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Note

Visible light-induced trifluoromethylation and perfluoroalkylation of cysteine residues in batch and continuous flow

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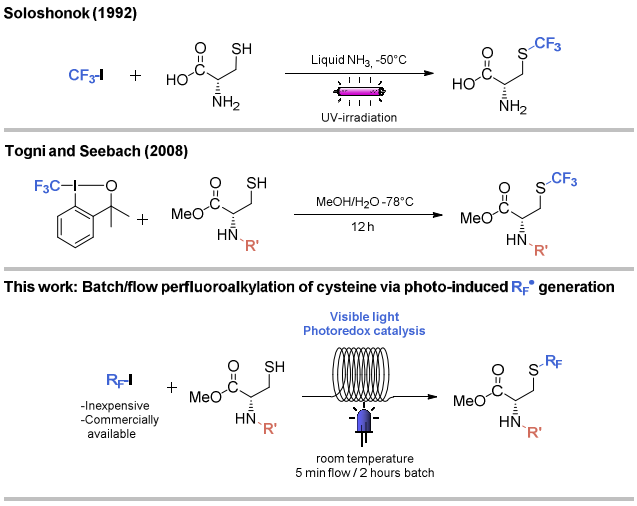
approaches were troubled with low yields and limited scope.[10] A more convenient method was developed by Togni, Seebach *et al.* utilizing hypervalent iodine(III) trifluoromethylating reagents but still required cryogenic reaction conditions.[6c, 11] Furthermore, introduction of other perfluoroalkylated analogues requires the synthesis of unique hypervalent iodine(III) perfluorinating reagents, which are either expensive, not commercially available, or difficult to synthesize. In order to develop a general protocol for the perfluoroalkylation of cysteines, we turned our attention to R_F–I reagents (R_F = perfluoroalkyl) which can generate electrophilic perfluoroalkyl radicals under visible light photocatalytic reactions conditions and are commercially available and cost efficient (Scheme 1).[12] We anticipated that such electrophilic perfluoroalkyl radicals can be used to functionalize cysteine residues, thereby rendering a more general and practical approach to access perfluoroalkylated cysteines. We also demonstrate that the use of continuous-flow photochemistry allows to accelerate this transformation, which provides a convenient and scalable method able to handle gaseous reactants (e.g. CF_3I) efficiently.

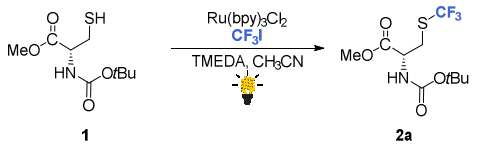


Scheme 1: Trifluoromethylation strategies for cysteine modification

Based on our experience with the visible-light induced photocatalytic trifluoromethylation of aromatic thiols,[13] we chose to initiate our investigations by trifluoromethylating cysteine **1** with gaseous CF_3I in the presence of $Ru(bpy)_3Cl_2$ as a photocatalyst and tetramethylethane-1,2-diamine (TMEDA) in acetonitrile (Table 1). Irradiation of the reaction mixture was achieved by a 24 W white CFL (compact fluorescent light). In the absence of any light or nitrogen base, no reaction product (**2a**) could be obtained (Table 1, Entries 1 and 2). The formation of SCF_3 product in the absence of any photocatalyst occurs via homolytic cleavage of the CF_3–I bond upon irradiation (Bond Dissociation Energy [CF_3–I] = 52.6 ± 1.1 kcal/mol which corresponds with 544 nm photons) (Table 1, Entry 3).[14] However, a more efficient and faster reaction was observed in the presence of $Ru(bpy)_3Cl_2$ (Table 1, Entry 4). When the reaction was conducted in MeOH, a lower product yield was obtained (Table 1 Entry 5), while water proved to be an incompatible solvent which is mainly caused by solubility issues (Table1, Entry 6). Further, the amount of CF_3I could be lowered (from a large excess of 10 equivalents to 4 equivalents) without any impact on the reaction yield (Table 1, Entries 4 and 7). The use of an inorganic base proved to be ineffective for this

transformation (Table 1, Entries 8 and 9). Satisfyingly, in contrast to our observations with aromatic and other aliphatic thiols, no disulfide byproduct formation could be observed in all cases (Table 1).

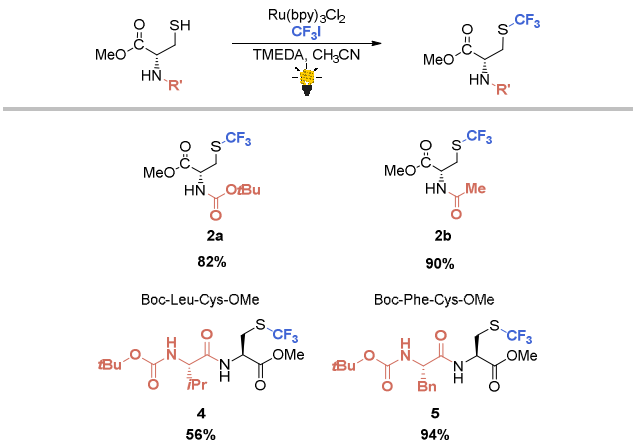
Table 1 Optimization studies for the visible light-induced trifluoromethylation of cysteine 1 with CF_3I



