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Copper-Catalyzed O-Difluoromethylation of Functionalized Aliphatic Alcohols: Access to Complex Organic Molecules with an OCF_2H Group

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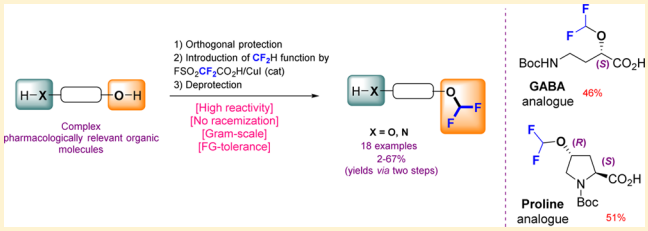
Supporting Information

ABSTRACT: A two-step synthetic strategy toward difluoromethyl ethers via a CuI-catalyzed reaction of the alcohols, bearing additional protected functionalities, with $FSO_2CF_2CO_2H$ has been developed. The high potential of the developed protocol has been shown by preparing novel OCF_2H-analogues of GABA and L-proline. The described transformation has good functional group compatibility and can serve as a powerful synthetic tool for late-stage preparation of complex OCF_2H-containing organic compounds as well as building blocks for drug discovery.



INTRODUCTION

The isosteric substitution of hydrogen atoms with fluorine and the introduction of fluorine-bearing functionalities into complex organic molecules are well-established strategies in medicine and life science for the design and optimization of biologically active molecules as well as in material science for devising new functional materials.[1,2] The fluorine atom is similar in size to hydrogen. This feature is accepted to be the main reason why biological objects, like microorganisms and enzymes, under particular circumstances, do not recognize the difference between a natural substrate and its fluorine-modified analogue, obtained via the replacement of the particular C−H bond by C−F bond. This phenomenon is often considered as the "mimic effect" of fluorine for hydrogen.[1b] However, the C−F bond compared with C−H has much stronger bonding energy, which results in increased stability of the C−F bond. These structural alterations are the main reasons for the changes in the metabolic pathways of fluorinated compounds and, in particular, augmentation of the in vivo stability toward various enzymes. For instance, introduction of a fluorine into the aromatic core is a well-known strategy to improve the stability of the lead compounds, for instance, toward the cytochrome C enzymes of liver cells, which dramatically changes the clearance and longevity of the drug candidate in vivo.[3] Nonetheless, 27 of the worldwide 150 best-selling drugs in the year 2013 are fluorinated compounds.[1b,d]

The effects associated with stereoelectronic interplays of fluorine atom with other fluorines or fluorine-containing groups, as well as with various polar or charged functional groups including, oxygen and nitrogen, are commonly used in the medicinal chemistry[1c,d,4] and in catalytic science for the development of pharmacologically significant substances, catalysts,[5,6] and/or catalytic moieties with enhanced properties, edited efficacy, and performance. In medicinal chemistry, however, these particular tools deliver a practical handle for "fine-tuning" of biological and physicochemical profiles of lead structures.[1c,d] In this context, several fluorine modifications of naturally occurring and pharmacologically relevant structures were undertaken.[1b]

In a continuation of our ongoing medicinal chemistry program dedicated to engineering fluorinated pharmacologically relevant scaffolds,[7] we have undertaken the current study aimed at the synthesis of OCF_2H-containing complex organic molecules. Our choice of this group is not random but was stipulated by a pivotal role this functionality plays as a pharmacophore in the marketed drugs;[3] for instance, such well-known medicines as roflumilast **I**[1b,c,3] and pentaprazole **II**[1b,c,3] contain this group (Figure 1). In addition, the OCF_2H group is a commonly occurring structural motif found in numerous pharmaceuticals and biologically active compounds[8] including

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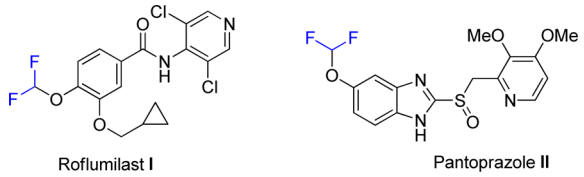


Figure 1. Pharmacologically relevant aromatic OCF_2H compounds.

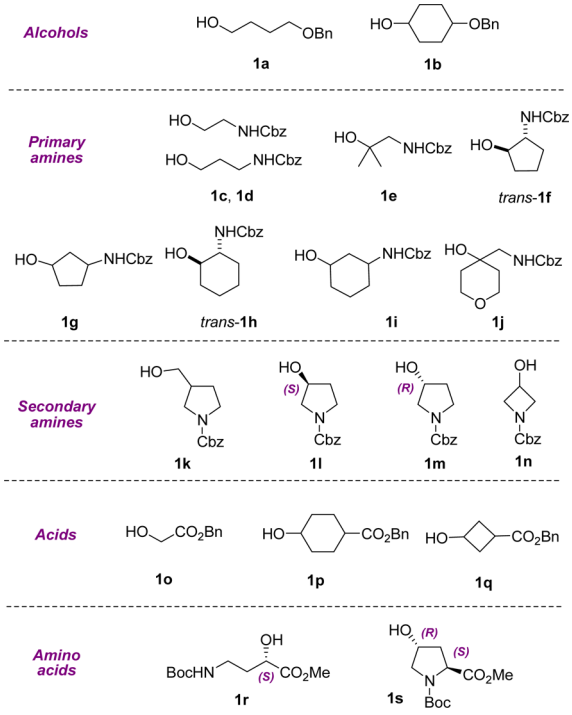
enzyme inhibitors, anti-HIV agents, and antimicrobial agents. In the life sciences, this group is presented by several OCF_2H-containing nucleosides,[1c,d] having a visible impact on the conformational preferences of the nucleosides themselves and the DNA double strand in particular. In addition to that, the OCF_2R functionalities are commonly used for the stereocontrol of the rotational profile[9] in organic molecules of different types. The elevated interest in the difluoromethyl group can be also explained by the fact that it acts as a bioisostere of alcohols and thiols.[1b,4] This makes the OCF_2R groups and OCF_2H, in particular, desirable pharmacophores and valuable tools to tune the properties of organic molecules and their conformational bias.

When analyzing the OCF_2H drugs presently available on the market as well as the drug candidates in clinical and preclinical studies, we noticed the lack of aliphatic OCF_2H molecules. In a view of recent trends in the field of medicinal chemistry related to the design of architecturally more complex molecules with greater three-dimensionality (3D-shape), via the formal saturation of aromatic precursors,[10] the functionalized OCF_2H aliphatic building blocks with a high degree of saturation are highly desirable scaffolds for drug discovery. The deficit of OCF_2H aliphatic structural motives is a result of underdeveloped synthetic methodologies enabling the preparation of such scaffolds.

Concerning the synthetic routes known to date for furnishing of organic compounds with the OCF_2H group, there are four main strategies. Namely, (i) the O-difluoromethylation[11] of phenols and alcohols using various sources of difluorocarbene; (ii) the C−O coupling reaction using the chemical equivalents[12] of the $[OCF_2H]^-$ synthon; (iii) the transformation of CO and CS groups;[13] and (iv) the nucleophilic exchange[14] of other halogens to fluorine in the $OCHal_2H$ groups. Concerning strategy i, there are a number of sources amenable for generation of difluorocarbene; for instance, chemical synthons such as $HalCF_2CO_2Na$, $FSO_2CF_2CO_2TMS$, $FSO_2CF_2CO_2H$, $TMSCF_2R$ (R = F, Cl, Br), $(Et_2O)_2POCF_2Br$, and $CF_3SO_3CF_2H$, etc., are commonly used for this purpose.[11a] However, $FSO_2CF_2CO_2H$, due to its high reaction efficiency, low price, and synthetic availability, is often considered to be the optimal reagent of choice for O-difluoromethylation, in particular for large-scale synthesis. Despite the diversity of the strategies known to date, the most commonly used synthetic route toward difluoromethyl ethers from alcohols requires the use of ozone-depleting HCF_2Cl, the so-called Freon 22.[15] The environmentally friendly preparative methods, however, often require elevated temperatures, are not compatible with many functional groups, and are only efficient on the structurally simple substrates.[11] Due to the aforementioned limitations of the presently used methodologies, the development of new, simple, straightforward, and concise methods to convert functional alcohols to difluoromethyl ethers are of considerable interests.

Herein, we report a practical entry toward structurally diverse difluoromethyl ethers using the set of readily available alcohols, bearing an additional functional group, and $FSO_2CF_2CO_2H$[11] as a source CF_2 structural motif. Our methodology commenced with the preparation of the protected substrates **1a−s**. For the current study, we selected O-protected aliphatic diols **1a,b**, N-protected amino alcohols **1c−n**, carboxyl-protected hydroxyl acids **1m−q**, as well as N- and carboxyl- protected amino acids bearing a free hydroxyl group **1r,s** (Table 1). The method we

Table 1. List of Starting Materials Used



are communicating here is an extension of the methodology for nonfunctionalized alcohols developed by Chen at al.[16] that in our case covers the functionalized aliphatic alcohols and results in improved reaction efficiency and overall yields. Within the current research program, we have developed diverse libraries of complex OCF_2H-containing organic compounds; however, here we are communicating only 18 examples (Table 3).

RESULTS AND DISCUSSION

With the set of the starting compounds **1a−s** in hand (Table 1), we focused on determining the standard reaction conditions applicable for the title transformation (Scheme 1 and Table 2). We chose the reaction conditions that were used in the early

Scheme 1. Synthesic Scenario for the Preparation of OCF_2H-Substituted Intermediates and Final PG-Free Products

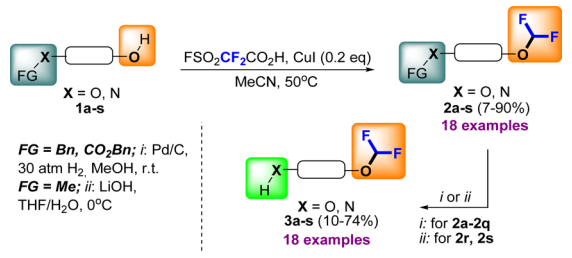


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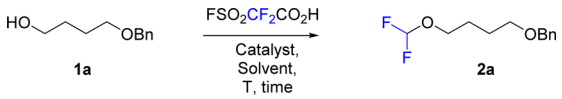
Table 2. Optimization of Reaction Conditions for the Synthesis of 2a[a]



entry	catalyst/solvent	T (°C)	time	yield (%)
1	CuBr (0.2 equiv)/C_6H_6	60	45 min	traces
2	CuBr (0.2 equiv)/C_6H_6	60	3 h	traces
3	CuBr (0.2 equiv)/C_6H_6	100	3 h	traces
4	CuBr (0.2 equiv)/MeCN	60	2 h	5[b]
5	CuI (0.2 equiv)/C_6H_6	50	1 h	17[b]
6	CuI (0.2 equiv)/C_6H_6	90	2 h	12[b]
7	CuI (0.2 equiv)/MeCN	50	2 h	67 (75)[b]
8	CuI (0.2 equiv)/MeCN	80	2 h	60 (69)[b]
9	CuI (0.2 equiv)/MeCN	50	45 min	73 (82)[b]
10	CuI (0.1 equiv)/MeCN	50	45 min	58[b]
11	CuI (0.3 equiv)/MeCN	50	45 min	81[b]
12	$NiBr_2$ (0.2 equiv)/MeCN	60	1 h	15[b]
13	NiI_2 (0.2 equiv)/MeCN	60	1 h	19[b]
14	$Cu(OAc)_2$ (0.2 equiv)/MeCN	60	1 h	
15	$Cu(OTf)_2$ (0.2 equiv)/MeCN	60	1 h	25[b]
16	$Rh_2(OAc)_4$ (0.1 equiv)/C_6H_6	60	3 h	45[b]
17	$Rh_2(O_2CCF_3)_4$ (0.1 equiv)/C_6H_6	60	3 h	38[b]

[a]Optimization of the reaction condition was performed on the 10 mmol scale taking 1.5 equiv of $FSO_2CF_2CO_2H$. [b]GC/MS detected yields.

works of Chen[17] as a starting point of our research. It is noteworthy that these conditions require a 2- to 3-fold excess of alcohol along with elevated temperatures and in our opinion cannot be used for the multigram preparation of structurally diverse OCF_2H compounds. At the same time, many synthetic methods known to date utilize strong bases for the difluorocarbene generation; these methods usually demonstrate low functional group tolerance and cannot be employed for the late-stage functionalization of complex organic molecules.

