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Synthesis and Reactions of Fluorous Carbobenzyloxy (^{F}Cbz) Derivatives of α-Amino Acids

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Fluorous carbobenzyloxy (^{F}Cbz) reagents $RfCH_2CH_2C_6H_4CH_2OC(O)OSu$ (where Su is succinimidoyl and Rf is C_6F_{13} and C_8F_{17}) have been used to make ^{F}Cbz derivatives of 18 of the 20 natural amino acids. The potential utility of this new family of reagents in both standard fluorous synthesis with spe separation and fluorous quasiracemic synthesis is illustrated with representative reactions of the ^{F}Cbz-Phe derivatives.

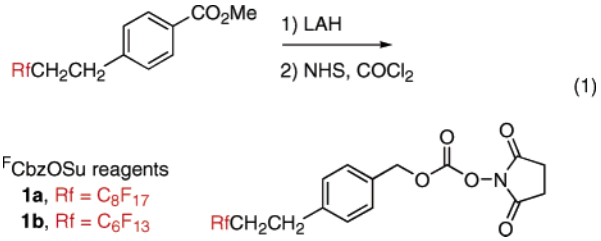
Introduction

Fluorous tagging methods for small molecule synthesis appeal because they couple the breadth of solution-phase reaction chemistry with convenient yet effective methods of separation.[2] In standard fluorous synthesis methods, solid-phase extraction over fluorous silica gel quickly bifurcates mixtures into fluorous-tagged and untagged fractions.[3] In fluorous mixture synthesis, fluorous chromatography is used to separate fluorous-tagged molecules from each other based on the tag.[4] The applicability of these methods is directly proportional to the availability of fluorous tags.

Fluorous tags are often fashioned after standard protecting groups for organic functionalities by addition of one or more fluoroalkyl substituents. A small assortment of fluorous oxygen protecting groups is known,[2,4,5] and fluorous Boc (^{F}Boc) groups show good potential for nitrogen protection.[6] Carbobenzyloxy (Cbz) groups are popular for nitrogen protection,[7] and very recently van Boom and co-workers reported the synthesis of several fluorous Cbz reagents.[8] They used these reagents for tagging and purification in solid-phase synthesis of small peptides. We describe herein the synthesis of two families of ^{F}Cbz-tagged α-amino acids, and we validate the utility of representative family members in both standard fluorous synthesis and fluorous mixture synthesis applications.

Results and Discussion

Fluorous CbzOSu reagents **1a** and **1b** with the *N*-hydroxysuccinimide group were readily prepared as shown in eq 1. Reduction of the appropriate methyl ester[9]



(Rf = C_8F_{17} or C_6F_{13}) with LAH followed by exposure of the resulting alcohol to phosgene and *N*-hydroxysuccinimide (NHS) gave **1a**,**b**. These reagents are now commercially available from Fluorous Technologies, Inc.[9]

^{F}Cbz reagents **1a**,**b** are white solids that are transferred in the open atmosphere by standard techniques, and their reactions with amines and amino acids are straightforward. The tagging of (L)-phenylalanine with larger ^{F}Cbz reagent **1a** is typical (Figure 1).

A solution of **1a** (1.44 mmol) in THF (30 mL) was added to (L)-phenylalanine (2.1 mmol) and triethylamine (2.1 mmol) in water (5 mL). After 1 h, the mixture was

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(9) www.fluorous.com. DPC is the Founder of FTI and holds an equity stake in the company.

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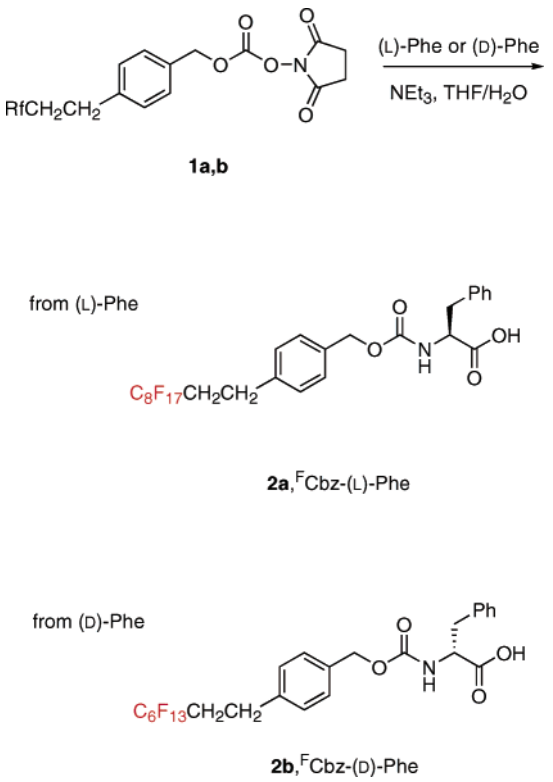


FIGURE 1. FCbz reagents and tagged phenylalanine quasi-enantiomers.

acidified to pH 2 with HCl and extracted with ethyl acetate. The ethyl acetate phase was washed, dried, and evaporated to provide substantially pure FCbz-(L)-Phe **2a** in 97% yield. The product could be further purified by recrystallization from acetonitrile, if desired. Similarly, (D)-phenylalanine was tagged with the smaller Cbz reagent **1b** to give FCbz-(D)-Phe **2b** in 95% yield.

