ChemPubSoc Europe

DOI: 10.1002/ejoc.201901572

EurJOC European Journal of Organic Chemistry
Communication

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Peptide Labeling

Selective Photoredox Trifluoromethylation of Tryptophan-Containing Peptides

Bo Ding,[a] Yue Weng,*[a,b] Yunqing Liu,[a] Chunlan Song,[a] Le Yin,[a] Jiafan Yuan,[a] Yanrui Ren,[a] Aiwen Lei,*[a] and Chien-Wei Chiang*[a]

Abstract: For application in drug discovery and biomedicine, it is crucial to develop new biocompatible methods to modify polypeptides. Herein, a visible-light-induced photoredox trifluoromethylation of tryptophan-containing peptides is reported. Under a mild, biocompatible, and straightforward condition, this strategy could incorporate the trifluoromethyl group into tryptophan residue with excellent chemo- and site-selectivity. The use of lower photocatalyst loading in 2 mol-% and cheap CF_3SO_2Na salt represents a great catalytic activity and economic CF_3 source. This direct trifluoromethylation strategy allows the ready study of fluorinated peptides exploiting ^{19}F-NMR. Additionally, the development of this protocol enables the study of biochemical systems and potentially modulates the function of biomolecules. Careful mechanistic studies (Stern-Volmer fluorescence quenching, EPR, and radical inhibition/trapping experiments) indicate that the reaction would proceed with a radical–radical cross-coupling procedure.

Introduction

Since the exquisite target potency and selectivity of peptides and proteins, a great interest in drug discovery has shifted to modify biomolecules, taking on a significant role as pharmaceuticals in the last decade.[1] Consequently, it is crucial to explore the possibility of biomolecular modification for discovering new therapeutic drugs. The growing importance of biomolecules has stimulated the chemistry field to develop new biocompatible reactions for the functionalization and bioconjugation of biomolecules.[2] In a living system, tryptophan (Trp) is the lowest abundance amino acid with a frequency of about 1.4 %,[3] but around 90 % of native proteins contain at least one Trp residue in their sequence.[4] Therefore, targeting Trp residue as well as maintaining structural integrity is a promising strategy for the modification of biomolecules due to its important roles.[5] Additionally, the C-2 position modification of the indole group of Trp, such as arylation, alkynylation, and allylation, has been recognized to be the most facile route of derivatization.[6,7]

Within pharmaceutical chemistry, the incorporation of the trifluoromethyl (CF_3) group to medicinal molecules could enhance the pharmacokinetic properties generally and improve its surface hydrophobicity, among other benefits.[8] Previously, peptide-based drugs and probes have proven particularly useful in biology.[1,9] Correspondingly, designing the fluorine-containing peptides with special properties and functions is attractive to researchers. In addition, due to the high sensitivity, extreme responsiveness to the local environment and broad chemical shift range of the ^{19}F-NMR, fluorinated peptides and proteins can often be detected by ^{19}F-NMR spectroscopy.[10] Although fluorine-containing biomolecules rarely exist in nature, the ^{19}F-labeled amino acids can be used to accelerate fluorine-containing drug design, respond to fundamental biological problems and illustrate the pharmacological mechanism.[11] Furthermore, fluorine-containing biomolecules could significantly support the study of a living system and potentially modulate the function of biomolecules.[12] Previously, the introduction of fluorine into biomolecules, such as reports from Davis,[6e,13] Gouverneur,[14] Parish and Krska,[11] as well as others[15] have provided numerous useful trifluoromethyl synthons with unique properties.

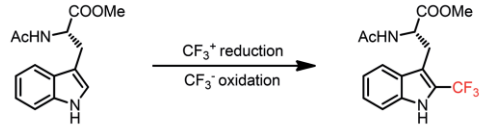
According to the literature, methods of merging the CF_3 group into (hetero)aryl compounds through the radical process have been reported.[16] However, on account of the problem of N–H interference, only a few studies have reported the trifluoromethylation on Trp (Scheme 1a).[6e,15b,17] Particularly, the research of applying the radical trifluoromethylation to the Trp-containing biomolecules was reported by the Davis and coworkers (Scheme 1b).[6e] Despite the utility of these approaches, to date, the reports of applying visible-light-induced photoredox catalytic trifluoromethylation to peptide substrates are still quite rare.[11,15a] Recently, photoredox catalysis has overcome several problems in traditional organic synthesis. Therefore, this strategy becomes a powerful tool for synthesizing complex molecules.[3,11,18] Previously, our group has utilized photoredox catalysis for the C–H bond activation of organic

[a] College of Chemistry and Molecular Sciences, Wuhan University, Wuhan, Hubei 430072, P. R. China
E-mail: cwchiang@whu.edu.cn
aiwenlei@whu.edu.cn
wengyue@whu.edu.cn
http://aiwenlei.whu.edu.cn/lawsys/
[b] TLS BL23A, National Synchrotron Radiation Research Center, Hsinchu Science Park, Hsinchu, Taiwan, R. O. C

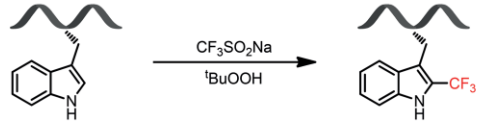
Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under https://doi.org/10.1002/ejoc.201901572.

compounds towards C–C and C–X bond generation.[19] Consequently, we envisioned that a mild and straightforward pathway to construct the fluorine-tagged biomolecules would be attained by exploiting the photoredox strategy. In addition, as a stable and inexpensive trifluoromethylation reagent, Langlois reagent (CF_3SO_2Na) has been wildly used as the CF_3 source in the field of C–H trifluoromethylation.[18b,20,21] Herein, we reported the visible-light-induced photocatalytic procedure to perform the trifluoromethylation on tryptophan-containing peptides with CF_3SO_2Na. This protocol provided a simple, mild, and biocompatible condition for the generation of Trp-CF_3 peptides (Scheme 1c).

a) Trifluoromethylation of Trp:



b) Radical trifluoromethylation of Trp in proteins *(by the Davis group)*:



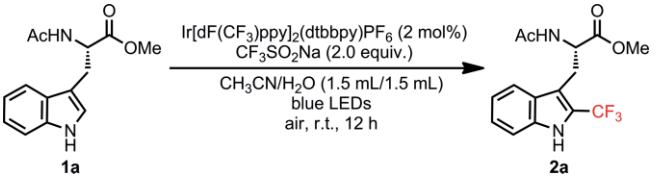
c) Photoredox selective trifluoromethylation of Trp in peptides *(this work)*:

Scheme 1. Trifluoromethylation of Trp residue.

Results and Discussion

Our initial experimental efforts focused on the development of reaction conditions for photocatalytic trifluoromethylation using CF_3SO_2Na, as this would provide a mild and direct condition for introducing the CF_3 group into Trp residue. The screening of photosensitizers and solvents was performed with CF_3SO_2Na and Ac-Trp-CO_2Me (**1a**) under the irradiation of blue LEDs at room temperature. We found that using 2 mol-% of Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 as the photosensitizer and CH_3CN as solvent under air atmosphere, the desired product **2a** could be observed in 62 % yield (Table 1, entry 1). Besides, for applying to polypeptide substrates, the tolerance of the photocatalytic conditions to mixed-aqueous systems is essential. Encouragingly, carrying out the photoredox trifluoromethylation of **1a** in a 1:1 mixture of CH_3CN/H_2O also gave 51 % yield of **2a** (Table 1, entry 2). However, using Ru(bpy)$_3$(PF_6)$_2$ or Ir(ppy)$_3$ as the photosensitizer delivered only trace amounts of the corresponding product (Table 1, entries 3 and 4). After that, the co-solvent effect was also explored. In comparison with CH_3CN, the co-solvent of DMSO displayed poor reactivity, but acetone showed moderate yield (Table 1, entries 5 and 6). Moreover, K_2HPO_4 was added to the reaction as the additive, resulting in a poor transformation (Table 1, entry 7). In contrast, the weak acid of HOAc had no effect on the formation of **2a** (Table 1, entry 8). Therefore, these results indicated that the basic system was not favored in this reaction, and the acidic condition could keep the generation of the product and inhibit the decomposition of the indole ring under oxidative conditions.[22] Moreover, control experiments showed that no product could be found in the absence of light, photocatalyst, or CF_3SO_2Na (Table 1, entries 9–11). In addition, the yield was decreased to less than 5 % by using N_2 or O_2 instead of air (Table 1, entries 12 and 13). The significant impact of air on the trifluoromethylation reaction, which led us realized that as a terminal oxidant, air would be milder than O_2, avoiding the over-oxidization of the reaction intermediate.[23]

Table 1. Optimization of the reaction conditions.[a]



1a **2a**

Entry	Variation from standard conditions	Yield [%]
1	CH_3CN (2 mL), 4 h	62 (60[b])
2	standard conditions	51 (52[b])
3	Ru(bpy)$_3$(PF_6)$_2$ as the photosensitizer	trace
4	Ir(ppy)$_3$ as the photosensitizer	trace
5	DMSO instead of CH_3CN	5
6	acetone instead of CH_3CN	47
7	added 1.0 equiv. K_2HPO_4	3
8	added 1.0 equiv. HOAc	48
9	no light	n.d.
10	no Ir photocatalyst	trace
11	no CF_3SO_2Na	n.d.
12	N_2 instead of air	4
13	O_2 instead of air	5

[a] Reaction conditions: **1a** (0.20 mmol), CF_3SO_2Na (0.40 mmol), Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 (2 mol-%), CH_3CN/H_2O (1.5 mL/1.5 mL), air, 3 W blue LEDs, room temperature, 12 h, ^{19}F-NMR yield. n.d. = not detected; dF(CF_3)ppy = 2-(2,4-difluorophenyl)-5-(trifluoromethyl)pyridine; dtbbpy = 4, 4′-di-*tert*-butyl-2,2′-bipyridine. [b] Isolated yield.

