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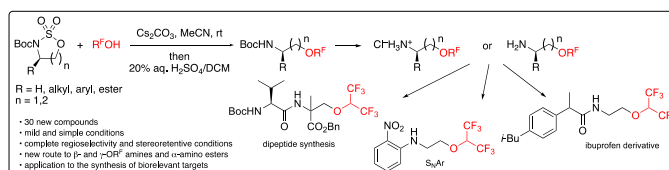
Amphiphilic Polyfluorinated Amino Ethers from Cyclic Sulfamidates

Nicolas Marie,[†] Jun-An Ma,[‡] Dominique Cahard^{*,†}

[†] UMR 6014 COBRA, CNRS, Université de Rouen-Normandie, INSA Rouen, IRCOF, 76821 Mont Saint Aignan, France

[‡] Department of Chemistry, Tianjin Key Laboratory of Molecular Optoelectronic Sciences, and Collaborative Innovation Center of Chemical Science and Engineering, Tianjin University, Tianjin 300072, China

Supporting Information Placeholder



ABSTRACT: The regioselective ring-opening of cyclic sulfamidates was achieved by means of nucleophilic polyfluorinated alkoxides to access achiral and chiral β - and γ -OR^F amines and α -amino esters. Subsequent transformations provide free-amines ready for incorporation into bioactive substances through amide bond formation or nucleophilic aromatic substitution.

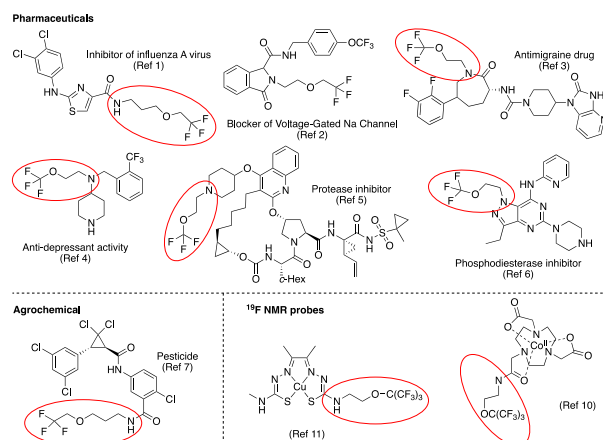
INTRODUCTION

There are many bioactive molecules featuring the N-(CH₂)_n-OR^F fragment that exhibit, to cite but a few, inhibition activity against the influenza A virus,¹ blocker of voltage-gated sodium channel Na_v 1.7 activity,² effect in the relief of migraine,³ dual inhibition of serotonin and norepinephrine reuptake,⁴ HCV NS3/4a protease inhibition,⁵ phosphodiesterase 5 inhibition,⁶ as well as pesticidal activity⁷ (Figure 1). Of particular interest, the amino nonafluoro-*tert*-butyl ether motif was developed in diverse applications such as in materials science as spacer in layered hybrid perovskites⁸ or as water-repellent perovskites,⁹ in medical ¹⁹F nuclear magnetic resonance imaging,¹⁰⁻¹² and in chemical tagging¹³ that include amino acid derivatives for studying dynamic biological processes (Figure 1).^{14,15} Because retention in the human body of polyfluorinated chemicals represents a health concern, these amphiphilic assemblies featuring a hydrophobic R^F motif tethered to a hydrophilic ionic amino function have the benefit of an enhanced body clearance than unfunctionalized R^F compounds.¹⁶

The N-(CH₂)_n-OCF₃ fragment was previously obtained via an oxidative desulfurization-fluorination step of intermediate xanthates using HF/Pyridine.^{17,18} Since polyfluoro alcohols are sufficiently acidic to be used as nucleophiles,¹⁹ the Mitsunobu etherification allowed to access N-(CH₂)_n-OCH(CF₃)₂²⁰ and N-(CH₂)_n-OC(CF₃)₃ derivatives.^{8,13,21} This latter motif could also be constructed by bromide displacement with NaOC(CF₃)₃ and NaI in DMF at 80 °C.^{11,22} However, it was found that these methods are limited and not suitable for all possible R^F groups. We thought it would be interesting to provide a new method that could meet the expectations for a wide variety of polyfluorinated moieties. In this context, we propose cyclic sulfamidates as the chemical platform of choice for ring-opening operation by means of polyfluorinated alkoxides. However, the reaction of cyclic sulfamidates was reputed challenging with “classic” alkoxides. Indeed, strong oxygen nucleophiles such as sodium methoxide turned out to be reluctant partners in this reaction.²³⁻²⁵ Phenoxide and derivatives are weaker bases than alkoxides and a class of oxygen

nucleophiles that has demonstrated synthetic utility in the ring-opening of cyclic sulfamidates.²⁶⁻³² We surmised that the electron-withdrawing property of fluorine atoms in polyfluorinated alkoxides could impart appropriate nucleophilicity to allow smooth reaction with cyclic sulfamidates.

Figure 1. Representative bioactive molecules featuring a polyfluoroalkoxy alkylamino motif.



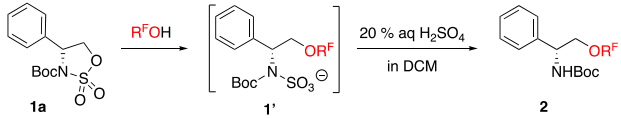
Hereafter, we report our investigation of the nucleophilic displacement on cyclic sulfamidates by means of polyfluorinated alkoxides, the access to β - and γ -OR^F amines and α -amino esters, and their introduction into bioactive substances for pharmaceutical and agrochemical applications.^{33,34}

RESULTS AND DISCUSSION

We initially examined the nucleophilic displacement of the readily available D-phenylglycine-derived cyclic sulfamidate **1a** with two of the most popular fluorinated alcohols, 2,2,2-trifluoroethanol (TFE) and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP). The reaction proceeded through the sulfamic acid

intermediate **1'** (Table 1), which is further converted into the desired product **2** by hydrolysis with the aid of a 20% aqueous H₂SO₄ solution. We selected alkali metal carbonates as base to generate the requested alkoxides; in particular, the use of cesium carbonate in DMF efficiently provided alkoxides of TFE and HFIP to end up with products **2a,b** in 71-75% yields (Table 1, entries 1-2). Additional experiments exploiting HFIP as oxygen nucleophile revealed that 1.5 equiv of both the base and HFIP enhanced the yield in **2a** to 80% (Table 1, entry 3). Changing the solvent to acetonitrile together with investigation of the carbonate base allowed on one hand to determine that acetonitrile, a polar and lower boiling point solvent compared to DMF, is suitable for the reaction and, on the other hand, to confirm Cs₂CO₃ as the optimum base (Table 1, entries 4-7). The nature of the base cation was important as the more covalent lithium carbonate did not provide the desired product **2** while increasing the ionic character of the base from Na, K and Cs allowed to reach increasing yields. We also noticed that the reaction time can be reduced to 3 h without erosion of the yield (Table 1, entries 7-9). Finally, an increase in the amount of alkoxide from 1.5 to 2 equiv nor a longer reaction time gave improved yields (Table 1, entry 10). Retention of the chiral integrity of the stereogenic center in **2a** (R^F = CH(CF₃)₂) was ascertained by HPLC analysis (see chromatograms in SI). This optimization

Table 1. Optimization of the reaction parameters with sulfamidate **1a**.^a



Entry	R ^F OH	Base	Solvent	Time (h)	Yield ^b (%)
1	TFE (1.2 eq)	Cs ₂ CO ₃ (1.2 eq)	DMF	20	71
2	HFIP (1.2 eq)	Cs ₂ CO ₃ (1.2 eq)	DMF	20	75
3	HFIP	Cs ₂ CO ₃	DMF	20	80
4	HFIP	Li ₂ CO ₃	CH ₃ CN	20	NR
5	HFIP	Na ₂ CO ₃	CH ₃ CN	20	29
6	HFIP	K ₂ CO ₃	CH ₃ CN	20	81
7	HFIP	Cs ₂ CO ₃	CH ₃ CN	20	82
8	HFIP	Cs ₂ CO ₃	CH ₃ CN	6	82
9	HFIP	Cs ₂ CO ₃	CH ₃ CN	3	82
10	HFIP (2.0 eq)	Cs ₂ CO ₃ (2.0 eq)	CH ₃ CN	20	82

^a Reaction conditions: cyclic sulfamidate **1a** (0.167 mmol), R^FOH (1.5 equiv unless otherwise noted), base (1.5 equiv unless otherwise noted), solvent (0.76 mL), 25 °C; then, 20% aq. H₂SO₄/DCM (1:1). ^b Isolated yields. NR: No reaction.

study demonstrated a straightforward ring-opening of cyclic sulfamidate **1a** by regioselective nucleophilic substitution at the C–O bond with two polyfluorinated alkoxides. Therefore, the sulfamidate scope as well as the alkoxide scope must be explored (Scheme 1). For this purpose, we first examined eight different poly- or perfluorinated alcohols (Scheme 1, left). Under the optimized conditions, the reactions performed

well with linear, branched and aromatic fluorinated alkoxides featuring 3 to up to 17 fluorine atoms to afford the desired products **2a-g** in 55-90% yield. Even a diol was effective in order to get a symmetrical difunctional compound with a polyfluorinated spacer arm **2h** as potential structure for the construction of new materials.³⁵ All the synthesized molecules were new and were fully characterized (see SI).

