# A Library of Fluorinated Electrophiles for Chemical Tagging and Materials Synthesis

Jonathan J. Kasper, Jamie E. Hitro, Sabrina R. Fitzgerald, Joseph M. Schnitter, James J. Rutowski, John A. Heck, and Jeremy L. Steinbacher*

Department of Chemistry and Biochemistry, Canisius College, 2001 Main Street, Buffalo, New York 14208-1098, United States

S *Supporting Information*

ABSTRACT: Various applications could benefit from new fluorinated molecules that offer chemical handles for quickly functionalizing reactive surfaces and molecules. Herein, we report the synthesis of a library of fluorinated molecules that contain nonafluoro-*tert*-butyl groups and electrophilic handles, mostly acrylates and acrylamides. Featuring a variety of hydrophobic and hydrophilic linkers, these molecules could find use in polymer chemistry, biomaterials, biomedical imaging, and protein tagging.
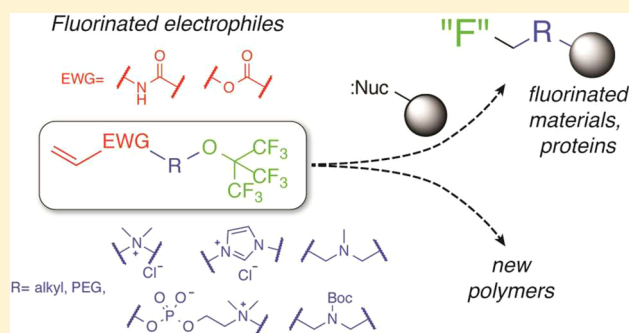
Fluorinated molecules and materials offer many unique properties in a wide-range of applications. The strong, nonpolarizable C−F bond leads to very low reactivity and weak van der Waals forces, and thus, highly fluorinated "fluorous" molecules have low solubility in both aqueous and organic solvents.[1,2] These useful properties have led to an entire segment of green chemistry that uses fluorous molecules in catalysis, reaction separations, and chemical synthesis.[3,4] Briefly, the phase separation of fluorinated solvents[1] and reagents[5−8] is used to greatly simplify purification of reaction mixtures. In related applications, fluorinated porous materials have been used to effect separations in the liquid and gas phases.[9−12] Also, the low reactivity of C−F bonds lends fluorinated materials an important place in materials chemistry, especially in high-performance engineering polymers like poly(tetrafluoroethylene) and perfluoroalkoxy alkanes, with remarkable chemical resistance, high thermal stability, and good mechanical properties.

Besides the interesting physical and chemical properties of fluorinated molecules, the ^{19}F nucleus possesses a large gyromagnetic ratio, making it nearly as sensitive as the ^{1}H nucleus in NMR spectroscopy. A large chemical shift dispersion and large paramagnetic term results in a great sensitivity to the chemical and solvation environment.[13,14] These characteristics make fluorine nuclei useful NMR probes for solvation, conformation, and dynamics[15] in biological macromolecules like proteins and peptides[16,17] and cellular structures like lipids.[18,19] These NMR characteristics also allow fluorine-containing molecules to be used as magnetic resonance imaging (MRI) contrast agents to complement the usual agents that enhance proton-based MRI.[20−22]

From the heavily fluorous "tags" of organic substrates envisioned by Horváth and Rábai[3] to more lightly fluorinated molecules needed for labeling biomolecules[16] many of these varied applications could benefit from new fluorinated molecules that offer chemical handles for quickly functionalizing reactive surfaces and molecules. Acrylates and acrylamides exhibit good reactivity with a variety of nucleophiles in Michael-type conjugate additions, making them attractive functional groups for such applications. Moreover, these electrophiles are also advantageous due to their myriad potential uses in polymer chemistry. Unfortunately, few highly fluorinated acrylates are currently commercially available, and many of those that are available contain long (>6 carbon) perfluoroalkyl chains that have known issues with biopersistence in the environment.[23] Those with smaller, compact perfluorinated groups, which are expected to be less persistent,[24] are rare. Herein, we report the synthesis of a small library of new fluorinated electrophiles (F-electrophiles) that all contain the compact nonafluoro-*tert*-butyl group with potential uses in diverse applications like protein tagging, ^{19}F NMR contrast agents, modification of materials, and polymer synthesis. We have avoided "heavy fluorous" molecules to permit their use in applications where separate fluorous phases are not needed, such as polymer science and biomedical materials.

For the reasons listed above, acrylate and acrylamide functional groups are the electrophilic chemical handles for most of the members of this library. F-electrophiles **3**, **7**, and **10** are relatively hydrophobic and could find use as monomers in acrylate polymerizations. F-electrophiles **4**, **12**, **13**, and **14** contain hydrophilic linkers (tetraethylene glycol, quaternary aminium, imidazolium, and phosphorylcholine, respectively) for applications that require hydrophilicity. F-electrophiles **17** and **20** contain 3° and 2° amines, respectively, that could

Scheme 1. Synthesis of 3 and 4
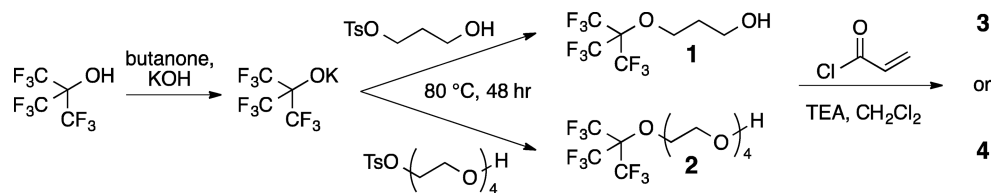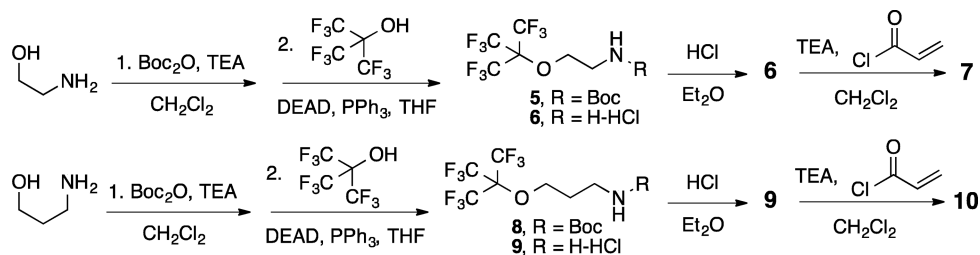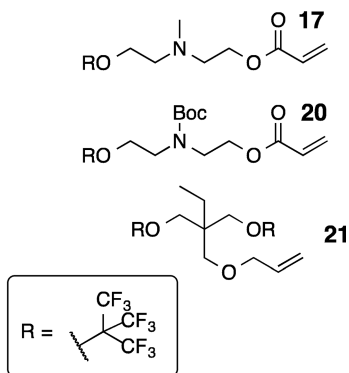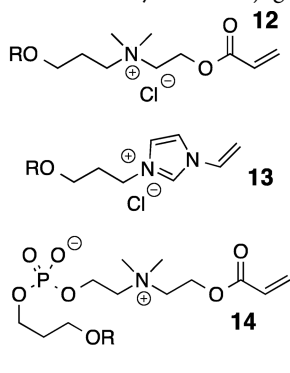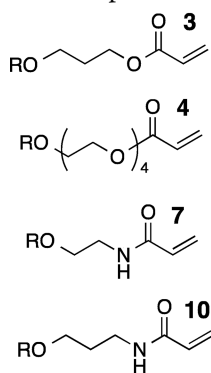

Scheme 2. Syntheses of 7 and 10

exhibit sensitivity to pH changes in biological applications. Lastly, allyl ether F-electrophile **21** contains 18 chemically

equivalent fluorine atoms and is reactive in the radical thiol−ene conjugation.

The syntheses of these compounds generally followed known synthetic organic transformations. The preparation of acrylates **3** and **4** (Scheme 1) began with the alkylation of nonafluoro-*tert*-butoxide generated *in situ* from the corresponding alcohol with KOH by reaction with monotosylated 1,3-propanediol and tetraethylene glycol, respectively. Despite the steric bulk of this alkoxide, it is a reasonably good nucleophile under these conditions,[25,26] yielding the fluorinated alcohols **1** and **2**, of which the former is a known fluorinated compound.[5] Esterification with acryloyl chloride then gave **3** and **4** in 24 and 18% overall yields, respectively.

The preparation of acrylamides **7** and **10** followed the same synthetic procedures except for the choice of amino alcohol starting materials (Scheme 2). Boc protection of the amines allowed the subsequent use of the Mitsunobu reaction to install the nonafluoro-*tert*-butyl ether groups in **5** and **8**. Unlike most alcohols, nonafluoro-*tert*-butanol is sufficiently acidic to use as a nucleophile in the Mitsunobu (pK_a ∼5),[26] as demonstrated previously by others.[27,26] Deprotection of the Boc groups with HCl in diethyl ether leads to fluorinated amines **6** and **9** as their hydrochloride salts, both crystalline solids. Conveniently, the isolation of both salts was facilitated by fluorous-promoted phase separations when diethyl ether was added to concentrated methanolic solutions of both. Ethylene derivative **6** was previously reported as its free base.[28] Lastly, **6** and **9** were acylated using acryloyl chloride to give F-electrophiles **7** and **10** in 13 and 16% overall yields from the initial aminoalcohols, respectively.