Sixteen of the twenty common amino acids were tagged in similar reactions, and the results of this series of experiments are summarized in Table 1.

In preparation for a mixture or quasiracemic synthesis applications, all the natural (L)-amino acids were given the larger C_8F_{17} tag, while the unnatural (D)-amino acids got the smaller C_6F_{13} tag. Achiral glycine was tagged with both reagents. Scales ranged from several hundred milligrams to several grams. All 32 of the products were isolated as white solids in good to excellent yield. Further purification by recrystallization was conducted for a little over half of the products. The remainder were deemed sufficiently pure to be used in crude form, although they could almost certainly be recrystallized if desired.

Two different protected forms of cysteine were generated, as shown in Figure 2. Reaction of (L)-cystine with **1a** and (D)-cystine with **1b** gave the corresponding dimeric FCbz derivatives, while reactions of (L)-*S*-benzyl cysteine ((L)-CysSBn) with **1a**,**b** gave the corresponding FCbz-SBn derivative. Once again, all derivatives were white solids. The enantiomers of (ϵ)-Boc-Lys were also tagged in the standard fashion to give the corresponding (ϵ)-Boc-FCbz-Lys analogues in good yields. Finally, preliminary attempts to make FCbz derivatives from free arginine and histidine did not succeed, so either modified procedures or suitably protected amino acids will be needed to generate FCbz analogues of these functionalized amino acids.

TABLE 1. Preparation of FCBz-Tagged Amino Acids[a]

entry	amino acid	FCbz rgt	yield[b]
1	Gly	**1a**	88 (46)
2	(L)-Ala	**1a**	81 (58)
3	(L)-Val	**1a**	89 (46)
4	(L)-Leu	**1a**	84 (52)
5	(L)-Ile	**1a**	89 (66)
6	(L)-Ser	**1a**	100 (69)
7	(L)-Phe	**1a**	97
8	(L)-Asn	**1a**	92
9	(L)-Gln	**1a**	97
10	(L)-Thr	**1a**	82 (65)
11	(L)-Met	**1a**	84 (70)
12	(L)-Asp	**1a**	61 (38)
13	(L)-Gle	**1a**	92 (39)
14	(L)-Trp	**1a**	83 (67)
15	(L)-Tyr	**1a**	92 (69)
16	(L)-Pro[c]	**1a**	87
17	Gly	**1b**	95
18	(D)-Ala	**1b**	92
19	(D)-Val	**1b**	95
20	(D)-Leu	**1b**	85
21	(D)-Ile	**1b**	89
22	(D)-Ser	**1b**	80 (69)
23	(D)-Phe	**1b**	95
24	(D)-Asn	**1b**	92
25	(D)-Gln	**1b**	97
26	(D)-Thr	**1b**	88 (72)
27	(D)-Met	**1b**	95
28	(D)-Asp	**1b**	97
29	(D)-Gle	**1b**	85 (83)
30	(D)-Trp	**1b**	72 (64)
31	(D)-Tyr	**1b**	92 (66)
32	(D)-Pro[c]	**1b**	81

[a] Et_3N, THF/H_2O, 25 °C, 2−24 h. [b] Crude yield (recrystallized yield). [c] $NaHCO_3$ was used as base.

Several reactions of the phenylalanine derivatives (L)-**2a** and (D)-**2b** were undertaken to show the utility of the FCbz-tagged amino acids and to validate separations over fluorous silica gel. Coupling reactions of **2a**,**b** were conducted with four different amines under standard conditions (EDCI, HOBt) as shown in Table 2. The amines were used in excess (4 equiv) and the excess amine and other reagents were removed by rapid solid-phase extraction[3b] of the crude reaction products through Fluoro*Flash* silica gel cartridges.[9] The crude coupled products were isolated in moderate to excellent yields in very good states of purity (see Supporting Information for ^1H NMR spectra). Although the spe's with the C_6F_{13} derivatives succeeded, the retention times of these products on fluorous silica are moderate (see below), so we recommend C_8F_{17} derivatives as first choices for standard fluorous synthesis applications.