The second part of the scope involved the sulfamidate keeping HFIP as the oxygen nucleophile (Scheme 1, right). 1,2-Sulfamidate **1a** synthesized from D-phenylglycine, **1i** (from L-phenylalanine), **1j** (from L-leucine), **1k** (from L-valine), **1l** (from L-isoleucine), **1m** (from L-alanine) gave excellent yields (85-96%) of the corresponding β-OR^F amines **2a,i-m**. Simpler achiral five-membered ring sulfamidate **1n** provided the corresponding β-OR^F amine **2n** in a good 85% yield. A modification of the *N*-protection of the sulfamidate from Boc to Cbz afforded the β-OR^F amine **2o** in an excellent 95% yield whereas the *p*-methoxybenzyl protective group (PMB) failed to give the desired product (Scheme 1, reluctant sulfamidate **1aa**). In this latter case, the first step of nucleophilic displacement took place leading to **1'** intermediate but the acidic treatment did not release the sulfamic moiety. We next synthesized and investigated six-membered cyclic 1,3-sulfamidates that possess a lower ring strain. Simple sulfamidate **1p** did allow access to the γ-OR^F amine **2p** but in a moderate 43% yield because of its volatility. As a limitation, we found that the more hindered cyclic sulfamidate analogue that features a *gem*-dimethyl group failed to react (Scheme 1, reluctant sulfamidate **1ab**).³⁶ Higher yields were obtained as soon as we employed 1,3-sulfamidates **1q** and **1r** featuring a phenyl ring; these two examples provided γ-OR^F amines **2q** and **2r** in 83 and 85% yield, respectively.

To further illustrate the potential of the method, we focused on ester functionalized sulfamidates **1x** and **1y** that were prepared from L-serine ethyl and benzyl ester, respectively (Table 2). The aim was to deliver non-proteogenic fluorinated amino acids that are important tools in the design of new peptide-based biomaterials.^{37,38} In this context, we attempted to prepare β-OR^F tertiary α-amino esters **2x** and **2y** but it failed and only dehydroalanine elimination products **3x** and **3y** were isolated (Table 2). The formation of such side-products is a recurrent problem in the chemistry of sulfamidates that is caused by a competition between nucleophilic displacement and deprotonation of the α-hydrogen atom followed by elimination.²³ In order to avoid or at least to limit this undesirable event, we surmised that replacing the ester by an amide function as in **1z** (Table 2) would render less acidic the α-hydrogen atom.

Scheme 1. Synthesis of β - and γ -OR^F amines from sulfamidates **1**.

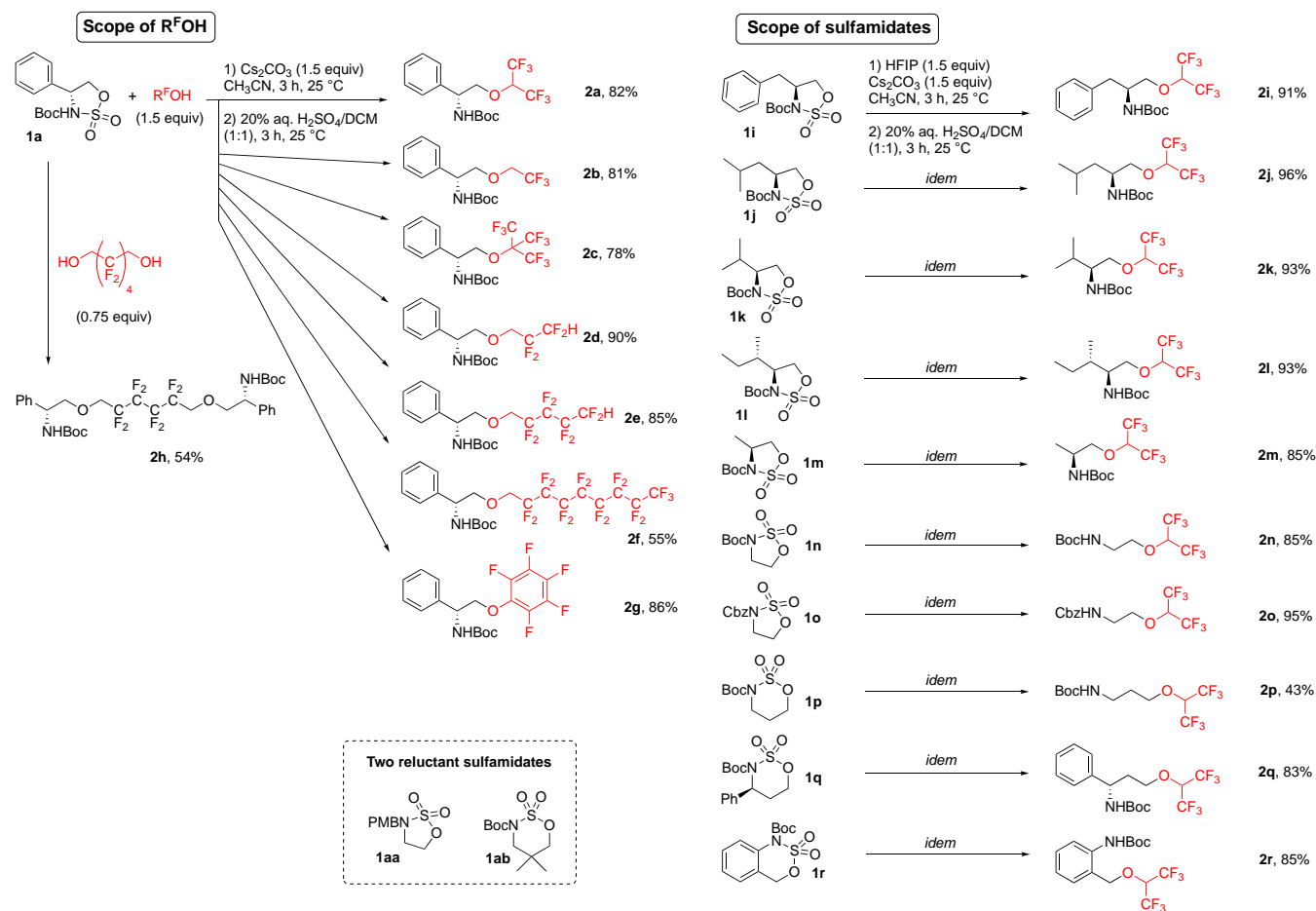


Table 2. Attempts to prepare β -OR^F tertiary α -amino esters.

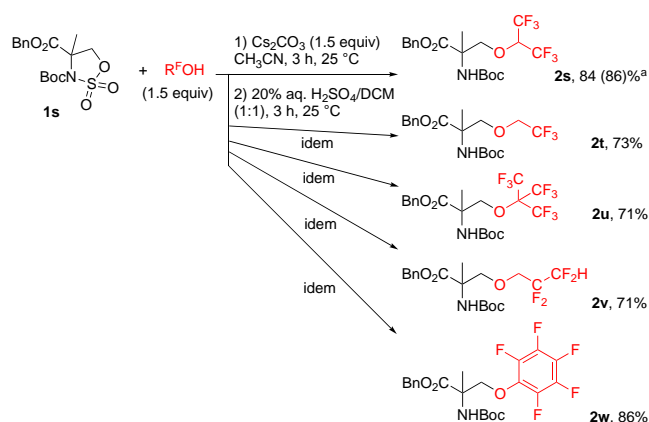
Sulfamidate	Expected product	Obtained product
1x	2x	3x
1y	2y	3y
1z	2z	2z + 3z 100% conv 2z/3z 54:46 2z, 17% yield ^a

^a Yield of isolated pure product was low because of difficult chromatographic separation from **3z**.