Entry	Conditions[a]	Solvent	Base	Eq. of CF_3I[b]	Yield (%)[c]
1	No light	CH_3CN	TMEDA	10	n.r.
2	CFL	CH_3CN	No base	10	n.r.
3	CFL, no catalyst	CH_3CN	TMEDA	10 / 4	43 / 23
4	CFL	CH_3CN	TMEDA	10	84
5	CFL	MeOH	TMEDA	10	49
6	CFL	H_2O	TMEDA	Sat.	n.r.
7	CFL	CH_3CN	TMEDA	4	82
8	CFL	CH_3CN	KOAc	4	35
9	CFL	CH_3CN	Na_3PO_4	4	23

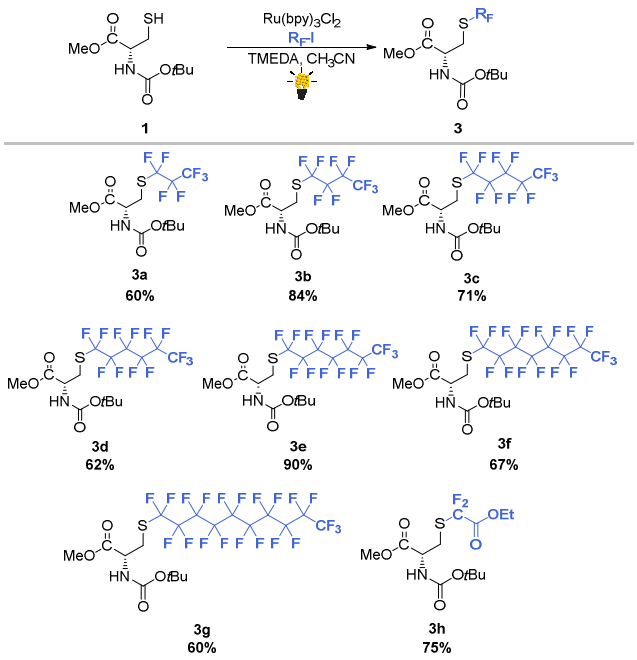
[a]Standard reaction conditions: N-Boc-L-Cys-OMe (**1**) (0.5 mmol), $Ru(bpy)_3Cl_2 \cdot 6H_2O$ (3.75 mg, 1mol%) TMEDA (1 mmol), and CF_3I in 5 ml CH_3CN. [b]CF_3I added directly to the reaction mixture or via a stock solution in CH_3CN, visible light irradiation, 2 hours. [c]Yield determined by ^{19}F-NMR with addition of an internal standard (α,α,α-trifluorotoluene, 0.5 mmol).

With optimal conditions in hand, we investigated the scope of this photo-induced trifluoromethylation protocol (Scheme 2). Two *L*-cysteine derivatives with a different amine protecting group were efficiently trifluoromethylated in excellent isolated yield (compounds **2a** and **2b**). Notably, good to excellent yields were also obtained for dipeptides Boc-Leu-Cys-OMe (**4**, 56%) and Boc-Phe-Cys-OMe (**5**, 94%), thus showing the selectivity of our methodology in the presence of other amino acid residues.



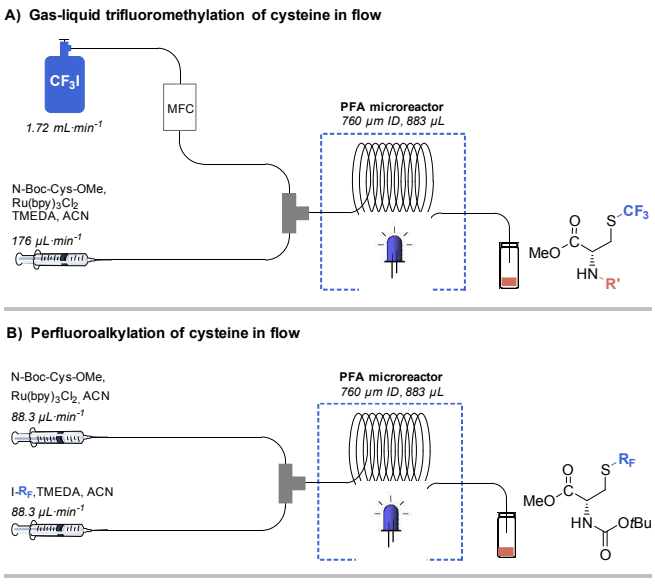
Scheme 2: Direct photo-induced trifluoromethylation of cysteine residues in batch. Reaction conditions: Cysteine derivative (0.5 mmol), $Ru(bpy)_3Cl_2 \cdot 6H_2O$ (1mol%), TMEDA (1 mmol), and CF_3I (2 mmol) in 5 ml CH_3CN. 24 W white CFL, 2 hours.

Several studies have shown that the introduction of multiple highly fluorinated amino acids can significantly alter the properties of proteins.[15] For example, due to the less polarizable nature of C–F bonds compared to C–H bonds, a perfluoroalkylated cysteine residue could change the overall acidity of the protein or could easily participate in hydrophobic interactions in a biological environment. Specifically, the modified residue could be harbored within hydrophobic pockets of proteins and enzymes, therefore providing an enabling tool for the investigation of hydrophobic protein-protein or even protein-membrane interactions.[5b] Moreover, the synthetic access to various perfluoroalkylated amino acids would be of high interest to generate a small library of compounds, which can be used for rapid screening of such interactions. In addition, long fluorous tags can be used to recover peptides and proteins by enabling extraction techniques with fluorinated solvents.[16] To showcase the utility of our methodology for the preparation of highly fluorinated cysteine residues, the scope of the perfluoroalkyl coupling partner was further expanded by using a wide variety of commercially available perfluoroalkylated iodides (Scheme 3). A complete range of perfluoroalkyl-substituted cysteines, bearing perfluoroalkylated chains of variable length (C_3 to C_{10}), was obtained in good to excellent yields (60-90% isolated yield). Moreover, derivative **3h**, bearing an ethyl difluoroacetyl moiety, could be obtained in good yield (75% isolated yield). This compound constitutes an intermediate of interest for the preparation of difluoromethyl-substituted compounds or for the introduction of ^{18}F via Ag-catalyzed decarboxylative fluorination.[3a]



