Visible-Light-Mediated Iodoperfluoroalkylation of Alkenes in Flow and Its Application to the Synthesis of a Key Fulvestrant Intermediate

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A. General Experimental Information

A1. Materials and Methods

Commercial reagents and solvents were purchased (Sigma-Aldrich, Fluka, Alfa Aesar, Fluorochem or VWR) and used as received, without further purification, unless otherwise stated.

1-Octene (1a), cyclohexene (1b), cyclooctene (1c), allylbenzene (1d), allyl alcohol (1e), 1-hexyne (1f), diphenylacetylene (1g), propargyl alcohol (1h), perfluorohexyl iodide (2a), nonafluoro-1-iodobutane (2b), heptafluoro-2-iodopropane (2c), trifluoroiodomethane (2d), pentafluoroiodoethane (2e), triethylamine, pyridine and benzoyl chloride were all commercially available.

Chromatographic purification of products was accomplished using flash chromatography on silica gel (35-70 mesh) or using a Biotage Isolera automated flash chromatography system with cartridges packed with KP-SIL, 60 Å (32–63 μ m particle size).

For thin layer chromatography (TLC) analysis, Merck pre-coated TLC plates (silica gel 60 GF254, 0.25 mm) were employed, using UV light as the visualizing agent (254 nm), basic aqueous potassium permanganate (KMnO₄) stain solution or iodine and heat as developing agents.

Organic solutions were concentrated under reduced pressure on a Büchi rotatory evaporator.

NMR spectra were recorded on Bruker 300 MHz spectrometer (¹H: 300 MHz, ¹³C: 75 MHz and 282 MHz for ¹⁹F). The chemical shifts (δ) for ¹H, ¹³C and ¹⁹F are given in ppm relative to residual signals of the solvent (CHCl₃ at 7.26 ppm ¹H-NMR and 77.16 ppm ¹³C-NMR). Coupling constants are given in Hertz (Hz). The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; ddd, doublet of doublets; m, multiplet.

GC-FID analyses were performed on a ThermoFisher Focus GC with a flame ionization detector, using a TR-5MS column (30 m × 0.25 mm ID × 0.25 μ m) and helium as carrier gas (1 mL/min constant flow). The injector temperature was set to 280 °C. After 1 min at 50 °C, the temperature was increased by 25 °C/min to 300 °C and kept constant at 300 °C for 4 min. The detector gases used for flame ionization were hydrogen and synthetic air (5.0 quality).

High resolution mass spectrometry (HRMS) measurements were performed using a Q-Exactive Hybrid Quadrupole-Orbitrap MS following flow injection analysis of the re-dissolved sample with a Dionex Ultimate 3000 series HPLC-system (Thermo Fisher Sci., Erlangen, Germany). The injection volume was $5 \,\mu$ L and the flow was 200 μ L/min of acetonitrile (>99.9 % HPLC-grade; Chem-Lab NV, Zedelgem, Germany). The HR-MS was fitted with, either a HESI-II atmospheric pressure electrospray ionization source, or a combination of an APCI Ion Max heated probe source with an APPI Photo Mate® UV light

source for mixed atmospheric pressure chemical and photo ionization. Nitrogen was used as nebulizer and drying gas.

ESI measurements were performed in negative ionization mode using the following settings: spray voltage - 2.5 kV, capillary temperature 250 °C, sheath gas flow rate 45 instrument units (IU), auxiliary gas temperature 300 °C, auxiliary gas flow rate 10 IU, automatic gain control target 3e⁶, maximum injection time 100 ms, and the resolution was 70000 (FWHM).

APCI+APPI measurements were performed in positive ionization mode using the following settings: corona discharge current +4 μ A, sheath gas flow rate 20 IU, auxiliary gas flow rate 5 IU, and the remaining settings were the same as for ESI. High resolution mass spectra were extracted from a scanned mass range of m/z 220-390 in both ionization modes.

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

UV-Vis spectra were recorded using a fiber-coupled Avantes Starline AvaSpec-2048 spectrometer, with an Avantes AvaLight-DHc lamp as the light source. These spectra were processed using Avasoft 8.7 software. Dehalogenation reactions using PtO₂ catalyst (commercially available 70 mm CatCart®, supplied by Thales Nano) under continuous flow were performed using an H-CUBE Pro® system from ThalesNano, with a Knauer HPLC pump.

A2. Photoreactor Setup

All photochemical reactions were conducted in a commercial continuous-flow reactor: Corning AdvancedFlow Lab Photo Reactor (Figure S1).



Figure S1. Photograph of commercial photoreactor setup: a) temperature control for reaction plate; b) control module, containing pumps, mass flow controller, Huber controller and data logger; c) fluidic module housing, with tinted plastic panels for light containment; d) temperature control for LED panels; e) wireless receiver for LED control.

Reactor module (G1 "low flow" fluidic module): A compact glass fluidic module ($155 \times 125 \times 8$ mm size, 0.3 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 center of the reaction layer). 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 webbased interface, connected wirelessly to a router.

