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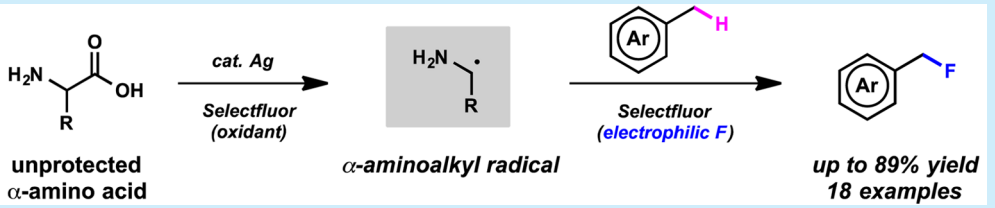
Radical C−H Fluorination Using Unprotected Amino Acids as Radical Precursors

Alyssa M. Hua, Duy N. Mai, Ramon Martinez, and Ryan D. Baxter*

Department of Chemistry and Chemical Biology, University of California, 5200 North Lake Road, Merced, California 95343, United States

Supporting Information

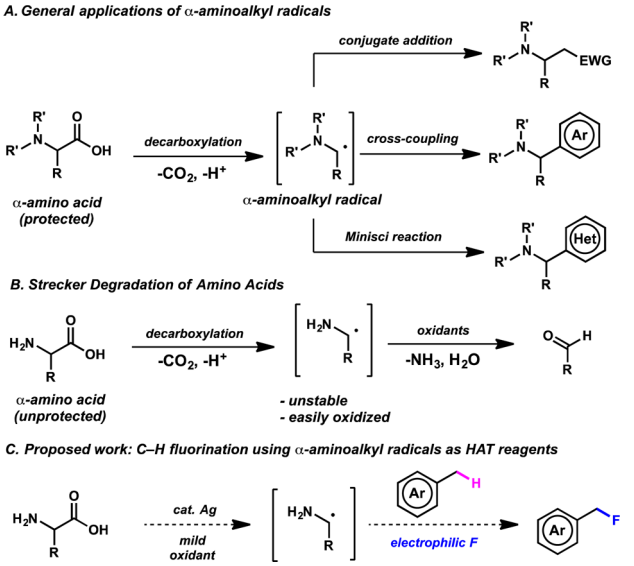


ABSTRACT: We report a unique example of utilizing unprotected amino acids for benzylic C−H fluorination via a radical process. α-Aminoalkyl radicals are readily generated via oxidative decarboxylation of unprotected amino acids using a simple silver(I) catalyst and Selectfluor, which serves as both a mild oxidant and source of electrophilic fluorine. Mechanistic investigation shows that coordination of the unprotected amino acid plays a crucial role in lowering the oxidation potential of Ag(I), enabling oxidation under mild conditions. Mono- or difluorination is possible by controlling the stoichiometry of amino acid and fluorine source.

α-Aminoalkyl radicals are important and highly reactive intermediates for the synthesis of substituted amines. Common strategies for generating α-aminoalkyl radicals involve direct oxidation of an amine to an *N*-centered radical cation via UV light or photocatalyst, followed by α-deprotonation.[1] However, site-specific formation of the α-aminoalkyl radical can be problematic with substrates containing multiple sites of deprotonation. Recent work has shown that radical decarboxylation of amino acids is an attractive, regioselective alternative (Scheme 1). Because α-aminoalkyl radicals are highly reducing and prone to oxidation, their synthetic utility depends on substitution at nitrogen to attenuate stability and reactivity.[2] Strong chemical oxidants and light-mediated photocatalysis have both been shown to be effective for the radical decarboxylation of *N*-substituted amino acids. The resulting α-aminoalkyl radicals have been shown to participate in a range of C−C bond-forming reactions such as conjugate additions, cross-coupling, and Minisci reactions with electron-deficient heteroarenes (Scheme 1a).[3−5] To the best of our knowledge, unprotected α-aminoalkyl radicals have not been successfully used as synthetic intermediates due to their propensity for rapid oxidation. Our interest in developing new and mild methods for C−H radical functionalizations led us to question whether it was possible to use unprotected α-aminoalkyl radicals as useful synthetic intermediates. Herein we report a new strategy for radical C−H fluorination using unprotected α-amino acids as stable radical precursors. Our mild protocol enables radical fluorination in the presence of sensitive functional groups and is effective under mild reaction conditions.

