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On the Mechanism of Silver-Catalyzed Decarboxylative Fluorination

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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. While 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 the 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 support the generation of a Ag(II) intermediate; data enabling 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 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 aromatic⁸ 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,8g-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, 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-BF₄, 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 material 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.

The Journal of Organic Chemistry

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 co-solvent, (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 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 equivalents of Selectfluor in 1:1 acetone/water media (Scheme 1). After examining a number of conditions, we found that increasing the concentration of **1** from 0.05 M to 0.1 M enabled the reaction to proceed to completion in 2 hours. Using these synthetic reaction conditions, kinetic studies were performed on the decarboxylative fluorination reaction of **1**.

Scheme 1. Ag(I)-catalyzed fluorination of aliphatic carboxylic acid using Selectfluor



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 ¹⁹F NMR and an internal standard. (Figure 1). A significant amount of initiation was observed (approximately 600 seconds, Figure 1) in the reaction, a feature that will be discussed *vide infra*.

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 [AgNO₃] 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 M to 0.15 M. The [AgNO₃] in Run 2 was the same employed in Run 1. If [AgNO₃] remained constant during the course of the reaction, the rates of Runs 1 and 2 would be the same. If [AgNO₃] decreased as the reaction proceeded through catalyst deactivation, 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 [AgNO₃] over the course of the reaction (Figure 2).¹² Catalyst stability during the course of the reaction suggested that AgNO₃ loading could be lowered significantly. We were able to lower $AgNO_3$ loading from 20 mol% to

5 mol% to generate **2** in 90% yield by increasing concentration the concentration of **1** from 0.1 M to 0.2 M and allowing the reaction to proceed overnight.





Run	[1] (M)	$[AgNO_3](M)$	[Selectfluor] (M)	Excess [Selectfluor] (M
- 100%	0.1	0.02	0.2	0.1

0.15

0.1

Table 1. Reaction	conditions f	for catalyst	stability studie	S
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2 - 50%

0.05

0.02



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

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 mol% to 40 mol%, a first-order rate dependence was found for AgNO₃. 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 M 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 was equal to the rate (see Supporting Information).^{12a} We observed an rate order of -1.5 for **1**, suggesting that the substrate was inhibiting reaction progress.

Interaction of Carboxylic Acid with AgNO3. The formation of silver-carboxylates is well-established in the literature.¹³ To investigate whether the inverse order found in carboxylic

The Journal of Organic Chemistry

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-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, are consistent with the interaction of substrate with Ag(I).

Kinetic studies were also performed on three other substrates to confirm 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 nitrate and Selectfluor were first order and carboxylic acid was found to show inverse first order dependency. The inverse orders observed for these mono-carboxylic 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.



Scheme 2. Ag(I)-catalyzed fluorination of additional aliphatic carboxylic acids^a

Interaction of Selectfluor with AgNO₃. 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 ¹H and ¹³C 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 ¹⁹F 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 ¹⁹F 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 (Ag²⁺, d⁹). 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 turnoverlimiting step of the catalytic cycle, activation parameters were obtained for the reaction of **1** under synthetic conditions at temperatures ranging between 23-40 °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 (ΔH^{\ddagger}) and the large negative entropy of activation (ΔS^{\ddagger}) are indicative of a highly ordered transition state.

Role of Water. In the original work of Li and coworkers, 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 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. 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.

Ratio of water ^a	% Yield ^b		
100% acetone	9		
100% acetone + 0.1 mmol H ₂ O	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		

Table 2. Fluorination of 2 with increasing amounts of water

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

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 ¹H 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 CO₂ 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 seconds 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, ¹⁹F 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 AgNO₃ 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 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 Selectfluor, and (B) which of those intermediate species oxidize the carboxylic acid to generate an alkyl radical after the rate-limiting step? Based on the data obtained to this point and previous literature reports, the mechanism likely proceeds through one of three pathways: (1) the twoelectron oxidation of Ag(I) to Ag(III) by Selectfluor, where Ag(III) oxidizes a carboxylic acid to produce an alkyl radical.^{9d,9h,16} (2) single electron oxidation of Ag(I) to Ag(II) by Selectfluor to also generate TEDA-BF₄ 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-BF₄ 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 the Li 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} Though Ag(III) complexes are capable of oxidizing carboxylic acids ($E^{o} = 1.8 \text{ V}, \text{ Ag}^{3+}/\text{Ag}^{2+}$),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-BF₄, 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-BF₄ radical cation as a reaction intermediate.^{9g,24} In a recent paper describing mechanistic studies of Cu(I)-catalyzed alkyl fluorination employing Selectfluor, the Leckta group revealed the role of Cu(I) as an initiator, and TEDA-BF₄ 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-BF₄ radical cation could function as an oxidant in this reaction, we employed triethylborane as an initiator to generate TEDA-BF₄ radical cation in the absence of AgNO₃ 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 ¹⁹F NMR after allowing the reaction to proceed overnight (Scheme 4). This result suggests that TEDA-BF₄ radical cation is likely not functioning as the oxidant of carboxylic acid in this reaction, and that the presence of AgNO₃ is critical for the success of the decarboxylative fluorination.