The tagging of the (L)- and (D)-amino acids with different tags sets the stage for the formation and reactions of amino acid quasiracemates.[4a,d] To demonstrate the potential, an FCbz-Phe quasiracemate was made by mixing equal portions of (L)-**2a** and (D)-**2b** to give M-**2a**,**b** (where the prefix "M" stands for "mixture"). Quasiracemate M-**2a**,**b** was then reacted with tetrahydroisoquinoline under standard coupling conditions (see Figure 3), and the crude product was both purified and demixed (resolved into its quasienantiomeric components) by HPLC with a preparative Fluoro*Flash* column.[9] Elution was conducted with a linear gradient of

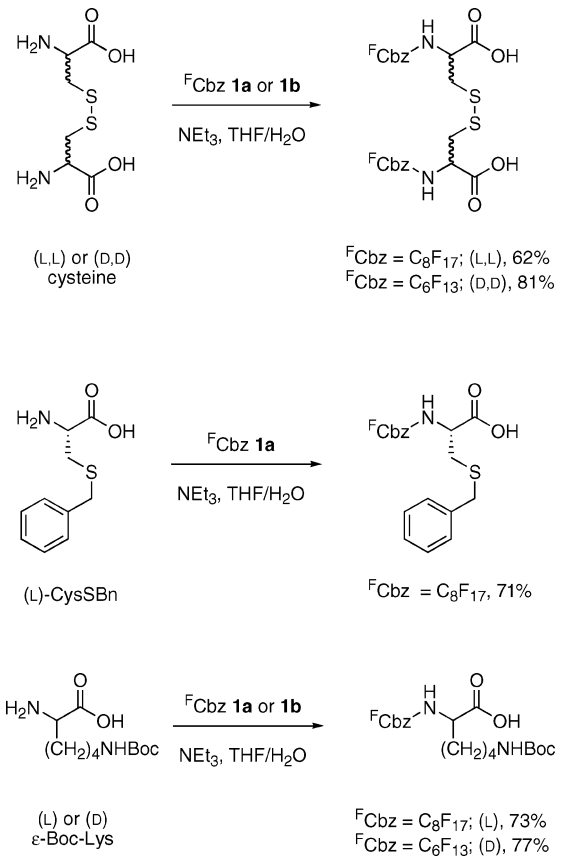
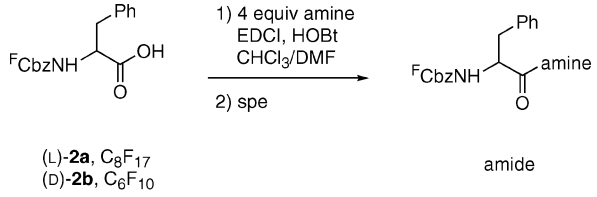
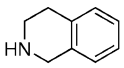
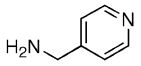
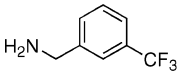


FIGURE 2. FCbz derivatives of cysteine and lysine.

TABLE 2. Reactions of FCBz-Tagged Phenylalanines



Entry	FCbz-Phe	Amine	Amide yield
1	(L)-**2a**		72%
2	(D)-**2b**	"	65%
3	(L)-**2a**	NH_2-C_6H_{11}	62%
4	(D)-**2b**	"	62%
5	(L)-**2a**		44%
6	(D)-**2b**	"	50%
7	(L)-**2a**		90%
8	(D)-**2b**	"	96%

80% acetonitrile water up to 100% acetonitrile over 30 min. Excess amine and coupling reagents eluted with the solvent front at about 2 min (for reference, the standard Cbz-tagged product lacking a fluoroalkyl group also elutes with the solvent front under these conditions). Pure quasienantiomer (D)-**3b** eluted after 10.2 min (83%) and pure quasienantiomer (L)-**3a** eluted after 16.0 min (81%).

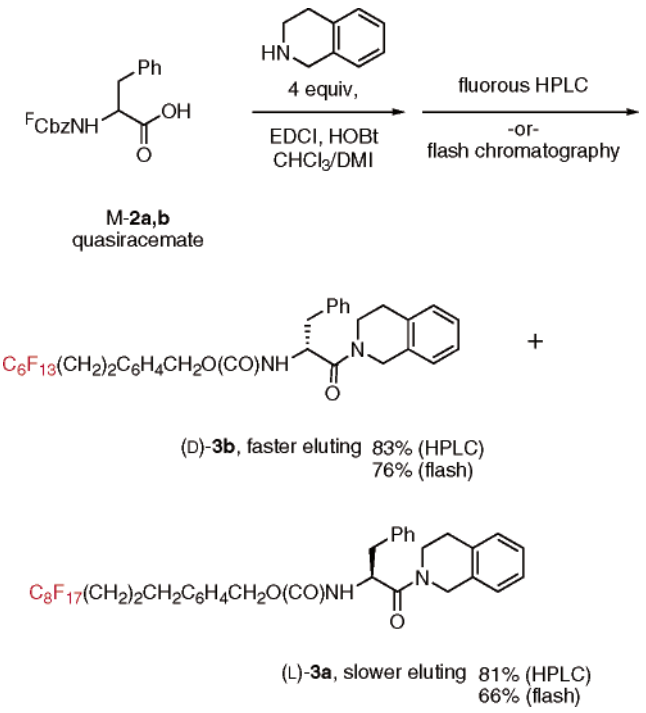


FIGURE 3. Reactions of phenylalanine quasienantiomers.