With the optimized reaction conditions in hand, the residue selectivity of this photocatalytic trifluoromethylation protocol was studied. Various amino acid substrates, especially those with active function groups, were tested by using the optimized reaction conditions (see Supporting Information). According to the evidence of ^{19}F-NMR, high levels of trifluoromethylation products were detected with Trp and cysteine (Cys) as substrates. On the other hand, low levels of products from tyrosine (Tyr) and phenylalanine (Phe) appeared as mixtures of regioisomers. The trifluoromethylation could not occur on histidine (His) residue. Notably, competition assays using mixtures of equimolar Cys, Phe, Tyr, or/and His with Trp were applied to assess residue-specific selectivity (Figure 1). The results revealed that the selectivity favored achieving the formation of Trp-CF_3. The transformation of **1a** was decreased obviously when the mixture contained His residue, implying that the His residue might inhibit the reaction process. These results supported the

photoredox trifluoromethylation on Trp was able to achieve in chemo- and site-selective way.

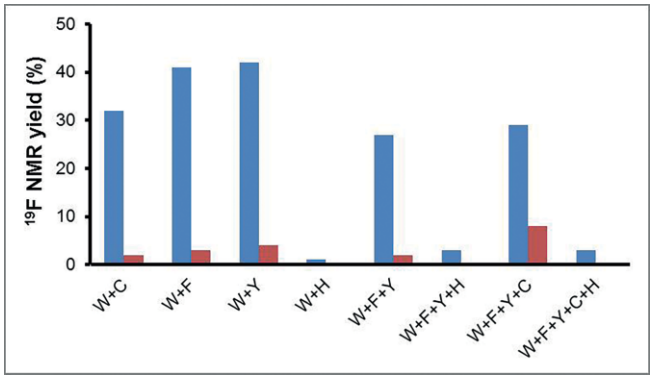


Figure 1. The competition experiments of derivatized amino acids analog revealed chemo- and site-selectivity toward **1a**. (For details, see Supporting Information). Blue columns represent the generation of Trp-CF_3; Red columns represent the generation of Cys-CF_3, Phe-CF_3, or/and Tyr-CF_3.

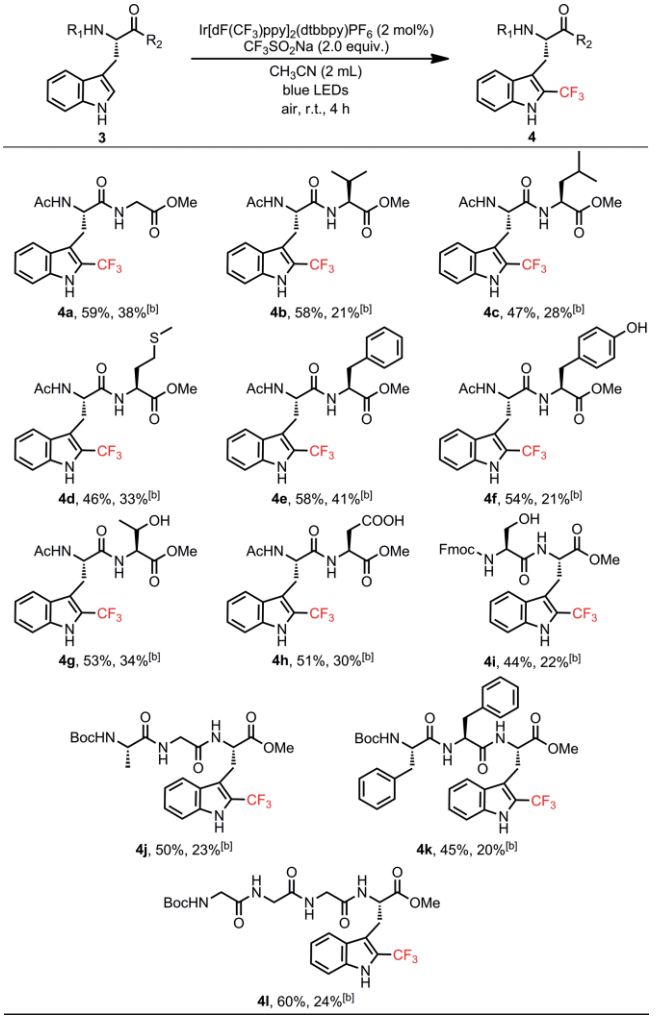
Subsequently, we attempted to investigate the functional group compatibility of this transformation by applying the reaction to a range of polypeptides (Table 2). For example, dipeptides containing relatively inert amino acid partners, such as glycine, valine, and leucine, afforded the corresponding products in moderate yields (**4a**–**4c**). Besides, when the readily oxidizable methionine was applied as a dipeptide partner to test the reactivity, this dipeptide also gave the desired product in 46 % yield (**4d**). Moreover, dipeptides with aromatic amino acids (Phe and Tyr) as the neighboring amino acids showed good selective trifluoromethylation at the Trp residue and provided the corresponding products in the yields of 58 % and 54 %, respectively (**4e** and **4f**). For dipeptides **3g**, **3h** and **3i**, the adjacent amino acids containing unprotected alcohol or carboxylic acid group would not interrupt the efficiency and selectivity of the trifluoromethylation of Trp residue (**4g**–**4i**). Furthermore, when other polypeptides were used as the substrates, the results demonstrated the successful trifluoromethylation of Trp residue as well (**4j**–**4l**).

To our delight, the photoredox trifluoromethylation of peptides could also be tolerated to the mixed-aqueous environment. While polypeptides were introduced to a 1:1 mixed-solvent of CH_3CN/H_2O, the reaction could achieve the trifluoromethylation of Trp in acceptable yields. Notably, these Trp-containing polypeptides exhibited the excellent trifluoromethylation selectivity on the Trp residue, which would provide the opportunity to discover and explore the development of peptide medicines.

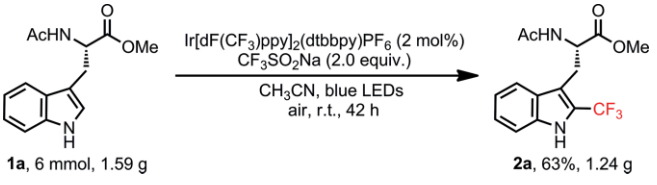
Additionally, to further explore the utilities of this method, the gram-scale synthesis experiment was implemented. A comparable yield of 63 % (1.24 g) was attained when the model reaction was conducted in 6 mmol (1.59 g) scale (Scheme 2). This result indicated the potential of promising application in preparative synthesis.

To get more insight into the reaction mechanism, the investigations of Stern-Volmer emission quenching experiments, electron paramagnetic resonance (EPR) spectroscopy and radical inhibition/trapping experiments have been performed. The

Table 2. Scope of selective trifluoromethylation of polypeptides.[a]



[a] Reaction conditions: peptide **3** (0.20 mmol), CF_3SO_2Na (0.40 mmol), $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (2 mol-%), CH_3CN (2 mL), air, 3 W blue LEDs, room temperature, 4 h, isolated yield. $dF(CF_3)ppy$ = 2-(2,4-difluorophenyl)-5-(trifluoromethyl)pyridine; dtbbpy = 4, 4′-di-*tert*-butyl-2,2′-bipyridine. [b] CH_3CN/H_2O (1.5 mL/1.5 mL) as solvent, 14 h, ^{19}F-NMR yield.



Scheme 2. Gram-scale synthesis experiment.

fluorescence intensity of the excited state of $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ could be linearly quenched by Ac-Trp-CO_2Me (**1a**) and CF_3SO_2Na individually in the analysis of Stern-Volmer emission quenching studies (see Figure S6–S8 in the Supporting Information). Noteworthy, **1a** had a more obvious quenching effect. In the EPR studies, under the irradiation of blue LEDs, a signal of nitrogen radical of Trp could be detected in the mixture of **1a** and photocatalyst (g = 2.0060, A_N = 10.1). Alternatively, when the radical spin trapping agent DMPO (5,5-di-

methyl-1-pyrroline *N*-oxide) was presented to the solution of CF_3SO_2Na with photocatalyst, a significant signal of CF_3 radical could also be found with *g* value of 2.0066 (A_N = 13.6 G, A_H = 16.2 G) (Figure 2). In addition, as DMPO was treated to the model reaction system, we still could observe a CF_3 radical signal in EPR spectroscopy (see Figure S9 in the Supporting Information).

