

Note

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

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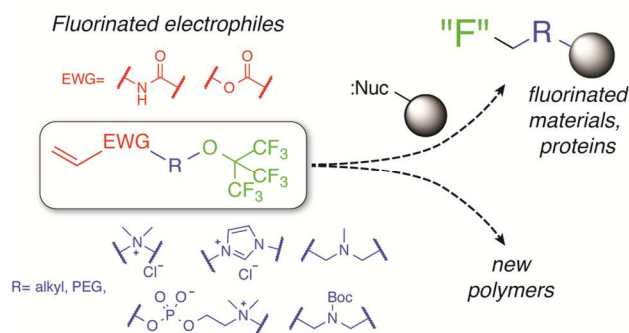
A Library of Fluorinated Electrophiles for Chemical Tagging and Materials Synthesis

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
NY, 14208-1098

*Corresponding author: steinbaj@canisius.edu, 716-888-2343 (T), 716-888-3112 (F)



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, non-polarizable C-F bond leads to very low reactivity and weak Van der Waals forces, respectively, and thus, highly fluorinated – “fluorous” – molecules have low solubility in both aqueous and organic solvents.^{1,2} These useful properties have lead to an entire segment of green chemistry that uses fluorous molecules in catalysis, reaction separations, and

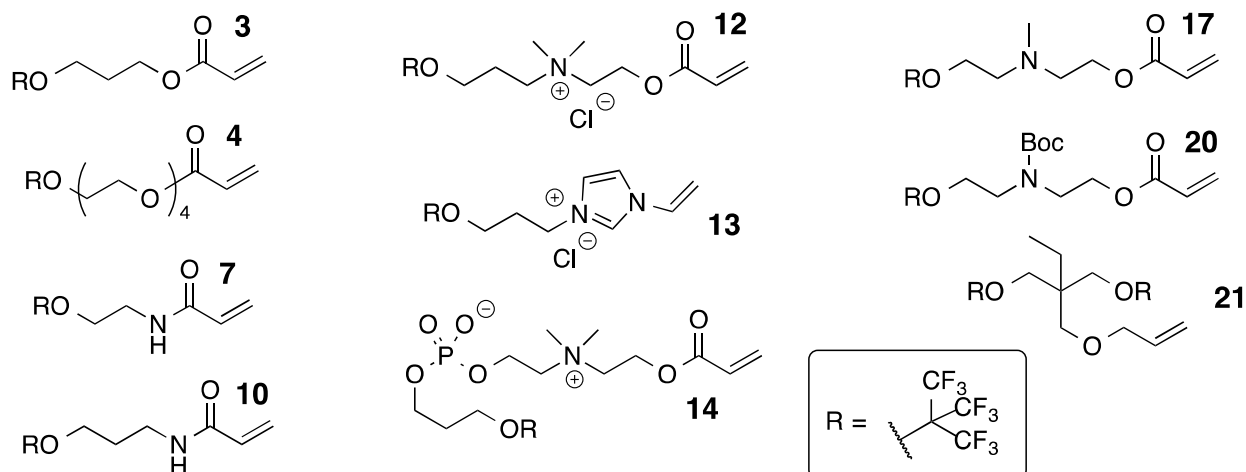
chemical synthesis.^{3,4} Briefly, the phase separation of fluorinated solvents¹ and reagents⁵⁻⁸ is used to greatly simplify purification of reaction mixtures. In related applications, fluorinated porous materials have been used to effect separations in the liquid and gas phases.⁹⁻¹² Also, the low reactivity 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.

Beside the interesting physical and chemical properties of fluorinated molecules, the ¹⁹F nucleus possesses a large gyromagnetic ratio, making it nearly as sensitive as the ¹H nucleus in NMR spectroscopy. A large chemical shift dispersion and large paramagnetic term results in a great sensitivity to chemical and solvation environment.^{13,14} These characteristics make fluorine nuclei useful NMR probes for solvation, conformation, and dynamics¹⁵ 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 Rábai³ to more lightly fluorinated molecules needed for labeling biomolecules¹⁶ 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

