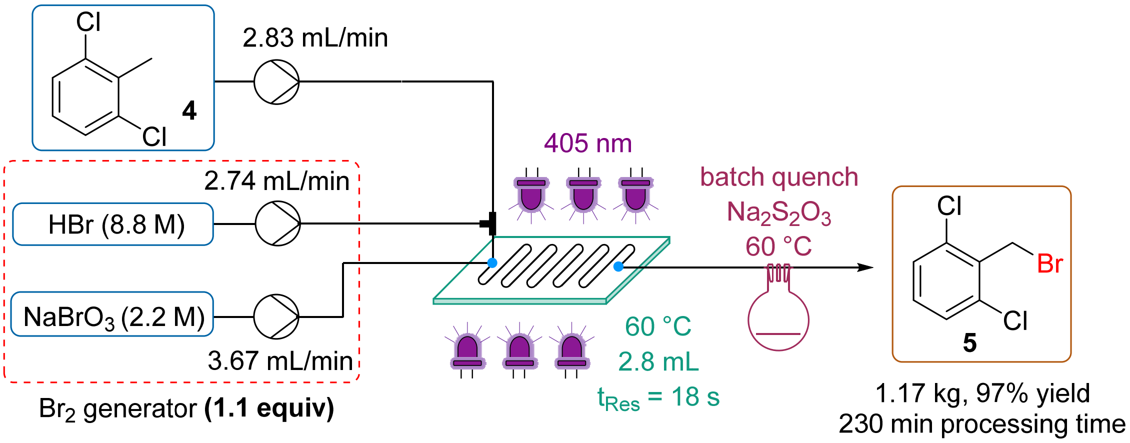


Fig. S13. Schematic showing the reaction setup for the scale-out run.

It should be noted that the conditions were slightly altered in the scale-out run, compared to the smaller scale isolation. The slower flow rates minimize the effect of pump pulsation, allowing improved stability throughout the longer operating period. Nevertheless, a small amount of starting material remained in some of these fractions (see Fig. S15 for details).

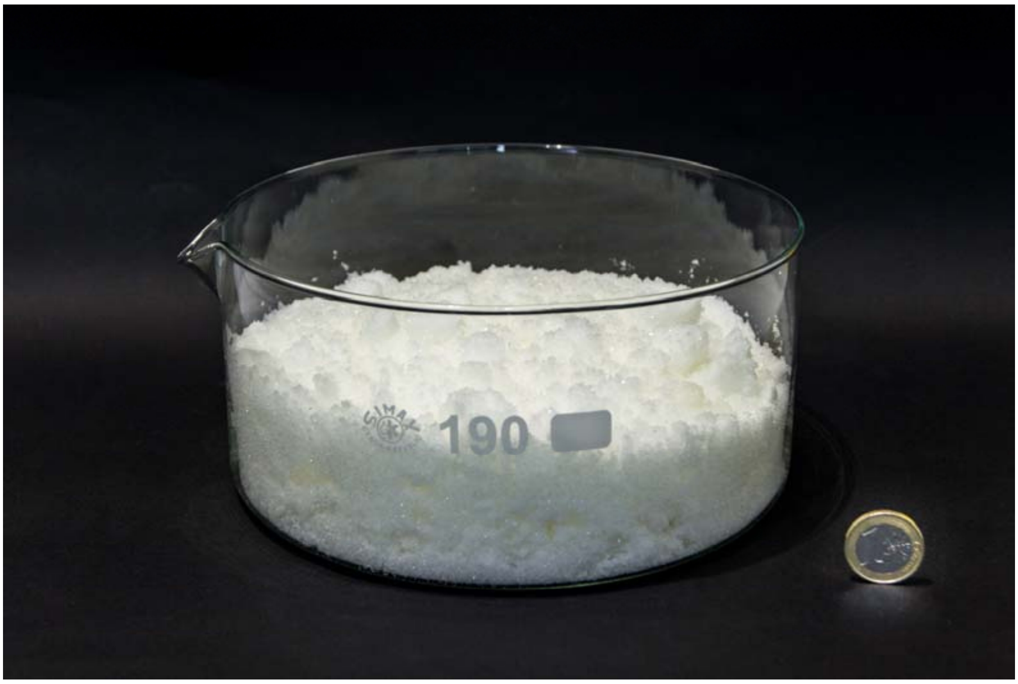


Fig. S14. Photo of 1.17 kg isolated product **5** from scale-out reaction (coin present for scale).

PMI calculation:

Reagent	kg consumed per kg product
HBr (8.8 M aqueous solution)	0.80
$NaBrO_3$ (2.2 M aqueous solution)	0.89
Substrate	0.70
$Na_2S_2O_3$ (2.64 M aqueous solution)	0.69
Total (PMI)	**3.08**

This calculation takes into account the mass of all starting materials and quench mixture (including water). The reaction workup (in this case, filtration and washing with a small volume of water) is not included.