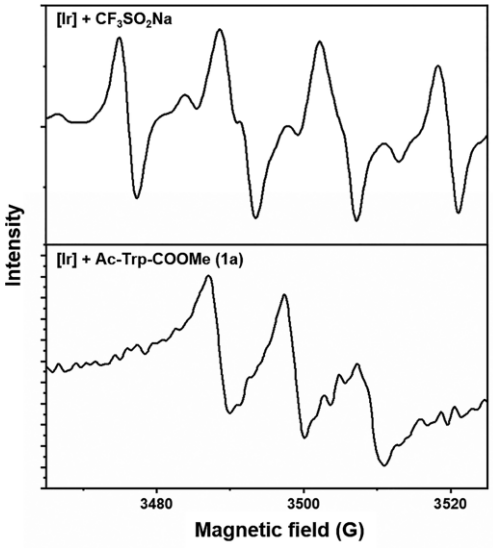
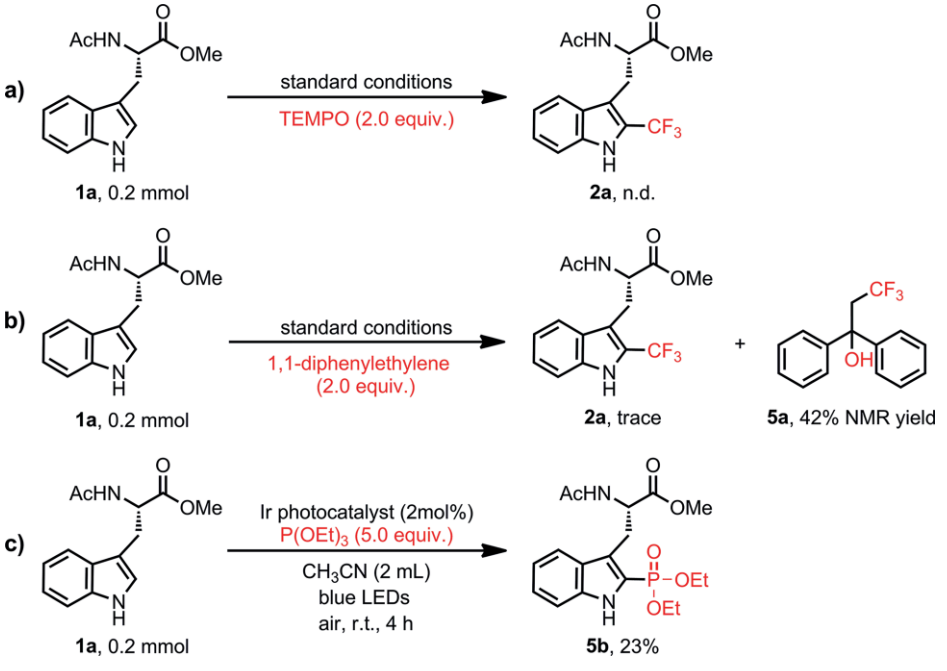


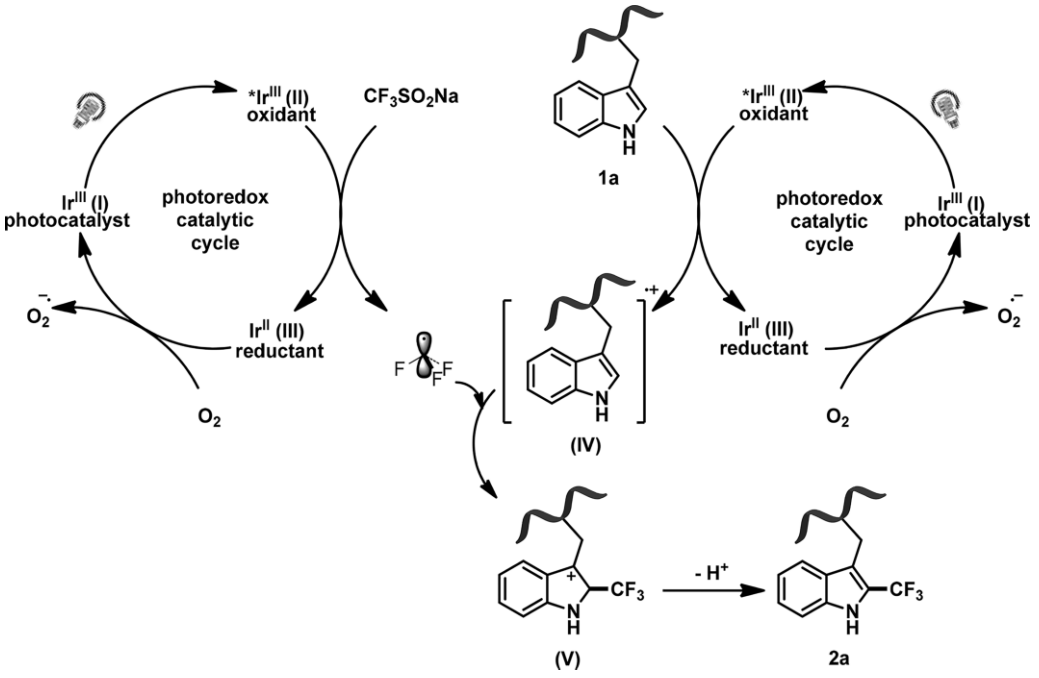
Figure 2. EPR spectroscopy. (For details, see Supporting Information).

To further confirm the formation of radical species and the possibility of radical–radical coupling mechanism. Radical inhibition/trapping reactions were conducted by adding the external TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl), 1,1-diphenylethylene, and $P(OEt)_3$ (triethyl phosphite), respectively. When 2.0 equiv. of TEMPO was added to the reaction solution, no corresponding product **2a** was detected in the resulting mixture (Scheme 3a). Accordingly, preliminary evidence of the radical-involved reaction would be verified. In addition, as the reaction mixture was treated with 1,1-diphenylethylene, an CF_3 radical bound adduct 3,3,3-trifluoro-1,1-diphenylpropan-1-ol (**5a**) could be identified. Nevertheless, **2a** was still difficult to obtain in this system (Scheme 3b). While $P(OEt)_3$ was introduced to the solution of **1a** and photocatalyst, the diethylphosphonate-bound tryptophan adduct (**5b**) could be gained in 23 % yield after the irradiation of blue LEDs (Scheme 3c). Therefore, based on the above mechanistic experiments, we could suppose that the reaction was proceeded by the radical-radical cross-coupling between Trp radical cation and the CF_3 radical. Furthermore, light on/off experiments confirmed the indispensability of visible light, suggesting that continuous visible-light irradiation was necessary for the trifluoromethylation of Trp. (see Figure S5 in the Supporting Information).

According to the above observations and literature reports, a reaction mechanism for this photoredox trifluoromethylation of Trp was proposed (Scheme 4).[3,24] Firstly, the excited state of the photosensitizer (**II**) would be generated under the irradiation of the blue LEDs. Afterwards, it performed individually single-electron transfer (SET) oxidation with CF_3SO_2Na and Trp (**1a**) and then produced the CF_3 radical and Trp radical cation species (**IV**). Subsequently, the reduced state of the photosensitizer (**III**) was oxidized to its ground-state **I** and completed the photoredox catalytic cycle. Meanwhile, the CF_3 radical reacted directly with the Trp radical cation (**IV**) to form the intermediate **V**. After facile deprotonation of the cation intermediate **V**, the desired product (**2a**) could be obtained eventually. On the other hand, based on the previous reports,[6e,18b,21] we might not exclude the possibility of the CF_3 radical addition with the indole ring of Trp (see Figure S10 in the Supporting Information).



Scheme 3. The radical inhibition/trapping experiments.



Scheme 4. Proposed mechanism.

Conclusions

In conclusion, we have introduced a visible-light-induced photoredox method that allowed direct trifluoromethylation of Trp and Trp-containing polypeptides without the prefunctionalization under a mild, biocompatible, and straightforward condition. This method offered a selective photoredox Trp bioconjugation strategy, complementing previous reports of Cys and Lys bioconjugation reactions. Furthermore, this protocol featured excellent site- and chemo-selectivity, along with good catalytic efficacy at photocatalyst loading as low as 2 mol-%. The evidences of Stern-Volmer emission quenching studies, EPR spectroscopy and radical inhibition/trapping experiments could demonstrate the reaction would proceed through a radical-radical coupling procedure between the tryptophan radical cation and the CF_3 radical. The value of this transformation was highlighted via the trifluoromethylation of biologically peptides with CF_3SO_2Na at room temperature under the easy-handle LED irradiation.

Experimental Section

General Information: All glassware was oven-dried at 110 °C for hours and cooled down under vacuum. All manipulations were carried out by using standard Schlenk techniques. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. The $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ was prepared following literature procedures.[25] Thin-layer chromatography (TLC) employed glass 0.25 mm silica gel plates. Flash chromatography columns were packed with 200–300 mesh silica gel. Gradient flash chromatography was conducted eluting with a continuous gradient from dichloromethane to the ethyl acetate or methanol. All new compounds were characterized by m.p., IR, ^{1}H-NMR, ^{13}C-NMR and HRMS. The known compounds were characterized by ^{1}H-NMR and ^{13}C-NMR. The ^{1}H-, ^{13}C- and ^{19}F-NMR spectra were recorded on a Bruker 400 MHz NMR spectrometer. For ^{1}H-NMR, chemical shifts (δ) were given in ppm relatives to the internal standard (TMS at 0 ppm, $[D_6]$DMSO at 2.50 ppm, CD_3CN at 1.94 ppm, $[D_6]$Acetone at 2.05 ppm). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, m = multiplet, br = broad. Coupling constants are reported as a *J* value in Hertz (Hz). The number of protons (*n*) for a given resonance is indicated as *n*H and is based on spectral integration values. For ^{13}C-NMR, chemical shifts (δ) were reported in ppm using solvent as internal standard ($CDCl_3$ at 77.16 ppm, $[D_6]$DMSO at 39.52 ppm, CD_3CN at 118.26 ppm, $[D_6]$Acetone at 29.84 ppm). High-resolution mass spectra (HRMS) were measured with a Bruker UltiMate3000 & Compact instrument and accurate masses were reported for the molecular ion + Hydrogen [M + H] or molecular ion + Sodium [M + Na].

General Procedure for Synthesis Protected Amino Acids 1a–1e:[26] In an oven-dried round-bottom flask (100 mL), L-amino acid (10 mmol) was dissolved in anhydrous MeOH (40 mL). Stirred, cooled to 0 °C. Carefully added $SOCl_2$ (20 mmol) to the solution. The reaction mixture was then warmed to room temperature and stirred overnight. The solvent was removed by rotary evaporation to afford amino ester hydrochloride residue. Without further purification, the residue and triethylamine (20 mmol) was added in anhydrous DCM (40 mL) and stirred for 15 min at 0 °C. Acetyl chloride (10 mmol) was added to the reaction solution dropwise. Stirring was continued for 12 h while allowing the mixture to warm up to room temperature. The reaction was washed with saturated $NaHCO_3$ solutions (50 mL × 2) and 10 % HCl (50 mL × 1) to remove any unreacted starting material. The combined organic extracts were dried (anhydrous Na_2SO_4), filtered, and concentrated in vacuo. Then, purification of the residue by column chromatography on silica gel (dichloromethane/ethyl acetate) to afford corresponding protected amino acid **1a**–**1e**.

