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Pentafluoroethylation of Carbonyl Compounds Using HFC-125 in a Flow Microreactor System

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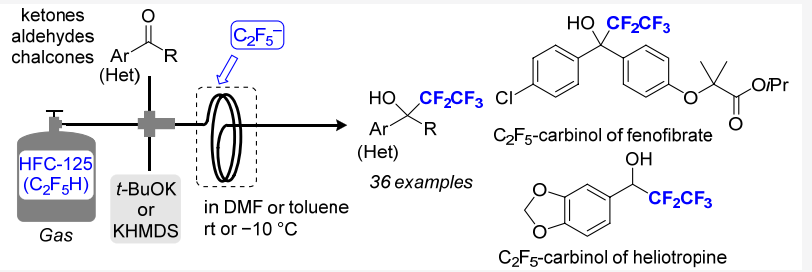

ABSTRACT: The protocol of micro-flow nucleophilic pentafluoroethylation using pentafluoroethane (HC_2F_5, HFC-125), a nontoxic, inexpensive, and commercially available greenhouse gas, is described. The micro-flow pentafluoroethylation by HFC-125 proceeded smoothly at room temperature or at −10 °C in DMF or toluene in the presence of a potassium base, namely, *t*-BuOK or KHMDS. A broad range of ketones, aldehydes, and chalcones with various substituted benzene rings were successfully converted to the corresponding pentafluoroethyl carbinols instantly with good to high yields.

INTRODUCTION

Organofluorine compounds have been an integral component of pharmaceutical, agrochemical, and fine chemical industries for more than half a century.[1] Fluorination (F) and trifluoromethylation (CF_3) reactions are the two most widely employed synthetic methods for the fluoro-functionalization of target substrates.[2,3] As a result, more than 80% of fluoro-pharmaceuticals and fluoro-agrochemicals on the market can be categorized into F^-- and CF_3-containing compounds.[1,4] After fluorination (C0 unit) and trifluoromethylation (C1 unit), pentafluoroethylation (C_2F_5), entailing a two-carbon extension, is the next most relevant fluoro-modification. Among the reported pentafluoroethylation reaction methods,[5] our focus is on the nucleophilic pentafluoroethylation reaction of carbonyl compounds providing pentafluoroethyl carbinols ($RC(OH)C_2F_5$), due to their potential broad utility in organic synthesis. Examples of biologically attractive compounds having a pentafluoroethyl carbinol moiety is shown in Figure 1a.[6] However, taming the pentafluoroethyl anion ($^-C_2F_5$) is complicated as it is thermally unstable,[7] spontaneously decomposing into notoriously explosive tetrafluoroethylene (TFE, $CF_2{=}CF_2$) and fluoride (F^-),[8] specially in the case of the reactive pentafluoroethyl lithium species generated by halogen-lithium exchange reactions of pentafluoroethyl halide ($X\text{-}C_2F_5$) (Figure 1b).[9] Copper or zinc pentafluoroethyl species ($Cu\text{-}C_2F_5$, $Zn\text{-}C_2F_5$) can be used as stable alternatives to pentafluoroethyl anions,[5a,10] but their utility is somewhat limited owing to their low reactivity. Pentafluoroethyl trialkylsilanes ($R_3SiC_2F_5$) have been generally used for nucleophilic pentafluoroethylation reactions under fluoride catalysis.[11] In 2011, Nagaki, Amii, and Yoshida et al. elegantly addressed this intractable problem by employing flow microreactor systems.[12] The flow microreactor is an effective device for controlling unstable, reactive intermediates in organic reactions.[13] They achieved the nucleophilic pentafluoroethylation of benzaldehyde with pentafluoroethyl lithium generated from pentafluoroethyl iodide ($I\text{-}C_2F_5$) under a flow microreactor system at 0 °C (Figure 1c). Although this method is potentially useful for various carbonyl compounds, only a single example was reported.

We have recently disclosed a novel protocol for the direct nucleophilic pentafluoroethylation of carbonyl compounds using pentafluoroethane (HC_2F_5, HFC-125) in the presence of potassium bases in glyme (Figure 1d).[14] The key to this transformation is the generation of glyme-encapsulated K^+, resulting in the stabilization of $C_2F_5^-$ derived from HFC-125 by ion separation. The encapsulation of K^+ by glyme effectively restricts contact between $C_2F_5^-$ and K^+, preventing β-elimination to $CF_2{=}CF_2$ and KF. Isolated $C_2F_5^-$ is rather exposed and is sufficiently nucleophilic for the pentafluoroethylation of various carbonyl compounds. HFC-125 is a

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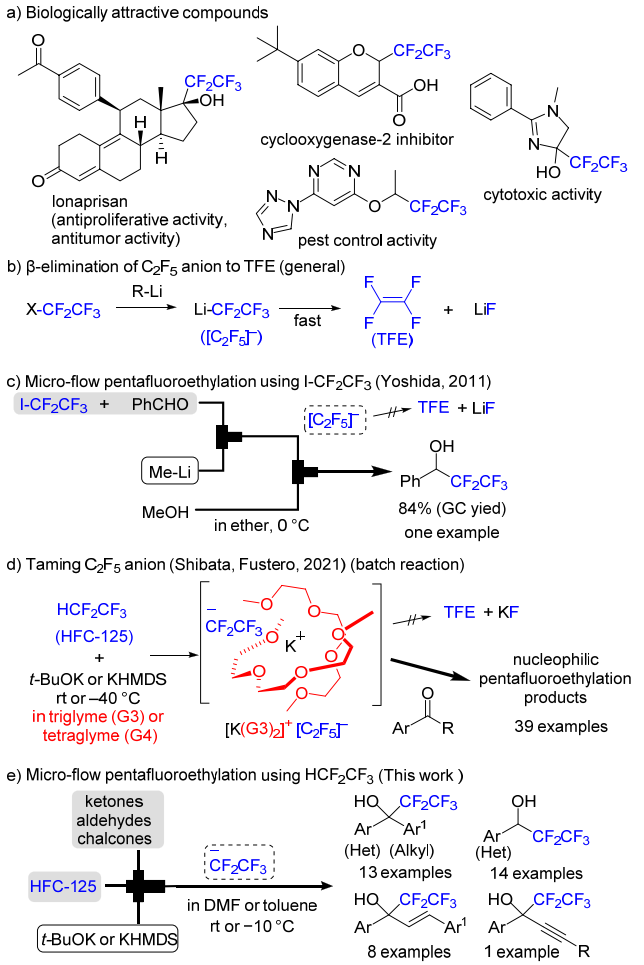


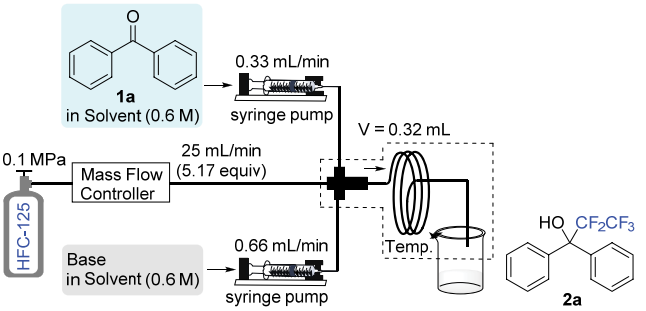
Figure 1. Pentafluoroethylation using pentafluoroethyl halides or HFC-125. (a) Biologically attractive compounds having a pentafluoroethyl carbinol moiety. (b) *β*-elimination in pentafluoroethyl lithium, yielding TFE. (c) Micro-flow pentafluoroethylation of benzaldehyde using I-CF_2CF_3 and MeLi. (d) Pentafluoroethylation of carbonyl compounds using HFC-125 and a potassium base in glyme. (e) Micro-flow pentafluoroethylation of carbonyl compounds using HFC-125 and a potassium base in DMF or toluene (this work).

nontoxic and inexpensive greenhouse gas, and it does not contribute to ozone layer depletion.[15] As HFC-125 is a more atom economical reagent than C_2F_5I, we focused on the micro-flow pentafluoroethylation of carbonyl compounds using HFC-125. The advantage of being able to control an unstable anion by harnessing the compatibility between flow microreactors and gaseous reagents should yield an ideal method for direct pentafluoroethylation using HFC-125. Herein, we report the pentafluoroethylation of various carbonyl compounds using HFC-125 in a flow microreactor system, as part of our project aimed at devising efficient protocols that utilize fluorocarbons in organic synthesis.[16] Indeed, nucleophilic pentafluoroethylation of a broad range of ketones, chalcones, and aldehydes was achieved in a flow microreactor system at temperatures ranging from room temperature to −10 °C in the presence of potassium bases such as potassium *tert*-butoxide (*t*-BuOK) and potassium bis(trimethylsilyl)amide (KHMDS) (Figure 1e). As expected, the use of a micro-flow system allowed for a highly efficient pentafluoroethylation protocol, which did not require glyme as a stabilization solvent or low-temperature conditions ordinarily employed in batch systems. Besides, this micro-flow protocol enables the reaction within minutes, while the batch system requires more than hours.[14] Thus, this continuous flow microreactor protocol for pentafluoroethylation would be advantageous for large-scale industrial preparation.[17]

RESULTS AND DISCUSSION

Optimization of conditions for the micro-flow pentafluoroethylation of benzophenone (**1a**) as a model substrate was investigated. On the basis of our previous report,[16f] we selected a three-inlet mixer to combine the substrate, HFC-125, and base (Table 1). It took about 2 min to stabilize the gas flow.