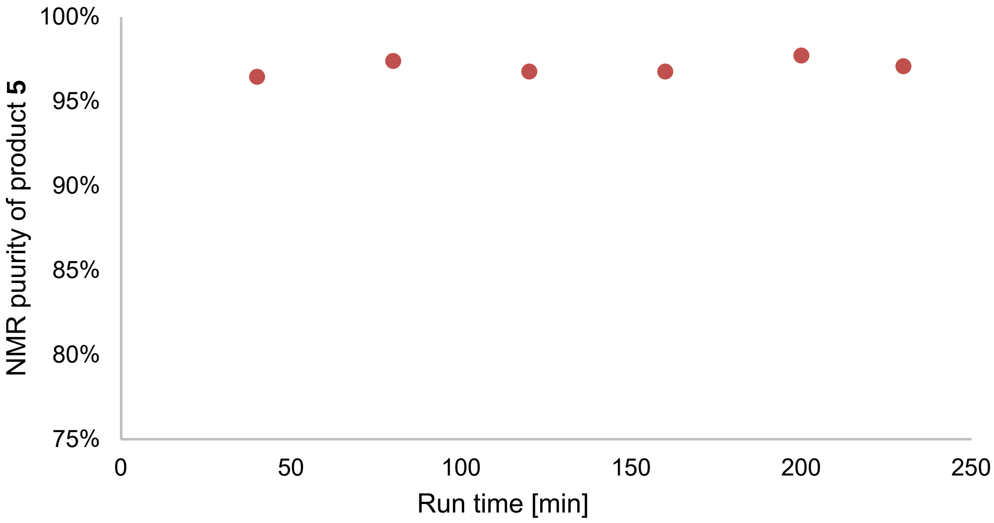
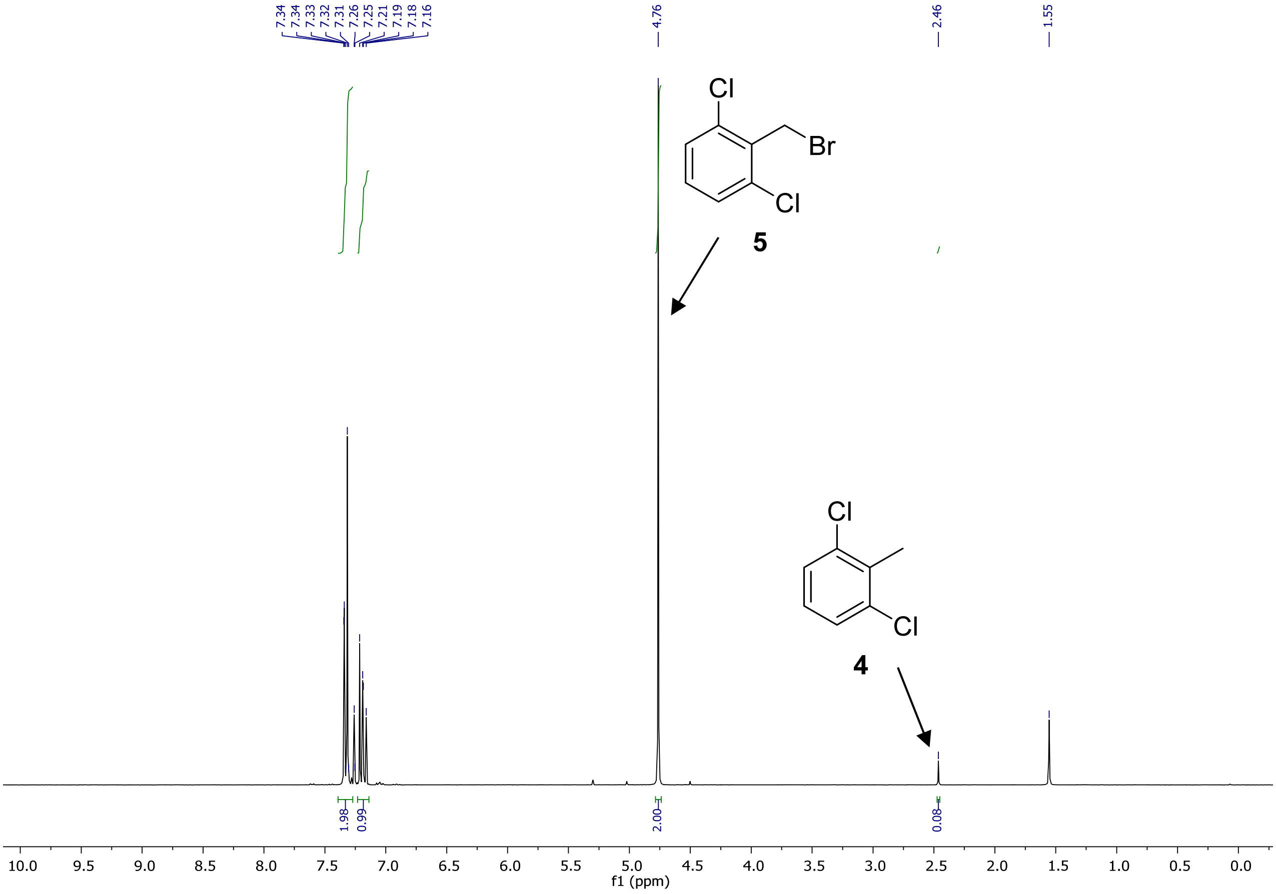


Fig. S15. Purity of fractions during scale-out run, measured by ^{1}H NMR.

Representative NMR spectrum from scale-out run, showing 2.6% remaining starting material:



3.6. Dibromination of 2,4-dichlorotoluene

3.6.1. Optimization studies

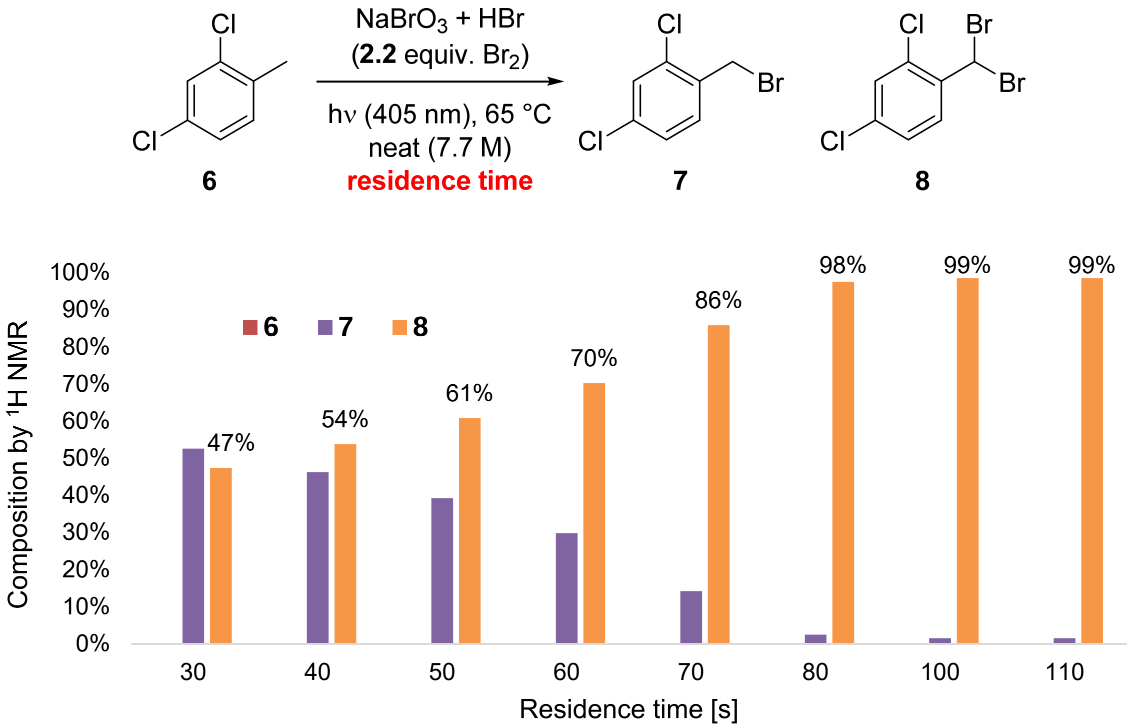


Fig. S16. Optimization of residence time for the dibromination of **6**.

