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Mechanistic Study of Silver-Catalyzed Decarboxylative Fluorination

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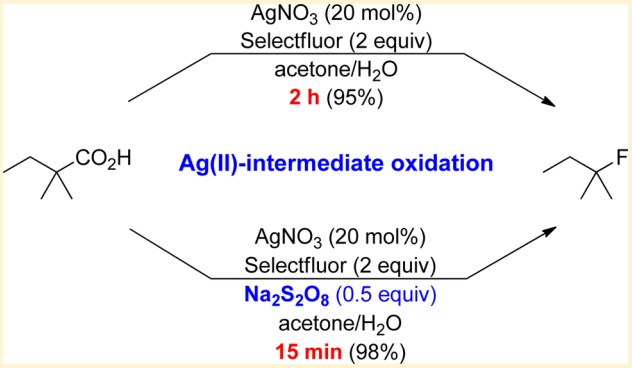
Supporting Information

ABSTRACT: The silver-catalyzed fluorination of aliphatic carboxylic acids by Selectfluor in acetone/water provides access to fluorinated compounds under mild and straightforward reaction conditions. Although this reaction provides efficient access to fluorinated alkanes from a pool of starting materials that are ubiquitous in nature, little is known about the details of the reaction mechanism. We report spectroscopic and kinetic studies on the role of the individual reaction components in decarboxylative fluorination. The studies presented herein provide evidence that Ag(II) is the intermediate oxidant in the reaction. In the rate-limiting step of the reaction, Ag(I)-carboxylate is oxidized to Ag(II) by Selectfluor. Substrate inhibition of the process occurs through the formation of a silver-carboxylate. Water is critical for solubilizing reaction components and ligates to Ag(I) under the reaction conditions. The use of donor ligands on Ag(I) provides evidence of oxidation to Ag(II) by Selectfluor. The use of sodium persulfate as an additive in the reaction as well as NFSI as a fluorine source further supports the generation of a Ag(II) intermediate; this data will enable the development of a more efficient set of reaction conditions for the fluorination.



INTRODUCTION

Carbon−fluorine bond formation is becoming increasingly important in the synthesis of fine chemicals and pharmaceuticals.[1] There has been a sharp increase in the development of fluorination methods due to the importance of C−F bonds in a large number of compounds of biological importance.[2] Fluorine substitution into drugs and other compounds alters their lipophilicity and metabolic stability, which can enhance the bioavailability and efficacy of a drug compound.[1a,3] In addition to pharmaceutical and agrochemical compounds, the presence of fluorine is vital in polymers[4] and materials[5] and for molecular positron emission tomography (PET) imaging.[6] Despite the abundance of fluorine in nature, as well as the vast utility of this functional group, there are only a small number of naturally occurring organic compounds.[7] For these reasons, the development of facile and versatile fluorination methods is essential.

In recent years, significant progress has been made in the development of transition metal-catalyzed methods for the fluorination of aromatic[8] and aliphatic substrates.[9] In particular, a great emphasis has been placed on the use of electrophilic fluorinating reagents in conjunction with metal catalysts,[8d,e,g,h,9c,i] as well as the reaction of radical intermediates with these reagents.[10] A greater understanding of metal-catalyzed fluorinations would be of considerable importance for the optimization of existing methods, expansion of substrate scope, and enhancement of chemoselectivity, as well as the development of new synthetic reactions. The recent development of a silver-catalyzed decarboxylative fluorination reaction using the electrophilic fluorinating reagent 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (F-TEDA-BF_4, Selectfluor) is of particular importance due to its procedural ease, mild reaction conditions, and extensive substrate scope.[9d] In addition, carboxylic acids are ubiquitous in nature, widely available, and straightforward to synthesize. As a consequence, there is a large pool of starting materials available for conversion to C−F containing compounds. It is our supposition that understanding the mechanism of this reaction will aid synthetic chemists in the design of improved or novel protocols that proceed through single-electron oxidation.

Herein, we present a detailed mechanistic investigation of the silver-catalyzed fluorination of carboxylic acids to produce alkyl fluorides. We (1) determine the stability of the silver nitrate catalyst during the course of the reaction, (2) present kinetic data describing the role of each of the components in the reaction, providing evidence for the rate-determining step, (3) explore the role of water as a cosolvent, (4) discuss the identity of likely reaction intermediates in this reaction, and (5) use the mechanistic information gleaned from our studies to develop an efficient catalytic process.

RESULTS AND DISCUSSION

The goal of this research was to explore the role of Ag(I) catalyst and Selectfluor in the silver-catalyzed fluorination of aliphatic carboxylic acids, a reaction recently developed by the Li group.[9d] In the original report, fluorination of tertiary acid **1** proceeded in

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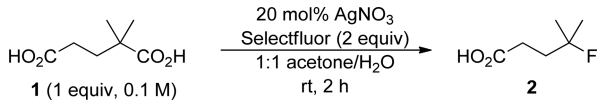
excellent yield. Fluorination of this compound displayed selectivity of the tertiary carboxylic acid over the primary acid moiety at room temperature.[9d] The reactions generally call for the use of 20 mol % catalyst and 2 equiv of Selectfluor in 1:1 acetone/water media (Scheme 1). After examining a number of

Scheme 1. Ag(I)-Catalyzed Fluorination of Aliphatic Carboxylic Acid Using Selectfluor



1 (1 equiv, 0.1 M) **2**

conditions, we found that increasing the concentration of **1** from 0.05 to 0.1 M enabled the reaction to proceed to completion in 2 h. Using these synthetic reaction conditions, kinetic studies were performed on the decarboxylative fluorination reaction of **1**.

Catalyst Stability Studies. To study the mechanism of this system, we sought to first do a thorough kinetic study of each component in the system. All kinetic studies were performed under synthetically relevant conditions.[11] Before beginning comprehensive studies, it was important to determine catalyst stability during the course of the reaction. Using the reaction in Scheme 1, we designated **1** as the limiting substrate with all other components added in excess and extracted kinetic information by monitoring the [**2**] using ^{19}F NMR and an internal standard (Figure 1). A significant amount of initiation was observed (approximately 600 s, Figure 1) in the reaction, a feature that will be discussed *vide infra*.