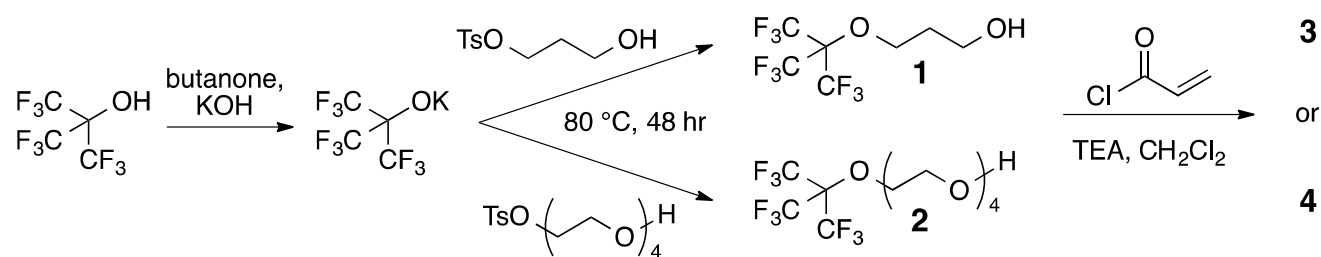
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3 fluorinated acrylates are currently commercially available, and many of those available contain
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5 long (>6 carbon) perfluoroalkyl chains that have known issues with biopersistence in the
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7 environment.²³ Those with smaller, compact perfluorinated groups, which are expected to be less
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9 persistent,²⁴ are rare. Herein we report the synthesis of a small library of new fluorinated
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11 electrophiles (“F-electrophiles”) that all contain the compact nonafluoro-*tert*-butyl group with
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13 potential uses in diverse applications like protein tagging, ¹⁹F NMR contrast agents, modification
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15 of materials, and polymer synthesis. We have avoided “heavy fluorous” molecules to permit
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17 their use in applications where separate fluorous phases are not needed, such as polymer science
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19 and biomedical materials.
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24 For the reasons listed above, acrylate and acrylamide functional groups are the
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26 electrophilic chemical handles for most of the members of this library. F-electrophiles **3**, **7**, and
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28 **10** are relatively hydrophobic and could find use as monomers in acrylate polymerizations. F-
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30 electrophiles **4**, **12**, **13**, and **14** contain hydrophilic linkers (tetraethylene glycol, quaternary
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32 aminium, imidazolium, and phosphorylcholine, respectively) for applications that require
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34 hydrophilicity. F-electrophiles **17** and **20** contain 3° and 2° amines, respectively, that could
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36 exhibit sensitivity to pH changes in biological applications. Lastly, allyl ether F-Electrophile **21**
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38 contains 18-chemically equivalent fluorine atoms and is reactive in the radical thiol-ene
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40 conjugation.
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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.

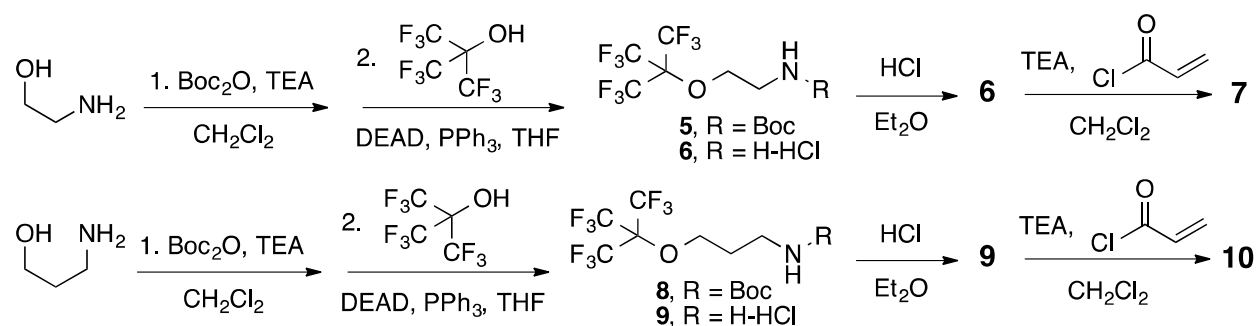
Scheme 1. Synthesis of **3** and **4**.



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 ($\text{pK}_a \sim 5$),²⁶ as demonstrated previously by others.^{27,26} Deprotection of the Boc groups with HCl in diethyl ether lead to the 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. The 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.

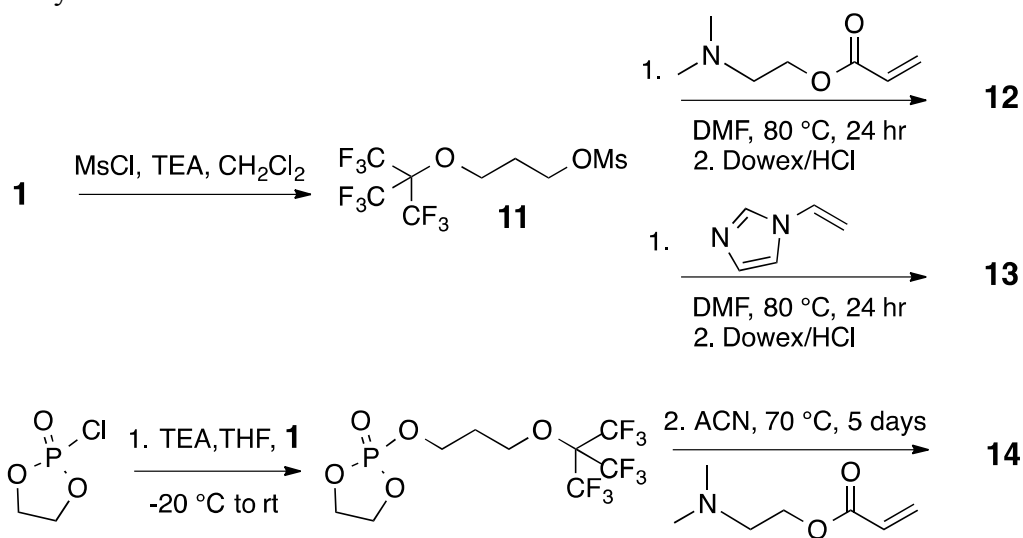
Scheme 2. Syntheses of **7** and **10**



The aminium, imidazolium, and phosphorylcholine F-electrophiles **12**, **13**, and **14** were prepared in only a handful of steps from the fluorinated alcohol **1** (Scheme 3). For **12** and **13**, 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 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 H₂O in the ¹H NMR spectrum (DMSO-₆). ¹H-¹H TOCSY NMR spectroscopy alleviated the interference by H₂O 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 the zwitterionic F-electrophile **14** in 34% yield from **1**.