The aminium, imidazolium, and phosphorylcholine F-electrophiles **12**, **13**, and **14** were prepared in only a handful of steps from fluorinated alcohol **1** (Scheme 3). For **12** and **13**,

Scheme 3. Synthesis of 12−14
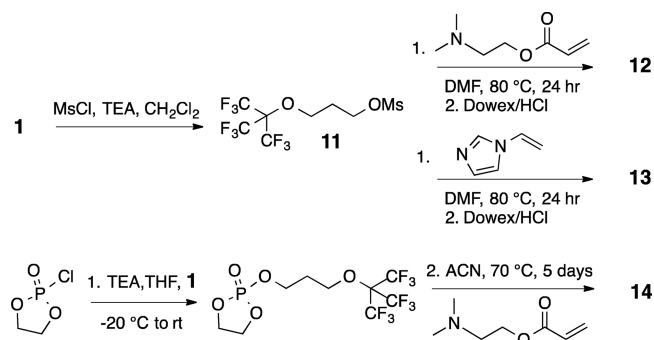
conversion to the mesylate proceeded quantitatively and in high yield with only a trace of unreacted mesyl chloride, which was not purified further. Mesylate **11** was then used to alkylate *N,N*-dimethylaminoethyl acrylate or 1-vinylimidazole in DMF at 80 °C. Both nucleophiles managed conversions of 50% or less when reacted with only the mesylate, as determined by NMR analysis of reaction crudes after evaporation of the DMF by short-path distillation. Thankfully, we found that catalytic

Scheme 4. Synthesis of 17 and 20
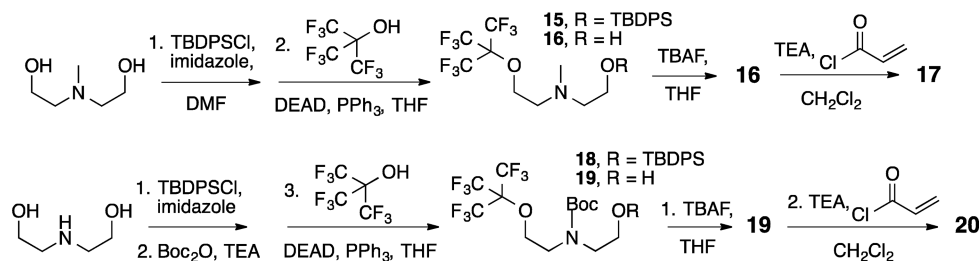
sodium iodide (5 mol %) increased conversion by generating the iodide in situ. After removal of DMF, F-electrophiles **12** and **13** were isolated as their chloride salts through anion exchange on sulfonic acid Dowex resin in 82 and 75% yields, respectively, from fluorinated alcohol **1**. For aminium **12**, there was an intense interference on one of the methylene groups by H_2O in the ^1H NMR spectrum (DMSO-$_6$). ^1H–^1H TOCSY NMR spectroscopy alleviated the interference by H_2O and clarified the methylene assignments (see the Supporting Information). Phosphorylcholine F-electrophile **14** was synthesized following the recent protocol reported by Hu and Emrick.[29] Fluorinated alcohol **1** was phosphorylated with 2-chloro-2-oxo-1,3,2-dioxaphospholane to give the phospholane intermediate shown in Scheme 3. This phospholane was prone to hydrolysis over the span of a few days, so we found it best to immediately subject it to nucleophilic ring-opening by *N,N*-dimethylaminoethyl acrylate to give zwitterionic F-electrophile **14** in 34% yield from **1**.

Amine-containing F-electrophiles **17** and **20** followed a synthetic pathway similar to those of acrylamides **7** and **10** (Scheme 4). Protection of *N*-methyldiethanolamine with *tert*-butyldiphenylsilyl chloride using an excess of the diol cleanly afforded the monoprotected species, which was subsequently submitted to Mitsunobu conditions using nonafluoro-*tert*-butanol as the nucleophile to give **15**. A similar sequence, including a Boc-protection of the secondary amine, resulted in **18**. Deprotection with TBAF afforded the fluorinated alcohols **16** and **19**, and subsequent esterification with acryloyl chloride gave acrylates **17** and **20** in 25 and 17% yields overall from the diol starting materials. Perhaps unsurprisingly, attempts to deprotect the Boc group from **20** resulted in the formation of inter- and intramolecular conjugate addition products. In practice, the secondary amine could be deprotected after polymerization or reaction onto a substrate.

Highly fluorinated allylic ether **21** was readily synthesized in one step from the commercially available diol derived from pentaerythritol shown in Scheme 5. Once again, the Mitsunobu

Scheme 5. Synthesis of 21
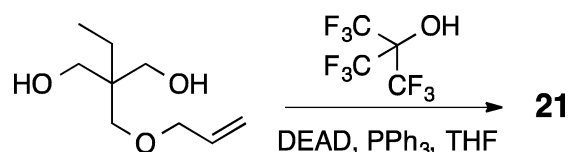
reaction proved quite capable of installing the nonafluoro-*tert*-butyl ethers, even in sterically congested **21**. On standard silica gel, highly fluorinated **21** exhibited a very large R_f even in a nonpolar eluent (0.82 in 90:10 petroleum ether/ethyl acetate), eluting even before unreacted triphenylphosphine from the Mitsunobu coupling. We isolated **21** in 49% yield. Spectroscopic characterization of **21** was interesting in that the methylenes

adjacent to the nonafluoro-*tert*-butyl ether groups appeared as a heavily skewed doublet of doublets, owing to the diastereotopic nature of the methylene protons. However, ^{13}C–^1H HMBC NMR spectroscopy proved particularly useful at confirming the connectivity, as the methylene protons (the doublet of doublets) displayed weak coupling to the quaternary carbons of the nonafluoro-*tert*-butyl groups across the ether bonds (see the Supporting Information). The pentaerythritol methylene adjacent to the allyloxy group appeared as a singlet, as expected.

In conclusion, we have synthesized a library of fluorinated electrophiles that could find use in biomaterials, omniphobic materials, polymer chemistry, and fluorous tagging of biological molecules. The fluorous group in each is a nonafluoro-*tert*-butyl ether, which is distinct from the few highly fluorinated acrylates and methacrylates now commercially available. Our current priority is to use some of these molecules to synthesize new fluorous/hydrophilic diblock copolymers and to rapidly and selectively modify nucleophiles (amines and thiols) immobilized to inorganic nanoparticles. To demonstrate feasibility, we performed preliminary kinetic experiments on an NMR scale, confirming that F-electrophiles **4**, **12**, and **17** reacted quickly and quantitatively with thiol and amine nucleophiles using DBU as a basic catalyst (see reactions and spectra in the Supporting Information). Also, toward preparing superhydrophobic materials,[30] we have synthesized thiol-modified silica nanoparticles via the well-known Stöber[31] method. Conjugation of F-electrophiles **3** and **21** to the nanoparticles using DBU as a catalyst or a photoinitiator and UV$_{254}$, respectively, resulted in useful degrees of functionalization for silica materials (~2.0 nonafluoro-*tert*-butoxy groups per nm^2, see thermogravimetric data in the Supporting Information). These experiments are proof-of-principle that just begin to demonstrate the full suite of applications for the F-electrophiles presented here.

■ EXPERIMENTAL SECTION

General Information. All reagents were purchased from commercial sources in the United States and were used without further purification unless otherwise noted. The petroleum ether (PE) used in our experiments was the 35–60 °C fraction. Dichloromethane, tetrahydrofuran, and diethyl ether were dried in a house-built solvent purification system using activated alumina. *N,N*-Dimethylformamide and acetonitrile were dried by vacuum distillation from calcium hydride and stored under an inert atmosphere. All column chromatography and TLC were performed using silica with 40–63 µm particle size. TLC was visualized with UV$_{254}$ and/or basic permanganate stain. NMR spectra were acquired on a 400 MHz instrument and are reported in ppm referenced to tetramethylsilane (^1H in CDCl$_3$), solvent (all ^{13}C and ^1H in DMSO-d_6), and fluorotrichloromethane (all ^{19}F). High resolution mass spectrometry was performed with a double-focusing magnetic sector instrument; three exceptions (**3**, **14**, and **21**, indicated below) used a time-of-flight (TOF) instrument.