3.6.2. Isolation run

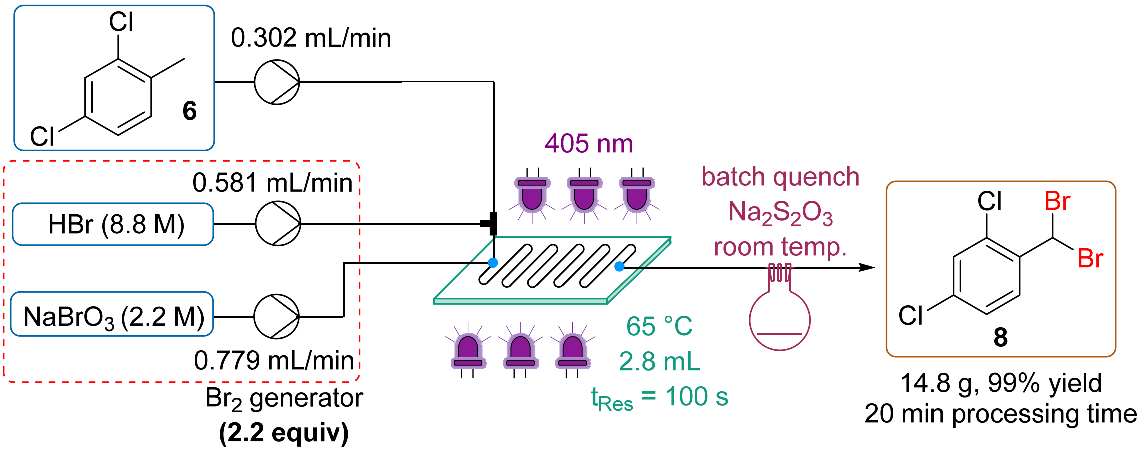


Fig. S17. Schematic of the setup used for isolation of dibrominated product **8**.

PMI calculation:

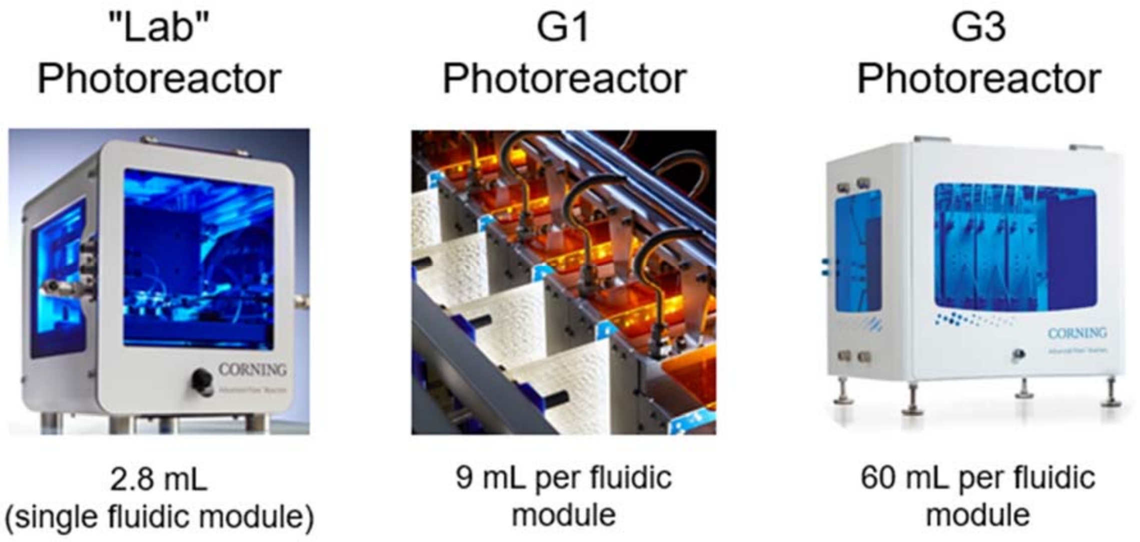
Reagent	**kg consumed per kg product**
HBr (8.8 M aqueous solution)	1.16
$NaBrO_3$ (2.2 M aqueous solution)	1.29
Substrate	0.50
$Na_2S_2O_3$ (2.64 M aqueous solution)	0.69
Total (PMI)	**3.64**

This calculation takes into account the mass of all starting materials and quench solution (including water). The reaction workup (in this case, extraction with DCM and washing with Na_2CO_3) is not included.

4. Linear scale up strategy

The linear scale up strategy, detailed in the conclusions section of the main paper, implies the use of Corning Advanced-Flow Photo Reactors:

Reactor	Fluidic module volume	Throughput per fluidic module	Throughput with 5 × fluidic modules
“Lab” (used in this study)[S1]	2.8 mL	0.30 kg/h	-
G1 Photo Reactor[S2]	9 mL	0.96 g/h	4.8 kg/h
G3 Photo Reactor[S3]	60 mL	6.4 kg/h	32 kg/h



2.8 mL (single fluidic module)

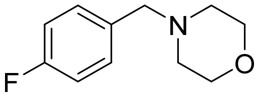
9 mL per fluidic module

60 mL per fluidic module

Fig. S18. Images of three photoreactor scales, with their respective fluidic module sizes.

5. Isolation procedures and compound characterization

4-(4-fluorobenzyl)morpholine **2a**:



2a

A waste collection flask was charged with a small volume of saturated sodium thiosulfate and was stirred with a magnetic stirrer. The reactor was turned on (405 nm LEDs and thermostats) and the reaction thermostat was set to 58 °C. After the temperature of the reactor had stabilized, the pumps were turned on. Flow rates: substrate = 2.116 mL/min, HBr = 3.04 mL/min and $NaBrO_3$ = 4.08 mL/min. Solutions: 4-Fluorotoluene (neat, 9.08 M, 9.62 mmol per 30 sec), HBr (48%, 13.4 mmol, 1.4 equiv.) and $NaBrO_3$ (2.2 M, 4.49 mmol, 0.47 equiv.). The system was given time to equilibrate, then for 30 seconds the mixture was collected into a stirred round bottom flask containing sodium thiosulfate solution (2.2 M). The quenched reaction mixture was extracted with DCM (2 × 20 mL) and the organic phase was transferred into a round bottom flask. The organic phase was analyzed using ^{19}F benchtop NMR, indicating a yield of 68% of the desired product, 27% dibrominated side product and about 5% of the starting material. Morpholine (~4 mL, ~46 mmol, ~4.8 equiv.) was added and ^{19}F NMR analysis showed full conversion of the benzyl bromide to the morpholine adduct after 3 min (shift of the product signal from 111.6 ppm to 114.5 ppm). The reaction mixture was washed with water (2 × 20 mL) and the organic phase was dried with Na_2SO_4. After concentrating under reduced pressure the product was purified by flash chromatography on silica using 40-60 petroleum ether and EtOAc (with 1% v/v Et_3N) as eluent (gradient: 0-50% EtOAc over 20 column volumes) to afford 1.36 g (73% yield) of the desired product **2a** as a pale yellow oil.

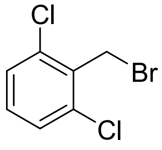
^{1}H NMR (300 MHz,$CDCl_3$) δ = 7.22 (ddd, *J* = 8.8, 5.4, 2.5 Hz,p 2H), 6.99 – 6.88 (m, 2H), 3.67 – 3.60 (m, 4H), 3.46 (s, 2H), 2.42 – 2.30 (m, 4H)

^{13}C NMR (75 MHz, $CDCl_3$) δ = 162.1 (d, *J* = 244.9 Hz), 133.6 (d, *J* = 3.2 Hz), 130.7 (d, *J* = 7.9 Hz), 115.1 (d, *J* = 21.2 Hz), 67.1, 62.7, 53.6.