With substrate **1z**, we were pleased to observe the expected β -OR^F tertiary α -amino amide **2z** (mixture of rotamers) albeit accompanied by elimination product **3z** in a 54:46 ratio (Table 2). Further modifications of the experimental conditions did not improve the yield of **2z**. In the literature, one report by Peregrina and coworkers described the ring-opening of a cyclic sulfamidate derived from α -methylserine with carbohydrates C1-O-nucleophiles.³⁹ This sulfamidate featured a quaternary α -carbon atom to preclude the elimination side-reaction. In the same vein, the same research group disclosed access to α -hydroxy and α -alkoxy $\beta^{2,2}$ -amino acids from α -methyl isoserine.⁴⁰⁻⁴² We thus prepared the sulfamidate **1s** from racemic α -methylserine and it was engaged in the construction of β -OR^F quaternary α -amino esters with five different polyfluorinated alcohols (Scheme 2). When HFIP was used, the desired product **2s** was obtained in 84% yield and 86% on a gram-scale experiment. Other linear, branched and aromatic polyfluorinated alcohols afforded the β -OR^F α -amino esters **2t-w** in yields ranging from 71 to 86% (Scheme 2).

Although we carried out this series of experiments using racemic α -methylserine, we have established the experimental conditions for possible extension to optically pure quaternary amino esters.

Scheme 2. Synthesis of β -OR^F quaternary α -amino esters.



^a All reactions were carried out on a 0.167 mmol scale except this case in which 2.42 mmol of $1\mathbf{s}$ was used (yield in brackets).

The development of this strategy offered a range of novel *N*-Boc β - and γ -OR^F amines and α -amino esters as a class of R^FO-containing building blocks. The *N*-Boc deprotection could easily be achieved by treatment with trifluoroacetic acid in DCM at rt for 2 h to access non-volatile amines such as $4\mathbf{a}$ and $4\mathbf{s}$ (Scheme 3a). The resulting free amine $4\mathbf{s}$ was engaged in a coupling reaction with Boc-Val-OH in the presence of 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (HATU) and *N,N*-diisopropylethylamine (DIPEA) in DMF at rt for 18 h. The dipeptide 5 was isolated in 81% yield as a mixture of two diastereomers due to the use of racemic $4\mathbf{s}$ (Scheme 3b). In the case of volatile amines, the *N*-deprotection was carried out with the aid of HCl/dioxane (4 M) to end up with the corresponding hydrochloride such as 6 from $2\mathbf{n}$ (Scheme 3c). Next, 6 was engaged in the synthesis of an ibuprofen derivative 7 (Scheme 3d). Alternative use of 6 was illustrated in a nucleophilic aromatic substitution of 1-fluoro-2-nitrobenzene to afford compound 8 (Scheme 3e).

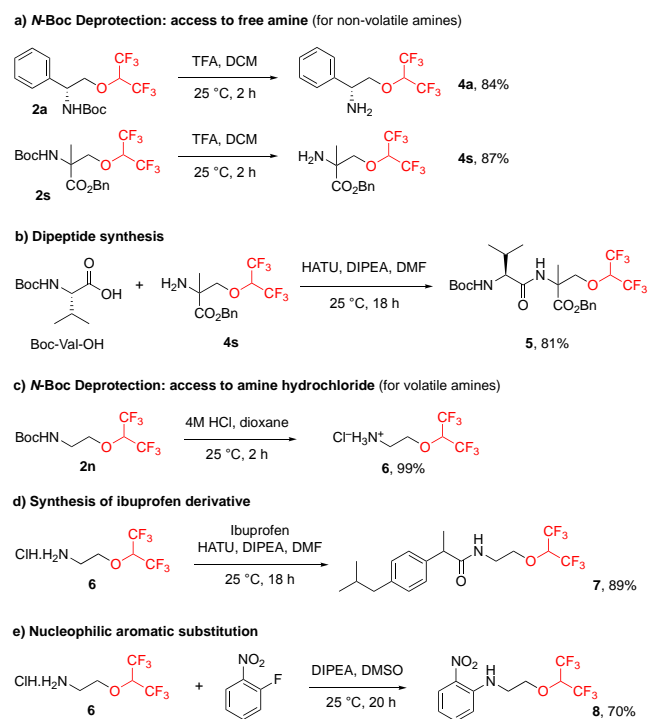
CONCLUSIONS

The ring-opening of versatile cyclic sulfamidates by means of fluorinated nucleophiles was reported in the literature that include formation of C-F,^{29,43-46} C-R,⁴⁷ and C-SCF₃⁴⁸ bonds but the construction of C-OR^F is still a rare disconnection.⁴⁹ We have filled this gap by investigating the regioselective ring-opening of 1,2- and 1,3-cyclic sulfamidates with diverse polyfluorinated alkoxides. Our approach offered a straightforward access to β - and γ -OR^F amines and α -amino esters via an unprecedented disconnection. Facile *N*-Boc deprotection afforded amphiphilic free amine or hydrochloride ready for nucleophilic aromatic substitutions or amide coupling as demonstrated in a dipeptide synthesis. As the N-(CH₂)_n-OR^F fragment is becoming more easily available, we expect it will be frequently exploited for the functionalization of relevant biomolecules.

Experimental section

All experiments were conducted under a fume-hood. Analytical thin-layer chromatographies were performed on silica gel aluminum plates with F-254 indicator and visualized by UV

Scheme 3. Post-transformation reactions and synthetic applications.



light (254 nm) and visualized by UV light (254 nm) and/or chemical staining with a ninhydrin or a KMnO₄ solution. Column chromatographies were performed with irregular silica (40-63 μm). NMR spectra were recorded on a Bruker DXP 300 instrument at 300 MHz for ¹H, 75.5 MHz for ¹³C{¹H} and 282 MHz for ¹⁹F in CDCl₃ at room temperature unless otherwise stated. Chemical shifts (δ) were quoted in parts per million (ppm) relative to the residual peak of CHCl₃ ($\delta_{\text{H}} = 7.26$ ppm and $\delta_{\text{C}} = 77.16$ ppm) and internal standard CFCl₃ ($\delta_{\text{F}} = 0.00$ ppm). Spectra are reported as follows: chemical shift δ (ppm), multiplicity (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, td = triplet of doublets, q = quartet, quint = quintet, sext = sextet, sept = septet, m = multiplet or complex pattern), integration and coupling constant. Infrared spectra were recorded on a PerkinElmer Spectrum 100. High-resolution mass spectra (HRMS) were recorded on a Waters LCT Premier with micro-TOF analyzer. Optical rotations were recorded on a PerkinElmer Polarimeter 341 at 20 °C in chloroform. Chiral HPLC analyses were carried out on a ThermoFisher UHPLC system Ultimate with a PDA detector, wavelengths were monitored at 210 nm and controlled with Chromeleon. Chiral HPLC analyses were performed with chiral stationary phase from Daicel (250 mm x 4.6 mm, 5 μm particle size) at 20 °C. Commercially available chemicals were obtained from Fisher scientific, Sigma Aldrich, Alfa Aesar, TCI, Fluorochem and used as received unless otherwise stated.

Tetrahydrofuran (THF), diethyl ether (Et₂O), and toluene were distilled from sodium / benzophenone prior to use; CH₂Cl₂ was distilled from CaH₂. Other dry solvents were used as received from suppliers.

Synthesis of cyclic sulfamidates 1.

A slightly modified procedure by Brimble and co-workers was followed.⁵⁰ A solution of thionyl chloride (2.4 equiv) and imidazole (3.1 equiv) in anhydrous acetonitrile (0.23 M) was cooled to -40 °C under nitrogen atmosphere. *N*-Protected hydroxy-amino ester or aminoalcohol (1.0 equiv) in anhydrous acetonitrile (0.28 M) was added dropwise to the mixture. The reaction was stirred for 10 minutes then triethylamine (1.7 equiv) was added. The mixture was allowed to warm to room temperature and was stirred for one hour. The reaction was diluted with water and EtOAc, the aqueous phase was extracted with EtOAc (3 x), the combined organic layers were washed with brine, dried over MgSO₄, filtered and the solvent was removed under reduced pressure to afford the cyclic sulfamidite. The crude sulfamidite was dissolved in anhydrous acetonitrile (0.14 M) and cooled to 0 °C. To this solution was added NaIO₄ (1.05 equiv), RuCl₃·H₂O (0.7 mol%) and water (0.28 M) successively. The mixture was stirred for 1 hour, diluted with water and filtered through a pad of Celite. The filtrate was extracted with EtOAc (3x). The combined organic layers were washed with saturated NaHCO₃ solution and brine, dried over MgSO₄, filtered and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (eluent: cyclohexane/EtOAc 8:2) to give the desired product. All sulfamidates are known compounds.⁴⁸

General procedure for the ring-opening of cyclic sulfamidates 1.

