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Synthesis of Quaternary α-Fluorinated α-Amino Acid Derivatives via Coordinating Cu(II) Catalytic α-C(sp^3)−H Direct Fluorination

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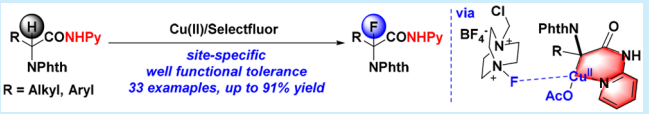
Supporting Information

ABSTRACT: A coordinating, copper-catalyzed direct α-C(sp^3)−H fluorination method has been developed to prepare vital quaternary α-fluorinated α-amino acid derivatives. A Cu(II) catalytic SET oxidative addition mechanism is proposed, involving a key fluoride-coupled Cu(II) charge transfer complex. The protocol can tolerate a rich variety of α-amino acids, for which the auxiliary group is removed in high yield and substituted for the direct preparation of dipeptide derivatives with detachable, single absolute configurations of the target compounds.



With the rapid development of peptide-based drugs[1] and proteomic investigations[2] in recent years, more innovative and efficient methods are urgently needed to modify natural α-amino acids (α-AAs). Fluorine-containing α-AAs have found a variety of applications in peptide or protein modifications, including enhanced hydrolytic stability, restricted conformation, and even tagging for imaging.[3] However, to date, the introduced fluorine has been limited to the side chains of the α-AAs,[3i] although a fluorine on the α-site could more effectively improve the peptide or protein's physicochemical or even pharmacological properties, such as tolerating the hydrolytic ability of peptide bonds to proteinase, increasing the optical stability of α-stereocenter, but with minimal impact on the native activity of the α-AA.[4]

α-Fluorinated glycines are generally prepared by a Gabriel reaction, which form the bonds between α-halogenated carboxyl acid ester and amines.[5] α-Fluorinated quaternary AAs, including α-fluorinated α-aryl glycines and 3′-fluorothalidomide, can be prepared by the direct fluorination of α-carbanions or enolates (deprotonation of α-AAs with excess strong base, such as LiHMDS/KHMDS, at extremely low temperature)[6] that lack functional group tolerance or regiospecificity. Li's group recently developed the α-fluorinated α-aryl glycine derivatives by the direct N−F bond insertion of diazocarbonyl compounds.[7] Transition-metal-catalyzed C−H direct functionalization to form new C−C, C−N, C−O, and C−X bonds has been widely applied to the site-specific modification of α-AAs, addressing the involved multiple steps, harsh conditions, and the use of stoichiometric and/or toxic reagents in traditional methods.[8] However, its C(α)−H modifications of α-AAs were limited to C(α)−C bonds via a pivotal reductive elimination mechanism of enolate-Pd(II) and C(α)-Pd(II) intermediates (Figure 1A)[9] Hartwig's group prepared α-arylation glycine derivatives utilizing Pd-catalysis. To achieve the quaternary α-arylation AAs, they had to previously fuse the tertiary C(α)−H in azlactones (an AA derivative with more acidic α-protons and less hindrance due to their cyclic structures, Figure 1A).[10] Trost's group developed asymmetric Pd-catalyzed alkylation based on azlactones to form chiral quaternary α-AAs.[11] As an improvement, recently, You's group has successfully realized a coordinating Fe-catalyzed or Ni-catalyzed radical oxidative cross-dehydrogenative-coupling reaction with a picolinamide auxiliary to prepare quaternary α-AA esters, which substituted the role of azlactones to activate the C(α)−H with a broader

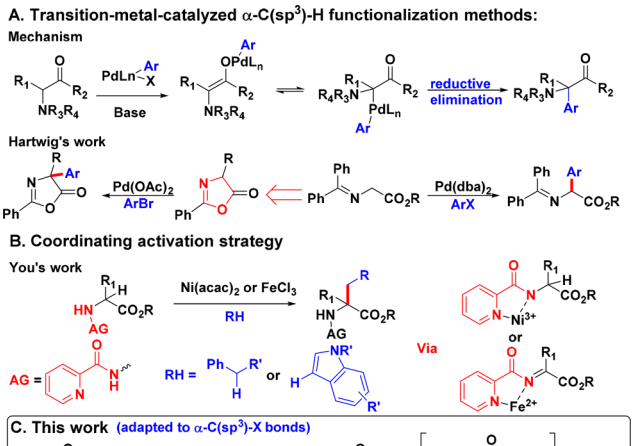


Figure 1. Transition-metal-catalyzed α-C(sp^3)−H functionalization methods of α-AA derivatives.