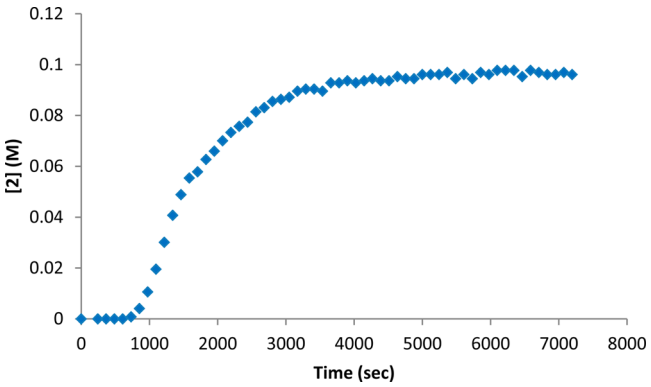


Figure 1. Growth of fluorinated product **2** over time monitored by ^{19}F NMR.

Under ideal conditions, at the first half-life of the reaction in Scheme 1, equivalent amounts of **1** and Selectfluor are consumed and [$AgNO_3$] remains constant. A second reaction initiated at the concentrations of reaction components at the half-life of the first reaction should follow the reaction profile of the first reaction and provide graphical overlay as long as [$AgNO_3$] is constant. Given the initiation period described above, reaction progress was monitored once product formation commenced. The reaction shown in Scheme 1 was monitored under the conditions shown in Table 1, Run 1. A second reaction was initiated at the first half-life of Run 1 (Table 1, Run 2). To do this, [**1**] was decreased to 0.05 M, one-half of that in Run 1, and [Selectfluor] was adjusted by an equivalent amount with respect to [**1**], decreased from 0.2 to 0.15 M. The [$AgNO_3$] in Run 2 was the same employed in Run 1. If [$AgNO_3$] remained constant during the course of the reaction, then the rates of Runs 1 and 2

Table 1. Reaction Conditions for Catalyst Stability Studies

Run	[**1**] (M)	[$AgNO_3$] (M)	[Selectfluor] (M)	Excess [Selectfluor] (M)
1 (100%)	0.1	0.02	0.2	0.1
2 (50%)	0.05	0.02	0.15	0.1

would be the same. If [$AgNO_3$] decreased as the reaction proceeded through catalyst deactivation, then the rates of Runs 1 and 2 would be different and their rate profiles would not overlay. To compare the rate profiles of both reactions on the same concentration scale, [**2**] was converted to [**1**]. When time-adjusted, both rate profiles show graphical overlay, consistent with constant [$AgNO_3$] over the course of the reaction (Figure 2).[12] Catalyst stability during the course of the reaction suggested

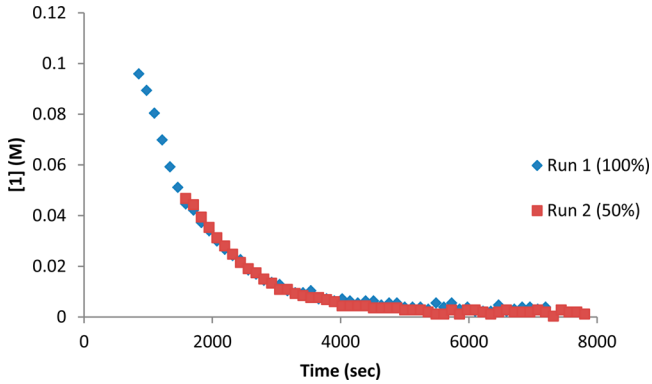


Figure 2. Time-adjusted profiles of [**1**] vs time for Runs **1** and **2**.

that $AgNO_3$ loading could be lowered significantly. We were able to lower $AgNO_3$ loading from 20 to 5 mol % to generate **2** in 90% yield by increasing the concentration of **1** from 0.1 to 0.2 M and allowing the reaction to proceed overnight.

Kinetic Order Studies. Next, the role of each substrate in the reaction was elucidated by determining their rate orders. Kinetic orders of substrates were found by using reaction progress kinetic analysis, in which the concentration of each substrate was varied individually to observe its effect on the rate of reaction.[11] When catalyst loading was increased from 20 to 40 mol %, a first-order rate dependence was found for $AgNO_3$. To determine the rate order of Selectfluor, its concentration was adjusted to 0.15 M while keeping the concentration of all other reactants constant. Decreasing [Selectfluor] resulted in a decrease of overall reaction rate, and a first-order rate dependence on Selectfluor was determined for the reaction. The order of **1** proved to be more complex. When lowering the amount of **1** from 0.1 to 0.075 M, an increase in reaction rate was observed. The rate plots of each reaction were fit to straight lines, in which the slope corresponds to the rate (see Supporting Information).[12a] We observed a rate order of −1.5 for **1**, suggesting that the substrate was inhibiting reaction progress.

Interaction of Carboxylic Acid with $AgNO_3$. The formation of silver-carboxylates is well-established in the literature.[13] To investigate whether the inverse order found in carboxylic acids could be due to an interaction resulting in silver-carboxylate formation, **1** was mixed with silver nitrate and allowed to stir overnight, forming a solid precipitate. The precipitation is likely a result of oligomers formed between diacid **1** and Ag(I). An FTIR spectrum of the precipitate showed the loss of the −OH peak and shift of the carbonyl peak to lower wavenumbers, consistent with the formation of a silver-

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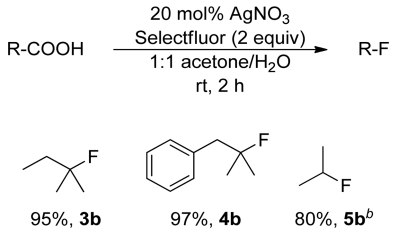
carboxylate.[13] The formation of this product, along with results found in the catalyst stability study and the inverse order found for the carboxylic acid, is consistent with the interaction of substrate with Ag(I).