To a solution of the cyclic sulfamidate (0.167 mmol, 1.0 equiv) in 0.76 mL of anhydrous acetonitrile were added sequentially R^FOH (0.251 mmol, 1.5 equiv) and Cs₂CO₃ (0.251 mmol, 1.5 equiv). The reaction mixture was stirred under nitrogen atmosphere at 25 °C for 3 h. Upon completion of the reaction (monitoring by TLC), the solvent was evaporated and the residue was dissolved back in dichloromethane (0.76 mL) and 20 % aqueous H₂SO₄ (0.76 mL). The resulting mixture was stirred vigorously at 25 °C for 3 h. Upon completion of the reaction (monitoring by TLC), NaHCO₃ saturated aqueous solution was then slowly added to the mixture until effervescence ceased. The aqueous layer was extracted with diethyl ether (3 x 15 mL). The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified by normal phase chromatography (irregular silica, 40-63 μm, 12 g, liquid loading, mobile phase gradient: from petroleum ether/ethyl acetate 100/0 to 80/20). The fractions containing the desired compound were combined and solvents evaporated in vacuo to give the pure compound. All β- and γ-ORF amines and α-amino esters are new compounds. Elimination products **3x-z** shown in Table 2 are known compounds (**3x** CAS [96846-37-6], **3y** CAS [94882-75-4], **3z** CAS [93953-13-0]). All compounds were purified under the conditions described above.

Tert-butyl (*R*)-2-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-1-phenylethyl)carbamate **2a**: White solid (53.0 mg, 82% yield); [α]_D²⁰ -15.9 (c 1.00, CHCl₃); HPLC analysis: Daicel Chiralcel

OJ-H, 250 mm, Ø 4.6 mm, heptane/iso-propanol = 95/5, 1.0 mL/min, λ = 210 nm, t(major) = 6.82 min, t(minor) = 6.07 min. ¹H NMR (300 MHz, CDCl₃) δ 7.35–7.17 (m, 5H), 5.09 (m, 1H), 4.83 (m, 1H), 4.14–3.94 (m, 3H), 1.37 (s, 9H); ¹⁹F NMR (282 MHz, CDCl₃) δ -74.31 (m, 6F); ¹³C{¹H} NMR (75 MHz, CDCl₃) δ 155.4, 138.7, 128.8, 128.1, 126.9, 121.5 (q, *J* = 286.7 Hz), 80.2, 76.3 (sept, *J* = 32.2 Hz), 75.9, 54.4, 28.4; ATR-FTIR (cm⁻¹): 3373, 2925, 1680, 1526, 1372, 1284, 1221, 1161, 1102, 699; HRMS (ESI⁻) *m/z*: [M+HCO₂]⁻ calcd for C₁₇H₂₀F₆NO₅ 432.1246, found: 432.1262.

Tert-butyl (*R*)-(1-phenyl-2-(2,2,2-trifluoroethoxy)ethyl)carbamate **2b**: White solid (43.1 mg, 81% yield); [α]_D²⁰ -24.6 (c 1.00, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.39–7.26 (m, 5H), 5.19 (m, 1H), 4.86 (m, 1H), 3.94–3.73 (m, 4H), 1.42 (s, 9H); ¹⁹F NMR (282 MHz, CDCl₃) δ -74.55 (t, *J* = 8.6 Hz, 3F); ¹³C{¹H} NMR (75 MHz, CDCl₃) δ 155.4, 139.6, 128.7, 127.8, 126.8, 123.9 (q, *J* = 279.8 Hz), 80.0, 75.4, 68.7 (q, *J* = 34.1 Hz), 54.2, 28.3; ATR-FTIR (cm⁻¹): 3386, 2980, 1679, 1519, 1366, 1281, 1239, 1151, 1100, 699; HRMS (ESI⁻) *m/z*: [M-H]⁻ calcd for C₁₅H₁₉F₃NO₃ 318.1317, found: 318.1306.

Tert-butyl (*R*)-(2-((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)-1-phenylethyl)carbamate **2c**: Colorless oil (59.1 mg, 78% yield); [α]_D²⁰ -14.2 (c 1.00, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.40–7.27 (m, 5H), 5.12–4.87 (m, 2H), 4.34–4.14 (m, 2H), 1.43 (s, 9H); ¹⁹F NMR (282 MHz, CDCl₃) δ -70.77 (s, 9F); ¹³C{¹H} NMR (75 MHz, CDCl₃) δ 155.2, 138.1, 128.9, 128.2, 126.9, 121.1 (q, *J* = 293.5 Hz), 80.3, 79.8 (m), 71.8, 54.4, 28.4; ATR-FTIR (cm⁻¹): 3377, 2982, 1688, 1526, 1368, 1245, 1151, 1012, 970, 698; HRMS (ESI⁻) *m/z*: [M+HCO₂]⁻ calcd for C₁₈H₁₉F₉NO₅ 500.1120, found: 500.1123.

Tert-butyl (*R*)-(1-phenyl-2-(2,2,3,3-tetrafluoropropoxy)ethyl)carbamate **2d**: White solid (53.0 mg, 90% yield); [α]_D²⁰ -20.7 (c 1.00, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.41–7.24 (m, 5H), 5.71 (tt, *J* = 53.1, 5.1 Hz, 1H), 5.15 (m, 1H), 4.87 (m, 1H), 3.94–3.67 (m, 4H), 1.43 (s, 9H); ¹⁹F NMR (282 MHz, CDCl₃) δ -125.70 (s, 2F), -140.32 (d, *J* = 53.1 Hz, 2F); ¹³C{¹H} NMR (75 MHz, CDCl₃) δ 155.4, 139.5, 128.8, 127.9, 126.7, 115.3 (tt, *J* = 249.7, 25.6 Hz), 108.5 (tt, *J* = 250.2, 33.3 Hz), 80.0, 75.4, 68.3 (t, *J* = 28.6 Hz), 54.2, 28.4; ATR-FTIR (cm⁻¹): 3364, 2992, 1682, 1530, 1352, 1275, 1165, 1139, 1100, 699; HRMS (ESI⁻) *m/z*: [M+H]⁺ calcd for C₁₆H₂₂F₄NO₃ 352.1536, found: 352.1530.

Tert-butyl (*R*)-(2-((2,2,3,3,4,4,5,5-octafluoropentyl)oxy)-1-phenylethyl)carbamate **2e**: White solid (64.2 mg, 85% yield) [α]_D²⁰ -18.8 (c 1.00, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.39–7.27 (m, 5H), 6.00 (tt, *J* = 52.2, 5.3 Hz, 1H), 5.19 (m, 1H), 4.87 (m, 1H), 3.98–3.77 (m, 4H), 1.42 (s, 9H); ¹⁹F NMR (282 MHz, CDCl₃) δ -120.25 (m, 2F), -126.17 (m, 2F), -130.90 (m, 2F), -137.81 (dm, 2F); ¹³C{¹H} NMR (75 MHz, CDCl₃) δ 155.4, 139.5, 128.7, 127.8, 126.8, 118.9–112.1 (m, 3CF₂), 107.5 (tt, *J* = 253.4, 31.2 Hz, CF₂H), 80.0, 75.8, 68.0 (t, *J* = 25.8 Hz), 54.2, 28.4; ATR-FTIR (cm⁻¹): 3383, 2984, 1682, 1519, 1364, 1279, 1163, 1127, 1054, 703; HRMS (API⁻) *m/z*: [M-H]⁻ calcd for C₁₈H₂₀F₈NO₃ 450.1315, found: 450.1311.

Tert-butyl (*R*)-(2-((2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,9-heptafluorononyl)oxy)-1-phenylethyl)carbamate **2f**: White solid, (61.0 mg, 55% yield); [α]_D²⁰ -13.9 (c 1.00,

CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.39–7.26 (m, 5H), 5.18 (m, 1H), 4.87 (m, 1H), 4.00–3.77 (m, 4H), 1.42 (s, 9H); ¹⁹F NMR (282 MHz, CDCl₃) δ -81.27 (t, *J* = 9.6 Hz, 3F), -119.96 (m, 2F), -122.44 (m, 6F), -123.22 (m, 2F), -123.82 (m, 2F), -126.64 (m, 2F); ¹³C{¹H} NMR (75 MHz, CDCl₃) δ 155.4, 139.6, 128.7, 127.8, 126.8, 122.6–108.3 (7 CF₂ + CF₃), 80.0, 75.8, 68.3 (t, *J* = 25.8 Hz), 54.2, 28.4; ATR-FTIR (cm⁻¹): 3377, 2994, 1687, 1526, 1368, 1280, 1196, 1151, 1012, 696; HRMS (ESI⁻) *m/z*: [M-H]⁻ calcd for C₂₂H₁₉F₁₇NO₃ 668.1093, found: 668.1089.