^{19}F NMR (282 MHz, $CDCl_3$) δ = -115.71 (ddd, *J* = 14.2, 8.8, 5.4 Hz)

The NMR data is in agreement with previous reports.[S4,S5]

2,6-Dichlorobenzyl bromide **5**, smaller scale isolation:



5

A waste collection flask was charged with a small volume of saturated sodium thiosulfate solution and was stirred with a magnetic stirrer. A 3-necked flask was charged with ~50 mL sodium thiosulfate solution (2.64 M) and equipped with a stirrer bar. The reactor was turned on (405 nm LEDs and thermostats) and the reactor thermostat was set to 55 °C. After the temperature of the reactor stabilized, the pumps were turned on. Flow rates: substrate 3.39 mL/min, HBr 3.29 mL/min and $NaBrO_3$ 4.40 mL/min. Solutions: 2,6-dichlorotoluene (neat, 7.79 M), HBr (8.8 M, 1.1 equiv.) and $NaBrO_3$ (2.2 M, 0.37 equiv.). The system was allowed to equilibrate for ~5 min, then the reactor output was collected into the stirred 3-necked flask for 5 min (heated to 60 °C during product collection). The collection flask was then allowed to cool gradually for 16 h, before the product was filtered, washed with water (~200 mL) and then dried under reduced pressure to afford 30.7 g (97% yield, >99% NMR purity) of the desired product as a white crystalline solid.

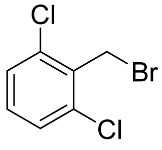
^{1}H NMR (300 MHz,$CDCl_3$) δ = 7.34 – 7.31 (m, 2H), 7.21 – 7.16 (m, 1H), 4.76 (s, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 136.0, 133.8, 130.2, 128.7, 27.6.

The NMR data is in agreement with previous reports.[S6]

Melting point: 55.0 °C (Literature value = 55 °C).[S7]

2,6-Dichlorobenzyl bromide **5**, scale-out run:



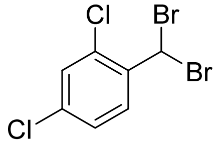
5

A waste collection flask was charged with a small volume of saturated sodium thiosulfate solution and was stirred with a magnetic stirrer. 6 × 500 mL Erlenmeyer flasks were each charged with ~100 mL sodium thiosulfate solution (2.64 M) and equipped with a stirrer bar. The reactor was turned on (405 nm LEDs and thermostats) and the reactor thermostat was set to 60 °C. After the temperature of the reactor stabilized, the pumps were turned on. Flow rates: substrate 2.826 mL/min, HBr 2.74 mL/min and $NaBrO_3$ 3.67 mL/min. Solutions: 2,6-dichlorotoluene (neat, 7.79 M, 5.06 mol), HBr (8.8 M, 5.57 mol, 1.1 equiv.) and $NaBrO_3$ (2.2 M, 1.86 mol, 0.37 equiv.). The system was allowed to equilibrate for ~10 min, then for 230 min (5 × 40 min and 1 × 30 min) the mixture was collected into the six stirred Erlenmeyer flasks (heated to 60 °C during product collection). When each collection was finished, the respective flask was allowed to cool to room temperature whilst stirring, to allow crystallization of the product. The collection flasks were then allowed to stand for 16 h, before the product was filtered, washed with water (~200 mL per batch) and then dried under reduced pressure at 30 °C to afford 1.17 kg (97% yield, 97% NMR purity) of the desired product as a white crystalline solid.

NMR spectra are coherent with that of the previous isolation experiment, but contain a small quantity of remaining starting material (<4% in all fractions collected). See section 3.5.3. for further details.

Melting point: 53.9 °C (Literature value = 55 °C).[S7]

2,4-Dichloro-1-(dibromomethyl)benzene **8**:



8

A waste collection flask was charged with a saturated solution of sodium thiosulfate and was stirred with a magnetic stirrer. The reactor was turned on (405 nm LEDs and thermostats) and the reactor thermostat was set to 65 °C. After the temperature of the reactor stabilized, the pumps were turned on. Flow rates: substrate 0.302 mL/min, HBr 0.581 mL/min and $NaBrO_3$ 0.779 mL/min. Solutions: 2,4-Dichlorotoluene (neat, 7.74 M, 46.7 mmol in 20 min), HBr (48%, 103 mmol, 2.2 equiv) and $NaBrO_3$ (2.2 M, 34.3 mmol, 0.73 equiv). The system was allowed to equilibrate for ~15 min, then for 20 min the mixture was collected in a stirred round bottom flask containing sodium thiosulfate solution (2.2 M). The quenched reaction mixture was extracted with DCM (3 × 20 mL) and the organic phase was then washed with sodium bicarbonate solution (1 × 20 mL) and dried with Na_2SO_4. After removal of the solvent under reduced pressure, 14.8 g (99% yield) of the desired product was obtained as a pale yellow oil.

^{1}H NMR (300 MHz,$CDCl_3$) δ = 7.95 – 7.92 (m, 1H), 7.37 – 7.34 (m, 2H), 7.04 (s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 137.6, 136.3, 132.0, 130.5, 129.2, 128.5, 35.6.

IR (ATR, neat, cm^{-1}): 3090, 3028, 1585, 1557, 1469, 1384, 1146, 1100, 1048.

6. References

S1 https://www.corning.com/media/worldwide/Innovation/documents/Lab%20Reactor.pdf, accessed 10th October 2019

S2 https://www.corning.com/media/worldwide/Innovation/documents/G1photo_WEB.pdf, accessed 10th October 2019

S3 https://www.corning.com/media/worldwide/Innovation/documents/G3%20Photo%20Reactor_brochure_FINAL_1.28.19.pdf, accessed 10th October 2019