Recent studies showcased that the transition metals enable the transfer of the carbene moieties by formation of the corresponding carbene complexes. Additionally, the existence of such adducts and their stability were supported by spectroscopic means along with the chemical transformations of the aforementioned metallic species.[18] The difluorocarbene complexes of transition metals were studied; however, their existence as intermediates was proven in several catalytic processes.[19] This, in particular, turned our attention toward transition-metal-mediated protocols and prompted us to being the reaction trials by applying Cu(I) salts, which are known to be capable of trapping carbenes to form suitable carbene complexes.[18a,d] On the other hand, the recent progress on the application of $CuCF_3$ as an intermediate of choice for the catalytic trifluoromethylation as well as difluoromethylation[20] gave us the idea that the O-difluoromethylation can also follow the second possible mechanistic route, namely, via the formation of a CF_3 metal species. Since we were not sure about the mechanism the reaction undergoes within the designed and tested reaction conditions, we decided to consider both possible routes mentioned above. Accordingly, we have selected a set of transition metals capable for formation of metal−carbene complexes and CF_3 metal species.

The substance **1a** was chosen as a model compound. After reaction condition optimization, consisting of various solvents, amounts and type of transition metals, temperatures, and times of reaction, the optimal reaction conditions were developed (Table 2 entry 9). We mainly focused on the exploration of CuBr and CuI as catalysts, enabling introduction of the CF_2H group. First, the CuBr was checked (Table 2, entries 1−4); accordingly, to our great disappointment we did observe the formation of the desired product but in trace amounts. The best result was showcased by utilizing the combination of CuBr with MeCN as a solvent. Under these conditions, the product **2a** was detected by GC/MS in 5% yield. Furthermore, the CuI/C_6H_6 system improved the situation dramatically, delivering the desired product in 17% GC/MS yield (Table 2, entry 5). Nonetheless, these results were not sufficient enough to deploy a chemistry using these reaction conditions. The important improvement in terms of yields appeared to be the usage of MeCN as a solvent, which increased the GC/MS yield up to 75% (Table 2, entry 7). The crucial parameters during the reaction condition optimization were the screening of time and the temperature. We encountered the problem of thermal instability of the product **2a** under Cu catalysis (Table 2, entry 8). This observation prompted us to decrease the reaction time up to 45 min and the reaction temperature to 50 °C. Finally, we reached the synthesis of the corresponding difluoromethyl ether **2a** in 82% GC/MS yield and 73% isolated yield (Scheme 1 and Table 2). The best yield was obtained using 1.5 equiv of difluoromethylation agent ($FSO_2CF_2CO_2H$) and 0.2 equiv of CuI in MeCN as reaction medium at 50 °C (Table 2, entry 9). Further, increasing the amount of CuI to 0.3 equiv did not visibly improve the efficiency of the title reaction. However, when we used 0.1 equiv of CuI, the GC/MS yield dropped significantly (entry 10). At the same time, other transition metals, such as Ni(II) (Table 2, entries 12 and 13) and Cu(II) (Table 2, entries 14 and 15) salts, were not prone to catalyze the title reaction in a sufficient manner. On the contrary, the Rh(II) salts, known previously to promote the formation of carbene metallo complexes,[18c] demonstrated promising results when applied to the title reaction (Table 2, entries 16 and 17). However, owing to the availability and overall costs of Rh-based catalysts, we excluded this option for the further optimization of the reaction conditions based on the goal of the gram-scale production of the desired OCF_2H-substituted substances.

Prompted by these results and having optimized the reaction conditions, we turned our attention toward evaluation of the generality of the developed synthetic protocol. We found that the O-protected diol **1b** under the aforementioned reaction conditions can be swiftly converted to the corresponding protected intermediate compound **2b** (Table 3). The same results were observed for a variety of N-protected amino alcohols **1c−n** and carboxyl-protected hydroxyl acids **1o−q** (Tables 1 and 3). To our delight, the developed reaction conditions appeared to be general and allowed the synthesis of the corresponding difluoromethyl ethers **2a−q** bearing various functionalities. From the results summarized in Table 3, it is evident that the described CuI-catalyzed difluoromethylation reaction turned out to be rather general. The obtained compounds were either highly viscous oils or liquids; thus, the purification was accomplished by distillation in vacuum or preparative column chromatography on the silica gel. In the case of compounds **2e**, **2j**, and **3c**, we observed a drop in the yields. For **2e** and **2j**, most probably this can be attributed to the sterical bulkiness of the corresponding substrates **1e,j**. The rather low yield of the amine **3c** can be explained by its high volatility. Upon scaled-up production of compounds **2d**, **2l**, **2m**,

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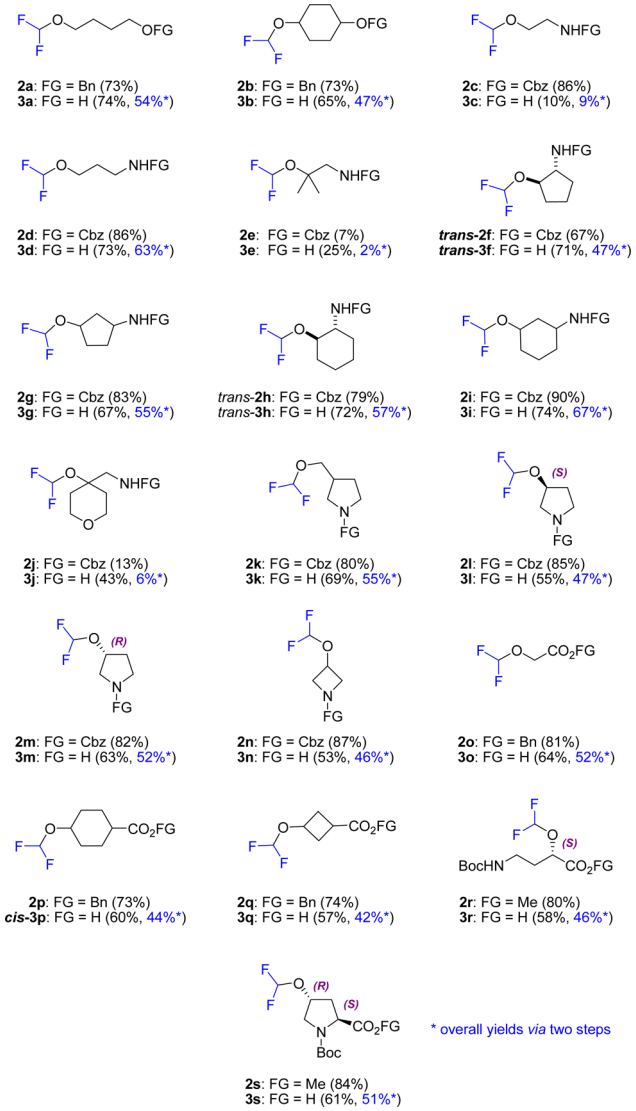
Table 3. Scope of the OCF_2H Intermediates as Well as Final Protecting-Group-Free Products



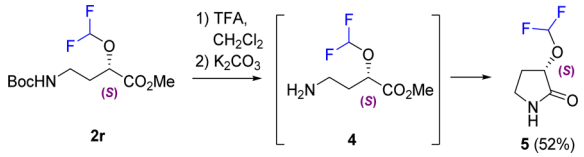
2r, and **2s**, the amount of $FSO_2CF_2CO_2H$ could be decreased up to 1.2−1.3 equiv without visible losses in yields.

The removal of the concrete protecting group was achieved following the standard reaction conditions commonly used for the given case (Scheme 1). For instance, the Bn and CO_2Bn moieties, present in compounds **2a−q**, were easily removed from the corresponding ethers and amides by the high-pressure catalytic hydrogenation. The reaction was conducted in methanol using 5% Pd/C as catalyst under 30 atm of H_2 at room temperature. The title reaction can be easily scaled up on gram and decagram scales without further optimization. Of note, the mildness of the developed methodology enabled the synthesis of enantiomerically pure compounds **3l** and **3m** from the corresponding (*S*) and (*R*) precursors without any notable racemization.

In the light of these results, we anticipated that the title reaction could be also applicable for the late-stage diversification of pharmacologically relevant compounds, for instance, hydroxy amino acids. In a view of our current interests in fluorine-modified natural and seminatural products[7] like amino acids and nucleosides, for this study two model amino acids were selected, namely, the (4*R*)-4-hydroxy-L-proline and (2*S*)-2-hydroxy GABA ((2*S*)-4-amino-2-hydroxybutanoic acid). Following the known synthetic methods,[21] these compounds were converted into the protected derivatives **1r** and **1s**, which were suitable for the subsequent CF_2 functionalization (Table 1). Using the optimal conditions, the corresponding compounds were successfully converted into intermediate structures **2r** and **2s** in good yields (80% and 84%, respectively). The further saponification of these amino acid esters by solution of LiOH in THF afforded *N*-Boc-protected (4*R*)-4-(difluoromethoxy)-L-proline **3r** and *N*-*t*-Boc-protected (2*S*)-4-amino-2-(difluoromethoxy)butanoic acid **3s** in 61% and 58% yield, respectively. The Boc and *t*-Boc protecting groups on the amino function were not removed since, according to our actual research plans, those building blocks will be used further for the peptide synthesis. Attempts to incorporate the synthesized OCF_2H-analogue of L-proline into the oligo- and polypeptide strings[7a−c,22] are currently underway in our laboratories.

In order to illustrate the follow-up chemistry, the synthetic transformation of the **2r** was undertaken. The cyclization of the protected (2*S*)-2-hydroxy GABA was achieved by treatment of the title compound with TFA followed by basic neutralization with K_2CO_3, which afforded to the pharmacologically relevant (3*S*)-3-(difluoromethoxy)pyrrolidin-2-one **5** in 52% yield as a pure (*S*)-enantiomer (Scheme 2). The racemization in the course of the reaction was not detected. At the same time, in order to cut off two extra steps related to protection and deprotection, we had a notion to set under investigation the unprotected hydroxy amino substrates including hydroxy amino acids. Unfortunately, these attempts experienced a failure; the corresponding reactions led to the formation of a mixture of unidentified products accompanied by tar formation.

