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Synthesis of α -Fluoro- α -Amino Acid Derivatives via Photoredox-Catalyzed Carbofluorination

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Abstract

A mild, metal-free, regioselective carbofluorination of dehydroalanine derivatives has been developed. Alkyl radicals resulting from visible-light photoredox catalysis engage in a radical conjugate addition to dehydroalanine, with subsequent fluorination of the newly generated radical to afford an α -fluoro- α -amino acid. By using a highly oxidizing organic photocatalyst, this process incorporates non-stabilized primary, secondary, and tertiary alkyl radicals derived from commercially available alkyltrifluoroborates to furnish a wide range of fluorinated unnatural amino acids.

Graphical Abstract

Keywords

Photoredox-catalysis; carbofluorination; amino acid; radical; dehydroalanine

Fluorinated amino acids have drawn considerable attention as powerful building blocks that possess physiochemical and biological properties unique from those of canonical amino acids.¹ The polar hydrophobicity² inherent in the C-F bond is known to increase lipophilicity, biological potency, stability to enzymatic degradation, and bioavailability of peptide-derived drugs and proteins. Although the synthetic strategies that produce various fluorinated amino acid analogues have been well developed, most of them involve fluorination of amino acid side chains³ and synthesis of fluorinated β -amino acids.⁴ In contrast, synthetic methods to access α -fluoro- α -amino acids have not been well established

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Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental details and spectral data (PDF)

X Crystal data for compound **1a** (CIF) Crystallography data for **1a** was deposited in the Cambridge Structural Database (CCDC 1872093)

because of challenges associated with the site-specific incorporation of fluorine as well as their chemical instability.

Previously established methods to access α -fluoro- α -amino acids include: A) nucleophilic or electrophilic α -fluorination of amino acid backbones via two electron transfer chemistry;⁵ B) Gabriel-type amination to give α -fluoroglycine;⁶ and C) Michael addition to a fluorinated nitro ester (Figure 1).⁷ These approaches lack substrate generality and typically require harsh conditions, thus rendering them ineffective and impractical. Therefore, the development of a mild and useful platform, affording diverse and versatile α -fluorinated amino acids, remains a challenge.

Since the groups of Davis and Park independently demonstrated that alkylation of dehydroalanine (Dha) via single-electron chemistry allows site-specific chemical mutagenesis of proteins,⁸ photoredox-catalyzed Dha modifications have been intensively investigated to provide unprecedented unnatural amino acids.⁹ Drawing from the mechanistic evidence amassed in these studies and recent reports on radical fluorination,¹⁰ we envisioned that carbofluorination of Dha could provide a variety of fluorinated amino acid derivatives. Herein, we disclose a mild and metal-free photoredox-catalyzed three component carbofluorination for the synthesis of α -fluoro- α -amino acids.

To investigate the tenability of this strategy, optimization studies were explored using bis-Boc dehydroalanine benzyl ester **1a** as the amino acid backbone in combination with Selectfluor and mesityl acridinium photocatalyst. Inspired by our previous studies on photochemical generation of alkyl radicals from alkyltrifluoroborate salts, we selected potassium benzyltrifluoroborate **2a** as the alkyl radical precursor (Table 1).¹¹

Initial screening showed that solvent played a crucial role in the effectiveness of fluorination after Giese-type alkylation. DMF was found to be essential for selective production of fluorinated product **3a** (entry 1). Use of THF, acting as a hydrogen atom source, gave only protonated product **4**, whereas acetone solvent selectively gave α,β -dialkylated product **5** in the presence of adequate fluorine source (entries 2–4). Next, several photocatalysts with varying reduction potentials were examined (entries 5 and 6 and see Supporting Information). In terms of chemical yield, cost efficiency, and high reduction potential to generate the alkyl radical from primary alkyltrifluoroborate ($E_{\text{red}} = +1.90$ V vs. SCE^{11c}), we moved forward with mesityl acridinium organophotocatalyst ($*E_{\text{red}} = +2.06$ V vs. SCE¹²). The choice of fluorine sources was critical for successful C-F bond formation. Interestingly, less electrophilic *N*-fluorobenzenesulfonimide and *N*-fluoropyridinium tetrafluoroborate barely induced fluorination (entries 7 and 8).¹³

As expected, control experiments confirmed that both light and photocatalyst are prerequisites for this transformation (entries 9 and 10 and see Supporting Information). Using an excess of radical precursor (2.0 equiv) and Selectfluor (4.0 equiv) is necessary to obtain synthetically useful yields (entries 10 and 11). Furthermore, other radical precursors, such as 4-alkyl-1,4-dihydropyridines (DHPs), and alkyl bis(catecholato)silicates gave no desired product (see Supporting Information).

