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Visible Light-Induced Trifluoromethylation and Perfluoroalkylation of Cysteine Residues in Batch and Continuous Flow

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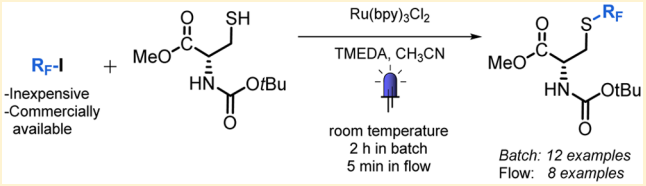
Supporting Information

ABSTRACT: We report a visible light-induced trifluoromethylation and perfluoroalkylation for cysteine conjugation using $Ru(bpy)_3^{2+}$ as photocatalyst and inexpensive R_FI as coupling partner. The protocol allows the introduction of a variety of perfluoro alkyl groups (C1−C10) and a CF_2COOEt moiety. The reaction is high yielding (56−94% yield) and fast (2 h in batch, 12 examples). Process intensification in a photomicroreactor accelerated the reaction (5 min reaction time) and increased the yields (8 examples). Quantum yield investigations support a radical chain mechanism.



The incorporation of fluorinated moieties is of great interest as it improves the metabolic stability, lipophilicity, and bioavailability of biologically active compounds.[1] In addition, access to fluorinated biomolecules allows one to use ^{19}F-NMR spectroscopy to investigate complex biological interactions.[2] Recent advances in ^{18}F-radiochemistry also provide access to ^{18}F-labeled small molecules, peptides, and proteins, thus rendering positron emission tomography (PET) techniques suitable for in vivo monitoring of biochemical processes.[3]

Several biosynthetic approaches have been developed allowing the introduction of fluorinated amino acids through protein engineering.[4] However, most of these methods fail to provide efficient strategies for the incorporation of highly fluorinated amino acids, which are often prepared through post-translational chemical modification of native sequences or through insertion of fluorinated residues via standard solid phase peptide synthesis.[5] In this regard, examples from the literature showed viable synthetic pathways toward trifluoromethylated amino acids or peptides.[6] As part of our interest in developing efficient synthetic tools for chemical biology purposes, we have been evaluating the use of visible light photoredox catalysis for efficient cysteine conjugation.[7] A cysteine residue provides unique reactivity that allows it to engage in radical or ionic reaction processes (Scheme 1).[8] Soloshonok et al. utilized CF_3I to construct the cysteine S−CF_3 bond, but the method suffered from unpractical reaction conditions (such as liquid ammonia, −50 °C, and UV irradiation).[9] Also other radical approaches suffered from low yields and limited scope.[10] A more convenient method was developed by Togni and Seebach et al. utilizing hypervalent iodine(III) trifluoromethylating reagents, but the method 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. 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 for acceleration of this transformation, which provides a convenient and scalable method able to handle gaseous reactants (e.g., CF_3I) efficiently.

On the basis of our experience with 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 to 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), and water proved to be an incompatible solvent, which is mainly caused by solubility

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Scheme 1. Trifluoromethylation Strategies for Cysteine Modification

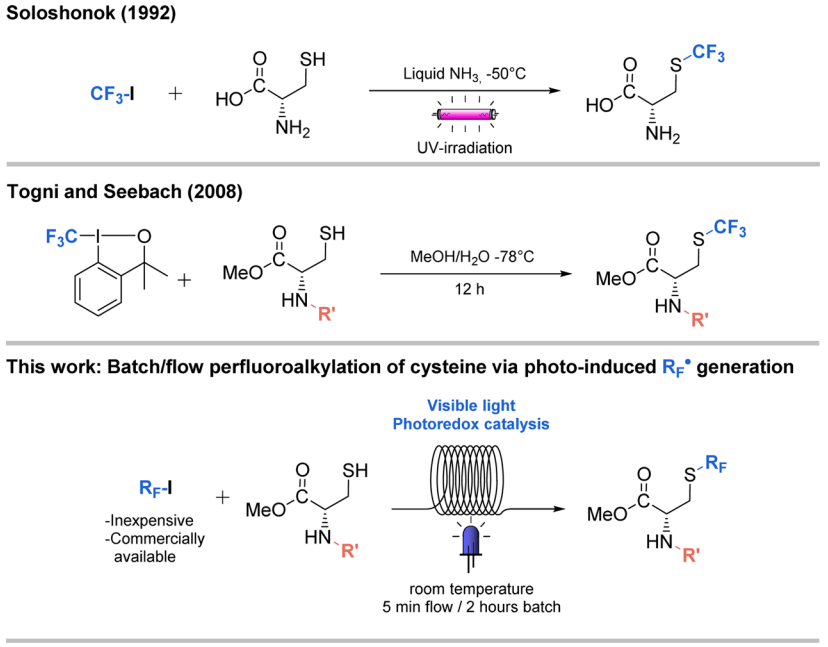
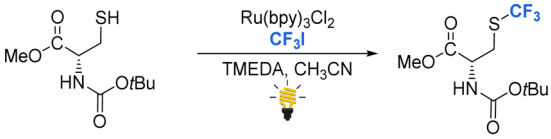