Kinetic studies were also performed on three other substrates to confirm that the inverse order observed for **1** was not a substrate-specific effect. The substrates studied were 2,2-dimethylbutyric acid (**3a**), 2,2-dimethylpropanoic acid (**4a**), and isobutyric acid (**5a**), to form products **3b**, **4b**, and **5b**, respectively, in excellent yields (Scheme 2). In all cases, silver

Scheme 2. Ag(I)-Catalyzed Fluorination of Additional Aliphatic Carboxylic Acids[a]



[a]Yields determined by ^{19}F NMR compared to α,α,α-trifluorotoluene standard. [b]Reaction run for 4 h.

nitrate and Selectfluor were first-order and carboxylic acid was found to show inverse first-order dependency. The inverse orders observed for these monocarboxylic acids suggest that the order of **1** is not a result of the presence of an additional carboxylic acid moiety but, rather, is indicative of a general phenomenon for all carboxylic acids examined in this study.

Interaction of Selectfluor with $AgNO_3$. The oxidation of Ag(I) to high-valent complexes is often the rate-limiting step in silver-catalyzed reactions.[11f,14] To probe the role of Selectfluor as both a fluorinating reagent as well as an oxidant, the interaction of silver nitrate and Selectfluor was investigated by NMR. Upfield shifts of Selectfluor protons and carbons were observed in the ^{1}H and ^{13}C NMR spectra, respectively, upon addition of an equivalent of silver nitrate to Selectfluor in acetone-d_6/D_2O. In addition, a disappearance of the N−F peak of Selectfluor was observed in the ^{19}F NMR under the same conditions. These spectroscopic results are consistent with defluorination of Selectfluor. While the loss of the N−F signal was observed in the ^{19}F NMR, the appearance of another fluorine signal was not observed. This is consistent with reaction between Selectfluor and silver. The resulting species may be paramagnetic (Ag^{2+}, d^9). This could prevent observation of the product fluoride in the reaction. Attempts to characterize the proposed high-valent silver intermediate by a range of techniques including XPS, LC-MS, or X-ray crystallography were unsuccessful.

Activation Parameters. To obtain more insight into the transition state of the turnover-limiting step of the catalytic cycle, activation parameters were obtained for the reaction of **1** under synthetic conditions at temperatures ranging between 23 and 40 °C. The data were fit to the linear form of the Eyring equation. The following activation parameters were found: $\Delta H^{\ddagger} = 6.2 \pm 0.5$ kcal/mol, $\Delta S^{\ddagger} = -51 \pm 4$ cal/K·mol, and $\Delta G^{\ddagger} = 21 \pm 2$ kcal/mol (at 23 °C). The relatively small enthalpy of activation ($\Delta H^{\ddagger}$) and the large negative entropy of activation ($\Delta S^{\ddagger}$) are indicative of a highly ordered transition state.

Role of Water. In the original work of Li and co-workers, water was proposed to be essential for reaction success.[9d] When the reaction was performed in neat acetone, **2** is formed in 9% yield; as shown in Scheme 1, **2** is formed in 95% yield when run in a 50:50 ratio of acetone/water. To examine the impact of water on the reaction, various concentrations of water in the reaction milieu were examined, and the results are displayed in Table 2.

Table 2. Fluorination of 2 with Increasing Amounts of Water

ratio of water[a]	% yield[b]
100% acetone	9
100% acetone + 0.1 mmol H_2O	12
99.1:0.9 (acetone/water)	17
98.2:1.8 (acetone/water)	34
96.4:3.6 (acetone/water)	57
94.6:5.4 (acetone/water)	65
90:10 (acetone/water)	95
80:20 (acetone/water)	94
50:50 (acetone/water)	95

[a]Reactions run at 0.1 M concentration of **2** [b]Yields were determined by ^{19}F NMR with α,α,α-trifluoromethyltoluene as a standard.

While large amounts of water in the medium correlated with an increase in formation of fluorinated product, these studies showed that only a 9:1 ratio of acetone/water was necessary to produce **2** in 95% yield. Under these conditions, solubility of the substrates is maintained. Given this finding, it is our supposition that one role of water in the reaction is to solubilize the Selectfluor, which has very limited solubility in acetone alone.

To further examine the role of water, $AgNO_3$ was added to 9:1 solution of acetone-d_6/D_2O containing trace water. The ^{1}H NMR of this solution displayed a downfield shift of the water signal in the presence of $AgNO_3$ compared to the spectrum in the absence of $AgNO_3$, suggesting that water is ligated to Ag, thus solvating the metal center (Supporting Information). Given the critical role of water proposed by Li, these findings could allow for water to potentially be replaced as a solvating ligand in this reaction.

Induction Period. As previously mentioned, an induction period is observed in this reaction. Since the oxidation of carboxylic acid substrate results in the generation of CO_2 and H^+ during conversion of starting material to product, the pH of the system was monitored over the time course of the reaction (see Supporting Information). During the initial 600 s of the reaction, the pH was found to increase from 3 to approximately 4.4. Interestingly, the time of the pH increase correlates to the time required for initiation. Once the maximum pH is obtained, the pH drops during the course of the reaction. In an attempt to obtain insight into the induction period, ^{19}F NMR was initiated at the start of the reaction. Interestingly, there is no loss of Selectfluor observed during the induction, suggesting that it is not involved in the initiation. This leaves $AgNO_3$ and carboxylic acid. The infrared spectroscopic experiments described above indicate that the Ag and carboxylic acid form a Ag-carboxylate. We hypothesize the induction period occurs as a result of Ag-carboxylate formation. In addition, the inverse order observed for carboxylic acid is a result of an equilibrium of Ag-carboxylate and Ag(carboxylate)$_2$ formation,[15] in which Ag-carboxylate is the resting state. This point will be discussed *vide infra*.