Having suitable conditions in hand, the scope with regard to alkyltrifluoroborates was assessed. For consistency, most of the reactions were conducted with the same number of equivalents of the reagents for 12 h under irradiation of blue LEDs. As shown in Table 2, these conditions generally tolerated a wide variety of differentially substituted alkyl radical precursors and diverse functional groups, such as protected amines (**3g**, **3u**, **3v**), alkyne **3o**, and electron-neutral alkene **3p**. Secondary alkyltrifluoroborates, which are commonly used in photoredox catalysis, provided the desired α -fluoro-alkylated amino acids in good yield (**3b-3h**), including F-leucine **3b**. Cyclic secondary radicals bearing 6- and 4-membered rings as well as heterocycles were also well established (**3d-3h**). It is noteworthy that non-stabilized primary alkyltrifluoroborates with higher oxidation potentials ($E_{\text{red}} = +1.90$ V vs. SCE^{11c}), from homobenzylic to tertiary pentyl radical precursors (**3i-3l**), were broadly applicable by using the strongly oxidizing MesAcr⁺ catalyst. The employment of sterically demanding tertiary alkyl groups (**3m**, **3n**) was also successful. α -Alkoxyethyltrifluoroborates, which are known to give more stabilized radicals, were smoothly transformed to their corresponding amino acid derivatives (**3o-3t**). However, they exhibited lower selectivity for fluorinated products over protonated byproducts (such as **4**).

Our attention was next turned to accessing amine and carbonyl functional groups to provide fluorinated natural amino acid mimics. We found that α -aminoalkyl (**3u**) and β -aminoalkyl (**3v**) radicals reacted to give amine-containing products. Notably, amide (**3w**) and ester (**3x**) and ketone (**3y**) moieties were also successfully introduced with β -carbonyl-substituted alkyltrifluoroborates. As expected, cyclopropylcarbinyl trifluoroborate **2z** formed a homoallylic radical via radical clock rearrangement to afford **3z** in modest yield. Finally, the less nucleophilic radical generated from electron-deficient (bromomethyl)trifluoroborate presumably induced hydrogen atom transfer (HAT) to generate an acyl radical from DMF solvent. Following radical addition to Dha **1a**, **3aa** was selectively obtained in 64% yield.

To increase the utility of these fluorinated amino acid derivatives as building blocks for peptides and proteins, the carbofluorination of Dha with different protecting groups was evaluated (Table 3). Bis-Boc-Dha-OMe was effectively transformed into the corresponding amino acids with different radical precursors (**3aa-3ac**). Phthalimide protection (**3ad-3ae**) was also compatible with the reaction conditions. Fluorinated amino acids protected with two different amine protecting groups were readily prepared (**3af-3ah**). Additionally, the carbofluorination process was applied to a substrate that afforded a dipeptide derivative (**3ai**).

Based on our observations, a plausible mechanism of the photoredox-catalyzed α -fluorinated- α -amino acid synthesis is outlined in Scheme 1. Under irradiation by blue LEDs, the mesityl acridinium photocatalyst is transformed to the highly oxidizing excited state ($E_{\text{red}} = +2.06$ V vs. SCE), which undergoes single electron transfer (SET) reductive quenching with radical precursor **2** to furnish alkyl radical **6**. Stern-Volmer quenching experiments indicate that alkyltrifluoroborate **2** ($E_{\text{red}} = +1.10$ V vs. SCE for benzylic alkyltrifluoroborate) is a more effective quencher of the excited organic photocatalyst than Dha **1** and Selectfluor (see Supporting Information). The generated radical **6** adds to Dha **1** to generate α -amino radical **7** by radical conjugate addition or reacts with Selectfluor to

undergo direct alkylfluorination. To obtain fluorinated amino acid **3**, the reaction of **6** with Dha **1** must be favored over that with Select-fluor. For this reason, the specific dehydroalanine derivatives bearing two electron-withdrawing groups on the amine were required. The radical **7** would subsequently engage with Selectfluor, resulting in formation of the desired α -fluoro amino acid **3**. The intermediacy of radical **7** was established by the presence of protonated **4** and dialkylated product **5**. We propose that aminyl radical cation **8** is converted to amine **9** to regenerate ground-state photocatalyst ($E_{\text{red}} = -0.57 \text{ V vs. SCE}$) and complete the catalytic cycle.