Table 1. Optimization of Reaction Conditions for the Micro-flow Pentafluoroethylation of Benzophenone (1a) Using HFC-125



entry	solvent	base	temp	yield (%)[a]
1	DMF	*t*-BuOK	rt	92
2	toluene	*t*-BuOK	rt	15
3	THF	*t*-BuOK	rt	33
4	DMF	KHMDS	rt	81
5	DMF	*t*-BuOK	−10 °C	89
6	DMF	*t*-BuOK	−50 °C	89
7	triglyme	*t*-BuOK	rt	74
8	tetraglyme	*t*-BuOK	rt	60

[a]Yields were determined by ^{19}F NMR of the crude product with trifluorotoluene as an internal standard.

We examined the flow process time and found that 1 min is enough to get good reproducible yields. When the reaction was conducted by mixing **1a** in DMF (0.6 M, 0.33 mL/min), *t*-BuOK in DMF (2.0 equiv, 0.66 mL/min), and gaseous HFC-125 (25 mL/min, 5.17 equiv, 0.1 MPa) at room temperature, the desired pentafluoroethylated product **2a** was obtained in 92% yield (entry 1). The use of toluene or THF as a solvent decreased the product yield (entries 2 and 3). When KHMDS was used instead of *t*-BuOK, the yield was lower (entry 4). Decreasing the reaction temperature (−10 or −50 °C) did not significantly affect the yield (entries 5 and 6). Despite our expectation,[14] tri- or tetraglyme as solvent was not adequate for the micro-flow protocol (entries 7 and 8).

To reduce the amount of HFC-125, we further optimized the concentration of **1a** and the flow rates of **1a**, *t*-BuOK, and HFC-125 in DMF (Table 2). An increase in the concentration of **1a** resulted in a lower product yield (entries 1−3). Decreasing the HFC-125 flow rate also resulted in a lower yield of **2a** (entries 4 and 5). A decrease in the flow rate of *t*-BuOK to 0.6 mL/min (i.e., increasing the residence time) improved the yield of **1a** to 94% (entry 6). Reducing the number of equivalents of *t*-BuOK (1.5 equiv) (entry 7) or the flow rates of *t*-BuOK and HFC-125 (entry 8) resulted in a lower yield (85−87%). These results suggest that the reactivity

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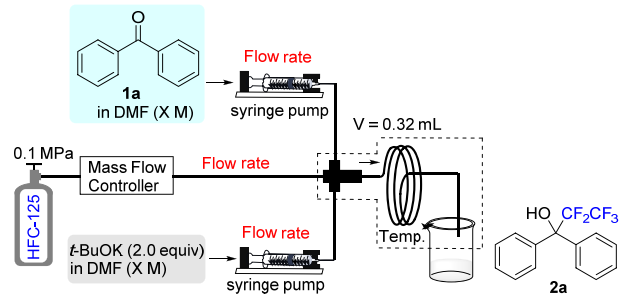
Table 2. Optimization of Flow Parameters for the Pentafluoroethylation of Benzophenone Using HFC-125



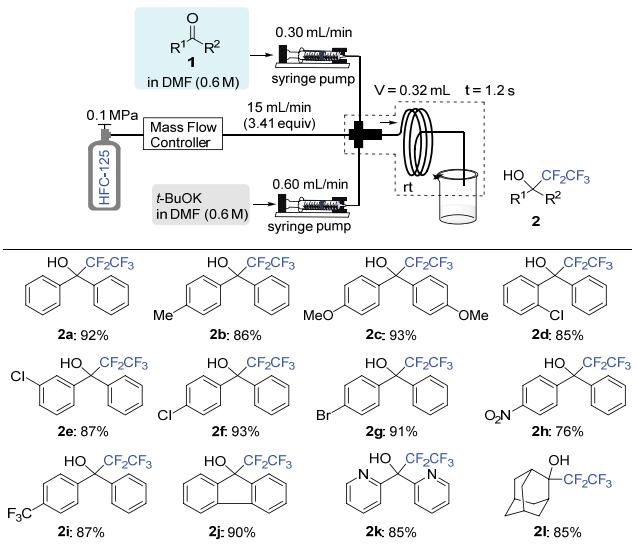
		flow rate (mL/min)				
entry	X (M)	**1a**	*t*-BuOK	HFC-125	equiv of HFC-125	yield (%)[a]
1	0.6	0.33	0.66	25	5.17	92
2	0.9	0.33	0.66	25	3.44	91
3	1.2	0.33	0.66	25	2.58	73
4	0.6	0.33	0.66	15	3.10	88
5	0.6	0.33	0.66	13.5	2.79	79
6	0.6	0.30	0.60	15	3.41	94
7	0.6	0.30	0.45[b]	15	3.41	87
8	0.6	0.30	0.60	13.5	3.07	85

[a]Yields were determined by ^{19}F NMR of crude product with trifluorotoluene as an internal standard. [b]1.5 equiv of *t*-BuOK.

of HFC-125-mediated pentafluoroethylation is highly dependent on the concentration of the reactants, viscosity, and slug flow in the microtube.

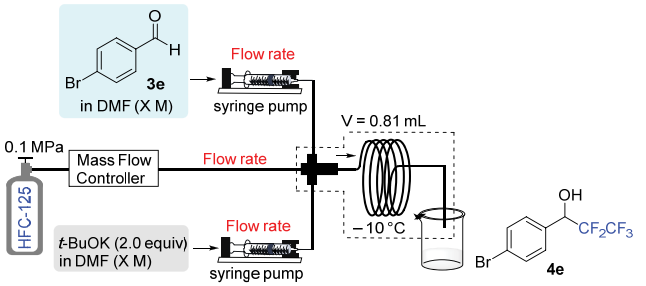
Next, we examined the substrate generality of the flow pentafluoroethylation protocol using various ketone substrates with a range of substituents on the aromatic ring (Scheme 1). Benzophenones bearing electron-donating groups or halogens (**1a**–**g**) provided the corresponding pentafluoroethylated products (**2a**–**g**) in high yield (85–93% yield). Substitution with electron-withdrawing groups (**1h**: NO_2, **1i**: CF_3) provided the pentafluoroethylated products in good yield (**2h**: 76%, **2i**: 87%). The pentafluoroethylation reaction of 9-fluorenone (**1j**), di-2-pyridyl ketone (**1k**), and 2-adamantanone (**1l**) proceeded smoothly to provide the corresponding products in high yield (**2j**: 90%, **2k**: 85%, **2l**: 85%).

Scheme 1. Flow Pentafluoroethylation of Ketones Using HFC-125



Next, we examined the micro-flow pentafluoroethylation of aldehyde **3** (Table 3). The reaction was first conducted by mixing **3a** in DMF (0.6 M, 0.33 mL/min), *t*-BuOK in DMF (2.0 equiv, 0.66 mL/min), and HFC-125 (25 mL/min, 5.17 equiv, 0.1 MPa) at room temperature; however, the desired product was not observed (entry 1). This outcome could be explained by the occurrence of the Cannizzaro reaction. Thus, we performed the reaction at −10 °C. After a number of attempts (entries 2–10), optimal conditions were established as follows: **3a** in DMF (0.6 M, 0.33 mL/min), *t*-BuOK in DMF (1.50 equiv, 0.50 mL/min), and HFC-125 (15 mL/min, 3.10 equiv, 0.1 MPa) at −10 °C (entry 6).

Table 3. Optimization of Reaction Conditions for the Flow Pentafluoroethylation of Benzaldehyde Using HFC-125



		flow rate (mL/min)				
entry	X (M)	**3e**	*t*-BuOK	HFC-125	equiv of HFC-125	yield (%)[a]
1[b]	0.6	0.33	0.66	25	5.17	0
2[c]	0.6	0.33	0.66	25	5.17	75
3	0.6	0.33	0.66	25	5.17	89
4	0.6	0.33	0.66	15	3.10	93
5	0.6	0.33	0.66	13.5	2.79	88
6	0.6	0.33	0.50[d]	15	3.10	92
7	0.6	0.30	0.60	13.5	3.07	85
8	0.6	0.30	0.45[d]	13.5	3.07	84
9	0.6	0.30	0.33[e]	13.5	3.07	70
10	0.9	0.30	0.30	20	3.03	89

[a]Yields were determined by ^{19}F NMR of the crude product with trifluorotoluene as an internal standard. [b]Reaction was performed at room temperature. [c]Reaction was performed at 0 °C. [d]1.5 equiv of *t*-BuOK. [e]1.1 equiv of *t*-BuOK.