Identification of Intermediates and Active Oxidant after the Rate-Limiting Step. Beyond substrate inhibition of the catalyst by carboxylic acid and the oxidation of Ag(I) by Selectfluor, we wanted to explore the reaction mechanism after the rate-limiting step. The questions that arise are (A) what intermediates are generated upon oxidation of Ag(I) by

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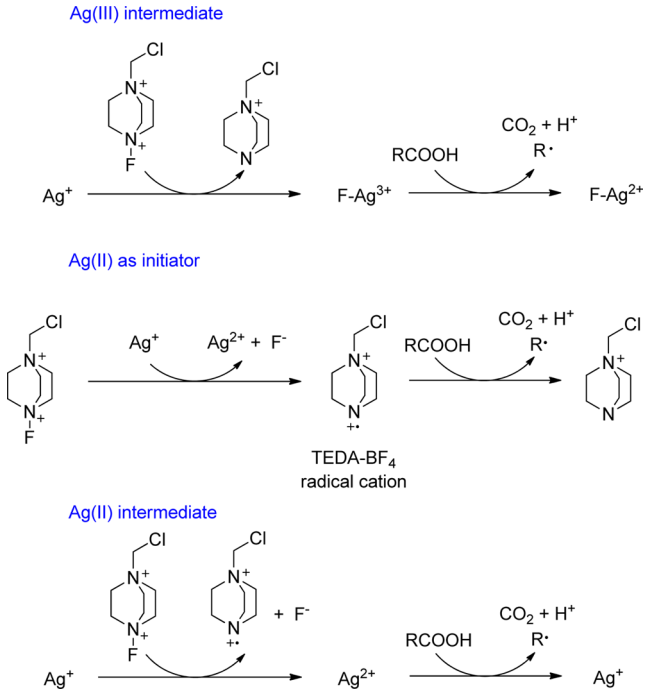
Selectfluor and (B) which of those intermediate species oxidize the carboxylic acid to generate an alkyl radical after the rate-limiting step? On the basis of the data obtained to this point and previous literature reports, the mechanism likely proceeds through one of three pathways: (1) the two-electron oxidation of Ag(I) to Ag(III) by Selectfluor, where Ag(III) oxidizes a carboxylic acid to produce an alkyl radical,[9d,h,16] (2) single-electron oxidation of Ag(I) to Ag(II) by Selectfluor to also generate TEDA-BF_4 radical cation, in which Ag(I) acts only as an initiator in the reaction and the radical cation oxidizes the carboxylic acid, or (3) the oxidation of Ag(I) by Selectfluor to generate Ag(II) and TEDA-BF_4 radical cation, where Ag(II) oxidizes the carboxylic acid to produce a radical (Scheme 3). We probed each of these hypotheses to determine the likely intermediate and silver oxidation state in this reaction.

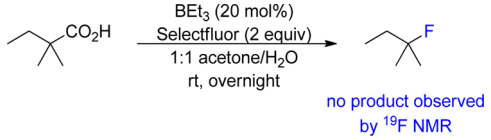
Scheme 3. Mechanistic Possibilities for Ag(I)-Catalyzed Decarboxylation



Ag(III) Intermediate. In the original report by Li's group, the reaction is proposed to proceed through the oxidation of Ag(I) by Selectfluor to form Ag(III), followed by decarboxylation of an acid to produce an alkyl radical through single-electron oxidation.[9d] Although Ag(III) complexes are capable of oxidizing carboxylic acids (E° = 1.8 V, Ag^{3+}/Ag^{2+}),[17] such complexes are known but are typically generated under a narrow range of conditions. Known complexes require specific ligands,[18] including biguanidines,[19] carbaporphyrins,[20] and N-heterocyclic carbenes,[21] or generation under basic conditions,[22] instances providing the electron density required to stabilize Ag(III). In addition, several studies have demonstrated that reduction of Ag(III) to Ag(I) is typically a one-step, two-electron process.[23] Due to the requirement of electron density, the lack of ligands other than TEDA-BF_4, and acidic medium in the present system, it is unlikely that Ag(III) is performing the oxidation of the carboxylic acid in this reaction.

Ag(II) as Initiator. Several recent papers involving Selectfluor-mediated fluorination propose generation of TEDA-BF_4 radical cation as a reaction intermediate.[9g,24] In a recent paper describing mechanistic studies of Cu(I)-catalyzed alkyl fluorination employing Selectfluor, Leckta's group revealed the role of Cu(I) as an initiator and TEDA-BF_4 radical cation as the intermediate responsible for H-atom abstraction of an alkane to generate an intermediate radical and chain propagation.[9g] To probe whether TEDA-BF_4 radical cation could function as an oxidant in this reaction, we employed triethylborane as an initiator to generate TEDA-BF_4 radical cation in the absence of $AgNO_3$ using a method similar to that described by Leckta.[9g] When using a substoichiometric amount of triethylborane in oxygenated acetone/water, no fluorination product was observed by ^{19}F NMR after allowing the reaction to proceed overnight (Scheme 4). This result suggests that TEDA-BF_4 radical cation is likely not

Scheme 4. Decarboxylative Fluorination Reaction with Triethylborane



functioning as the oxidant of carboxylic acid in this reaction and that the presence of $AgNO_3$ is critical for the success of the decarboxylative fluorination.

Ag(II) Intermediate. Since TEDA-BF_4 radical cation is most likely not acting as an oxidant responsible for conversion of the carboxylic acid to a radical, we sought to probe whether Ag(II) could be performing the oxidation. Ag(I)-persulfate catalysis has a long-established history in the literature,[14,25] in which Ag(II) is generated upon oxidation of Ag(I).[14] Work performed by Kochi and co-workers in the early 1970s on the Ag(I)-persulfate-catalyzed oxidation of aliphatic carboxylic acids to produce alkyl radicals revealed that Ag(II) was the active oxidant.[14,26] Since the combination of $AgNO_3$ and persulfate provides a rapid means for producing Ag(II), we sought to probe the impact of persulfate on the decarboxylative fluorination. Addition of $Na_2S_2O_8$ resulted in acceleration of the reaction rate. The addition of 0.1−1.0 equiv of $Na_2S_2O_8$ (with respect to **1**) to the reaction in Scheme 1 was examined. The reaction rate was monitored by observing the appearance of **2** by ^{19}F NMR. Exponential fits were used to determine k_{obs} for each reaction. In nearly every case, the exponential fit was greater than R^2 = 0.99. The reaction proceeded rapidly in the presence of $Na_2S_2O_8$, and saturation was observed at concentrations higher than 0.5 equiv (Figure 3). To examine this further, several other reactions were carried out by adding 0.5 equiv of $Na_2S_2O_8$.