Scheme 4. Decarboxylative fluorination reaction with triethylborane

 BEt₃ (20 mol%)

 CO₂H
 Selectfluor (2 equiv)

 1:1 acetone/H₂O
 rt, overnight no product observed by ¹⁹F NMR

The Journal of Organic Chemistry

Ag(II) intermediate. Since TEDA-BF₄ 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 longestablished history in the literature,^{14,25} in which Ag(II) is generated upon oxidation of Ag(I).¹⁴ Work performed by Kochi and coworkers 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 AgNO₃ and persulfate provides a rapid means for producing Ag(II), we sought to probe the impact of persulfate on the decarboxylative fluorination. Addition of Na₂S₂O₈ resulted in acceleration of the reaction rate. The addition of 0.1-1.0 equivalents 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 every case, the exponential fit was greater than The reaction proceeded rapidly in the presence of $Na_2S_2O_8$ and saturation was $(R^2 0.99).$ observed at concentrations higher than 0.5 equivalents (Figure 3). To examine this further, several other reactions were carried out by adding 0.5 equivalents of Na₂S₂O₈.



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

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When 0.5 equivalents of $Na_2S_2O_8$ was combined with 2 equivalents of Selectfluor and 20 mol% AgNO₃, reaction time decreased from 2 hours to 15 minutes 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, suggests that this approach may be useful for ¹⁸F labeling.



Scheme 5. Decarboxylative fluorination reaction with Na₂S₂O₈ as additive

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 AgNO₃ catalyst during the course of the reaction. In addition, kinetic studies showed that AgNO₃ and Na₂S₂O₈ were consistent with a first order dependence, and **3a** and Selectfluor were zero order. 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 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-BF₄ radical cation, is the oxidant responsible for decarboxylation.

Scheme 6. Proposed catalytic cycle of Ag(I)-catalyzed fluorination using Na₂S₂O₈ and



Selectfluor

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, line broadening would occur, whereas if Ag(III)

was generated, 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 AgNO₃, 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 (d⁹) 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 coworkers heated the combination of tert-butyl-2-ethyltetradecaneperoxoate and Selectfluor in a sealed tube to 120 °C for 2 hours. 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. Based on 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 heated tube for 2 hrs. 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 only be present 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

The Journal of Organic Chemistry

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, 7) An alkyl radical is abstracting fluorine from Selectfluor, not from a Ag(II)-F intermediate.

If Ag(II) is the active oxidant in this reaction in the presence of persulfate, Selectfluor is no longer required to oxidize Ag(I) to Ag(II), but should still function as a fluorine atom source. Either the TEDA-BF₄ 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, 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) ($E^{o} = -0.78$ V, NFSI; $E^{o} = 1.98$ V, Ag²⁺/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 allowed to react with a catalytic amount of $AgNO_3$ in the presence of 0.5 equiv Na₂S₂O₈ and 2 equiv NFSI. After

Scheme 7. Proposed catalytic cycle of Ag(I)-catalyzed fluorination using NFSI and





reacting overnight, fluorinated product **2** was observed in 51% yield by ¹⁹F NMR (Scheme 8). When increasing persulfate from 0.5 equiv to 1.1 equiv, 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.





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Proposed Mechanism. Based on 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-BF₄ 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 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-BF₄ radical cation which can oxidize Ag(I) to Ag(II).

Scheme 9. Proposed catalytic cycle of Ag(I)-catalyzed fluorination using Selectfluor



Conclusions

The mechanistic studies described herein show the complex roles of AgNO₃ 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-BF₄ radical cation. In addition, substrate inhibition of the AgNO₃ catalyst by the carboxylic acid is proposed to occur as a result of Ag(carboxylate)₂ formation. Catalyst stability enabled AgNO₃ loading to be decreased significantly. Kinetic studies utilizing Na₂S₂O₈ as an additive are consistent with Ag(II) as the intermediate oxidant responsible for decarboxylation leading 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 ¹⁸F 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, ¹³C: 125 MHz, ¹⁹F: 470 MHz). GC-MS analyses were done with a gas chromatograph with a mass selector detector. Chromatography was performed using an automated system. Reaction products were separated using pre-packed silica gel columns with a