Scheme 2 shows the substrate scope of the flow pentafluoroethylation of substituted benzaldehydes (**3a**–**j**), naphthalene aldehydes (**3i** and **3j**), and heteroaryl aldehydes (**3k** and **3l**). Benzaldehydes bearing electron-donating groups, halogens, and electron-withdrawing groups gave the corresponding pentafluoroethylated products (**4a**–**h**) in high yield (86–92% yield). Likewise, 1- and 2-naphthalene aldehydes (**3i** and **3j**) also delivered the desired products in high yield (**4i**: 91%, **4j**: 82%). The flow pentafluoroethylation of heteroaromatic aldehydes (**3k** and **3l**) afforded lower yields (**4k**: 65%, **4l**: 69%).

The flow pentafluoroethylation of chalcone **5a** was examined next (Table 4). In this case, KHMDS was used based on the reported batch system.[14] The desired 1,2-addition product **6a** was obtained in 45% yield (entry 1). The reagent concentrations, solvent, and HFC-125 flow rate were further

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Scheme 2. Flow Pentafluoroethylation of Aldehydes Using HFC-125

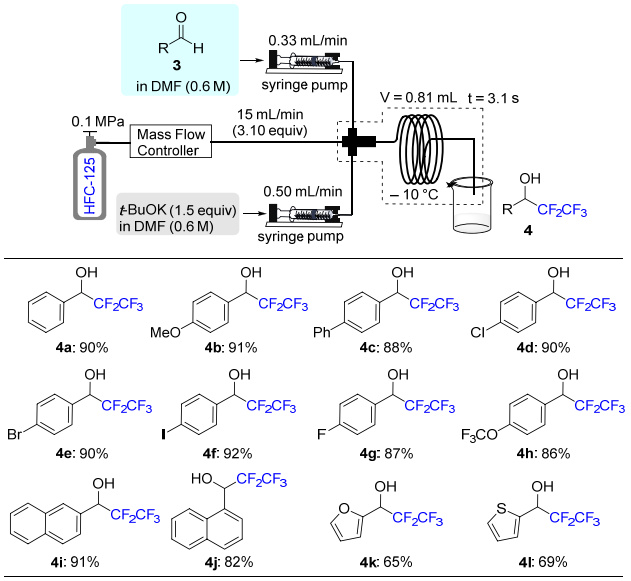
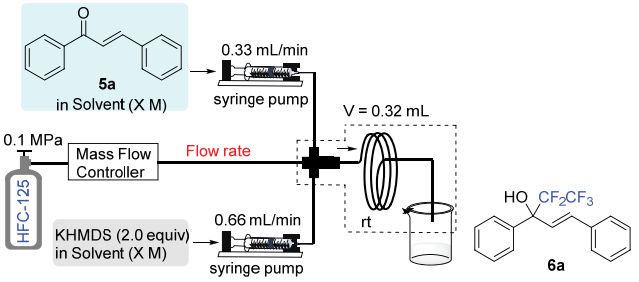


Table 4. Optimization of Conditions for the Flow Pentafluoroethylation of Chalcones Using HFC-125



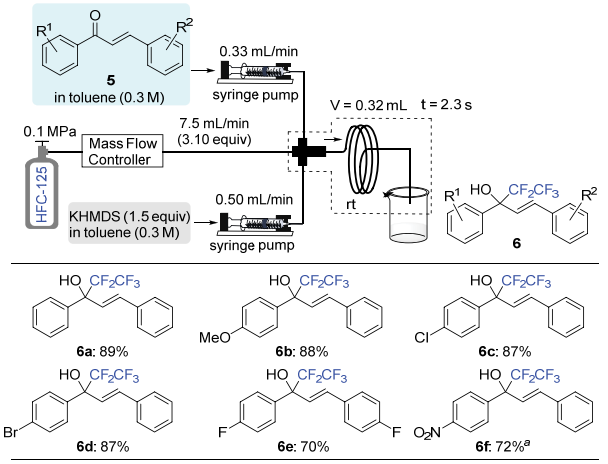
			HFC-125		
entry	X (M)	solvent	flow rate (mL/min)	equiv	yield (%)[a]
1[b]	0.6	DMF	25	5.17	45
2	0.6	DMF	25	5.17	65
3	0.6	THF	25	5.17	85
4	0.6	toluene	25	5.17	85
5	0.3	toluene	12.5	5.17	90
6[c]	0.3	toluene	12.5	5.17	90
7	0.3	toluene	7.5	3.10	90
8	0.3	toluene	6.5	2.69	85
9[d]	0.3	toluene	7.5	3.10	90

[a]Yields were determined by ^{19}F NMR of the crude product with trifluorotoluene as an internal standard. [b]*t*-BuOK was used instead of KHMDS. [c]Reaction was performed at −10 °C. [d]1.5 equiv of KHMDS was used.

optimized (entries 2−9), and the ideal conditions were determined as follows: chalcone **5a** in toluene (0.3 M, 0.33 mL/min), KHMDS (1.5 equiv, 0.50 mL/min) in toluene, and HFC-125 (7.5 mL/min, 3.10 equiv, 0.1 MPa) were reacted at room temperature to afford product **6a** in 90% yield (entry 9).

Thus, we demonstrated the flow pentafluoroethylation of chalcones **5** under optimized reaction conditions (Scheme 3). Methoxy- (**5b**) and halogen-substituted (**5c**−**e**) chalcones were converted to the corresponding 1,2-addition products (**6b**−**e**) in good to high yields (70−88%). The flow

Scheme 3. Flow Pentafluoroethylation of Chalcones Using HFC-125

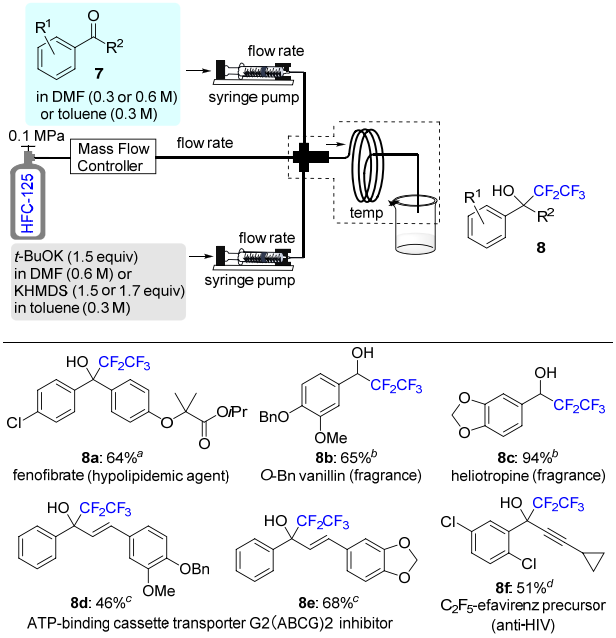


[a]THF was used as the solvent.

pentafluoroethylation of nitro-substituted **5f** also provided the desired pentafluoroethylated product **6f** in 72% yield when conducted in THF instead of toluene.

Finally, we extended the protocol to the pentafluoroethylation of biologically attractive substrates (Scheme 4). The

Scheme 4. Flow Pentafluoroethylation of Bioactive Carbonyl Derivatives



[a]Conditions for ketones **1** (Scheme 1). [b]Conditions for aldehydes **3** (Scheme 2). [c]Conditions for chalcones **5** (Scheme 3). [d]Modified conditions of chalcones **5**; see the details in the Experimental Section.

pentafluoroethylation of fenofibrate (**7a**, hypolipidemic agent) furnished the pentafluoroethyl carbinol product **8a** in good yield (64%) by the ketone's conditions (Scheme 1). Fragrance aldehydes such as *O*-Bn-vanillin (**7b**) and heliotropin (**7c**) were transformed into pentafluoroethyl carbinol products (**8b** and **8c**) in good to high yield (65% and 94%) under the conditions for aldehydes (Scheme 2). The ABCG2 inhibitory

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active chalcones (**7d** and **7e**) gave the corresponding pentafluoroethyl carbinols (**8d** and **8e**) in moderated yield (46% and 68%) by the conditions for chalcones (Scheme 3). Interestingly, a conjugated, alkynyl ketone, 3-cyclopropyl-1-(2,5-dichlorophenyl)prop-2-yn-1-one (**7f**, a building block for the preparation of anti-HIV drug, efavirenz) was also transformed into the desired C_2F_5-variant of efavirenz precursor **8f**, under the slightly modified conditions for chalcones (1.7 equiv of KHMDS in toluene (0.3 M), 1.1 mL/min, −30 °C) in moderated yield (51%).