When 0.5 equiv of $Na_2S_2O_8$ was combined with 2 equiv of Selectfluor and 20 mol % $AgNO_3$, the reaction time decreased from 2 h to 15 min for all substrates, forming alkyl fluorides in excellent yields (Scheme 5). The significant acceleration of rate in the decarboxylative fluorination has led to a more efficient process, suggesting that this approach may be useful for ^{18}F labeling.

Since the addition of persulfate changes the system, kinetic studies were performed on the reaction of **3a** to determine the mechanistic role of persulfate in the reaction. Catalyst stability studies showed that there was no deactivation of $AgNO_3$ catalyst during the course of the reaction. In addition, kinetic studies showed that $AgNO_3$ and $Na_2S_2O_8$ were consistent with a first-order dependence and that **3a** and Selectfluor were zero-order.

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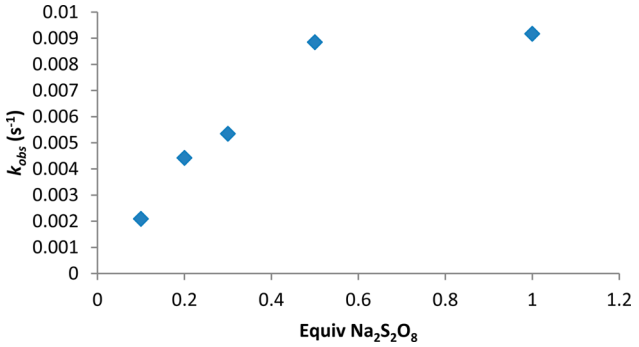
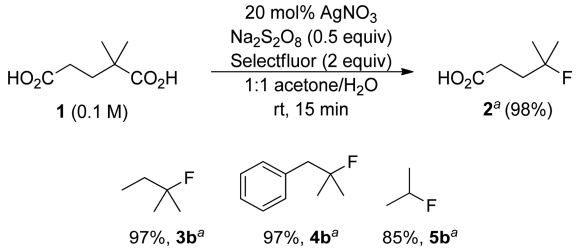


Figure 3. Equivalents of $Na_2S_2O_8$ vs k_{obs} for the fluorination of **1**.

Scheme 5. Decarboxylative Fluorination Reaction with $Na_2S_2O_8$ as an Additive



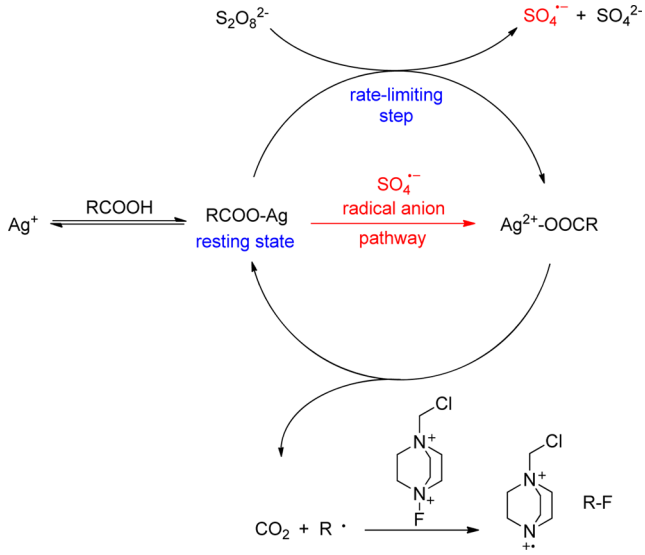
[a]Yields determined by ^{19}F NMR compared to α,α,α-trifluorotoluene standard.

The zero order observed for **3a** implies that, in the presence of persulfate, Ag-(carboxylate)$_2$ formation is slower than Ag(I) oxidation by persulfate and therefore does not result in substrate inhibition. The first-order rate dependence on silver and persulfate suggest that Ag(I) is oxidized to Ag(II) by persulfate. The zero-order dependence in Selectfluor for the reaction in Scheme 5 not only suggests that it does not play a role before the rate-limiting step but also that it is not oxidizing Ag(I) to Ag(II) under these conditions; therefore, its role is likely that of a fluorine atom source after the alkyl radical is produced by oxidation of the carboxylic acid by Ag(II) after the rate-limiting step (Scheme 6). The generation of Ag(II) by persulfate, along with the zero-order rate dependence on Selectfluor, suggests that Ag(II), not TEDA-BF_4 radical cation, is the oxidant responsible for decarboxylation.

One of the challenges with this system is that the absence of supporting ligands makes it difficult to characterize the oxidation state of the metal. To probe the oxidation state of Ag and gain further information on the active oxidant in this reaction, we chose to employ a strong donor ligand with a characteristic ^1H NMR signal. It was our supposition that if Ag(II) was formed as an intermediate upon mixing with Selectfluor then line broadening would occur, whereas if Ag(III) was generated, then no line broadening would occur.[18,20a] When an equivalent of Selectfluor was added to a premixed equimolar combination of 2,9-dimethyl-1,10-phenanthroline and $AgNO_3$, significant line broadening was observed in the ^1H NMR spectrum. Similar line broadening occurred when terpyridine was employed as a donor ligand as well. These findings are consistent with the formation of a paramagnetic (d^9) Ag(II) complex (see Supporting Information).