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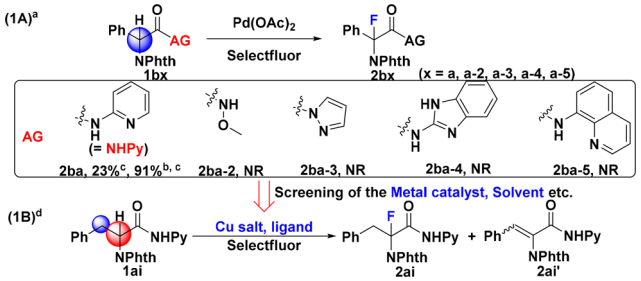
scope and milder conditions (Figure 1B).[12] Inspired by this progress, we investigated the first α-C(sp^3)−H direct fluorination of α-AAs (Figure 1C) via a coordinating metal-catalyzed strategy.[13]

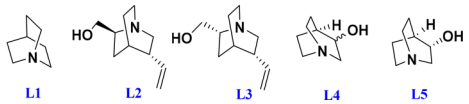
To resolve the kinetically disfavored C(sp^3)−Metal−F reductive elimination,[14] an appropriate auxiliary group (AG) should be introduced first to assist with the transformation (Figure 1C, **INTx**). Initially, we tested various AGs containing N- or O-atoms by the designed reaction using $Pd(OAc)_2$, fluorinating agent Selectfluor, and phthaloyl(Phth)-amino-protected phenylglycine derivatives **1bx** (Table 1A), and

Table 1. Design and Optimization of α-C(sp^3)−H Fluorination



entry	Cu Salt	ligand	**2ai** (%)[e]	**1ai** (%)[e]	**2ai′** (%)[e]
1	$Cu(OAc)_2$	–	39	10	42
2	$Cu(OTf)_2$	–	30	10	28
3	CuCl	–	26	49	11
4	CuI	–		no conversion	
5	CuF_2	–		no conversion	
6	$Cu(acac)_2$	–	0	30	53
7	$Cu(eaa)_2$	–	21	40	24
8	Cu_2O	–		no conversion	
9	$Cu(OAc)_2$	**L1** (40%)	49	0	42
10	$Cu(OAc)_2$	**L2** (40%)	43	27	19
11	$Cu(OAc)_2$	**L3** (40%)	62	18	9
12	$Cu(OAc)_2$	**L4** (40%)	50	28	11
13	$Cu(OAc)_2$	**L5** (40%)	78	12	trace
14	$Cu(OAc)_2$	**L5** (80%)	59	24	trace
15	$Cu(OAc)_2$	**L5** (20%)	81	trace	10
16	$Cu(OAc)_2$	**L5** (10%)	56	23	13

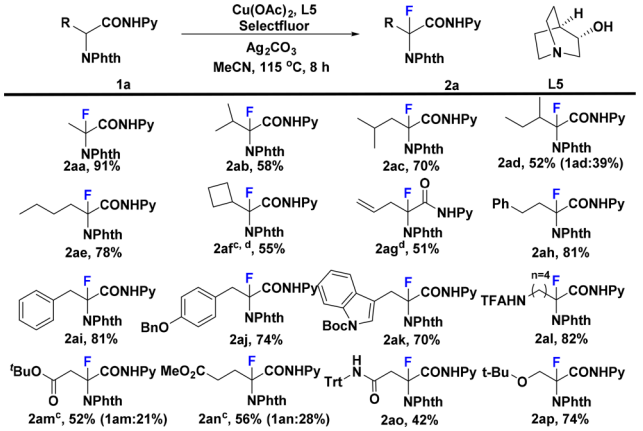
[a]Conditions: **1ba** (0.1 mmol), selectfluor (0.15 mmol), $Pd(OAc)_2$ (10 mol %), Ag_2CO_3 (0.2 mmol), and 1,4-dioxane (1.5 mL) at 115 °C under Ar for 16 h. [b]2-Picoline (10 mol %). [c]Yield was determined by ^1H NMR using internal standard DEM. [d]**1ai** (0.1 mmol), selectfluor (0.15 mmol), Cu salt (40 mol %), Ag_2CO_3 (0.2 mmol), Ligand X (x mol %), and MeCN (1.5 mL) at 115 °C under Ar for 8 h. [e]Isolated yield.