The large differences in retention time suggested that the crude product could also be purified and demixed by flash chromatography. The reaction was repeated and this time the product was separated by rapid manual ("flash") chromatography over a Fluoro*Flash* cartridge (instead of an HPLC column). Fractions from elution with 80% MeOH/water containing reagents and excess amine were discarded. Fractions from elution with 90% MeOH/water yielded pure quasienantiomer (D)-**3b** (76%). Eluting with absolute MeOH gave pure quasienantiomer (L)-**3a** (66%).

Finally, we briefly investigated the cleavage of the FCbz group by hydrogenation. Adduct **3b** was stirred in MeOH with Pd−C under a hydrogen atmosphere for 5 h. After filtration and flash chromatography, we isolated 83% yield of the corresponding free amine (not shown) alongside 75% of the fluorous toluene $C_6F_{13}CH_2CH_2C_6H_4$-*p*-CH_3. This suggests that FCbz removal under conditions used for standard Cbz groups will be possible.

Conclusions

We suggest that the FCbz amino acids described in this Article and related compounds will be useful reagents in medicinal chemistry, peptide chemistry, and other areas. In traditional applications, the individual reagents function like standard Cbz-protected amino acids with the advantage that the FCbz-tagged products can readily be separated from nonfluorous products by either fluorous spe or chromatography. We currently recommend the longer C_8F_{17} tag for spe separations, but either tag is useful for chromatographic separations.

The quasiracemates generated by deliberate mixing are useful reagents in their own right. For example, coupling of a library of *n* nucleophiles with one quasiracemate followed by *n* chromatographic purifications will give 2*n* products (the products after detagging are enantiomers if the nucleophile is achiral and diastereomers if it is chiral). Further efficiency increases can be extracted if more homologous tags are introduced and structurally different tagged amino acids are mixed for use in fluorous mixture synthesis.[4] Finally, either the fluorous tagging reagents **1a**,**b** or the fluorous amino acids themselves can be used for tagging and purification purposes in solid-phase peptide synthesis.[8]

Experimental Section

Synthesis of 4-(1*H*,1*H*,2*H*,2*H*-Perfluorodecyl)benzyl Alcohol. Under N_2 atmosphere, $LiAlH_4$ (0.80 g, 20 mmol) was dissolved in anhydrous ether (50 mL). The mixture was cooled to 0−5 °C internal temperature (ice−water bath). To this was added dropwise a solution of methyl benzoate (11.37 g, 20 mmol) in ether (40 mL). The reaction was stirred at 0−5 °C for 1 h. Water (1 mL) was added dropwise very slowly to quench the reaction, then 2 N HCl (55 mL) was added and the mixture was stirred well. The layers were separated and the aqueous layer was extracted with ether (1 × 50 mL). The combined ether layers were washed with 1 N HCl (1 × 5 mL) and brine (1 × 50 mL). The product was dried over $MgSO_4$, filtered, and concentrated in vacuo to give a yield of 10.61 g (19.1 mmol, 90%). A similar procedure was used for the lower homolog.

Synthesis of Rf8 Cbz-OSu Reagent 1b. Phosgene (20% in toluene, 7.9 mL, 15 mmol) was charged to a flask and cooled to 0−5 °C (ice water bath). [**CAUTION**: Phosgene is highly toxic and must be handled with appropriate precautions.] To this was added a solution of 4-(1*H*,1*H*,2*H*,2*H*-perfluorodecyl)-benzyl alcohol (5.54 g, 10 mmol) in THF (25 mL). The mixture was stirred at room temperature for 18 h. After evaporation to dryness, the product was taken up in chloroform (50 mL). *N*-Hydroxysuccinimide dicyclohexylamine salt (3.26 g, 11 mmol) was added portionwise over 10 min, and the mixture was stirred at room temperature for 3 h. The reaction was quenched with H_2O (100 mL). The product was extracted with chloroform (3 × 100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was recrystallized in toluene (100 mL) to give 5.55 g (80%) of **1b**. A similar procedure was used for the lower homolog.

Preparation of 3-Phenyl-2-[4-(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)benzyloxycarbonylamino]propionic Acid (2b). To a solution of D-phenylalanine (416 mg, 2.52 mmol) and carbonic acid 2,5-dioxopyrrolidin-1-yl ester 4-(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluoro-octyl) benzyl ester **1b** (1 g, 1.68 mmol) in THF/H_2O (30 mL/5 mL) was added triethylamine (354 μL, 2.52 mmol). The mixture was stirred at room temperature for 1 h. After the reaction was complete, the mixture was acidified with aqueous HCl to pH ∼2 and diluted with ethyl acetate (60 mL). The organic layer was extracted with water three times and dried with magnesium sulfate. After drying, magnesium sulfate was filtered off and the filtrate was evaporated to give product (1.06 g, 98%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.30−7.14 (m, 9H), 5.14 (d, J = 7.97 Hz, 1H), 5.08 (s, 2H), 4.70 (dd, J = 13.4, 5.98 Hz, 1H), 3.22 (dd, J = 13.7, 5.35 Hz, 1H), 3.12 (dd, J = 14.2, 6.39 Hz, 1H), 2.95−2.89 (m, 2H), 2.45−2.27 (m, 2H).