Two separate panels were used for various experiments in this study (panel 1 = 365, 385, 405, 485, 610 nm and "4000K" white light; panel 2 = 340, 375, 395, 422, 450, 540 nm; see emission spectra below, Figure S2 and Figure S3).

Waxalangth (nm)	Single LED Luminous	Entire Array Luminous	Entire Array Photon
wavelength (IIII)	Flux (W) ^[a]	Flux (W) ^[b]	Flux (mmol h ⁻¹) ^[c]
340	0.0725	2.9	30
365	1.09	43.6	477
375	1.16	46.4	522
385	1.34	53.6	619
395	1.34	53.6	635
405	1.42	56.8	690
422	0.91	36.4	461
450	1.19	47.6	650
485	<i>n.a.</i> ^[d]	<i>n.a.</i> ^[d]	<i>n.a.</i> ^[d]
540	0.47	18.8	299
610	<i>n.a.</i> ^[d]	<i>n.a.</i> ^[d]	<i>n.a.</i> ^[d]
4000 K	1.52	60.8	<i>n.a.</i> ^[d]

Table S1. Power and photon flux of all LEDs used in this study.

^[a]LED luminous flux data taken from its corresponding data sheet (output power). ^[b]"Entire array" consists of 40 individual LEDs. ^[c]Photon flux for the entire array, calculated by:

moles per hour = λ (nm) × power (W) × 3 × 10⁻⁵

as previously described in the literature.^{S1 [d]}*n.a.* denotes that this LED power value is not available.







Figure S3. Emission spectra of LEDs on "Panel 2" used in this study. Note: this graph gives no impression of light intensity, since emission intensities are normalized.

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

Back pressure regulator: For experiments using gaseous perfluoroalkyl iodides, a dome-type back pressure regulator (BPR-10, Zaiput Flow Technologies) was installed after the reactor exit with a set point of 3 bar.

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 PEEK fittings.

Sample loop: For optimization and substrate scope experiments, an Upchurch 6-way switching valve was used (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 internal diameter PFA tubing) installed.

B. Synthesis of *N*,*N*-bis(2,6-diisopropylphenyl)perylene-3,4,9,10-bis(dicarboximide) (PDI)



PDI was prepared according to the literature procedure:

A mixture of 2,6-diisopropylaniline (2.07 mL, 11 mmol), perylene-3,4:9,10-tetracarboxylic dianhydride (1.96 g, 5 mmol) and imidazole (10 g) was stirred at 140 °C for 4 h, then diluted with ethanol. This was followed by the addition of HCl (2 M, 200 mL). The reaction mixture was then allowed to settle. The precipitate thus formed was collected through vacuum filtration. Further purification by silica gel chromatography using dichloromethane as the eluent provided the desired product (**PDI**) in 75% yield (2.70 g). The characterization of the compound matches the data reported in the literature.^{S2}

C. General Procedures

C1. General Procedure (PDI as catalyst)

Iodoperfluoroalkylation of Alkenes at 450 nm with PDI photocatalyst



Scheme S1. Flow diagram showing general reaction setup for 450 nm experiments using PDI as photocatalyst.

The 40 LED array was switched on at 450 nm and its thermal fluid was set to 15 °C. The reaction plate thermostat was set to 20 °C. A solution of 1-octene **1a** (1 mmol, 1 equiv) perfluorohexyl iodide **2a** (1.2 mmol, 1.2 equiv), PDI (0.05 mol% = 500 ppm, with respect to alkene **1a**, 0.35 mg) and triethylamine (0.2 mmol, 0.2 equiv) was made up in degassed acetonitrile/methanol in 4:3 ratio (5 mL total volume in a volumetric flask, solvent was degassed prior to use by sparging with argon for 15 minutes, $[1a]_0 = 0.2$ M), then loaded into a 5 mL injection loop (fitted to an Upchurch 6-way valve). Acetonitrile was pumped through the 2.77 mL reaction plate at 0.554 mL/min flow rate, corresponding to 5 min residence time. After allowing the reactor to equilibrate for roughly 15 min, the reaction mixture was injected from the sample loop. The central 1 mL portion of this sample was collected for analysis by gas chromatography (GC-FID). For the isolation run, additional volume was removed under reduced pressure and the residue was purified by column chromatography (eluent: petroleum ether/ethyl acetate) to give the corresponding iodoperfluoroalkyl compound **3aa**.



1,1,1,2,2,3,3,4,4,5,5,6,6-tridecafluoro-8-iodotetradecane (3aa). Prepared according to the general procedure C1 using 1-octene 1a (1 mmol, 157 μ L) and perfluorohexyl iodide 2a (1.2 mmol, 260 μ L). The product 3aa was obtained as colorless oil (503 mg, 90%

yield). The characterization of the compound matches the data reported in the literature.^{S3}

C2. General Procedure (Catalyst-free)



Iodoperfluoroalkylation of Alkenes at 405 nm in the absence of PDI

Scheme S2. Flow diagram showing general reaction setup for 405 nm experiments.