3-(Nonafluoro-tert-butoxy)propan-1-ol (1).
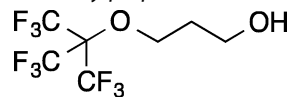
First, 3-hydroxypropyl tosylate was synthesized: 1,3-propanediol (3.63 mL, 50.0 mmol) was added to a round-bottomed flask (RBF) along with CH_2Cl_2 (20 mL) and TEA (1.53 mL, 11 mmol). A dripping funnel equipped with a rubber septum was placed on the RBF, which was then flushed with nitrogen and placed in an ice bath. Separately, tosyl chloride (1.91 g, 10.0 mmol) was dissolved in CH_2Cl_2 (15 mL) and added to the dripping funnel. The tosyl chloride solution was then dripped into the RBF over the span of 30 min, and the reaction was stirred overnight for 18 h, warming to room temperature. Then, the solvent was removed by rotary evaporation, yielding a viscous, slightly yellow slurry with solid TEA·HCl. This slurry was taken up in minimal Et_2O (~5 mL) and vacuum filtered through a fritted funnel. Removal of the solvent by rotary evaporation left a viscous oil, and column chromatography with 60:40 EtOAc:PE yielded 1.96 g (81%) of product tosylate ($R_f \approx 0.38$ in 60:40 EtOAc:PE) as a viscous, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, $J = 8.0$ Hz, 2H), 7.35 (d, $J = 8.0$ Hz, 2H), 4.19 (t, $J = 6.2$ Hz, 2H), 3.72 (q, $J = 5.6$ Hz, 2H), 2.45 (s, 3H), 1.89 (quint, $J = 6.0$ Hz, 2H), 1.48 (broad t, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.0, 133.1, 130.0, 128.0, 67.6, 58.5, 31.8, 21.8. These spectroscopic data match the literature values.[32]

Next, powdered potassium hydroxide (0.34 g, 6.0 mmol) was added to an RBF along with 2-butanone (5 mL), forming a slurry. The flask was sealed with a rubber septum and placed in an ice bath. Nonafluoro-*tert*-butanol (0.84 mL, 6.0 mmol) was added dropwise via syringe over 20 min, at which point the mixture was heterogeneous. Then, the tosyl alcohol (1.52 g, 6.60 mmol) dissolved in 2-butanone (2 mL) was added to the RBF via syringe. The RBF was then placed in a hot sand bath (80 °C) and refluxed for 20 h overnight. The solvent was removed by rotary evaporation to yield a viscous slurry, to which was added water (10 mL), saturated bicarbonate (10 mL), and CH_2Cl_2 (10 mL). Upon separation, the aqueous phase was washed with another aliquot of CH_2Cl_2 (10 mL); then, the combined organic layers were washed sequentially with saturated bicarbonate (8 mL) and brine (8 mL), dried with anhydrous sodium sulfate, and vacuum filtered. The solvent was removed by rotary evaporation to yield a pale-yellow oil. Column chromatography with 15:85 EtOAc:PE yielded 0.90 g (51%) of product 1 ($R_f \approx 0.16$ in 15:85 EtOAc:PE) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 4.18 (q, $J = 6.0$ Hz, 2H), 3.79 (q, $J = 5.5$ Hz, 2H), 1.94 (quint, $J = 5.9$ Hz, 2H), 1.38 (t, $J = 5.0$ Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 120.5 (q, $J = 293$ Hz), 80.0 (m), 67.1, 59.0, 32.6. ^{19}F NMR (376 MHz, $CDCl_3$): δ −70.95 (s). These spectroscopic data match the literature values.[5]

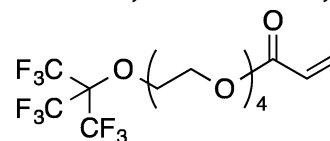*3-(Nonafluoro-tert-butoxy)propyl acrylate (3).*
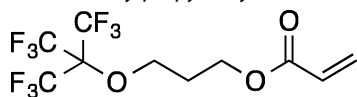
Fluoroalcohol 1 (0.588 g, 2.00 mmol) and dry CH_2Cl_2 (10 mL) were added to an RBF. The flask was stoppered with a rubber septum, placed in an ice bath, and flushed with nitrogen, and TEA (0.56 mL, 4.0 mmol) was added via syringe. Acryloyl chloride (0.49 mL, 6.0 mmol) was then added dropwise via syringe over a span of 20 min, and the reaction was allowed to stir overnight, warming to room temperature. After 18 h, the solvent was removed by rotary evaporation to yield a sticky, yellow semisolid. Column chromatography with 1:99 EtOAc:PE yielded 0.41 g (58%) of product 3 ($R_f \approx 0.18$ in 1:99 EtOAc:PE) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.41 (dd, $J = 17.4, 1.4$ Hz, 1H), 6.12 (dd, $J = 17.6, 10.0$ Hz, 1H), 5.85 (dd, $J = 10.2, 1.4$ Hz, 1H), 4.28 (t, $J = 6.2$ Hz, 2H), 4.14 (t, $J = 6.0$ Hz, 2H), 2.07 (quint, $J = 6.0$ Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.1, 131.1, 128.3, 120.5 (q, $J = 293$ Hz), 80 (m, $J = 29.7$ Hz), 66.4, 60.4, 29.2. ^{19}F NMR (376 MHz, $CDCl_3$): δ −70.88 (s). HRMS (+ESI TOF) m/z: [M + H]$^+$ calcd for $C_{10}H_{10}F_9O_3$ 349.0481; found 349.0478.

*11-(Perfluoro-tert-butoxy)-3,6,9-trioxaundecan-1-ol (2).*
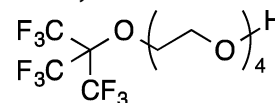
First, 2-(2-(2-(2-hydroxyethoxy)ethoxy)ethoxy)ethyl tosylate (TsO-TEG) was synthesized. Tetraethylene glycol (3.45 mL, 20.0 mmol) was added to an RBF along with CH_2Cl_2 (30 mL) and TEA (1.67 mL, 12.0 mmol). A dripping funnel equipped with a rubber septum was placed on the RBF, which was then flushed with nitrogen and placed in an ice bath. Separately, tosyl chloride (1.91 g, 10.0 mmol) was dissolved in CH_2Cl_2 (6 mL) in an Erlenmeyer flask and added to the dripping funnel via syringe; the flask was rinsed with a second aliquot of CH_2Cl_2 (4 mL) into the dripping funnel. The tosyl chloride solution was then dripped into the RBF over the span of 30 min, and the reaction was stirred overnight for 18 h, warming to room temperature. Then, the solvent was removed by rotary evaporation, yielding a viscous, slightly yellow slurry with solid TEA·HCl. This slurry was taken up in minimal cold CH_2Cl_2 (~5 mL) and vacuum filtered through a fritted funnel. Removal of the solvent by rotary evaporation left a viscous oil, and column chromatography with 98:2 changing to 96:4 CH_2Cl_2:MeOH yielded 1.78 g (51%) of product TsO-TEG ($R_f \approx 0.32$ in 95:5 CH_2Cl_2:MeOH) as a viscous, colorless oil. ^{1}H NMR ($CDCl_3$): δ 7.80 (d, $J = 8.0$ Hz, 2H), 7.34 (d, $J = 8.0$ Hz, 2H), 4.17 (t, $J = 4.8$ Hz, 2H), 3.56−3.73 (m, 14H), 2.45 (s, 3H), 2.4 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.0, 133.1, 130.0, 128.1, 72.6, 70.90, 70.81, 70.70, 70.63, 70.49, 69.4, 68.9, 61.9, 21.8. These spectroscopic data match the literature values.[33]

Next, powdered potassium hydroxide (0.42 g, 7.5 mmol) was added to an RBF along with 2-butanone (10 mL), forming a slurry. The flask was sealed with a rubber septum and placed in an ice bath. Nonafluoro-*tert*-butanol (1.05 mL, 7.5 mmol) was added dropwise via syringe over 20 min, at which point the mixture was heterogeneous. Then, TsO-TEG (2.86 g, 8.23 mmol) dissolved in 2-butanone (5 mL) was added to the RBF via syringe. The RBF was then placed in a hot sand bath (80 °C) and refluxed for 20 h overnight. The solvent was removed by rotary evaporation to yield a viscous slurry, which was vacuum filtered and washed with CH_2Cl_2 (3 × 5 mL) to remove precipitated potassium tosylate. The solvent was removed by rotary evaporation to yield a viscous, pale-yellow oil. Column chromatography with 75:25 EtOAc:PE yielded 2.27 g (73%) of product 2 ($R_f \approx 0.18$ in 75:25 EtOAc:PE) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 4.16 (t, $J = 4.8$ Hz, 2H), 3.60−3.75 (m, 14H), 2.42 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 120.5 (q, $J = 291$ Hz), 79.9 (m), 72.6, 71.2, 70.8, 70.7, 70.5, 69.6, 69.4, 61.9. ^{19}F NMR (376 MHz, $CDCl_3$): δ −70.83 (s). HRMS (+ESI) m/z: [M + Na]$^+$ calcd for $C_{12}H_{17}F_9O_5Na$ 435.0835; found 435.0839.

11-(Nonafluoro-tert-butoxy)-3,6,9-trioxaundecyl Acrylate (4).

Fluoro-TEG (1.5 g, 3.6 mmol) and dry CH_2Cl_2 (15 mL) were added to an RBF. The flask was stoppered with a rubber septum, placed in an ice bath, and flushed with nitrogen; then, TEA (1.0 mL, 7.2 mmol) was added via syringe. Acryloyl chloride (0.86 mL, 11 mmol) was then added dropwise via syringe over a span of 20 min, and the reaction was allowed to stir overnight, warming to room temperature. After 18 h, the solvent was removed by rotary evaporation to yield a viscous slurry with solid TEA·HCl. This slurry was taken up in minimal CH_2Cl_2 (~5 mL) and vacuum filtered through filter paper with rinsing, and the solvent was removed by rotary evaporation. Column chromatography with 20:80 EtOAc:PE yielded 0.78 g (47%) of product 4 ($R_f \approx 0.21$ in 20:80 EtOAc:PE) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 6.43 (dd, $J = 17.4, 1.4$ Hz, 1H), 6.15 (dd, $J = 17.4, 10.2$ Hz, 1H), 5.83 (dd, $J = 10.2, 1.4$ Hz, 1H), 4.32 (t, $J = 4.8$ Hz, 2H), 4.15 (t, $J = 5$ Hz, 2H), 3.74 (q, $J = 4.8$ Hz, 4H), 3.64−3.69 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.3, 131.1, 128.4, 120.5 (q, $J = 293$ Hz), 79.7 (m), 71.2, 70.8, 69.6, 69.4, 69.2, 63.8. ^{19}F NMR (376 MHz, $CDCl_3$): δ −70.90 (s). HRMS (+ESI) m/z: [M + Na]$^+$ calcd for $C_{15}H_{19}F_9O_6Na$ 489.0941; found 489.0932.