CONCLUSIONS

In summary, we have developed a micro-flow pentafluoroethylation method using HFC-125. Ketones, aldehydes, and chalcones were promptly converted to the corresponding pentafluoroethylated products in good to high yields. HFC-125 is a nontoxic, inexpensive, and commercially available greenhouse gas. The reaction can be performed at room temperature or at −10 °C, and the system does not require the use of glyme as a stabilization solvent, nor very low-temperature conditions employed in batch systems. While the glyme protocol is efficient,[14] the reaction should be carried out for 12 h. On the other hand, this micro-flow protocol enables the reaction within minutes. Besides, large-scale production can be performed without a particular large-scale variant since the protocol is a continuous flow system. Moreover, we never experienced any explosions through all the experiments.[8] Since we experienced the substrates with an enolizable ketone moiety was unreacted due to the α-deprotonation of ketones, the issue should be the next challenge. The application of this flow system in asymmetric pentafluoroethylation reactions is currently under investigation.

EXPERIMENTAL SECTION

General Information. All reagents were used as received from commercial sources unless specified otherwise. The solvents were transferred via syringe. All reactions were monitored by thin-layer chromatography (TLC) performed on 0.25 mm Merck silica gel (60-F_{254}). The TLC plates were visualized under UV light and stained with 7% phosphomolybdic acid or $KMnO_4$ in water, followed by heating. Column chromatography was performed on silica gel 60N spherical neutral size 40−50 μm (Kanto Kagaku), 64−210 μm (FUJIFILM Wako). NMR spectra were recorded on a Varian Mercury 300 spectrometer for ^{1}H NMR (300 MHz) and ^{19}F NMR (282 MHz), and a Bruker Avance 500 for ^{1}H NMR (500 MHz) and ^{13}C{^{1}H} NMR (125 MHz). The chemical shifts (δ) were measured in parts per million with respect to solvent (^{1}H: $CDCl_3$, δ = 7.26 ppm; ^{19}F: $CDCl_3$, δ = −162.2 ppm with C_6F_6 as internal standard; ^{13}C{^{1}H}: $CDCl_3$, δ = 77.16 ppm), and coupling constants (J) are given in hertz. The following abbreviations denoted the corresponding multiplicities: s, singlet; d, doublet; t, triplet; q, quadruplet; dd, doublet of doublets; td, triplet of doublets; dt, doublet of triplets; m, multiplet; br, broad. Mass spectra were recorded using an LCMS-2020EV (ESI-MS) system. Infrared spectra were recorded on a JASCO FT/IR-4100 spectrometer. High-resolution mass spectrometry (HR-MS) was performed on a Waters Synapt G2 HDMS (ESI-TOF-MS) instrument. Melting points were recorded using a BUCHI L3abortehnik AG M-565 apparatus. Ketones **1**, aldehydes **3**, and chalcones **5a**, **7b**, and **7c** were purchased from Aldrich, TCI, and Wako Chemical. Substrates **5b−f**, **7b**, and **7d−f** were prepared according to the reported methods.[18−22]

Components of Flow System. A syringe pump (YMC) was used for addition of solutions of substrate and base. The mass flow controller (Fujikin, FCST1005MLC) was used to control the flow rate of gaseous HFC-125. The pressure of HFC-125 was regulated by the regulator connected to the HFC-125 cylinder. The three-inlet mixer (4 direction swirl mixer, Sugiyama Shoji, SUS316, 60 μL internal volume, 16YSM-0.8-0.5-S)[23] was used for a mixing of solutions and HFC-125. All flow stuffs (syringes, three inlets mixer, reaction coil, tubes) were dried and filled with N_2 gas before using. The residence tube (SUS316, ID = 0.8 mm; residence volume V = 0.32 or 0.81 mL) was used for the reaction coil.

General Procedure 1: Flow Pentafluoroethylation of Benzophenones Using HFC-125. A solution of ketone **1** (1.2 mmol, 1.0 equiv) in dry DMF (2.0 mL) was fed into a three-inlet mixer (0.30 mL/min) using a syringe pump; simultaneously *t*-BuOK (2.4 mmol, 2.0 equiv) in dry DMF (4.0 mL) was fed into the mixer (0.60 mL/min) using another syringe pump. HFC-125 (3.41 equiv) was introduced into the mixer at 0.1 MPa and 15 mL/min controlled by a mass flow controller. The combined mixture was passed through residence tubing (residence volume V = 0.32 mL) at room temperature. After the gas flow rate stabilized (about 2 min), we collected the product for 1 min. The product stream was quenched with sat. NH_4Cl aq. The aqueous layer was extracted with Et_2O, and the combined organic layers were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure, and purified by column chromatography on silica gel to give products **2**.

*2,2,3,3,3-Pentafluoro-1,1-diphenylpropan-1-ol (**2a**).* Following the general procedure 1, crude product was purified by silica gel column chromatography with hexane/CH_2Cl_2 (1:1) to give the product **2a** (50.0 mg, 92% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.63−7.53 (m, 4H), 7.41−7.32 (m, 6H), 2.95−2.93 (m, 1H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −77.6 (br s, 3F), −116.9 (br s, 2F) ppm. MS (ESI, m/z) 301 [M − H]$^-$. Analytical data are consistent with reported values.[13]

*2,2,3,3,3-Pentafluoro-1-phenyl-1-(p-tolyl)propan-1-ol (**2b**).* Following the general procedure 1, crude product was purified by silica gel column chromatography with hexane/CH_2Cl_2 (1:1) to give the product **2b** (49.1 mg, 86% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.55 (d, J = 6.8 Hz, 2H), 7.43 (d, J = 7.6 Hz, 2H), 7.35−7.33 (m, 3H), 7.15 (d, J = 7.9 Hz, 2H), 2.81 (s, 1H), 2.34 (s, 3H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −77.5 (s, 3F), −116.9 (s, 2F) ppm. MS (ESI, m/z) 315 [M − H]$^-$. Analytical data are consistent with reported values.[14]

*2,2,3,3,3-Pentafluoro-1,1-bis(4-methoxyphenyl)propan-1-ol (**2c**).* Following the general procedure 1, crude product was purified by silica gel column chromatography with hexane/EtOAc (9:1) to give the product **2c** (60.8 mg, 93% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.45 (d, J = 8.8 Hz, 4H), 6.85 (d, J = 8.8 Hz, 4H), 3.79 (s, 6H), 2.89 (s, 1H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −77.6 (s, 3F), −117.0 (s, 2F) ppm. MS (ESI, m/z) 361 [M − H]$^-$. Analytical data are consistent with reported values.[24]

*1-(2-Chlorophenyl)-2,2,3,3,3-pentafluoro-1-phenylpropan-1-ol (**2d**).* Following the general procedure 1, crude product was purified by silica gel column chromatography with hexane/CH_2Cl_2 (2:1) to give the product **2d** (51.7 mg, 85% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.99 (d, J = 7.1 Hz, 1H), 7.43−7.35 (m, 8H), 4.03 (s, 1H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −76.7 (s, 3F), −114.0 (d, $^2J_{F\text{-}F}$ = 275.9 Hz, 1F), −116.6 (d, $^2J_{F\text{-}F}$ = 275.9 Hz, 1F) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ: 138.1, 137.2, 133.3, 132.6, 130.1, 129.1 (t, $^3J_{C\text{-}F}$ = 5.9 Hz), 128.7, 128.0, 127.9, 126.6, 119.3 (qt, $^1JC\text{-}F$ = 288.4, 35.0 Hz), 117.7−112.6 (m), 80.6 (t, $^2J_{C\text{-}F}$ = 23.2 Hz). ATR-FTIR (neat): ν = 3555, 3067, 1452, 1336, 1223, 1134, 1050, 910, 863, 755 cm^{-1}. HRMS (ESI) m/z: [M − H]$^-$ calcd. for $C_{15}H_9ClF_5O$; 335.0262 Found: 335.0258.