The 40 LED array was switched on at 405 nm and its thermal fluid was set to 15 °C. The reaction plate thermostat was set to 20 °C. A solution of alkene **1** (1.25 mmol, 1 equiv) perfluoroalkyl iodide **2** (1.5 mmol, 1.2 equiv), for **2d** and **2e**: 5 mmol, 4 equiv from a 2 M solution in acetonitrile), and triethylamine (0.25 mmol, 0.2 equiv) was made up in degassed acetonitrile (5 mL total volume in a volumetric flask, solvent was degassed prior to use by sparging with argon for 15 minutes, $[1]_0 = 0.25$ M), then loaded into a 5 mL injection loop (fitted to an Upchurch 6-way valve). Using a Zaiput back pressure regulator, a pressure of 3 bar was set before using perfluoroalkyl iodides **2d** and **2e**. Acetonitrile was pumped through the 2.77 mL reaction plate at 0.554 to 0.139 mL/min flow rate, corresponding to 5, 10 or 20 min residence time. After allowing the reactor to equilibrate for roughly 15 min, the reaction mixture was injected from the sample loop. The central 1 mL portion of this sample was collected to ensure that none of the 5 mL reaction mixture was lost due to longitudinal diffusion. The solvent was removed under reduced pressure and the residue was purified by column chromatography (eluent: petroleum ether/ethyl acetate) to give the corresponding iodoperfluoroalkyl compound **3**.

C3. Characterization Data



1,1,1,2,2,3,3,4,4,5,5,6,6-tridecafluoro-8-iodotetradecane (3aa). Prepared according to the general procedure C2 using 1-octene 1a (1.25 mmol, 196 μ L) and perfluorohexyl iodide 2a (1.5 mmol, 325 µL) in a residence time of 5 min. The product 3aa was obtained

as colorless oil (660 mg, 95% yield). The characterization of the compound matches the data reported in the literature.^{S3}



1-iodo-2-(perfluorohexyl)cyclohexane (3ba). Prepared according to the general procedure C2 using cyclohexene 1b (1.25 mmol, 127 µL) and perfluorohexyl iodide 2a (1.5 mmol, 325 μ L) in a residence time of 10 min. The product **3ba** was obtained as colorless oil (340 mg,

52% yield d.r. = 3:1). The characterization of the compound matches the data reported in the literature.^{S4}



(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluoro-2-iodononyl)benzene (3da). Prepared according to the general procedure C2 using allylbenzene 1d (1.25 mmol, 166 μ L) and perfluorohexyl iodide 2a (1.5 mmol, 325 µL) in a residence time of 10 min. The product 3da was obtained as colorless oil (618 mg, 88% yield). The characterization of the compound matches the data reported in the literature.^{S5}



4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluoro-2-iodononan-1-ol (3ea). Prepared according to the general procedure C2 using allyl alcohol 1e (1.25 mmol, 85 μ L) and perfluorohexyl iodide 2a (1.5 mmol, 325 µL) in a residence time of 5 min. The product 3ea was obtained as white solid (573

mg, 91% yield). The characterization of the compound matches the data reported in the literature.^{S6}



(E)-7,7,8,8,9,9,10,10,11,11,12,12,12-tridecafluoro-5-iodododec-5-ene (3fa). Prepared according to the general procedure C2 using 1-hexyne 1f (1.25 mmol, 144 μ L) and perfluorohexyl iodide 2a (1.5 mmol, 325 μ L) in a residence time of 5 min. The product

3fa was obtained as colorless oil (465 mg, 70% yield, E/Z ratio = 5.7:1). The characterization of the compound matches the data reported in the literature.^{S7}



1,1,1,2,2,3,3,4,4-nonafluoro-6-iodododecane (3ab). Prepared according to the general procedure C2 using 1-octene 1a (1.25 mmol, 196 µL) and nonafluoro-1-iodobutane 2b (1.5 mmol, 258 μ L) in a residence time of 5 min. The product **3ab** was obtained as colorless oil

(499 mg, 87% yield). The characterization of the compound matches the data reported in the literature.⁵⁸



1-iodo-2-(perfluorobutyl)cyclooctane (3cb). Prepared according to the general procedure C2 using cyclooctene 1c (1.25 mmol, 162 µL) and nonafluoro-1-iodobutane 2b (1.5 mmol, 258 µL) in a residence time of 10 min. The product 3cb was obtained as colorless oil (417 mg, 73% yield, d.r. = 1.9:1). The characterization of the compound matches the data reported in the literature.59



1,1,1,2-tetrafluoro-4-iodo-2-(trifluoromethyl)decane (3ac). Prepared according to the general procedure C2 using 1-octene 1a (1.25 mmol, 196 µL) and heptafluoro-2iodopropane 2c (1.5 mmol, 213 µL) in a residence time of 10 min. The product 3ac was

obtained as colorless oil (378 mg, 74% yield). The characterization of the compound matches the data reported in the literature.^{S10}