Scheme 2. Follow-up Chemistry: Synthesis of (*S*)-3-(Difluoromethoxy)pyrrolidin-2-one 5 by Base-Promoted Cyclization of (*S*)-Methyl 4-Amino-2-(difluoromethoxy)butanoate 4



To confirm the constitution of the obtained structural scaffolds **2**, **3**, and **5**, we mainly used NMR. The characteristic features of the OCF_2H products in ^1H and ^{13}C NMR spectra are accompanied by the equal volume of corresponding J_{C-F}, J_{F-H} coupling constants in ^1H and ^{19}F NMR spectra. For the structures with the chiral carbon in the close proximity to the OCF_2H group, we observed the diastereotopism of two geminal fluorine atoms with the characteristic spin pictures and coupling patterns.[23] The chemical shifts of the OCF_2H function are in accordance with the previously communicated data.[23]

SUMMARY

In summary, we developed an operationally simple protocol for O-difluoromethylation of various functional alcohols with 1.2−1.5 excess amounts of $FSO_2CF_2CO_2H$, which is so far an optimal difluoromethylation reagent. The CuI-catalyzed reaction of the polyfunctional alcohols provides the corresponding difluoromethyl ethers in moderate to high yields.

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Furthermore, this protocol is distinguished by a wide substrate scope, including aliphatic alcohols bearing additional protected OH, NH_2, or CO_2H groups, without compromising its efficiency and scalability. As the following task to be solved in the frame of this research program, we see the extension of the developed protocol on the synthesis of other OCF_2H-modified amino acids and natural products as well as subsequent assembly of OCF_2H analogues of several pharmacologically relevant peptides. At the same time, we are intended to disclose the mechanism of the title CuI-catalyzed reaction by spectroscopic (1D, 2D NMR, IR) and rational means. These attempts are currently underway in our laboratory.

EXPERIMENTAL SECTION

Solvents were purified according to standard procedures. Column chromatography was performed using Merck Kieselgel 60 (230−400 mesh) as the stationary phase. ^{1}H, ^{19}F, and ^{13}C NMR spectra were recorded at 499.9, 470.3, and 124.9 MHz. Chemical shifts are reported in ppm downfield from TMS (1H, ^{13}C) or $CFCl_3$ (^{19}F) as internal standards. The information associated with preparation of the compounds **1a−s** is available in the SI.

((4-(Difluoromethoxy)butoxy)methyl)benzene (2a). Compound **1a** (15 g, 0.083 mol, 1 equiv) was dissolved in 200 mL of acetonitrile, and copper iodide (3.16 g, 0.017 mol, 0.2 equiv) was added. The mixture was heated to 50 °C, and a solution of 2-fluorosulfonyl-2,2-difluoroacetic acid (22.3 g, 0.125 mol, 1.5 equiv) in 100 mL of acetonitrile was added dropwise over a period of 45 min. The reaction mixture was heated for an additional 30 min at 50 °C. Then acetonitrile was evaporated, the remaider was dissolved in EtOAc, and the solid phase was filtered out. The EtOAc solution was concentrated under vacuum to give the product **2a**. Yield = 73% (14 g).

The product is a transparent, colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.71−1.74 (m, 4H), 3.20, 3.49 (s, 2H), 3.85, 4.18 (t, 2H, ^3J = 5.4 Hz), 4.49 (s, 2H), 6.16 (t, 1H, $^2J_{H-F}$= 75.3 Hz, CF_2H), 7.27−7.32 (m, 5H). ^{19}F NMR (376 MHz, $CDCl_3$): δ = −842 (d, 2F, ^2J = 76.0 Hz). ^{13}C{^{1}H} NMR (125.7 MHz, $CDCl_3$): δ = 25.9, 26.0, 63.4 (t, J = 5.9 Hz), 69.5, 72.8, 116.1 (t, $^1J_{C-F}$ = 259.0 Hz, CF_2H), 127.4, 127.5, 128.3, 138.5. Anal. Calcd for $C_{12}H_{16}F_2O_2$: C, 62.60; H, 7.00. Found: C, 62.74; H, 7.07.

4-(Difluoromethoxy)butan-1-ol (3a). Compound **2a** (14 g, 0.061 mol, 1 equiv) was dissolved in 100 mL of methanol. and 1.5 g of 5% Pd/C was added. The mixture was stirred under 30 atm of H_2 for 96 h at room temperature. Then Pd/C was filtered out, and the resulting mixture was concentrated under vacuum to give compound **3a**. Yield = 74% (6.3 g).

The product is a pale liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.60−1.73 (m, 4H), 2.78 (br s, 1H), 3.63 (t, 2H, ^3J = 6.8 Hz), 3.85 (t, 2H, ^3J = 6.7 Hz), 6.17 (t, 1H, $^2J_{H-F}$ = 73.3 Hz, CF_2H). ^{19}F NMR (376 MHz, $CDCl_3$): δ = −84.5 (d, 2F, $^2J_{H-F}$ = 75.1 Hz). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 25.1, 29.3, 62.1, 63.0 (t, J = 5.5 Hz), 115.7 (t, $^1J_{C-F}$ = 256.3 Hz, CF_2H). Anal. Calcd for $C_5H_{10}F_2O_2$: C, 42.86; H, 7.19. Found: C, 42.72; H, 7.22.

(((4-(Difluoromethoxy)cyclohexyl)oxy)methyl)benzene (2b) (Mixture of Diastereomers). Compound **1b** (28.8 g, 0.14 mol, 1 equiv) was dissolved in 300 mL of acetonitrile, and copper iodide (5.3 g, 0.028 mol, 0.2 equiv) was added. The mixture was heated to 50 °C, and a solution of 2-fluorosulfonyl-2,2-difluoroacetic acid (37.3 g, 0.21 mol, 1.5 equiv) in 100 mL of acetonitrile was added dropwise over a period of 45 min. The reaction mixture was heated for an additional 30 min at 50 °C. Then acetonitrile was evaporated, the remainder was dissolved in EtOAc, and the insoluble solid was filtered out. The resulting solution of EtOAc was evaporated, and the crude of **2b** was purified by column chromatography (EtOAc/hexane 1:6, R_f = 0.65). Yield = 73% (27.6 g). We encountered problems related to the prefabrication of the compound **2b**; however, the impurities of the batch did not affect the purity of the final product **3b**.

The product is a transparent colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of diastereomers): δ = 1.15−1.19 (m, 2H), 1.69−1.72 (m, 2H), 1.95−1.99 (m, 2H), 2.07−2.14 (m, 2H), 3.50−3.53 (m, 1H), 4.20−4.25 (m, 1H), 4.58 (s, 2H), 6.27 (dt, 1H, $^2J_{H-F}$ = 75.6 Hz, J = 9.0 Hz, CF_2H), 7.33−7.34 (m, 1H), 7.39−7.40 (m, 4H). ^{19}F NMR (376 MHz, $CDCl_3$): δ = −81.1 (t, 2F, $^2J_{H-F}$ = 77.0 Hz). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) (mixture of diastereomers): δ = 27.4, 28.2, 28.4, 29.4, 69.3, 69.7, 74.3, 75.0, 117.7 (dt, $^1J_{C-F}$= 258.5 Hz, J = 12.2 Hz, CF_2H), 127.6, 127.7, 128.6, 139.6, 139.6 (d, J = 14.0 Hz). Anal. Calcd for $C_{14}H_{18}F_2O_2$: C, 65.61; H, 7.08. Found: C, 65.43; H, 7.11.

4-(Difluoromethoxy)cyclohexanol (3b) (Mixture of Diastereomers). Compound **2b** (25.5 g, 0.1 mol) was dissolved in 200 mL of methanol, and 3.5 g of 5% Pd/C was added. The mixture was stirred under 30 atm of H_2 for 96 h at room temperature. Then Pd/C was filtered out, and the resulting mixture was concentrated under vacuum. The crude product was distilled under vacuum (1 Torr, 54 °C) to give compound **3b**. Yield = 64.7% (10.7 g).

The product is a pale liquid. ^{1}H NMR (500 MHz, $CDCl_3$) (mixture of diastereomers): δ = 1.25−1.71 (m, 4H), 1.75 (s, 1H), 1.90−2.02 (m, 4H), 3.73−3.75 (m, 1H), 4.18 (m, 1H), 6.22 (dt, 1H, $^2J_{H-F}$ = 75.9 Hz, J = 7.8 Hz, CF_2H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) (mixture of diastereomers): δ = 28.2, 29.3, 29.8, 31.5, 35.1, 68.2, 72.6, 115.9 (t, $^1J_{C-F}$ = 259.6 Hz, CF_2H). Anal. Calcd for $C_7H_{12}F_2O_2$: C, 50.60; H, 7.28. Found: C, 50.39; H, 7.25.

Benzyl (2-(Difluoromethoxy)ethyl)carbamate (2c). Compound **1c** (6 g, 0.0307 mol, 1 equiv) was dissolved in 60 mL of acetonitrile, and copper iodide (1.15 g, 0.006 mol, 0.2 equiv) was added. The reaction mixture was heated to 50 °C, and a solution of 2-fluorosulfonyl-2,2-difluoroacetic acid (8.2 g, 0.046 mol, 1.5 equiv) in 10 mL of acetonitrile was added dropwise over a period of 30 min. The reaction mixture was heated for an additional 30 min at 50 °C. Then acetonitrile was evaporated, the remainder was dissolved in EtOAc, and the insoluble solids were filtered out. The resulting solution of EtOAc was evaporated, and the crude of **2c** was purified by column chromatography (hexane/EtOAc 4:1, R_f = 0.65). Yield = 86% (6.35 g).

The product is a transparent colorless thick oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.40 (br s, 2H), 3.86 (m, 2H), 5.07 (s, 2H), 5.32 (br s, 1H), 6.15 (t, 1H, $^2J_{H-F}$ = 71.4 Hz, CF_2H), 7.31 (s, 5H). ^{19}F NMR (376 MHz, $CDCl_3$): δ = −84.6 (d, 2F, $^2J_{H-F}$ = 79.6 Hz, CF_2H). ^{13}C{^{1}H} NMR (125.7 MHz, $CDCl_3$): δ = 40.2, 62.5, 66.9, 115.8 (t, $^1J_{C-F}$ = 260.0 Hz, CF_2H), 127.9, 128.0, 128.4, 136.3, 156.3. Anal. Calcd for $C_{11}H_{13}F_2NO_3$: C, 53.88; H, 5.34; N, 5.71. Found: C, 54.00; H, 5.40; N, 5.65.

2-(Difluoromethoxy)ethanamine (3c). Compound **2c** (6.35g, 0.026 mol, 1 equiv) was dissolved in 65 mL of methanol, and 0.6 g of 5% Pd/C was added. The mixture was stirred under 30 atm of H_2 for 12 h at room temperature. Then Pd/C was filtered out, and the reaction mixture was concentrated under atmospheric pressure. Product **3c** was purified by distilled under vacuum (18 Torr, 35 °C). Yield = 10% (0.29 g); the main reason for low yield is the high volatility of the product.

The product is a transparent colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.22 (s, 2H), 2.85 (t, 2H, ^3J = 5.0 Hz), 3.78 (t, 2H, ^3J = 5.0 Hz), 6.17 (t, 1H, $^2J_{H-F}$= 76.3 Hz, CF_2H). ^{19}F NMR (376 MHz, $CDCl_3$): δ = −74.1 (d, 2F, $^2J_{H-F}$= 74.7 Hz). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 40.8, 65.5, 115.7 (t, $^1J_{C-F}$ = 258.8 Hz, CF_2H). Anal. Calcd for $C_3H_7F_2NO$: C, 32.43; H, 6.35; N, 12.61. Found: C, 32.22; H, 6.28; N, 12.50.