General Procedure for Synthesis of Starting Materials Dipeptides 3a - 3f:[26] In a round-bottomed flask (250 mL), equipped with a stir bar, *N*-acetyl-L-tryptophan (5.0 mmol), HOBT (1-hydroxybenzo-

triazole) (7.5 mmol), HBTU (*O*-benzotriazole-*N*,*N*,*N*′,*N*′-tetramethyl-uronium-hexafluorophosphate) (7.5 mmol), dichloromethane (100 mL) and triethylamine (6.0 mmol) were combined and added. The mixture was stirred for 30 min at room temperature, and then, L-amino acids methyl ester hydrochloride (5.0 mmol) and triethylamine (5.0 mmol) were added to the solution. The reaction was stirred overnight. After regular workup, the reaction mixture washed by saturated $NaHCO_3$ solution (100 mL × 3), 2 M hydrochloric acid solution (100 mL × 3) and H_2O (100 mL × 3). The organic layers were combined, dried with Na_2SO_4, and concentrated. The resulting crude product was purified by flash column chromatography on silica gel (dichloromethane/ethyl acetate) to afford corresponding dipeptides **3a** – **3f**.

Ac-Trp-Gly-OMe (3a):[15b] White solid. ^{1}H NMR (400 MHz, CD_3CN) δ = 9.36 (s, 1H), 7.59 (d, *J* = 7.9 Hz, 1H), 7.38 (d, *J* = 8.1 Hz, 1H), 7.26 (t, *J* = 5.8 Hz, 1H), 7.18–7.08 (m, 2H), 7.03 (t, *J* = 7.3 Hz, 1H), 6.97 (d, *J* = 7.8 Hz, 1H), 4.70 (td, *J* = 8.1, 5.4 Hz, 1H), 3.86 (d, *J* = 5.9 Hz, 2H), 3.64 (s, 3H), 3.27 (dd, *J* = 14.8, 5.4 Hz, 1H), 3.07 (dd, *J* = 14.8, 8.1 Hz, 1H), 1.83 (s, 3H). ^{13}C NMR (101 MHz, CD_3CN) δ = 173.2, 171.1, 171.0, 137.2, 128.4, 124.5, 122.3, 119.7, 119.2, 112.2, 111.0, 54.6, 52.5, 41.6, 28.4, 22.9. HRMS (ESI) calculated for $C_{16}H_{19}N_3O_4$, $[M + Na]^+$, 340.1268, found 340.1265.

Ac-Trp-Val-OMe (3b):[27] White solid. ^{1}H NMR (400 MHz, $[D_6]$DMSO) δ = 10.83 (s, 1H), 8.30 (d, *J* = 8.1 Hz, 1H), 8.08 (d, *J* = 8.1 Hz, 1H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.16–7.11 (m, 1H), 7.06 (t, *J* = 7.3 Hz, 1H), 6.98 (t, *J* = 7.3 Hz, 1H), 4.69 (td, *J* = 8.7, 5.0 Hz, 1H), 4.21 (dd, *J* = 8.1, 6.4 Hz, 1H), 3.62 (s, 3H), 3.09 (dd, *J* = 14.7, 5.0 Hz, 1H), 2.91 (dd, *J* = 14.7, 9.1 Hz, 1H), 2.12–2.00 (m, 1H), 1.78 (s, 3H), 0.89 (dd, *J* = 9.4, 6.7 Hz, 6H). ^{13}C NMR (101 MHz, $[D_6]$DMSO) δ = 172.3, 172.0, 169.2, 136.1, 127.4, 123.6, 120.9, 118.6, 118.2, 111.3, 110.1, 57.5, 53.1, 51.7, 30.0, 27.8, 22.6, 19.0, 18.4. HRMS (ESI) calculated for $C_{19}H_{25}N_3O_4$, $[M + Na]^+$, 382.1737, found 382.1737.

Ac-Trp-Leu-OMe (3c):[6f] White solid. ^{1}H NMR (400 MHz, $[D_6]$DMSO) δ = 10.82 (s, 1H), 8.42 (d, *J* = 7.7 Hz, 1H), 8.06 (d, *J* = 8.3 Hz, 1H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.32 (dt, *J* = 8.1, 0.9 Hz, 1H), 7.14 (d, *J* = 2.2 Hz, 1H), 7.10–7.03 (m, 1H), 7.02–6.95 (m, 1H), 4.59 (td, *J* = 8.8, 4.8 Hz, 1H), 4.37–4.28 (m, 1H), 3.61 (s, 3H), 3.10 (dd, *J* = 14.7, 4.7 Hz, 1H), 2.88 (dd, *J* = 14.7, 9.3 Hz, 1H), 1.76 (s, 3H), 1.68–1.54 (m, 2H), 1.54–1.45 (m, 1H), 0.90 (d, *J* = 6.3 Hz, 3H), 0.85 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (101 MHz, $[D_6]$DMSO) δ = 172.9, 172.1, 169.1, 136.1, 127.4, 123.6, 120.9, 118.6, 118.2, 111.3, 110.1, 53.0, 51.9, 50.3, 38.3, 27.8, 24.2, 22.8, 22.6, 21.4. HRMS (ESI) calculated for $C_{19}H_{25}N_3O_4$, $[M + Na]^+$, 396.1894, found 396.1889.

Ac-Trp-Met-OMe (3d):[6f] White solid. ^{1}H NMR (400 MHz, CD_3CN) δ = 9.44 (s, 1H), 7.57 (d, *J* = 7.9 Hz, 1H), 7.44 (d, *J* = 7.8 Hz, 1H), 7.38 (d, *J* = 8.1 Hz, 1H), 7.16 (d, *J* = 7.9 Hz, 1H), 7.14–7.08 (m, 2H), 7.06–6.98 (m, 1H), 4.75 (td, *J* = 7.8, 5.6 Hz, 1H), 4.53 (td, *J* = 8.3, 4.8 Hz, 1H), 3.64 (s, 3H), 3.24 (dd, *J* = 14.7, 5.6 Hz, 1H), 3.08 (dd, *J* = 14.7, 7.8 Hz, 1H), 2.49–2.31 (m, 2H), 2.07–2.02 (m, 1H), 2.00 (s, 3H), 1.93–1.86 (m, 1H), 1.84 (s, 3H). ^{13}C NMR (101 MHz, CD_3CN) δ = 173.0, 172.9, 171.2, 137.2, 128.3, 124.6, 122.2, 119.6, 119.2, 112.1, 110.8, 54.7, 52.7, 52.2, 31.5, 30.3, 28.4, 22.9, 15.1. HRMS (ESI) calculated for $C_{19}H_{25}N_3O_4S$, $[M + Na]^+$, 414.1458, found 414.1452.

Ac-Trp-Phe-OMe (3e):[6f] White solid. ^{1}H NMR (400 MHz, CD_3CN) δ = 9.37 (s, 1H), 7.57 (d, *J* = 7.9 Hz, 1H), 7.38 (dt, *J* = 8.2, 1.0 Hz, 1H), 7.29–7.21 (m, 3H), 7.17 (d, *J* = 7.8 Hz, 1H), 7.15–7.09 (m, 3H), 7.08–7.01 (m, 2H), 6.97–6.90 (m, 1H), 4.72–4.61 (m, 2H), 3.61 (s, 3H), 3.19 (dd, *J* = 14.8, 5.6 Hz, 1H), 3.10–2.98 (m, 2H), 2.93 (dd, *J* = 13.8, 7.7 Hz, 1H), 1.81 (s, 3H). ^{13}C NMR (101 MHz, CD_3CN) δ = 172.5, 172.4, 171.1, 137.5, 137.2, 130.1, 129.2, 128.3, 127.6, 124.5, 122.3, 119.7, 119.2, 112.2, 110.9, 54.53, 54.47, 52.6, 37.9, 28.2, 22.8. HRMS (ESI) calculated for $C_{23}H_{25}N_3O_4$, $[M + Na]^+$, 430.1737, found 430.1735.

Ac-Trp-Tyr-OMe (3f):[6c] White solid. ^{1}H NMR (400 MHz, CD_3CN) δ = 9.39 (s, 1H), 7.82 (br, 1H), 7.57 (d, *J* = 7.9 Hz, 1H), 7.38 (d, *J* = 8.1 Hz, 1H), 7.18–7.09 (m, 2H), 7.08 (d, *J* = 2.4 Hz, 1H), 7.06–7.00 (m, 2H), 6.95–6.89 (m, 2H), 6.73–6.66 (m, 2H), 4.69 (td, *J* = 7.9, 5.6 Hz, 1H), 4.59 (td, *J* = 7.5, 5.7 Hz, 1H), 3.60 (s, 3H), 3.20 (dd, *J* = 14.8, 5.6 Hz, 1H), 3.04 (dd, *J* = 14.8, 8.0 Hz, 1H), 2.96 (dd, *J* = 13.9, 5.8 Hz, 1H), 2.84 (dd, *J* = 13.9, 7.4 Hz, 1H), 1.82 (s, 3H). ^{13}C NMR (101 MHz, CD_3CN) δ = 172.54, 172.53, 171.6, 156.7, 137.2, 131.2, 128.3, 128.1, 124.5, 122.3, 119.7, 119.2, 116.0, 112.2, 110.8, 54.72, 54.68, 52.6, 37.1, 28.2, 22.8. HRMS (ESI) calculated for $C_{23}H_{25}N_3O_5$, $[M + Na]^+$, 446.1686, found 446.1684.