Preparation of 3-Phenyl-2-[4-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluoro-decyl)benzyloxycarbonylamino]propionic Acid (2a). To a solution of L-phenylalanine (356.8 mg, 2.16 mmol) and carbonic acid 2,5-dioxopyrrolidin-1-yl ester 4-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluoro-decyl) benzyl ester (1 g, 1.44 mmol) in THF/H_2O (30 mL/5 mL) was added triethylamine (300.5 μL, 2.16 mmol). The mixture was stirred at room temperature for 1 h. After the reaction was complete, the mixture was acidified with aqueous HCl to pH ∼2 and diluted with ethyl acetate (60 mL). The organic layer was extracted with water three times and dried with magnesium sulfate. After drying, magnesium sulfate was filtered off. The filtrate was evaporated and the residue was recrystallized from acetonitrile to give a solid, which was washed with distilled hexane to give product (0.722 g, 67%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.29−7.07 (m, 9H), 5.14 (d, J = 7.89 Hz, 1H), 5.07 (s, 2H), 4.69 (dd, J = 13.2, 6.05 Hz, 1H), 3.21 (dd, J = 13.7, 5.35 Hz, 1H), 3.11 (dd, J = 14.2, 6.39 Hz, 1H), 2.93−2.88 (m, 2H), 2.44−2.26 (m, 2H).

General Procedures for Couplings in Table 2. Synthesis of [1-Benzyl-2-(3,4-dihydro-1*H*-isoquinolin-2-yl)-2-oxoethyl]carbamic Acid 4-(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl) Benzyl Ester (Table 2, entry 2). To a solution of **2b** (50 mg, 0.078 mmol), EDCI (22.2 mg, 0.12 mmol), and HOBt (15.7 mg, 0.12 mmol) in chloroform/DMF (0.65 mL/0.65 mL) was added 1,2,3,4-tetrahydroisoquinoline (38.8 μL, 0.31 mmol) and triethylamine (16.3 μL, 0.12 mmol). The mixture was stirred at room temperature for 18 h. After the reaction, the solvents were evaporated and the product was purified by fluorous solid-phase extraction (F-SPE). The crude reaction mixture dissolved in THF (0.7 mL) was loaded to a 2-g Fluoro*Flash* column purchased from Fluorous Technologies, Inc. After elution of the organic compounds with 80/20 MeOH/H_2O, the fluorous product was eluted with ether and evaporation of solvents gave product (38.2 mg, 65%) as a white oily solid: ^{1}H NMR ($CDCl_3$) δ 7.32−7.03 (m, 12H), 6.87 (d, J = 6.21 Hz, 1H), 5.78 (br, 1H), 5.07 (s, 2H), 4.98 (dd, J = 15.5, 7.24 Hz, 1H), 4.65 (dd, J = 59.5, 17.1 Hz, 1H), 4.21 (dd, J = 155, 16.0 Hz, 1H), 3.85−3.62 (m, 1H), 3.59−3.10 (m, 1H), 3.07−2.98 (m, 2H), 2.94−2.89 (m, 2H), 2.78−2.68 (m, 2H), 2.45−2.27 (m, 2H); ^{19}F NMR ($CDCl_3$) δ −79.5 (3F), −113.4 (2F), −120.7 (2F), −121.6 (2F), −122.3 (2F), −124.9 (2F); ^{13}C NMR ($CDCl_3$) δ 170.2, 155.7, 139.1−126.1 (m), 118.4−110.8 (m), 66.6, 52.2, 47.1, 44.6, 43.1, 40.3, 32.8, 29.1, 26.2; LRMS *m*/*z* (rel intensity) 437 (100), 132 (87); HRMS calcd for $C_{34}H_{29}F_{13}N_2O_3$ 760.1970, found 760.2003; IR (KBr) 3292, 1717, 1637, 1455, 1239, 1144 cm^{-1}; $[\alpha]^{25}_D$ −0.0803 (*c* 0.4, CH_2Cl_2).