found that the desired C(α)-fluorinated product **2ba** was formed in 23% yield only when a pyridine was used as the AG. Then, a 91% yield was obtained by adding 10% of a 2-picoline ligand (Table S1, Supporting Information (SI)). Unfortunately, this condition did not work completely for the phenylalanine derivative **1ai** with the more inert aliphatic tertiary α-C(sp^3)−H bond (Table 1B). Further attempts using many other metal salts undertaken for **1ai** (Table S2, SI). Fortunately, $Cu(OAc)_2$ successfully gave the anticipated product **2ai** (39%), accompanied by the β-H elimination byproduct **2ai′** (42%, Table 1, entry 1). Other copper salts did not give better results (entries 2−8). Considering the role of a ligand in promoting metal-catalyzed activity and inhibiting β-H elimination,[15] we further tested many *N*-hetero ligands (Table S3, SI). We found that quinuclidine (**L1**) increased the yield of **2ai** to 49%, but **2ai′** (42%) still occurred (Table 1, entry 9). Other quinuclidine ligands were then screened (entries 10−13), and amazingly we found that (*R*)-3-hydroxy quinuclidine (**L5**, entry 13) significantly decreased **2ai′** which consequently resulted in an increased yield of desired **2ai** (78%). Further increasing or decreasing the **L5** amount did not improve the yield of **2ai** (entry 14 or 16). Finally, an 81% isolated yield was achieved when optimal **L5** (20%, entry 15) was used.

The reaction scope was next examined with the gained optimal conditions. For the aliphatic methyne α-C(sp^3)−H bonds, branched and unbranched alkanes (Scheme 1, **2aa**−

Scheme 1. Fluorination of Aliphatic Methyne C(sp^3)−H Bonds[a,b]



[a]Conditions: **1a** (0.1 mmol), selectfluor (0.15 mmol), $Cu(OAc)_2$ (40 mol %), Ag_2CO_3 (0.2 mmol), **L5** (20 mol %), and MeCN (1.5 mL) at 115 °C under Ar for 8 h. [b]Isolated yield. [c]$Cu(OAc)_2$ (80 mol %), 10 h.

2ae), cycloalkanes (**2af**), olefins (**2ag**), aromatics (**2ah**−**2ak**), amides (**2al** and **2ao**), esters (**2am**−**2an**), and ethers (**2ap**) were compatible with this fluorination protocol in moderate to high yields (42−91%). The steric hindrance next to the α-C(sp^3)−H (**2ab** and **2ad**) and the highly active β-C(sp^3)−H (**2af**, **2ag**, **2am**, and **2ao**) were the main reason for the variation in yield. For the benzylic methyne α-C(sp^3)−H bonds, whether electron-donating or -withdrawing substituents were used, a higher yield (65−91%, Scheme 2) and efficiency (80 °C, 2 h) were attained than those in the former Pd catalytic system (23%, 115 °C, 16 h, Table 1A).

To explore the application of such α-fluorinated α-AAs, it was necessary to find mild conditions for effective removal of the AG. Unfortunately, over many trials, the literature methods[16] did not convert the amide to a corresponding carboxyl group or its derivatives without affecting the newly introduced C(α)−F bond. Triflic anhydride (Tf_2O) is known as an excellent activating agent for the amide bond with exceptional functional group tolerance.[17] Therefore, Tf_2O and catalytic amounts of $CoCl_2$[18] were tested, and the carboxylic acid **3ai** (65%) and ester **4ai** (70%) were herein acquired in high yield (Scheme 3). Importantly, dipeptides (**5ai**, **6ai**, **7ai**) could be directly prepared by using L-amino acid esters with

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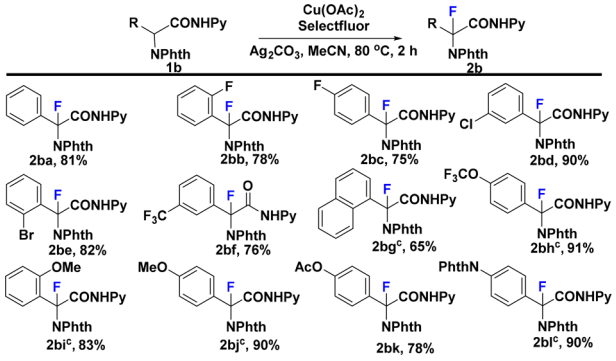
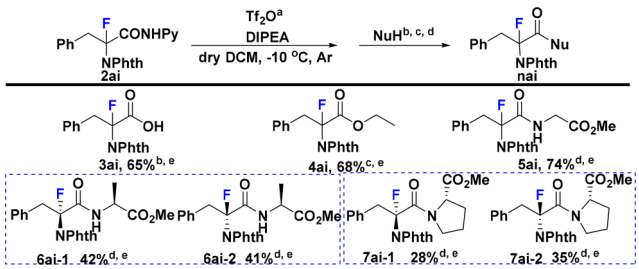
Scheme 2. Fluorination of Benzylic Methyne C(sp^3)−H Bonds[a,b]



