Fluorinated amino acids (FAAs) are a class of amino acids with specific biological activity and medicinal value. The incorporation of FAAs is one of the most common strategies in peptide and protein science as biological tracers, mechanistic probes, and enzyme inhibitors. The introduction of fluorine-containing amino acids and their derivatives into polypeptide drugs, due to their strong hydrophobicity, can usually improve the thermal and chemical stability of drugs and increase lipid solubility, thereby greatly improving biology and pharmacology activity. Thus, the intrinsic functionalities of FAAs make them versatile precursors for the synthesis of more architecturally complex compounds. As a consequence, the development of new methodologies that allow streamlined access to fluorinated amino acids has been an important challenge for chemical synthesis.

Site-selective fluorination of amino acids has been applied in various medicinal scenarios, including blood pressure control, allergy treatment, and tumor growth inhibition. The synthesis of trifluoromethyl-containing amino acids can be generally achieved following the strategies shown in Scheme 1b. The successful trifluoromethylation of amino acids heavily relies on suitable fluorinating reagents, for example, nucleophilic trifluoromethylation of α-ketimino esters, electrolytic amination of fluorinated ketones, and carboxylation of fluorinated amines. However, these strategies often suffer from the limited scope of substrates and require specific fluorinated building blocks. The photocatalyzed radical additions to imines have been well-documented. The addition of alkyl nucleophiles to trifluoromethyl α-ketimino esters, which are readily accessible from trifluoroacrylic acid and primary amines, represents an attractive approach to construct fluorinated amino acids. However, this appealing path continues to be underdeveloped. The main challenge lies in the high nucleophilicity of the organometallic alkyl precursor and inertness of keto imines.

Considering the mismatched reactivities of these species, we envisioned that using commonly available dihydropyridine (DHP)-derived Hantzsch ester as a versatile nucleophilic alkyl radical surrogate, the trifluoromethyl α-ketimino ester could be rapidly derived to furnish a class of α-CF₃-substituted amino acids in mild conditions. The innate issue of low fusion efficiency in the batch reaction can be addressed by continuous flow technique. A significantly enhanced mass transfer and high surface-to-volume ratio are expected with commercially available apparatus setup. Especially during the photochemical process, the microfluidic reactor could benefit from the precise residence/reaction time control, the easiness of scale-up, and multistep synthesis. Herein we report a general catalyst-free photoredox protocol to prepare a range of trifluoromethylated natural α-amino acid analogues under microfluidic conditions.

To pursue the goal, we started our investigation using α-CF₃ ketimine ester 1a and Hantzsch ester 4-benzyl-1,4-dihydropyridine 1b as the model substrates. When a solution of 1a (1 equiv) and 1b (2 equiv) in MeCN was irradiated by a 365 nm LED light for 24 h, the desired α-trifluoromethyl amino acid was generated in 93% isolated yield at ambient temperature (entry 1). Further investigation revealed that...
when 395 nm LED and 460 nm LED were used as light sources, the yield decreased remarkably to 75% and 40% respectively (entries 2 and 3), and no reaction occurred in the absence of LEDs. The solvent was found to be important for this transformation, as evidenced by the unsatisfactory yield obtained when using DMF, NMP, DCM, etc. as the solvent (Table S2). For the optimization of reaction time, the yield decreased with shortened time (entry 5). When 1 equiv of 1b was used, the reaction occurred in a slightly lower yield (55%) with a small amount of unreacted starting material (entry 7).

Subsequently, in order to improve the reaction efficiency, we examined the conditions of continuous flow under the above optimized conditions in batch. A series of residence times in the continuous-flow reactor were investigated, and 2 h was the best residence time to give a product in 90% yield (entry 8 and Table S5).

Fluorinated natural amino acids, especially α-CF₃-substituted precursors, are often inaccessible and costly due to the innate reactivity of fluorination and limited substrate scope. With the optimized microfluidic conditions in hand, this simple process allows for rapid access to a series of α-CF₃-derived natural amino acid analogues (Scheme 2a). The CF₃-modified isoleucine (1), tyrosine (2), phenylalanine (3), and alanine (4) were smoothly obtained in high yields with much lower costs ($100–120/g by this method vs commercial prices of over $1000/g from Sigma-Aldrich). Even the challenging primary-alkyl-derived Hantzsch ester was tolerated to furnish CF₃-leucine (5) in moderate yield, which has not been reported by other methods. We next examined the generality of this transformation with different amines (Scheme 2b). Anilines bearing an electron-donating group (7–11), halogen atom (12–14), or electron-withdrawing group (15) at the ortho, meta, or para position reacted smoothly to afford the products in moderate to excellent yields (61–91%). Bisubstituted (16–18) and polysubstituted (6, 19) substrates could also be converted to the products in good yields. Benzylamine (20) and secondary alkyamine delivered a slightly lower yields, which may be due to the unstable imine intermediate.

Next, we explored the reaction scope with varied Hantzsch esters using α-CF₃ ketimine ester 1a as the coupling partner (Scheme 2c). The benzyl- (21–23), cycloalkyl- (24–27), and secondary-alkyl-substituted (28–30) Hantzsch ester derivatives were employed for the photoinduced radical alkylation, and the desired products were obtained in excellent yields. Both natural and non-natural fluorine-containing amino acids could be constructed by this feasible method.