Table 1. Optimization Studies for the Visible Light-Induced Trifluoromethylation of Cysteine 1 with CF_3I

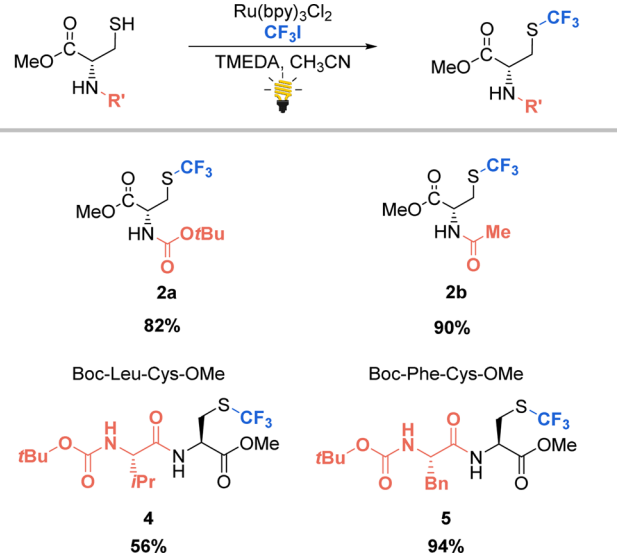


1 2a

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), $Ru(bpy)_3Cl_2·6H_2O$ (3.75 mg, 1 mol %), TMEDA (1 mmol), and CF_3I in 5 mL of CH_3CN. [b]CF_3I added directly to the reaction mixture or via a stock solution in CH_3CN, visible light irradiation, 2 h. [c]Yield determined by ^{19}F-NMR with the addition of an internal standard (α,α,α-trifluorotoluene, 0.5 mmol).

Scheme 2. Direct Photo-Induced Trifluoromethylation of Cysteine Residues in Batch[a]



[a]Reaction conditions: cysteine derivative (0.5 mmol), $Ru(bpy)_3Cl_2·6H_2O$ (1 mol %), TMEDA (1 mmol), and CF_3I (2 mmol) in 5 mL of CH_3CN; 24 W white CFL, 2 h.

issues (Table 1, entry 6). Furthermore, the amount of CF_3I could be lowered (from a large excess of 10 equiv to 4 equiv) 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).

With the optimal conditions in hand, we investigated the scope of this photoinduced trifluoromethylation protocol (Scheme 2). Two L-cysteine derivatives with different amine protecting groups 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.

Several studies have shown that the introduction of multiple highly fluorinated amino acids can significantly alter the properties of proteins.[15] For example, because of the less polarizable nature of C−F bonds compared to that of 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. Specif-