[1-Benzyl-2-(3,4-dihydro-1*H*-isoquinolin-2-yl)-2-oxoethyl]carbamic Acid 4-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadecafluorodecyl) Benzyl Ester (Table 2, entry 1). ^{1}H NMR ($CDCl_3$) δ 7.32−7.03 (m, 12H), 6.87 (d, J = 6.30 Hz, 1H), 5.78 (br, 1H), 5.07 (s, 2H), 4.98 (dd, J = 15.3, 7.11 Hz, 1H), 4.65 (dd, J = 59.4, 17.1 Hz, 1H), 4.22 (dd, J = 155, 16.0 Hz, 1H), 3.85−3.62 (m, 1H), 3.59−3.09 (m, 1H), 3.07−2.98 (m, 2H), 2.94−2.89 (m, 2H), 2.78−2.68 (m, 2H), 2.45−2.27 (m, 2H); ^{19}F NMR ($CDCl_3$) δ −79.5 (3F), −113.4 (2F), −120.4 (2F), −120.6 (4F), −121.4 (2F), −122.2 (2F), −124.8 (2F); ^{13}C NMR ($CDCl_3$) δ 170.4, 155.7, 139.1−126.1 (m), 118.4−110.8 (m), 66.6, 52.2, 47.1, 44.6, 43.1, 40.3, 32.8, 29.1, 26.2; LRMS *m*/*z* (rel intensity) 537 (74), 427 (69), 187 (100), 132 (85); HRMS calcd for $C_{36}H_{29}F_{17}N_2O_3$ 860.1906, found 860.1893; IR (KBr) 3298, 1717, 1641, 1455, 1205, 1148 cm^{-1}; $[\alpha]^{25}_D$ +0.05 (*c* 0.4, CH_2Cl_2).

(1-Cyclohexylcarbamoyl-2-phenylethyl)carbamic Acid 4-(3,3,4,4,5,5,6,6,7,7,8,8,8-Tridecafluorooctyl) Benzyl Ester (Table 2, entry 4). ^{1}H NMR ($CDCl_3$) δ 7.32−7.03 (m, 12H), 5.49 (br, 1H), 5.35 (br, 1H), 5.07 (s, 2H), 4.28 (dd, J = 13.8, 7.52 Hz, 1H), 3.72−3.59 (m, 1H), 3.13 (dd, J = 13.3, 5.70 Hz, 1H), 2.98−2.89 (m, 3H), 2.45−2.27 (m, 2H), 1.79−0.78 (m, 10H); ^{19}F NMR ($CDCl_3$) δ −79.5 (3F), −113.4 (2F), −120.7 (2F), −121.6 (2F), −122.3 (2F), −124.9 (2F); ^{13}C NMR ($CDCl_3$) δ 169.5, 155.8, 139.3−127.1 (m), 119.1−110.8 (m), 66.7, 56.6, 48.3, 39.3, 32.9, 25.4, 24.7; LRMS *m*/*z* (rel intensity) 556 (30), 437 (100), 229 (35), 164 (45); HRMS calcd for $C_{31}H_{31}F_{13}N_2O_3$ 726.2127, found 726.2094; IR (KBr) 3303, 1692, 1646, 1535, 1244, 1144 cm^{-1}; $[\alpha]^{25}_D$ −0.0665 (*c* 0.4, CH_2Cl_2); mp 127−129 °C.

(1-Cyclohexylcarbamoyl-2-phenylethyl)carbamic Acid 4-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadecafluoro-

decyl) Benzyl Ester (Table 2, entry 3). ^{1}H NMR ($CDCl_3$) δ 7.32−7.03 (m, 12H), 5.50 (br, 1H), 5.35 (br, 1H), 5.07 (s, 2H), 4.28 (dd, J = 13.5, 7.51 Hz, 1H), 3.70−3.60 (m, 1H), 3.14 (dd, J = 13.3, 5.57 Hz, 1H), 2.98−2.89 (m, 3H), 2.45−2.27 (m, 2H), 1.79−0.78 (m, 10H); ^{19}F NMR ($CDCl_3$) δ −79.5 (3F), −113.4 (2F), −120.4 (2F), −120.7 (4F), −121.5 (2F), −122.2 (2F), −124.8 (2F); ^{13}C NMR ($CDCl_3$) δ 169.5, 155.8, 139.3−127.1 (m), 119.1−110.8 (m), 66.7, 56.6, 48.2, 39.3, 32.9, 25.4, 24.7; LRMS *m*/*z* (rel intensity) 656 (8), 537 (60), 230 (35), 164 (22); HRMS calcd for $C_{33}H_{31}F_{17}N_2O_3$ 826.2063, found 826.2088; IR (KBr) 3301, 1693, 1647, 1536, 1204, 1148 cm^{-1}; $[\alpha]^{25}_D$ +0.051 (*c* 0.4, CH_2Cl_2); mp 135−137 °C.