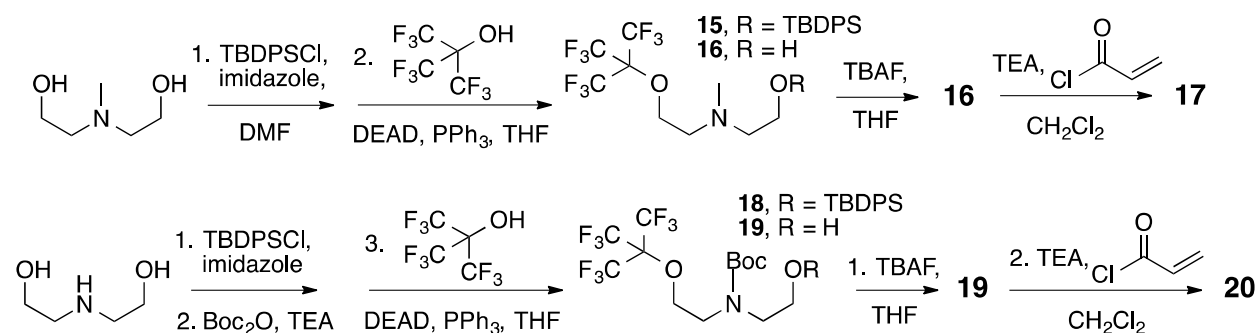
Scheme 3. Synthesis of **12** – **14**



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**

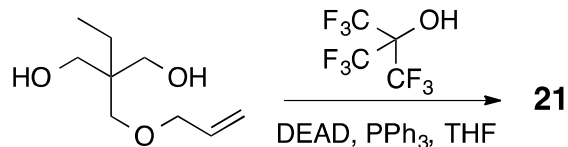
and **19**, and subsequent esterification with acryloyl chloride gave acrylates **17** and **20** in 25% and 17% yields overall from the diol starting materials. Perhaps unsurprisingly, attempts to deprotect the Boc group from **20** resulted in the formation of inter- and intramolecular conjugate addition products. In practice, the secondary amine could be deprotected after polymerization or reaction onto a substrate.

Scheme 4. Synthesis of **17** and **20**



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 reaction proved quite capable of installing the nonafluoro-*tert*-butyl ethers, even in the sterically congested **21**. On standard silica gel, the highly-fluorinated **21** exhibited a very large R_f even in a non-polar 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, ¹³C-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.

Scheme 5. Synthesis of **21**



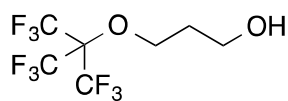
In conclusion, we have synthesized a library of fluorinated electrophiles that could find use in biomaterials, omniphobic materials, polymer chemistry, and fluorous tagging of biological molecules. The fluorous group in each is a nonafluoro-*tert*-butyl ether, which is distinct from the few highly-fluorinated 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, preliminary kinetic experiments on an NMR scale confirmed 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 Stöber³¹ method. Conjugation of F-electrophiles **3** and **21** to the nanoparticles using DBU as a catalyst or a photoinitiator and UV₂₅₄, respectively, resulted in useful degrees of functionalization for silica materials (~2.0 nonafluoro-*tert*-butoxy groups per nm², see thermogravimetric data in the Supporting Information). These experiments are proofs-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**)

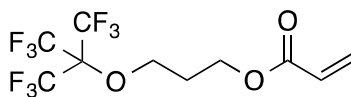


First, 3-hydroxypropyl tosylate was synthesized: 1,3-propanediol (3.63 mL, 50.0 mmol) was added to a RBF along with CH_2Cl_2 (20 mL) and TEA (1.53 mL, 11 mmol). A dripping funnel equipped with a rubber septum was placed on the RBF, which was then flushed with nitrogen and placed in an ice bath. Separately, 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 thirty minutes, and the reaction was stirred overnight for 18 hours, warming to room temperature. Then, the solvent was removed by rotary evaporation, yielding a viscous, slightly-yellow slurry with solid $\text{TEA}\cdot\text{HCl}$. 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 ~0.38 in 60:40 EtOAc:PE) as a viscous, colorless oil. ^1H 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 a 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 twenty minutes, 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 $^\circ\text{C}$) and refluxed for 20 hours 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

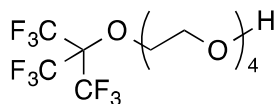
organic layers were washed sequentially with saturated bicarbonate (8 mL) and brine (8 mL), dried with anhydrous sodium sulfate, and vacuum filtered. The solvent was removed by rotary evaporation to yield a pale-yellow oil. Column chromatography with 15:85 EtOAc:PE yielded 0.90 g (51%) of product **1** ($R_f \sim 0.16$ in 15:85 EtOAc:PE) as a colorless oil. ^1H 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 a RBF. The flask was stoppered with a rubber septum, placed in an ice bath, 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 twenty minutes, and the reaction was allowed to stir overnight, warming to room temperature. After 18 hours, the solvent was removed by rotary evaporation to yield a sticky, yellow semi-solid. Column chromatography with 1:99 EtOAc:PE yielded 0.41 g (58%) of product **3** ($R_f \sim 0.18$ in 1:99 EtOAc:PE) as a colorless oil. ^1H 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 : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{10}\text{H}_{10}\text{F}_9\text{O}_3$ 349.0481; Found 349.0478.