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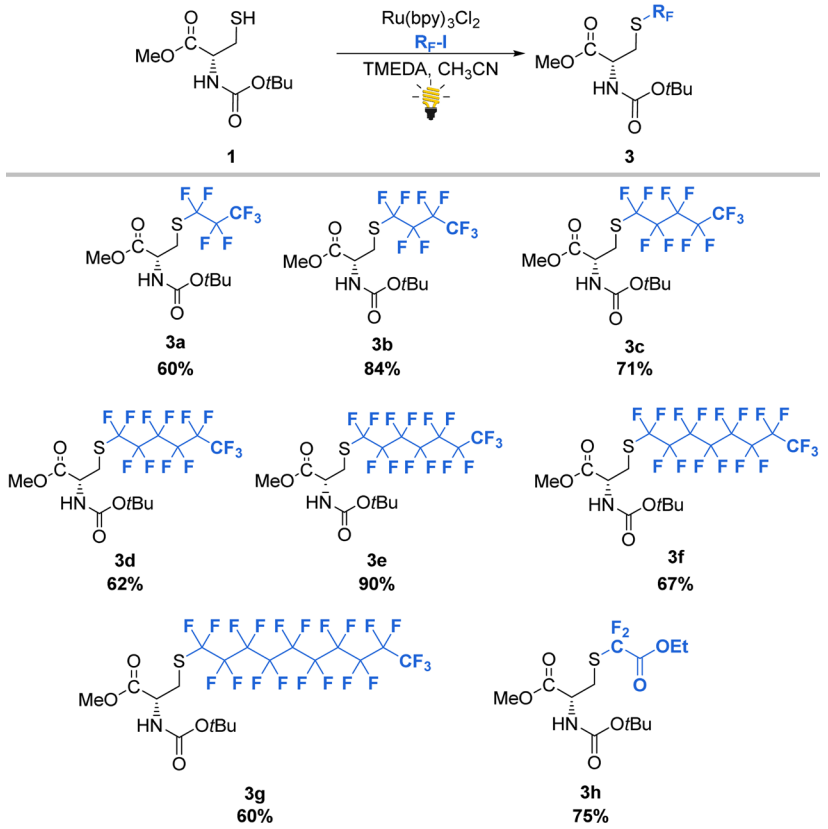
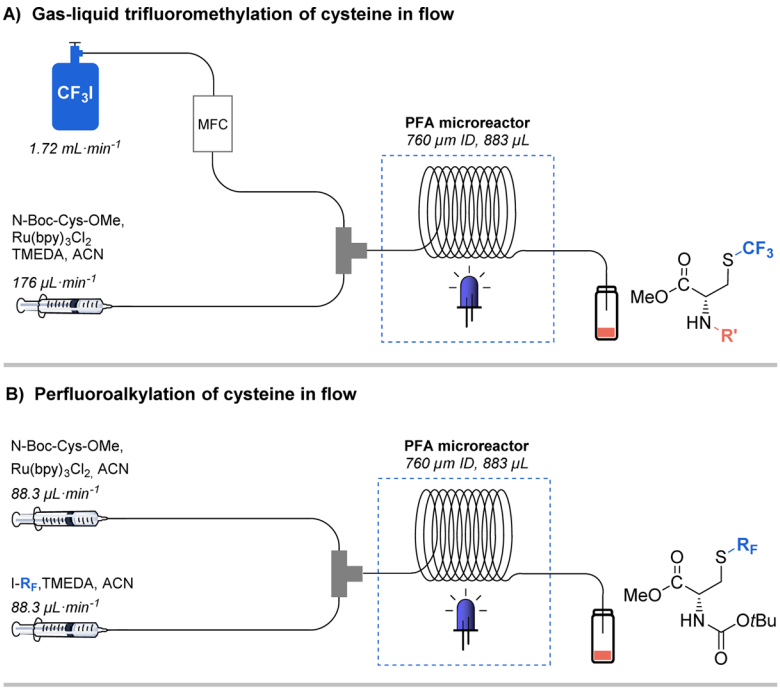
Scheme 3. Direct Photo-Induced Perfluoroalkylation of Cysteine in Batch[a]



[a]Reaction conditions: *N*-Boc-L-Cys-OMe (0.5 mmol), $Ru(bpy)_3Cl_2·6H_2O$ (1 mol %), TMEDA (1 mmol), and R_F-I (1 mmol) in 5 mL of CH_3CN; 24 W white CFL, 2 h.



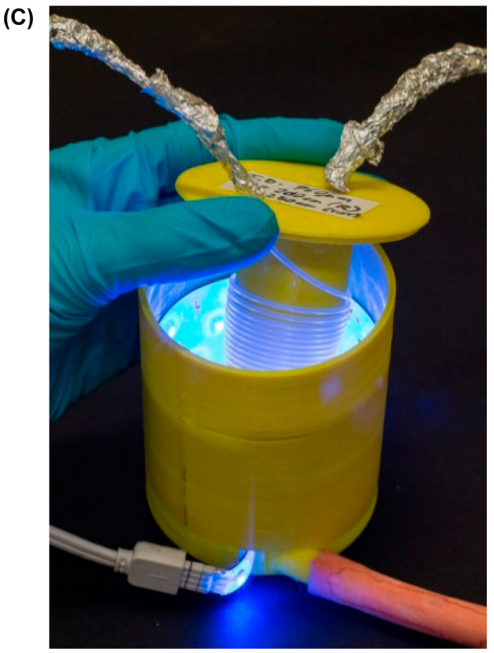


Figure 1. Schematic representation of the microflow setups for (A) gas–liquid trifluoromethylation and (B) perfluoroalkylation of cysteine. (C) Picture of the photomicroreactor (more details regarding the setup can be found in the Supporting Information).