Benzyl (3-(Difluoromethoxy)propyl)carbamate (2d). Compound **1d** (60 g, 0.287 mol, 1 equiv) was dissolved in 600 mL of acetonitrile, and copper iodide (10.95 g, 0.058 mol, 0.2 equiv) was added. The mixture was heated to 50 °C, and a solution of 2-fluorosulfonyl-2,2-difluoroacetic acid (61.3 g, 0.344 mol, 1.2 equiv) in 100 mL of acetonitrile was added dropwise over a period of 45 min. The reaction mixture was heated for an additional 30 min at 50 °C. Then acetonitrile was evaporated, the remainder was dissolved in EtOAc, and the insoluble solids were filtered out. The resulting solution of EtOAc was evaporated, and the crude of **2d** was purified by

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column chromatography (hexane/EtOAc 4:1, R_f = 0.65). Yield = 86% (63 g).

The product is a transparent colorless thick oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.85−1.87 (m, 2H), 3.31 (br s, 2H), 3.91 (m, 2H), 4.99 (br s, 1H), 5.10 (s, 2H), 6.20 (t, 1H, $^2J_{H-F}$ = 72.4 Hz, CF_2H), 7.36 (s, 5H, Ph). ^{19}F NMR (376 MHz, $CDCl_3$): δ = −81.8 (dd, F, $^2J_{H-F}$ = 76.8 Hz), −81.0 (dd, F, $^2J_{H-F}$ = 76.8 Hz). $^{13}C\{^1H\}$ NMR (125.7 MHz, $CDCl_3$): δ = 29.4, 38.00, 61.4, 66.8, 116.2 (t, $^1J_{C-F}$ = 261.3 Hz, CF_2H), 128.2, 128.6, 136.7, 156.7. Anal. Calcd for $C_{12}H_{15}F_2NO_3$: C, 55.59; H, 5.83; N, 5.40. Found: C, 55.75; H, 5.87; N, 5.31.

3-(Difluoromethoxy)propan-1-amine (3d). Compound **2d** (63 g, 0.243 mol, 1 equiv) was dissolved in 300 mL of methanol, and 5 g of 5% Pd/C was added. The mixture was stirred under 30 atm of H_2 for 36 h at room temperature. Then Pd/C was filtered out, and the reaction mixture was concentrated under atmospheric pressure. Product **3d** was purified by distilled under vacuum (18 Torr, 43 °C). yield = 72.6% (22.1 g).

The product is a transparent colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.42 (s, 2H), 1.77 (quint, 2H, ^3J = 6.5 Hz), 2.81 (t, 2H, ^3J = 7.0 Hz), 3.92 (t, 2H, ^3J = 6.0 Hz), 6.18 (t, 1H, $^2J_{H-F}$ = 75.2 Hz, CF_2H). ^{19}F NMR (376 MHz, $CDCl_3$): δ = −84.6 (d, 2F, $^2J_{H-F}$ = 76.1 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 32.6, 38.6, 61.4, 116.0 (t, $^1J_{C-F}$ = 272.0 Hz, CF_2H). Anal. Calcd for $C_4H_9F_2NO$: C, 38.40; H, 7.25; N, 11.19. Found: C, 38.55; H, 7.19; N, 11.13.

Benzyl (2-Hydroxy-2-methylpropyl)carbamate (1e). Benzyl chloroformate (CbzCl) (94.95 g, 0.557 mol, 1 equiv) was added dropwise to the stirred solution of amino alcohol (49.6 g, 0.557 mol, 1 equiv) and potassium carbonate (153.8 g, 1.115 mol, 2 equiv) in a mixture of THF/water (800:400) at 0 °C. Then the reaction mixture was stirred 18 h at room temperature. After completion of the reaction, THF was rotary evaporated, and the rest was extracted three times with DCM. DCM was dried with sodium sulfate and then filtration evaporated. The crude product was purified by flash chromatography (EtOAc−petroleum ether 1:3). Yield = 71.9% (89.3 g).

The product is a transparent yellowish oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.19 (s, 6H), 2.66 (s, 1H), 3.17 (s, 2H), 5.09 (br s, 2H), 5.45 (s, 1H), 7.33 (br s, 5H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 27.1, 51.8, 67.0, 71.0, 128.2, 128.3, 128.6, 136.6, 157.5. Anal. Calcd for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.67; N, 6.27; O, 21.50. Found: C, 64.34; H, 7.79; N, 6.18.

Benzyl (2-(Difluoromethoxy)-2-methylpropyl)carbamate (2e). Compound **1e** (89.3 g, 0.4 mol, 1 equiv) was dissolved in 750 mL of acetonitrile, and copper iodide (15.25 g, 0.08 mol, 0.2 equiv) was added. The mixture was heated to 50 °C, and a solution of 2-fluorosulfonyl-2,2-difluoroacetic acid (106.85g, 0.6 mol, 1.5 equiv) in 200 mL of acetonitrile was added dropwise over a period of 45 min. The reaction mixture was heated for an additional 30 min at 50 °C. Then acetonitrile was evaporated, the remainder was dissolved in EtOAc, and the insoluble solid was filtered out. The resulting solution of EtOAc was evaporated, and the crude product **2e** was purified by column chromatography (hexane/EtOAc 3:1, R_f = 0.6). Yield = 6.8% (7.4 g).

The product is a transparent colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.34 (s, 6H), 3.32 (d, 2H, ^3J = 6.7 Hz), 5.10 (br s, 3H), 6.25 (t, 1H, $^2J_{H-F}$ = 76.4 Hz, CF_2H), 7.34 (br s, 5H). ^{19}F NMR (376 MHz, $CDCl_3$): δ = −79.3 (d, 2F, $^2J_{H-F}$ = 76.5 Hz). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 24.0, 50.3, 67.0, 80.3, 115.6 (t, $^1J_{C-F}$ = 250.8 Hz, CF_2H), 128.2, 128.3, 128.7, 136.6, 157.0. Anal. Calcd for $C_{13}H_{17}F_2NO_3$: C, 57.14; H, 6.27; N, 5.13. Found: C, 56.98; H, 6.30; N, 5.20.

2-(Difluoromethoxy)-2-methylpropan-1-amine (3e). Compound **2e** (7.4 g, 0.027 mol, 1 equiv) was dissolved in 100 mL of methanol, and 1 g of 5% Pd/C was added. The mixture was stirred under 30 atm of H_2 for 48 h at room temperature. Then Pd/C was filtered out, and the reaction mixture was concentrated under atmospheric pressure. The product **3e** was purified by distillation under vacuum (18 Torr, 32 °C). Yield = 25.2% (0.95 g).

The product is a transparent colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.33 (s, 6H), 1.37 (s, 2H), 2.73 (s, 2H), 6.35 (t, 1H, $^2J_{H-F}$ = 75.9 Hz, CF_2H). ^{19}F NMR (376 MHz, $CDCl_3$): δ = −76.9 (d, 2F, $^2J_{H-F}$ = 77.1 Hz). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 23.6, 51.6, 80.3, 115.1 (t, $^1J_{C-F}$ = 250.0 Hz, CF_2H). Anal. Calcd for $C_5H_{11}F_2NO$: C, 43.16; H, 7.97; N, 10.07. Found: C, 43.08; H, 8.02; N, 10.01.

Benzyl *trans*-2-(Difluoromethoxy)cyclopentyl)carbamate (2f). Compound **1f** (41.6 g, 0.177 mol, 1 equiv) was dissolved in 400 mL of acetonitrile, and copper iodide (6.7 g, 0.035 mol, 0.2 equiv) was added. The mixture was heated to 50 °C, and a solution of 2-fluorosulfonyl-2,2-difluoroacetic acid (47.2 g, 0.265 mol, 1.5 equiv) in 100 mL acetonitrile was added dropwise over a period of 45 min. The reaction mixture was heated for additional 30 min at 50 °C. Then acetonitrile was evaporated, the remainder was dissolved in EtOAc, and the insoluble solid was filtered out. The resulting solution of EtOAc was evaporated, and the crude of **2f** was purified by column chromatography (hexane/EtOAc 2:1, R_f = 0.6). Yield = 67% (33.6 g).

The product is a transparent colorless thick oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.49−2.03 (m, 6H), 3.97 (br s, 1H), 4.39 (br s, 1H), 5.10 (br s, 3H), 6.32 (t, 1H, $^2J_{H-F}$ = 75.2 Hz, CF_2H), 7.34 (br s, 5H). ^{19}F NMR (376 MHz, $CDCl_3$): δ = −81.7 (m, 2F). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 29.3, 30.1, 53.1, 57.3, 66.3, 80.1, 116.0 (t, $^1J_{C-F}$ = 255.9 Hz, CF_2H), 127.7, 127.8, 128.1, 136.0, 155.6. Anal. Calcd for $C_{14}H_{17}F_2NO_3$: C, 58.94; H, 6.01; N, 4.91. Found: C, 58.81; H, 6.05; N, 4.82.

***trans*-2-(Difluoromethoxy)cyclopentanamine (3f).** Compound **2f** (33.6 g, 0.1177 mol, 1 equiv) was dissolved in 300 mL of methanol, and 4 g of 5% Pd/C was added. The mixture was stirred under 30 atm of H_2 for 36 h at room temperature. Then Pd/C was filtered out, and the reaction mixture was concentrated under vacuum. The product **3f** was purified by distillation under vacuum (18 Torr, 67 °C). Yield = 71% (12.6 g).

The product is a transparent colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.21−1.27 (m, 3H), 1.60−1.66 (m, 3H), 1.88−1.98 (m, 2H), 3.16−3.20 (m, 1H), 4.01−4.03 (m, 1H), 6.16 (t, 1H, $^2J_{H-F}$ = 76.3 Hz, CF_2H). ^{19}F NMR (376 MHz, $CDCl_3$): δ = −81.5 (dd, F, $^2J_{F-F}$ = 164.6 Hz, $^2J_{H-F}$ = 75.4 Hz), −80.9 (dd, F, $^2J_{F-F}$ = 160.4 Hz, $^2J_{H-F}$ = 76.0 Hz). $^{13}C\{^1H\}$NMR (125 MHz, $CDCl_3$): δ = 19.8, 30.0, 31.3, 57.5, 83.5, 115.8 (t, $^1J_{C-F}$ = 257.7 Hz, CF_2H). Anal. Calcd for $C_6H_{11}F_2NO$: C, 47.68; H, 7.34; N, 9.27. Found: C, 47.80; H, 7.38; N, 9.30.

Benzyl (3-(Difluoromethoxy)cyclopentyl)carbamate (2g) (Mixture of Diastereomers). Compound **1g** (35.7 g, 0.152 mol, 1 equiv) was dissolved in 350 mL of acetonitrile, and copper iodide (5.8 g, 0.03 mol, 0.2 equiv) was added. The mixture was heated to 50 °C, and a solution of 2-fluorosulfonyl-2,2-difluoroacetic acid (40.5 g, 0.227 mol, 1.5 equiv) in 100 mL of acetonitrile was added dropwise over a period of 45 min. The reaction mixture was heated for an additional 30 min at 50 °C. Next, acetonitrile was evaporated, the remainder was dissolved in EtOAc, and the insoluble solid was filtered out. The resulting solution of EtOAc was evaporated and the crude of **2g** was purified by column chromatography (hexane/EtOAc 2:1, R_f = 0.6). Yield = 83% (36 g).