Tert-butyl (2*R*)-(2-(perfluorophenoxy)-1-phenylethyl)carbamate **2g**: White solid (58.0 mg, 86% yield) [α]_D²⁰ -7.3 (*c* 1.00, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.40–7.28 (m, 5H), 5.30 (m, 1H), 5.07–4.96 (m, 1H), 4.49–4.32 (m, 2H), 1.44 (s, 9H); ¹⁹F NMR (282 MHz, CDCl₃) δ -156.79 (m, 2F), -163.49 (m, 3F); ¹³C{¹H} NMR (75 MHz, CDCl₃) δ 155.3, 143.3 (m), 140.0 (m), 138.6 (m), 136.4 (m), 133.4 (m), 128.9, 128.1, 126.9, 80.2, 77.2, 54.5, 28.4; ATR-FTIR (cm⁻¹): 3378, 2982, 1680, 1514, 1281, 1158, 1028, 996, 756, 699; HRMS (API⁻) *m/z*: [M+HCO₂]⁻ calcd for C₂₀H₁₉F₅NO₅ 448.1183, found: 448.1188.

Di-*tert*-butyl ((*R,R'*)-(2,2,3,3,4,4,5,5-octafluorohexane-1,6-diyl)bis(oxy))bis(1-phenylethane-2,1-diyl)dicarbamate **2h**: Pale yellow solid (63.2 mg, 54% yield); [α]_D²⁰ -27.3 (*c* 1.00, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.44–7.28 (m, 10H), 5.35–5.12 (m, 2H), 4.95–4.77 (m, 2H), 4.06–3.62 (m, 8H), 1.41 (s, 18H); ¹⁹F NMR (282 MHz, CDCl₃) δ -120.23 (m, 4F), -124.42 (m, 4F); ¹³C{¹H} NMR (75 MHz, CDCl₃) δ 155.3, 139.6, 129.3 (m), 128.6, 127.6, 126.7, 126.2 (m), 79.8, 75.6, 68.2 (t, *J* = 24.8 Hz), 54.0, 28.3; ATR-FTIR (cm⁻¹): 3373, 2924, 1683, 1524, 1368, 1281, 1167, 1115, 1098, 700; HRMS (ESI⁻) *m/z*: [M-H]⁻ calcd for C₃₂H₃₉F₈N₂O₆ 699.2680, found: 699.2659.

Tert-butyl (*S*)-(1-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-3-phenylpropan-2-yl)carbamate **2i**: White solid (61.0 mg, 91% yield); [α]_D²⁰ -22.3 (*c* 1.00, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.38–7.23 (m, 5H), 4.81 (m, 1H), 4.13–3.95 (m, 2H), 3.89–3.76 (m, 2H), 2.92 (d, *J* = 7.5 Hz, 2H), 1.46 (s, 9H); ¹⁹F NMR (282 MHz, CDCl₃) δ -74.28 (m, 6F); ¹³C{¹H} NMR (75 MHz, CDCl₃) δ 155.4, 137.4, 129.4, 128.8, 126.9, 121.5 (q, *J* = 284.5 Hz), 79.9, 76.3 (sept, *J* = 32.2 Hz), 75.0, 51.7, 37.2, 28.4; ATR-FTIR (cm⁻¹): 3367, 2984, 1686, 1531, 1372, 1281, 1234, 1184, 1104, 687; HRMS (API⁻) *m/z*: [M-H]⁻ calcd for C₁₇H₂₀F₆NO₃ 400.1347, found: 400.1342.

Tert-butyl (*S*)-(1-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-4-methylpentan-2-yl)carbamate **2j**: White solid (58.7 mg, 96% yield); [α]_D²⁰ -35.0 (*c* 1.00, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 4.56 (m, 1H), 4.06 (sept, *J* = 5.9 Hz, 1H), 3.95–3.64 (m, 3H), 1.70–1.61 (m, 1H), 1.43 (s, 9H), 1.41–1.30 (m, 2H), 0.93 (d, *J* = 2.9 Hz, 3H), 0.90 (d, *J* = 2.8 Hz, 3H); ¹⁹F NMR (282 MHz, CDCl₃) δ -74.49 (m, 6F); ¹³C{¹H} NMR (75 MHz, CDCl₃) δ 155.4, 121.4 (q, *J* = 283.6 Hz), 79.5, 76.3 (sept, *J* = 32.2 Hz), 75.8, 48.5, 40.2, 28.3, 24.7, 22.9, 22.0; ATR-FTIR (cm⁻¹): 3363, 2976, 1683, 1531, 1370, 1278, 1220, 1186, 1099, 688; HRMS (API⁻) *m/z*: [M-H]⁻ calcd for C₁₄H₂₂F₆NO₃ 366.1504, found: 366.1506.

Tert-butyl (*S*)-(1-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-3-methylbutan-2-yl)carbamate **2k**: White solid (55.0 mg, 93% yield); [α]_D²⁰ -33.3 (*c* 1.00, CHCl₃); ¹H NMR (300 MHz,

CDCl₃) δ 4.65 (m, 1H), 4.06 (sept, *J* = 5.9 Hz, 1H), 3.97 (dd, *J* = 9.3, 3.4 Hz, 1H), 3.83 (dd, *J* = 9.3, 4.2 Hz, 1H), 3.54–3.40 (m, 1H), 1.97–1.80 (m, 1H), 1.43 (s, 9H), 0.96 (d, *J* = 5.2 Hz, 3H), 0.93 (d, *J* = 5.1 Hz, 3H); ¹⁹F NMR (282 MHz, CDCl₃) δ -74.47 (m, 6F); ¹³C{¹H} NMR (75 MHz, CDCl₃) δ 155.9, 121.6 (q, *J* = 283.6 Hz), 79.6, 76.3 (sept, *J* = 32.2 Hz), 75.4, 55.7, 29.0, 28.4, 19.5, 18.8; ATR-FTIR (cm⁻¹): 3366, 2986, 1683, 1517, 1376, 1277, 1210, 1191, 1101, 689; HRMS (ESI⁻) *m/z*: [M+Cl]⁻ calcd for C₁₃H₂₁F₆NO₃Cl 388.1114, found: 388.1124.

Tert-butyl ((2*S*,3*S*)-1-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-3-methylpentan-2-yl)carbamate **2l**: White solid (57.0 mg, 93% yield); [α]_D²⁰ -34.3 (*c* 1.00, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 4.67 (m, 1H), 4.06 (sept, *J* = 5.9 Hz, 1H), 3.99 (dd, *J* = 9.2, 3.1 Hz, 1H), 3.85 (dd, *J* = 9.2, 3.9 Hz, 1H), 3.58–3.47 (m, 1H), 1.69–1.49 (m, 2H), 1.42 (s, 9H), 1.23–1.07 (m, 1H), 0.94–0.85 (m, 6H); ¹⁹F NMR (282 MHz, CDCl₃) δ -74.46 (m, 6F); ¹³C{¹H} NMR (75 MHz, CDCl₃) δ 155.8, 121.6 (q, *J* = 283.9 Hz), 79.6, 76.3 (sept, *J* = 32.2 Hz), 75.3, 54.5, 35.4, 28.4, 25.4, 15.5, 11.2; ATR-FTIR (cm⁻¹): 3368, 2969, 1683, 1515, 1374, 1278, 1210, 1191, 1100, 688; HRMS (ESI⁻) *m/z*: [M-H]⁻ calcd for C₁₄H₂₂F₆NO₃ 366.1504, found: 366.1492.

Tert-butyl (*S*)-(1-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)propan-2-yl)carbamate **2m**: White solid (46.0 mg, 85% yield) [α]_D²⁰ -22.7 (*c* 1.00, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 4.61 (m, 1H), 4.07 (sept, *J* = 5.9 Hz, 1H), 3.90–3.76 (m, 3H), 1.43 (s, 9H), 1.21 (d, *J* = 6.4 Hz, 3H); ¹⁹F NMR (282 MHz, CDCl₃) δ -74.52 (m, 6F); ¹³C{¹H} NMR (75 MHz, CDCl₃) δ 155.3, 121.6 (q, *J* = 286.9 Hz), 79.8, 78.0, 76.4 (sept, *J* = 32.2 Hz), 46.1, 28.4, 17.3; ATR-FTIR (cm⁻¹): 3360, 2982, 1685, 1533, 1371, 1280, 1237, 1190, 1099, 687; HRMS (API⁻) *m/z*: [M-H]⁻ calcd for C₁₁H₁₆F₆NO₃ 324.1034, found: 324.1042.