(4,5,5,5-tetrafluoro-2-iodo-4-(trifluoromethyl)pentyl)benzene (3dc). Prepared according to the general procedure C2 using allylbenzene 1d (1.25 mmol, 166 μ L) and heptafluoro-2-iodopropane 2c (1.5 mmol, 213 µL) in a residence time of 10

min. The product **3dc** was obtained as colorless oil (405 mg, 78% yield). The characterization of the compound matches the data reported in the literature.^{S11}



1,1,1-trifluoro-3-iodononane (3ad). Prepared according to the general procedure C2 using 1-octene 1a (1.25 mmol, 196 µL) and trifluoroiodomethane 2d (5 mmol, 2.5 mL of a 2 M solution in acetonitrile) in a residence time of 10 min. The product 3ad was obtained as

colorless oil (348 mg, 90% yield). The characterization of the compound matches the data reported in the literature.^{S12}



(4,4,4-trifluoro-2-iodobutyl)benzene (3dd). Prepared according to the general procedure C2 using allylbenzene 1d (1.25 mmol, 166 μ L) and trifluoroiodomethane 2d (5 mmol, 2.5 mL of a 2 M solution in acetonitrile) in a residence time of 20 min. The product 3dd was obtained as colorless oil (327 mg, 83% yield). The characterization of the compound matches the data reported in the literature.^{S13}

4,4,4-trifluoro-2-iodobutan-1-ol (3ed). Prepared according to the general procedure C2 F₃C OH using allyl alcohol **1e** (1.25 mmol, 85 μ L) and trifluoroiodomethane **2d** (5 mmol, 2.5 mL) of a 2 M solution in acetonitrile) in a residence time of 20 min. The product 3ed was obtained as colorless oil (255 mg, 80% yield). ¹H-NMR $(300 \text{ MHz}, \text{CDCl}_3) \delta 4.33-4.22 \text{ (m, 1H)}, 3.77 \text{ (t, } J = 4.9 \text{ Hz}, 2\text{H}), 3.10-2.64 \text{ Hz}$ (m, 2H), 2.49 (s, 1H); ¹³C-NMR (75 MHz, CDCl₃) δ 125.62 (q, J = 278.1 Hz), 67.59 (d, J = 0.7 Hz), 40.75 $(q, J = 29.1 \text{ Hz}), 22.75 (q, J = 2.6 \text{ Hz}); {}^{19}\text{F-NMR} (282 \text{ MHz}, \text{CDCl}_3) \delta -64.26 (t, J = 10.3 \text{ Hz}, 3F); IR (ATR, C) = 10.3 \text{ Hz}, 3F + 10.3 \text{ Hz}, 3F$ neat, cm⁻¹): 3371, 1250, 1136, 1111, 1069, 1040, 1006; HRMS (ESI, negative mode) calculated for C₄H₅OF₃I [M-H]⁻: 252.9337, found: 252.9344.

(4,4,5,5,5-pentafluoro-2-iodopentyl)benzene (3de). Prepared according to the C_2F_5 general procedure C2 using allylbenzene 1d (1.25 mmol, 166 μ L) and pentafluoroiodoethane 2e (5 mmol, 2.5 mL of a 2 M solution in acetonitrile) in a residence time of 20 min. The product **3de** was obtained as colorless oil (394 mg, 87% yield). ¹H-NMR (300 MHz, CDCl₃) δ 7.41– 7.29 (m, 3H), 7.25–7.18 (m, 2H), 4.47 (ddd, J = 12.8, 8.8, 6.4 Hz, 1H), 3.26 (ddd, J = 23.4, 14.6, 7.3 Hz, 2H), 3.02–2.71 (m, 2H).); ¹³C-NMR (75 MHz, CDCl₃) δ 138.70 (s), 129.09 (s), 128.78 (s), 127.48 (s), 47.06 (d, J = 1.6 Hz), 40.77 (t, J = 20.8 Hz), 19.54 (s); ¹⁹F-NMR (282 MHz, CDCl₃) δ -85.79 (s, 3F), -115.88 (ddd, J = 265.0, 24.7, 12.2 Hz, 1F), -117.91 (ddd, J = 265.1, 22.7, 11.7 Hz, 1F); IR (ATR, neat, cm⁻¹): 1318, 1188, 1115, 1009, 743, 697, 508; HRMS (APCI+APPI, positive mode) calculated for C₁₁H₁₀F₅I [M]⁺: 363.9747, found: 363.9732; HRMS (APCI+APPI, positive mode) calculated for C₁₁H₁₀F₅ [M-I]⁺: 237.0703, found: 237.0694.