The oxidative decomposition of α-amino acids by strong oxidants has been known for more than eight decades. The Strecker degradation produces aldehydes via a sequence involving decarboxylation, oxidation, and iminium hydrolysis (Scheme 1b).[6] Our laboratory has recently utilized this transformation as a means to generate and use aldehydes as alkyl radical precursors for C−H heterocycle functionalization.[7] During our studies, we contemplated the fate of the α-aminoalkyl radical species formed immediately after amino acid decarboxylation. We hypothesized

Scheme 1. α-Aminoalkyl Radicals from Amino Acids



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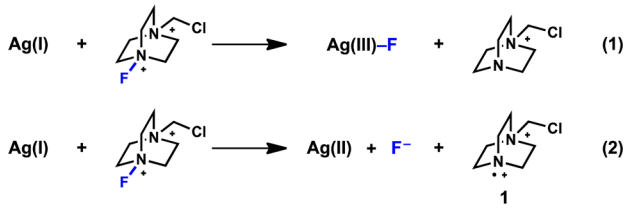
that if a mild oxidant could be employed to facilitate radical decarboxylation, this would diminish the prevalence for α-aminoalkyl radical oxidation, allowing alternative radical termination pathways to proceed.

Based on analysis of bond dissociation energies, we believed that α-aminoalkyl radicals should be capable of hydrogen atom abstraction from benzylic sp^3 C−H bonds.[8] Hydrogen atom transfer (HAT) strategies have been used to generate α-oxy, α-amino, or α-aryl radicals from metal complexes, but the use of carbon-centered radicals as HAT agents is less common.[9,10] Because electrophilic sources of fluorine can serve as both oxidant and a source of atomic fluorine, we sought to establish the feasibility of using α-aminoalkyl radicals as HAT reagents by developing a new protocol for C−H fluorination (Scheme 1c).[11,12]

At the outset of our studies, we considered two possible mechanistic scenarios for reaction initiation (Scheme 2). Direct

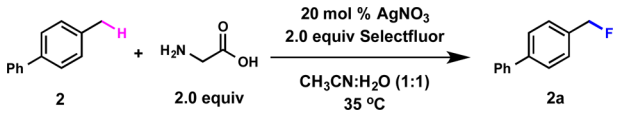
Scheme 2. Mechanistic Scenarios for Ag(I) Oxidation



addition of Ag(I) into the N−F bond of Selectfluor, as originally proposed by Li, would promote fluorination via a Ag(I)/(III)/(II) catalytic cycle (eq 1).[13] Alternatively, single-electron oxidation of Ag(I) by Selectfluor, as suggested by Flowers, would facilitate decarboxylation via a Ag(I)/(II) catalyst cycle (eq 2).[14] This second scenario could be complicated by the stoichiometric formation of radical dication **1** from Selectfluor, potentially obscuring the identity of the dominant HAT agent. Lectka has previously implicated dication **1** in HAT processes involving radical chain reactions for C−H fluorinations involving Selectfluor.[15] Studies involving ReactIR, analytical electrochemistry, and deuterium labeling have led us to support a Ag(I)/(II) cycle involving HAT predominately from an α-aminoalkyl radical (*vide infra*).

As shown in Table 1, 4-methylbiphenyl (**2**) was chosen as a model system to develop radical C−H fluorinations using amino acids. Through our optimization, we discovered that catalytic $AgNO_3$, Selectfluor, glycine, and a 1:1 mixture of CH_3CN/H_2O at slightly elevated temperatures led to formation of **2a** in good yield. The reaction was shown to be ineffective at room temperature, and higher temperatures led to diminished conversion (entry 2). The reaction may be performed open to air (entry 3), although higher conversion was observed under an inert atmosphere. Several unprotected amino acids were capable of benzylic fluorination (entries 4−6) although competing oxidation was observed in some cases, and glycine generally led to the highest conversion across all substrates examined. Interestingly, *N*-protected amino acids, such as *N*-Boc-glycine, did not promote radical fluorination (entry 7), although these results were later rationalized through mechanistic investigation (*vide infra*). Carboxylic acids were not effective at promoting benzylic fluorination, suggesting the presence of nitrogen plays a key role in the reaction (entry 8). *N*-Fluorobenzenesulfonamide (NFSI) was ineffective as an electrophilic fluorine source, which may be rationalized by its lower reduction potential ($E^\circ = -0.78$ V) compared to Selectfluor ($E^\circ = -0.04$ V) (entry 9).[16] Alternative solvents led to diminished reaction conversions (entries 10−11). Other silver(I) catalysts, such as $Ag(Bpy)_2OTf$ or $Ag(Phen)_2OTf$, did not promote radical fluorination (entries 12−13). Control reactions showed that both a silver catalyst and an amino acid were necessary for reaction (entries 14−15).