The product is a transparent colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of diastereomers): δ = 1.66−1.93 (m, 2H), 1.96−2.21 (m, 4H), 4.20 (br s, 1H), 4.68 (m, 1H), 5.05 (br s, 1H), 5.10 (s, 2H), 6.18 (dt, 1H, $^2J_{H-F}$ = 74.6 Hz, J = 6.7 Hz, CF_2H), 7.33−7.36 (m, 5H). ^{19}F NMR (376 MHz, $CDCl_3$): δ = −82.4 to −81.9 (m, 2F). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) (mixture of diastereomers): δ = 31.1, 31.5, 40.1, 50.5, 53.0, 60.0, 66.3, 115.6 (t, $^1J_{C-F}$ = 259.6 Hz, CF_2H), 127.8, 128.2, 136.1, 144.5, 155.3. Anal. Calcd for $C_{14}H_{17}F_2NO_3$: C, 58.94; H, 6.01; N, 4.91. Found: C, 58.81; H, 6.06; N, 4.87.

3-(Difluoromethoxy)cyclopentanamine (3g) (Mixture of Diastereomers). Compound **2g** (36 g, 0.1261 mol, 1 equiv) was dissolved in 300 mL of methanol, and 4 g of 5% Pd/C was added. The mixture was stirred under 30 atm of H_2 for 36 h at room temperature. Then Pd/C was filtered out, and the reaction mixture was concentrated under vacuum. Finally, product **3g** was purified by distillation under vacuum (18 Torr, 65 °C). Yield = 66.6% (12.7 g).

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The product is a transparent colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of diastereomers): δ = 1.24 (s, 2H), 1.42−1.69 (m, 2H), 1.75−1.87 (m, 2H), 1.91−2.15 (m, 2H), 3.24, 3.48 (quintet, 1H, ^3J = 6.0 Hz), 4.50−64 (m, 1H), 6.10 (dt, 1H, $^2J_{H-F}$= 75.7 Hz, J = 13.7 Hz, CF_2H). ^{19}F NMR (376 MHz, $CDCl_3$): δ = −82.2 to −81.7 (m, 2F). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) (mixture of diastereomers): δ = 31.2, 31.5, 33.2, 33.8, 42.7, 42.8, 50.5, 51.1, 76.1, 76.2, 115.8 (t, $^1J_{C-F}$ = 258.1 Hz, J = 12.8 Hz). Anal. Calcd for $C_6H_{11}F_2NO$: C, 47.68; H, 7.34; N, 9.27. Found: C, 47.81; H, 7.40; N, 9.23.

Benzyl (*trans*-2-(Difluoromethoxy)cyclohexyl)carbamate (2h). Compound **1h** (39 g, 0.156 mol, 1 equiv) was dissolved in 350 mL of acetonitrile, and copper iodide (6 g, 0.032 mol, 0.2 equiv) was added. The mixture was heated to 50 °C, and a solution of 2-fluorosulfonyl-2,2-difluoroacetic acid (41.8 g, 0.235 mol, 1.5 equiv) in 100 mL of acetonitrile was added dropwise over a period of 45 min. The reaction mixture was heated for an additional 30 min at 50 °C. Then acetonitrile was evaporated, the remainder was dissolved in EtOAc, and the insoluble solid was filtered out. The resulting solution of EtOAc was evaporated, and the crude **2h** was purified by column chromatography (hexane/EtOAc 2:1, R_f = 0.6). Yield = 78.6% (36.8 g).

The product is a transparent colorless thick oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.28−1.75 (m, 6H), 2.04−2.08 (m, 2H), 3.56 (br s, 1H), 3.92 (m, 1H), 4.97 (br s, 1H), 5.11 (s, 2H), 6.22 (t, 1H, $^2J_{H-F}$ = 74.6 Hz, CF_2H), 7.30−7.34 (m, 5H). ^{19}F NMR (376 MHz, $CDCl_3$): δ = −81.0 (m, 2F). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 23.5, 31.2, 31.9, 53.3, 60.0, 66.2, 75.6, 115.6 (t, $^1J_{C-F}$ = 257.3 Hz, CF_2H), 127.6, 128.1, 136.3, 155.7. Anal. Calcd for $C_{15}H_{19}F_2NO_3$: C, 60.19; H, 6.40; N, 4.68. Found: C, 60.23; H, 6.35; N, 4.60.

***trans*-2-(Difluoromethoxy)cyclohexanamine (3h).** Compound **2h** (30 g, 0.1 mol, 1 equiv) was dissolved in 300 mL of methanol, and 4 g of 5% Pd/C was added. The mixture was stirred under 30 atm of H_2 for 36 h at room temperature. Then Pd/C was filtered out, and the reaction mixture was concentrated under vacuum. The product **3h** was purified by destination under vacuum (18 Torr, 75 °C). Yield = 72.5% (12 g).

The product is a transparent colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.96−1.14 (m, 4H), 1.19−1.25 (m, 4H), 1.49−1.57 (m, 2H), 1.73−1.87 (m, 2H), 2.47−2.53 (m, 1H), 3.43−3.48 (m, 1H), 6.14 (t, 1H, $^2J_{H-F}$ = 75.0 Hz, CF_2H). ^{19}F NMR (376 MHz, $CDCl_3$): δ = −80.7 (dd, F, $^2J_{F-F}$ = 161.0 Hz, $^2J_{H-F}$ = 70.0 Hz), −79.0 (dd, 2F, $^2J_{F-F}$ = 155.0 Hz, $^2J_{H-F}$ = 75.0 Hz). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 23.7, 23.8, 31.3, 33.0, 53.6, 81.5, 116.1 (t, $^1J_{C-F}$ = 258.9 Hz, CF_2H). Anal. Calcd for $C_7H_{13}F_2NO$: C, 50.90; H, 7.93; N, 8.48. Found: C, 50.79; H, 7.96; N, 8.53.

Benzyl (3-(Difluoromethoxy)cyclohexyl)carbamate (2i) (Mixture of Diastereomers). Compound **1i** (49.8 g, 0.2 mol, 1 equiv) was dissolved in 450 mL of acetonitrile, and copper iodide (7.6 g, 0.04 mol, 0.2 equiv) was added. The mixture was heated to 50 °C, and a solution of 2-fluorosulfonyl-2,2-difluoroacetic acid (53.4 g, 0.3 mol, 1.5 equiv) in 100 mL of acetonitrile was added dropwise over a period of 45 min. The reaction mixture was heated for an additional 30 min at 50 °C. Then acetonitrile was evaporated, the remainder was dissolved in EtOAc, and the insoluble solids were filtered out. The resulting solution of EtOAc was evaporated, and the crude of **2i** was purified by column chromatography (hexane/EtOAc 2:1, R_f = 0.6). Yield = 90.3% (54 g).

The product is a transparent colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) (mixture of diastereomers): δ = 1.16−2.26 (m, 6H), 3.62, 3.90 (br s, 1H), 4.11, 4.48 (m, 1H), 5.01−5.18 (m, 3H), 5.26 (s, 2H), 6.20 (dt, 1H, $^2J_{H-F}$ = 75.3 Hz, J = 5.4 Hz, CF_2H), 7.31−7.34 (m, 5H). ^{19}F NMR (376 MHz, $CDCl_3$): δ = −81.8 (d, F, ^2J = 74.0 Hz), −81.0 (d, F, ^2J = 74.0 Hz). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) (mixture of diastereomers): δ = 18.9, 20.2, 30.3, 31.5, 37.3, 38.7, 45.5. 47.8, 53.1, 66.1, 70.5, 72.3, 115.9 (dt, $^1J_{C-F}$ = 258.1 Hz, J = 10.6 Hz, CF_2H), 127.7, 128.1, 136.3, 155.2. Anal. Calcd for $C_{15}H_{19}F_2NO_3$: C, 60.09; H, 6.40; N, 4.68. Found: C, 60.22; H, 6.42; N, 4.76.

3-(Difluoromethoxy)cyclohexanamine (3i) (Mixture of Diastereomers). Compound **2i** (30 g, 0.1 mol, 1 equiv) was dissolved in 300 mL of methanol, and 4 g of 5% Pd/C was added. The mixture was stirred under 30 atm of H_2 for 36 h at room temperature. Then Pd/C was filtered out, and the reaction mixture was concentrated under vacuum. The product **3i** was purified by destination under vacuum (18 Torr, 77 °C). Yield = 74.3% (12.3 g).

The product is a transparent colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of diastereomers): δ = 0.97−1.46 (m, 4H), 1.52 (s, 2H), 1.49−1.57 (m, 2H), 1.62−2.18 (m, 2H), 2.68−3.11 (m, 1H), 4.02−4.49 (m, 1H), 6.19 (dt, 1H, $^2J_{H-F}$ = 76.0 Hz, J = 4.6 Hz, CF_2H). ^{19}F NMR (376 MHz, $CDCl_3$): δ = −81.4 to −81.0 (m, 2F). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) (mixture of diastereomers): δ = 19.2, 21.7, 30.8, 32.2, 35.1, 35.3, 40.8, 43.2, 45.4, 49.0, 71.6, 73.0, 116.1, 116.4 (t, $^1J_{H-F}$ = 253.4 Hz, CF_2H). Anal. Calcd for $C_{15}H_{19}F_2NO_3$: C, 60.19; H, 6.40; F, 12.69; N, 4.68. Found: C, 60.15; H, 6.42; F, 12.65; N, 4.65.

Benzyl ((4-Hydroxytetrahydro-2*H*-pyran-4-yl)methyl)-carbamate (1j). Benzyl chloroformate (CbzCl) (43 g, 0.252 mol, 1 equiv) was added dropwise to the stirring solution of amino alcohol (31.5 g, 0.516 mol, 2 equiv) and potassium carbonate (66.4 g, 0.481 mol, 1.9 equiv) in the mixture THF/water (400/200 mL) at 0 °C. Afterward, the reaction mixture was stirred for additional 18 h at room temperature. Upon completion, the THF was evaporated, and the rest was extracted 3 times with DCM. The organic layer was dried with sodium sulfate, filtered, and evaporated to dryness. The crude product **1j** was purified by flash chromatography (EtOAc/petroleum ether 1:3). Yield = 75.1% (47.85 g).

The product is a white solid. Mp = 143−146 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.48−1.51 (m, 2H), 1.59−1.64 (m, 2H), 2.72 (s, 1H), 3.21 (br s, 2H), 3.72 (br s, 4H), 5.09 (s, 2H), 5.41 (br s, 1H), 7.34 (s, 5H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 35.5, 51.3, 63.7, 67.2, 69.2, 128.2, 128.4, 128.7, 136.4, 157.7. Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.22; H, 7.27; N, 5.25.

Benzyl ((4-(Difluoromethoxy)tetrahydro-2*H*-pyran-4-yl)-methyl)carbamate (2j). Compound **1j** (47.85 g, 0.18 mol, 1 equiv) was dissolved in 450 mL of acetonitrile, and copper iodide (6.9 g, 0.036 mol, 0.2 equiv) was added. The mixture was heated to 50 °C, and a solution of 2-fluorosulfonyl-2,2-difluoroacetic acid (48.3 g, 0.271 mol, 1.5 equiv) in 100 mL of acetonitrile was added dropwise over a period of 45 min. The reaction mixture was heated for an additional 30 min at 50 °C. Afterward, acetonitrile was evaporated, the remainder was dissolved in EtOAc, and the solid phase was filtered out. The resulting solution of EtOAc was evaporated, and the crude of **2j** was purified by column chromatography (EtOAc/hexane 3:1, R_f = 0.65). Yield = 12.8% (7.3 g).