General Procedure for Synthesis of Starting Materials Dipeptides 3g–3i:[26] In a round-bottomed flask (250 mL), equipped with a stir bar, *N*-acetyl-L-tryptophan (5.0 mmol), HOBT (7.5 mmol), HBTU (7.5 mmol), dichloromethane (100 mL) and triethylamine (6.0 mmol) were combined and added. The mixture was stirred for 30 min at room temperature, and then, L-amino acids methyl ester hydrochloride (5.0 mmol) whose residues are protected and triethylamine (5.0 mmol) was added to the solution. The reaction was stirred overnight. After regular workup, the reaction mixture washed by saturated $NaHCO_3$ solution (100 mL × 3), 2 M hydrochloric acid solution (100 mL × 3) and H_2O (100 mL × 3). The organic layers were combined, dried with Na_2SO_4, and concentrated. Without further purification, the 50 % TFA/DCM solution (40 mL) was added dropwise and the mixture was stirred for 2–4 h at room temperature. When the reaction finished, the reaction mixture was concentrated in vacuo. The resulting crude product was purified by flash column chromatography on silica gel (dichloromethane/ethyl acetate) to afford corresponding dipeptides **3g**–**3i**.

Ac-Trp-Thr-OMe (3g): Pale yellow solid. M.p. 63–66 °C. IR (film)/cm^{-1} 3298, 3060, 2928, 1742, 1653, 1541, 1438, 1206, 744. ^{1}H NMR (400 MHz, $[D_6]$DMSO, diastereomer) δ = 10.84 (s, 1H), 8.18 (d, *J* = 8.3 Hz, 0.82H) & 8.13 (d, *J* = 8.3 Hz, 0.18H), 8.09 (d, *J* = 8.3 Hz, 0.17H) & 8.02 (d, *J* = 8.6 Hz, 0.82H), 7.62 (d, *J* = 7.7 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.15 (d, *J* = 2.4 Hz, 1H), 7.05 (t, *J* = 7.3 Hz, 1H), 6.97 (t, *J* = 7.3 Hz, 1H), 5.03 (d, *J* = 5.6 Hz, 0.20H) & 5.01 (d, *J* = 5.9 Hz, 0.76H), 4.69 (td, *J* = 8.8, 5.1 Hz, 1H), 4.33 (dd, *J* = 8.4, 3.4 Hz, 0.18H) & 4.29 (dd, *J* = 8.6, 3.3 Hz, 0.81H), 4.18–4.11 (m, 0.25H) & 4.11–4.02 (m, 0.80H), 3.64 (s, 2.27H) & 3.63 (s, 0.78H), 3.13 (dd, *J* = 15.0, 5.7 Hz, 1H), 2.91 (dd, *J* = 14.5, 9.2 Hz, 1H), 1.78 (s, 2.33H) & 1.77 (s, 0.72H), 1.07 (d, *J* = 6.4 Hz, 0.46H) & 0.95 (d, *J* = 6.4 Hz, 2.60H). ^{13}C NMR (101 MHz, $[D_6]$DMSO, diastereomer) δ = 172.5 & 172.4, 171.12 & 171.08, 169.2, 136.1, 127.41 & 127.37, 123.6, 120.9, 118.5, 118.2, 111.3, 110.24 & 110.20, 66.4, 57.9 & 57.8, 53.5 & 53.3, 51.9, 28.1, 22.6, 20.1 & 20.0. HRMS (ESI) calculated for $C_{18}H_{23}N_3O_5$, $[M + H]^+$, 384.1530, found 384.1526.

Ac-Trp-Asp-OMe (3h): Pale yellow solid. M.p. 52–55 °C. IR (film)/cm^{-1} 3316, 3059, 2954, 1732, 1647, 1539, 1437, 1229, 744. ^{1}H NMR (400 MHz, $[D_6]$DMSO) δ = 12.58 (br, 1H), 10.83 (s, 1H), 8.54 (d, *J* = 7.7 Hz, 1H), 8.11 (dd, *J* = 8.5, 3.1 Hz, 1H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.33 (d, *J* = 7.9 Hz, 1H), 7.14 (d, *J* = 2.4 Hz, 1H), 7.07 (t, *J* = 7.5 Hz, 1H), 6.99 (t, *J* = 7.4 Hz, 1H), 4.78–4.45 (m, 2H), 3.62 (s, 3H), 3.13 (dd, *J* = 14.5, 4.6 Hz, 1H), 2.89 (dd, *J* = 14.4, 9.4 Hz, 1H), 2.75 (dd, *J* = 16.7, 5.9 Hz, 1H), 2.62 (dd, *J* = 16.8, 6.8 Hz, 1H), 1.77 (s, 3H). ^{13}C NMR (101 MHz, $[D_6]$DMSO) δ = 172.3, 172.0, 171.8, 169.6, 136.5, 127.8, 124.1, 121.3, 118.9, 118.6, 111.7, 110.5, 53.5, 52.6, 49.1, 36.2, 28.3, 23.0. HRMS (ESI) calculated for $C_{18}H_{21}N_3O_6$, $[M + Na]^+$, 398.1323, found 398.1316.

Fmoc-Ser-Trp-OMe (3i): White solid. M.p. 79–81 °C. IR (film)/cm^{-1} 3327, 3062, 2952, 1724, 1666, 1525, 1450, 1232, 759, 740. ^{1}H NMR

(400 MHz, CD_3CN) δ = 9.33 (s, 1H), 7.79 (d, J = 7.6 Hz, 2H), 7.68–7.58 (m, 2H), 7.52 (d, J = 7.9 Hz, 1H), 7.42–7.32 (m, 4H), 7.32–7.23 (m, 2H), 7.16–7.08 (m, 2H), 7.04 (t, J = 7.3 Hz, 1H), 6.33 (d, J = 7.8 Hz, 1H), 4.80 (dt, J = 7.7, 6.0 Hz, 1H), 4.35–4.24 (m, 3H), 4.18 (t, J = 7.0 Hz, 1H), 3.87–3.68 (m, 2H), 3.58 (s, 3H), 3.43 (br, 1H), 3.33–3.19 (m, 2H). ^{13}C NMR (101 MHz, CD_3CN) δ = 172.9, 171.3, 157.2, 144.83, 144.76, 141.9, 137.1, 128.5, 128.2, 127.9, 126.0, 124.8, 122.4, 120.8, 119.9, 119.1, 112.3, 110.0, 67.5, 63.0, 57.3, 54.1, 52.7, 47.7, 27.9. HRMS (ESI) calculated for $C_{30}H_{29}N_3O_6$, $[M + Na]^+$, 550.1949, found 550.1949.

General Procedure for Synthesis of Starting Materials Peptides 3j–3l:[26] Refer to the synthesis method of **3a–3f**.

Boc-Ala-Gly-Trp-OMe (3j): White solid. M.p. 74–76 °C. IR (film)/cm^{-1} 3309, 3057, 2978, 2931, 1736, 1663, 1522, 1457, 1367, 1249, 1166, 744. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.99 (s, 1H), 7.45 (d, J = 7.8 Hz, 1H), 7.28 (d, J = 8.0 Hz, 1H), 7.20–7.08 (m, 3H), 7.05 (t, J = 7.3 Hz, 1H), 6.97 (d, J = 2.0 Hz, 1H), 5.45 (d, J = 6.8 Hz, 1H), 4.77 (q, J = 6.3 Hz, 1H), 4.19–4.03 (m, 1H), 3.81–3.62 (m, 2H), 3.60 (s, 3H), 3.24 (d, J = 5.7 Hz, 2H), 1.42 (s, 9H), 1.21 (d, J = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 173.9, 172.4, 169.2, 155.9, 136.2, 127.3, 123.9, 121.9, 119.3, 118.2, 111.6, 109.0, 80.5, 52.7, 52.6, 50.3, 42.8, 28.4, 27.3, 18.4. HRMS (ESI) calculated for $C_{22}H_{30}N_4O_6$, $[M + Na]^+$, 469.2058, found 469.2057.

Boc-Phe-Phe-Trp-OMe (3k): White solid. M.p. 48–51 °C. IR (film)/cm^{-1} 3292, 3061, 2930, 1743, 1648, 1517, 1456, 1383, 1250, 1169, 742, 700. ^{1}H NMR (400 MHz, [D$_6$]DMSO) δ = 10.93 (s, 1H), 8.67 (d, J = 5.8 Hz, 0.16H) & 8.62 (d, J = 6.9 Hz, 0.78H), 8.11 (d, J = 7.7 Hz, 0.16H) & 8.03 (d, J = 8.0 Hz, 0.76H), 7.52 (d, J = 7.7 Hz, 1H), 7.37 (d, J = 7.9 Hz, 1H), 7.34–7.24 (m, 5H), 7.24–7.13 (m, 6H), 7.09 (t, J = 7.5 Hz, 1H), 7.02 (t, J = 7.4 Hz, 1H), 6.91 (d, J = 8.8 Hz, 1H), 4.79–4.65 (m, 1H), 4.60 (q, J = 7.1 Hz, 1H), 4.23–4.12 (m, 0.82H) & 4.12–3.99 (m, 0.25H), 3.57 (s, 3H), 3.22 (dd, J = 14.6, 6.3 Hz, 1H), 3.18–3.01 (m, 2H), 2.95–2.77 (m, 2H), 2.66 (dd, J = 13.8, 10.4 Hz, 1H), 1.29 (s, 7.80H) & 1.11 (s, 1.48H). ^{13}C NMR (101 MHz, [D$_6$]DMSO) δ = 172.1, 171.5, 171.2, 155.2, 138.2, 137.5, 136.2, 129.5, 129.2, 128.1, 128.0, 127.2, 126.4, 126.2, 123.9, 121.1, 118.5, 118.1, 111.5, 109.2, 78.2, 55.9, 53.5, 53.3, 51.9, 37.9, 37.7, 28.2 & 27.8, 27.2. HRMS (ESI) calculated for $C_{35}H_{40}N4O_6$, $[M + Na]^+$, 635.2840, found 635.2836.