11-(perfluoro-*tert*-butoxy)-3,6,9-trioxaundecan-1-ol (**2**)

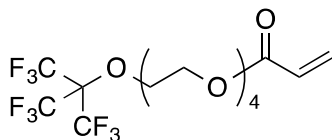


First, 2-(2-(2-(2-hydroxyethoxy)ethoxy)ethoxy)ethyl tosylate, TsO-TEG, was synthesized. Tetraethylene glycol (3.45 mL, 20.0 mmol) was added to a RBF along with CH_2Cl_2 (30 mL) and TEA (1.67 mL, 12.0 mmol). A dripping funnel equipped with a rubber septum was placed on the RBF, which was then flushed 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 thirty minutes, and the reaction was stirred

overnight for 18 hours, 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 CH₂Cl₂ (~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 CH₂Cl₂:MeOH yielded 1.78 g (51%) of product TsO-TEG (*R_f* ~0.32 in 95:5 CH₂Cl₂:MeOH) as a viscous, colorless oil. ¹H NMR (CDCl₃): 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). ¹³C NMR (100 MHz, CDCl₃): 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 a 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 twenty minutes, 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 hours overnight. The solvent was removed by rotary evaporation to yield a viscous slurry, which was vacuum filtered and washed with CH₂Cl₂ (3 x 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* ~0.18 in 75:25 EtOAc:PE) as a colorless oil. ¹H NMR (CDCl₃): δ 4.16 (t, *J* = 4.8 Hz, 2H), 3.60 – 3.75 (m, 14H), 2.42 (bs, 1H). ¹³C NMR (100 MHz, CDCl₃): δ. ¹⁹F NMR (376 MHz, CDCl₃): δ -70.83 (s). HRMS (+ESI) *m/z*: [M + Na]⁺ Calcd for C₁₂H₁₇F₉O₅Na 435.0835; Found 435.0839.

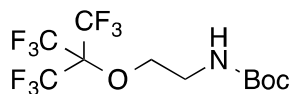
11-(nonafluoro-*tert*-butoxy)-3,6,9-trioxaundecyl acrylate (**4**)



Fluoro-TEG (1.5 g, 3.6 mmol) and dry CH₂Cl₂ (15 mL) were added to a 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 twenty minutes, and the reaction was allowed to stir overnight, warming to room temperature. After 18 hours, the solvent was removed by rotary evaporation to yield a viscous slurry with solid TEA·HCl. This slurry was taken up in minimal CH₂Cl₂ (~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* ~0.21 in 20:80 EtOAc:PE) as a colorless oil. ¹H

NMR (CDCl₃): 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). ¹³C NMR (100 MHz, CDCl₃): 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. ¹⁹F NMR (376 MHz, CDCl₃): δ -70.90 (s). HRMS (+ESI) m/z : [M + Na]⁺ Calcd for C₁₅H₁₉F₉O₆Na 489.0941; Found 489.0932.

N-(*tert*-butyloxycarbonyl)-2-amino-1-(nonafluoro-*tert*-butoxy)ethane (**5**)

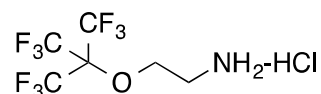


First, *N*-(*tert*-butyloxycarbonyl)-2-aminoethanol was synthesized. TEA (13.9 mL, 100 mmol), di-*tert*-butyl dicarbonate, Boc₂O (5.24 g, 24.0 mmol), and THF (25 mL) were added to a RBF, which was stoppered with a rubber septum and placed in an ice bath. 2-aminoethanol (1.21 mL, 20.0 mmol) was added to the RBF via syringe over the span of five minutes, and the reaction was stirred for three hours, 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 %) of unreacted Boc₂O, and 21 mol % (7 w/w%) ethyl acetate. This crude was used in further steps without additional purification. ¹H NMR (CDCl₃): 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). ¹³C NMR (100 MHz, CDCl₃): 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 minutes. 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 five minutes, at which point the flask was raised from the ice-water bath and allowed to warm to room temperature over 20 minutes. 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 hours, 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 ~0.26 in 95:5 PE:EtOAc, mp = 33.7-34.5 °C). ¹H NMR (400 MHz, CDCl₃): δ

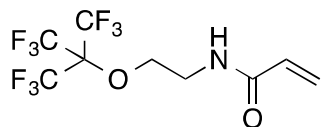
4.83 (bs, 1H), 4.12 (t, $J = 5.0$ Hz, 2H), 3.41 (q, $J = 5.3$ Hz, 2H), 1.45 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3): δ 155.9, 120.4 (q, $J = 291$ Hz), 79.98, 79.87 (m, $J = 29.7$ Hz), 69.2, 40.5, 28.4. ^{19}F NMR (376 MHz, CDCl_3): δ -70.90 (s). HRMS (+ESI) m/z : $[\text{M} - \text{C}_4\text{H}_7]^+$ Calcd for $\text{C}_7\text{H}_7\text{F}_9\text{NO}_3$ 324.0288, found 324.02771.