Page 21 of 30

The Journal of Organic Chemistry

gradient elution of ethyl acetate and hexanes. The pH of the reaction was monitored using a pH sensor and related software. AgNO₃, Selectfluor, **1**, **3a**, **5a**, BEt₃ (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 bottom flask equipped with stir bar was added diisopropylamine and 30 mL 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 diethyl either and 200 mL water. The aqueous layer was acidified by addition of conc. HCl (36%, ca. 10 mL). The resulting mixture was extracted with 3 x 50 mL diethyl ether. The combined organic phase was dried with Na₂SO₄, filtered and concentrated. The colorless oil was then solidified under high vac. ¹H NMR (500 MHz, CDCl₃) δ (ppm): 7.29 (5H, m), 2.92 (2H, s), 1.22 (6H, s); ¹³C NMR (125 MHz, CDCl₃) 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 was added carboxylic acid (1 mmol), Selectfluor (708 mg, 2 mmol), and AgNO₃ (34 mg, 0.2 mmol). Acetone (5 mL) and DI water (5 mL) were added, and the mixture was allowed to react between 2-4 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 $acetoned_6/D_2O$. Upon completion of the reaction, CDCl₃ 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 at synthetically relevant conditions. To an NMR tube, carboxylic acid and Selectfluor were combined. To the tube was added 0.5 mL acetone and 0.5 mL of AgNO₃ solution (in water), and α,α,α -trifluoromethyltoluene (10µL, internal standard). The tube was shaken and inserted into the NMR. Reactions were monitored *in situ* by ¹⁹F 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 AgNO₃. 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 was added AgNO₃ (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. ¹H, ¹³C, and ¹⁹F 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 was added 2,2-dimethylgluatric acid (160.17mg, 1 mmol), AgNO₃ (34 mg,

The Journal of Organic Chemistry

0.2mmol), 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 hours. The pH of acetone/water without any additives was also monitored for 2 hours. No change in pH was observed.

General Procedure for Reaction with BEt₃. To an NMR tube was added carboxylic acid (0.1 mmol), NFSI (63.1 mg, 0.2 mmol), and BEt₃ (0.02 mmol, 1M 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 ¹⁹F 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 was added carboxylic acid (1 mmol), Selectfluor (708 mg, 2 mmol), Na₂S₂O₈ (119 mg, 0.05 mmol), and AgNO₃ (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 was added carboxylic acid (0.1 mmol), NFSI (63.1 mg, 0.2 mmol), Na₂S₂O₈ (11.9 mg, 0.05 mmol), and AgNO₃ (3.4 mg, 0.02 mmol). Acetone (0.5 mL) and DI water (0.5 mL) was added, and the mixture was allowed to react overnight. Product yield was determined by ¹⁹F 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 CDCl₃. Separately, Selectfluor was subject to heating to 120 $^{\circ}$ C in acetone-d₆/D₂O for 2 h in a sealed tube under the

conditions describe by Li.^{9d} After 2 hours, an aliquot was taken and a ¹H NMR spectrum obtained.

Spectroscopic data for 2 (4-fluoro-4-methylpentanoic acid): ¹H NMR (500 MHz, CDCl₃/acetone-d₆) δ (ppm): 2.34 (2H, m), 1.87 (2H, m), 1.26 (6H, d); ¹³C NMR (125 MHz, CDCl₃/acetone-d₆) δ (ppm): 174.7, 94.5 (d), 36.0 (d), 28.5, 21.4 (d) ; ¹⁹F NMR (470 MHz, CDCl₃/acetone-d₆): -135.4 (m).

Spectroscopic data for 3b (2-fluoro-2-methylbutane): ¹H NMR (500 MHz, CDCl₃/acetone-d₆) δ (ppm): 1.55 (2H, m), 1.23 (6H, dd), 0.86 (3H, t); ¹³C NMR (125 MHz, CDCl₃/acetone-d₆) δ (ppm): 34.0, 25.9, 8.1; ¹⁹F NMR (470 MHz, CDCl₃/acetone-d₆): -134.3 (m).

Spectroscopic data for 4b (2-fluoro-2-methylpropyl)-benzene: ¹H NMR (500 MHz, CDCl₃/acetone-d₆) δ (ppm): 7.19 (5H, m), 2.82 (2H, d); 1.23 (6H, d); ¹³C NMR (125 MHz, CDCl₃/acetone-d₆) δ (ppm): 137.1, 130.4, 128.1, 126.5, 95.6, 94.3, 47.5, 47.4, 26.6, 26.4; ¹⁹F NMR (470 MHz, CDCl₃/acetone-d₆): -138.1 (m).

Spectroscopic data for 5b (2-fluoropropane): ¹H NMR (500 MHz, CDCl₃/acetone-d₆) δ (ppm): 4.73 (1H, ds), 1.24 (6H, dd); ¹³C NMR (125 MHz, CDCl₃/acetone-d₆) δ (ppm): 88.0, 22.7; ¹⁹F NMR (470 MHz, CDCl₃/acetone-d₆): -162.9 (m).

Associated Content

Supporting Information

Experimental procedures, kinetic and spectral data. This material is available free of charge via the Internet at <u>http://pubs.acs.org</u>.

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Notes

The authors declare no competing financial interest.

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The Journal of Organic Chemistry

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