4,4,5,5,5-pentafluoro-2-iodopentan-1-ol (3ee). Prepared according to the general C₂F₅ OH procedure C2 using allyl alcohol 1e (1.25 mmol, 85 µL) and pentafluoroiodoethane 2e (5 mmol, 2.5 mL of a 2 M solution in acetonitrile) in a residence time of 20 min. The product 3ee was obtained as pale yellow oil (330 mg, 87% yield). ¹H-NMR (300 MHz, CDCl₃) δ 4.47-4.32 (m, 1H), 3.80 (s, 2H), 3.09-2.56 (m, 2H), 2.44 (s, 1H); ¹³C-NMR (75 MHz, CDCl₃) δ 67.96 (d, J = 2.1 Hz), 37.36 (t, J = 21.0Hz), 21.64 (s); ¹⁹F-NMR (282 MHz, CDCl₃) δ -85.90 (s, 3F), -116.73 (ddd, J = 264.9, 28.4, 9.1 Hz, 1F), -118.47 (ddd, J = 264.9, 26.1, 8.9 Hz, 1F); IR (ATR, neat, cm⁻¹): 3410, 2924, 2853, 1193, 1029, 722; HRMS (ESI, negative mode) calculated for $C_5H_5OF_5I [M-H]^-$: 302.9305, found: 302.9314.

C₂F₅ .OH

4,4,5,5,5-pentafluoro-2-iodopent-2-en-1-ol (3ie). Prepared according to the general procedure C2 using propargyl alcohol 1i (1.25 mmol, 73 µL) and pentafluoroiodoethane 2e (5 mmol, 2.5 mL of a 2 M solution in acetonitrile) in a residence time of 20 min. The product 3ie was obtained as pale yellow oil (287 mg, 76% yield, E/Z ratio = 1:1). The characterization of the compound matches the data reported in the literature.^{S14}

D. Optimization of the Reaction Conditions

D1. Optimization of the Reaction Conditions at 450 nm Using PDI as Photocatalyst

A series of optimization studies were performed using 1-octene (1a) and perfluorohexyl iodide (2a) as model reagents in order to explore the reaction parameters. These experiments were carried out following General Procedure C1. Conversions and yields were determinate by calibrated GC-FID analysis using *n*-dodecane as the internal standard.

$$[3aa] = \left(\frac{Area\,(3aa)}{Area\,(IS)} - c\right) \times \frac{[IS]}{k}$$



Figure S4. GC-FID calibration curve.

Table S2. Optimization of the residence time. Reactions were performed on 0.5 mmol scale. ^[a]Conversions and yields were determined by GC-FID using n-dodecane as the internal standard.

+		C ₆ F ₁₃ —I	PDI (Et ₃	(0.05 mol%) N (2 equiv)		~~/	
1a 1 equ	1a 1 equiv.		CH ₃ CN/CH ₃ OH (4:3) LED (450 nm) 20°C		3aa		
Entry	Conc.	Flow	Rate	Residence Time	Conv. ^[a]	Yield ^[a]	
1	0.1 M	0.554 ı	mL/min	5 min	>99%	93%	
2	0.1 M	1.108 ı	mL/min	2.5 min	99%	91%	
3	0.1 M	2.77 n	nL/min	1 min	71%	71%	
4	0.1 M	5.54 n	nL/min	30 sec	30%	26%	

Table S3. Optimization of the triethylamine amount. Reactions were performed on 0.5 mmol scale. ^[a]Conversions and yields were determined by GC-FID using *n*-dodecane as the internal standard.

+ C		C ₆ F ₁₃ —I	PDI (0.05 mol%) Et ₃ N		~~/		
1a 1 equiv	Ι.	CH ₃ t 2a ل 2 equiv.		CH ₃ CN/CH ₃ OH 2a LED (450 nm 2 equiv. 20°C		/CH ₃ OH (4:3) 0 (450 nm) 20°C	3aa	
Entry	Conc.	Residence T	īme	Et ₃ N	Conv. ^[a]	Yield ^[a]		
1	0.1 M	5 min		2 equiv	>99%	93%		
2	0.1 M	5 min		1 equiv	>99%	94%		
3	0.1 M	5 min		0.5 equiv	>99%	94%		
4	0.1 M	5 min		0.2 equiv	>99%	95%		
5	0.1 M	5 min		0.1 equiv	98%	93%		

 Table S4. Screening of the LEDs wavelength. Reactions were performed on 0.5 mmol scale. ^[a]Conversions and yields were determined by GC-FID using *n*-dodecane as the internal standard.



Entry	Conc.	Residence Time	Wavelength	Conv. ^[a]	Yield ^[a]
1	0.1 M	5 min	340 nm	>99%	95%
2	0.1 M	5 min	365 nm	>99%	95%
3	0.1 M	5 min	375 nm	>99%	94%
4	0.1 M	5 min	385 nm	>99%	97%
5	0.1 M	5 min	395 nm	>99%	96%
6	0.1 M	5 min	405 nm	>99%	97%
7	0.1 M	5 min	422 nm	98%	95%
8	0.1 M	5 min	450 nm	>99%	95%
9	0.1 M	5 min	485 nm	>99%	95%
10	0.1 M	5 min	540 nm	90%	88%
11	0.1 M	5 min	610 nm	0%	0%
12	0.1 M	5 min	4000 K	98%	90%

Table S5. Optimization of the perfluorohexyl iodide amount. Reactions were performed on 0.5 mmol scale. ^[a]Conversions and yields were determined by GC-FID using n-dodecane as the internal standard.