N-(tert-Butyloxycarbonyl)-2-amino-1-(nonafluoro-tert-butyoxy)-ethane (5).
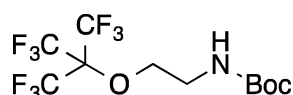
First, N-(*tert*-butyloxycarbonyl)-2-aminoethanol was synthesized. TEA (13.9 mL, 100 mmol), di-*tert*-butyl dicarbonate, Boc$_2$O (5.24 g, 24.0 mmol), and THF (25 mL) were added to an RBF, which was stoppered with a rubber septum and placed in an ice bath. 2-Aminoethanol (1.21 mL, 20.0 mmol) was added to the RBF via syringe over the span of 5 min, and the reaction was stirred for 3 h, warming to room temperature. The solvent was then removed under reduced pressure to yield a colorless oil that was transferred to a separatory funnel with deionized water (50 mL) and ethyl acetate (30 mL). The aqueous layer was washed with two additional aliquots of ethyl acetate, and the combined organic layers were washed with saturated sodium bicarbonate (30 mL) and brine (30 mL), dried with anhydrous sodium sulfate, and vacuum filtered. The solvent was removed by rotary evaporation to give 4.31 g of extracted crude, which consisted of 63 mol % (69 w/w %) Boc-protected aminoalcohol (92% yield), 15 mol % (14 w/w %) unreacted Boc$_2$O, and 21 mol % (7 w/w%) ethyl acetate. This crude mixture was used in further steps without additional purification. ^{1}H NMR (CDCl$_3$): δ 4.95 (bs, 1H), 3.71 (distorted t, 2H), 3.30 (distorted q, J = 4.8 Hz, 2H), 2.2 (bs, 1H), 1.45 (s, 9H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 157.0, 79.8, 62.7, 43.4, 28.5. These spectroscopic data match the literature values.[34]

Then, triphenylphosphine (1.97 g, 7.50 mmol) was added to a flame-dried RBF containing a stir bar along with the N-Boc-protected aminoalcohol (0.80 g, 5.0 mmol). The flask was stoppered with a rubber septum and was purged with nitrogen for 15 min. Dry THF (13 mL) was added via syringe, and the flask was placed in an ice-bath. DEAD (1.18 mL, 7.50 mmol) was added via syringe over 5 min, at which point the flask was raised from the ice-water bath and allowed to warm to room temperature over 20 min. Then, nonafluoro-*tert*-butanol (1.05 mL, 7.50 mmol) was added quickly by syringe; the septum was replaced with a Teflon-taped glass stopper secured with a Keck clip, and the flask was placed in a sand bath at 50 °C. The reaction continued overnight for 22 h, at which point the solvent was removed by rotary evaporation, yielding a yellow, viscous slurry of precipitated triphenylphosphine oxide. Column chromatography with 95:5 PE:EtOAc yielded 0.89 g (47%) of **5** as a white, crystalline solid after drying under vacuum ($R_f \approx$ 0.26 in 95:5 PE:EtOAc, mp 33.7−34.5 °C). ^{1}H NMR (400 MHz, CDCl$_3$): δ 4.83 (bs, 1H), 4.12 (t, J = 5.0 Hz, 2H), 3.41 (q, J = 5.3 Hz, 2H), 1.45 (s, 9H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 155.9, 120.4 (q, J = 291 Hz), 79.98, 79.87 (m, J = 29.7 Hz), 69.2, 40.5, 28.4. ^{19}F NMR (376 MHz, CDCl$_3$): δ −70.90 (s). HRMS (+ESI) m/z: [M − C$_4$H$_7$]$^+$ calcd for C$_7$H$_7$F$_9$NO$_3$ 324.0288; found 324.02771.

2-Amino-1-(nonafluoro-tert-butyoxy)ethane Hydrochloride (6).
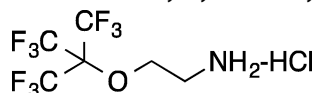

To an RBF were added **5** (0.485 g, 1.23 mmol) along with Et$_2$O (2 mL). Concentrated HCl (205 μL, 2.46 mmol) was dripped into the flask over 10 min. The flask was stoppered and allowed to stir for a day, yielding an off-white, precipitated slurry. The solvent was removed by rotary evaporation to give a thick, pale yellow slurry, which was taken up in a minimal amount of methanol (~1 mL). The addition of 10 mL of Et$_2$O caused a phase separation, and a small pipet was used to transfer the lower layer to a clean RBF. The methanol in the dense layer was then removed by rotary evaporation, yielding 0.116 g (30%) of product **6**, a white, powdery solid (mp 241−244 °C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.2 (bs, 3H), 4.30 (t, J = 5.0 Hz, 2H), 3.15 (t, J = 5.2 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 119.8 (q, J = 292 Hz), 79.2 (m, J = 29.6 Hz), 66.8, 38.3. ^{19}F NMR (376 MHz, DMSO-d_6): δ −69.22 (s). MS (+ESI) m/z: [M − Cl]$^+$ found 294.20. These spectroscopic data are consistent with the literature values for the free base.[28]

N-(2-(Nonafluoro-tert-butoxy)ethyl)acrylamide (7).
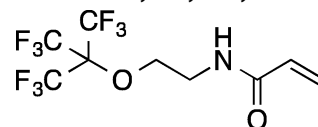
Fluorinated amine **6** (0.157 g, 0.50 mmol) and dry CH$_2$Cl$_2$ (2.5 mL) were added to an RBF. The flask was stoppered with a rubber septum, placed in an ice bath, and flushed with nitrogen, and TEA (0.127 mL, 1.5 mmol) was added via syringe. Acryloyl chloride (0.082 mL, 1.0 mmol) was then added dropwise via syringe over a span of 20 min, and the reaction was allowed to stir overnight, warming to room temperature. After 20 h, the reaction was quenched by the addition of saturated aqueous NaHCO$_3$ (10 mL) and poured into a separatory funnel. The aqueous layer was washed with CH$_2$Cl$_2$ (3 × 7 mL), and the combined organic layers were washed with brine (5 mL), dried with NaSO$_4$, and vacuum filtered. The solvent was removed by rotary evaporation to yield a clear oil. Column chromatography with 20:80 EtOAc:PE yielded 0.118 g (71%) of product **7** ($R_f \approx$ 0.34 in 30:70 EtOAc:PE) as a colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.30 (dd, J = 17.8, 1.2 Hz, 1H), 6.12 (dd, J = 17.8, 10.4 Hz, 1H), 6.0 (bs, 1H), 5.69 (dd, J = 10.4, 1.2 Hz, 1H), 4.15 (t, J = 5.0 Hz, 2H), 3.62 (q, J = 5.0 Hz, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 165.9, 130.4, 127.3, 120.4 (q, J = 292 Hz), 80.0 (m, J = 29.6 Hz), 68.9, 39.3. ^{19}F NMR (376 MHz, CDCl$_3$): δ −70.89 (s). HRMS (+ESI) m/z: [M + H]$^+$ calcd for C$_9$H$_9$F$_9$NO$_2$ 334.0495; found 334.0497.

*N-(tert-Butyloxycarbonyl)-3-amino-1-(nonafluoro-tert-butyoxy)-propane (8).*
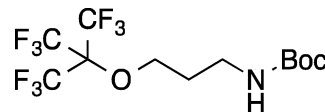
First, N-(*tert*-butyloxycarbonyl)-3-aminopropan-1-ol was synthesized. TEA (13.9, 100 mmol), di-*tert*-butyl dicarbonate, Boc$_2$O (5.24 g, 24.0 mmol), and THF (25 mL) were added to an RBF, which was stoppered with a rubber septum and placed in an ice bath. Then, 3-aminoethanol (1.58 mL, 20.0 mmol) was added to the RBF via syringe over the span of 5 min, and the reaction was stirred overnight for 20 h, warming to room temperature. The solvent was then removed under reduced pressure to yield a yellow oil that was transferred to a separatory funnel with deionized water (50 mL) and ethyl acetate (30 mL). The aqueous layer was washed with two additional aliquots of ethyl acetate, and the combined organic layers were washed with saturated sodium bicarbonate (20 mL) and brine (20 mL), dried with anhydrous sodium sulfate, and vacuum filtered. The solvent was removed by rotary evaporation to give 3.65 g of extracted crude, which consisted of 93 mol % (94 w/w %) product (98% yield) and 7 mol % (6 w/w%) of unreacted Boc$_2$O. This crude was used in further steps without additional purification. ^{1}H NMR (400 MHz, CDCl$_3$): δ 4.9 (bs, 1H), 3.66 (q, J = 5.7 Hz, 2H), 3.29 (q, J = 6.0 Hz, 2H), 3.1 (broad t, $J \approx$ 6 Hz 1H), 1.67 (quint, J = 6.2 Hz, 2H), 1.45 (s, 9H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 157.3, 79.7, 59.4, 37.0, 33.0, 27.9. These spectroscopic data match the literature values.[35]