We carried out further mechanistic studies to gain insight into this transformation. First, the UV/vis absorption spectra of CH₃CN solutions of α-CF₃ ketimine ester 1a (5 × 10⁻⁵ M), 4-benzyl-1,4-dihydropyridine 1b (5 × 10⁻⁵ M), and a mixture
of 1a (5 × 10⁻⁵ M) and 1b (5 × 10⁻⁵ M) are shown in Figure S1. A strong absorption band of the mixture [1a + 1b] with a maximum absorption wavelength at 343 nm and the fact that there is no significant red shift relative to the respective absorption may indicate that an electron donor–acceptor (EDA) complex between 1a and 1b was unlikely to be the case. In addition, the radical trapping agent TEMPO was added under the standard conditions, and almost no target product was formed, which supported the radical mechanism. In order to verify the type of free radical reaction, quantum yield experiments were carried out. The average photon flux was thus calculated to be 9.276 × 10⁻⁸ einstein s⁻¹. The reaction quantum yield (Φ) was thus determined to be Φ = 0.04 according to the reaction rate curve (Scheme 3a). Also, a light on–off experiment was carried out between 1a and 1b. The reaction mixture was sequentially stirred under irradiation with 365 nm LED and in the dark and analyzed every 10 min by ¹⁹F NMR spectroscopy (Scheme 3b). The above results indicated that the reaction was a catalytic radical pathway instead of a radical chain mechanism. In addition, scalability
was also evaluated, and the gram-scale reaction with continuous flow also furnished the final product in equally high yield (1.6 g, 85%).

Based on the above results and previous reports, a feasible mechanism is proposed (Scheme 3c). Under visible-light excitation, the excited state $1b^*$, as a strong reducing agent ($E(1b^*/1b) = -1.09$ V vs SCE, as determined by cyclic voltammetry and UV spectrometry; see the Supporting Information), was triggered by the pyridinium ion ($\text{Pyr-H}^+$) to form the unstable DHP radical cation intermediate I via a SET process. It is noteworthy that the pyridinium ion has lower redox potential ($E(\text{Pyr-H}^+/\text{Pyr-H}) = -1.0$ V) than imine $1a$ ($E(1a/1a^*) = -1.51$ V) in order to accept an electron from $1b^*$. Subsequently, the homolytic cleavage of intermediate I yielded the benzyl radical II, which then added to $1a$ to afford the radical intermediate III. Then the radical species III was reduced by $\text{PyrH}^+$ through a SET process to produce the nitrogen anion IV, which is eventually protonated by $\text{PyrH}^+$ to form the desired product and pyridine residue V.

In conclusion, we have developed a visible-light-mediated metal-free radical alkylation of trifluoromethyl-containing imino esters for the construction of trifluoromethyllated amino acids using continuous flow technology. This efficient and controllable protocol provides a powerful tool to construct CF$_3$-derived natural amino acid scaffolds, which has great value in large-scale preparation of fluorine-incorporated peptides and proteins.

### ASSOCIATED CONTENT

**Data Availability Statement**

The data underlying this study are available in the published article and its Supporting Information.

**Supporting Information**

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.3c00915.

Synthetic procedures and characterization data (PDF)

### AUTHOR INFORMATION

**Corresponding Authors**

Yi Wang — State Key Laboratory of Coordination Chemistry, Jiangsu Key Laboratory of Advanced Organic Materials, Collaborative Innovation Center of Advanced Microstructures, School of Chemistry and Chemical Engineering, Nanjing University, Nanjing 210023, China; orcid.org/0000-0002-8700-7621; Email: yiwang@nju.edu.cn

Liang Yan — State Key Laboratory of Coordination Chemistry, Jiangsu Key Laboratory of Advanced Organic Materials, Collaborative Innovation Center of Advanced Microstructures, School of Chemistry and Chemical Engineering, Nanjing University, Nanjing 210023, China; School of Basic Medicine, Wannan Medical College, Wuhu 241000, China; Email: liyan@wnmc.edu.cn
Organic Letters

Authors

Jiyang Liu — State Key Laboratory of Coordination Chemistry, Jiangsu Key Laboratory of Advanced Organic Materials, Collaborative Innovation Center of Advanced Microstructures, School of Chemistry and Chemical Engineering, Nanjing University, Nanjing 210023, China

Weigang Zhang — State Key Laboratory of Coordination Chemistry, Jiangsu Key Laboratory of Advanced Organic Materials, Collaborative Innovation Center of Advanced Microstructures, School of Chemistry and Chemical Engineering, Nanjing University, Nanjing 210023, China

Xiangzhang Tao — State Key Laboratory of Coordination Chemistry, Jiangsu Key Laboratory of Advanced Organic Materials, Collaborative Innovation Center of Advanced Microstructures, School of Chemistry and Chemical Engineering, Nanjing University, Nanjing 210023, China

Qing Wang — State Key Laboratory of Coordination Chemistry, Jiangsu Key Laboratory of Advanced Organic Materials, Collaborative Innovation Center of Advanced Microstructures, School of Chemistry and Chemical Engineering, Nanjing University, Nanjing 210023, China

Yi Pan — State Key Laboratory of Coordination Chemistry, Jiangsu Key Laboratory of Advanced Organic Materials, Collaborative Innovation Center of Advanced Microstructures, School of Chemistry and Chemical Engineering, Nanjing University, Nanjing 210023, China

Jinzhu Ma — School of Basic Medicine, Wannan Medical College, Wuhu 241000, China

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.3c00915

Notes

The authors declare no competing financial interest.

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