In the seminal work of Li, a Ag(II) fluoride is proposed as the active fluorine atom source in the reaction as opposed to Selectfluor.[9d] To support this supposition, Li and co-workers

Scheme 6. Proposed Catalytic Cycle of Ag(I)-Catalyzed Fluorination Using $Na_2S_2O_8$ and Selectfluor



heated the combination of *tert*-butyl-2-ethyltetradecaneperoxoate and Selectfluor in a sealed tube to 120 °C for 2 h. When the reaction was run in acetone, a 22% yield of 3-fluoropentadecane was obtained, whereas when the reaction was run in 50:50 acetone/water, only a 4% of fluorinated product was obtained. On the basis of these findings, Li proposed that fluorine atom transfer from Selectfluor to alkyl radicals is unlikely to be involved in the Ag-catalyzed process. Selectfluor is reported to be unstable in water at high temperature, forming HF through reaction of the reagent and water.[27] To examine this, we heated Selectfluor in acetone-d_6/D_2O to 120 °C in a sealed tube for 2 h. After cooling to room temperature, a sample was removed and examined by ^1H NMR, showing that 80% of the reagent decomposed to the defluorinated chloromethyl derivative (see Supporting Information). This shows that the conditions of the experiment were likely not conducive to testing whether radicals can abstract a fluorine atom from Selectfluor. In addition, if a Ag(II)−F intermediate was formed during the reaction, it can be present only in a catalytic amount (at most). During its formation, radicals are also generated in a catalytic amount, so the likelihood of a small amount of radical being fluorinated by a small amount of Ag(II)−F in the presence of excess Selectfluor is unlikely. Finally, there is a large body of evidence showing that Selectfluor and similar electrophilic fluorinating reagents react with radicals to form C−F bonds.[10]

The data presented to this point in the discussion are consistent with the following: (1) it is unlikely that Ag(III) is an intermediate in the reaction, (2) Ag(II) does not act as an initiator in the reaction, (3) the radical cation of Selectfluor does not oxidize the carboxylic acid, (4) water is critical for solubilizing the reaction components and may ligate to Ag(I) under the reaction conditions, (5) the addition of persulfate significantly accelerates the rate of the reaction and only a half equivalent is required to achieve the highest rate of conversion to product, (6) the use of donor ligands in conjunction with Ag(I) and Selectfluor provided spectroscopic evidence that Ag(II), not Ag(III), is the intermediate in the reaction, and (7) an alkyl radical is abstracting fluorine from Selectfluor, not from a Ag(II)−F intermediate.

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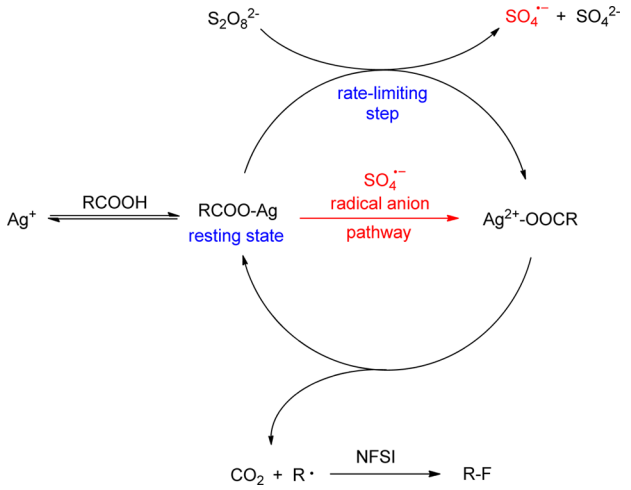
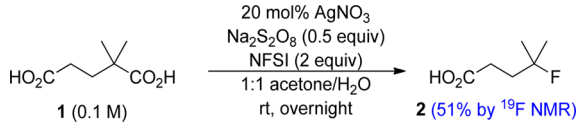
If Ag(II) is the active oxidant in this reaction in the presence of persulfate, then Selectfluor is no longer required to oxidize Ag(I) to Ag(II) but should still function as a fluorine atom source. Either the TEDA-BF_4 radical cation produced by this process or the sulfate radical anion can turn over (oxidize) Ag(I) to continue the catalytic cycle (Scheme 6). If this is the case, then the alkyl radical can abstract a fluorine from another N−F source. In the seminal report on this reaction, Li showed that upon replacement of Selectfluor with *N*-fluorobenzenesulfonimide (NFSI) no reaction occurred.[9d] This finding is likely due to the fact that NFSI it is not a strong enough oxidant to oxidize Ag(I) to Ag(II) (E° = −0.78 V, NFSI; E° = 1.98 V, Ag^{2+}/Ag^{+}).[8a,9d,17] However, in the presence of persulfate, which can readily oxidize Ag(I), the addition of NFSI can potentially result in alkyl fluoride formation through fluorine abstraction by the alkyl radical formed after decarboxylation.[10a,c] In addition, the resulting sulfate radical anion formed after the initial oxidation of Ag(I) by persulfate can carry out the subsequent oxidation of Ag(I) to Ag(II) after the rate-limiting step. A representation of this process is shown in Scheme 7. To test this supposition, **1** was

Scheme 7. Proposed Catalytic Cycle of Ag(I)-Catalyzed Fluorination Using NFSI and Persulfate



allowed to react with a catalytic amount of $AgNO_3$ in the presence of 0.5 equiv of $Na_2S_2O_8$ and 2 equiv of NFSI. After reacting overnight, fluorinated product **2** was observed in 51% yield by ^{19}F NMR (Scheme 8). When increasing persulfate from