2-amino-1-(nonafluoro-*tert*-butoxy)ethane hydrochloride (6)



To a RBF was added **5** (0.485 g, 1.23 mmol) along with Et_2O (2 mL). Concentrated HCl (205 μL , 2.46 mmol) was dripped into the flask over 10 minutes. 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_2O caused a phase separation, and a small pipette 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 $^\circ\text{C}$). ^1H NMR (400 MHz, $\text{DMSO}-d_6$): 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, $\text{DMSO}-d_6$): δ 119.8 (q, $J = 292$ Hz), 79.2 (m, $J = 29.6$ Hz), 66.8, 38.3. ^{19}F NMR (376 MHz, $\text{DMSO}-d_6$): δ -69.22 (s). MS (+ESI) m/z : $[\text{M} - \text{Cl}]^+$ Found 294.20. These spectroscopic data are consistent with the literature values for the free base.²⁸

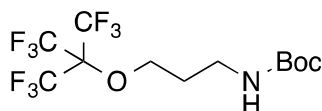
N-(2-(nonafluoro-*tert*-butoxy)ethyl)-acrylamide (7)



Fluorinated amine **6** (0.157 g, 0.50 mmol) and dry CH_2Cl_2 (2.5 mL) were added to a RBF. The flask was stoppered with a rubber septum, placed in an ice bath, 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 twenty minutes, and the reaction was allowed to stir overnight, warming to room temperature. After 20 hours, 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_2Cl_2 (3 x 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** ($R_f \sim 0.34$ in 30:70 EtOAc:PE) as a colorless oil. ^1H 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 : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_9\text{H}_9\text{F}_9\text{NO}_2$ 334.0495; Found 334.0497.

***N*-(*tert*-butyloxycarbonyl)-3-amino-1-(nonafluoro-*tert*-butoxy)propane (8)**

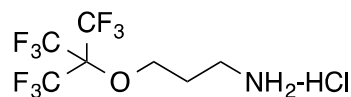


First, *N*-(*tert*-butyloxycarbonyl)-3-aminopropan-1-ol was synthesized. TEA (13.9, 100 mmol), di-*tert*-butyl dicarbonate, Boc_2O (5.24 g, 24.0 mmol), and THF (25 mL) were added to a RBF, which was stoppered with a rubber septum and placed in an ice bath. Then, 3-aminoethanol (1.58 mL, 20.0 mmol) was added to the RBF via syringe over the span of five minutes, and the reaction was stirred overnight for 20 hours, 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_2O . This crude was used in further steps without additional purification. ^1H 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, $J \sim 6$ 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 was purged with nitrogen for 15 minutes. 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 five minutes, at which point the flask was raised from the ice-water bath and allowed to warm to room temperature over 20 minutes. 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 hours, 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** ($R_f \sim 0.37$ in 90:10 PE:EtOAc) as a colorless oil. ^1H 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,

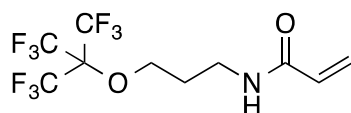
2H), 1.89 (quint, $J = 6.2$ Hz, 2H), 1.44 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3): δ 156.2, 120.6 (q, $J = 293$ Hz), 79.95 (m, $J = 29.7$ Hz), 79.46, 68.0, 37.3, 30.3, 28.3. ^{19}F NMR (376 MHz, CDCl_3): δ -70.82 (s). HRMS (+ESI) m/z : $[\text{M} - \text{C}_4\text{H}_7]^+$ Calcd for $\text{C}_8\text{H}_9\text{F}_9\text{NO}_3$ 338.0444, found 338.04395.

3-amino-1-(nonafluoro-*tert*-butoxy)propane hydrochloride (**9**)



To a RBF was added **8** (0.635 g, 1.62 mmol) along with Et_2O (3 mL). Concentrated HCl (270 μL , 3.2 mmol) was dripped into the flask over 10 minutes. The flask was stoppered and allowed to stir for 20 hr, 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_2O caused a phase separation, and a small pipette 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 $^\circ\text{C}$). ^1H NMR (400 MHz, $\text{DMSO}-d_6$): 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, $\text{DMSO}-d_6$): 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, $\text{DMSO}-d_6$): δ -69.56 (s). HRMS (+ESI) m/z : $[\text{M}]^+$ Calcd for $\text{C}_7\text{H}_9\text{F}_9\text{NO}$ 294.0546; Found 294.0555.

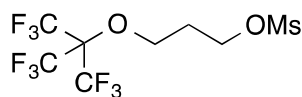
N-(3-(nonafluoro-*tert*-butoxy)propyl)acrylamide (**10**)



Fluorinated amine **9** (0.230 g, 0.697 mmol) and dry CH_2Cl_2 (2.0 mL) were added to a RBF. The flask was stoppered with a rubber septum, placed in an ice bath, 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 twenty minutes, and the reaction was allowed to stir overnight, warming to room temperature. After 20 hours, 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_2Cl_2 (3 x 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 $\text{EtOAc}:\text{PE}$, increasing to 50:50 $\text{EtOAc}:\text{PE}$, yielded 0.151 g (62%) of product **10** (R_f ~0.50 in 50:50 $\text{EtOAc}:\text{PE}$) as a colorless oil. ^1H 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, $J = 6.3$

