JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

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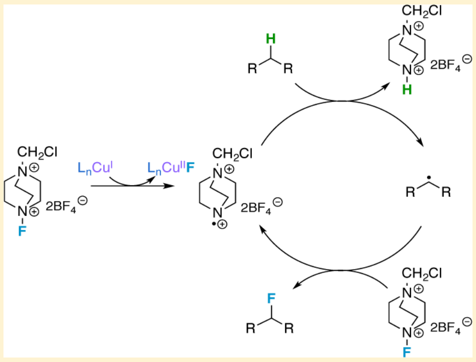
Direct, Catalytic Monofluorination of sp^3 C−H Bonds: A Radical-Based Mechanism with Ionic Selectivity

Cody Ross Pitts,[†] Steven Bloom,[†] Ryan Woltornist,[†] Dillon Jay Auvenshine,[†] Lev R. Ryzhkov,[‡] Maxime A. Siegler,[†] and Thomas Lectka*,[†]

[†]Department of Chemistry, Johns Hopkins University, 3400 North Charles Street, Baltimore, Maryland 21218, United States
[‡]Department of Chemistry, Towson University, 8000 York Road, Towson, Maryland 21252, United States

Ⓢ *Supporting Information*

ABSTRACT: Recently, our group unveiled a system in which an unusual interplay between copper(I) and Selectfluor effects mild, catalytic sp^3 C−H fluorination. Herein, we report a detailed reaction mechanism based on exhaustive EPR, ^{19}F NMR, UV−vis, electrochemical, kinetic, synthetic, and computational studies that, to our surprise, was revealed to be a radical chain mechanism in which copper acts as an initiator. Furthermore, we offer an explanation for the notable but curious preference for monofluorination by ascribing an ionic character to the transition state.



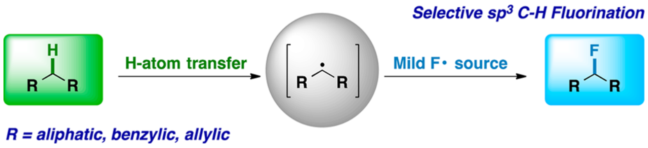
INTRODUCTION

Selective functionalization of sp^3 C−H bonds represents an area of invaluable and economical chemistry. The direct formations of alcohols, alkenes, alkyl halides, and other functional groups from inactivated C−H bonds are impressive, seemingly effortless reactions accomplished by enzymes that are often challenging to effect in a laboratory setting. However, selective *fluorination* has proven an arduous undertaking for both Nature and the synthetic chemist alike. Biologically, very few fluorinase enzymes are known, and none of them operate on the basis of direct C−H functionalization.[1] Synthetically, a conceivable radical fluorination method using hazardous and difficult-to-use F$_2$, similar to the well-established bromination and chlorination reactions, is actually highly exothermic, which causes great selectivity and safety concerns.[2] For organofluorine chemists, this issue and other existing challenges call for a more innovative approach to C−H fluorination (Scheme 1).

Arguably one of the most significant developments in the field of organofluorine chemistry was the advent of the N−F reagents (containing a nitrogen−fluorine bond) intended as mild sources of electrophilic fluorine in the late 1980s.[3] Considering that these reagents were solid, stable, and effective compounds, they quickly superseded the use of the high-energy electrophilic fluorinating reagents such as fluorine gas, xenon difluoride, perchloryl fluoride, and hypofluorites, making fluorination reactions significantly more accessible to the synthetic chemist.[4] Among the top ranks of the N−F reagents are *N*-fluorobenzenesulfonimide (NFSI), *N*-fluoropyridinium salts (NFPy), and 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor), vide infra (Figure 1). These unique and versatile compounds have proven their worth as reagents for fluorofunctionalization as mediators and catalysts, but are also ideal candidates for mechanistic studies.[5]

Recent findings suggest that some of these so-called “electrophilic” N−F reagents can also act as F atom transfer

Scheme 1



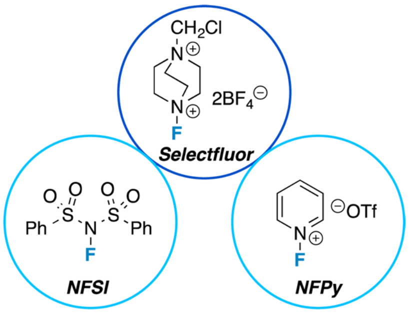


Figure 1. Common “N−F” reagents.