Tert-butyl (2-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)ethyl)carbamate **2n**: Colorless oil (44.2 mg, 85% yield); ¹H NMR (300 MHz, CDCl₃) δ 4.88 (br s, 1H), 4.07 (sept, *J* = 6.0 Hz, 1H), 3.91 (t, *J* = 5.1 Hz, 2H), 3.38 (m, 2H), 1.44 (s, 9H); ¹⁹F NMR (282 MHz, CDCl₃) δ -74.58 (d, *J* = 5.8 Hz, 6F); ¹³C{¹H} NMR (75 MHz, CDCl₃) δ 156.0, 121.5 (q, *J* = 283.6 Hz), 79.9, 76.3 (sept, *J* = 32.2 Hz), 74.6, 40.4, 28.4; ATR-FTIR (cm⁻¹): 3361, 2982, 1695, 1511, 1369, 1288, 1217, 1191, 1101, 687; HRMS (ESI⁻) *m/z*: [M-H]⁻ calcd for C₁₀H₁₄F₆NO₃ 310.0878, found: 310.0868.

Benzyl (2-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)ethyl)carbamate **2o**: White solid (54.9 mg, 95% yield); ¹H NMR (300 MHz, CDCl₃) δ 7.44–7.29 (m, 5H), 5.19 (br s, 1H), 5.11 (s, 2H), 4.06 (sept, *J* = 5.5 Hz, 1H), 3.91 (t, *J* = 5.1 Hz, 2H), 3.45 (q, *J* = 5.4 Hz, 2H); ¹⁹F NMR (282 MHz, CDCl₃) δ -74.55 (d, *J* = 6.0 Hz, 6F); ¹³C{¹H} NMR (75 MHz, CDCl₃) δ 156.5, 136.5, 128.7, 128.3, 128.2, 121.5 (q, *J* = 283.4 Hz), 76.3 (sept, *J* = 32.2 Hz), 74.4, 67.1, 40.8; ATR-FTIR (cm⁻¹): 3303, 2927, 1693, 1549, 1284, 1217, 1190, 1102, 736, 687; HRMS (ESI⁺) *m/z*: [M+H]⁺ calcd for C₁₃H₁₄F₆NO₃ 346.0878, found: 346.0863.

Tert-butyl (3-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)propyl)carbamate **2p**: Colorless oil (23.3 mg, 43% yield); ¹H NMR (300 MHz, CDCl₃) δ 4.67 (br s, 1H), 4.05 (sept, *J* = 6.0 Hz, 1H), 3.89 (t, *J* = 5.9 Hz, 2H), 3.24 (m, 2H), 1.85 (m, 2H), 1.43 (s, 9H); ¹⁹F NMR (282 MHz, CDCl₃) δ -74.61 (d, *J* = 5.8 Hz, 6F); ¹³C{¹H} NMR (75 MHz, CDCl₃) δ

156.2, 121.6 (q, $J = 284.2$ Hz), 79.5, 76.2 (sept, $J = 32.2$ Hz), 73.4, 37.5, 30.1, 28.5; ATR-FTIR (cm^{-1}): 3352, 2981, 1693, 1512, 1369, 1287, 1217, 1190, 1101, 687; HRMS (API) m/z : [M-H]⁻ calcd for C₁₁H₁₆F₆NO₃ 324.1034, found: 324.1041.

Tert-butyl (*S*)-3-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-1-phenylpropyl)carbamate **2q**. White solid (55.7 mg, 83% yield); [α]_D²⁰ -31.2 (*c* 1.00, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.39–7.25 (m, 5H), 5.23–4.97 (m, 1H), 4.91–4.69 (m, 1H), 4.04 (sept, $J = 6.0$ Hz, 1H), 3.92–3.75 (m, 2H), 2.24–2.03 (m, 2H), 1.42 (s, 9H); ¹⁹F NMR (282 MHz, CDCl₃) δ -74.42 (m, 6F); ¹³C{¹H} NMR (75 MHz, CDCl₃) δ 155.4, 141.8, 128.9, 127.7, 126.4, 121.5 (q, $J = 283.4$ Hz), 79.7, 76.2 (sept, $J = 32.2$ Hz), 72.6, 52.3, 36.6, 28.4; ATR-FTIR (cm^{-1}): 3384, 2980, 1682, 1514, 1372, 1281, 1216, 1193, 1103, 697; HRMS (API) m/z : [M-H]⁻ calcd for C₁₇H₂₀F₆NO₃ 400.1347, found: 400.1340.

Tert-butyl (2-(((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)methyl)phenyl)carbamate **2r**. White solid (53.0 mg, 85% yield); ¹H NMR (300 MHz, CDCl₃) δ 7.95 (d, $J = 7.8$, 1H), 7.40 (m, 1H), 7.20 (m, 1H), 7.07 (m, 1H), 6.98 (s, 1H), 4.88 (s, 2H), 4.16 (sept, $J = 5.9$ Hz, 1H), 1.52 (s, 9H); ¹⁹F NMR (282 MHz, CDCl₃) δ -73.88 (d, $J = 5.7$ Hz, 6F); ¹³C{¹H} NMR (75 MHz, CDCl₃) δ 153.1, 138.4, 130.9, 130.7, 123.6, 123.5, 122.0, 121.6 (q, $J = 284.2$ Hz), 80.8, 74.3, 73.8 (sept, $J = 32.2$ Hz), 28.3; ATR-FTIR (cm^{-1}): 3338, 2986, 1699, 1525, 1369, 1284, 1185, 1102, 762, 687; HRMS (API) m/z : [M-H]⁻ calcd for C₁₅H₁₆F₆NO₃ 372.1034, found: 372.1038.

Benzyl 2-((*tert*-butoxycarbonyl)amino)-3-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-2-methylpropanoate **2s**. White solid (64.1 mg, 84% yield); the same reaction carried out on a 2.42 mmol scale gave the white solid (952.0 mg, 86% yield); ¹H NMR (300 MHz, CDCl₃) δ 7.39–7.31 (m, 5H), 5.40 (br s, 1H), 5.19 (m, 2H), 4.39 (m, 1H), 4.27 (m, 1H), 4.09 (sept, $J = 5.9$ Hz, 1H), 1.50 (s, 3H), 1.41 (s, 9H); ¹⁹F NMR (282 MHz, CDCl₃) δ -74.49 (d, $J = 6.0$ Hz, 6F); ¹³C{¹H} NMR (75 MHz, CDCl₃) δ 172.0, 154.5, 135.2, 128.7, 128.6, 128.4, 121.5 (q, $J = 281.4$ Hz), 80.2, 76.4 (sept, $J = 32.2$ Hz), 75.6, 67.8, 59.7, 28.3, 20.7; ATR-FTIR (cm^{-1}): 3382, 2986, 1718, 1697, 1522, 1371, 1290, 1191, 1103, 685; HRMS (ESI) m/z : [M+HCO₂]⁻ calcd for C₂₀H₂₄F₆NO₇ 504.1457, found: 504.1438.

Benzyl 2-((*tert*-butoxycarbonyl)amino)-2-methyl-3-(2,2,2-trifluoroethoxy)propanoate **2t**. Colorless oil (47.5 mg, 73% yield); ¹H NMR (300 MHz, CDCl₃) δ 7.37–7.31 (m, 5H), 5.41 (br s, 1H), 5.19 (m, 2H), 4.07 (m, 1H), 3.97 (m, 1H), 3.79 (m, 2H), 1.52 (s, 3H), 1.42 (s, 9H); ¹⁹F NMR (282 MHz, CDCl₃) δ -74.76 (t, $J = 8.7$ Hz, 3F); ¹³C{¹H} NMR (75 MHz, CDCl₃) δ 172.5, 154.6, 135.5, 128.7, 128.5, 128.3, 123.9 (q, $J = 280.0$ Hz), 80.0, 74.5, 69.0 (q, $J = 34.4$ Hz), 67.6, 60.0, 28.4, 20.6; ATR-FTIR (cm^{-1}): 3432, 2980, 1712, 1497, 1368, 1279, 1155, 1120, 1063, 697; HRMS (ESI) m/z : [M-H]⁻ calcd for C₁₈H₂₃F₃NO₅ 390.1528, found: 390.1526.