Boc-Gly-Gly-Gly-Trp-OMe (3l): White solid. M.p. 72–75 °C. IR (film)/cm^{-1} 3314, 3059, 2979, 2932, 1739, 1663, 1528, 1458, 1368, 1251, 1168, 741. 1H NMR (400 MHz, [D$_6$]Acetone) δ = 7.54 (d, J = 7.8 Hz, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.24 (s, 1H), 7.09 (ddd, J = 8.2, 6.9, 1.3 Hz, 1H), 7.02 (ddd, J = 8.0, 7.0, 1.1 Hz, 1H), 4.75 (t, J = 6.3 Hz, 1H), 3.92 (d, J = 3.1 Hz, 2H), 3.88 (s, 2H), 3.81 (s, 2H), 3.61 (s, 3H), 3.38–3.16 (m, 2H), 1.40 (s, 9H). ^{13}C NMR (101 MHz, [D$_6$]Acetone) δ = 172.9, 171.7, 170.6, 169.8, 157.2, 137.2, 128.2, 124.7, 122.0, 119.5, 118.9, 112.2, 110.1, 79.7, 53.9, 52.4, 44.6, 43.3, 43.0, 28.5, 28.0. HRMS (ESI) calculated for $C_{23}H_{31}N_5O_7$, $[M + Na]^+$, 512.2116, found 512.2115.

General Procedure for Photoredox Catalysis Trifluoromethylation of 1a: A solution of methyl *N*-acetyl-L-tryptophanate **1a** (0.20 mmol), CF_3SO_2Na (0.40 mmol) and Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 (2 mol-%) in CH_3CN/H_2O (1.5 mL/1.5 mL) was stirred under air atmosphere and irradiated by 3 W blue LEDs for 12 h. When the reaction finished, the reaction mixture was analyzed by ^{19}F-NMR using α,α,α-trifluorotoluene as an internal standard to determine solution yields. The solvent was removed under reduced pressure by an aspirator. Then, the pure product **2a** was obtained by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 3:1).

Methyl *N*-acetyl-2-trifluoromethyl-L-tryptophanate (2a):[15b] White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.59 (s, 1H), 7.67 (d, J = 8.1 Hz, 1H), 7.32 (d, J = 8.2 Hz, 1H), 7.26 (t, J = 7.5 Hz, 1H), 7.15 (t, J = 7.3 Hz, 1H), 6.27 (d, J = 8.1 Hz, 1H), 4.98 (dt, J = 8.2, 6.3 Hz, 1H), 3.65 (s, 3H), 3.49–3.32 (m 2H), 1.94 (s, 3H). ^{19}F NMR (377 MHz, $CDCl_3$) δ = –57.71. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.3, 170.3, 135.6, 127.3, 124.9, 122.8 (q, $J_{C\text{-}F}$ = 36.8 Hz), 122.0 (q, $J_{C\text{-}F}$ = 269.8 Hz), 120.8, 119.9, 112.2, 111.7 (q, $J_{C\text{-}F}$ = 2.6 Hz), 52.8, 52.6, 27.0, 23.0. HRMS (ESI) calculated for $C_{15}H_{15}F_3N_2O_3$, $[M + Na]^+$, 351.0927, found 351.0924.

Methyl *N*-Acetyl-S-trifluoromethyl-L-cysteinate (2e):[15a] White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.84 (d, J = 7.4 Hz, 1H), 4.82 (dt, J = 7.1, 5.0 Hz, 1H), 3.73 (s, 3H), 3.43 (dd, J = 14.3, 4.8 Hz, 1H), 3.27 (dd, J = 14.3, 5.2 Hz, 1H), 2.00 (s, 3H). ^{19}F NMR (377 MHz, $CDCl_3$) δ = –41.06. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 170.4, 170.1, 130.5 (q, $J_{C\text{-}F}$ = 307.4 Hz), 53.0, 51.8, 31.5, 22.8.

General Procedure for Trifluoromethylation of Di-, Tri- and Tetrapeptides: A solution of peptide **3** (0.20 mmol), CF_3SO_2Na (0.40 mmol) and Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 (2 mol-%) in CH_3CN (2 mL) was stirred under air atmosphere and irradiated by 3 W blue LEDs for 4 h. When the reaction finished, the solvent was removed under reduced pressure by an aspirator. Then, the product was obtained by flash column chromatography on silica gel (dichloromethane/ethyl acetate) to afford corresponding trifluoromethylation of peptide **4**.

Ac-Trp(CF_3)-Gly-OMe (4a):[15b] White solid. ^{1}H NMR (400 MHz, CD_3CN) δ = 10.18 (s, 1H), 7.76 (d, J = 8.1 Hz, 1H), 7.42 (d, J = 8.2 Hz, 1H), 7.29 (t, J = 7.6 Hz, 1H), 7.15 (t, J = 7.5 Hz, 1H), 7.07 (t, J = 6.0 Hz, 1H), 6.93 (d, J = 8.6 Hz, 1H), 4.71 (td, J = 8.2, 5.8 Hz, 1H), 3.81 (qd, J = 17.7, 5.9 Hz, 2H), 3.63 (s, 3H), 3.41 (dd, J = 14.5, 5.7 Hz, 1H), 3.18 (dd, J = 14.4, 8.1 Hz, 1H), 1.79 (s, 3H). ^{19}F NMR (377 MHz, CD_3CN) δ = –58.10. ^{13}C NMR (101 MHz, CD_3CN) δ = 172.2, 170.84, 170.79, 136.6, 128.0, 125.4, 123.1 (q, $J_{C\text{-}F}$ = 269.3 Hz), 123.0 (q, $J_{C\text{-}F}$ = 36.6 Hz), 121.14, 121.11, 113.9 (q, $J_{C\text{-}F}$ = 2.7 Hz), 112.9, 54.5, 52.5, 41.5, 27.6, 22.8. HRMS (ESI) calculated for $C_{17}H_{18}F_3N_3O_4$, $[M + Na]^+$, 408.1142, found 408.1141.

Ac-Trp(CF_3)-Val-OMe (4b): White solid. M.p. 96–98 °C. IR (film)/cm^{-1} 3281, 3077, 2966, 1743, 1651, 1543, 1438, 1215, 1165, 1118, 748. ^{1}H NMR (400 MHz, [D$_6$]DMSO) δ = 11.94 (s, 1H), 8.10 (t, J = 8.1 Hz, 2H), 7.81 (d, J = 8.2 Hz, 1H), 7.42 (d, J = 8.2 Hz, 1H), 7.26 (t, J = 7.6 Hz, 1H), 7.10 (t, J = 7.4 Hz, 1H), 4.70 (q, J = 7.4 Hz, 1H), 4.29–4.11 (m, 1H), 3.55 (s, 3H), 3.27 (dd, J = 14.2, 5.8 Hz, 1H), 3.09 (dd, J = 13.9, 7.4 Hz, 1H), 2.04–1.91 (m, 1H), 1.77 (s, 3H), 0.83 (dd, J = 6.8, 5.6 Hz, 6H). ^{19}F NMR (377 MHz, [D$_6$]DMSO) δ = –56.20. ^{13}C NMR (101 MHz, [D$_6$]DMSO) δ = 171.7, 171.2, 169.2, 135.8, 127.2, 124.2, 122.4 (q, $J_{C\text{-}F}$ = 269.7 Hz), 121.8 (q, $J_{C\text{-}F}$ = 36.4 Hz), 120.7, 119.8, 112.8 (q, $J_{C\text{-}F}$ = 2.7 Hz), 112.2, 57.4, 53.7, 51.7, 30.4, 27.2, 22.6, 18.9, 18.4. HRMS (ESI) calculated for $C_{20}H_{24}F_3N_3O_4$, $[M + Na]^+$, 450.1611, found 450.1609.

Ac-Trp(CF_3)-Leu-OMe (4c): White solid. M.p. 211–213 °C. IR (film)/cm^{-1} 3283, 3077, 2958, 1740, 1650, 1545, 1439, 1386, 1211, 1163, 1117, 747. ^{1}H NMR (400 MHz, [D$_6$]DMSO) δ = 11.91 (s, 1H), 8.23 (d, J = 7.9 Hz, 1H), 8.05 (d, J = 8.9 Hz, 0.54H) & 7.99 (d, J = 9.0 Hz, 0.12H), 7.83 (d, J = 8.1 Hz, 0.82H) & 7.77 (d, J = 8.3 Hz, 0.15H), 7.41 (d, J = 8.2 Hz, 1H), 7.26 (t, J = 7.6 Hz, 1H), 7.11 (t, J = 7.5 Hz, 1H), 4.75–4.57 (m, 0.88H) & 4.57–4.47 (m, 0.15H), 4.42–4.25 (m, 1H), 3.61 (s, 0.44H) & 3.55 (s, 2.60H), 3.28 (dd, J = 14.2, 5.1 Hz, 1H), 3.05 (dd, J = 14.1, 8.3 Hz, 1H), 1.73 (s, 3H), 1.65–1.40 (m, 3H), 0.84 (dd, J = 12.8, 6.2 Hz, 6H). ^{19}F NMR (377 MHz, [D$_6$]DMSO) δ = –56.15. ^{13}C NMR (101 MHz, [D$_6$]DMSO) δ = 172.73 & 172.71, 171.1 & 171.0, 169.1 & 169.0, 135.8, 127.2, 124.2, 122.4 (q, $J_{C\text{-}F}$ = 269.7 Hz), 121.8 (q, $J_{C\text{-}F}$ = 35.4 Hz), 120.7, 119.8, 112.9 (q, $J_{C\text{-}F}$ = 2.8 Hz), 112.2, 53.5 & 53.4, 51.9 & 51.8, 50.3 & 50.2, 40.0, 27.2, 24.22 & 24.17, 22.84 & 22.80, 22.60 & 22.56, 21.53 & 21.47. HRMS (ESI) calculated for $C_{21}H_{26}F_3N_3O_4$, $[M + Na]^+$, 464.1768, found 464.1760.