Scheme 3: Direct photo-induced perfluoroalkylation of cysteine in batch. Reaction conditions: N-Boc-L-Cys-OMe (0.5 mmol), $Ru(bpy)_3Cl_2 \cdot 6H_2O$ (1mol%) TMEDA (1 mmol), and R_F-I (1 mmol) in 5 ml CH_3CN. 24 W white CFL, 2 hours.

Next, we focused our research efforts to transfer our trifluoromethylation and perfluoroalkylation protocol to a continuous-flow microreactor. In general, such devices provide a more homogeneous irradiation/energy distribution and an increased gas-liquid mass transfer.[17] The observed process intensification of photochemical transformations in microreactors often results in increased yields, reduced reaction times and easy scale-up.[18] The microflow setup consists of perfluoroalkoxyalkane microcapillary tubing (PFA, 760 µm ID, 2.0 m, 883 µL) wrapped around a plastic holder, which is placed into a 3D-printed beaker (See Figure 1C and *Supporting Information*).[19] The reactor is subjected to irradiation generated by a blue LED stripe (1 m length, 78 Lumen, 3.12 Watt). The use of such miniaturized light sources, instead of CFL light sources, allows to increase the overall photonic efficiency and to minimize unproductive heat generation.[20] For the trifluoromethylation protocol, CF_3I gas was dosed into the liquid stream via a mass flow controller (Figure 1A). For the perfluoroalkylation protocol, the two liquid phases were introduced in the reactor by means of syringe pumps (Figure 1B). For both, the two streams were combined in a Tefzel T-micromixer (500 µm ID) upon entering the photomicroreactor. Notably, because of the high solubility of CF_3I gas in acetonitrile, the formation of a slug flow regime was not observed. A significant acceleration of the reaction rate was observed for both the trifluoromethylation and perfluoroalkylation chemistry, thus affording the formation of the desired products in higher yields than in batch and within only 5 minutes residence time (Scheme 4, 62-92%).



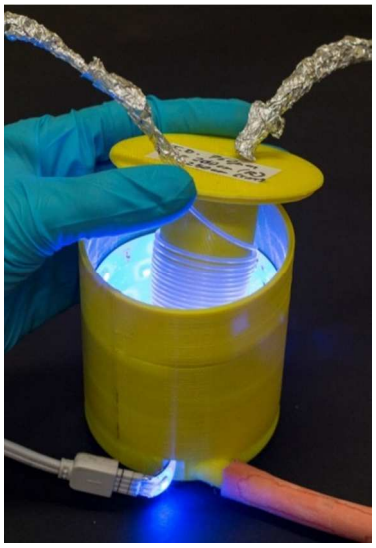
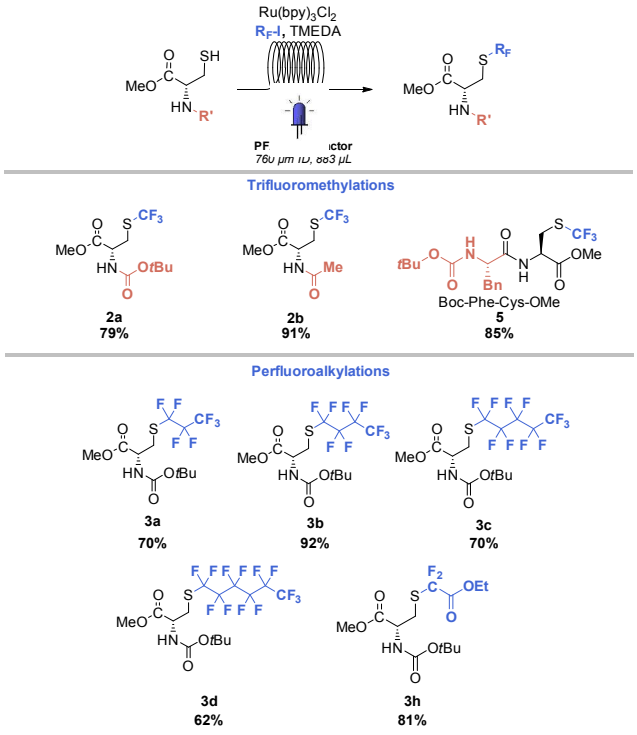
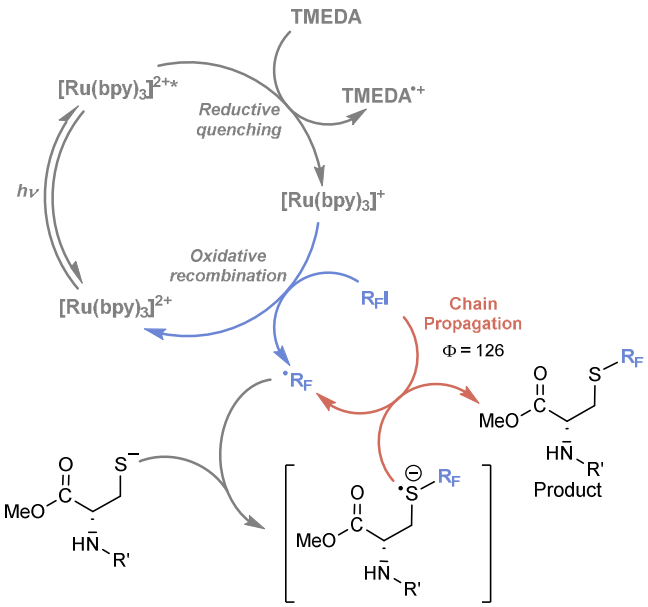


Figure 1. Schematic representation of the microflow setups for (A) gas-liquid trifluoromethylation and (B) perfluoroalkylation of cysteine. (C) Picture of the photomicroreactor. (More details about the setup can be found in the *Supporting Information*.