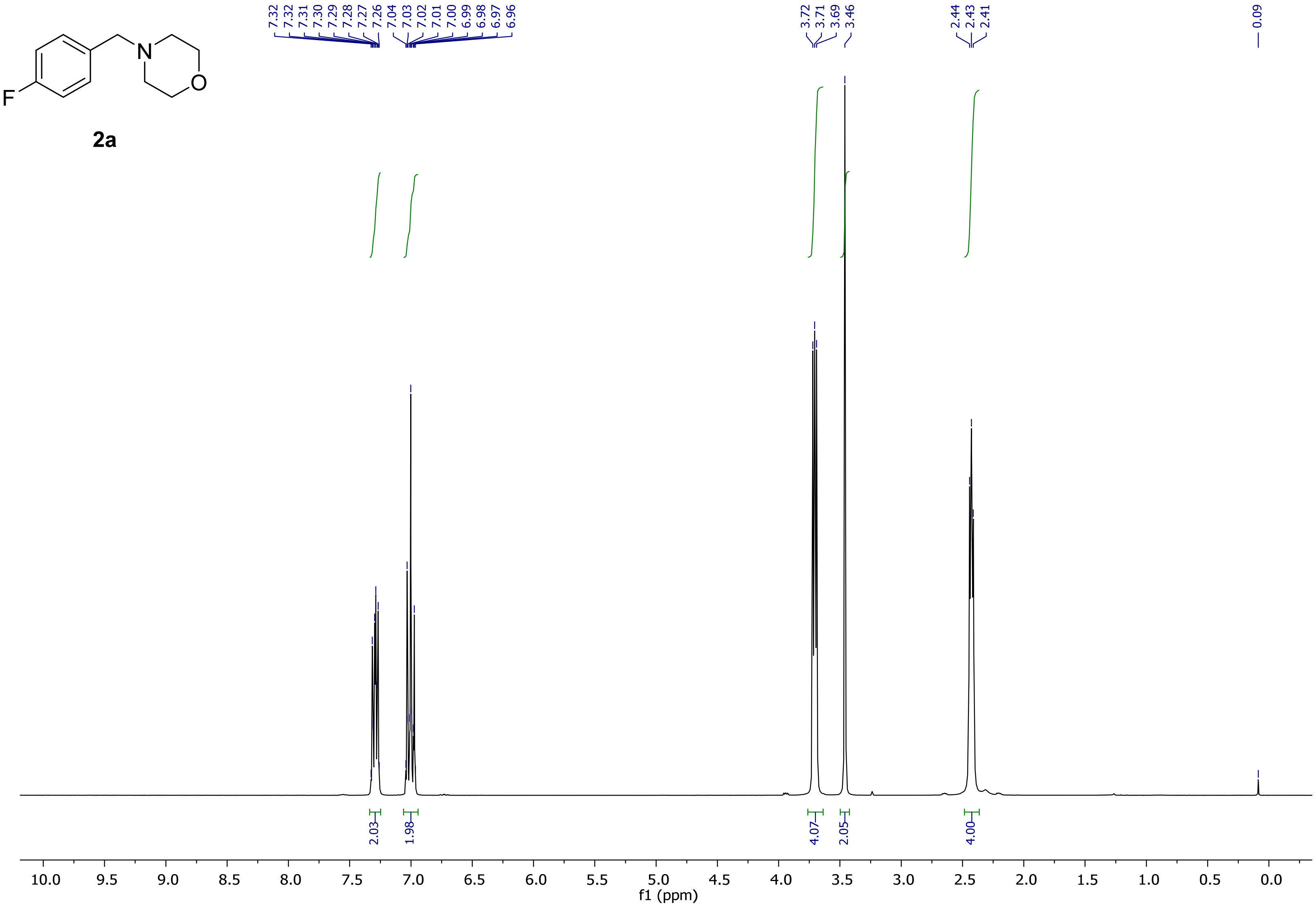
S4 T. R. Long, P. K. Maity, T. B. Samarakoon and P. R. Hanson, *Org. Lett.*, 2010, **12**, 2904–2907.

S5 A. Tillack, I. Rudloff and M. Beller, *Eur. J. Org. Chem.*, 2001, **2001**, 523–528.

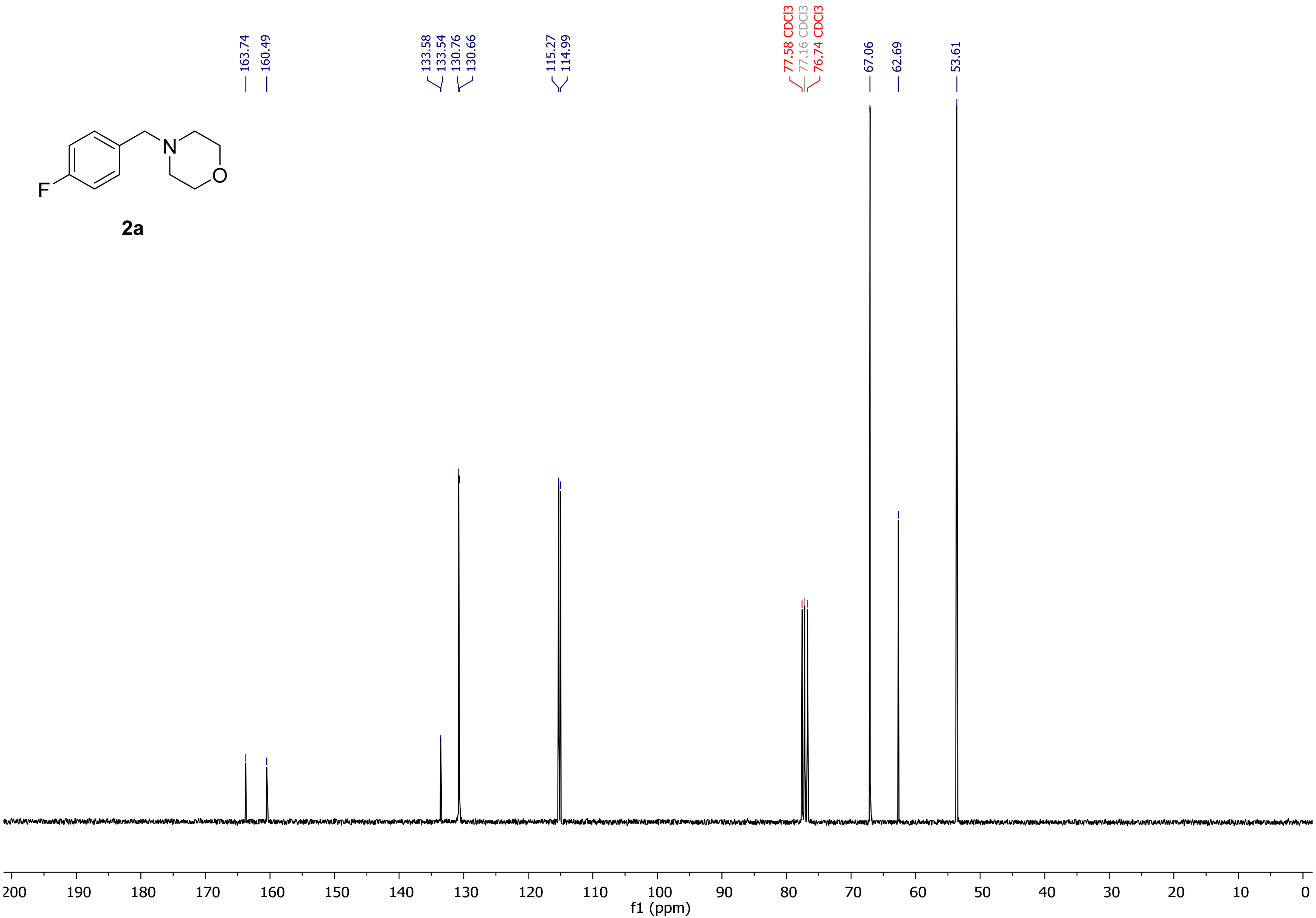
S6 X. Tan, T. Song, Z. Wang, H. Chen, L. Cui and C. Li, *Org. Lett.*, 2017, **19**, 1634–1637.