Next, triphenylphosphine (1.97 g, 7.50 mmol) was added to a flame-dried RBF containing a stir bar along with the N-Boc-protected aminoalcohol (0.88 g, 5.0 mmol). The flask was stoppered with a rubber septum and purged with nitrogen for 15 min. Dry THF (20 mL) was added via syringe, and the flask was placed in an ice-bath. DEAD (1.18 mL, 7.50 mmol) was added via syringe over 5 min, at which point the flask was raised from the ice-water bath and allowed to warm to room temperature over 20 min. Then, nonafluoro-*tert*-butanol (1.05 mL, 7.50 mmol) was added quickly by syringe; the septum was replaced with a Teflon-taped glass stopper secured with a Keck clip, and the flask was placed in a sand bath at 55 °C. The reaction continued overnight for 22 h, at which point the solvent was removed by rotary evaporation, yielding a light yellow, viscous oil. Column chromatography with 90:10 changing to 80:20 PE:EtOAc yielded 1.10 g (56%) of product **8** ($R_f \approx$ 0.37 in 90:10 PE:EtOAc) as a colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ 4.6 (bs, 1H), 4.09 (t, J = 5.8 Hz, 2H), 3.25 (q, J = 6.4 Hz, 2H),

1.89 (quint, J = 6.2 Hz, 2H), 1.44 (s, 9H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 156.2, 120.6 (q, J = 293 Hz), 79.95 (m, J = 29.7 Hz), 79.46, 68.0, 37.3, 30.3, 28.3. ^{19}F NMR (376 MHz, CDCl$_3$): δ −70.82 (s). HRMS (+ESI) m/z: [M − C$_4$H$_7$]$^+$ calcd for C$_8$H$_9$F$_9$NO$_3$ 338.0444; found 338.04395.

3-Amino-1-(nonafluoro-tert-butyoxy)propane Hydrochloride (9).
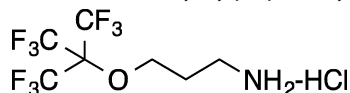
To an RBF was added **8** (0.635 g, 1.62 mmol) along with Et$_2$O (3 mL). Concentrated HCl (270 μL, 3.2 mmol) was dripped into the flask over 10 min. The flask was stoppered and allowed to stir for 20 h, yielding an off-white, precipitated slurry. The solvent was removed by rotary evaporation to give a thick, pale yellow slurry, which was taken up in a minimal amount of methanol (~1 mL). The addition of 10 mL of Et$_2$O caused a phase separation, and a small pipet was used to transfer the lower layer to a clean RBF. The methanol in the dense layer was then removed by rotary evaporation, yielding 0.251 g (47%) of product **9**, a white solid with small, clumpy crystals (mp 229−231 °C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.0 (bs, 3H), 4.19 (t, J = 6.2 Hz, 2H), 2.86 (distorted q, 2H), 1.96 (quint, J = 7 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 120.4 (q, J = 291 Hz), 79.6 (m, J = 29.6 Hz), 68.3, 35.7, 27.9 ^{19}F NMR (376 MHz, DMSO-d_6): δ −69.56 (s). HRMS (+ESI) m/z: [M]$^+$ calcd for C$_7$H$_9$F$_9$NO 294.0546; found 294.0555.

N-(3-(Nonafluoro-tert-butoxy)propyl)acrylamide (10).
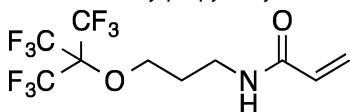
Fluorinated amine **9** (0.230 g, 0.697 mmol) and dry CH$_2$Cl$_2$ (2.0 mL) were added to an RBF. The flask was stoppered with a rubber septum, placed in an ice bath, and flushed with nitrogen, and TEA (0.293 mL, 2.1 mmol) was added via syringe. Acryloyl chloride (0.112 mL, 1.4 mmol) was then added dropwise via syringe over a span of 20 min, and the reaction was allowed to stir overnight, warming to room temperature. After 20 h, the reaction was quenched by the addition of saturated aqueous NaHCO$_3$ (10 mL) and poured into a separatory funnel. The aqueous layer was washed with CH$_2$Cl$_2$ (3 × 7 mL), and the combined organic layers were washed with brine (5 mL), dried with NaSO$_4$, and vacuum filtered. The solvent was removed by rotary evaporation to yield a clear oil. Column chromatography with 20:80 EtOAc:PE, increasing to 50:50 EtOAc:PE, yielded 0.151 g (62%) of product **10** ($R_f \approx$ 0.50 in 50:50 EtOAc:PE) as a colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.26 (dd, J = 17.2, 1.2 Hz, 1H), 6.07 (dd, J = 17.2, 10.4 Hz, 1H), 5.9 (bs, 1H), 5.65 (dd, J = 10.4, 1.2 Hz, 1H), 4.13 (t, J = 5.8 Hz, 2H), 3.47 (q, J = 6.3 Hz, 2H), 1.98 (quint, J = 6.2 Hz, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 165.9, 130.7, 126.7, 120.5 (q, J = 292 Hz), 79.8 (m, J = 29.6 Hz), 68.5, 36.9, 29.5. ^{19}F NMR (376 MHz, CDCl$_3$): δ −70.86 (s). HRMS (+ESI) m/z: [M + H]$^+$ calcd for C$_{10}$H$_{11}$F$_9$NO$_2$ 348.0652; found 348.0649.

3-(Nonafluoro-tert-butoxy)propyl Mesylate (11).
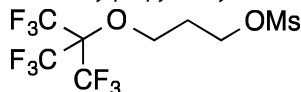
Fluorinated alcohol **1** (1.44 g, 4.89 mmol) was added to a flame-dried RBF along with TEA (1.14 mL, 8.00 mmol) and CH$_2$Cl$_2$ (12 mL). The flask was sealed with a rubber stopper and placed in an ice bath. After 5 min, mesyl chloride (0.62 mL, 8.0 mmol) was added via syringe over the span of 5 min. The reaction was stirred for an hour and allowed to warm to room temperature, at which time the reaction was transferred to a separatory funnel with water (20 mL) and CH$_2$Cl$_2$ (10 mL). Upon separation, the aqueous phase was washed with another aliquot of CH$_2$Cl$_2$ (10 mL); then, the combined organic layers were washed sequentially with saturated bicarbonate (15 mL) and brine (15 mL), dried with anhydrous sodium sulfate, and vacuum filtered. The solvent was removed by rotary evaporation to yield 1.75 g of a colorless, thin oil, which consisted of 88 mol % (96 w/w %) product **11** (92% yield) and 12 mol % (4 w/w %) unreacted mesyl chloride. This crude was used in

further steps without additional purification. ^{1}H NMR (CDCl$_3$): δ 4.35 (t, J = 6.0 Hz, 2H), 4.18 (t, 5.8 Hz, 2H), 3.02 (s, 3H), 2.15, (quint, J = 5.8 Hz, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 120.4 (q, J = 293 Hz), 79.8 (m, J = 29.7 Hz), 65.5, 37.2, 29.6. ^{19}F NMR (376 MHz, CDCl$_3$): δ −70.88 (s). HRMS (+ESI) m/z: [M + Na]$^+$ calcd for C$_8$H$_9$F$_9$O$_4$SNa 394.9981; found 394.9974.

N-(2-(Acryloyloxy)ethyl)-N,N-dimethyl-3-(nonafluoro-tert-butoxy)propan-1-aminium Chloride (12).
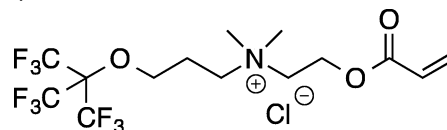

Fluorinated mesylate **11** (0.744 g, 2.00 mmol) was added to an RBF along with 2-(dimethylamino)ethyl acrylate (0.258 g, 1.80 mmol), sodium iodide (0.015 g, 0.10 mmol), and DMF (4 mL). The flask was stoppered tightly and placed into a sand bath at 78 °C for 44 h after which time the DMF was removed via short-path distillation under reduced pressure. The resulting viscous, orange, oily slurry was purified via anion exchange chromatography on Dowex 8X-100 (−SO$_3$H form) by first eluting noncharged constituents with Et$_2$O. Then, aminium **12** was eluted with a solution of HCl (2.5 M) in MeOH, and the solvent was removed by rotary evaporation and high vacuum to give 0.734 g (89%) of **12** as a viscous, slightly orange oil. ^{1}H NMR (DMSO-d_6): δ 6.38 (dd, J = 17.2, ~1 Hz, 1H), 6.19 (dd, J = 17.2 Hz, J = 10.6 Hz, 1H), 6.02 (dd, J = 10.6, ~1 Hz, 1H), 4.54 (s, 2H), 4.17 (t, 5.8 Hz, 2H), 3.78 (t, 4.6 Hz, 2H), 3.48 (m, 2H), 3.15 (s, 6H), 2.16 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.8, 132.5, 127.7, 119.9 (q, J = 292 Hz), 79.2 (m, J = 29.9 Hz), 67.8, 61.9, 60.3, 57.9, 50.8, 23.0. ^{19}F NMR (376 MHz, DMSO-d_6): δ −69.92 (s). HRMS (+ESI) m/z: [M]$^+$ calcd for C$_{14}$H$_{19}$F$_9$NO$_3$ 420.1227; found 420.1219.