The product is a transparent colorless thick oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.70−1.83 (m, 4H), 3.44−3.46 (m, 2H), 3.74 (br s, 4H), 5.11 (s, 2H), 5.23 (br s, 1H), 6.36 (t, 1H, $^2J_{H-F}$ = 76.0 Hz, CF_2H), 7.35 (s, 5H). ^{19}F NMR (376 MHz, $CDCl_3$): δ = −77.6 (d, 2F, $^2J_{H-F}$ = 77.7 Hz). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 33.3, 47.6, 63.3, 67.3, 78.8, 114.7 (t, $^1J_{C-F}$= 264.6 Hz, CF_2H), 127.7, 127.8, 128.2, 135.8, 156.4. Anal. Calcd for $C_{15}H_{19}F_2NO_4$: C, 57.14; H, 6.07; N, 4.44. Found: C, 57.01; H, 6.13; N, 4.41.

(4-(Difluoromethoxy)tetrahydro-2*H*-pyran-4-yl)-methanamine (3j). Compound **2j** (7.3 g, 0.232 mol, 1 equiv) was dissolved in 100 mL of methanol, and 1 g of 5% Pd/C was added. The mixture was stirred under 30 atm of H_2 for 48 h at room temperature. Then Pd/C was filtered out, and the reaction mixture was concentrated under vacuum. The product **3j** was purified by distillation under vacuum (1 Torr, 44 °C). Yield = 42.9% (1.8 g).

The product is a transparent colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.24 (m, 2H), 1.64−1.86 (m, 4H), 2.87 (s, 2H), 3.74−3.76(m, 4H), 6.54 (t, 1H, ^2J = 77.8 Hz, CF_2H). ^{19}F NMR (376 MHz, $CDCl_3$): δ = −77.2 (d, 2F, $^2J_{H-F}$ = 84.7 Hz). $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ = 33.2, 49.3, 63.1, 79.4, 115.2 (t, $^1J_{C-F}$ = 231.2 Hz, CF_2H). Anal. Calcd for $C_7H_{13}F_2NO_2$: C, 46.40; H, 7.23; N, 7.73. Found: C, 46.53; H, 7.27; N, 7.68.

Benzyl 3-((Difluoromethoxy)methyl)pyrrolidine-1-carboxylate (2k). Compound **1k** (40g, 0.17 mol, 1 equiv) was dissolved in 400 mL of acetonitrile, and copper iodide (6.5 g, 0.034 mol, 0.2 equiv) was added. The mixture was heated to 50 °C, and a solution of 2-fluorosulfonyl-2,2-difluoroacetic acid (45.4 g, 0.2549 mol, 1.5 equiv) in

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100 mL acetonitrile was added dropwise over a period of 45 min. The reaction mixture was heated for an additional 30 min at 50 °C. Next, acetonitrile was evaporated, the remainder was dissolved in EtOAc, and the insoluble solid was filtered out. The resulting solution of EtOAc was evaporated, and the crude of **2k** was purified by column chromatography (hexane/EtOAc 7:1, R_f = 0.6). Yield = 80% (39 g).

The product is a transparent thick oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.67 (m, 1H), 1.99 (br s, 1H), 2.48 (m, 1H, $CH_{pyrrolidine}$), 3.14−3.37 (m, 2H), 3.49−3.81 (m, 4H), 5.08 (s, 2H), 6.16 (t, 1H, $^2J_{H-F}$ = 74.7 Hz, CF_2H), 7.28−7.33 (m, 5H). ^{19}F NMR (376 MHz, $CDCl_3$): δ = −85.0 (d, F, $^2J_{H-F}$ = 74.2 Hz), −84.9 (d, F, $^2J_{H-F}$ = 74.2 Hz). ^{13}C{^{1}H} NMR (125.7 MHz, $CDCl_3$): δ = 27.5, 28.3, 37.6, 38.5, 45.2, 45.6, 48.5, 48.9, 63.3, 66.9, 115.9 (t, $^1J_{C-F}$ = 262.3 Hz, CF_2H), 128.0, 128.1, 128.6, 137.1, 154.9. Anal. Calcd for $C_{14}H_{17}F_2NO_3$: C, 58.99; H, 6.01; N, 4.91. Found: C, 58.93; H, 6.07; N, 4.83.

3-((Difluoromethoxy)methyl)pyrrolidine (3k). Compound **2k** (30 g, 0.105 mol, 1 equiv) was dissolved in 150 mL of methanol, and 3 g of 5% Pd/C was added. The mixture was stirred under 30 atm of H_2 for 36 h at room temperature. After completion of the reaction, Pd/C was filtered out, and the reaction mixture was concentrated under vacuum. The product **3k** was purified by distillation under vacuum (18 Torr, 57 °C). Yield = 68.6% (10.9 g).

The product is a transparent colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.15−1.20 (m, 1H), 1.61−1.70 (m, 1H), 1.75 (s, 1H), 2.11−2.18 (m, 1H), 2.41−2.45 (m, 1H), 2.59−2.80 (m, 3H), 3.46−3.56 (m, 2H), 5.95 (t, 1H, $^2J_{H-F}$ = 75.1 Hz, CF_2H). ^{19}F NMR (376 MHz, $CDCl_3$): δ = −84.5 (d, 2F, $^2J_{H-F}$ = 77.0 Hz). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 28.4, 37.8, 46.2, 49.5, 65.5 (t, J = 4.7 Hz), 115.4 (t, $^1J_{C-F}$ = 258.8 Hz, CF_2H). Anal. Calcd for $C_6H_{11}F_2NO$: C, 47.68; H, 7.34; N, 9.27. Found: C, 47.81; H, 7.29; N, 9.21.

(*S*)-Benzyl 3-(Difluoromethoxy)pyrrolidine-1-carboxylate (2l). Compound **1l** (50g, 0.226 mol, 1 equiv) was dissolved in 400 mL of acetonitrile, and copper iodide (8.6 g, 0.045 mol, 0.2 equiv) was added. The mixture was heated to 50 °C, and a solution of 2-fluorosulfonyl-2,2-difluoroacetic acid (52.3 g, 0.294 mol, 1.3 equiv) in 100 mL of acetonitrile was added dropwise over a period of 45 min. The reaction mixture was heated for additional 30 min at 50 °C. Next, acetonitrile was evaporated, the remainder was dissolved in EtOAc, and the insoluble solids were filtered out. The resulting solution of EtOAc was evaporated, and the crude of **2l** was purified by column chromatography (hexane/EtOAc 7:1, R_f = 0.6). Yield = 84.8% (52 g).

The product is a transparent colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, ethyl acetate inside): δ = 2.06 (br s, 2H), 3.50−3.58 (m, 4H), 4.79 (m, 1H), 5.11 (s, 2H), 6.20 (t, 1H, $^2J_{H-F}$ = 74.8 Hz, CF_2H), 7.28−7.34 (m, 5H). ^{19}F NMR (376 MHz, $CDCl_3$): δ = −83.1 (d, 2F, $^2J_{H-F}$ = 72.5 Hz). ^{13}C{^{1}H} NMR (125.7 MHz, $CDCl_3$): δ = 31.6, 32.4, 43.6, 44.0, 52.0, 52.3, 66.9, 72.5, 73.1, 115.8 (t, $^1J_{C-F}$ = 273.0 Hz, CF_2H), 127.9, 128.0, 128.5, 136.8, 154.8. Anal. Calcd for $C_{13}H_{15}F_2NO_3$: C, 57.56; H, 5.57; N, 5.16. Found: C, 57.70; H, 5.61; N, 5.11.

(*S*)-3-(Bifluoromethoxy)pyrrolidine (3l). Compound **2l** (52 g, 0.192 mol, 1 equiv) was dissolved in 300 mL of methanol, and 5 g of 5% Pd/C was added. The mixture was stirred under 30 atm of H_2 for 36 h at room temperature. Then Pd/C was filtered out, and the reaction mixture was concentrated under vacuum. The product **3l** was purified by distillation under vacuum (18 Torr, 51 °C). Yield = 55.2% (14.5 g).

The product is a transparent colorless liquid, $[\alpha]_D$ = −9.03 (EtOH, c = 72.925 mmol/L). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.87−2.00 (m, 3H), 2.81−3.11 (m, 4H), 4.71 (br s, 1H), 6.17 (t, 1H, $^2J_{H-F}$ = 74.6 Hz, CF_2H). ^{19}F NMR (376 MHz, $CDCl_3$): δ = −82.1 (d, 2F, $^2J_{H-F}$ = 74.1 Hz). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 33.6, 45.5, 54.0, 75.8, 116.0 (t, $^1J_{C-F}$ = 258.4 Hz, CF_2H). Anal. Calcd for $C_5H_9F_2NO$: C, 43.79; H, 6.62; N, 10.21. Found: C, 43.65; H, 6.65; N, 10.15.

(*R*)-Benzyl 3-(Difluoromethoxy)pyrrolidine-1-carboxylate (2m). Compound **1m** (40 g, 0.181 mol, 1 equiv) was dissolved in 400 mL of acetonitrile, and copper iodide (6.9 g, 0.036 mol, 0.2 equiv) was added. The mixture was heated to 50 °C, and a solution of 2-fluorosulfonyl-2,2-difluoroacetic acid (41.9 g, 0.235 mol, 1.3 equiv) in 100 mL acetonitrile was added dropwise over a period of 45 min. The reaction mixture was heated for additional 30 min at 50 °C. Then acetonitrile was evaporated, the remainder was dissolved in EtOAc, and the insoluble solids were filtered out. The resulting solution of EtOAc was evaporated, and the crude of **2m** was purified by column chromatography (hexane/EtOAc 7:1, R_f = 0.6). Yield = 82.6% (40.5 g).

The product is a transparent colorless oil. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.08 (br s, 2H), 3.55−3.57 (m, 4H), 4.79 (m, 1H), 5.12 (s, 2H), 6.21 (t, 1H, $^2J_{H-F}$ = 74.4 Hz, CF_2H), 7.29−7.35 (m, 5H). ^{19}F NMR (376 MHz, $CDCl_3$): δ = −83.0 (d, 2F, $^2J_{H-F}$ = 74.5 Hz). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 31.2, 31.9, 43.2, 43.5, 51.5, 51.9, 66.5, 72.2, 72.9, 115.5 (t, $^1J_{C-F}$ = 261.9 Hz, CF_2H), 127.5, 128.1, 136.4, 155.3. Anal. Calcd for $C_{13}H_{15}F_2NO_3$: C, 57.56; H, 5.57; N, 5.16. Found: C, 57.41; H, 5.52; N, 5.13.

(*R*)-3-(Difluoromethoxy)pyrrolidine (3m). Compound **2m** (40.5 g, 0.149 mol, 1 equiv) was dissolved in 300 mL of methanol and 5 g of 5% Pd/C was added. The mixture was stirred under 30 atm of H_2 for 36 h at room temperature. Then Pd/C was filtered out, and the mixture was concentrated under vacuum. The product **3m** was purified by distillation under vacuum (18 Torr, 51 °C). Yield = 63.5% (13 g).

The product is a transparent colorless liquid, $[\alpha]_D$ = +6.31 (EtOH, c = 72.925 mmol/L). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.95−2.05 (m, 2H), 2.92−3.14 (m, 3H), 3.43 (s, 2H), 4.75 (s, 1H), 6.20 (t, 1H, $^2J_{H-F}$ = 74.4 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ = −82.3 (d, 2F, $^2J_{H-F}$ = 74.5 Hz). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 33.3, 45.1, 53.5, 75.4, 116.0 (t, $^1J_{C-F}$ = 295.8 Hz, CF_2H). Anal. Calcd for $C_5H_9F_2NO$: C, 43.79; H, 6.62; N, 10.21. Found: C, 43.72; H, 6.70; N, 10.15.