Received: May 22, 2014

reagents. Sammis et al. have reported the ability of NFSI to react with alkyl radicals,[6] Baran et al. have suggested the ability of Selectfluor to participate in single-electron transfer (SET) chemistry and the homolytic cleavage of C−H bonds,[7] and within the last year both our laboratory and the Groves laboratory have independently published methods on metal-catalyzed sp^3 C−H monofluorination. Where the Groves system utilizes silver(I) fluoride (a nucleophilic fluorine source) and iodosobenzene to generate a manganese(IV) fluoride porphyrin catalyst in situ instead of an aforementioned N−F reagent,[8] our system, as will be shown in this full paper, relies fundamentally on radical-based chemistry between Selectfluor and a copper(I) promoter to effect both H atom abstraction and subsequent installation of fluorine.[9]

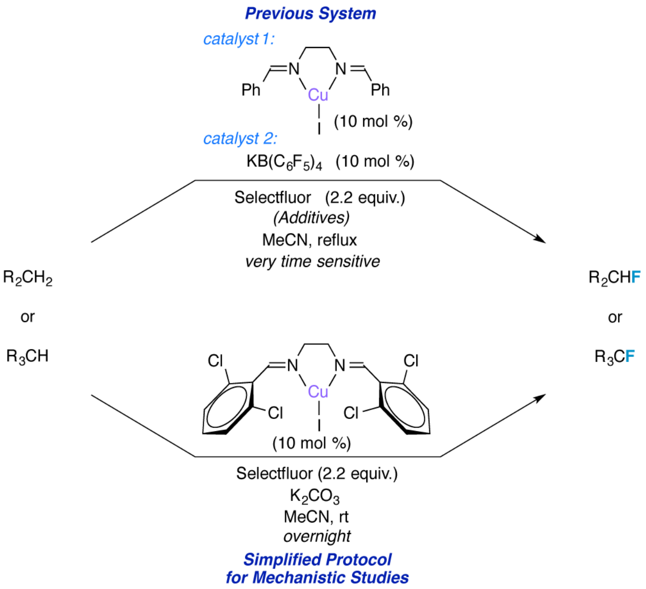
Groves's and our work were among the first direct, catalytic methodologies for the monofluorination of aliphatic substrates. These discoveries prompted further investigations in our laboratory, viz., (1) simplification of the conditions for our originally fairly complex system, (2) exploration of the chemistry of other redox-active transition metals with Selectfluor,[10] and especially (3) in-depth mechanistic studies of the system(s) we devised. In this article, we propose a detailed mechanism for the copper-initiated aliphatic fluorination method that is consistent with exhaustive EPR, ^{19}F NMR, UV−vis, electrochemical, kinetic, synthetic, and computational studies. Furthermore, we offer a possible explanation for the notable, useful, but curious preference for monofluorination.

The article is structured to present a logical narrative whereby the mechanistic studies were conducted. With this regard, the article is organized respectively as to (1) establish the simplified protocol used for mechanistic analysis, (2) discuss the experiments used to determine the role of copper as an initiator, (3) examine the H atom abstraction/fluorination steps of the mechanism (illuminating the involvement of radical intermediates), (4) illustrate our conclusions drawn from kinetic analyses, (5) propose a reasonable mechanism in accord with all experimental observations, and (6) offer an explanation for the observed selectivity of our reaction as a manifestation of the "polar effect" by ascribing an ionic character to the H atom abstraction transition state and, finally, subjecting the system to computational analysis to confirm experimental results.

Simplified Protocol. Our original discovery combined Selectfluor and transition metal catalysts (especially copper(I) based complexes) in effecting direct aliphatic, benzylic, and, in special cases, allylic monofluorination.[9,10] However, the copper system that focused on aliphatic fluorination, albeit intriguing, is admittedly less practical for large-scale applications as it involves the use of several additives. Thus, our immediate goal was to establish a simplified protocol that is more accessible, cost-effective, scalable, less time-sensitive, and easier to subject to mechanistic studies. A logical approach was to strip the system back down to the minimum number of necessary components (i.e., Selectfluor, a copper salt, acetonitrile) and address possible problems more directly.