+ 1a 1 equiv.		C ₆ F ₁₃ —I	PDI (Et ₃ N	0.05 mol%) (0.2 equiv.)		~ ~ /
		2a	CH ₃ CN/CH ₃ OH (4:3) LED (450 nm) 20°C		3aa	
Entry	Conc.	Residence	e Time	C ₆ F ₁₃ I	Conv. ^[a]	Yield ^[a]
1	0.1 M	5 mi	n	2 equiv.	>99%	95%
2	0.1 M	5 mi	n	1.5 equiv.	90%	87%
3	0.1 M	5 mi	n	1.2 equiv.	86%	83%
4	0.1 M	5 mi	n	1 equiv.	84%	79%

Table S6. Optimization of the concentration with respect to alkene 1b. Reactions were performed on 0.5 mmol scale. ^[a]Conversions and yields were determined by GC-FID using *n*-dodecane as the internal standard. ^[b]1 mmol scale reaction. Isolated yield in parentheses.



D2. Optimization of the Reaction Conditions at 405 nm in Absence of PDI

Prior to evaluating the synthetic potential of the transformation, a series of optimization studies were performed using 1-octene (1a) and perfluorohexyl iodide (2a) as model reagents in order to explore the reaction parameters. These experiments were carried out following General Procedure C2.

Table S7. Screening of the LEDs wavelength. Reactions were performed on 0.5 mmol scale. ^[a]Conversions and yields were determined by GC-FID using n-dodecane as the internal standard.

+ 1a 1 equiv.		· +	C ₆ F ₁₃ −I Et ₃ N (0.2 equiv) CH ₃ CN/CH ₃ OH (4:3) 2a LED 2 equiv. 20°C		C ₆ F ₁₃	3aa
	Entry	Conc.	Residence Time	Wavelength	Conv. ^[a]	Yield ^[a]
	1	0.1 M	5 min	340 nm	>99%	94%
	2	0.1 M	5 min	365 nm	>99%	94%
	3	0.1 M	5 min	375 nm	>99%	97%
	4	0.1 M	5 min	385 nm	>99%	94%
	5	0.1 M	5 min	395 nm	>99%	94%
	6	0.1 M	5 min	405 nm	>99%	94%
	7	0.1 M	5 min	422 nm	40%	34%
	8	0.1 M	5 min	450 nm	0%	0%
	9	0.1 M	5 min	485 nm	0%	0%
	10	0.1 M	5 min	540 nm	0%	0%
	11	0.1 M	5 min	610 nm	0%	0%

Table S8. Screening of the solvents. Reactions were performed on 0.5 mmol scale. ^[a]Conversions and yields were determined by GC-FID using *n*-dodecane as the internal standard.

$\sim\sim\sim$	+ C ₆ F ₁₃ —I _	Et ₃ N (0.2 equiv.)	
1a	2a	Solvent	399
1 equiv.	1.2 equiv.	20°C	ouu

Entry	Conc.	Residence Time	Solvent	Conv. ^[a]	Yield ^[a]
1	0.1 M	5 min	CH ₃ CN/CH ₃ OH (4:3)	84%	82%
2	0.1 M	5 min	CH ₃ CN/CH ₃ OH (9:1)	95%	90%
3	0.1 M	5 min	CH₃CN	96%	92%
				J	

Table S9. Screening of the reaction concentration with respect to alkene **1a**. Isolated yields after chromatography purification. Reactions were performed on ^[a]1.25 mmol scale, ^[b]1.5 mmol scale and ^[c]2.5 mmol scale.



Perfluorohexyl iodide (2a) is poorly soluble in acetonitrile at concentrations higher than 0.25 M with respect to alkene 1a.

E. Mechanistic Investigations

E1. Determination of Binding Stoichiometry and Association Constant by ¹⁹F NMR

¹⁹F NMR spectra of seven mixtures of perfluorohexyl iodide (**2a**) and triethylamine (TEA) were recorded in the CD₃CN. Fluorobenzene was used as the internal standard (25 μ L, δ = -114.85 ppm). The total volume of the solution was 0.7 mL. The total amount of **2a** and TEA was kept constant at 0.35 mmol (0.5 M). The amount of **2a** was varied from 0 to 0.35 mmol, corresponding to 0.0, 0.2, 0.4, 0.5, 0.6, 0.8, 1.0 molar ratio. The chemical shift difference ($\Delta\delta$) between –CF₂I in the different mixtures was calculated and the binding stoichiometry was then determined using Job's plot analysis,^{S15} plotting [2a]/[2a + TEA] *vs* [2a] × $\Delta\delta$.



Figure S5. $^{19}\text{F-NMR}$ spectra showing the $\Delta\delta$ of the various $C_6F_{13}I$ and TEA mixtures.

Molar Ratio	[2a]	[TEA]	Δδ	[2a]/[2a + TEA]	[2a] × Δδ
0.0	0	0.5	0	0	0
0.2	0.1	0.4	4.58	0.2	0.458
0.4	0.2	0.3	4	0.4	0.8
0.5	0.25	0.25	3.08	0.5	0.77
0.6	0.3	0.2	2.61	0.6	0.783
0.8	0.4	0.1	1.25	0.8	0.5
1.0	0.5	0	0	1	0

Table S10. Experimental data for Job plot analysis.