Benzyl 3-(Difluoromethoxy)azetidine-1-carboxylate (2n). Compound **1n** (44.7 g, 0.218 mol, 1 equiv) was dissolved in 400 mL of acetonitrile, and copper iodide (8.2 g, 0.043 mol, 0.2 equiv) was added. The mixture was heated to 50 °C, and a solution of 2-fluorosulfonyl-2,2-difluoroacetic acid (57.65 g, 0.324 mol, 1.5 equiv) in 100 mL of acetonitrile was added dropwise over a period of 45 min. The reaction mixture was heated for an additional 30 min at 50 °C. Then acetonitrile was evaporated, the remainder was dissolved in EtOAc, and the insoluble solid was filtered out. Afterward, the resulting solution of EtOAc was evaporated, and the crude of **2n** was purified by column chromatography (hexane/EtOAc 7:1, R_f = 0.6). Yield = 86.5% (48 g).

The product is a transparent yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.06−4.09 (m, 2H), 4.26−4.31 (m, 2H), 4.93−4.94 (m, 1H), 5.11 (s, 2H), 6.24 (t, 1H, $^2J_{H-F}$ = 73.0 Hz, CF_2H), 7.36 (br s, 5H). ^{19}F NMR (376 MHz, $CDCl_3$): δ = −84.9 (d, 2F, $^2J_{H-F}$ = 74.9 Hz). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 56.8, 62.1 (t, 66.3 J = 6.5 Hz), 66.8, 115.3 (t, $^1J_{C-F}$ = 260.6 Hz, CF_2H), 127.9, 128.0, 128.4, 136.3, 156.1. Anal. Calcd for $C_{12}H_{13}F_2NO_3$: C, 56.03; H, 5.09; N, 5.45. Found: C, 55.89; H, 5.16; N, 5.39.

3-(Difluoromethoxy)azetidine (3n). Compound **2n** (48 g, 0.187 mol, 1 equiv) was dissolved in 300 mL of methanol, and 5 g of 5% Pd/C was added. The mixture was stirred under 30 atm of H_2 for 36 h at room temperature. Then Pd/C was filtered out, and the reaction mixture was concentrated under vacuum. The product **3n** was purified by distillation under vacuum (18 Torr, 47 °C). Yield = 53.5% (12.3 g).

The product is a transparent colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.08 (s, 1H), 3.70−3.71 (m, 4H), 4.91 (quintet, 1H, ^3J = 7.0 Hz), 6.21 (t, 1H, $^2J_{H-F}$ = 73.9 Hz, CF_2H). ^{19}F NMR (376 MHz, $CDCl_3$): δ = −84.1 (d, 2F, $^2J_{H-F}$ = 74.4 Hz). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 54.3, 66.3, 115.4 (t, $^1J_{C-F}$ = 261.1 Hz, CF_2H). Anal. Calcd for $C_4H_7F_2NO$: C, 39.03; H, 5.73; N, 11.38. Found: C, 39.11; H, 5.79; N, 11.34.

Benzyl 2-(Difluoromethoxy)acetate (2o). Compound **1o** (50.15 g, 0.302 mol, 1 equiv) was dissolved in 500 mL of acetonitrile, and copper iodide (11.5 g, 0.06 mol, 0.2 equiv) was added. The mixture was heated to 50 °C, and a solution of 2-fluorosulfonyl-2,2-difluoroacetic acid (80.65 g, 0.453 mol, 1.5 equiv) in 100 mL of acetonitrile was added dropwise over a period of 45 min. The reaction mixture was heated for additional 30 min at 50 °C. Then acetonitrile was evaporated, the remainder was dissolved in EtOAc and the solid phase was filtered out. The resulting solution of EtOAc was evaporated

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and the crude of **2o** was purified by column chromatography (hexane/EtOAc - 1:7, R_f = 0.7). Yield =81.2% (53g).

The product is a transparent colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.44 (s, 2H), 5.21 (s, 2H), 6.34 (t, 1H, $^2J_{H-F}$ = 73.9 Hz, CF_2H), 7.36 (br s, 5H).

^{19}F NMR (376 MHz, $CDCl_3$): δ = −86:6 (d, 2F, $^2J_{H-F}$ = 73.6 Hz).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 59.9, 67.3, 115.3 (t, $^1J_{C-F}$ = 272.0 Hz, CF_2H), 128.5, 128.8, 134.9, 167.6.

Anal. Calcd for $C_{10}H_{10}F_2O_3$: C, 55.56; H, 4.66; F, 17.58. Found: C, 55.67; H, 4.71; F, 17.52.

2-(Difluoromethoxy)acetic acid (3o). Compound **2o** (53 g, 0.245 mol, 1 equiv) was dissolved in 300 mL of methanol, and 7 g of 5% Pd/C was added. The mixture was stirred under 30 atm of H_2 for 72 h at room temperature. After completion of the reaction, Pd/C was filtered out, and the reaction mixture was concentrated under vacuum. The product **3o** was dissolved in a concentrated solution of sodium bicarbonate, and the obtained solution was washed three times with EtOAc. Then the solution was carefully acidified with a concentrated solution of citric acid and extracted three times with EtOAc. The combined organic layer was washed twice with brine, dried over magnesium sulfate, and concentrated under vacuum to give the product **3o**. Yield = 64.1% (19.8 g).

The product is a white solid, mp =46−48 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.51 (s, 2H), 6.36 (t, 1H, $^2J_{H-F}$ = 75.9 Hz, CF_2H), 10.62 (br s, 1H). ^{19}F NMR (376 MHz, $CDCl_3$): δ = −86.8 (d, 2F, $^2J_{H-F}$ = 87.9 Hz). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 59.1, 115.2 (t, $^1J_{C-F}$ = 285.6 Hz, CF_2H), 173.7. Anal. Calcd for $C_3H_4F_2O_3$: C, 28.58; H, 3.20. Found: C, 28.52; H, 3.10.

1,4-Benzyl 4-(Difluoromethoxy)cyclohexanecarboxylate (2p) (Mixture of Diastereomers). Compound **1p** (as a mixture of *cis*- and *trans*-isomers 7:3) (42 g, 0.179 mol, 1 equiv) was dissolved in 500 mL of acetonitrile, and copper iodide (6.85 g, 0.36 mol, 0.2 equiv) was added. The mixture was heated to 50 °C, and a solution of 2-fluorosulfonyl-2,2-difluoroacetic acid (47.9 g, 0.269 mol, 1.5 equiv) in 100 mL of acetonitrile was added dropwise over a period of 45 min. The reaction mixture was heated for an additional 30 min at 50 °C. Then acetonitrile was evaporated, the remainder was dissolved in EtOAc, and the insoluble solids were filtered out. The resulting solution of EtOAc was evaporated, and the crude of **2p** was purified by column chromatography (hexane/EtOAc 1:7, R_f = 0.6). Yield = 73.4% (37.4 g).

The product is a transparent colorless thick oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.47−2.42 (m, 8H), 4.06, 4.33 (s, 1H), 5.10 (br s, 1H), 5.26 (s, 2H), 6.21 (t, 1H, $^2J_{H-F}$ = 73.9 Hz, CF_2H), 7.34 (br s, 5H). ^{19}F NMR (376 MHz, $CDCl_3$): δ = −83.6 (d, 2F, $^2J_{H-F}$ = 73.7 Hz), −83.1 (d, 2F, $^2J_{H-F}$ = 73.7 Hz). ^{13}C NMR{^{1}H} (100 MHz, DMSO-d_6) (mixture of diastereomers): δ = 14.0, 22.1, 23.2, 26.3, 29.3, 31.3, 40.8, 65.5, 74.3, 117.2 (t, $^1J_{C-F}$ = 253.0 Hz, CF_2H), 117.4 (t, $^1J_{C-F}$ = 253.0 Hz, CF_2H), 127.8, 128.0, 128.5, 136.3, 136.4, 174.2, 174.2. Anal. Calcd for $C_{15}H_{18}F_2O_3$: C, 63.37; H, 6.38. Found: C, 63.22; H, 6.43.

1,4-*cis*-(Difluoromethoxy)cyclohexanecarboxylic Acid (3p). Compound **2p** (30 g, 0.106 mol, 1 equiv) was dissolved in 300 mL of methanol, and 6.5 g of 5% Pd/C was added. The mixture was stirred under 30 atm of H_2 for 72 h at room temperature. Then Pd/C was filtered out, and the reaction mixture was concentrated under vacuum. The crude was dissolved in a concentrated solution of sodium bicarbonate, and the obtained solution was washed three times with EtOAc. Then the solution was carefully acidified with a concentrated solution of citric acid and extracted three times with EtOAc. Combined organic layer was washed twice with brine, dried over magnesium sulfate, and concentrated under vacuum and recrystallized from petroleum ether−ethyl acetate (10:1) to give the product **3p**. Yield = 60% (12.3 g). Compound **3p** was obtained as a pure *cis*-isomer.

The product is a white solid. Mp = 117−119 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.45−1.61 (m, 4H), 2.07−2.10 (m, 4H), 2.32−2.37 (m, 1H), 4.09 (br s, 1H), 6.23 (t, 1H, $^2J_{H-F}$ = 74.6 Hz, CF_2H), 11.0 (br s, 1H). ^{19}F NMR (376 MHz, $CDCl_3$): δ = −81.2 (d, 2F, $^2J_{H-F}$ = 76.4 Hz). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 28.3, 31.6, 41.4, 73.0, 116.2 (t, $^1J_{C-F}$ = 258.4 Hz, CF_2H), 181.6. Anal. Calcd for $C_8H_{12}F_2O_3$: C, 49.48; H, 6.23; F, 19.57. Found: C, 49.33; H, 6.19.

Benzyl 3-(Difluoromethoxy)cyclobutanecarboxylate (2q) (Mixture of Diastereomers). Compound **1q** (12.2 g, 0.059 mol, 1 equiv) was dissolved in 200 mL of acetonitrile, and copper iodide (2.25 g, 0.012 mol, 0.2 equiv) was added. The mixture was heated to 50 °C, and a solution of 2-fluorosulfonyl-2,2-difluoroacetic acid (15.8 g, 0.089 mol, 1.5 equiv) in 100 mL of acetonitrile was added dropwise over a period of 45 min. The reaction mixture was heated for an additional 30 min at 50 °C. Then acetonitrile was evaporated, the remainder was dissolved in EtOAc, and the insoluble solid was filtered out. The resulting solution of EtOAc was evaporated, and the crude of **2q** was purified by column chromatography (hexane/EtOAc 1:7, R_f = 0.6). Yield = 73.9% (11.2 g).

The product is a transparent colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of diastereomers): δ = 2.40−2.47 (m, 2H), 2.57−2.59 (m, 2H), 2.71−2.75 (m, 1H), 4.51−4.57 (m, 1H), 5.11 (s, 2H), 6.13 (t, 1H, $^2J_{H-F}$ = 74.0 Hz, CF_2H), 7.34 (br s, 5H). ^{19}F NMR (376 MHz, $CDCl_3$): δ = −83.6 (d, 2F, $^2J_{H-F}$ = 72.0 Hz). ^{13}C{^{1}H}NMR (125.7 MHz, $CDCl_3$): δ = 29.9, 34.4, 63.9, 66.7, 115.7 (t, $^1J_{C-F}$ = 259.8 Hz, CF_2H), 128.3, 128.4, 128.7, 136.0, 173.7. Anal. Calcd for $C_{13}H_{14}F_2O_3$: C, 60.93; H, 5.51. Found: C, 61.03; H, 5.45.