[a]Conditions: **1b** (0.1 mmol), selectfluor (0.15 mmol), $Cu(OAc)_2$ (40 mol %), Ag_2CO_3 (0.2 mmol), and MeCN (1.5 mL) at 80 °C under Ar for 2 h. [b]Isolated yield. [c]$Cu(OAc)_2$ (20 mol %) at 60 °C for 2 h.

Scheme 3. Conversion of AG

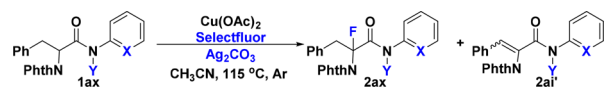


[a]Conditions: **2ai** (0.1 mmol), Tf_2O (0.15 mmol), DIPEA (0.5 mmol), DCM (1.5 mL) at −10 °C under Ar for 2 h. [b]LiOH (0.2 mmol)/H_2O (1 mL) was added at rt for 18 h. [c]$CoCl_2$ (10 mol %)/EtOH (1 mL) was added at rt for 18 h. [d]$CoCl_2$ (10 mol %)/AA methyl esters (0.25 mmol) were added at rt for 18 h. [e]Isolated yield.

relatively high yields (63−83%), and a pair of diastereoisomers of the α-fluorinated dipeptide derivatives (**6ai-1**, **6ai-2**; **7ai-1**, **7ai-2**) were easily separated and optical isomers were indisputably identified by circular dichroism (Scheme 3 and Figures S1−S10, SI).

To illuminate the mechanism, several studies were performed in Table 2. A blank experiment without an auxiliary *N*-atom (entry 1) was first investigated. As expected, **1aq** could not be fluorinated, which indicated the coordinating role of

Table 2. Mechanistic Studies[a]



entry	conditions	results[b]
1	X = CH, Y = H (**1aq**)	no conv
2	**1ai**, no selectfluor	**2ai**: 0%, **2ai′**: 70%
3	**1ai** + TEMPO (2 equiv)	**2ai**: 11%, **2ai′**: 62%
4	**1ai** + TEMPO (5 equiv)	**2ai**: 0%, **2ai′**: 71%
5	**1ai** + BHT (2 equiv)	no conv
6	X = N, Y = Me (**1ar**)	no conv
7	no **1ai**, CD_3CN, rt, 1 h	δ −150.95
8	**1ai**, CD_3CN, rt or 80 °C, 1 h	δ −150.75, −150.95

[a]Conditions: **1ax** (0.1 mmol), selectfluor (0.15 mmol), $Cu(OAc)_2$ (40 mol %), Ag_2CO_3 (0.15 mmol), and MeCN (1.5 mL) at 115 °C under Ar for 8 h. [b]Isolated yield or δ value of ^{19}F NMR.

pyridine. Thus, two possible pathways to reach **2ai** exist: pathway **A** is the direct nucleophilic reaction of the generated enolate-Cu(II) intermediate **INT2**, and **B** is the oxidation addition of the formed α-C(sp^3)−Cu(II) intermediate **INT3** by highly oxidative selectfluor (Figure 2, pathway **A** and **B**).

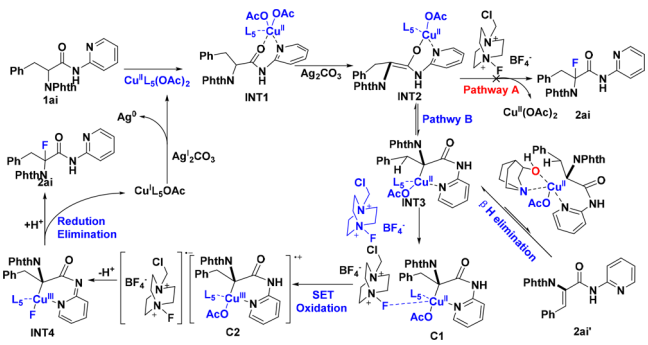


Figure 2. Proposed mechanism.