Scheme 4: Direct photo-induced trifluoromethylation and perfluoroalkylation of cysteine in batch and continuous flow. Reaction conditions: N-Boc-L-Cys-OMe (0.5 mmol), $Ru(bpy)_3Cl_2$•$6H_2O$ (1mol%) TMEDA (1 mmol), and R_F-I (4 equiv. for CF_3I, 2 equiv. for R_F-I) in CH_3CN are mixed with a T-mixer and irradiated with an array of. 3.12 W blue LEDs, 5 minutes residence time.

A plausible mechanism for this process is outlined in Scheme 5. Upon absorption of blue light, $[Ru(bpy)_3]^{2+}$ undergoes a metal-to-ligand charge transfer which is subsequently reductively quenched by TMEDA. Stern-Volmer quenching experiments indeed demonstrated that this step occurs under our reaction conditions. Next, $[Ru(bpy)_3]^{+}$ is oxidized to its ground state generating an electrophilic R_F radical. This radical can subsequently react with cysteine to establish the S–R_F linkage. In order to generate a neutral species, the radical anion needs to undergo another single electron transfer step (SET). This can be either done with $[TMEDA]^{\bullet+}$ (chain-terminating SET) or with R_FI (chain propagating SET) to generate another R_F radical. In order to elucidate this step and to update our previously proposed mechanism on the photocatalytic trifluoromethylation of aromatic thiols, we calibrated the quantum yield of this transformation against the oxidation of 1,9-diphenylanthracene with singlet oxygen.[13, 21] The obtained quantum yield value was Φ = 126 which demonstrates that indeed a chain propagating SET step is present in the light-induced perfluoroalkylation of cysteine (see *Supporting Information*).[22]



Scheme 5 Proposed mechanism of the $Ru(bpy)_3^{2+}$-catalyzed radical perfluoroalkylation of cysteine residues.

In summary, we have developed a visible light-induced photocatalytic route to prepare a wide variety of trifluoromethylated and perfluoroalkylated cysteine residues. The mild reaction conditions and the broad scope renders our methodology amenable to the synthesis of perfluoroalkylated cysteines, which can be subsequently introduced in standard peptide synthesis protocols. Moreover, the implementation of a continuous-flow photomicroreactor afforded increased product yields (on average 10% more product formation compared to batch) and reduced reaction times (5 minutes vs 2 hours in batch).

Experimental Section

All components as well as reagents and solvents were used as received without further purification, unless stated otherwise. The product isolation was performed using silica, and TLC analysis was performed using silica on aluminum foils TLC plates with visualization under ultraviolet light (254 nm and 365 nm) or appropriate TLC staining. ^{1}H-NMR, ^{13}C-NMR and ^{19}F-NMR spectra were recorded on ambient temperature using a 400 MHz spectrometer. ^{1}H-NMR spectra are reported in parts per million (ppm) downfield relative to TMS (0.00 ppm) and all ^{13}C NMR spectra are reported in ppm relative to $CDCl_3$ (77.23 ppm). Known products were characterized by comparing to the corresponding ^{1}H-NMR and ^{13}C-NMR from literature. All reactions were monitored by TLC, and ^{19}F-NMR. The IR spectra were recorded on an FT-IR spectrometer. HRMS (ESI/APCI multimode ionization source, TOF-MSD analyzer), were measured with direct infusion in a 50:50 flow of 5mM NH_4OAc in water / MeOH.

General procedure for the trifluoromethylation of cysteine residues in batch (GP1, for compounds 2a-b, 4, 5): In an oven-dried vial equipped with a magnetic stirrer and a PTFE septum, 3.75 mg (1 mol %) of $Ru(bpy)_3Cl_2$•$6H_2O$ was added to a mixture of N-Boc-L-Cys-OMe (117.65 mg, 0.5 mmol), *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) (116.24 mg, 1.0 mmol) and α,α,α-Trifluorotoluene (73.1 mg, 0.5 mmol, internal standard) in CH_3CN. The fluorinating agent (2 mmol, 4 equiv. for CF_3I) was added dropwise to the reaction mixture. For the insertion of CF_3I, stock solutions of known concentrations in CH_3CN were prepared and immediately used for the reaction. The vial was subjected to visible light irradiation with a 24W white CFL. The reaction was stirred at 1000 rpm for 2 hours. The reaction mixture was pre-adsorbed onto silica, dried in vacuo and purified by flash chromatography to yield the fluorinated product.