ically, 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

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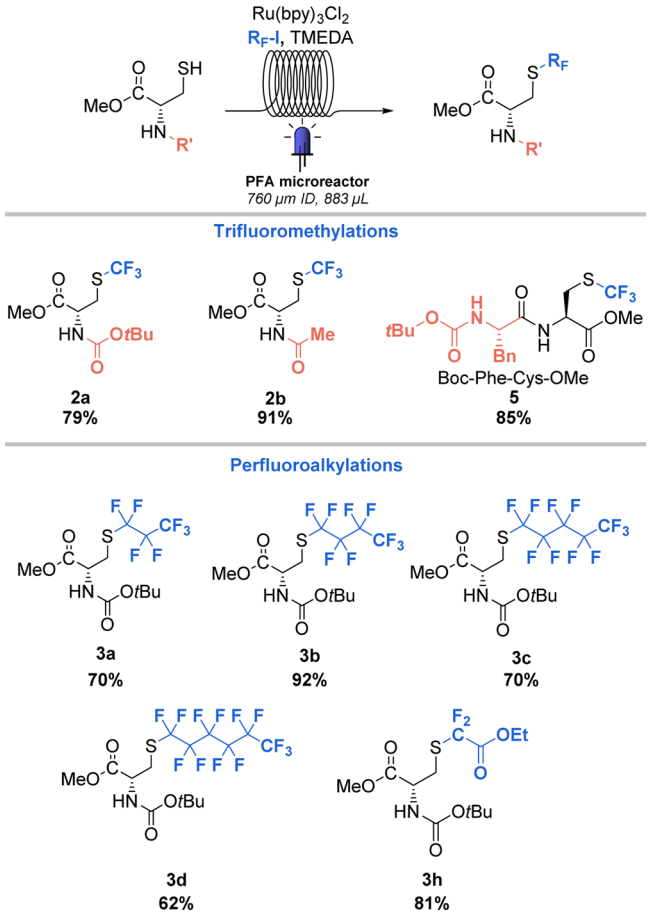
of compounds, which can be used for rapid screening of such interactions. In addition, long fluorous tags can be used to recover peptides and proteins by enabling extraction techniques with fluorinated solvents.[16] For the utility of our methodology for the preparation of highly fluorinated cysteine residues to be showcased, 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]

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 strip (1 m length, 78 Lumen, 3.12 W). The use of such miniaturized light sources, instead of CFL light sources, allows for increasing the overall photonic efficiency and minimizing 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 min residence time (Scheme 4, 62−92%).

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 that 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. For a neutral species to be generated, the radical anion needs to undergo another single electron transfer step (SET). This can be done either with $[TMEDA]^{\bullet+}$ (chain-terminating SET) or with R_FI (chain-propagating SET) to generate another R_F radical. To elucidate this step and 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 a chain propagating SET step is indeed present in the light-induced perfluoroalkylation of cysteine (see Supporting Information).[22]

Scheme 4. Direct Photo-Induced Trifluoromethylation and Perfluoroalkylation of Cysteine in Batch and Continuous Flow[a]



[a]Reaction conditions: *N*-Boc-L-Cys-OMe (0.5 mmol), $Ru(bpy)_3Cl_2 \cdot 6H_2O$ (1 mol %), 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 with 5 min residence time.

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 broad scope render 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 min vs 2 h 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 foil TLC plates with visualization under ultraviolet light (254 and 365 nm) or appropriate TLC staining. ^1H NMR, ^{13}C NMR, and ^{19}F-NMR spectra were recorded at ambient temperature using a 400 MHz spectrometer. ^1H 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