Previously, we observed that our newly fluorinated substrates were prone to ionization in situ over time, which led to a decrease in product yields if the reactions were not quenched at the appropriate time intervals. Perhaps this is attributable to a gradual accumulation of hydrogen fluoride (HF) as a byproduct of the reaction, which was observed by ^{19}F NMR under our published conditions. To prevent the buildup of HF, we screened a variety of bases and noted that whereas amines tend to impede the reaction altogether, 0.1 equiv of potassium carbonate is often enough to effect the reaction and eliminate any traces of HF by ^{19}F NMR for 16−24 h. This small modification allows us to let a variety of substrates stir at room temperature for longer, generalized periods of time without having vigilantly to monitor and optimize each one individually. To our satisfaction, we also obtained comparable conversions to monofluorinated products in the presence of potassium carbonate. However, at this time we did not conclude anything about the true role of the potassium carbonate in the system.

Scheme 2



Hoping to circumvent the dependency on potassium tetrakis(pentafluorophenyl)borate, *N*-hydroxyphthalimide, and potassium iodide for higher yields, we decided to focus on modifying the ligand. In the original system, we had the most success with *N*,*N*′-bis(benzylidene)ethane-1,2-diamine. Making minor modifications to the ligand scaffold, we quickly found a substantial increase in percent conversions at room temperature by using *N*,*N*′-bis(2,6-dichlorobenzylidene)ethane-1,2-diamine instead.[11] At this juncture in our laboratory, we have established that a standard reaction using 2.2 equiv of Selectfluor, 0.1 equiv of cuprous iodide, 0.1 equiv of the aforementioned ligand, and 0.1−1.0 equiv of potassium carbonate in MeCN under N_2 at room temperature overnight was a suitable, generalized protocol for aliphatic and benzylic monofluorination (Scheme 2). Under these conditions, the reaction has also proven amenable to gram-scale synthesis of monofluorinated products (e.g., 1-fluorocyclododecane was obtained in 50% yield after 8 h). Using this simplified protocol, we sought to address the most fundamental concerns surrounding the reaction mechanism, i.e., the role of copper, how the fluorine atom is installed, how the reaction kinetics behave, and the preference for monofluorination.

Loss of Fluoride from Copper(I)−Selectfluor Interaction. Intuitively, copper can be either a species actively involved in the catalytic cycle or an initiator to the reaction. With these potential roles in mind, a large array of experiments were designed to probe the behavior of copper over the course of the reaction.

Considering that the minimum necessary components to effect sp^3 C−H fluorination are simply Selectfluor and copper(I), we first studied their interaction by NMR. A ^{19}F

NMR spectrum of Selectfluor in CD_3CN displays an N−F signal at +47.1 ppm and a BF_4 signal at −152.1 ppm, relative to 3-chlorobenzotrifluoride.[12] A spectrum of a 1:1 mixture of Selectfluor and cuprous iodide in CD_3CN, taken after 45 min of stirring, displays a BF_4 signal at −152.4 ppm and the standard peak. No N−F fluorine signal is observed at +47.1 ppm, nor are any additional signals from +400 ppm to −300 ppm present.

Preliminary EPR experiments reveal the formation of a copper(II) species, but no Cu−F coupling is observed at room temperature, as well. So where did the fluorine atom go? The most logical scenario is the formation of a copper fluoride species that is undetectable by ^{19}F NMR due to extreme signal broadening induced by the paramagnetic copper(II) center (unlikely), formation of a copper(II) bifluoride exhibiting fluxional behavior in solution,[13] or the fact that, after rapid solvolysis, it exists as a solvent separated ion pair.[14] Attempts were made to "freeze out" a copper(II) bifluoride signal at −10 °C and −40 °C, but no evidence for this type of species or any other signal was seen. Notably, a simple ^{19}F NMR of cupric fluoride in MeCN supports the notion of solvent separation: no fluorine signal is observed.