General procedure for the perfluoroalkylation of cysteine residues in batch (GP2, for compounds 3a-h): In an oven-dried vial equipped with a magnetic stirrer and a PTFE septum, 3.75 mg (1 mol %) of $Ru(bpy)_3Cl_2$•$6H_2O$ was added to a mixture of N-Boc-L-Cys-OMe (117.65 mg, 0.5 mmol), *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) (116.24 mg, 1.0 mmol) and α,α,α-Trifluorotoluene (73.1 mg, 0.5 mmol, internal standard) in CH_3CN. The fluorinating agent (I-CF_2R, 1 mmol, 2 equiv) was added dropwise to the reaction mixture. The vial was subjected to visible light irradiation with a 24W white CFL. The reaction was stirred at 1000 rpm for 2 hours. The reaction mixture was pre-adsorbed onto silica, dried in vacuo and purified by flash chromatography to yield the fluorinated product.

General procedure for the trifluoromethylation of cysteine residues in a continuous-flow microreactor (GP3, for compounds 2a-b, 5): A 10 mL syringe containing 7.5 mg (1 mol%) of $Ru(bpy)_3Cl_2$•$6H_2O$, N-Boc-L-Cys-OMe (235.3 mg, 1 mmol, 0.1 M), α,α,α-Trifluorotoluene (146.1 mg, 1 mmol, internal standard) and TMEDA (232.4 mg, 2.0 mmol) in 10 mL CH_3CN was mounted on a syringe pump. The liquid flowrate was fixed at 176.6 µL/min. The liquid stream was merged with gaseous CF_3I in a T-Mixer before entering the reactor. CF_3I was added to the reaction mixture at a flowrate of 1.72 mL/min by means of a mass flow controller. After reaching steady state, a reaction sample was collected until 0.5 mmol of product was collected in a vial kept in the dark. The reaction mixture was pre-adsorbed onto silica, dried in vacuo and purified by flash chromatography to yield the trifluoromethylated product

General procedure for the perfluoroalkylation of cysteine residues in a continuous-flow microreactor (GP4, for compounds 3a-d, 3h): A 5 mL syringe containing 7.5 mg (1 mol%) of $Ru(bpy)_3Cl_2$•$6H_2O$, N-Boc-L-Cys-OMe (235.3 mg, 1.0 mmol, 0.2 M), α,α,α-Trifluorotoluene (146.1 mg, 1 mmol, internal standard) in 5 mL CH_3CN and a 5 mL syringe containing TMEDA (232.4 mg, 2.0 mmol) and the fluorinating agent (I-CF_2R, 2 mmol,2 eq.) in 5 mL CH_3CN were mounted on a single syringe pump. The liquid flowrate (per syringe) was fixed at 88.3 µL/min. The two liquid streams were merged in a T-Mixer. After reaching steady state, a reaction sample was collected until 0.5 mmol of product was collected in a vial kept in the dark. The reaction mixture was pre-adsorbed onto silica, dried in vacuo and purified by flash chromatography to yield the fluorinated product.

General procedure for the synthesis of dipeptides Boc-Leu-Cys-OMe and Boc-Phe-Cys-OMe: The dipeptides used as starting materials for the synthesis of derivatives **4** and **5** and were prepared through a two-step procedure adapted from literature.[23] **Step 1: Formation of the thioester derivative:** *L*-Boc-Leu-OH or *L*-Boc-Leu-OH (1.0 equiv.) and DCM or ethyl acetate (0.5 mmol/mL) were added to an oven-dried flask and placed in an ice bath (0°C). Then, DCC (1 equiv.) and HOBt•H_2O (1 equiv.) were added together with thiophenol (1 equiv.). The flask was closed with a PTFE septum and the reaction mixture was placed under argon atmosphere. The reaction was checked for completion by TLC (4 -24 hours). The reaction mixture was washed with HCl (1M), $NaHCO_3$ (sat) and brine. The organic layer was dried with $MgSO_4$. The crude was absorbed on silica gel and purified with PE:EtOAC 7:1. **Step 2: Native chemical ligation**: L-Cysteine methyl ester HCl (1.0 equiv.) and the thioester derivative (1.0 equiv.) were added to MeOH (0.25 mmol/mL) in an oven-dried flask kept under argon atmosphere and closed with a PTFE septum. Next tributylphopshine (0.6 equiv.) was added by the use of a disposable syringe and the reaction mixture was stirred at r.t. until completion (24 hours). The crude was evaporated under vacuo, and redissolved in EtOAc. The organic layer was extracted with H_2O (3 times) and with brine (3 times). The organic layer was then dried with $MgSO_4$ and concentrated on silica gel under vacuo. The purification by column chromatography afforded the desired dipeptides Boc-Leu-Cys-OMe (45%) and Boc-Phe-Cys-OMe (24%) (DCM:MeOH 9:1 + 1% acetic acid).

Methyl *N*-(*tert*-butoxycarbonyl)-*S*-(trifluoromethyl)-*L*-cysteinate (2a)[11] was made according to **GP1** on a 0.5 mmol scale. The crude product was purified by flash chromatography (petroleum ether: ethyl acetate 100:0 to 90:10) yielding 124.4 mg (0.41 mmol, 82%) of derivative **2a** as a white solid (Mp: 67.6-67.9 °C). The reaction according to **GP3** on a 0.5 mmol scale afforded. 120 mg (0.39 mmol, 79 %) of product **2a** after 5 minutes residence time. ^{1}H NMR (399 MHz, Chloroform-*d*) δ 5.35 (s, 1H), 4.62 (s, 1H), 3.79 (s, 3H), 3.58 – 3.23 (m, 2H), 1.45 (s, 9H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 170.1, 154.9, 130.5 (q, *J* = 306.4 Hz), 80.6, 53.0, 52.9, 32.1, 28.2. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -41.0 HRMS (ESI) calculated for $C_5H_9F_3NO_2S$ $[M\text{-}Boc+H]^+$: 204.0306; found: 204.0308. IR (ATR, cm^{-1}): 3358, 3000, 1724, 1674, 1519, 1369, 1342, 1328, 1292, 1251, 1161, 1145.