Benzyl 2-((*tert*-butoxycarbonyl)amino)-3-((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)-2-methylpropanoate **2u**. Colorless oil (62.7 mg, 71% yield); ¹H NMR (300 MHz, CDCl₃) δ 7.42–7.29 (m, 5H), 5.41 (br s, 1H), 5.25 (d, $J = 12.1$ Hz, 1H), 5.11 (d, $J = 12.2$ Hz, 1H), 4.58 (m, 1H), 4.40 (d, $J = 8.6$ Hz, 1H), 1.53 (s, 3H), 1.41 (s, 9H); ¹⁹F NMR (282 MHz, CDCl₃) δ -70.86 (s, 9F); ¹³C{¹H} NMR (75 MHz, CDCl₃) δ 171.7, 154.2, 135.1, 128.8, 128.7, 128.5, 120.3 (q, $J = 292.4$ Hz), 80.2, 79.4, 70.1, 68.0, 59.5, 28.3,

20.4; ATR-FTIR (cm^{-1}): 3436, 2982, 1716, 1498, 1369, 1246, 1154, 1019, 970, 726; HRMS (ESI) m/z : [M-H]⁻ calcd for C₂₀H₂₁F₉NO₅ 526.1276, found: 526.1281.

Benzyl 2-((*tert*-butoxycarbonyl)amino)-2-methyl-3-(2,2,3,3-tetrafluoropropoxy)propanoate **2v**. Colorless oil (50.1 mg, 71% yield); ¹H NMR (300 MHz, CDCl₃) δ 7.45–7.28 (m, 5H), 5.75 (tt, $J = 53.3$, 5.1 Hz, 1H), 5.41 (br s, 1H), 5.22 (d, $J = 12.3$ Hz, 1H), 5.16 (d, $J = 12.2$ Hz, 1H), 4.06 (m, 1H), 3.90 (d, $J = 9.5$ Hz, 1H), 3.86–3.69 (m, 2H), 1.51 (s, 3H), 1.42 (s, 9H); ¹⁹F NMR (282 MHz, CDCl₃) δ -125.84 (s, 2F), -140.34 (d, $J = 53.0$ Hz, 2F); ¹³C{¹H} NMR (75 MHz, CDCl₃) δ 172.5, 154.5, 135.4, 128.8, 128.6, 128.4, 115.2 (tt, $J = 249.7$, 25.6 Hz, 2F), 108.3 (tt, $J = 250.2$, 33.3 Hz, 2F), 80.1, 74.3, 68.7 (t, $J = 28.5$ Hz), 67.7, 60.1, 28.4, 20.5; ATR-FTIR (cm^{-1}): 3432, 2981, 1712, 1497, 1368, 1232, 1157, 1105, 1063, 697; HRMS (ESI) m/z : [M-H]⁻ calcd for C₁₉H₂₄F₄NO₅ 422.1591, found: 422.1581.

Benzyl 2-((*tert*-butoxycarbonyl)amino)-2-methyl-3-(perfluorophenoxy)propanoate **2w**. Colorless oil (68.0 mg, 86% yield); ¹H NMR (300 MHz, CDCl₃) δ 7.40–7.30 (m, 5H), 5.50 (br s, 1H), 5.26 (d, $J = 12.2$ Hz, 1H), 5.19 (d, $J = 12.2$ Hz, 1H), 4.66 (d, $J = 10.0$ Hz, 1H), 4.54 (d, $J = 9.8$ Hz, 1H), 1.59 (s, 3H), 1.38 (s, 9H); ¹⁹F NMR (282 MHz, CDCl₃) δ -156.64 (m, 2F), -163.64 (m, 3F); ¹³C{¹H} NMR (75 MHz, CDCl₃) δ 172.0, 154.3, 143.3 (m), 140.0 (m), 136.3 (m), 135.2, 133.8 (m), 128.7, 128.6, 128.4, 80.1, 75.9, 67.9, 60.1, 28.3, 20.6; ATR-FTIR (cm^{-1}): 3432, 2981, 1713, 1513, 1455, 1247, 1158, 1031, 994, 697; HRMS (ESI) m/z : [M-H]⁻ calcd for C₂₂H₂₁F₅NO₅ 474.1340, found: 474.1342.

Tert-butyl (*S*)-1-(benzyl(methyl)amino)-3-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-1-oxopropan-2-yl)carbamate **2z**. White solid (15.0 mg, 17% yield, mixture of rotamers, ¹³C{¹H} NMR was recorded; however, the low quantity available as well as the presence of rotamers did not allow to provide a good spectrum); [α]_D²⁰ -28.2 (*c* 1.00, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.38–7.17 (m, 5H), 5.53–5.11 (m, 1H), 5.06–4.90 (m, 1H), 4.83–4.45 (m, 2H), 4.21–3.88 (m, 3H), 3.08–2.92 (m, 3H), 1.48–1.36 (m, 9H); ¹⁹F NMR (282 MHz, CDCl₃) δ -74.43 (m, 6F); ATR-FTIR (cm^{-1}): 3292, 2921, 1685, 1639, 1539, 1368, 1187, 1100, 867, 687; HRMS (ESI) m/z : [M+H]⁺ calcd for C₁₉H₂₅F₆N₂O₄ 459.1719, found: 459.1702.

Procedures for the deprotection of *N*-Boc products **2a**, **2s**.

To a solution of **2a** (50.0 mg, 0.129 mmol) in dichloromethane (0.178 mL) was added dropwise trifluoroacetic acid (0.178 mL, 2.32 mmol). The reaction mixture was stirred for 2 h at 25 °C. Then, an aqueous solution 10% of NaHCO₃ was added. The mixture was extracted with DCM three times, the organic layer was dried over MgSO₄, filtered and evaporated to give the desired compound **4a**.

(*R*)-2-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-1-phenylethan-1-amine **4a**. Yellow oil (31.3 mg, 84% yield); [α]_D²⁰ -12.7 (*c* 1.00, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.44–7.23 (m, 5H), 4.30 (dd, $J = 9.0$, 3.5 Hz, 1H), 4.14 (sept, $J = 5.9$ Hz, 1H), 3.98 (dd, $J = 9.0$, 3.5 Hz, 1H), 3.85–3.69 (m, 1H), 1.87 (s, 2H); ¹⁹F NMR (282 MHz, CDCl₃) δ -74.36 (d, $J = 5.7$ Hz, 6F); ¹³C{¹H} NMR (75 MHz, CDCl₃) δ 140.7, 128.8, 128.1, 127.0, 121.6 (q, $J = 283.9$ Hz), 81.3, 76.4 (sept, $J = 32.2$ Hz), 55.6; ATR-FTIR (cm^{-1}): 3370, 2921, 1518, 1287, 1263, 1219,

1156, 1099, 864, 695; HRMS (ESI⁺): *m/z*: [M+H]⁺ calcd for C₁₁H₁₂F₆NO 288.0823, found: 288.0828.

To a solution of **2s** (588.0 mg, 1.28 mmol) in dichloromethane (1.76 mL) was added dropwise trifluoroacetic acid (1.76 mL, 23.04 mmol). The reaction mixture was stirred for 2 h at 25 °C. Then, an aqueous solution 10% K₂CO₃ was added. The mixture was extracted with DCM (3 x 10 mL), the organic layer was dried over MgSO₄, filtered and evaporated to give the desired compound **4s**, which was used for the next step without any further purification.

Benzyl 2-amino-3-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-2-methylpropanoate **4s**. Yellow oil (398.0 mg, 87% yield); ¹H NMR (300 MHz, CDCl₃) δ 7.42–7.30 (m, 5H), 5.20 (d, *J* = 12.2 Hz, 1H), 5.12 (d, *J* = 12.2 Hz, 1H), 4.20–4.08 (m, 2H), 3.79 (d, *J* = 8.7 Hz, 1H), 1.86 (br s, 2H), 1.30 (s, 3H); ¹⁹F NMR (282 MHz, CDCl₃) δ -74.35 (m, 5.9 Hz); ¹³C{¹H} NMR (75 MHz, CDCl₃) δ 175.2, 135.5, 128.8, 128.6, 128.3, 121.5 (q, *J* = 281.4 Hz), 119.6, 81.0, 76.5 (sept, *J* = 32.2 Hz), 67.6, 58.8, 22.9; ATR-FTIR (cm⁻¹): 3411, 2944, 1736, 1605, 1373, 1288, 1191, 1102, 1019, 687; HRMS (ESI⁺) *m/z*: [M+H]⁺ calcd for C₁₄H₁₆F₆NO₃ 360.1034, found: 360.1042.