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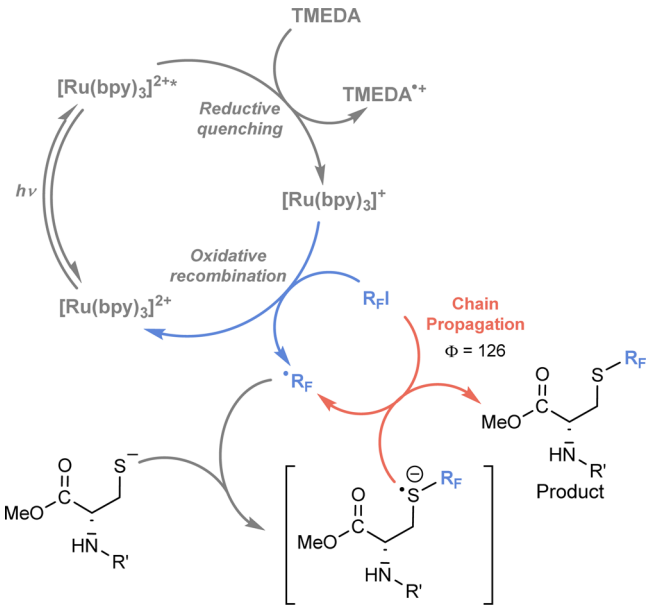
Scheme 5. Proposed Mechanism of the $Ru(bpy)_3^{2+}$-Catalyzed Radical Perfluoroalkylation of Cysteine Residues



corresponding ^1H NMR and ^{13}C NMR data from the 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) was measured with direct infusion in a 50:50 flow of 5 mM NH_4OAc in water/MeOH.

General Procedure for the Trifluoromethylation of Cysteine Residues in Batch (GP1, for Compounds 2a–b, 4, and 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 24 W white CFL. The reaction was stirred at 1000 rpm for 2 h. The reaction mixture was preadsorbed 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), 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 24 W white CFL. The reaction was stirred at 1000 rpm for 2 h. The reaction mixture was preadsorbed 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, 2b, and 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 of CH_3CN was mounted on a syringe pump. The liquid flow rate 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 flow rate 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 preadsorbed 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 and 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), and *α,α,α*-trifluorotoluene (146.1 mg, 1 mmol, internal standard) in 5 mL of 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 equiv) in 5 mL of CH_3CN were mounted on a single syringe pump. The liquid flow rate (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 preadsorbed 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** were prepared through a two-step procedure adapted from the literature.[23] Step 1 is 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 h). The reaction mixture was washed with HCl (1M), $NaHCO_3$ (sat), and brine. The organic layer was dried with $MgSO_4$. The crude mixture was absorbed on silica gel and purified with PE:EtOAC 7:1. Step 2 is the 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, tributylphosphine (0.6 equiv) was added by the use of a disposable syringe, and the reaction mixture was stirred at rt until completion (24 h). The crude mixture was evaporated under vacuo and redissolved in EtOAc. The organic layer was extracted with H_2O (3 times) and brine (3 times). The organic layer was then dried with $MgSO_4$ and concentrated on silica gel under vacuo. 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] Compound **2a** 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 min residence time. ^1H 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 − 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] Compound **2b** 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**. ^1H 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.

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*Methyl N-(tert-Butoxycarbonyl)-S-(perfluoropropyl)-L-cysteinate (**3a**).* Compound **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 a 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 to −82.31 (m), −84.76 to −89.66 (m), −124.08. HRMS (ESI) calculated for $C_7H_9F_7NO_2S^+$ [M − 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**).* Compound **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 a 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 to −88.16 (m), −119.94 to −121.26 (m), −125.32 to −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**).* Compound **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 a 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 to −81.14 (m), −85.48 to −87.66 (m), −119.18 to −120.38 (m), −121.60 to −122.76 (m), −125.63 to −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**).* Compound **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 a 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 to −81.65 (m), −85.12 to −88.04 (m), −119.78, −121.51, −122.94, −125.67 to −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**).* Compound **3e** was made according to GP2 on a 0.5 mmol scale. The crude product was purified by flash chromatography (petroleum ether:diethyl ether 16:1 to 8:1) yielding 269.5 mg (0.44 mmol, 90%) of derivative **3e** as a 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 to −88.54 (m), −119.78, −121.39, −122.18, −122.93, −126.00 to −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**).* Compound **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 a 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 to −89.24 (m), −119.59 to −119.88 (m), −121.20 to −121.46 (m), −121.80 to −122.27 (m), −122.74 to −123.14 (m), −126.25 to −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**).* Compound **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 to −81.23 (m), −85.58 to −87.69 (m), −119.21 to −119.96 (m), −120.84 to −121.55 (m), −121.55 to −122.26 (m), −122.62 to −123.05 (m), −125.67 to −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**).* Compound **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 a 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 to −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**).* Compound **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] Compound **5** 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

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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.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01031.

Description of reaction setups, light sources and their emission spectra, quantum yield measurements, and spectral data of all products (PDF)

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Notes

The authors declare no competing financial interest.

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