3-(3-(Nonafluoro-tert-butoxy)propyl)-1-vinyl-1H-imidazol-3-ium Chloride (13).
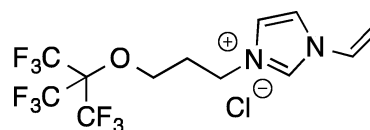
Fluorinated mesylate **11** (0.744 g, 2.00 mmol) was added to an RBF along with vinyl imidazole (0.169 g, 1.80 mmol), sodium iodide (0.015 g, 0.10 mmol), and DMF (7 mL). The flask was stoppered tightly and placed in a sand bath at 80 °C for 24 h after which time the DMF was removed via short-path distillation under reduced pressure. The resulting viscous, orange, oily slurry was purified via anion exchange chromatography on Dowex 8X-100 (−SO$_3$H form) by first eluting noncharged constituents with Et$_2$O. Then, imidazolium **13** was eluted with a solution of HCl (2.5 M) in MeOH, and the solvent was removed by rotary evaporation and high vacuum to give 0.591 g (81%) of **13** as a very viscous, colorless oil. ^{1}H NMR (DMSO-d_6): δ 9.55 (s, 1H), 8.20 (s, 1H), 7.95 (s, 1H), 7.30 (dd, J = 15.6, 8.4 Hz, 1H), 5.95 (dd, J = 15.6 Hz, J = 2.4 Hz, 1H), 5.43 (dd, J = 8.4, 2.4 Hz, 1H), 4.33 (t, J = 7.2 Hz, 2H), 4.22 (t, 5.4 Hz, 2H), 2.30 (quint, J = 6.4 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 135.5, 128.9, 123.3, 119.9 (q, J = 292 Hz), 119.2, 108.8, 79.2 (m, J = 28.9 Hz), 68.4, 46.6, 29.3. ^{19}F NMR (376 MHz, DMSO-d_6): δ −69.83 (s). HRMS (+ESI) m/z: [M]$^+$ calcd for C$_{12}$H$_{12}$F$_9$N$_2$O 371.0811; found 371.0814.

2-((2-(Acryloyloxy)ethyl)dimethylammonio)ethyl (3-(nonafluoro-tert-butoxy)propyl)phosphate (14).
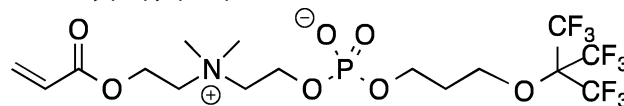
First, 2-(3-(nonafluoro-*tert*-butoxy)propoxy)-1,3,2-dioxaphospholane 2-oxide was synthesized. Fluorinated alcohol **1** (1.47 g, 5.00 mmol) was added to a flame-dried RBF. The flask was then subjected to vacuum for several minutes and recharged with nitrogen; this was repeated a second time. Next, dry THF (8 mL) and TEA (0.695 mL, 5.25 mmol) were added via syringe, and the flask was cooled to −20 °C in an acetone/N$_2$(l) slurry. 2-Chloro-2-oxo-1,3,2-dioxaphospholane (0.46 mL,

5.0 mmol) was added via syringe over 25 min; then, the reaction was allowed to warm to room temperature while stirring under nitrogen. After 3 h, the copious white precipitate was filtered off with repeated washing with Et$_2$O (6 × 2 mL), and the solvent was removed by rotary evaporation to yield a light yellow oil. Column chromatography with 60:40 EtOAc:PE, increasing to 70:30 EtOAc:PE, yielded 1.02 g (51%) of the fluorinated phospholane product ($R_f \approx 0.24$ in 60:40 EtOAc:PE) as a colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ 4.41−4.50 (m, 2H), 4.32−4.41 (m, 2H), 4.27 (dt, J = 8.6, 6.2, 2H), 4.16 (t, J = 5.8 Hz, 2H), 2.10 (quint, J = 5.9 Hz, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 120.4 (q, J = 292 Hz), 79.8 (m, J = 29.6 Hz), 66.2 (d, J = 3.1 Hz), 65.6 (d, J = 2.8 Hz), 64.6 (d, J = 6.1 Hz), 30.8 (d, J = 6.9 Hz). ^{19}F NMR (376 MHz, CDCl$_3$): δ −70.98 (s). ^{31}P NMR (162 MHz, CDCl$_3$): δ 17.4 (s).

Next, 2-(dimethylamino)ethyl acrylate (0.426 mL, 2.79 mmol) and anhydrous sodium sulfate (∼0.3 g, ∼4 mmol) were added directly to the RBF used to isolate the fluorinated phospholane (1.02 g, 2.54 mmol) from the above reaction. The flask was then subjected to vacuum for several minutes and recharged with nitrogen; this was repeated a second time. Acetonitrile (2 mL, dried by distillation over CaH$_2$) was then added via syringe, and the slurry was stirred under nitrogen for 30 min. Afterward, the solution was transferred via cannula to a flame-dried RBF; the sodium sulfate was rinsed with 3 × 1.5 mL of dry acetonitrile, which was also transferred via cannula into the new RBF. The septum was quickly replaced with a Teflon-taped glass stopper secured with a Keck clip, and the flask was placed in a sand bath at 70 °C and allowed to stir for 5 days. After cooling to room temperature, Et$_2$O (15 mL) was added, causing a white precipitate to form, and the flask was placed in the freezer overnight. The off-yellow supernatant was removed via pipet, and the resulting gummy white solid was washed three times with Et$_2$O through a settling/pipet sequence. A second crop of product was collected from the first supernatant by removing the solvent by rotary evaporation to yield a gummy solid. This solid was dissolved in ∼1 mL of acetonitrile and then precipitated by the addition of Et$_2$O (10 mL). The resulting gummy white solid was washed similarly to the first crop. Together, 0.91 g (66%) of product **14** was collected as a sticky, slightly off-white gum. ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.39 (d, J = 17.5, 1H), 6.21 (dd, J = 17.3, 10.3 Hz, 1H), 6.02 (d, J = 10.2, 1H), 4.55 (bs, 1H), 4.14 (t, J = 6.0 Hz, 2H), 4.02 (bs, 1H), 3.80 (m, J = 3.9 Hz, 2H), 3.70 (q, J = 6.5 Hz, 2H), 3.60 (m, J = 4.7 Hz, 2H), 3.17 (s, 6H), 1.88 (quint, J = 6.2 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.8, 132.2, 127.9, 120.1 (q, J = 292 Hz), 79.3 (m, J = 28.9 Hz), 67.7, 64.1, 62.6, 60.0 (d, J = 5.3 Hz), 58.13 (d, J = 4.5 Hz), 58.00, 51.4, 30.9 (d, J = 6.8 Hz). ^{19}F NMR (376 MHz, DMSO-d_6): δ −69.77 (s). ^{31}P NMR (162 MHz, DMSO-d_6): δ −0.86 (s). HRMS (+ESI TOF) m/z: [M + H]$^+$ calcd for C$_{16}$H$_{24}$F$_9$NO$_7$P 544.1141; found 544.1138.

*2-((tert-Butyldiphenylsilyl)oxy)-N-methyl-N-(2-((nonafluoro-tert-butoxy)ethyl)-ethan-1-amine (15).*
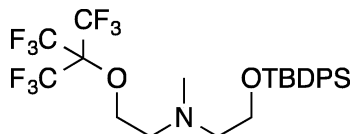
First, 2-((2-((*tert*-butyldiphenylsilyl)oxy)ethyl)(methyl)amino)ethan-1-ol was synthesized: N-methyldiethanolamine (2.28 g, 20.0 mmol), imidazole (0.68 g, 10.0 mmol), and DMF (15 mL) were added to a flame-dried RBF equipped with a rubber septum and flushed with nitrogen. *tert*-Butyldiphenylsilyl chloride (1.28 mL, 5.0 mmol) was added via syringe over a span of 25 min. Stirring was continued overnight at room temperature until the reaction was quenched by the addition of Et$_2$O (40 mL), deionized H$_2$O (20 mL), and saturated sodium bicarbonate (20 mL). The aqueous layer was washed with a second aliquot of Et$_2$O (30 mL); then, the combined organic layers were washed sequentially with saturated bicarbonate (20 mL) and brine (20 mL), dried with anhydrous sodium sulfate, and vacuum filtered. The solvent was removed by rotary evaporation to give 1.666 g of extracted crude, which consisted of 96 mol % monoprotected product (79% yield) and 4 mol % disubstituted product. This crude mixture, a colorless oil, was used in further steps without additional purification. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.67−7.69 (m, 4H), 7.37−7.43 (m, 6H), 3.73

(t, J = 5.8 Hz, 2H), 3.54 (t, J = 5.2 Hz, 2H), 2.61 (t, J = 6.0 Hz, 2H), 2.57 (t, J = 5.4 Hz, 2H), 2.27 (s, 3H), 1.05 (s, 9H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 135.6, 133.7, 129.7, 127.8, 62.1, 59.16, 59.13, 58.5, 42.4, 26.9, 19.2.