We observed that starting material was fully recovered with Boc-Me-Dha **1b** and mono-Boc-Dha **1c**, providing benzyl fluoride (R-F) by direct alkylfluorination under the same reaction conditions. The disparate reactivity observed with substrates **1a** and **1b** compared to **1c** warranted further investigation to understand the correlation between their structures and reactivity. Quantum mechanical calculations were employed to determine the energy-minimized conformations of the Dhas.¹⁴ As seen in Figure 2, the ground state structure of each adduct displays a unique torsional angle [$\omega(\text{C}=\text{C}-\text{N}-\text{C})$] between the plane of the olefin and the carbamate. The torsional angle correlates with the degree of conjugation of the nitrogen lone pair into the adjoining π system, impacting the electronic density of each olefin. In the calculated structure of adduct **1c**, the olefin and carbamate are coplanar, whereas in **1a** they are nearly perpendicular (consistent with the X-ray crystal structure, Figure 2B). The electrostatic potential at the terminus of the olefin (C-3) in each structure was calculated using the HLY method (Figure 2C).¹⁵ As anticipated, **1c** and **1b** display higher electronic density than **1a** because of the difference in the torsional angle, which is consistent with the observed experimental reactivity.¹⁶ The more deshielded ^{13}C NMR chemical shift value of **1a** at C-3 also supports this result. We examined the equilibria between the energy-minimized structure of **1a** and other rotational conformers via a coordinate scan of the torsional angle (see Supporting Information). The energetic penalty to rotate the carbamate plane coplanar with the olefin was found to be 10.8 kcal/mol. Under standard reaction conditions, the associated equilibrium constant ($K_{\text{eq}} = 1.24 \times 10^{-8}$) clearly suggests that **1a** exists almost exclusively in the conformation shown in Figure 2A. We assume that this orthogonal conformation and the electron-withdrawing nature of the protecting groups in **1a** provides the observed reactivity under the developed reaction conditions.

In conclusion, a mild, metal-free protocol for the preparation of diverse and unprecedented α -fluoro- α -amino acids by photoredox-catalyzed carbofluorination has been developed. This method introduces not only a fluorine atom at the α -position of amino acids, which is tremendously useful in the field of medicinal chemistry, agrochemistry, and chemical biology, but additionally, various alkyl chains, including primary, secondary, and tertiary alkyl groups were employed from commercially available and bench-stable alkyltrifluoroborate reagents. The wide variety of functional groups that are tolerated enable further modification toward analogues of natural amino acids.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Synthetic Routes toward α -Fluoro- α -Amino Acids

Figure 2. 3D Structure of Dha adducts (A) Energy-minimized conformations were calculated at B3LYP/6–31G(d) level of theory using Gaussian 09 visualized via WebMO. (B) X-ray crystal structure of **1a**. (C) Computed torsion angles, ESP (electrostatic potential) values, and ^{13}C chemical shifts at C-3 of Dhas.

Scheme 1.
Plausible Mechanism for Dha Carbofluorination

Table 1.

Optimization for Carbofluorination of Dehydroalanine.

entry	^a deviation from standard condition	3a (%) ^b	4(%)	5(%)
1	None	81	<5	8
2	acetone	<5	<5	79
3	THF	0	87	0
4	MeCN	45	<5	38
5	Ir[dF(CF ₃)ppy] ₂ bpy] ^c	80	<5	14
6	4CzIPN ^d	24	58	13
7	NSFI ^e	0	0	87
8	<i>N</i> -fluoropyridinium salt ^f	0	22	47
9	No light	0	0	0
10	No photocatalyst	0	0	0
10	BnBF ₃ K 2a (1.5 equiv)	59	<5	9
11	Selectfluor (2 equiv)	18	21	31

^aReactions were run with Dha (1.0 equiv), trifluoroborate (2.0 equiv), photocatalyst (5.0 mol %), and Selectfluor (4.0 equiv) in DMF on 0.1 mmol scale.

^bYields determined by ¹H NMR using 4-methoxybiphenyl as an internal standard.

^cHexafluorophosphate salt.

^d2,4,5,6-Tetra(9H-carbazol-9-yl)isophthalonitrile.

^e*N*-Fluorobenzenesulfonimide.

^fTetrafluoroborate.

Table 2.Synthesis of α -Fluoro- α -Amino Acid: Scope of Alkyltrifluoroborates^{a,b}

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Radical precursor scope

Secondary alkyl radical

Primary alkyl radical

Tertiary alkyl radical

α -Alkoxyethyl radical

α -Aminomethyl radical

β -Aminoethyl radical

β -Carbonyl alkyl radical

Radical clock reaction

Acyl radical

^a All values indicate the yield of the isolated product.

^b General reaction conditions: dehydroalanine (1.0 equiv, 0.5 mmol), potassium alkyltrifluoroborate (2.0 equiv, 1.0 mmol), Selectfluor (4.0 equiv, 2.0 mmol), MesAcr⁺ (5 mol %, 0.025 mmol), DMF (0.1 M), 12 h, irradiating with blue LEDs.

^c Diastereomeric ratio determined by ¹H and ¹⁹F NMR.

^d Separated by preparative HPLC.

^e Conducted using 2.0 equiv of potassium (bromomethyl)trifluoroborate.

Table 3.Synthesis of α -Fluoro- α -Amino Acid: Scope of Dehydroalanine^{a, b}

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Dehydroalanine scope

^a All values indicate the yield of the isolated product.

^b General reaction conditions: dehydroalanine (1.0 equiv, 0.5 mmol), potassium alkyltrifluoroborate (2.0 equiv, 1.0 mmol), Selectfluor (4.0 equiv, 2.0 mmol), MesAcr⁺ (5 mol %, 0.025 mmol), DMF (0.1 M), 12 h, irradiating with blue LEDs.

^c Separated by preparative HPLC.