Table 1. Optimization of Benzylic Fluorination[a]



2 2.0 equiv 2a

entry	deviation from standard conditions	yield (%)
1	none	76
2	50 °C	46
3	open to air	48
4	proline instead of glycine	62
5	valine instead of glycine	72
6	phenylalanine instead of glycine	59
7	*N*-Boc-glycine instead of glycine	0
8	mandelic acid instead of glycine	0
9	NFSI as fluorine source	0
10	CH_2Cl_2/H_2O	0
11	acetone/H_2O	48
12	20 mol % $Ag(Bpy)_2OTf$	0
13	20 mol % $Ag(Phen)_2OTf$	0
14	no $AgNO_3$	0
15	no glycine	0

[a]Yields refer to chromatographically pure material. Reaction conditions: 4-methylbiphenyl (**2**) (0.2 mmol), glycine (0.4 mmol), Selectfluor (0.4 mmol), $AgNO_3$ (0.04 mmol), 2 mL of CH_3CN/H_2O (1:1).

With optimized experimental conditions established, the scope of radical fluorination was explored. As shown in Scheme 3, good yields and functional group tolerance were observed. In most cases, unreacted starting material accounted for the mass balance of incomplete reactions. Mono- or difluorinated products may be accessed for select electron-rich substrates by controlling reaction stoichiometry (**2a**, **2b**, both from 4-methylbiphenyl; **3a**, **3b**, both from 4-ethylbiphenyl). Although secondary sites can be suitably fluorinated (**5a**, **14a**), primary benzylic positions were shown to be the most reactive under our conditions. Tertiary benzylic sites were not reactive, yielding only trace product (**6a**). Analogous selectivity (1° > 2° > 3°) has been shown in previous radical fluorinations and may be the result of a proton-coupled electron transfer mechanism that is sensitive to stereoelectronic effects.[12c] Both electron-rich (**2a**−**8a**) and electron-poor (**9a**, **10a**) arenes are tolerated, although higher conversions are noted for electron-rich substrates, consistent with fluorination from a nucleophilic benzylic radical. Boronic acid pinacol esters are typically sensitive to oxidative cleavage, but are tolerated under our reaction conditions (**12a**−**13a**). Although direct heterobenzylic fluorination is a challenge, nitrogen-containing substrates were successfully fluorinated (**15a**−**17a**), supporting the feasibility of late-stage fluorination on pharmaceutically relevant scaffolds.

Based simply on the analysis of reduction potentials, Selectfluor should not be capable of generating Ag(II) from Ag(I) via single-electron transfer. To provide spectroscopic evidence for the formation of Ag(III)−F, we studied the radical fluorination of substrate **10** by *in situ* ReactIR.[17] We were surprised to find that no significant change in Selectfluor concentration was observed when exposed to stoichiometric $AgNO_3$ (Figure 1a). Upon the

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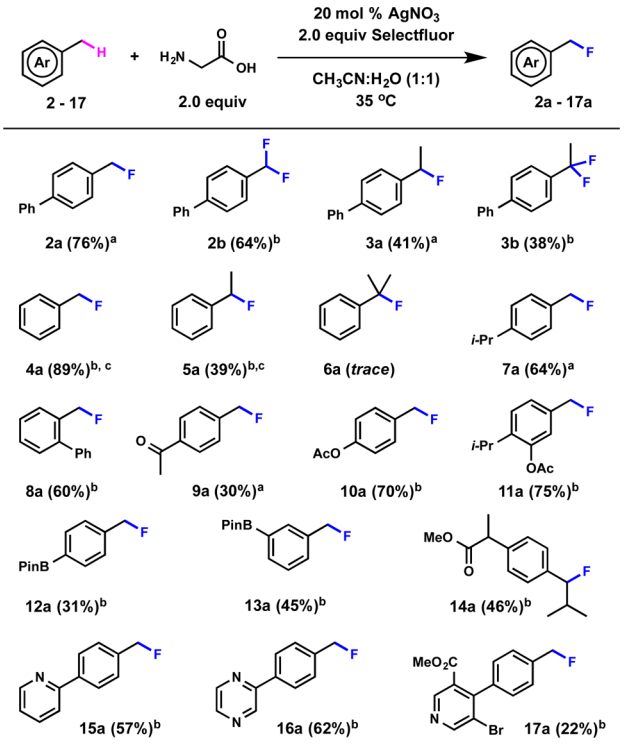
Scheme 3. Scope of Benzylic Fluorination