*1-(3-Chlorophenyl)-2,2,3,3,3-pentafluoro-1-phenylpropan-1-ol (**2e**).* Following the general procedure 1, crude product was purified by silica gel column chromatography with hexane/CH_2Cl_2 (2:1) to give the product **2e** (52.7 mg, 87% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.63 (s, 1H), 7.59−7.56 (m, 2H), 7.46 (d, J = 7.1 Hz, 1H), 7.39−7.29 (m, 5H), 2.97 (s, 1H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −77.6 (s, 3F), −116.4 (d, $^2J_{F\text{-}F}$ = 279.3 Hz, 1F), −117.6 (d, $^2J_{F\text{-}F}$ = 279.3 Hz, 1F) ppm. MS (ESI, m/z) 335 [M − H]$^-$. Analytical data are consistent with reported values.[14]

*1-(4-Chlorophenyl)-2,2,3,3,3-pentafluoro-1-phenylpropan-1-ol (**2f**).* Following the general procedure 1, crude product was purified by

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silica gel column chromatography with hexane/CH_2Cl_2 (2:1) to give the product **2f** (56.3 mg, 93% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.56−7.52 (m, 4H), 7.38−7.32 (m, 5H), 2.92 (s, 1H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −77.6 (s, 3F), −116.5 (d, $^2J_{F\text{-}F}$ = 279.3 Hz, 1F), −117.7 (d, $^2J_{F\text{-}F}$ = 277.6 Hz, 1F) ppm. MS (ESI, m/z) 335 $[M - H]^-$. Analytical data are consistent with reported values.[14]

*1-(4-Bromophenyl)-2,2,3,3,3-pentafluoro-1-phenylpropan-1-ol (**2g**).* Following the general procedure 1, crude product was purified by silica gel column chromatography with hexane/CH_2Cl_2 (1:1) to give the product **2g** (62.4 mg, 91% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.53−7.35 (m, 9H), 2.90 (d-like, J = 6.5 Hz, 1H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −77.5 (s, 3F), −116.4 (d, $^2J_{F\text{-}F}$ = 277.6 Hz, 1F), −117.6 (d, $^2J_{F\text{-}F}$ = 277.6 Hz, 1F) ppm. MS (ESI, m/z) 404 $[M + Na]^+$. Analytical data are consistent with reported values.[14]

*2,2,3,3,3-Pentafluoro-1-(4-nitrophenyl)-1-phenylpropan-1-ol (**2h**).* Following the general procedure 1, crude product was purified by silica gel column chromatography with hexane/EtOAc (9:1) to give the product **2h** (47.6 mg, 76% yield) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.18 (d, J = 8.8 Hz, 2H), 7.76 (d, J = 8.2 Hz, 2H), 7.54−7.52 (m, 2H), 7.39−7.37 (m, 3H), 3.16 (s, 1H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −77.5 (s, 3F), −115.9 (d, $^2J_{F\text{-}F}$ = 279.3 Hz, 1F), −118.0 (d, $^2J_{F\text{-}F}$ = 279.3 Hz, 1F) ppm. MS (ESI, m/z) 346 $[M - H]^-$. Analytical data are consistent with reported values.[14]

*2,2,3,3,3-Pentafluoro-1-phenyl-1-(4-(trifluoromethyl)phenyl)-propan-1-ol (**2i**).* Following the general procedure 1, crude product was purified by silica gel column chromatography with hexane/EtOAc (9:1) to give the product **2i** (58.1 mg, 87% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.70 (d, J = 8.5 Hz, 2H), 7.61 (d, J = 8.2 Hz, 2H), 7.56−7.53 (m, 2H), 7.41−7.33 (m, 3H), 2.99 (s, 1H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −63.3 (s, 3F), −77.5 (s, 3F), −116.3 (d, $^2J_{F\text{-}F}$ = 279.3 Hz, 1F), −117.8 (d, $^2J_{F\text{-}F}$ = 277.6 Hz, 1F) ppm. MS (ESI, m/z) 369 $[M - H]^-$. Analytical data are consistent with reported values.[14]

*9-(Perfluoroethyl)-9H-fluoren-9-ol (**2j**).* Following the general procedure 1, crude product was purified by silica gel column chromatography with hexane/CH_2Cl_2 (1:1) to give the product **2j** (48.7 mg, 90% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.73−7.63 (m, 4H), 7.48 (t-like, J = 7.4 Hz, 2H), 7.35 (t-like, J = 7.5 Hz, 2H), 2.78 (s, 1H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −79.4 (s, 3F), −122.2 (s, 2F) ppm. MS (ESI, m/z) 299 $[M - H]^-$. Analytical data are consistent with reported values.[14]

*2,2,3,3,3-Pentafluoro-1,1-di(pyridin-2-yl)propan-1-ol (**2k**).* Following the general procedure 1, crude product was purified by silica gel column chromatography with hexane/CH_2Cl_2 (1:1) to give the product **2k** (46.4 mg, 85% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.60−8.58 (m, 2H), 8.24 (d-like, J = 7.9 Hz, 2H), 7.79−7.73 (m, 2H), 7.58 (s, 1H), 7.31−7.26 (m, 2H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −78.5 (s, 3F), −118.3 (s, 2F) ppm. MS (ESI, m/z) 305 $[M + Na]^+$. Analytical data are consistent with reported values.[14]

*2-(Pentafluoroethyl)-2-adamantanol (**2l**).* Following the general procedure 1, crude product was purified by silica gel column chromatography with hexane/Et_2O (4:1) to give the product **2l** (41.4 mg, 85% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.27−2.12 (m, 6H), 1.92−1.75 (m, 7H), 1.61 (d, J = 12.4 Hz, 2H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −78.6 (s, 3F), −117.4 (s, 2F) ppm. MS (ESI, m/z) 269 $[M - H]^-$. Analytical data are consistent with reported values.[24]

General Procedure 2: Flow Pentafluoroethylation of Aldehydes Using HFC-125. A solution of aldehyde **3** (1.2 mmol, 1.0 equiv) in dry DMF (2.0 mL) was fed into a three-inlet mixer (0.33 mL/min) using a syringe pump; simultaneously *t*-BuOK (1.8 mmol, 1.5 equiv) in dry DMF (3.0 mL) was fed into the mixer (0.50 mL/min) using another syringe pump. HFC-125 (3.10 equiv) was introduced into the mixer at 0.1 MPa and 15 mL/min controlled by a mass flow controller. The combined mixture was passed through residence tubing (residence volume V = 0.81 mL) at −10 °C. After the gas flow rate stabilized (about 2 min), we collected the product for 1 min. The product stream was quenched with sat. NH_4Cl aq. The aqueous layer was extracted with Et_2O, and the combined organic layers were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure, and purified by column chromatography on silica gel to give products **4**.

*2,2,3,3,3-Pentafluoro-1-phenylpropan-1-ol (**4a**).* Following the general procedure 2, crude product was purified by silica gel column chromatography with hexane/CH_2Cl_2 (1:1) to give the product **4a** (40.3 mg, 90% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.45 (br s, 5H), 5.18−5.09 (m, 1H), 2.44 (d, J = 4.4 Hz, 1H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −81.7 (s, 3F), −122.3 (dd, $^2J_{F\text{-}F}$, $^3J_{F\text{-}F}$ = 275.9, 6.9 Hz, 1F), −129.9 (dd, $^2J_{F\text{-}F}$, $^3J_{F\text{-}F}$ = 275.9, 17.2 Hz, 1F) ppm. MS (ESI, m/z) 227 $[M + H]^+$. Analytical data are consistent with reported values.[14]

*2,2,3,3,3-Pentafluoro-1-(4-methoxyphenyl)propan-1-ol (**4b**).* Following the general procedure 2, crude product was purified by silica gel column chromatography with hexane/Et_2O (1:1) to give the product **4b** (46.2 mg, 91% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.36 (d, J = 8.8 Hz, 2H), 6.92 (d-like, J = 8.8 Hz, 2H), 5.08−4.99 (m, 1H), 3.81 (s, 3H), 2.75 (s, 1H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −81.7 (s, 3F), −122.7 (dd, $^2J_{F\text{-}F}$, $^3J_{F\text{-}F}$ = 274.1, 8.6 Hz, 1F), −129.9 (dd, $^2J_{F\text{-}F}$, $^3J_{F\text{-}F}$ = 275.0, 16.4 Hz, 1F) ppm. MS (ESI, m/z) 257 $[M + H]^+$. Analytical data are consistent with reported values.[14]

*1-([1,1′-Biphenyl]-4-yl)-2,2,3,3,3-pentafluoropropan-1-ol (**4c**).* Following the general procedure 2, crude product was purified by silica gel column chromatography with hexane/Et_2O (4:1) to give the product **4c** (52.7 mg, 88% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.67−7.37 (m, 9H), 5.23−5.14 (m, 1H), 2.56 (d, J = 4.1 Hz, 1H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −81.7 (s, 3F), −122.2 (dd, $^2J_{F\text{-}F}$, $^3J_{F\text{-}F}$ = 275.9, 6.9 Hz, 1F), −130.0 (dd, $^2J_{F\text{-}F}$, $^3J_{F\text{-}F}$ = 275.9, 17.2 Hz, 1F) ppm. MS (ESI, m/z) 303 $[M + H]^+$. Analytical data are consistent with reported values.[14]