However, the concomitant β-H elimination byproduct **2ai′** indicates the presence of **INT3,** which supports the pathway **B**. Interestingly, **1ai** was nearly converted into **2ai′** in the absence of selectfluor (Table 2, entry 2), confirming a competitive reaction between fluorination and β-H elimination mediated by **INT3** (Figure 2, **INT3** to **2ai′**). The radical trapping reagents TEMPO and BHT could markedly suppress the fluorination of **1ai** (Table 2, entries 3−5), suggesting the presence of free radicals in the reaction,[19] which almost rule out pathway **A**. Recent literature reported that selectfluor can fluorinate the benzyl C(sp^3)−H adjacent to *N*-heterocycles by a charge-transfer complex mediated SET route.[20] Ritter's group also developed an aromatic C−H fluorination via a SET from a fluoride-coupled Pd(III) electron transfer to a Pd(II) complex.[21] We observed that the radical trapping significantly increased **2ai′** (Table 2, entries 3 and 4) leading to the speculation that a SET oxidative addition from the **INT3** to α-C(sp^3)−Cu(III) intermediate **INT4** occurred in our fluorination which involved the key complexes **C1** and **C2** (Figure 2, **INT3-4**). Another control experiment showed that the *N*-methylated amide bond of the AG (Table 2, entry 6) did not proceed in the reaction, implying the participation of its H-atom in the fluorination (Figure 2, **C2** to **INT4**) and further excluding pathway **A**. Additionally, the observed silver mirror in reaction (SI) also explains the involved oxidation of Ag_2CO_3 in the reaction (Figure 2, $Ag^I_2CO_3$ to Ag^0).

A primary kinetic isotope effect (21% yield) was gained ($k_H/k_D \approx 4.0$) in the intermolecular competition experiments (Figure S11, SI), evidencing that our Cu(II) catalyzed α-C(sp^3)−H activation process was the rate-limiting step, which is distinguished from the more sluggish Pd(IV)−F reductive elimination.[14] The signal of the Cu(II) complex was not visible or appeared as a small broad peak in the NMR spectrum due to the paramagnetism of Cu(II) (Figures S13−S14, SI); therefore, we monitored the reaction intermediates by ^{19}F NMR in CD_3CN. The blank experiment without **1ai** showed the $Cu(OAc)_2$ noncoordinated ^{19}F NMR signal of selectfluor (δ −150.95). When **1ai** was added into the reaction at rt and 80 °C for 1 h respectively, an extra broad peak appeared at δ −150.75 that in all probability indicated the formed fluoride-coupled Cu(II) electron transfer complex **C1** with a weak coordinated ^{19}F NMR signal (Table 2, entry 9; Figure S12 in SI for details).

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Based on the above collected data, along with the previously proposed mechanisms in Figure 1A[9] and recent fluoride-coupled SET reactions,[20−22] a catalytic cycle for this reaction is described in Figure 2. The coordination of Cu(II) and the alkalinity of Ag_2CO_3 promote the generation of **INT1** and its enolate intermediate **INT2**. Highly nucleophilic **INT3** existing in equilibrium with its tautomer **INT2**[9] promotes the production of **C1** using selectfluor. Then, a SET oxidative addition generates the Cu(III) complex **C2**.[20,21] A H-ion transfer of **C2** then generates more stable **INT4**, following the reductive elimination which afforded the product **2ai**. The associated Cu(I) is reoxidized to Cu(II) by excessive Ag_2CO_3. Meanwhile, the β-H elimination of **INT3** is inhibited by **L5**, which may occur by occupying the empty metal orbital used to break C(β)−H.[15]

In summary, the first direct α-C(sp^3)−H fluorination of the α-AA derivatives has been realized by our coordinating Cu(II) catalytic method, which provides a wide range of α-AA substrates, including aliphatic and benzylic methyne α-C(sp^3)−H with rich substituents. Mechanism studies revealed a Cu(II) catalytic SET oxidative addition process, in which a key fluoride-coupled Cu(II) charge transfer complex **C1** is detected by ^{19}F NMR. The β-H elimination byproduct is effectively inhibited by the (*R*)-3-hydroxy quinuclidine ligand. Mild conditions for efficient removal of the AG are disclosed without affecting newly introduced C(α)−F, which allows us to directly synthesize and separate the α-fluorinated dipeptide derivatives with a single configuration. This work should potentially feature in forming corresponding peptides and proteins.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03044.

Experimental procedures, spectroscopic data, and copies of NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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