{**2-Phenyl-1-[(pyridin-4-ylmethyl)carbamoyl]-ethyl**}-**carbamic Acid 4-(3,3,4,4,5,5,6,6,7,7,8,8,8-Tridecafluorooctyl) Benzyl Ester (Table 2, entry 6).** ^{1}H NMR ($CDCl_3$) δ 8.45 (d, J = 3.81 Hz, 2H), 7.28−6.91 (m, 11H), 6.38 (br, 1H), 5.45 (br, 1H), 5.05 (s, 2H), 4.47 (dd, J = 14.6, 7.63 Hz, 1H), 4.39 (dd, J = 15.9, 6.22 Hz, 1H), 4.28 (dd, J = 15.9, 5.80 Hz, 1H), 3.16 (dd, J = 13.7, 6.26 Hz, 1H), 3.05 (dd, J = 13.6, 7.92 Hz, 1H), 2.94−2.88 (m, 2H), 2.44−2.26 (m, 2H); ^{19}F NMR ($CDCl_3$) δ −79.5 (3F), −113.4 (2F), −120.6 (2F), −121.6 (2F), −122.2 (2F), −124.9 (2F); ^{13}C NMR ($CDCl_3$) δ 171.4, 156.2, 150.1, 146.9, 139.4, 135.9, 134.3, 128.9−127.5 (m), 122.2−110.9 (m), 66.7, 56.3, 41.8, 38.6; LRMS *m*/*z* (rel intensity) 454 (84), 451 (100), 437 (18), 281 (29); HRMS calcd for $C_{31}H_{26}F_{13}N_3O_3$ 735.1766, found 735.1785; IR (KBr) 3303, 1696, 1651, 1531, 1256, 1137 cm^{-1}; $[\alpha]^{25}_D$ −0.000075 (*c* 0.4, CH_2Cl_2); mp 164−165 °C.

{**2-Phenyl-1-[(pyridin-4-ylmethyl)carbamoyl]ethyl**}-**carbamic Acid 4-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadecafluorodecyl) Benzyl Ester (Table 2, entry 5):** ^{1}H NMR ($CDCl_3$) δ 8.48 (d, J = 5.65 Hz, 2H), 7.30−6.98 (m, 11H), 6.16 (br, 1H), 5.30 (br, 1H), 5.08 (s, 2H), 4.45−4.30 (m, 3H), 3.18 (dd, J = 13.4, 5.79 Hz, 1H), 3.05 (dd, J = 13.4, 7.89 Hz, 1H), 2.95−2.89 (m, 2H), 2.44−2.26 (m, 2H); ^{19}F NMR ($CDCl_3$) δ −79.5 (3F), −113.4 (2F), −120.7 (6F), −121.5 (2F), −122.2 (2F), −124.9 (2F); ^{13}C NMR ($CDCl_3$) δ 171.1, 149.7, 147.0, 139.5, 136.2, 134.5, 129.4−127.3 (m), 122.2−110.9 (m), 66.7, 56.3, 42.3, 38.6; LRMS *m*/*z* (rel intensity) 554 (13), 537 (15), 281 (11); HRMS calcd. for $C_{33}H_{26}F_{17}N_3O_3$ 835.1702, found 835.1792; IR (KBr) 3301, 1696, 1652, 1533, 1204, 1146 cm^{-1}; $[\alpha]^{25}_D$ +0.00725 (*c* 0.4, CH_2Cl_2); mp 167−169 °C.

[2-Phenyl-1-(3-trifluoromethylbenzylcarbamoyl)ethyl]-carbamic Acid 4-(3,3,4,4,5,5,6,6,7,7,8,8,8-Tridecafluorooctyl) Benzyl Ester (Table 2, entry 8). ^{1}H NMR ($CDCl_3$) δ 7.53−7.14 (m, 11H), 6.13 (br, 1H), 5.40 (br, 1H), 5.07 (s, 2H), 4.42−4.34 (m, 3H), 3.16 (dd, J = 13.6, 6.05 Hz, 1H), 3.02 (dd, J = 13.6, 7.92 Hz, 1H), 2.96−2.85 (m, 2H), 2.44−2.26 (m, 2H); ^{19}F NMR ($CDCl_3$) δ −61.3 (3F), −79.5 (3F), −113.3 (2F), −120.6 (2F), −121.6 (2F), −122.3 (2F), −124.9 (2F); ^{13}C NMR ($CDCl_3$) δ 171.0, 156.0, 150.1, 139.4−110.7 (m), 66.9, 56.6, 43.1, 38.6, 32.9, 26.2; LRMS *m*/*z* (rel intensity) 600 (5), 454 (60), 437 (80), 305 (49), 159 (50); IR (KBr) 3297, 1690, 1660, 1528, 1330, 1247, 1134 cm^{-1}; $[\alpha]^{25}_D$ −0.0218 (*c* 0.4, CH_2Cl_2); mp 134−135 °C.

[2-Phenyl-1-(3-trifluoromethylbenzylcarbamoyl)ethyl]-carbamic Acid 4-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadecafluorodecyl) Benzyl Ester (Table 2, entry 7). ^{1}H NMR ($CDCl_3$) δ 7.53−7.17 (m, 11H), 6.01 (br, 1H), 5.33 (br, 1H), 5.06 (s, 2H), 4.44−4.38 (m, 3H), 3.17 (dd, J = 13.6, 6.00 Hz, 1H), 3.02 (dd, J = 13.5, 7.90 Hz, 1H), 2.94−2.89 (m, 2H), 2.44−2.27 (m, 2H); ^{19}F NMR ($CDCl_3$) δ −61.3 (3F), −79.5 (3F), −113.3 (2F), −120.4 (2F), −120.6 (4F), −121.4 (2F), −122.2 (2F), −124.8 (2F); ^{13}C NMR ($CDCl_3$) δ 170.9, 156.0, 139.4−107.5 (m), 66.9, 53.5, 43.1, 38.6, 32.9, 26.2; LRMS *m*/*z* (rel intensity) 554 (18), 536 (44), 305 (25), 159 (29); HRMS calcd for $C_{35}H_{26}F_{20}N_2O_3$???, found, XXX. IR (KBr) 3303, 1690, 1660, 1529, 1330, 1248, 1205, 1142 cm^{-1}; $[\alpha]^{25}_D$ +0.0265 (*c* 0.4, CH_2Cl_2); mp 142−144 °C.