3-(Difluoromethoxy)cyclobutanecarboxylic Acid (3q) (Mixture of Diastereomers). Compound **2q** (3.5 g, 0.014 mol, 1 equiv) was dissolved in 100 mL of methanol, and 0.9 g of 5% Pd/C was added. The mixture was stirred under 30 atm of H_2 for 36 h at room temperature. Then Pd/C was filtered out, and the reaction mixture was concentrated under vacuum. The product **3q** was dissolved in a concentrated solution of sodium bicarbonate, and the obtained solution was washed three times with EtOAc. Then the solution was carefully acidified with a concentrated solution of citric acid and extracted three times with EtOAc. The combined organic layer was washed twice with brine, dried over magnesium sulfate, and concentrated under vacuum to give the product **3q**. Yield = 57.3% (1.3 g).

The product is a transparent colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of diastereomers): δ = 2.43−2.48 (m, 2H), 2.61−2.63 (m, 2H$_{butyl}$), 2.71−2.76 (m, 1H), 4.55−4.59 (m, 1H), 6.15 (t, 1H, $^2J_{H-F}$ = 74.0 Hz, CF_2H), 12.0 (s, 1H). ^{19}F NMR (376 MHz, $CDCl_3$): δ = −83.9 (d, 2F, $^2J_{H-F}$ = 71.6 Hz). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 29.3, 31.6, 33.7, 63.1 (t, J = 5.6 Hz), 115.1 (t, $^1J_{C-F}$ = 261.2 Hz, CF_2H), 181.1. Anal. Calcd for $C_6H_8F_2O_3$: C, 43.38; H, 4.85. Found: C, 43.49; H, 4.91.

***tert*-Butyl (*S*)-3-(Methoxycarbonyl)-3-(difluoromethoxy)-propylcarbamate (2r).** Compound **1r** (3.2 g, 0.014 mol, 1 equiv) was dissolved in 50 mL of acetonitrile, and copper iodide (0.5 g, 0.0026 mol, 0.2 equiv) was added. The mixture was heated to 50 °C, and a solution of 2-fluorosulfonyl-2,2-difluoroacetic acid (2.95 g, 0.017 mol, 1.2 equiv) in 20 mL of acetonitrile was added dropwise over a period of 30 min. The reaction mixture was heated for an additional 30 min at 50 °C. Then acetonitrile was evaporated, the remainder was dissolved in EtOAc, and the insoluble solids were filtered out. The resulting solution of EtOAc was evaporated and the crude of **2r** was purified by column chromatography (hexane/EtOAc 3:1, R_f = 0.65). Yield = 79.8% (3.1 g).

The product is a transparent colorless oil, $[\alpha]_D$ = −20.2 (MeOH, c = 35.3 mmol/L). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.45 (s, 9H), 1.99−2.08 (m, 2H), 3.27 (br s, 2H), 3.79 (s, 3H), 4.65−4.68 (m, 2H), 6.36 (t, 1H, $^2J_{H-F}$ = 74.6 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ = −85.0 (dd, F, $^2J_{F-F}$ = 160.2 Hz, $^2J_{H-F}$ = 73.4 Hz), −83.9 (dd, F, $^2J_{F-F}$ = 158.5 Hz, $^2J_{H-F}$ = 71.8 Hz). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 27.7, 28.4, 32.4, 52.6, 69.8, 80.0, 115.5 (t, $^1J_{C-F}$ = 272.0 Hz, CF_2H), 155.8, 170.7. Anal. Calcd for $C_{11}H_{19}F_2NO_5$: C, 46.64; H, 6.76; N, 4.94. Found: C, 46.78; H, 6.70; N, 5.02.

(2*S*)-2-(Difluoromethoxy)-4-[[(1,1-dimethylethoxy)-carbonyl]amino]butanoic Acid (3r). Compound **2r** (1 g, 0.0035 mol, 1 equiv) was dissolved in 20 mL of THF, and a solution of $LiOHxH_2O$ (0.178 g, 0.0042 mol, 1.2 equiv) in 5 mL of water was added all at once at 0 °C. The reaction mixture was heated to room temperature and was stirred for 4 h. Afterward, the reaction mixture

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was diluted with 25 mL of EtOAc and 20 mL of water. The organic layer was separated and washed twice with 20 mL of water. The combined water solution was washed once with 25 mL of EtOAc, carefully acidified with 20 mL of a concentrated solution of citric acid, and extracted three times with 30 mL of EtOAc. The combined organic layer was washed with brine, dried with magnesium sulfate, and concentrated under vacuum to give compound **3r**. Yield = 57.9% (0.55 g).

The product is a white solid. Mp = 96−99 °C. $[\alpha]_D$ = −21.3 (MeOH, *c* = 37.14 mmol/L). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.37 (s, 9H), 1.76−1.91 (m, 2H), 3.01 (br s, 2H), 4.50−4.52 (m, 1H), 6.70 (t, 1H, $^2J_{H-F}$ = 76.0 Hz, CF_2H), 6.87 (br s, 1H), 13.20 (br s, 1H). ^{19}F NMR (376 MHz, DMSO-d_6): δ = −82.3 (d, 2F, $^2J_{H-F}$ = 75.5 Hz). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6): δ = 28.2, 32.0, 36.0, 71.5, 77.7, 116.9 (t, $^1J_{C-F}$ = 280.5 Hz, CF_2H), 155.6, 171.3. Anal. Calcd for $C_{10}H_{17}F_2NO_5$: C, 44.61; H, 6.36; N, 5.20. Found: C, 44.72; H, 6.30; N, 5.17.

(2*S*,4*R*)-1-*tert*-Butyl 2-Methyl 4-(difluoromethoxy)-pyrrolidine-1,2-dicarboxylate (2s). Compound **1s** (7.5 g, 0.031 mol, 1 equiv) was dissolved in 100 mL of acetonitrile, and copper iodide (1.18 g, 0.0062 mol, 0.2 equiv) was added. The mixture was heated to 50 °C, and a solution of 2-fluorosulfonyl-2,2-difluoroacetic acid (6.6 g, 0.037 mol, 1.2 equiv) in 30 mL of acetonitrile was added dropwise over a period of 30 min. The reaction mixture was kept for an additional 30 min at 50 °C. Then acetonitrile was evaporated, the remainder was dissolved in EtOAc, and the insoluble solids were filtered out. The resulting solution of EtOAc was evaporated, and the crude of **2s** was purified by column chromatography (hexane/EtOAc 1:4, R_f = 0.7). Yield = 84.2% (7.4 g).

The product is a transparent colorless oil, $[\alpha]_D$ = +20.2 (MeOH, *c* = 33.87 mmol/L). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.46 (s, 3H), 1.51 (s, 6H), 2.21−2.26 (m, 1H), 2.45−2.50 (m, 1H), 3.59−3.78 (m, 2H), 3.79 (s, 3H), 4.39−4.50 (m, 1H), 4.90 (s, 1H), 6.28 (t, 1H, $^2J_{H-F}$ = 74.8 Hz, CF_2H). ^{19}F NMR (376 MHz, $CDCl_3$): δ = −84.0- −82.8 (m, 2F). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 28.2, 28.3, 36.2, 37.2, 52.1, 52.3, 71.2, 71.9, 80.5, 115.6 (t, $^1J_{C-F}$ = 262.8 Hz, CF_2H), 153.4, 154.1, 172.6. Anal. Calcd for $C_{12}H_{19}F_2NO_5$: C, 48.83; H, 6.49; N, 4.74. Found: C, 48.68; H, 6.45; N, 4.69.

(2*S*,4*R*)-1-(*tert*-Butoxycarbonyl)-4-(difluoromethoxy)-pyrrolidine-2-carboxylic Acid (3s). Compound **2s** (2.75 g, 0.0093 mol, 1 equiv) was dissolved in 40 mL of THF, and a solution of LiOH·H_2O (0.47 g, 0.0112 mol, 1.2 equiv) in 10 mL of water was added all at once at 0 °C. The reaction mixture was heated to room temperature and was stirred for 4 h. Afterward, the reaction mixture was diluted with 75 mL of EtOAc and 40 mL of water. The organic layer was separated and washed twice with 20 mL of water. The combined water solution was washed once with 50 mL of EtOAc, carefully acidified with 35 mL of a concentrated solution of citric acid, and extracted three times with 40 mL of EtOAc. The combined organic layer was washed with brine, dried over magnesium sulfate, and concentrated under vacuum to give compound **3s**. Yield = 61.1% (1.6 g).

The product is a white solid. Mp = 70−75 °C. $[\alpha]_D$ = −36.6 (EtOH, *c* = 35.55 mmol/L). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.14 (s, 3H), 1.45 (s, 6H), 2.23−2.47 (m, 2H), 3.56−3.68 (m, 2H), 4.35−4.42 (m, 1H), 4.83 (s, $1H_{idine}$), 6.21 (t, 1H, $^2J_{H-F}$ = 73.5 Hz, CF_2H), 8.70 (br s, 1H). ^{19}F NMR (376 MHz, $CDCl_3$): δ = −84.0 to −82.9 (m, 2F). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 28.2, 28.3, 35.5, 37.2, 52.1, 52.5, 71.2, 71.5, 81.0, 81.8, 115.6 (t, $^1J_{C-F}$ = 262.6 Hz, CF_2H), 153.6, 155.7, 177.8. Anal. Calcd for $C_{11}H_{17}F_2NO_5$: C, 46.97; H, 6.09; N, 4.98. Found: C, 47.09; H, 6.15; N, 4.91.

(*S*)-3-(Difluoromethoxy)pyrrolidin-2-one (5). Compound **2r** (1.5 g, 0.0053 mol, 1 equiv) was dissolved in 5 mL of DCM and cooled to 0 °C using an ice bath. Afterward, trifluoroacetic acid (5 mL, 0.0653 mol, 12.3 equiv) was added all at once. The reaction mixture was stirred for 30 min at 0 °C and then basified with a concentrated solution of potassium carbonate. The obtained suspension was extracted three times with 30 mL of EtOAc. The combined organic layer was washed with brine, dried with magnesium sulfate, and concentrated under vacuum. The crude product was purified by flash chromatography (hexane/EtOAc 5:1) to give compound **5**. Yield = 52.5% (0.42 g).

The product is a white solid. Mp = 57−61 °C. $[\alpha]_D$ = −72.9 (MeOH, *c* = 66.18 mmol/L). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.16−2.53 (m, 2H), 3.28−3.45 (m, 2H), 4.67 (t, 1H, ^3J = 8.1 Hz), 6.48 (t, 1H, $^2J_{H-F}$ = 75.8 Hz), 7.50 (br s, 1H). ^{19}F NMR (376 MHz, $CDCl_3$): δ = −84.3 (dd, F, $^2J_{H-F}$ = 158.5 Hz, $^2J_{H-F}$ = 75.7 Hz), −83.4 (dd, F, $^2J_{F-F}$ = 158.5 Hz, $^2J_{H-F}$ = 73.5 Hz). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 28.7, 38.8, 70.8, 115.8 (t, $^1J_{C-F}$ = 258.4 Hz, CF_2H), 173.7. Anal. Calcd for $C_5H_7F_2NO_2$: C, 39.74; H, 4.67; N, 9.27. Found: C, 39.80; H, 4.71; N, 9.33.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00628.

Detailed experimental procedures and characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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