Methyl *N*-acetyl-*S*-(trifluoromethyl)-*L*-cysteinate (2b)[10] was made according to **GP1** on a 0.5 mmol scale. The crude product was purified by flash chromatography (petroleum ether: ethyl ether 1:1) yielding 110.3 mg (0.45 mmol, 90%) of derivative **2b** as a white solid (Mp: 68.6-69.4 °C). The reaction according to **GP3** on a 0.5 mmol scale afforded 111.5 mg (0.46 mmol, 91%) of product **2b**. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.72 (s, 1H), 5.01 – 4.60 (m, 1H), 3.74 (s, 3H), 3.59 – 3.10 (m, 2H), 2.00 (s, 3H^{13}C NMR (101 MHz, Chloroform-*d*) δ 170.3, 170.1, 130.5 (q, *J* = 306.4 Hz), 53.0, 51.9, 31.6, 22.8, 15.2.^{19}F NMR (376 MHz, Chloroform-*d*) δ -41.1. HRMS (ESI) calculated for $C_7H_{11}F_3NO_3S$ $[M+H]^+$: 246.0412; found: 246.0401. IR (ATR, cm^{-1}): 3317, 2958, 1741, 1734, 1641, 1537, 1340, 1255, 1105, 1039.

Methyl *N*-(*tert*-butoxycarbonyl)-*S*-(perfluoropropyl)-*L*-cysteinate (3a) was made according to **GP2** on a 0.5 mmol scale. The crude product was purified by flash chromatography (petroleum ether: ethyl acetate 100:0 to 90:10) yielding 121 mg (0.3 mmol, 60 %) of derivative **3a** as yellow oil. The reaction according to **GP4** on a 0.5 mmol scale afforded 141.2 mg (0.35 mmol, 70 %) of compound **3a**.^{1}H NMR (399 MHz, Chloroform-*d*) δ 5.37 (s, 1H), 4.61 (s, 1H), 3.78 (s, 3H), 3.60 – 3.28 (m, 2H), 1.44 (s, 9H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 170.2, 155.1, 128.0 – 120.8 (m), 117.4 (dt, *J* = 288.1, 33.3 Hz), 114.0 – 106.9 (m), 80.7, 53.2, 52.9, 30.9, 28.2. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -76.30 – -82.31 (m), -84.76 – -89.66 (m), -124.08. HRMS (ESI) calculated for $C_7H_9F_7NO_2S^+$ $[M\text{-}Boc+H]^+$: 304.0237; found: 304.0238: 254. IR (ATR, cm^{-1}): 3367, 2982, 1724, 1518, 1336, 1180, 1161, 1112.

Methyl *N*-(*tert*-butoxycarbonyl)-*S*-(perfluorobutyl)-*L*-cysteinate (3b) was made according to GP2 on a 0.5 mmol scale. The crude product was purified by flash chromatography (petroleum ether: ethyl acetate 100:0 to 90:10) yielding 190.2 mg (0.42 mmol, 84%) of derivative 3b as yellow oil. The reaction according to GP4 on a 0.5 mmol scale afforded 209.3.mg (0.46 mmol, 92 %) of compound **3b**.^{1}H NMR (399 MHz,

Chloroform-*d*) δ 5.49 (s, 1H), 4.58 (s, 1H), 3.74 (s, 3H), 3.56 – 3.25 (m, 2H), 1.40 (s, 9H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 170.2, 155.1, 127.8 – 123.4 (m), 122.7 – 120.5 (m), 117.4 (dt, *J* = 288.1, 33.3 Hz), 114.6 – 105.3 (m), 80.7, 53.2, 52.9, 30.9, 28.2. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -81.39 (t, *J* = 9.8 Hz), -85.67 – -88.16 (m), -119.94 – -121.26 (m), -125.32 – -126.23 (m). HRMS (ESI) calculated for $C_8H_9F_9NO_2S^+$ [M-Boc+H]$^+$: 354.0205; found: 354.0206. IR (ATR, cm^{-1}): 3370, 2997, 1724, 1681, 1518, 1348, 1225, 1198, 1163, 1136.

Methyl *N*-(*tert*-butoxycarbonyl)-*S*-(perfluoropentyl)-*L*-cysteinate (3c) was made according to **GP2** on a 0.5 mmol scale. The crude product was purified by flash chromatography (petroleum ether: ethyl acetate 100:0 to 90:10) yielding 178.7 mg (0.36 mmol, 71%) of derivative **3c** as yellow oil. The reaction according to **GP4** on a 0.5 mmol scale afforded 176.1.mg (0.35 mmol, 70%) of compound **3c**. ^{1}H NMR (399 MHz, Chloroform-*d*) δ 5.37 (s, 1H), 4.63 (s, 1H), 3.79 (s, 3H), 3.61 – 3.27 (m, 2H), 1.44 (s, 9H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 170.0, 154.8, 127.8 – 126.3 (m), 124.6 – 123.5 (m), 122.3 – 120.3 (m), 119.3 – 117.9 (m), 115.9 (d, *J* = 33.1 Hz), 80.6, 53.0, 52.9, 30.9, 28.1. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -80.47 – -81.14 (m), -85.48 – -87.66 (m), -119.18 – -120.38 (m), -121.60 – -122.76 (m), -125.63 – -127.13 (m). HRMS (ESI) calculated for $C_9H_9F_{11}NO_2S^+$ [M-Boc+H]$^+$: 404,0173; found: 404,0171. IR (ATR, cm^{-1}): 3371, 2997, 2949, 1726, 1680, 1518, 1288, 1223, 1099.