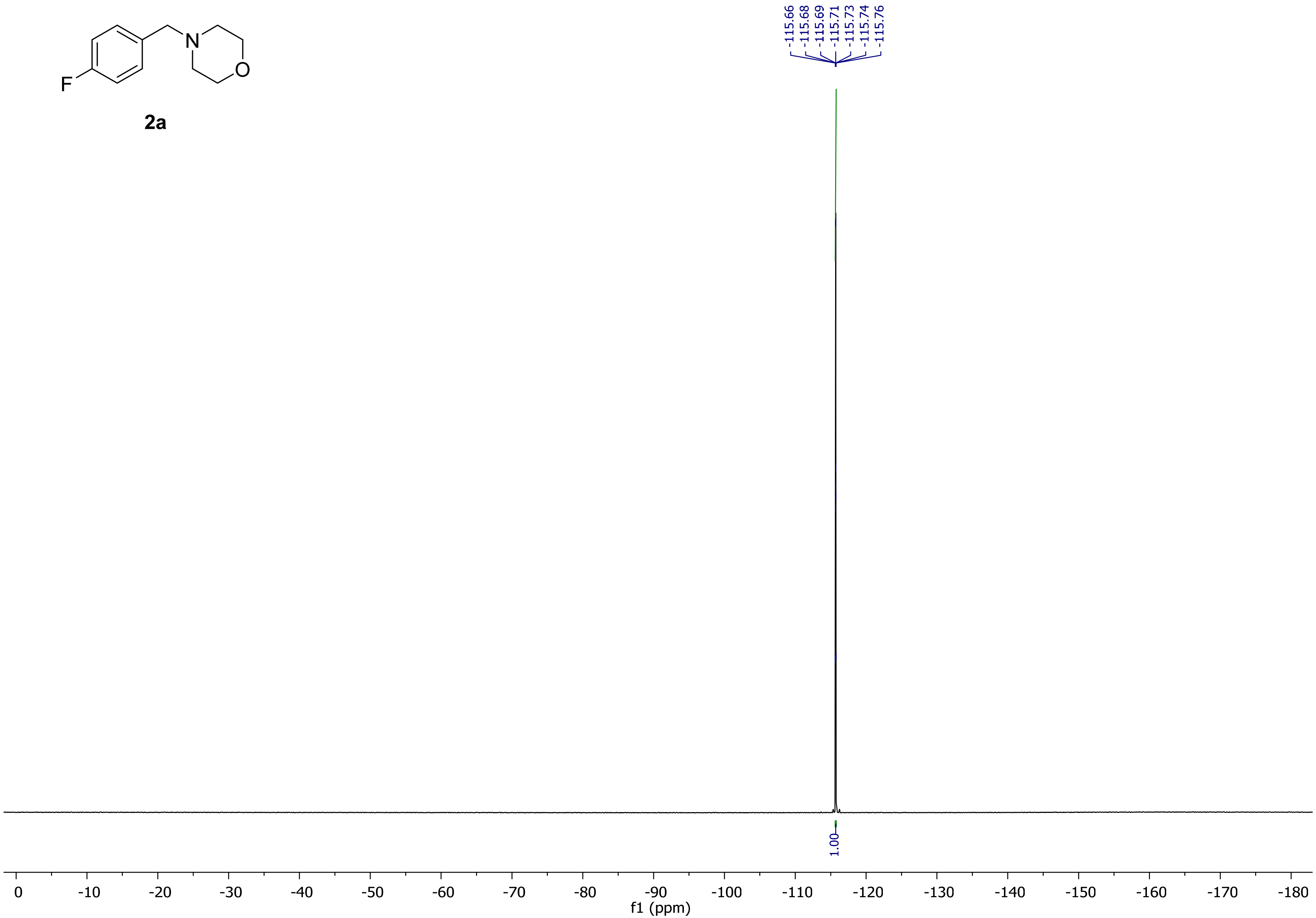
S7 M. J. Strauss, L. J. Andrews and R. M. Keefer, *J. Am. Chem. Soc.*, 1968, **90**, 3473–3478.

7. NMR Spectra



2a


F
N
O
2a
163.74
160.49
133.58
133.54
130.76
130.66
115.27
114.99
77.58 CDCl3
77.16 CDCl3
76.74 CDCl3
67.06
62.69
53.61
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



2a

-115.66
-115.68
-115.69
-115.71
-115.73
-115.74
-115.76
1.00
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
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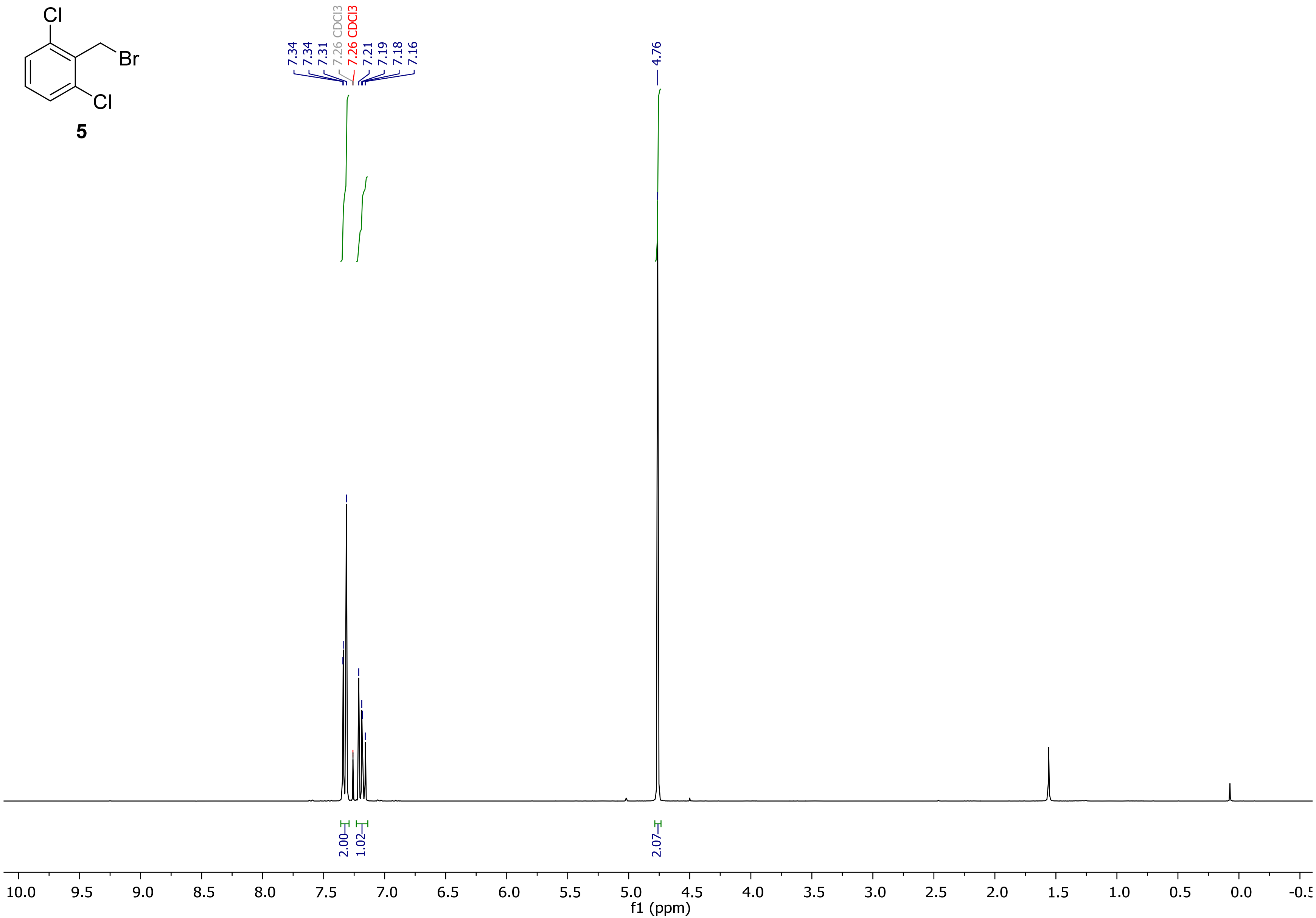
-180
f1 (ppm)
F
N
O