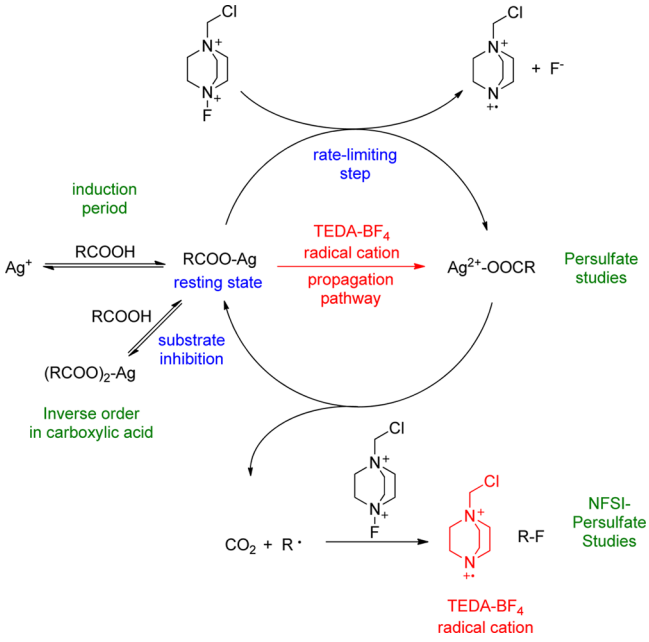
Scheme 8. Decarboxylative Fluorination Reaction with NFSI and $Na_2S_2O_8$



0.5 equiv to 1.1 equiv, the yield of **2** increased to 63%. On the basis of these findings, we propose that Ag(II) is the active oxidant in this decarboxylative fluorination reaction.

Proposed Mechanism. On the basis of the kinetic and spectroscopic studies described above, we propose a mechanism in which Ag(I) is oxidized to Ag(II) by Selectfluor to also generate TEDA-BF_4 radical cation in the rate-limiting step of the reaction (Scheme 9). There is also formation of Ag-carboxylate in the induction period, as well as substrate inhibition of silver

Scheme 9. Proposed Catalytic Cycle of Ag(I)-Catalyzed Fluorination Using Selectfluor



catalyst by carboxylic acid through formation of a Ag-(carboxylate)$_2$ intermediate.[15] Selectfluor oxidizes the Ag-carboxylate, and the resulting Ag(II) intermediate oxidizes the carboxylate ligand to produce an alkyl radical. Fluorine abstraction from Selectfluor yields product and the TEDA-BF_4 radical cation, which can oxidize Ag(I) to Ag(II).

CONCLUSIONS

The mechanistic studies described herein show the complex roles of $AgNO_3$ and Selectfluor in decarboxylative fluorination in acetone/water. In the turnover-limiting step of the reaction, Ag(I)-carboxylate is oxidized to Ag(II) by Selectfluor, also generating TEDA-BF_4 radical cation. In addition, substrate inhibition of the $AgNO_3$ catalyst by the carboxylic acid is proposed to occur as a result of Ag-(carboxylate)$_2$ formation. Catalyst stability enabled $AgNO_3$ loading to be decreased significantly. Kinetic studies utilizing $Na_2S_2O_8$ as an additive are consistent with Ag(II) as the intermediate oxidant responsible for decarboxylation that leads to a radical that abstracts fluorine from an electrophilic fluorinating source. This supposition is supported by the use of NFSI as a fluorine source in the presence of persulfate. While the addition of persulfate enabled us to uncover the active oxidant in this reaction, it was also shown to significantly accelerate the rate of decarboxylative fluorination, leading to a more efficient process. This suggests that this approach may be useful for ^{18}F labeling. It is our supposition that understanding the mechanism of this reaction will aid in the development of improved or novel fluorination methods that proceed through single-electron oxidation. We are currently examining the use of this approach in other fluorinations that proceed through single-electron oxidations to produce free radical intermediates. The results of these studies will be reported in due course.

EXPERIMENTAL SECTION

General Methods and Materials. Proton, carbon, and fluorine NMR were recorded on a 500 MHz instrument (^1H: 500 MHz; ^{13}C: 125 MHz; ^{19}F: 470 MHz). GC-MS analyses were done with a gas

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chromatograph with a mass selector detector. Chromatography was performed using an automated system. Reaction products were separated using prepacked silica gel columns with a gradient elution of ethyl acetate and hexanes. The pH of the reaction was monitored using a pH sensor and related software. $AgNO_3$, Selectfluor, **1**, **3a**, **5a**, BEt_3 (1 M in THF), sodium persulfate, and NFSI were purchased and used without further purification. Reagent grade acetone and deionized water were used.

Synthesis of 2,2-Dimethyl-3-phenylpropanoic acid (4a). To a round-bottomed flask equipped with stir bar were added diisopropylamine and 30 mL of dry THF under Ar. The solution was stirred and cooled to approximately 0 °C. A solution of 2.2 M *n*-BuLi in hexanes was added over 30 min via syringe pump and allowed to stir. Isobutyric acid was added over 10 min via syringe. The solution was allowed to warm to room temperature and stirred for 1.5 h. The stirred solution was cooled to approximately 15 °C. Benzyl chloride was added over 30 min via syringe pump, maintaining temperature below 5 °C. The resulting mixture was allowed to warm to ambient temperature and stirred under argon overnight. The reaction mixture was partitioned between 200 mL of diethyl either and 200 mL of water. The aqueous layer was acidified by addition of conc. HCl (36%, ca. 10 mL). The resulting mixture was extracted with 3 × 50 mL diethyl ether. The combined organic phase was dried with Na_2SO_4, filtered, and concentrated. The colorless oil was then solidified under high vacuum. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.29 (5H, m), 2.92 (2H, s), 1.22 (6H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 179.4, 132.5, 125.2, 123.0, 121.5, 40.8, 38.4, 19.6.

General Procedure for Synthesis of Fluorinated Products. The decarboxylative fluorination reaction was performed in open air without the need for degassed solvents. In a vial equipped with a magnetic stir bar were added carboxylic acid (1 mmol), Selectfluor (708 mg, 2 mmol), and $AgNO_3$ (34 mg, 0.2 mmol). Acetone (5 mL) and DI water (5 mL) were added, and the mixture was allowed to react between 2 and 4 h (depending on substrate). Reaction mixture was extracted thrice with dichloromethane. Organic layer was dried with magnesium sulfate and concentrated to obtain fluorinated product.

Due to the volatility of several of the fluorinated products, NMR spectra of products were obtained by running the reaction in acetone-d_6/D_2O. Upon completion of the reaction, $CDCl_3$ was added. The organic layer was extracted and analyzed by NMR.