[a]Yields refer to chromatographically pure material unless otherwise noted. Reaction conditions: arene (0.2 mmol), glycine (0.4 mmol), Selectfluor (0.4 mmol), $AgNO_3$ (0.04 mmol), 2 mL of CH_3CN/H_2O (1:1). [b]5.0 equiv of Selectfluor (1.0 mmol) and glycine (1.0 mmol). [c]NMR yield compared to benzotrifluoride as an internal standard.

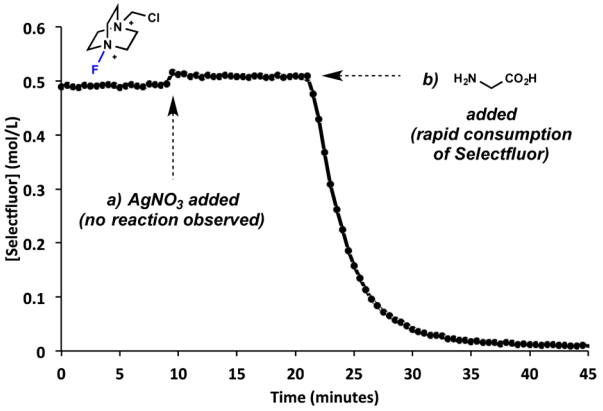


Figure 1. ReactIR monitoring of selectfluor concentration. Reaction conditions: **10** (0.2 mmol), glycine (0.4 mmol), Selectfluor (0.4 mmol), $AgNO_3$ (0.4 mmol), 2 mL of CH_3CN/H_2O (1:1). Reaction showed 25% conversion to **10a** by GCMS.

addition of glycine to this reaction mixture, a rapid decrease in Selectfluor concentration was observed, suggesting that glycine plays an important role in the reaction between Ag(I) and Selectfluor (Figure 1b).

This result led us to reconsider the possibility of a Ag(I)/Ag(II) catalyst cycle for decarboxylation of unprotected amino acids with Selectfluor. Measuring the onset oxidation potential of $AgNO_3$ in the presence of glycine, we noticed a significant decrease in the onset oxidation potential for the Ag(I)/Ag(II) couple (Figure 2b).[18] Conversely, when *N*-Boc-glycine was added to a solution of $AgNO_3$, a negligible shift in oxidation potential was observed.

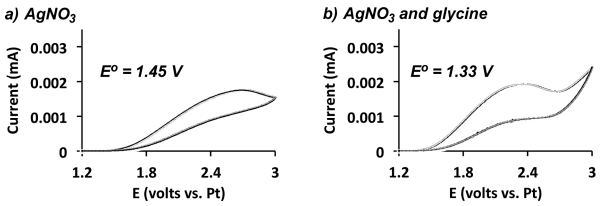
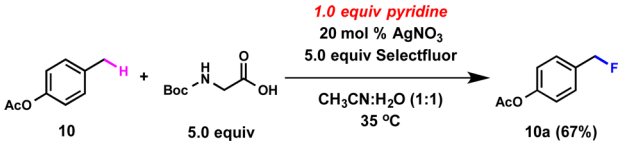


Figure 2. Cyclic voltammetry of Ag(I)/Ag(II) systems. Electrochemical conditions: $AgNO_3$ (0.4 mmol) in 5 mL of CH_3CN, tetrabutylammonium hexafluorophosphate supporting electrolyte (0.1 M), glycine (0.4 mmol). See Supporting Information for additional details.