Methyl *N*-(*tert*-butoxycarbonyl)-*S*-(perfluorohexyl)-*L*-cysteinate (3d) was made according to **GP2** on a 0.5 mmol scale. The crude product was purified by flash chromatography (petroleum ether: ethyl acetate 100:0 to 90:10) yielding 171.4 mg (0.31 mmol, 62%) of derivative **3d** as yellow oil. The reaction according to **GP4** on a 0.5 mmol scale afforded 171.6 mg (0.31 mmol, 62%) of compound **3d**. ^{1}H NMR (399 MHz, Chloroform-*d*) δ 5.40 (s, 1H), 4.62 (s, 1H), 3.78 (s, 3H), 3.55 – 3.25 (m, 2H), 1.43 (s, 9H ^{13}C NMR (100 MHz, Chloroform-*d*) δ 170.0, 154.8, 125.5 (dt, *J* = 292.5, 34.1 Hz), 121.6 – 120.8 (m), 117.1 (dt, *J* = 288.5, 33.2 Hz), 114.4 – 112.2 (m), 111.6 – 109.6 (m), 109.2 – 107.1 (m), 80.5, 53.0, 52.8, 30.8, 28.1. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -80.11 – -81.65 (m), -85.12 – -88.04 (m), -119.78, -121.51, -122.94, -125.67 – -127.15 (m). HRMS (ESI) calculated for $C_{10}H_9F_{13}NO_2S^+$ [M-Boc+H]$^+$: 454,0141; found: 454.0153. IR (ATR, cm^{-1}): 3379, 2980, 2951, 1728, 1695, 1682, 1518, 1317, 1199, 1188, 1163, 1147.

Methyl *N*-(*tert*-butoxycarbonyl)-*S*-(perfluoroheptyl)-*L*-cysteinate (3e) was made according to **GP2** on a 0.5 mmol scale. The crude product was purified by flash chromatography (petroleum ether : diethylether 16:1 to 8:1)yielding 269.5 mg (0.44 mmol, 90 %) of derivative **3e** as yellow oil. ^{1}H NMR (399 MHz, Chloroform-*d*) δ 5.42 (s, 1H), 4.62 (s, 1H), 3.77 (s, 3H), 3.61 – 3.27 (m, 2H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 170.2, 155.1, 127.8 – 123.6 (m), 122.2 – 120.3 (m), 117.3 (dt, *J* = 288.5, 33.0 Hz), 114.5 – 112.4 (m), 112.2 – 109.9 (m), 109.2 – 107.2 (m), 106.7 – 104.5 (m), 80.7, 53.2, 53.0, 31.0, 28.3. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -81.07 (t, *J* = 10.0 Hz), -84.97 – -88.54 (m), -119.78, -121.39, -122.18, -122.93, -126.00 – -126.69 (m). HRMS (ESI) calculated for $C_{11}H_9F_{15}NO_2S^+$ [M-Boc+H]$^+$: 504,0109; found: 504,0114. IR (ATR, cm^{-1}): 3377, 2991, 1728, 1693, 1681, 1518, 1321, 1230, 1193, 1149.

Methyl *N*-(*tert*-butoxycarbonyl)-*S*-(perfluorooctyl)-*L*-cysteinate (3f) was made according to **GP2** on a 0.5 mmol scale. The crude product was purified by flash chromatography (petroleum ether :ether 10:1 to 6:1) yielding 218.9 mg (0.34 mmol, 67%) of derivative **3f** as yellow oil. ^{1}H NMR (399 MHz, Chloroform-*d*) δ 5.40 (s, 1H), 4.63 (s, 1H), 3.78 (s, 3H), 3.56 – 3.30 (m, 2H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 170.2, 155.0, 127.4 (d, *J* = 33.4 Hz), 124.3 (t, *J* = 33.9 Hz), 119.5 – 118.2 (m), 118.1 – 117.2 (m), 115.8 (t, *J* = 33.4 Hz), 112.0 – 109.8 (m), 109.5 – 107.0 (m), 80.8, 53.2, 53.1, 31.1, 28.3.^{19}F NMR (376 MHz, Chloroform-*d*) δ -81.02 (t, *J* = 10.0 Hz), -84.55 – -89.24 (m), -119.59 – -119.88 (m), -121.20 – -121.46 (m), -121.80 – -122.27 (m), -122.74 – -123.14 (m), -126.25 – -126.46 (m). HRMS (ESI) calculated for $C_{12}H_9F_{17}NO_2S^+$ [M-Boc+H]$^+$: 554,0077; found: 554.0076. IR (ATR, cm^{-1}): 3383, 2991, 1695, 1681, 1516, 1369, 1195, 1118, 1082.