*1-(4-Chlorophenyl)-2,2,3,3,3-pentafluoropropan-1-ol (**4d**).* Following the general procedure 2, crude product was purified by silica gel column chromatography with hexane/CH_2Cl_2 (1:1) to give the product **4d** (46.5 mg, 90% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.41 (br s, 4H), 5.18−5.08 (m, 1H), 2.47 (d, J = 4.1 Hz, 1H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −81.7 (s, 3F), −122.3 (dd, $^2J_{F\text{-}F}$, $^3J_{F\text{-}F}$ = 275.9, 6.9 Hz, 1F), −129.8 (dd, $^2J_{F\text{-}F}$, $^3J_{F\text{-}F}$ = 275.9, 15.5 Hz, 1F) ppm. MS (ESI, m/z) 261 $[M + H]^+$. Analytical data are consistent with reported values.[14]

*1-(4-Bromophenyl)-2,2,3,3,3-pentafluoropropan-1-ol (**4e**).* Following the general procedure 2, crude product was purified by silica gel column chromatography with hexane/CH_2Cl_2 (1:1) to give the product **4e** (54.4 mg, 90% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.56 (d, J = 8.2 Hz, 2H), 7.34 (d, J = 8.2 Hz, 2H), 5.15−5.06 (m, 1H), 2.53−2.49 (m, 1H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −81.7 (s, 3F), −122.2 (dd, $^2J_{F\text{-}F}$, $^3J_{F\text{-}F}$ = 275.9, 6.9 Hz, 1F), −130.0 (dd, $^2J_{F\text{-}F}$, $^3J_{F\text{-}F}$ = 275.9, 17.2 Hz, 1F) ppm. MS (ESI, m/z) 306 $[M + H]^+$. Analytical data are consistent with reported values.[14]

*2,2,3,3,3-Pentafluoro-1-(4-iodophenyl)propan-1-ol (**4f**).* Following the general procedure 2, crude product was purified by silica gel column chromatography with hexane/CH_2Cl_2 (1:1) to give the product **4f** (64.0 mg, 92% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.76 (d, J = 8.2 Hz, 2H), 7.21 (d, J = 8.2 Hz, 2H), 5.14−5.05 (m, 1H), 2.52−2.49 (m, 1H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −81.7 (s, 3F), −122.2 (dd, $^2J_{F\text{-}F}$, $^3J_{F\text{-}F}$ = 275.9, 6.9 Hz, 1F), −129.9 (dd, $^2J_{F\text{-}F}$, $^3J_{F\text{-}F}$ = 275.9, 15.5 Hz, 1F) ppm. MS (ESI, m/z) 352 $[M + H]^+$. Analytical data are consistent with reported values.[14]

*2,2,3,3,3-Pentafluoro-1-(4-fluorophenyl)propan-1-ol (**4g**).* Following the general procedure 2, crude product was purified by silica gel column chromatography with hexane/CH_2Cl_2 (1:1) to give the product **4g** (42.1 mg, 87% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.46 (t-like, J = 6.5 Hz, 2H), 7.12 (t-like, J = 8.5 Hz, 2H), 5.18−5.09 (m, 1H), 2.45 (d, J = 4.4 Hz, 1H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −81.6 (s, 3F), −111.9 (s, 1F), −122.5 (dd, $^2J_{F\text{-}F}$, $^3J_{F\text{-}F}$ = 275.9, 6.9 Hz, 1F), −129.7 (dd, $^2J_{F\text{-}F}$, $^3J_{F\text{-}F}$ = 275.9, 15.5 Hz, 1F) ppm. MS (ESI, m/z) 245 $[M + H]^+$. Analytical data are consistent with reported values.[14]

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*2,2,3,3,3-Pentafluoro-1-(4-(trifluoromethoxy)phenyl)propan-1-ol (**4h**).* Following the general procedure 2, crude product was purified by silica gel column chromatography with hexane/CH_2Cl_2 (1:1) to give the product **4h** (52.8 mg, 86% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.52 (d, J = 8.5 Hz, 2H), 7.27 (d, J = 7.9 Hz, 2H), 5.21−5.12 (m, 1H), 2.60 (d, J = 4.4 Hz, 1H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −58.3 (s, 3F), −81.6 (s, 3F), −122.2 (dd, $^2J_{F\text{-}F}$, $^3J_{F\text{-}F}$ = 275.9, 6.9 Hz, 1F), −129.9 (dd, $^2J_{F\text{-}F}$, $^3J_{F\text{-}F}$ = 276.7, 16.4 Hz, 1F) ppm. MS (ESI, m/z) 311 $[M + H]^+$. Analytical data are consistent with reported values.[14]

*2,2,3,3,3-Pentafluoro-1-(naphthalen-2-yl)propan-1-ol (**4i**).* Following the general procedure 2, crude product was purified by silica gel column chromatography with hexane/CH_2Cl_2 (1:1) to give the product **4i** (49.8 mg, 91% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.95−7.87 (m, 4H), 7.59−7.53 (m, 3H), 5.36−5.26 (m, 1H), 2.58 (d, J = 4.7 Hz, 1H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −81.7 (s, 3F), −122.1 (dd, $^2J_{F\text{-}F}$, $^3J_{F\text{-}F}$ = 275.9, 6.9 Hz, 1F), −129.6 (dd, $^2J_{F\text{-}F}$, $^3J_{F\text{-}F}$ = 275.9, 15.5 Hz, 1F) ppm. MS (ESI, m/z) 277 $[M + H]^+$. Analytical data are consistent with reported values.[14]

*2,2,3,3,3-Pentafluoro-1-(naphthalen-1-yl)propan-1-ol (**4j**).* Following the general procedure 2, crude product was purified by silica gel column chromatography with hexane/acetone (7:1) to give the product **4j** (44.8 mg, 82% yield) as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.02 (d, J = 7.6 Hz, 1H), 7.94−7.91 (m, 2H), 7.82 (d, J = 7.4 Hz, 1H), 7.61−7.51 (m, 3H), 6.06−5.97 (m, 1H), 2.74 (br s, 1H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −81.8 (s, 3F), −122.1 (dd, $^2J_{F\text{-}F}$, $^3J_{F\text{-}F}$ = 274.1, 6.9 Hz, 1F), −130.5 (dd, $^2J_{F\text{-}F}$, $^3J_{F\text{-}F}$ = 274.1, 17.2 Hz, 1F) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ: 133.8, 131.4, 130.4, 130.2, 129.1, 127.0, 126.5, 126.1, 125.3, 122.8, 119.4 (qt, $^1J_{C\text{-}F}$, $^2J_{C\text{-}F}$ = 285.5, 34.4 Hz), 116.0−111.0 (m) 67.7 (dd, $^2J_{C\text{-}FA}$, $^2J_{C\text{-}FB}$ = 29.1, 21.8 Hz) ppm. ATR-FTIR (KBr): ν = 3465, 3059, 1514, 1351, 1185, 1134, 1080, 1026, 790, 720 cm^{-1}. HRMS (ESI) m/z: $[M - H]^-$ calcd. for $C_{13}H_8F_5O$; 275.0495 Found: 275.0497. Mp: 45.5−46.3 °C.

*2,2,3,3,3-Pentafluoro-1-(furan-2-yl)ethan-1-ol (**4k**).* Following the general procedure 2, crude product was purified by silica gel column chromatography with hexane/Et_2O (4:1) to give the product **4k** (27.8 mg, 65% yield) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.49 (s, 1H), 6.54 (s, 1H), 6.44 (s, 1H), 5.20−5.10 (m, 1H), 2.59 (d, J = 7.9 Hz, 1H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −82.4 (s, 3F), −123.2 (dd, $^2J_{F\text{-}F}$, $^3J_{F\text{-}F}$ = 274.1, 6.9 Hz, 1F), −129.3 (dd, $^2J_{F\text{-}F}$, $^3J_{F\text{-}F}$ = 275.0, 16.4 Hz, 1F) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ: 146.8, 144.0, 118.94 (qt, $^1J_{C\text{-}F}$, $^2J_{C\text{-}F}$ = 286.6, 35.2 Hz), 115.1−110.1 (m), 111.0, 110.8, 66.5 (q, $^2J_{C\text{-}F}$ = 17.3 Hz,) ppm. ATR-FTIR (KBr): ν = 3407, 2927, 1507, 1363, 1192, 1138, 1015, 929, 809, 744 cm^{-1}. HRMS (ESI) m/z: $[M + H]^+$ calcd. for $C_7H_6F_5O_2$; 217.0288 Found: 217.0278.