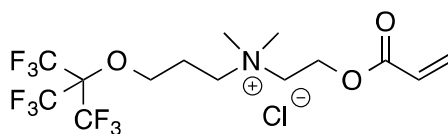
Hz, 2H), 1.98 (quint, $J = 6.2$ Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3): δ 165.9, 130.7, 126.7, 120.5 (q, $J = 292$ Hz), 79.8 (m, $J = 29.6$ Hz), 68.5, 36.9, 29.5. ^{19}F NMR (376 MHz, CDCl_3): δ -70.86 (s). HRMS (+ESI) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{10}\text{H}_{11}\text{F}_9\text{NO}_2$ 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_2Cl_2 (12 mL). The flask was sealed with a rubber stopper and placed in an ice bath. After five minutes, mesyl chloride (0.62 mL, 8.0 mmol) was added via syringe over the span of five minutes. 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_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 (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 %) of unreacted mesyl chloride. This crude was used in further steps without additional purification. ^1H 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 : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_8\text{H}_9\text{F}_9\text{O}_4\text{SNa}$ 394.9981; Found 394.9974.

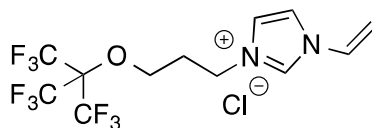
N-(2-(acryloyloxy)ethyl)-*N,N*-dimethyl-3-(nonafluoro-*tert*-butoxy)propan-1-aminium chloride (**12**)



Fluorinated mesylate **11** (0.744 g, 2.00 mmol) was added to a 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 hours 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_3H form) by first eluting non-charged constituents with Et_2O . 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. ^1H NMR ($\text{DMSO}-d_6$): δ 6.38 (dd, $J = 17.2$, ~ 1 Hz, 1H), 6.19 (dd, $J =$

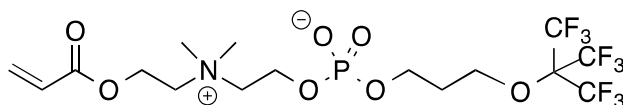
17.2 Hz, $J = 10.6$ Hz, 1H), 6.02 (dd, $J = 10.6$, ~ 1 Hz, 1H), 4.54 (s, 2H), 4.17 (t, 5.8 Hz, 2H), 3.78 (t, 4.6 Hz, 2H), 3.48 (m, 2H), 3.15 (s, 6H), 2.16 (m, 2H). ^{13}C NMR (100 MHz, DMSO- d_6): δ 164.8, 132.5, 127.7, 119.9 (q, $J = 292$ Hz), 79.2 (m, $J = 29.9$ Hz), 67.8, 61.9, 60.3, 57.9, 50.8, 23.0. ^{19}F NMR (376 MHz, DMSO- d_6): δ -69.92 (s). HRMS (+ESI) m/z : $[\text{M}]^+$ Calcd for $\text{C}_{14}\text{H}_{19}\text{F}_9\text{NO}_3$ 420.1227; Found 420.1219.

3-(3-(nonafluoro-*tert*-butoxy)propyl)-1-vinyl-1*H*-imidazol-3-ium chloride (**13**)



Fluorinated mesylate **11** (0.744 g, 2.00 mmol) was added to a 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 into a sand bath at 80 °C for 24 hours 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 (-SO₃H form) by first eluting non-charged constituents with Et₂O. 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. ^1H 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 : $[\text{M}]^+$ Calcd for $\text{C}_{12}\text{H}_{12}\text{F}_9\text{N}_2\text{O}$ 371.0811; Found 371.0814.

2-((2-(acryloyloxy)ethyl)dimethylammonio)ethyl 3-(3-(nonafluoro-*tert*-butoxy)propyl) phosphate (**14**)

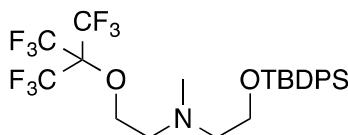


First, 2-(3-(nonafluoro-*tert*-butoxy)propoxy)-1,3,2-dioxaphospholane 2-oxide was synthesized. Fluorinated alcohol **1** (1.47 g, 5.00 mmol) was added to a flame-dried RBF. The flask was then subjected to vacuum for several minutes and recharged with nitrogen; this was repeated a second time. Next, dry 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/N₂(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 hours, the copious white precipitate was filtered off with repeated washing with Et₂O (6 x 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 ($R_f \sim 0.24$ in 60:40 EtOAc:PE) as a colorless oil. ^1H 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 x 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 $^\circ\text{C}$ and allowed to stir for 5 days. After cooling to room temperature, Et_2O (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 pipette, and the resulting gummy white solid was washed three times with Et_2O through a settling/pipette 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, then precipitated by the addition of Et_2O (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. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): 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, $\text{DMSO}-d_6$): 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, $\text{DMSO}-d_6$): δ -69.77 (s). ^{31}P NMR (162 MHz, $\text{DMSO}-d_6$): δ -0.86 (s). HRMS (+ESI TOF) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{16}\text{H}_{24}\text{F}_9\text{NO}_7\text{P}$ 544.1141; Found 544.1138.