Ac-Trp(CF_3)-Met-OMe (4d): White solid. M.p. 151–153 °C. IR (film)/cm^{-1} 3284, 2924, 1742, 1652, 1523, 1439, 1386, 1213, 1166, 1118, 748. ^{1}H NMR (400 MHz, CD_3CN) δ = 10.02 (s, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.44 (d, J = 8.3 Hz, 1H), 7.33–7.27 (m, 1H), 7.19–7.12 (m, 1H), 6.90 (d, J = 8.0 Hz, 1H), 6.77 (d, J = 8.5 Hz, 1H), 4.67 (td, J = 8.1, 6.4 Hz, 1H), 4.47 (td, J = 8.3, 4.8 Hz, 1H), 3.59 (s, 3H), 3.41–3.32 (m, 1H), 3.23–3.14 (m, 1H), 2.45–2.32 (m, 2H), 2.01 (s, 3H), 2.00–195 (m, 1H), 1.89–1.81 (m, 1H), 1.79 (s, 3H). ^{19}F NMR (377 MHz, CD_3CN) δ = –58.10. ^{13}C NMR (101 MHz, CD_3CN) δ = 172.6, 171.8, 170.6, 136.6, 128.0, 125.5, 123.14 (q, $J_{C\text{-}F}$ = 269.3 Hz), 123.05 (q, $J_{C\text{-}F}$ = 36.6 Hz), 121.2, 121.3, 113.9 (q, $J_{C\text{-}F}$ = 2.8 Hz), 112.9, 54.6, 52.7, 52.1, 31.9, 30.3, 27.5, 22.9, 15.1. HRMS (ESI) calculated for $C_{20}H_{24}F_3N_3O_4S$, $[M + Na]^+$, 482.1332, found 482.1334.

Ac-Trp(CF_3)-Phe-OMe (4e): White solid. M.p. 174–176 °C. IR (film)/cm^{-1} 3292, 3065, 2954, 1740, 1651, 1524, 1444, 1386, 1215, 1165, 1118, 744, 702. ^{1}H NMR (400 MHz, CD_3CN) δ = 10.00 (s, 1H), 7.72 (d, J = 8.1 Hz, 1H), 7.43 (d, J = 8.3 Hz, 1H), 7.32–7.20 (m, 4H), 7.17–7.09 (m, 3H), 6.83 (d, J = 7.8 Hz, 1H), 6.70 (d, J = 8.5 Hz, 1H), 4.69–4.53 (m, 2H), 3.57 (s, 3H), 3.36–3.27 (m, 1H), 3.16–3.08 (m, 1H), 3.04 (dd, J = 13.6, 5.8 Hz, 1H), 2.91 (dd, J = 13.8, 7.3 Hz, 1H), 1.76 (s, 3H). ^{19}F NMR (377 MHz, CD_3CN) δ = –58.12. ^{13}C NMR (101 MHz, CD_3CN) δ = 172.2, 171.5, 170.6, 137.5, 136.6, 130.2, 129.2, 128.0, 127.7, 125.5, 123.1 (q, $J_{C\text{-}F}$ = 269.3 Hz), 123.0 (q, $J_{C\text{-}F}$ = 36.7 Hz), 121.22, 121.18, 113.9 (q, $J_{C\text{-}F}$ = 2.8 Hz), 112.9, 54.6, 54.4, 52.6, 38.2, 27.4, 22.8. HRMS (ESI) calculated for $C_{24}H_{24}F_3N_3O_4$, $[M + Na]^+$, 498.1611, found 498.1616.

Ac-Trp(CF_3)-Tyr-OMe (4f): White solid. M.p. 102–104 °C. IR (film)/cm^{-1} 3296, 2956, 1740, 1654, 1517, 1445, 1229, 1166, 1118, 844, 749. ^{1}H NMR (400 MHz, CD_3CN) δ = 10.01 (s, 1H), 7.72 (d, J = 8.4 Hz, 1H), 7.43 (d, J = 8.3 Hz, 1H), 7.32–7.26 (m, 1H), 7.19–7.10 (m, 2H), 6.95–6.89 (m, 2H), 6.79 (d, J = 7.9 Hz, 1H), 6.74 (d, J = 8.5 Hz, 1H), 6.69–6.62 (m, 2H), 4.68–4.60 (m, 1H), 4.55–4.48 (m, 1H), 3.57 (s, 3H), 3.36–3.28 (m, 1H), 3.17–3.08 (m, 1H), 2.93 (dd, J = 13.9, 5.7 Hz, 1H), 2.82 (dd, J = 13.9, 7.2 Hz, 1H), 1.77 (s, 3H). ^{19}F NMR (377 MHz, CD_3CN) δ = –58.11. ^{13}C NMR (101 MHz, CD_3CN) δ = 172.3, 171.4, 170.8, 156.7, 136.6, 131.3, 128.3, 128.0, 125.5, 123.1 (q, $J_{C\text{-}F}$ = 269.3 Hz), 123.0 (q, $J_{C\text{-}F}$ = 36.6 Hz), 121.22, 121.16, 115.9, 113.9 (q, $J_{C\text{-}F}$ = 2.9 Hz), 112.9, 54.65, 54.62, 52.6, 37.3, 27.4, 22.8. HRMS (ESI) calculated for $C_{24}H_{24}F_3N_3O_5$, $[M + Na]^+$, 514.1560, found 514.1560.

Ac-Trp(CF_3)-Thr-OMe (4g): White solid. M.p. 94–97 °C. IR (film)/cm^{-1} 3292, 2925, 1740, 1649, 1523, 1437, 1383, 1212, 1163, 1116, 745. ^{1}H NMR (400 MHz, [D_6]DMSO, diastereomers) δ = 11.95 (s, 1H), 8.25 (d, J = 8.9 Hz, 1H), 7.91 (d, J = 8.3 Hz, 1H), 7.82 (d, J = 8.1 Hz, 1H), 7.41 (d, J = 8.2 Hz, 1H), 7.26 (t, J = 7.6 Hz, 1H), 7.11 (t, J = 7.5 Hz, 1H), 4.92 (d, J = 6.2 Hz, 0.83H) & 4.88 (d, J = 6.2 Hz, 0.12H), 4.73 (q, J = 7.8 Hz, 1H), 4.15 (dd, J = 8.3, 3.1 Hz, 0.87H) & 4.09 (dd, J = 8.3, 3.1 Hz, 0.21H), 4.05–3.94 (m, 1H), 3.62 (s, 2.53H) & 3.61 (s, 0.48H), 3.27 (dd, J = 14.3, 6.2 Hz, 1H), 3.08 (dd, J = 14.0, 7.6 Hz, 1H), 1.78 (s, 0.64H) & 1.77 (s, 2.36H), 0.73 (d, J = 6.4 Hz, 2.56H) & 0.64 (d, J = 6.4 Hz, 0.37H). ^{19}F NMR (377 MHz, [D_6]DMSO, diastereomers) δ = –56.16 & –56.19. ^{13}C NMR (101 MHz, [D_6]DMSO, diastereomers) δ = 171.6, 171.0, 169.2, 135.8, 127.1, 124.3, 122.4 (q, $J_{C\text{-}F}$ = 270.0 Hz), 121.7 (q, $J_{C\text{-}F}$ = 36.2 Hz), 120.7, 119.9, 112.9 (q, $J_{C\text{-}F}$ = 2.9 Hz), 112.2, 66.22 & 66.17, 58.0, 53.9, 52.0, 27.3, 22.6 & 22.5, 19.6 & 19.4. HRMS (ESI) calculated for $C_{19}H_{22}F_3N_3O_5$, $[M + Na]^+$, 452.1404, found 452.1404.

Ac-Trp(CF_3)-Asp-OMe(4h): Pale yellow solid. M.p. 81–84 °C. IR (film)/cm^{-1} 3408, 2990, 1712, 1661, 1400, 1273, 1165, 1119, 752. ^{1}H NMR (400 MHz, [D_6]DMSO) δ = 11.93 (s, 1H), 8.34 (d, J = 7.9 Hz, 1H), 8.13 (d, J = 9.0 Hz, 1H), 7.82 (d, J = 8.1 Hz, 1H), 7.41 (d, J = 8.3 Hz, 1H), 7.26 (t, J = 7.6 Hz, 1H), 7.10 (t, J = 7.5 Hz, 1H), 4.66–4.53 (m, 2H), 3.56 (s, 3H), 3.28 (dd, J = 14.5, 4.7 Hz, 1H), 3.02 (dd, J = 14.5, 8.9 Hz, 1H), 2.70 (dd, J = 16.8, 6.2 Hz, 1H), 2.56 (dd, J = 16.8, 6.3 Hz, 1H), 1.69 (s, 3H). ^{19}F NMR (377 MHz, [D_6]DMSO) δ = –56.13. ^{13}C NMR (101 MHz, [D_6]DMSO) δ = 171.7, 171.2, 170.9, 169.0, 135.7, 127.1, 124.2, 122.3 (q, $J_{C\text{-}F}$ = 270.0 Hz), 121.6 (q, $J_{C\text{-}F}$ = 36.2 Hz), 120.6, 119.8, 113.0 (q, $J_{C\text{-}F}$ = 2.9 Hz), 112.2, 53.5, 52.2, 48.6, 35.8, 27.0, 22.5. HRMS (ESI) calculated for $C_{19}H_{20}F_3N_3O_6$, $[M + Na]^+$, 466.1196, found 466.1193.