*2,2,3,3,3-Pentafluoro-1-(thiophene-2-yl)ethan-1-ol (**4l**).* Following the general procedure 2, crude product was purified by silica gel column chromatography with hexane/Et_2O (4:1) to give the product **4l** (31.7 mg, 69% yield) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.43 (d, J = 4.4 Hz, 1H), 7.21 (br s, 1H), 7.08−7.05 (m, 1H), 5.39 (dd, J = 16.5, 5.9 Hz, 1H), 2.69 (s, 1H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −81.8 (s, 3F), −122.1 (dd, $^2J_{F\text{-}F}$, $^3J_{F\text{-}F}$ = 274.1, 6.9 Hz, 1F), −130.5 (dd, $^2J_{F\text{-}F}$, $^3J_{F\text{-}F}$ = 274.1, 17.2 Hz, 1F) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ: 136.0, 128.2, 127.7, 127.1, 119.1 (qt, $^1J_{C\text{-}F}$, $^2J_{C\text{-}F}$ = 287.0, 35.4 Hz), 115.1−110.1 (m), 68.5 (q, $^2J_{C\text{-}F}$ = 17.6 Hz) ppm; ATR-FTIR (neat): ν = 3426, 2923, 1432, 1355, 1208, 1131, 1023, 809, 708 cm^{-1}. HRMS (ESI) m/z: $[M - H]^-$ calcd. for $C_7H_4F_5OS$; 230.9903 Found: 230.9911.

General Procedure 3: Flow Pentafluoroethylation of Chalcones Using HFC-125. A solution of chalcone **5** (0.6 mmol, 1.0 equiv) in dry toluene (2.0 mL) or dry THF (2.0 mL) was fed into a three-inlet mixer (0.33 mL/min) using a syringe pump; simultaneously KHMDS (1.2 mmol, 1.5 equiv) in dry toluene (4.0 mL) or dry THF (4.0 mL) was fed into the mixer (0.50 mL/min) using another syringe pump. HFC-125 (3.10 equiv) was introduced into the mixer with 0.1 MPa, 7.5 mL/min controlled by a mass flow controller. The combined mixture was passed through residence tubing (residence volume V = 0.32 mL) at rt. After the gas flow rate stabilized (about 2 min), we collected the product for 1 min. The product stream was quenched with sat. NH_4Cl aq. The aqueous layer was extracted with Et_2O, and the combined organic layers were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure, and purified by column chromatography on silica gel to give products **6**.

*(E)-4,4,5,5,5-Pentafluoro-1,3-diphenylpent-1-en-3-ol (**6a**).* Following the general procedure 3, crude product was purified by silica gel column chromatography with hexane/CH_2Cl_2 (1:2) to give the product **6a** (29.0 mg, 89% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.65 (d, J = 7.1 Hz, 2H), 7.44−7.29 (m, 8H), 6.86 (br s, 2H), 2.74 (s, 1H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −78.2 (s, 3F), −121.0 (d, $^2J_{F\text{-}F}$ = 279.3 Hz, 1F), −122.0 (d, $^2J_{F\text{-}F}$ = 277.6 Hz, 1F) ppm. MS (ESI, m/z) 327 $[M - H]^-$. Analytical data are consistent with reported values.[14]

*(E)-4,4,5,5,5-Pentafluoro-3-(4-methoxyphenyl)-1-phenylpent-1-en-3-ol (**6b**).* Following the general procedure 3, crude product was purified by silica gel column chromatography with hexane/EtOAc (9:1) to give the product **6b** (31.1 mg, 88% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.55 (d, J = 9.1 Hz, 2H), 7.44−7.29 (m, 5H), 6.93 (d, J = 9.1 Hz, 2H), 6.84 (br s, 2H), 3.82 (s, 3H), 2.69 (s, 1H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −78.2 (s, 3F), −121.1 (d, $^2J_{F\text{-}F}$ = 277.6 Hz, 1F), −122.1 (d, $^2J_{F\text{-}F}$ = 277.6 Hz, 1F) ppm. MS (ESI, m/z) 357 $[M - H]^-$. Analytical data are consistent with reported values.[14]

*(E)-3-(4-Chlorophenyl)-4,4,5,5,5-pentafluoro-1-phenylpent-1-en-3-ol (**6c**).* Following the general procedure 3, crude product was purified by silica gel column chromatography with hexane/EtOAc (9:1) to give the product **6c** (31.3 mg, 87% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.58 (d, J = 8.5 Hz, 2H), 7.43−7.28 (m, 7H), 6.82 (br s, 2H), 2.84−2.81 (m, 1H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −78.1 (s, 3F), −121.6 (s, 2F) ppm. MS (ESI, m/z) 361 $[M - H]^-$. Analytical data are consistent with reported values.[14]

*(E)-3-(4-Bromophenyl)-4,4,5,5,5-pentafluoro-1-phenylpent-1-en-3-ol (**6d**).* Following the general procedure 3, crude product was purified by silica gel column chromatography with hexane/EtOAc (9:1) to give the product **6d** (35.1 mg, 87% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.56−7.49 (m, 4H), 7.44−7.29 (m, 5H), 6.81 (br s, 2H), 2.66 (s, 1H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −78.1 (s, 3F), −121.6 (s, 2F) ppm. MS (ESI, m/z) 406 $[M - H]^-$. Analytical data are consistent with reported values.[14]

*(E)-4,4,5,5,5-Pentafluoro-1,3-bis(4-fluorophenyl)pent-1-en-3-ol (**6e**).* Following the general procedure 3, crude product was purified by silica gel column chromatography with hexane/EtOAc (9:1) to give the product **6e** (25.2 mg, 70% yield) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.61 (dd, J = 8.8, 5.3 Hz, 2H), 7.41−7.36 (m, 2H), 7.12−7.01 (m, 4H), 6.80 (d, J = 15.9 Hz, 1H), 6.73 (d, J = 16.2 Hz, 1H), 2.71 (s, 1H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −78.2 (s, 3F), −113.1 to −113.0 (m, 1F), −113.6 to −113.5 (m, 1F), −121.7 (s, 2F) ppm. MS (ESI, m/z) 363 $[M - H]^-$. Analytical data are consistent with reported values.[14]

*(E)-4,4,5,5,5-Pentafluoro-3-(4-nitrophenyl)-1-phenylpent-1-en-3-ol (**6f**).* Following the general procedure 3, crude product was purified by silica gel column chromatography with hexane/EtOAc (9:1) to give the product **6f** (26.6 mg, 72% yield) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.26 (d, J = 9.1 Hz, 2H), 7.84 (d, J = 8.8 Hz, 2H), 7.43−7.30 (m, 5H), 6.89−6.78 (m, 2H), 2.89 (s, 1H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −78.1 (s, 3F), −120.9 (d, $^2J_{F\text{-}F}$ = 279.3 Hz, 1F), −122.1 (d, $^2J_{F\text{-}F}$ = 279.3 Hz, 1F) ppm. MS (ESI, m/z) 372 $[M - H]^-$. Analytical data are consistent with reported values.[14]

Flow Pentafluoroethylation of Bioactive Substrates. *iso-Propyl 2-(4-(1-(4-Chlorophenyl)-2,2,3,3,3-pentafluoro-1-hydroxypropyl)phenoxy)-2-methylpropanoate (**8a**).* Following the general procedure 1, crude product was purified by silica gel column chromatography with hexane/EtOAc (4:1) to give the product **8a** (55.4 mg, 69% yield) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.45 (d, J = 8.5 Hz, 2H), 7.36 (d, J = 8.8 Hz, 2H), 7.30−7.27 (m, 2H), 6.78−6.75 (m, 2H), 5.06−4.98 (m, 1H), 3.17 (s, 1H), 1.57 (s, 6H), 1.17 (d, J = 2.1 Hz, 3H), 1.16 (d, J = 1.8 Hz, 3H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ: 173.6, 155.9, 138.4, 134.5, 132.8, 128.8, 128.4, 128.2, 122.9−117.6 (m), 118.3, 117.8−112.8 (m), 79.3, 78.4

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(t, J = 23.6 Hz), 69.3, 25.5, 25.4, 21.6. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −77.6 (s, 3F), −116.62 (d, $^2J_{F\text{-}F}$, $^3J_{H\text{-}F}$ = 277.6 Hz, 1F), −117.8 (d, $^2J_{F\text{-}F}$, $^3J_{H\text{-}F}$ = 277.6 Hz, 1F) ppm. ATR-FTIR (neat): ν = 3429, 2992, 1731, 1605, 1509, 1386, 1294, 1166, 1102, 1061, 1015, 909, 874, 828 cm^{-1}. HRMS (ESI) m/z: $[M + Na]^+$ calcd. for $C_{22}H_{22}O_4F_5Na$; 503.1024 Found: 503.1030. Mp: 94.5−94.7 °C.