Reaction of the M-2a,b with 1,2,3,4-Tetrahydroisoquinoline and Separation of 3b and 4a from the Reaction Mixture by F-SPE (Figure 3). To a solution of **2a** (50 mg, 0.078 mmol), **2b** (57.7 mg, 0.078 mmol), EDCI (44.4 mg, 0.23 mmol), and HOBt (31.4 mg, 0.23 mmol) in chloroform/DMF (1.3 mL/1.3 mL) was added 1,2,3,4-tetrahydroisoquinoline (77.6 μL, 0.62 mmol) and triethylamine (32.6 μL, 0.23 mmol). The mixture was stirred at room temperature for 18 h. The solvents were evaporated and the product was extracted by fluorous solid-phase extraction (F-SPE). The crude reaction mixture dissolved in THF (0.7 mL) was loaded to a 20-g Fluoro*Flash* column purchased from Fluorous Technologies, Inc. After elution of the organic compounds with 80/20 MeOH/H_2O, compound **3b** was eluted with 90/10 MeOH/H_2O and compound **3a** was eluted with 100% MeOH. After purification by regular silica gel column, **3b** (44.8 mg, 76%) and **3a** (44.2 mg, 66%) were obtained as white oily solids, which were identified by ^{1}H, ^{13}C, and ^{19}F NMR and mass spectroscopy as identical with the products in Table 2.

Reaction of the Mixture of 1 and 2 with 1,2,3,4-Tetrahydroisoquinoline and Separation of 3 and 4 from the Reaction Mixture by Preparative HPLC. After reaction as above, the solvents were evaporated and the crude reaction mixture (290.2 mg) was dissolved in 2 mL of acetonitrile and injected in two 1-mL portions onto a preparative Fluoro*Flash* HPLC column. The column was eluted with 80/20 acetonitrile/H_2O increasing to 100% acetonitrile for 30 min. The fractions of products were collected and evaporated to give **3b** (49.1 mg, 83%) and **3a** (53.9 mg, 81%) separately, which were identified by ^{1}H and ^{19}F NMR spectroscopy.

[1-Benzyl-2-(3,4-dihydro-1*H*-isoquinolin-2-yl)-2-oxoethyl]carbamic Acid Benzyl Ester Cbz-Phe-THQ. To a solution of *N*-(carbobenzyloxy)-L-phenylalanine (20 mg, 0.067 mmol), EDCI (19.2 mg, 0.10 mmol), and HOBt (13.5 mg, 0.10 mmol) in chloroform/DMF (0.65 mL/0.65 mL) was added 1,2,3,4-tetrahydroisoquinoline (33.4 μL, 0.267 mmol) and triethylamine (13.9 μL, 0.100 mmol). The mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with ether and 5% HCl (4 mL) was added. The organic layer was extracted with ethyl acetate three times and dried over magnesium sulfate. Magnesium sulfate was filtered off and after evaporation of solvents, the residue was purified by column chromatography with 2/1 pentane/ethyl acetate to give product (27.0 mg, 98%) as a white oil: ^{1}H NMR ($CDCl_3$) δ 7.35−6.86 (m, 14H), 5.79 (br, 1H), 5.10 (s, 2H), 4.98 (dd, J = 15.6, 7.63 Hz, 1H), 4.66 (dd, J = 55.8, 17.1 Hz, 1H), 4.23 (dd, J = 152, 15.9 Hz, 1H), 3.86−3.62 (m, 1H), 3.59−3.09 (m, 1H), 3.06−2.95 (m, 2H), 2.83−2.72 (m, 2H).

HPLC Analysis of the Mixture of 3a, 3b, and Cbz-Phe-THQ (Cbz-Phe-THQ is the standard, nonfluorous Cbz analogue of 3a and 3b). The equimolar mixture of **3a**, **3b**, and **Cbz-Phe-THQ** was injected onto an analytical HPLC column. The column was eluted with 80/20 acetonitrile/H_2O increasing to 100% acetonitrile over 30 min. Compounds **3a**, **3b**, and **Cbz-Phe-THQ** eluted individually at 16.0, 5.2, and 1.9 min.

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Supporting Information Available: Tables of HRMS data, optical rotations, and melting points of all the FCbz derivatives along with copies of all ^{1}H and ^{13}C NMR spectra and two representative IR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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