These experiments suggest that amino acid ligation of the Ag(I) catalyst is necessary for decarboxylation. Although *N*-Boc-glycine is incapable of promoting radical fluorination on its own, the addition of 1 equiv of pyridine enabled the fluorination of **10** in 67% isolated yield (Scheme 4).[19]

Scheme 4. Catalyst Activation via Pyridine as an Additive



[a]Yields refer to chromatographically pure material. Reaction conditions: **10** (0.2 mmol), *N*-Boc-glycine (1.0 mmol), Selectfluor (1.0 mmol), pyridine (0.2 mmol), $AgNO_3$ (0.04 mmol), 2 mL of CH_3CN/H_2O (1:1).

To validate the role of the α-aminoalkyl radical as a HAT reagent, we conducted deuterium-labeling studies. *In situ* carbon NMR provides evidence for the formation of methylamine from glycine during a standard reaction using toluene to produce **4a**. The analogous experiment using toluene-d8 (**4-D**) produces deuterated methylamine upon fluorination under standard conditions.[19] Unfortunately, several attempts at *in situ* protection of the resulting free amine were unsuccessful, precluding quantitative analysis of deuterium incorporation. As shown in Scheme 2, a consequence of a Ag(I)/(II) initiation would be the stoichiometric formation of dication **1**. It is possible that unprotected amino acids act merely to initiate a chain radical process that involves **1** as the active HAT agent. However, running fluorinations with catalytic amounts of glycine (20–40 mol %) yielded only trace amounts of product, supporting its action as a stoichiometric participant beyond radical chain initiation.

Based on our studies, we propose the following mechanism for radical C–H fluorination using amino acids as radical precursors (Figure 3). Precoordination of Ag(I) to one or more unprotected glycines generates an electron-rich silver catalyst capable of undergoing single-electron oxidation with Selectfluor.[20] As shown in Table 1 (entries 12–13), fully coordinated Ag(I) complexes do not participate in radical fluorination, suggesting that glycine reversibly associates with Ag(I). Fluorine NMR shows that an aqueous fluoride anion is produced continuously throughout the fluorination reactions, supporting a single-electron transfer event with Selectfluor, although at this time a Ag(I)/Ag(III) catalytic cycle cannot be fully ruled out. Rapid decarboxylation from Ag(II) produces the α-aminoalkyl radical, and hydrogen-atom transfer with a benzylic C–H bond generates a benzylic radical and methylamine. Finally, the nucleophilic benzylic radical reacts with Selectfluor to provide the desired

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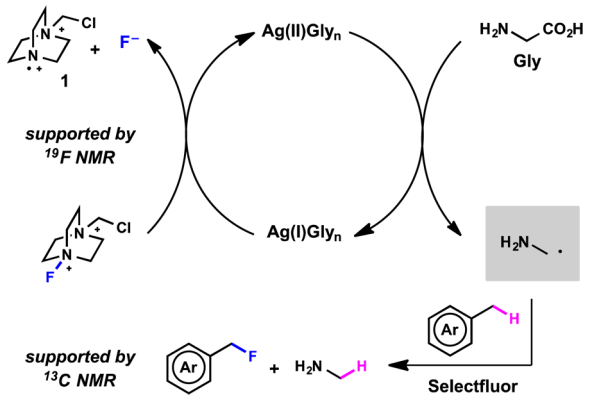

Figure 3. Proposed mechanism for benzylic fluorination.

product. As illustrated in Figure 2, amino acid coordination to Ag(I) is required to yield a catalyst of the appropriate oxidation potential for reaction with Selectfluor. Because the oxidation of glycine by Ag(II) is believed to occur rapidly from a metal-bound species, the concentration of Ag(II) in solution is expected to be low throughout the reaction. This has implications for the lifetime of the α-aminoalkyl radical which is expected to be readily oxidized by Ag(II). Based on the mechanism shown in Figure 3, Selectfluor and **1** are the strongest oxidants the α-aminoalkyl radical is likely to encounter, allowing HAT to occur prior to unwanted oxidation.

In conclusion, we have developed a new method for C−H benzylic fluorination using unprotected amino acids as radical precursors. Fluorination proceeds under mild conditions and is effective for several electron-rich benzylic substrates. Amino acid binding to the silver precatalyst is critical for lowering the oxidation potential of Ag(I), allowing oxidative decarboxylation under mildly oxidizing conditions. Additional work exploring the precise role of the amino acid throughout the reaction is ongoing.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01188.

Detailed experimental procedures, full characterization, and copies of all spectra data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: rbaxter@umcerced.edu.

ORCID

Ryan D. Baxter: 0000-0002-1341-5315

Notes

The authors declare no competing financial interest.

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