*1-(4-(Benzyloxy)-3-methoxyphenyl)-2,2,3,3,3-pentafluoropropan-1-ol (**8b**).* Following the general procedure 2, crude product was purified by silica gel column chromatography with hexane/EtOAc (4:1) to give the product **8b** (46.6 mg, 65% yield) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.43 (d, J = 7.3 Hz, 2H), 7.39−7.36 (m, 2H), 7.34−7.30 (m, 1H), 6.97 (s, 1H), 6.85−6.60 (m, 2H), 5.13 (s, 2H), 5.01−4.96 (m, 1H), 3.84 (s, 3H), 2.87 (d, J = 4.6 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ: 149.6, 149.2, 136.8, 128.7, 128.1, 127.4, 127.1, 120.8, 119.2 (qt, $^1J_{C\text{-}F}$, $^2J_{C\text{-}F}$ = 286.9, 35.8 Hz), 115.5−110.7 (m), 113.5, 111.3, 71.8 (q, $^2J_{C\text{-}F}$ = 17.0 Hz), 71.0, 56.1. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −81.9 (s, 3F), −122.5 (d, $^2J_{F\text{-}F}$ = 267.2 Hz, 1F), −130.1 (dd, $^2J_{F\text{-}F}$, $^3J_{H\text{-}F}$ = 275.0, 16.4 Hz, 1F) ppm. ATR-FTIR (neat): ν = 3673, 3425, 2967, 1721, 1466, 1387, 1235, 1130, 1040, 923, 860, 717, 650 cm^{-1}. HRMS (ESI) m/z: $[M + Na]^+$ calcd. for $C_{17}H_{15}O_3F_5Na$; 385.0839 Found: 385.0835. Mp: 85.3−85.9 °C.

*1-(Benzo[d][1,3]dioxol-5-yl)-2,2,3,3,3-pentafluoropropan-1-ol (**8c**).* Following the general procedure 2, crude product was purified by silica gel column chromatography with hexane/EtOAc (4:1) to give the product **8c** (50.3 mg, 94% yield) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.95 (s, 1H), 6.89 (dd, J = 7.9, 1.2 Hz, 1H), 6.82 (d, J = 7.9 Hz, 1H), 5.99 (s, 2H), 5.01 (dd, J = 16.2, 7.3 Hz, 1H), 2.67 (s, 1H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ: 148.8, 148.1, 127.7, 122.1, 119.2 (qt, $^1J_{C\text{-}F}$, $^2J_{C\text{-}F}$ = 285.8, 36.8 Hz), 115.6−110.6 (m), 108.4, 108.2, 101.6, 71.9 (q, $^2J_{C\text{-}F}$ = 16.7 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ: −81.8 (s, 3F), −122.7 (dd, $^2J_{F\text{-}F}$, $^3J_{H\text{-}F}$ = 275.0, 7.8 Hz, 1F), −130.0 (dd, $^2J_{F\text{-}F}$, $^3J_{H\text{-}F}$ = 275.0, 16.4 Hz, 1F) ppm. ATR-FTIR (neat): ν = 3372, 2911, 1855, 1507, 1450, 1308, 1258, 1105, 927, 867, 736, 683, 525 cm^{-1}. HRMS (ESI) m/z: $[M - H]^-$ calcd. for $C_{10}H_6O_3F_5Na$; 269.0237 Found: 269.0238. Mp: 46.7−47.0 °C.

*(E)-1-(4-(Benzyloxy)-3-methoxyphenyl)-4,4,5,5,5-pentafluoro-3-phenylpent-1-en-3-ol (**8d**).* Following the general procedure 3, crude product was purified by silica gel column chromatography with toluene to give the product **8d** (21.2 mg, 46% yield) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.63 (d, J = 7.0 Hz, 2H), 7.43−7.35 (m, 8H), 7.31−7.29 (m, 1H), 6.94 (d, J = 2.1 Hz, 1H), 6.90 (dd, J = 8.2, 1.8 Hz, 1H), 6.83 (d, J = 8.2 Hz, 1H), 6.74 (d, J = 15.9 Hz, 1H), 6.68 (d, J = 16.2 Hz, 1H), 5.16 (s, 2H), 3.91 (s, 3H), 2.67 (s, 1H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ: 149.9, 148.8, 137.7, 137.0 132.9, 129.2, 128.8, 128.7, 128.4, 128.1, 127.3, 126.8, 125.0, 120.2, 120.8−116.2 (m), 116.2−111.8 (m), 114.0, 110.1, 71.1, 56.2 (one carbon (-C(OH)-CF_2CF_3) was not observed). ^{19}F NMR (282 MHz, $CDCl_3$) δ: −78.2 (s, 3F), −121.4 (s, 2F) ppm. ATR-FTIR (neat): ν = 3860, 3730, 3707, 3666, 3644, 3396, 1601, 1514, 1452, 1134, 701, 516 cm^{-1}. HRMS (ESI) m/z: $[M - H]^-$ calcd. for $C_{25}H_{20}O_3F_5$; 463.1333 Found: 463.1340. Mp: 69.0−69.6 °C.

*(E)-1-(Benzo[d][1,3]dioxol-5-yl)-4,4,5,5,5-pentafluoro-3-phenylpent-1-en-3-ol (**8e**).* Following the general procedure 3, crude product was purified by silica gel column chromatography with toluene to give the product **8e** (50.0 mg, 68% yield) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.63 (d, J = 7.0 Hz, 2H), 7.43−7.36 (m, 3H), 6.96 (d, J = 1.5 Hz, 1H), 6.84 (dd, J = 7.9, 1.5 Hz, 1H), 6.77−6.66 (m, 3H), 5.96 (s, 2H), 2.72 (s, 1H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ: 148.3, 148.2, 137.7, 132.6, 130.1, 128.8, 128.4, 126.8, 125.0, 122.2, 119.3 (qt, $^1J_{C\text{-}F}$, $^2J_{C\text{-}F}$ = 239.6, 36.0 Hz), 114.1 (tq, $^1J_{C\text{-}F}$, $^2J_{C\text{-}F}$ = 244.4, 34.9 Hz), 108.5, 106.1, 101.4 (one carbon (−C(OH)-CF_2CF_3) was not observed). ^{19}F NMR (282 MHz, $CDCl_3$) δ: −78.2 (s, 3F), −121.5 (s, 2F) ppm. ATR-FTIR (neat): ν = 3459, 3072, 2915, 1604, 1451, 1220, 1072, 980, 859, 766, 703, 632, 540 cm^{-1}. HRMS (ESI) m/z: $[M - H]^-$ calcd. for $C_{18}H_{12}O_3F_5$; 371.0707 Found: 371.0713.

*1-Cyclopropyl-3-(2,5-dichlorophenyl)-4,4,5,5,5-pentafluoropent-1-yn-3-ol (**8f**).* A solution of **7f** (0.66 mmol, 1.0 equiv) in dry toluene (2.0 mL) was fed into a three-inlet mixer (0.33 mL/min) using a syringe pump; simultaneously KHMDS (1.8 mmol, 1.7 equiv) in dry toluene (6.0 mL) was fed into the mixer (1.1 mL/min) using another syringe pump. HFC-125 (22.5 equiv) was introduced into the mixer at 0.1 MPa and 50 mL/min, controlled by a mass flow controller. The combined mixture was passed through residence tubing (residence volume V = 0.81 mL) at −30 °C. After the gas flow rate stabilized (about 2 min), we collected the product for 1 min. The product stream was quenched with sat. NH_4Cl aq. The aqueous layer was extracted with Et_2O, and the combined organic layers were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure, and purified by column chromatography on silica gel with hexane/EtOAc (9:1) to give products **8f** (19.9 mg, 51% yield) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.90 (d, J = 2.4 Hz, 1H), 7.34 (d, J = 8.5 Hz, 1H), 7.29 (dd, J = 8.5, 2.4 Hz, 1H), 3.49 (s, 1H), 1.38−1.33 (m, 1H), 0.90−0.76 (m, 4H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ: 134.3, 133.0, 132.9, 131.6, 130.9, 130.6, 119.1 (qt, $^1J_{C\text{-}F}$, $^2J_{C\text{-}F}$ = 286.4, 35.5 Hz), 112.9 (tq, $^1J_{C\text{-}F}$, $^2J_{C\text{-}F}$ = 264.8, 33.3 Hz), 95.3, 72.3 (t, $^2J_{C\text{-}F}$ = 27.2 Hz), 69.3 (d, $^3J_{C\text{-}F}$ = 5.4 Hz), 8.4, 8.3, −0.4. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −78.3 (s, 3F), −116.9 (d, $^2J_{F\text{-}F}$ = 270.7 Hz, 1F), −120.9 (d, $^2J_{F\text{-}F}$ = 270.7 Hz, 1F) ppm. ATR-FTIR (neat): ν = 3738, 3651, 3453, 3109, 3016, 2246, 1457, 1390, 1336, 1221, 1109, 1049, 873, 818, 630, 514 cm^{-1}. HRMS (ESI) m/z: $[M - H]^-$ calcd. for $C_{14}H_8OF_5Cl_2$; 356.9872 Found: 356.9873.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00728.

Detailed optimization of reaction conditions, photos of flow reaction tubes, general procedures, and copies of ^{1}H, ^{19}F, and ^{13}C{^{1}H} NMR spectra of compounds **2**, **4**, **6**, and **8** (PDF)

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Notes

The authors declare no competing financial interest.

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