Cl
Br
Cl
5
7.34
7.34
7.31
7.26 CDCl3
7.26 CDCl3
7.21
7.19
7.18
7.16
4.76
2.00
1.02
2.07
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
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3.0
2.5
2.0
1.5
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0.5
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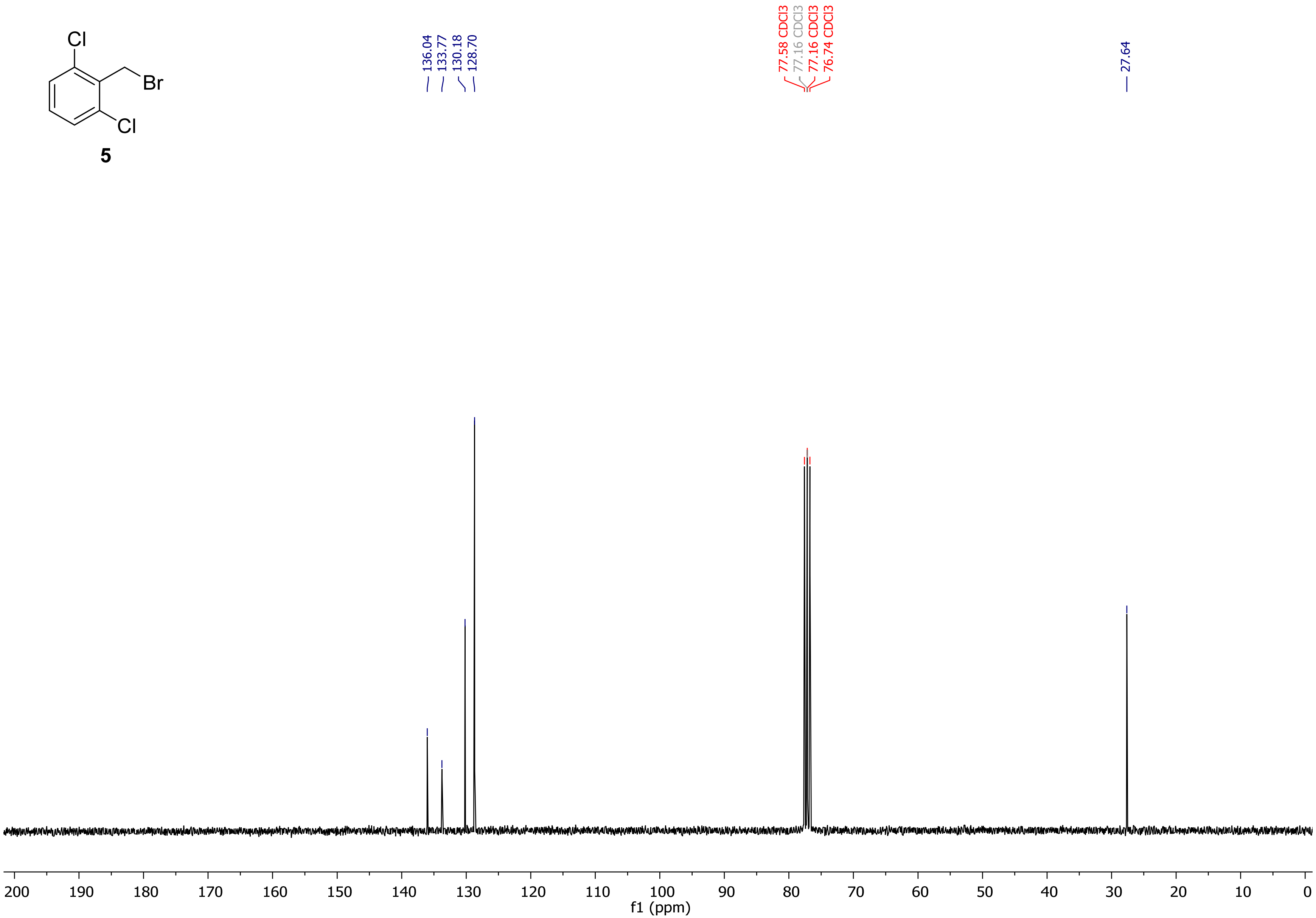
-0.5
f1 (ppm)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Br
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136.04
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130.18