General Procedure for Kinetic Studies. For kinetic studies, the concentration of reagents was kept under synthetically relevant conditions. To an NMR tube were combined carboxylic acid and Selectfluor. To the tube was added 0.5 mL of acetone, 0.5 mL of $AgNO_3$ solution (in water), and α,α,α-trifluoromethyltoluene (10 μL, internal standard). The tube was shaken and inserted into the NMR. Reactions were monitored *in situ* by ^{19}F NMR on a 470 MHz spectrometer. All reactions were performed at 23 °C. Peak integrations were analyzed using NMR processing software. Concentrations at each time point were determined with respect to an internal standard.

General Procedure for IR Studies. To a vial equipped with a magnetic stirrer were added **1** and $AgNO_3$. The reaction was allowed to react overnight, forming a small amount of precipitate. The precipitate was isolated, washed with water, and allowed to dry under vacuum. An FTIR spectrum was obtained.

General Procedure for Ag-Selectfluor NMR Studies. To one NMR tube was added Selectfluor, which was dissolved in 1:1 acetone-d_6/D_2O. In a second NMR tube were added $AgNO_3$ (0.1 mmol) and Selectfluor (0.1 mmol), which were then dissolved in 1:1 acetone-d_6/D_2O (0.25 mL each). The tubes were shaken and allowed to sit overnight. ^{1}H, ^{13}C, and ^{19}F NMR were obtained.

General Procedure for pH Studies. A pH probe was referenced with two buffer solutions of pH 4 and 7. To a vial were added 2,2-dimethylgluatric acid (160.17 mg, 1 mmol), $AgNO_3$ (34 mg, 0.2 mmol), and Selectfluor (708 mg, 2 mmol). The pH probe was inserted, and acetone (5 mL) and H_2O (5 mL) were added. The reaction vial was then sealed. The pH of the reaction was monitored over the course of 2 h. The pH of acetone/water without any additives was also monitored for 2 h. No change in pH was observed.

General Procedure for Reaction with BEt_3. To an NMR tube were added carboxylic acid (0.1 mmol), NFSI (63.1 mg, 0.2 mmol), and BEt_3 (0.02 mmol, 1 M soln in THF). Acetone (0.5 mL) and DI water (0.5 mL) were then added. The mixture was allowed to react overnight. Product yield was determined by ^{19}F NMR using α,α,α-trifluoromethyltoluene as an internal standard.

General Procedure for Fluorination Reaction Using Sodium Persulfate. To a vial equipped with a magnetic stir bar were added carboxylic acid (1 mmol), Selectfluor (708 mg, 2 mmol), $Na_2S_2O_8$ (119 mg, 0.05 mmol), and $AgNO_3$ (34 mg, 0.2 mmol). Acetone (5 mL) and DI water (5 mL) were added. The mixture was allowed to react for 15 min. Reaction mixture was extracted thrice with dichloromethane. Organic layer was dried with magnesium sulfate and concentrated to obtain fluorinated product.

General Procedure for Fluorination Reaction Using NFSI and Sodium Persulfate. To an NMR tube were added carboxylic acid (0.1 mmol), NFSI (63.1 mg, 0.2 mmol), $Na_2S_2O_8$ (11.9 mg, 0.05 mmol), and $AgNO_3$ (3.4 mg, 0.02 mmol). Acetone (0.5 mL) and DI water (0.5 mL) were added, and the mixture was allowed to react overnight. Product yield was determined by ^{19}F NMR using α,α,α-trifluoromethyltoluene as an internal standard.

General Procedure for Selectfluor Heating/Decomposition Studies. A proton NMR spectrum of Selectfluor from the commercially available bottle was obtained in $CDCl_3$. Separately, Selectfluor was subject to heating at 120 °C in acetone-d_6/D_2O for 2 h in a sealed tube under the conditions describe by Li.[9d] After 2 h, an aliquot was taken, and a ^{1}H NMR spectrum was obtained.

Spectroscopic Data for 2 (4-Fluoro-4-methylpentanoic acid). ^{1}H NMR (500 MHz, $CDCl_3$/acetone-d_6) δ (ppm): 2.34 (2H, m), 1.87 (2H, m), 1.26 (6H, d); ^{13}C NMR (125 MHz, $CDCl_3$/acetone-d_6) δ (ppm): 174.7, 94.5 (d), 36.0 (d), 28.5, 21.4 (d); ^{19}F NMR (470 MHz, $CDCl_3$/acetone-d_6): −135.4 (m).

Spectroscopic Data for 3b (2-Fluoro-2-methylbutane). ^{1}H NMR (500 MHz, $CDCl_3$/acetone-d_6) δ (ppm): 1.55 (2H, m), 1.23 (6H, dd), 0.86 (3H, t); ^{13}C NMR (125 MHz, $CDCl_3$/acetone-d_6) δ (ppm): 34.0, 25.9, 8.1; ^{19}F NMR (470 MHz, $CDCl_3$/acetone-d_6): −134.3 (m).

Spectroscopic Data for 4b (2-Fluoro-2-methylpropyl)-benzene. ^{1}H NMR (500 MHz, $CDCl_3$/acetone-d_6) δ (ppm): 7.19 (5H, m), 2.82 (2H, d); 1.23 (6H, d); ^{13}C NMR (125 MHz, $CDCl_3$/acetone-d_6) δ (ppm): 137.1, 130.4, 128.1, 126.5, 95.6, 94.3, 47.5, 47.4, 26.6, 26.4; ^{19}F NMR (470 MHz, $CDCl_3$/acetone-d_6): −138.1 (m).

Spectroscopic Data for 5b (2-Fluoropropane). ^{1}H NMR (500 MHz, $CDCl_3$/acetone-d_6) δ (ppm): 4.73 (1H, ds), 1.24 (6H, dd); ^{13}C NMR (125 MHz, $CDCl_3$/acetone-d_6) δ (ppm): 88.0, 22.7; ^{19}F NMR (470 MHz, $CDCl_3$/acetone-d_6): −162.9 (m).

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and kinetic and spectral data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00826.

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Notes

The authors declare no competing financial interest.

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