Figure S6. Job's plot analysis.

$$x_{max} = \frac{3.223}{-2 \times (-3.208)} = 0.50$$

The Job plot analysis has demonstrated that **2a** and TEA are associated in 1:1 ratio complex ratio through halogen bonding.

Finally, the association constant (Ka) of the complex has been calculated using Hanna and Ashbaugh's method.^{S16 19}F NMR spectra of seven mixtures of perfluorohexyl iodide (**2a**) and triethylamine (TEA) were recorded in the CD₃CN. Fluorobenzene was used as the internal standard (25 μ L, δ = -114.85 ppm). The total volume of the solution was 0.7 mL. The amount of **2a** was kept constant at 0.1 mmol (0.143 M). The amount of TEA was varied from 0 to 3 mmol, corresponding to 0, 1, 1.5, 3, 6, 12, 30 equivalents with respect to **2a**. The chemical shift difference ($\Delta\delta$) between $-CF_2I$ in the different mixtures was calculated and the binding stoichiometry was then determined plotting 1/[TEA] *vs* 1/ $\Delta\delta$.

Entry	[2a]	[TEA]	1/[TEA]	Δδ	1/Δδ
1	0.143	0.00	0.00	0	0.00
2	0.143	0.14	7.00	2.16	0.46
3	0.143	0.21	4.67	2.98	0.34
4	0.143	0.43	2.33	4.9	0.20
5	0.143	0.86	1.17	6.92	0.14
6	0.143	1.71	0.58	8.74	0.11
7	0.143	4.29	0.23	9.77	0.10

 Table S11. Experimental data for association constant determination.



Figure S7. Association constant determination.

$$K_a = \frac{intercept}{slope} = \frac{0.0837}{0.0539} = 1.57 \, M^{-1}$$

The association constant between 2a and TEA was calculated to be 1.57 M⁻¹ in CD₃CN.

E2. Kinetic profile and UV-Vis experiments

To determine the kinetic profile of the model reaction between 1a and 2a in presence of TEA as amine additive, the general procedure C2 was followed, adjusting the flow rate of the solvent to provide the corresponding residence time.

Entry	Flow Rate (mL/min)	Residence Time (s)	Conv. (%) ^[a]
1	0	0	0
2	9.78	17	0
3	5.54	30	46
4	2.77	60	74
5	1.85	90	84
6	1.38	120	87
7	1.11	150	89
8	0.92	180	90
9	0.79	210	91
10	0.69	240	92
11	0.62	270	93



Figure S8. Kinetic profile of the model reaction performed in flow, irradiated at 405 nm, without PDI.

The reaction under these conditions has an induction period of at least 30 seconds.

UV-Vis experiments of the crude mixture in acetonitrile highlighted the formation of five different bands during the reaction progress. Two of which are present in the UV region (250 and 350 nm) and three are centered in the visible (440, 500 and 570 nm). The first set of signals is observed using a concentration of 0.0025 M with respect to the alkene **1a** and the second set is clearly observable at 0.025 M. The reactor output was diluted accordingly, to reach the required concentration.

For comparison, the spectrum of the pure product **3aa** is also shown ($\lambda_{max} = 265$ nm).



Figure S9. Optical absorption spectra of the reaction output obtained at different residence times. Recorded in acetonitrile (0.0025 M). Optical path length = 1 cm.



Figure S10. Optical absorption spectra of the reaction output obtained at different residence times. Recorded in acetonitrile (0.025 M) Optical path length = 1 cm.



Figure S11. Optical absorption spectra recorded in acetonitrile of the pure product **3aa** in acetonitrile at 0.00025 M (blue line) and 0.0025 M (red line). Optical path length = 1 cm.

F. Fulvestrant Side Chain Synthesis

F1. Dehalogenation of 3ee

An H-CUBE Pro (ThalesNano Inc.) system was used for this procedure. The H-CUBE Pro has an internal hydrogen generator, then this hydrogen is introduced into the reaction mixture, which is pumped by an HPLC pump, prior to catalyst contact. The pressure of the system is dictated by the adjustable BPR (back pressure regulator). The system can be summarized by the following scheme:



Scheme S3. Flow diagram showing the reaction setup for dehalogenation of 3ee.

The crude mixture of **3ee** in acetonitrile (theoretically 1.25 mmol, 1 equiv) coming from the Corning Photo-Reactor was collected and diluted with acetonitrile to 0.1 M and sparged with argon for 30 min to remove the unreacted trifluoroiodomethane. Triethylamine (2.5 mmol, 348 μ L, 2 equiv) was then added and the resulting solution was loaded into an 8.5 mL injection loop (fitted to an Upchurch 6-way valve). Acetonitrile was pumped through the H-CUBE Pro reactor at 1 mL/min flow rate, corresponding to less than 1 min residence time. The system was equipped with a PtO₂ cartridge (70 mm, 4 mm diameter), heated up to 50 °C, pressurized to 20 bar by the adjustable back pressure regulator and set to "100% hydrogen amount". After allowing the reactor to equilibrate for roughly 30 min, the reaction mixture was injected from the sample loop. The output was collected and used directly in the following step without isolation nor purification of the dehalogenated alcohol **4**.