Typical procedure for dipeptide synthesis from **4s**.⁵¹

4s (0.193 mmol) and HATU (43.99 mg, 0.116 mmol) were dissolved in DMF (6.57 mL). Then, DIPEA (0.034 mL, 0.193 mmol) was added and the mixture was stirred for 10 min. Boc-Val-OH (20.94 mg, 0.096 mmol) was dissolved in DMF (0.22 mL) and added dropwise to the initial mixture. The reaction was stirred at room temperature for 18 h. The solvent was removed under vacuum. The resulting residue was dissolved in CH₂Cl₂ and washed with saturated aqueous NaHCO₃. The organic layer was dried over MgSO₄ and volatiles were removed under vacuum. The crude product was purified by normal phase chromatography (irregular silica, 40–63 μm, 12 g, liquid loading, mobile phase gradient: from petroleum ether/ethyl acetate 100/0 to 80/20) to yield 43.8 mg of the title compound as a white solid.

Benzyl 2-((*S*)-2-((tert-butoxycarbonyl)amino)-3-methylbutanamido)-3-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-2-methylpropanoate **5**. White solid (43.8 mg, 81% yield, mixture of two diastereomers and rotamers); ¹H NMR (300 MHz, CDCl₃) δ 7.41–7.28 (m, 5H), 6.88 (s, 0.54H), 6.68 (s, 0.46H), 5.24 (d, *J* = 12.2 Hz, 0.23H), 5.20 (d, *J* = 12.1 Hz, 0.76H), 5.17 (d, *J* = 12.1 Hz, 0.80H), 5.13 (d, *J* = 12.2 Hz, 0.24H), 5.05–4.86 (m, 1H), 4.55–4.48 (m, 1H), 4.28–4.07 (m, 2H), 3.94–3.86 (m, 1H), 2.18–2.01 (m, 1H), 1.55 (s, 3H), 1.43 (s, 9H), 0.97–0.87 (m, 6H); ¹⁹F NMR (282 MHz, CDCl₃) δ -74.22 – -74.58 (m, 6F); ¹³C{¹H} NMR (75 MHz, CDCl₃) δ 171.7, 171.52, 171.50, 155.9, 135.04, 135.01, 128.8, 128.75, 128.73, 128.5, 128.4, 121.4 (q, *J* = 286.0 Hz), 80.2, 76.25, 76.22, 75.2, 75.1, 68.1, 60.4, 60.3, 31.0, 30.6, 28.3, 20.3, 19.9, 19.3, 19.1, 17.6; ATR-FTIR (cm⁻¹): 3329, 2968, 1705, 1659, 1500, 1369, 1289, 1193, 1103, 1021, 687; HRMS (ESI⁺) *m/z*: [M+H]⁺ calcd for C₂₄H₃₃F₆N₂O₆ 559.2259, found: 559.2243.

Procedure for the deprotection of *N*-Boc product **2n**.⁵²

To a stirred solution of **2n** (75 mg, 0.241 mmol) in dioxane (1.80 mL), was added 4M HCl in dioxane (1.80 mL) at 0 °C. After stirring for 2 h at room temperature, the reaction mixture was concentrated in vacuo to afford 59.1 mg of the title compound as a pale-yellow solid.

2-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)ethan-1-amine hydrochloride **6**. Pale yellow solid (59.1 mg, 99% yield); ¹H NMR (300 MHz, D₂O) δ 4.94 (sept, *J* = 6.1 Hz, 1H), 4.17 (t, *J* = 5.0 Hz, 2H), 3.29 (t, *J* = 4.9 Hz, 2H); ¹⁹F NMR (282 MHz, D₂O) δ -74.41 (d, *J* = 6.1 Hz, 6F); ¹³C NMR (75 MHz, D₂O) δ 121.4 (q, *J* = 283.1 Hz), 75.0 (sept, *J* = 32.5 Hz), 70.2, 39.1; ATR-FTIR (cm⁻¹): 2909, 1507, 1376, 1284, 1193, 1126, 1101, 991, 864, 692; HRMS (ESI⁺) *m/z*: [M-Cl]⁺ calcd for C₅H₈F₆NO 212.0510, Found: 212.0511.

Typical procedure for synthesis of ibuprofen derivative **7**.⁵³

DIPEA (73.3 μL, 0.421 mmol) was added to a solution of ibuprofen (34.7 mg, 0.168 mmol) in DMF (1.68 mL) at 25 °C. Then, solution of HATU (64.0 mg, 0.168 mmol) and **6** (50.0 mg, 0.202 mmol) in DMF (0.84 mL) was added dropwise. The reaction mixture was stirred at 25 °C for 18 h. After completion, the reaction mixture was diluted with EtOAc (30 mL), washed with water and brine. The organic phase was dried over Na₂SO₄ and concentrated in vacuo. The crude product was purified by normal phase chromatography (irregular silica, 40–63 μm, 12 g, liquid loading, mobile phase gradient: from petroleum ether/ethyl acetate 100/0 to 70/30). The fractions containing the desired compound were combined in vacuo to give 60.0 mg of the desired compound as a white solid.

N-(2-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)ethyl)-2-(4-isobutylphenyl)propanamide **7**. White solid (60.0 mg, 89% yield); ¹H NMR (300 MHz, CDCl₃) δ 7.21–7.06 (m, 4H), 5.82 (br s, 1H), 4.04–3.92 (m, 1H), 3.90–3.76 (m, 2H), 3.54 (q, *J* = 7.3 Hz, 1H), 3.49–3.35 (m, 2H), 2.45 (d, *J* = 7.2 Hz, 2H), 1.84 (sept, *J* = 6.8 Hz, 1H), 1.51 (d, *J* = 7.2 Hz, 3H), 0.89 (d, *J* = 6.6 Hz, 6H); ¹⁹F NMR (282 MHz, CDCl₃) δ -74.63 (m, 6F); ¹³C{¹H} NMR (75 MHz, CDCl₃) δ 175.0, 141.1, 138.1, 129.8, 127.4, 121.4 (q, *J* = 283.4 Hz), 76.4 (sept, *J* = 32.2 Hz), 74.2, 46.8, 45.1, 39.3, 30.3, 24.0, 22.4, 18.3; ATR-FTIR (cm⁻¹): 3307, 2958, 1649, 1542, 1376, 1275, 1214, 1192, 1100, 691; HRMS (ESI⁺) *m/z*: [M+H]⁺ calcd for C₁₈H₂₄F₆NO₂ 400.1711, found: 400.1722.

Typical procedure for nucleophilic aromatic substitution with hydrochloride **6**.⁵⁴

To a stirred solution of **6** (50.0 mg, 0.202 mmol) in DMSO (0.381 mL), DIPEA (0.106 mL, 0.606 mmol) was added and the mixture was stirred 10 min at 25 °C and then 1-fluoro-2-nitrobenzene (21.3 μL, 0.202 mmol) was added dropwise. The mixture was stirred at 25 °C for 20 h. Next, the reaction mixture was diluted with water and ethyl acetate. The aqueous layer was extracted three times with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified by normal phase chromatography (irregular silica, 40–63 μm, 12 g, liquid loading, mobile phase gradient: from petroleum ether/ethyl acetate 100/0 to 80/20). The fractions containing the desired compound were combined in vacuo to give 47.3 mg of the desired compound as a yellow liquid.

N-(2-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)ethyl)-2-nitroaniline **8**. Yellow liquid (47.3 mg, 70% yield); ¹H NMR (300 MHz, CDCl₃) δ 8.20 (dd, *J* = 8.6, 1.6 Hz, 2H), 7.53–7.41 (m, 1H), 6.86 (dd, *J* = 8.7, 1.2 Hz, 1H), 6.76–6.66 (m, 1H), 4.19–4.05 (m, 3H), 3.63 (q, *J* = 5.5 Hz, 2H); ¹⁹F NMR (282 MHz, CDCl₃) δ -74.45 (d, *J* = 5.9 Hz, 6F); ¹³C{¹H} NMR (75

MHz, CDCl₃) δ 145.0, 136.4, 132.7, 127.2, 121.4 (q, *J* = 284.0 Hz), 116.2, 113.5, 76.4 (sept, *J* = 32.2 Hz), 73.4, 42.4; ATR-FTIR (cm⁻¹): 3379, 2951, 1619, 1513, 1353, 1189, 1099, 897, 737, 687; HRMS (ESI⁺) *m/z*: [M+H]⁺ calcd for C₁₁H₁₁F₆N₂O₃ 333.0674, found: 333.0674.

ASSOCIATED CONTENT

The data underlying this study are available in the published article and its online supplementary material.

Supporting Information

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

Copies of ¹H, ¹⁹F and ¹³C{¹H} NMR spectra of the products as well as HPLC chromatograms (pdf).

AUTHOR INFORMATION

Corresponding Author

* dominique.cahard@univ-rouen.fr

ORCID

Jun-An Ma: 0000-0002-3902-6799

Dominique Cahard: 0000-0002-8510-1315

Author Contributions

N.M. performed the experiments and analyzed the data. D.C. supervised the project, and J-A.M. co-supervised. The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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