Fmoc-Ser-Trp(CF_3)-OMe (4i): White solid. M.p. 91–93 °C. IR (film)/cm^{-1} 3308, 3066, 2954, 1717, 1666, 1521, 1450, 1229, 1165, 1118, 741. ^{1}H NMR (400 MHz, CD_3CN) δ = 9.97 (s, 1H), 7.83 (d, J = 7.5 Hz, 2H), 7.71 (d, J = 8.1 Hz, 1H), 7.69–7.60 (m, 2H), 7.48–7.38 (m, 3H), 7.37–7.27 (m, 3H), 7.27–7.21 (m, 1H), 7.19–7.11 (m, 1H), 5.91 (d, J = 8.0 Hz, 1H), 4.74 (q, J = 7.3 Hz, 1H), 4.33 (d, J = 7.5 Hz, 2H), 4.22 (t, J = 7.1 Hz, 1H), 4.16–4.07 (m, 1H), 3.70–3.56 (m, 2H), 3.54 (s, 3H), 3.42–327 (m, 2H), 3.22 (br, 1H). ^{19}F NMR (377 MHz, CD_3CN) δ = –58.31. ^{13}C NMR (101 MHz, CD_3CN) δ = 172.4, 171.0, 157.0, 145.0, 144.9, 142.0, 136.6, 128.6, 128.0, 127.9, 126.1, 125.7, 123.05 (q, $J_{C\text{-}F}$ = 269.2 Hz), 123.04 (q, $J_{C\text{-}F}$ = 36.8 Hz), 121.5, 120.9, 120.9, 113.2 (q, $J_{C\text{-}F}$ = 2.7 Hz), 113.0, 67.4, 62.9, 57.2, 54.1, 52.8, 47.9, 27.4. HRMS (ESI) calculated for $C_{31}H_{28}F_3N_3O_6$, $[M + Na]^+$, 618.1822, found 618.1833.

Boc-Ala-Gly-Trp(CF_3)-OMe (4j): White solid. M.p. 86–89 °C. IR (film)/cm^{-1} 3296, 3066, 2981, 1740, 1662, 1524, 1455, 1369, 1251, 1165, 1119, 743. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.79 (s, 1H), 7.61 (d, J = 8.0 Hz, 1H), 7.32 (d, J = 8.2 Hz, 1H), 7.27–7.17 (m, 2H), 7.16 –7.03 (m, 2H), 5.36 (d, J = 7.3 Hz, 1H), 4.88 (q, J = 7.0 Hz, 1H), 4.13 (q, J = 7.5 Hz, 1H), 3.85 (dd, J = 17.2, 5.5 Hz, 1H), 3.78–3.66 (m, 1H), 3.59 (s, 3H), 3.42 (dd, J = 14.7, 6.6 Hz, 1H), 3.32 (dd, J = 14.7, 6.7 Hz, 1H), 1.41 (s, 9H), 1.27 (d, J = 6.9 Hz, 3H). ^{19}F NMR (377 MHz, $CDCl_3$) δ = –57.74. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 173.5, 171.9, 168.8, 155.7, 135.6, 127.2, 124.8, 122.8 (q, $J_{C\text{-}F}$ = 37.4 Hz), 122.0 (q, $J_{C\text{-}F}$ = 269.7 Hz), 120.7, 119.8, 112.3, 111.7 (q, $J_{C\text{-}F}$ = 2.8 Hz), 80.3, 53.0, 52.5, 50.3, 42.8, 28.3, 26.9, 18.54. HRMS (ESI) calculated for $C_{23}H_{29}F_3N_4O_6$, $[M + Na]^+$, 537.1931, found 537.1929.

Boc-Phe-Phe-Trp(CF_3)-OMe (4k): White solid. M.p. 167–169 °C. IR (film)/cm^{-1} 3290, 3064, 2929, 1736, 1644, 1497, 1453, 1248, 1158, 1111, 742, 697. ^{1}H NMR (400 MHz, [D_6]DMSO) δ = 12.09 (s, 1H), 8.82 (d, J = 7.4 Hz, 0.18H) & 8.77 (d, J = 7.4 Hz, 0.70H), 8.05 (d, J = 7.7 Hz, 0.15H) & 7.97 (d, J = 8.2 Hz, 0.74H), 7.71 (d, J = 8.1 Hz, 1H), 7.45 (d, J = 8.3 Hz, 1H), 7.32–7.22 (m, 6H), 7.22–7.11 (m, 6H), 6.94 (d, J = 8.7 Hz, 1H), 4.71–4.60 (m, 1H), 4.59–4.49 (m, 1H), 4.19–4.08 (m, 0.86H) & 4.08–4.00 (m, 0.18H), 3.43 (s, 3H), 3.36–3.20 (m, 2H), 3.01 (dd, J = 13.9, 4.9 Hz, 1H), 2.91–2.78 (m, 2H), 2.66 (dd, J = 13.6, 10.7 Hz, 1H), 1.28 (s, 7.75H) & 1.11 (s, 1.44H). ^{19}F NMR (377 MHz, [D_6]DMSO) δ = –56.55. ^{13}C NMR (101 MHz, [D_6]DMSO) δ = 171.43, 171.40, 170.9, 155.2, 138.2, 137.4, 135.7, 129.4, 129.2, 128.1, 128.0, 126.7, 126.4, 126.2, 124.5, 122.2 (q, $J_{C\text{-}F}$ = 269.7 Hz), 121.6 (q, $J_{C\text{-}F}$ = 36.4 Hz), 120.2, 119.9, 112.4, 111.8 (q, $J_{C\text{-}F}$ = 2.8 Hz), 78.2, 56.0, 53.4, 51.8, 37.9, 37.5, 28.1 & 27.8, 26.5. HRMS (ESI) calculated for $C_{36}H_{39}F_3N_4O_6$, $[M + Na]^+$, 703.2714, found 703.2713.

Boc-Phe-Phe-Trp(CF_3)-OMe (4l): White solid. M.p. 99–101 °C. IR (film)/cm^{-1} 3304, 3067, 2981, 2933, 1739, 1662, 1531, 1455, 1369, 1269, 1165, 1119, 739. ^{1}H NMR (400 MHz, [D_6]Acetone) δ = 11.09 (s, 1H), 7.79 (d, J = 8.0 Hz, 2H), 7.71 (d, J = 7.7 Hz, 1H), 7.69–7.63 (m, 1H), 7.48 (d, J = 8.2 Hz, 1H), 7.29 (t, J = 7.6 Hz, 1H), 7.17 (t, J = 7.5 Hz, 1H), 6.41 (t, J = 5.8 Hz, 1H), 4.77 (q, J = 7.6 Hz, 1H), 3.94–3.87 (m, 3H), 3.86–3.82 (m, 1H), 3.82–3.76 (m, 2H), 3.52 (s, 3H), 3.48–3.40 (m, 1H), 3.40–3.32 (m, 1H), 1.40 (s, 9H). ^{19}F NMR (377 MHz, [D_6]Acetone) δ = –58.22. ^{13}C NMR (101 MHz, [D_6]Acetone) δ = 172.3, 171.5, 170.2, 169.6, 157.2, 136.9, 128.1, 125.4, 123.2 (q, $J_{C\text{-}F}$ = 269.4 Hz), 123.0 (q, $J_{C\text{-}F}$ = 36.7 Hz), 121.2, 121.0, 113.4 (q, $J_{C\text{-}F}$ =

2.8 Hz), 113.1, 79.6, 54.2, 52.3, 44.8, 43.5, 43.0, 28.5, 27.5. HRMS (ESI) calculated for $C_{24}H_{30}F_3N_5O_7$, $[M + Na]^+$, 580.1990, found 580.1989.

α-Phenyl-α-(2,2,2-trifluoroethyl)-benzenemethanol (5a): [28] Colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.44–7.39 (m, 4H), 7.36–7.30 (m, 4H), 7.29–7.23 (m, 2H), 3.20 (q, J = 10.3 Hz, 2H), 2.63 (q, J = 1.4 Hz, 1H). ^{19}F NMR (377 MHz, $CDCl_3$) δ = –58.17. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 145.2, 128.5, 127.7, 126.5 (q, J_{C-F} = 151.5 Hz), 125.7, 75.8 (q, J_{C-F} = 2.2 Hz), 45.0 (q, J_{C-F} = 25.6 Hz).

Methyl (*S*)-2-Acetamido-3-[2-(diethoxyphosphoryl)-1*H*-indol-3-yl]propanoate (5b): White solid. ^1H NMR (400 MHz, $CDCl_3$) δ = 9.69 (s, 1H), 8.08 (q, J = 6.3 Hz, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.42 (d, J = 8.3 Hz, 1H), 7.29 (td, J = 7.5, 5.9, 2.4 Hz, 1H), 7.16 (td, J = 7.6, 6.7, 1.9 Hz, 1H), 4.64 (dt, J = 10.4, 5.3 Hz, 1H), 4.27–4.06 (m, 4H), 3.70 (d, J = 2.1 Hz, 3H), 3.54–3.39 (m, 2H), 1.94 (s, 3H), 1.38–1.29 (m, 6H). ^{31}P NMR (162 MHz, $CDCl_3$) δ = 11.40. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.5, 170.8, 137.8 (dd, J_{C-P} = 11.5, 3.1 Hz), 127.1 (d, J_{C-P} = 16.1 Hz), 125.3, 122.1, 121.6 (dd, J_{C-P} = 18.7, 2.8 Hz), 120.2 (d, J_{C-P} = 129.8 Hz), 119.9, 112.3, 62.9 (d, J_{C-P} = 5.3 Hz), 54.1, 52.3, 26.5, 22.7, 16.30 (dd, J_{C-P} = 8.6, 6.4 Hz). HRMS (ESI) calculated for $C_{18}H_{25}N_2O_6P$, $[M + Na]^+$, 419.1342, found 419.1346.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (21701127, 21520102003, 21390402), the Hubei Province Natural Science Foundation of China (2017CFB152, 2017CFA010), the Fundamental Research Funds for the Central Universities (213413000050), and the Scientific Research Foundation of Wuhan University (413100043, 413100021). The Program of Introducing Talents of Discipline to Universities of China (111 Program) is also appreciated.

Keywords: Peptides · Photoredox catalysis · Synthetic methods · Trifluoromethylation · Tryptophan

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Received: October 27, 2019