F2. Benzoylation of 4 performed in batch



Scheme S4. Benzoylation of alcohol 4.

To the crude mixture of 4 in acetonitrile (theoretically 1,25 mmol, 1 equiv) coming from the H-CUBE Pro

reactor was added pyridine (10 mmol, 809 μ L, 8 equiv) and the solution was stirred at 0 °C for 10 min. Benzoyl chloride (6.25 mmol, 726 μ L, 5 equiv) was added dropwise and the solution was stirred at room temperature for 3 hours. The reaction was quenched by the addition of HCl 1 M (20 mL) and then extracted with ethyl acetate (3 × 20 mL). The organic phases were combined and dried over sodium sulfate. The solvent was removed under reduced pressure and the residue was purified by column chromatography (petroleum ether/ethyl acetate 95:5) to give the corresponding benzoylated alcohol **5** as a pale yellow oil (253 mg, 72% overall yield).

¹H-NMR (300 MHz, CDCl₃) δ 8.08–8.01 (m, 2H), 7.62–7.53 (m, 1H), 7.49–7.41 (m, 2H), 4.40 (t, *J* = 6.1 Hz, 2H), 2.33–2.02 (m, 4H); ¹³C-NMR (75 MHz, CDCl₃) δ 166.44 (s), 133.26 (s), 129.67 (s), 128.56 (s), 63.49 (s), 27.84 (t, *J* = 22.3 Hz), 20.35 (t, *J* = 3.8 Hz); ¹⁹F (282 MHz, CDCl₃) δ -85.51 (s), -118.32 (t, *J* = 17.8 Hz); IR (ATR, neat, cm⁻¹): 1720, 1271, 1188, 1109, 1025, 997, 705; HRMS (APCI+APPI, positive mode) calculated for C₁₂H₁₂O₂F₅ [M+H]⁺: 283.0757, found: 283.0748.

F3. Scale-out Synthesis of 5



Scheme S5. Flow diagram showing the reaction setup for scale-out synthesis of 30.

The 40 LED array was switched on at 405 nm and its thermal fluid was set to 15 °C. The reaction plate thermostat was set to 20 °C. A solution of allyl alcohol **1e** (12.5 mmol, 1 equiv), pentafluoroiodoethane **2e** (50 mmol, 4 equiv, taken from a 2 M solution in acetonitrile), and triethylamine (2.5 mmol, 0.2 equiv) was made up in degassed acetonitrile (50 mL total volume in a volumetric flask, solvent was degassed prior to use by sparging with argon for 15 minutes, $[1e]_0 = 0.25$ M). Using a Zaiput back pressure regulator, a pressure of 3 bar was set. The reaction solution was pumped through the 2.77 mL reaction plate at 0.139 mL/min flow rate, corresponding to 20 min residence time. After allowing the reactor to equilibrate for roughly 15 min, the processed mixture, containing compound **3ee**, was collected over a run time of 173 min (24 mL, 6 mmol theoretical yield).



Scheme S6. Flow diagram showing the reaction setup for scale-out synthesis of 4.

The crude mixture of **30** in acetonitrile (24 mL, theoretically 6 mmol, 1 equiv) coming from the Corning Photo-Reactor was diluted with acetonitrile to 0.1 M and sparged with argon for 30 min to remove the unreacted trifluoroiodomethane. Triethylamine (12 mmol, 1.67 mL, 2 equiv) was then added and the resulting solution was pumped through the H-CUBE Pro reactor at 1 mL/min flow rate, corresponding to less than 1 min residence time. The system was equipped with a PtO_2 cartridge (70 mm, 4 mm diameter), heated to 50 °C, pressurized to 20 bar by the adjustable back pressure regulator and set to "100% hydrogen amount". The output was collected and used directly in the following step without isolation nor purification of the dehalogenated alcohol **4** (6 mmol theoretical yield).



Scheme S7. Larger scale benzoylation of alcohol 4.

To the crude mixture of **4** in acetonitrile (6 mmol, 1 equiv) coming from the H-CUBE Pro reactor was added pyridine (48 mmol, 3.88 mL, 8 equiv) and stirred at 0 °C for 10 min. Benzoyl chloride (30 mmol, 3.49 mL, 5 equiv) was added dropwise and the solution was stirred at room temperature for 16 h. The reaction was quenched by the addition of HCl (1 M, 100 mL) and then extracted with ethyl acetate (3×100 mL). The organic phases were combined and dried over sodium sulfate. The solvent was removed under reduced pressure and the residue was purified by column chromatography (petroleum ether/ethyl acetate 95:5) to give the corresponding benzoylated alcohol **5** as a pale yellow oil (1.23 g, 73% yield over 3 steps).

H. References

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I. NMR Spectra


















































































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