Methyl *N*-(*tert*-butoxycarbonyl)-*S*-(perfluorodecyl)-*L*-cysteinate (3g) was made according to **GP2** on a 0.5 mmol scale. The crude product was purified by flash chromatography (petroleum ether : ether 12:1 to 8:1) yielding 225.9 mg (0.3 mmol, 60 %) of derivative **3g** as a white solid (Mp: 65.5-67.1 °C). ^{1}H NMR (399 MHz, Chloroform-*d*) δ 5.38 (s, 1H), 4.64 (s, 1H), 3.79 (s, 3H), 3.65 – 3.22 (m, 2H), 1.44 (s, 9H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 170.2, 155.0, 127.7 – 127.0 (m), 126.3 – 125.5 (m), 124.9 – 123.9 (m), 122.0 – 121.1 (m), 119.4 – 118.0 (m), 116.5 – 115.1 (m), 114.4 – 113.0 (m), 111.9 – 109.7 (m), 109.3 – 106.8 (m), 80.8, 53.2, 53.1, 31.1, 28.3. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -80.48 – -81.23 (m), -85.58 – -87.69 (m), -119.21 – -119.96 (m), -120.84 – -121.55 (m), -121.55 – -122.26 (m), -122.62 – -123.05 (m), -125.67 – -126.94 (m). HRMS (ESI) calculated for $C_{14}H_9F_{21}NO_2S^+$ [M-Boc+H]$^+$: 654,0013; found: 654,0019. IR (ATR, cm^{-1}): 3383, 2982, 1728, 1695, 1684, 1516, 1198, 1141.

Methyl *N*-(*tert*-butoxycarbonyl)-*S*-(2-ethoxy-1,1-difluoro-2-oxoethyl)-*L*-cysteinate (3h) was made according to **GP2** on a 0.5 mmol scale. The crude product was purified by flash chromatography (petroleum ether: ethyl acetate 100:0 to 90:10) yielding 134.2 mg (0.38 mmol, 75%) of derivative **3h** as yellow oil. The reaction according to **GP4** on a 0.5 mmol scale afforded 144.7.mg (0.40 mmol, 81%) of compound **3h**. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.36 (s, 1H), 4.55 (s, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 3.73 (s, 3H), 3.48 – 3.18 (m, 2H), 1.40 (s, 9H), 1.32 (t, *J* = 7.1 Hz, 3H).^{13}C NMR (101 MHz, Chloroform-*d*) δ = 170.4, 161.4 (t, *J*=32.6), 154.9, 120.0 (t, *J*=287.4), 80.4, 63.8, 53.0, 52.8, 30.9, 28.2, 13.8. ^{19}F NMR (376 MHz, Chloroform-*d*) δ = -80.9 – -82.4 (m). HRMS (ESI) calculated for $C_8H_{14}F_2NO_4S^+$ [M-Boc+H]$^+$: 258,0612; found: 258,0616. IR (ATR, cm^{-1}): 3387, 2980, 1755, 1714, 1504, 1247, 1161, 1010.

Methyl *N*-((*tert*-butoxycarbonyl)-*L*-leucyl)-*S*-(trifluoromethyl)-*L*-cysteinate (4) was made according to **GP1** on a 0.50 mmol scale. The crude product was purified by flash chromatography (petroleum ether: ether: 6:1 to 3:1) yielding 117 mg (0.28 mmol, 56%) of derivative **4** as a white solid (Mp: 78.8-79.3 °C). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.22 (s, 1H), 5.00 (s, 1H), 4.80 (q, *J* = 5.3 Hz, 1H), 4.14 (s, 1H), 3.75 (s, 3H), 3.52 – 3.24 (m, 2H), 1.74 – 1.58 (m, 2H), 1.51 – 1.44 (m, 1H), 1.42 (s, 9H), 0.91 (t, *J* = 6.8 Hz, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 172.8, 169.7, 155.6, 130.5 (q, *J* = 306.4 Hz), 80.2, 53.1, 52.9, 51.8, 40.8, 31.4, 28.2, 24.7, 22.8, 21.9. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -41.03. HRMS (ESI) calculated for $C_{16}H_{27}F_3N_2NaO_5S^+$ [M+Na]$^+$: 439,1485; found: 439,1487. IR (ATR, cm^{-1}): 3334, 2958, 1755, 1686, 1654, 1514, 1367, 1153, 1103.

Methyl *N*-((*tert*-butoxycarbonyl)-*L*-phenylalanyl)-*S*-(trifluoromethyl)-*L*-cysteinate (5)[6c] was made according to **GP1** on a 0.50 mmol scale. The crude product was purified by flash chromatography (petroleum ether: ethyl ether 50:50 to 0:100) yielding 211.5 mg (0.47 mmol, 94%) of derivative **5** as a white solid (Mp: 112.2-112.9 °C). The reaction according to **GP3** on a 0.5 mmol scale afforded 191.3.mg (0.43 mmol, 85%) of compound **5**. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.41 – 7.16 (m, 5H), 6.83 (s, 1H), 4.94 (s, 1H), 4.82 (s, 1H), 4.42 (s, 1H), 3.79 (s, 3H), 3.58 – 3.27 (m, 2H), 3.20 – 3.04 (m, 2H), 1.45 (s, 9H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 171.5, 169.5, 155.5, 141.8 – 129.7 (m), 129.4, 129.0, 128.9, 127.2, 80.7, 55.8, 53.1, 52.0, 38.0, 31.6 (d, *J* = 2.2 Hz), 28.4. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -40.9. HRMS (ESI) calculated for $C_{19}H_{25}F_3N_2NaO_5S^+$ [M+Na]$^+$: 473,1329; found: 473,1323. IR (ATR, cm^{-1}): 3325, 2972, 1741, 1681, 1666, 1516, 1439, 1298, 1220, 1153

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Supporting Information Available:

Description of reaction set-ups, light sources and their emission spectra, quantum yield measurements and spectral data of all products. This material is available free of charge via the Internet at http://pubs.acs.org

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