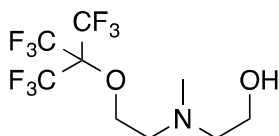
2-((*tert*-butyldiphenylsilyl)oxy)-*N*-methyl-*N*-(2-((nonafluoro-*tert*-butoxy)ethyl)-ethan-1-amine) (15)



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 minutes. Stirring was continued overnight at room temperature until the reaction was quenched by the addition of Et₂O (40 mL), deionized H₂O (20 mL), and saturated sodium bicarbonate (20 mL). The aqueous layer was washed with a second aliquot of Et₂O (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 % of the disubstituted product. This crude, a colorless oil, was used in further steps without additional purification. ¹H NMR (400 MHz, CDCl₃): 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). ¹³C NMR (100 MHz, CDCl₃): δ 135.6, 133.7, 129.7, 127.8, 62.1, 59.16, 59.13, 58.5, 42.4, 26.9, 19.2.

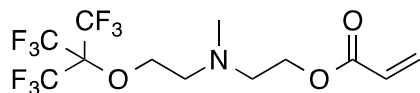
Next, triphenylphosphine (1.57g, 6.0 mmol) was added to a flame-dried RBF along with the TBDPS-protected alcohol from above (1.42 g, 4.0 mmol). The flask was stoppered with a rubber septum and was purged with nitrogen for 15 minutes. Dry THF (15 mL) was added via syringe and the flask was placed in an ice-bath. DEAD (0.94 mL, 6.0 mmol) was added via syringe over five minutes, at which point the flask was raised from the ice-water bath and allowed to warm to room temperature over 20 minutes. 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 hours, 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* ~0.25 in 90:10 PE:EtOAc) as a colorless oil. ¹H NMR (400 MHz, CDCl₃): 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). ¹³C NMR (100 MHz, CDCl₃): 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. ¹⁹F NMR (376 MHz, CDCl₃): δ -70.90 (s). HRMS (+ESI) *m/z*: [M + H]⁺ Calcd for C₂₅H₃₁F₉NO₂Si 576.1986; Found 576.1996.

2-(2-((nonafluoro-*tert*-butoxy)ethyl)(methyl)amino)ethan-1-ol (**16**)



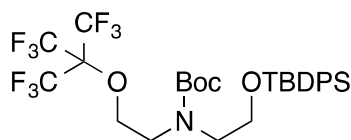
TBDPS-protected fluoro-alcohol **15** (1.72 g, 2.98 mmol) was added to a RBF along with TBAF·H₂O (1.89 g, 6.0 mmol) and stirred at room temperature for six hours. The solvent was then removed under reduced pressure to yield an oil that was transferred to a separatory funnel with a saturated solution 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* ~0.15 in 80:20 EtOAc:PE) as a colorless oil. ¹H NMR (400 MHz, CDCl₃): 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). ¹³C NMR (100 MHz, CDCl₃): δ 120.4 (q, *J* = 292 Hz), 79.9 (m, *J* = 29.7 Hz), 67.8, 59.1, 58.5, 56.6, 41.9. ¹⁹F NMR (376 MHz, CDCl₃): δ -70.86 (s). HRMS (+ESI) *m/z*: [M + H]⁺ Calcd for C₉H₁₃F₉NO₂ 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, cooled for five minutes, and acryloyl chloride (0.32 mL, 4.0 mmol) was added over 15 minutes. The reaction was stirred overnight, warming to room temperature, for 14 hours, then was 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* ~0.32 in 20:80 EtOAc:PE) as a very light yellow oil. ¹H NMR (400 MHz, CDCl₃): 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* ~ 6 Hz, 4H), 2.37 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): 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. ¹⁹F NMR (376 MHz, CDCl₃): δ -70.85 (s). HRMS (+ESI) *m/z*: [M + H]⁺ Calcd for C₁₂H₁₅F₉NO₃ 392.0914; Found 392.0903.

tert-butyl (2-((*tert*-butyldiphenylsilyl)oxy)ethyl)(2-(nonafluoro-*tert*-butoxy)ethyl)carbamate (**18**)