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77.16 CDCl3
77.16 CDCl3
76.74 CDCl3
27.64
200
190
180
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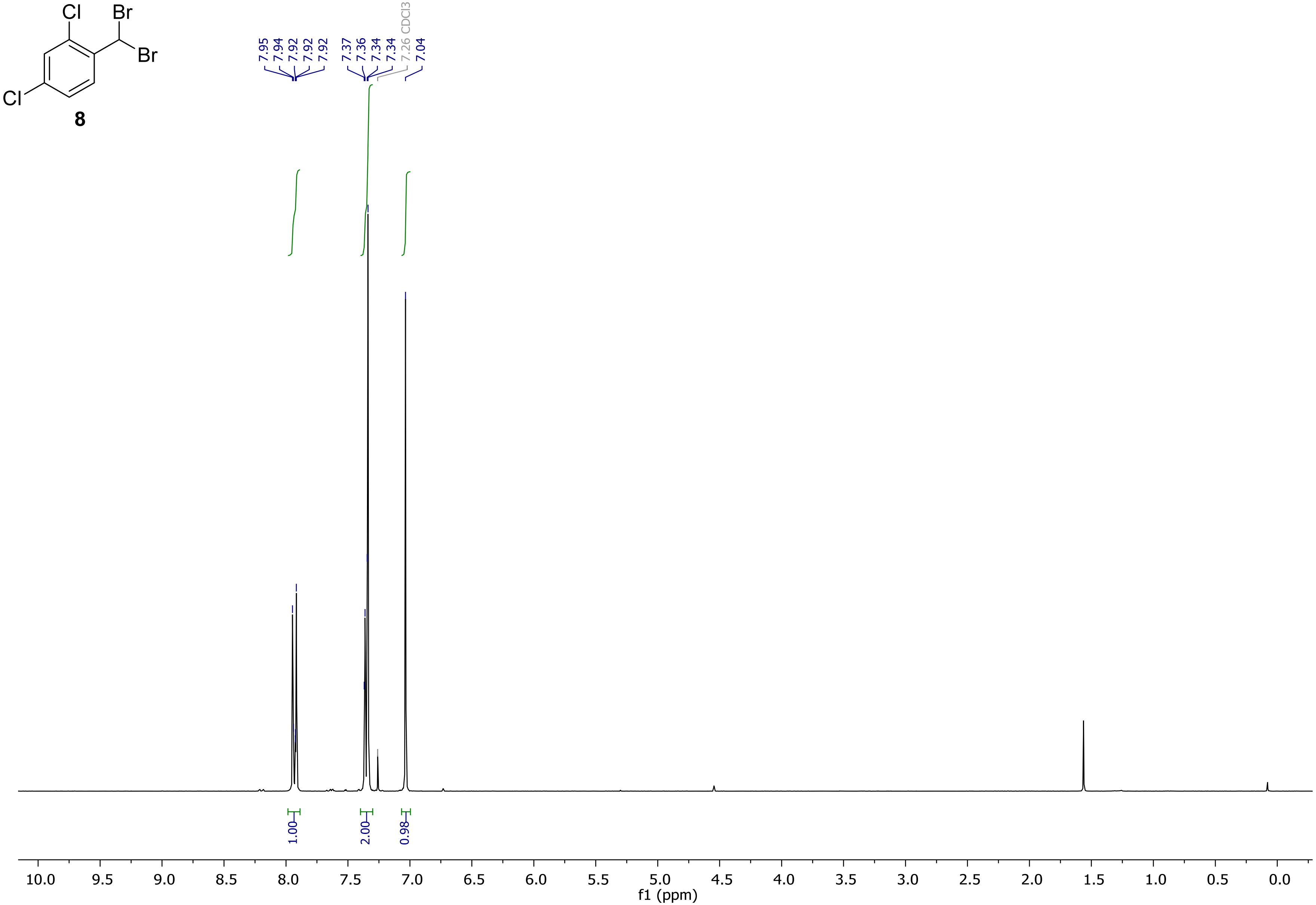
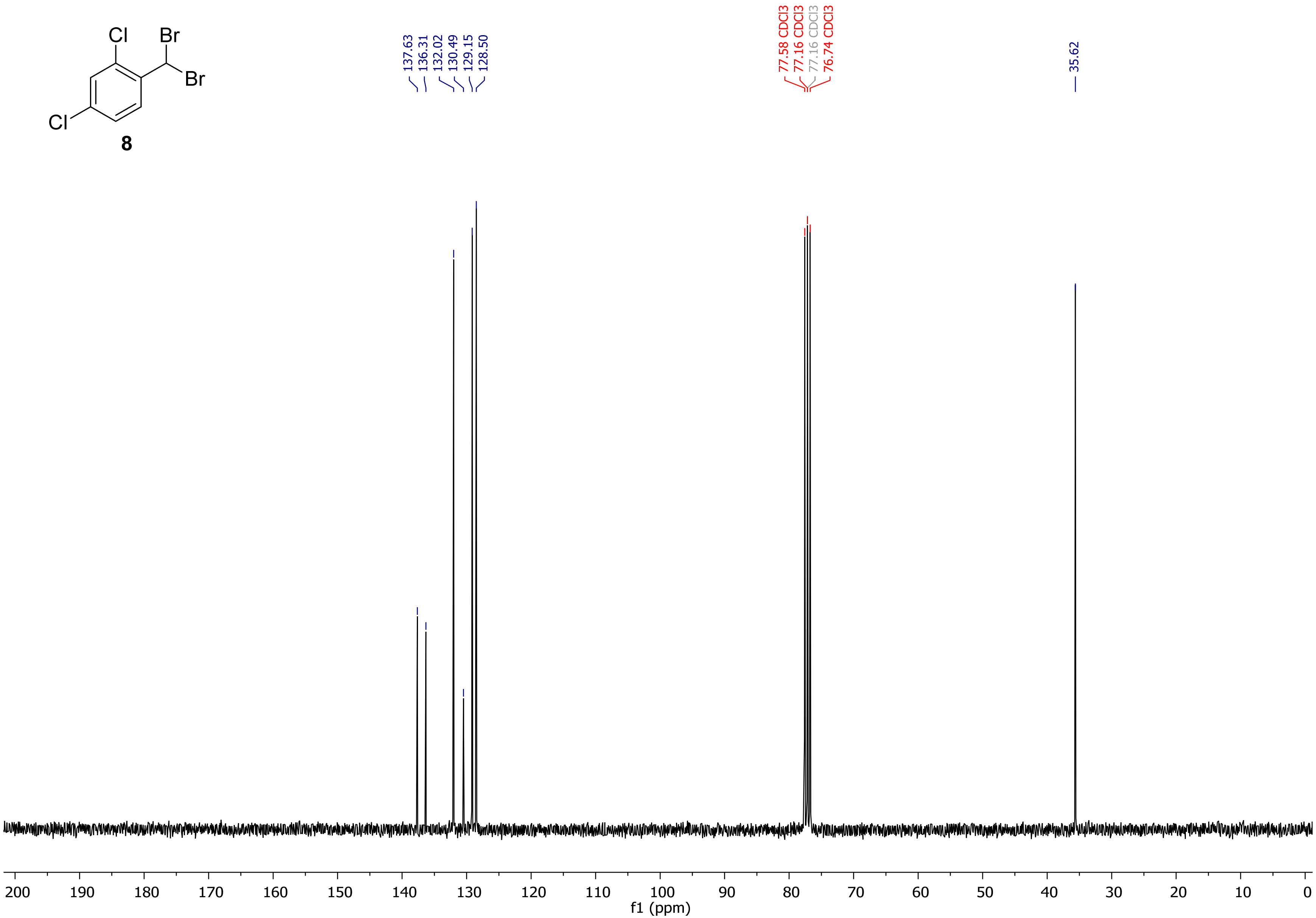
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



8

Cl
Br
Br
Cl
7.95
7.94
7.92
7.92
7.92
7.37
7.36
7.34
7.34
7.26 CDCl3
7.04
1.00
2.00
0.98
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


Cl
Br
Br
Cl
8
137.63
136.31
132.02
130.49
129.15
128.50
77.58 CDCl3
77.16 CDCl3
77.16 CDCl3
76.74 CDCl3
35.62
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)