Next, triphenylphosphine (1.57g, 6.0 mmol) was added to a flame-dried RBF along with the TBDPS-protected alcohol from above (1.42 g, 4.0 mmol). The flask was stoppered with a rubber septum and was purged with nitrogen for 15 min. Dry THF (15 mL) was added via syringe, and the flask was placed in an ice-bath. DEAD (0.94 mL, 6.0 mmol) was added via syringe over 5 min, at which point the flask was raised from the ice-water bath and allowed to warm to room temperature over 20 min. At this point, nonafluoro-*tert*-butanol (0.84 mL, 6.0 mmol) was added quickly by syringe; the septum was replaced with a Teflon-taped glass stopper secured with a Keck clip, and the flask was placed in a sand bath at 50 °C. The reaction continued overnight for 16 h, at which point the solvent was removed by rotary evaporation, yielding a light yellow, viscous oil. Column chromatography with 90:10 PE:EtOAc yielded 1.72 g (75%) of product **15** ($R_f \approx 0.25$ in 90:10 PE:EtOAc) as a colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.65−7.67 (m, 4H), 7.36−7.43 (m, 6H), 4.12 (t, J = 6.0 Hz, 2H), 3.78 (t, J = 6.0 Hz, 2H), 2.86 (t, J = 5.8 Hz, 2H), 2.68 (t, J = 6.0 Hz, 2H), 2.33 (s, 3H), 1.04 (s, 9H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 135.5, 133.7, 129.9, 128.1, 120.6 (q, J = 292 Hz), 79.7 (m, J = 29.7 Hz), 68.2, 62.3, 59.5, 56.7, 43.4, 26.9, 19.3. ^{19}F NMR (376 MHz, CDCl$_3$): δ −70.90 (s). HRMS (+ESI) m/z: [M + H]$^+$ calcd for C$_{25}$H$_{31}$F$_9$NO$_2$Si 576.1986; found 576.1996.

2-(2-((Nonafluoro-tert-butoxy)ethyl)(methyl)amino)ethan-1-ol (16).
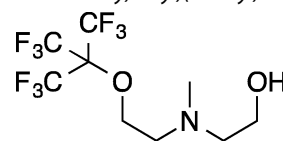
TBDPS-protected fluoro-alcohol **15** (1.72 g, 2.98 mmol) was added to an RBF along with TBAF·H$_2$O (1.89 g, 6.0 mmol) and stirred at room temperature for 6 h. The solvent was then removed under reduced pressure to yield an oil that was transferred to a separatory funnel with a saturated solution of sodium bicarbonate (20 mL) and ethyl acetate (20 mL). The aqueous layer was washed with two additional aliquots of ethyl acetate, and the combined organic layers were washed with brine (20 mL), dried with anhydrous sodium sulfate, and vacuum filtered. The solvent was removed by rotary evaporation to yield an oil. Column chromatography using 80:20 EtOAc:PE, then 90:10 EtOAc:PE ether, yielded 0.75 g (74%) of product **16** ($R_f \approx 0.15$ in 80:20 EtOAc:PE) as a colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ 4.10 (t, J = 5.4 Hz, 2H), 3.58 (t, J = 5.2 Hz, 2H), 2.79 (t, J = 5.6 Hz, 2H), 2.62 (t, J = 5.4 Hz, 3H), 2.34 (s, 3H), 2.3 (bs, 1H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 120.4 (q, J = 292 Hz), 79.9 (m, J = 29.7 Hz), 67.8, 59.1, 58.5, 56.6, 41.9. ^{19}F NMR (376 MHz, CDCl$_3$): δ −70.86 (s). HRMS (+ESI) m/z: [M + H]$^+$ calcd for C$_9$H$_{13}$F$_9$NO$_2$ 338.0808; found 338.0799.

2-((2-((Nonafluoro-tert-butoxy)ethyl)(methyl)amino)ethyl Acrylate (17).
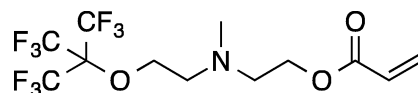
Fluorinated aminoalcohol **16** (0.67 g, 2.0 mmol) was added to a flame-dried RBF along with TEA (0.56 mL, 4.0 mmol) and dry dichloromethane (10 mL), and the flask was stoppered with a rubber septum. The flask was placed in an ice bath and cooled for 5 min, and acryloyl chloride (0.32 mL, 4.0 mmol) was added over 15 min. The reaction was stirred overnight, warming to room temperature for 14 h, and was then quenched by the addition of saturated sodium bicarbonate (10 mL) and additional dichloromethane (5 mL). After removing the organic layer, the aqueous layer was washed an additional time with dichloromethane (10 mL), and the organic layers were combined, dried with anhydrous sodium sulfate, and filtered. The solvent was removed by rotary evaporation to yield a light yellow oil. Column chromatography using 15:85 EtOAc:PE yielded 0.432 g (56%) of acrylate product **17** ($R_f \approx 0.32$ in 20:80 EtOAc:PE) as a very light yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.41 (dd, J = 17.4, 1.4 Hz, 1H), 6.13 (dd, J = 17.2, 10.4 Hz, 1H),

5.83 (dd, J = 10.2, 1.4 Hz, 1H), 4.24 (t, J = 5.6 Hz, 2H), 4.10 (t, J = 6.2 Hz, 2H), 2.75−2.81 (m, $J \approx$ 6 Hz, 4H), 2.37 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 166.2, 130.9, 128.3, 120.4 (q, J = 291 Hz), 79.9 (m, J = 29.7 Hz), 68.2, 62.3, 56.5, 56.0, 43.0. ^{19}F NMR (376 MHz, CDCl$_3$): δ −70.85 (s). HRMS (+ESI) m/z: [M + H]$^+$ calcd for C$_{12}$H$_{15}$F$_9$NO$_3$ 392.0914; found 392.0903.

tert-Butyl (2-((tert-Butyldiphenylsilyl)oxy)ethyl)(2-(nonafluoro-tert-butoxy)ethyl)carbamate (18).
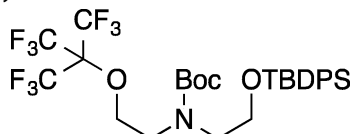

First, 2-((2-((*tert*-butyldiphenylsilyl)oxy)ethyl)amino)ethan-1-ol was synthesized: diethanolamine (2.47 g, 23.5 mmol), imidazole (1.06 g, 15.6 mmol), and DMF (20 mL) were added to a flame-dried RBF equipped with a rubber septum and flushed with nitrogen. *tert*-Butyldiphenylsilyl chloride (2.00 mL, 7.79 mmol) was added via syringe over a span of 25 min. Stirring was continued overnight at room temperature until the reaction was quenched by the addition of Et$_2$O (40 mL), deionized H$_2$O (20 mL), and saturated sodium bicarbonate (20 mL). The aqueous layer was washed with a second aliquot of Et$_2$O (30 mL); then, the combined organic layers were washed sequentially with saturated bicarbonate (20 mL) and brine (20 mL), dried with anhydrous sodium sulfate, and vacuum filtered. The solvent was removed by rotary evaporation to give 2.69 g of extracted crude mixture, which consisted of 89 mol % monoprotected product (5.8 mmol, 74% yield) and 11 mol % disubstituted product. This crude mixture, a colorless oil, was used in further steps without additional purification. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.65−7.68 (m, 4H), 7.37−7.43 (m, 6H), 3.76 (distorted t, J = 5.2 Hz, 2H), 3.60 (distorted t, J = 4.6 Hz, 2H), 2.74−2.77 (m, 4H), 1.7 (bs, 1H), 1.05 (s, 9H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 135.7, 133.7, 129.9, 127.8, 63.3, 61.0, 51.1, 50.7, 27.0, 19.4.

Next, *tert*-butyl (2-((*tert*-butyldiphenylsilyl)oxy)ethyl)(2-hydroxyethyl)carbamate was synthesized. To the RBF containing the TBDPS-protected amino alcohol from above (2.0 g, 5.8 mmol) was added TEA (2.8 mL, 20 mmol), di-*tert*-butyl dicarbonate, Boc$_2$O (1.32 g, 6.0 mmol), and THF (40 mL). The flask was stoppered with a rubber septum and placed in an ice bath, and the reaction was stirred overnight for 20 h, warming to room temperature. The solvent was then removed under reduced pressure to yield a yellow oil that was transferred to a separatory funnel with deionized water (30 mL) and ethyl acetate (30 mL). The aqueous layer was washed with two additional aliquots of ethyl acetate, and the combined organic layers were washed with saturated sodium bicarbonate (20 mL) and brine (20 mL), dried with anhydrous sodium sulfate, and vacuum filtered. The solvent was removed by rotary evaporation to give a light yellow oil, which was submitted to column chromatography with 70:30 PE:EtOAc to yield 2.43 g (94%) of the Boc-protected product ($R_f \approx$ 0.29 in 70:30 PE:EtOAc) as a colorless, viscous oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.64−7.67 (m, 4H), 7.37−7.43 (m, 6H), 3.82/3.75 (bs/t, J = 5.2 Hz, 2H, rotamers), 3.74 (t, J = 5.6 Hz, 2H), 3.47 (distorted q, $J \approx$ 4 Hz, 2 H), 3.4/2.7 (bs, 1H, rotamers), 3.39 (broad t, $J \approx$ 5 Hz 1H), 1.48/1.38 (s, 9H, rotamers), 1.05 (s, 9H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 157.4, 135.7, 133.2, 129.9, 127.9, 80.4/80.0 (rotamers), 62.97/62.2 (rotamers), 62.85, 52.0, 51.1/50.8 (rotamers), 28.5 (broad, rotamers), 26.9, 19.2.