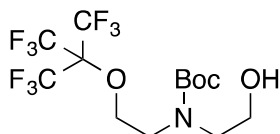


First, 2-((2-((tert-butylidiphenylsilyl)oxy)ethyl)amino)ethan-1-ol was synthesized: diethanolamine (2.47 g, 23.5 mmol), imidazole (1.06 g, 15.6 mmol), and DMF (20 mL) were added to a flame-dried RBF equipped with a rubber septum and flushed with nitrogen. *Tert*-butyldiphenylsilyl chloride (2.00 mL, 7.79 mmol) was added via syringe over a span of 25 minutes. Stirring was continued overnight at room temperature until the reaction was quenched by the addition of Et₂O (40 mL), deionized H₂O (20 mL), and saturated sodium bicarbonate (20 mL). The aqueous layer was washed with a second aliquot of Et₂O (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, which consisted of 89 mol % monoprotected product (5.8 mmol, 74% yield) and 11 mol % of the disubstituted product. This crude, a colorless oil, was used in further steps without additional purification. ¹H NMR (400 MHz, CDCl₃): 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). ¹³C NMR (100 MHz, CDCl₃): 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, Boc₂O (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 hours, 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* ~0.29 in 70:30 PE:EtOAc) as a colorless, viscous oil. ¹H NMR (400 MHz, CDCl₃): δ 7.64-7.67 (m, 4H), 7.37-7.43 (m, 6H), 3.82/3.75 (bs/t, *J* = 5.2 Hz, 2H, rotomers), 3.74 (t, *J* = 5.6 Hz, 2H), 3.47 (distorted q, *J* ~ 4 Hz, 2H), 3.4/2.7 (bs, 1H, rotomers), 3.39 (broad t, *J* ~ 5 Hz 1H), 1.48/1.38 (s, 9H, rotomers), 1.05 (s, 9H). ¹³C NMR (100 MHz, CDCl₃): δ 157.4, 135.7, 133.2, 129.9, 127.9, 80.4/80.0 (rotomers), 62.97/62.2 (rotomers), 62.85, 52.0, 51.1/50.8 (rotomers), 28.5 (broad, rotomers), 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 was purged with nitrogen for 15 minutes. 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 ten minutes, at which point the flask was raised from the ice-water bath and allowed to warm to room temperature over 20 minutes. 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 hours, 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 ~0.58 in 95:5 PE:EtOAc) as a colorless oil. ^1H 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, rotomers), 3.77/3.70 (t, J = 5.2/5.8 Hz, 2H, rotomers), 3.53-3.57 (m, 2H), 3.39-3.45 (m, 2H), 1.45/1.37 (s, 9H, rotomers), 1.04 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3): δ 155.4/155.1 (rotomers), 135.6, 133.5, 129.9, 127.9, 120.5 (q, J = 292 Hz), 80.16/80.03 (rotomers), 79.7 (m, J = 30 Hz), 69.07/68.56 (rotomers), 62.9, 51.2/50.5 (rotomers), 48.6/48.3 (rotomers), 28.48/28.42 (rotomers), 26.9, 19.2. ^{19}F NMR (376 MHz, CDCl_3): δ -70.98 (s). HRMS (+ESI) m/z : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{29}\text{H}_{36}\text{F}_9\text{NO}_4\text{SiNa}$ 684.2162; Found 684.2166.

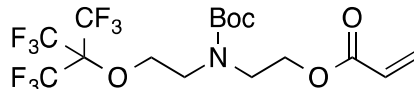
***tert*-butyl (2-(nonafluoro-*tert*-butoxy)ethyl)(2-hydroxyethyl)carbamate (**19**)**



TBDPS-protected fluoro-aminoalcohol **18** (0.731 g, 1.11 mmol) was added to a RBF along with TBAF·H₂O (1.11 g, 3.52 mmol) and stirred at room temperature for five hours. 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 ~0.37 in 60:40 PE:EtOAc) as a colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 4.22/4.15 (bs, 2H, rotomers), 3.75 (bs, 2H), 3.52 (distorted q, J ~ 5.2 Hz, 2H), 3.45 (distorted q, J ~ 4.4 Hz, 2H), 2.8 (bs, 1H), 1.46 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3): δ 156.8/155.5 (rotomers), 120.4 (q, J = 292 Hz), 81.05/80.63 (rotomers), 79.7 (m, J = 29.8 Hz), 68.9/68.5 (rotomers), 62.6/61.8 (rotomers), 51.8, 48.6,

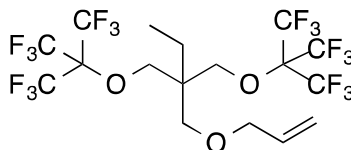
28.4. ^{19}F NMR (376 MHz, CDCl_3): δ -70.93/-70.96 (s, rotomers). HRMS (+ESI) m/z : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{13}\text{H}_{18}\text{F}_9\text{NO}_4\text{Na}$ 446.0984; Found 446.0996.

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, cooled for five minutes, and acryloyl chloride (0.16 mL, 2.0 mmol) was added over 15 minutes. The reaction was stirred overnight, warming to room temperature, for 14 hours, then was 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 ~0.31 in 90:10 PE:EtOAc) as a colorless oil. ^1H 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, rotomers), 4.21/4.14 (t, J = 5.2 Hz, 2H, rotomers), 3.49-3.58 (m, 4H), 1.456/1.450 (s, 9H, rotomers). ^{13}C NMR (100 MHz, CDCl_3): δ 166.1, 155.25/154.99 (rotomers), 131.3, 128.3, 120.4 (q, J = 29.2 Hz), 80.7, 79.9 (m, J = 29.6 Hz), 68.96/68.48 (rotomers), 62.98/62.91 (rotomers), 48.3/48.1 (rotomers), 47.5, 28.4. ^{19}F NMR (376 MHz, CDCl_3): δ -70.94/70.98 (s, rotomers). HRMS (+ESI) m/z : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{16}\text{H}_{20}\text{F}_9\text{NO}_5\text{Na}$ 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-ethylpropane-1,3-diol (0.435 g, 2.5 mmol). The flask was stoppered with a rubber septum and was purged with nitrogen for 15 minutes. 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 five minutes, at which point the flask was raised from the ice-water bath and allowed to warm to room temperature over 20 minutes. 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 hours, 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 ~0.82 in 90:10 PE:EtOAc) as a colorless liquid. ^1H 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 : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{17}\text{H}_{17}\text{F}_{18}\text{O}_3$ 611.0885; Found 611.0881.

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Supporting Information. NMR spectra of all numbered compounds and synthetic intermediates.

This material is available free of charge via the Internet at <http://pubs.acs.org>.

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