Lastly, triphenylphosphine (1.49 g, 5.68 mmol) was added to a flame-dried RBF along with the TBDPS-protected, Boc-protected alcohol from above (1.62 g, 3.65 mmol). The flask was stoppered with a rubber septum and purged with nitrogen for 15 min. Dry THF (15 mL) was added via syringe, and the flask was placed in an ice-bath. DEAD (0.94 mL, 6.0 mmol) was added via syringe over 10 min, at which point the flask was raised from the ice-water bath and allowed to warm to room temperature over 20 min. Then, nonafluoro-*tert*-butanol (0.84 mL, 6.0 mmol) was added quickly by syringe; the septum was replaced with a Teflon-taped glass stopper secured with a Keck clip, and the flask was placed in a sand bath at 50 °C. The reaction continued overnight for 48 h, at which point the solvent was removed by rotary evaporation, yielding a thick, oily slurry. Column chromatography with 95:5 PE:EtOAc yielded 0.75 g

(31%) of product **18** ($R_f \approx$ 0.58 in 95:5 PE:EtOAc) as a colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.63−7.65 (m, 4H), 7.37−7.41 (m, 6H), 4.18/4.11 (t, J = 4.6/5.6 Hz, 2H, rotamers), 3.77/3.70 (t, J = 5.2/5.8 Hz, 2H, rotamers), 3.53−3.57 (m, 2H), 3.39−3.45 (m, 2H), 1.45/1.37 (s, 9H, rotamers), 1.04 (s, 9H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 155.4/155.1 (rotamers), 135.6, 133.5, 129.9, 127.9, 120.5 (q, J = 292 Hz), 80.16/80.03 (rotamers), 79.7 (m, J = 30 Hz), 69.07/68.56 (rotamers), 62.9, 51.2/50.5 (rotamers), 48.6/48.3 (rotamers), 28.48/28.42 (rotamers), 26.9, 19.2. ^{19}F NMR (376 MHz, CDCl$_3$): δ −70.98 (s). HRMS (+ESI) m/z: [M + Na]$^+$ calcd for C$_{29}$H$_{36}$F$_9$NO$_4$SiNa 684.2162; found 684.2166.

tert-Butyl (2-(Nonafluoro-tert-butoxy)ethyl)(2-hydroxyethyl)-carbamate (19).
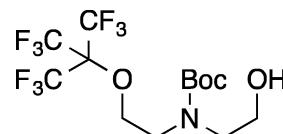
TBDPS-protected fluoro-aminoalcohol **18** (0.731 g, 1.11 mmol) was added to an RBF along with TBAF·H$_2$O (1.11 g, 3.52 mmol) and stirred at room temperature for 5 h. The solvent was then removed under reduced pressure to yield an oil that was transferred to a separatory funnel with a saturated solution of ammonium chloride (20 mL) and ethyl acetate (20 mL). The aqueous layer was washed with two additional aliquots of ethyl acetate, and the combined organic layers were washed with brine (20 mL), dried with anhydrous sodium sulfate, and vacuum filtered. The solvent was removed by rotary evaporation to yield an oil. Column chromatography using 60:40 PE:EtOAc yielded 0.432 g (92%) of product **19** ($R_f \approx$ 0.37 in 60:40 PE:EtOAc) as a colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ 4.22/4.15 (bs, 2H, rotamers), 3.75 (bs, 2H), 3.52 (distorted q, $J \approx$ 5.2 Hz, 2H), 3.45 (distorted q, $J \approx$ 4.4 Hz, 2H), 2.8 (bs, 1H), 1.46 (s, 9H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 156.8/155.5 (rotamers), 120.4 (q, J = 292 Hz), 81.05/80.63 (rotamers), 79.7 (m, J = 29.8 Hz), 68.9/68.5 (rotamers), 62.6/61.8 (rotamers), 51.8, 48.6, 28.4. ^{19}F NMR (376 MHz, CDCl$_3$): δ −70.93/-70.96 (s, rotamers). HRMS (+ESI) m/z: [M + Na]$^+$ calcd for C$_{13}$H$_{18}$F$_9$NO$_4$Na 446.0984; found 446.0996.

*2-((tert-Butoxycarbonyl)(2-(nonafluoro-tert-butoxy)ethyl)-amino)ethyl Acrylate (20).*
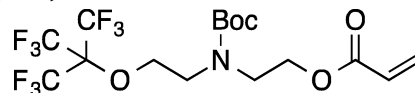
Fluorinated aminoalcohol **19** (0.43 g, 1.0 mmol) was added to a flame-dried RBF along with TEA (0.28 mL, 2.0 mmol) and dry dichloromethane (10 mL), and the flask was stoppered with a rubber septum. The flask was placed in an ice bath and cooled for 5 min, and acryloyl chloride (0.16 mL, 2.0 mmol) was added over 15 min. The reaction was stirred overnight, warming to room temperature for 14 h, and was then quenched by the addition of saturated sodium bicarbonate (10 mL) and additional dichloromethane (5 mL). After removing the organic layer, the aqueous layer was washed an additional time with dichloromethane (10 mL), and the organic layers were combined, dried with anhydrous sodium sulfate, and filtered. The solvent was removed by rotary evaporation to yield a light yellow oil. Column chromatography using 90:10 PE:EtOAc yielded 0.42 g (88%) of acrylate product **20** ($R_f \approx$ 0.31 in 90:10 PE:EtOAc) as a colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.42 (d, J = 16.8 Hz, 1H), 6.12 (dd, J = 17.4, 10.2 Hz, 1H), 5.86 (ddd, J = 10.4, 7.2, 1.2 Hz, 1H), 4.29/4.24 (t, J = 5.5 Hz, 2H, rotamers), 4.21/4.14 (t, J = 5.2 Hz, 2H, rotamers), 3.49−3.58 (m, 4H), 1.456/1.450 (s, 9H, rotamers). ^{13}C NMR (100 MHz, CDCl$_3$): δ 166.1, 155.25/154.99 (rotamers), 131.3, 128.3, 120.4 (q, J = 292 Hz), 80.7, 79.9 (m, J = 29.6 Hz), 68.96/68.48 (rotamers), 62.98/62.91 (rotamers), 48.3/48.1 (rotamers), 47.5, 28.4. ^{19}F NMR (376 MHz, CDCl$_3$): δ −70.94/70.98 (s, rotamers). HRMS (+ESI) m/z: [M + Na]$^+$ calcd for C$_{16}$H$_{20}$F$_9$NO$_5$Na 500.1090; found 500.1097.

1-(Allyloxy)-2,2-bis((nonafluoro-tert-butoxy)methyl)butane (21).
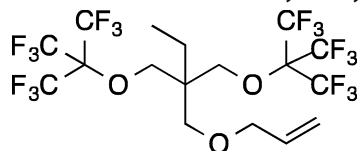
Triphenylphosphine (1.97 g, 7.50 mmol) was added to a flame-dried RBF containing a stir bar along with 2-((allyloxy)methyl)-2-ethyl-propane-1,3-diol (0.435 g, 2.5 mmol). The flask was stoppered with a rubber septum and was purged with nitrogen for 15 min. Dry THF (36 mL) was added via syringe, and the flask was placed in an ice-bath. DEAD (1.18 mL, 7.50 mmol) was added via syringe over 5 min, at which point the flask was raised from the ice-water bath and allowed to warm to room temperature over 20 min. Then, nonafluoro-*tert*-butanol (1.05 mL, 7.50 mmol) was added quickly by syringe; the septum was replaced with a Teflon-taped glass stopper secured with a Keck clip, and the flask was placed in a sand bath at 55 °C. The reaction continued overnight for 22 h, at which point the solvent was removed by rotary evaporation, yielding a light yellow, viscous oil. Column chromatography with 90:10 PE:EtOAc yielded 0.74 g (49%) of product **21** ($R_f \approx 0.82$ in 90:10 PE:EtOAc) as a colorless liquid. ^{1}H NMR (400 MHz, CDCl$_3$): δ 5.85 (ddt, J = 17.4, 10.2, 5.5 Hz, 1H), 5.23 (ddt, J = 17.4, 1.6, 1.4 Hz, 1H), 5.17 (ddt, J = 10.2, 1.6, 1.4 Hz, 1H), 3.95 (dd, J = 14.8, 8.4 Hz, 4H), 3.92 (dt, J = 5.5, 1.4 Hz, 2H), 3.28 (s, 2H), 1.50 (q, J = 7.6 Hz, 2H), 0.89 (t, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 134.6, 120.7 (q, J = 291 Hz), 117.0, 80.0 (m, J = 29.6 Hz), 72.6, 68.4, 67.9, 44.2, 21.7, 6.8. ^{19}F NMR (376 MHz, CDCl$_3$): δ −70.82 (s). HRMS (+ESI TOF) *m/z*: [M + H]$^+$ calcd for C$_{17}$H$_{17}$F$_{18}$O$_3$ 611.0885; found 611.0881.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01572.

NMR spectra of all numbered compounds and synthetic intermediates (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: steinbaj@canisius.edu; phone: 716-888-2343; fax: 716-888-3112.

Notes

The authors declare no competing financial interest.

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