To rule out the possibility of a copper fluoride formed in situ being the key player for H atom abstraction and subsequent installation of fluorine, several control experiments were run using preformed copper fluorides (cupric fluoride and $(PPh_3)_3CuF \cdot 2MeOH$)[15] in the absence of Selectfluor.[16] Although these experiments provide no evidence for/against a copper fluoride as the source of fluorine during the fluorination step of the mechanism,[17] they do help confirm that an interaction between copper and Selectfluor is necessary to generate the species responsible for effecting H atom abstraction.[18]

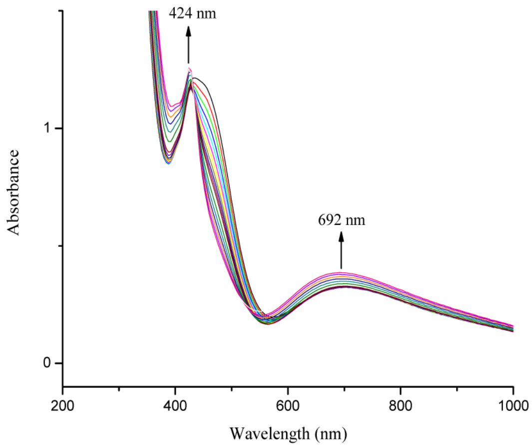


Figure 2. UV−vis spectra of CuI, ligand, and Selectfluor.

UV−Vis and EPR Analyses Indicate Copper(II) Species.

This copper(I)−Selectfluor interplay may best be elucidated by direct observation of copper. Formation of a copper(II) species was recognized early on in the investigation by UV−vis and EPR analyses, and was subsequently studied intently.

UV−Vis Spectroscopy. UV−vis spectroscopy was used to monitor changes in the copper species early in the reaction (ca. $t = 5$ min to $t = 15$ min displayed in Figure 2). Figure 2 displays visible bands at 426, 456, and 692 nm upon the addition of cuprous iodide and our bis(imine) ligand to Selectfluor in MeCN under N_2. The broad band at 692 nm, a new copper(II) absorbance, grows in concomitantly with the sharp absorbance at 426 nm, which disappears in the absence of ligand and is conceivably a charge-transfer band from a copper−ligand interaction. The decreasing absorbance at 456 nm was determined to result from an interaction between iodide and Selectfluor: this absorbance was duplicated when taking a UV−vis spectrum upon mixing Selectfluor with tetrabutylammonium iodide (note that the interaction between iodide and Selectfluor alone will not effect the fluorination reaction; copper is necessary). Interestingly, when the reaction was run in a cuvette under standard conditions (in the presence of substrate), the spectrum obtained was virtually identical. Furthermore, a UV−vis spectrum taken after several hours still shows a strong copper(II) absorbance.

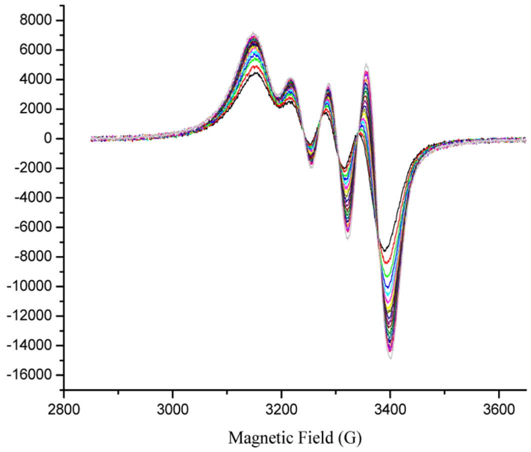


Figure 3. Flat-cell liquid phase spectra of copper(II) over time.

X-Band CW EPR Flat-Cell Experiments. The formation of a paramagnetic copper(II) species presents an opportunity for analysis via EPR spectroscopy. For liquid phase EPR experiments, a flat cell was used in place of a cylindrical sample configuration in order to minimize the absorption of microwaves by the solvent.[19] The copper(II) spectra of reaction conditions with and without a substrate present consist of four hyperfine lines (from copper; $I = 3/2$) of unequal intensities that grow in and *persist* over time. Subsequent observation of a reaction in the absence of a substrate over time revealed gradual shifts in intensities and resonances (Figure 3). This could indicate a change in geometry or ligand environment of the original copper(II) species formed. For better clarification, we turned to solid-state EPR.

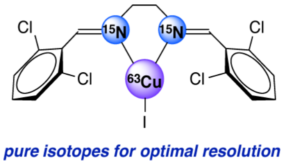


Figure 4. Isotopically enriched ligand for solid state EPR.

Solid-State X-Band CW EPR. The added complexity of solid-state EPR spectra due to anisotropic effects can illuminate details about the geometry of a complex, symmetry, and the nature of any neighboring atoms.[20] In an attempt to achieve optimal resolution, spectra were collected at 8 K using isotopically enriched ^{63}CuI and ^{15}N-labeled ligand (Figure 4).[21] To our knowledge, this is the best approach to determine

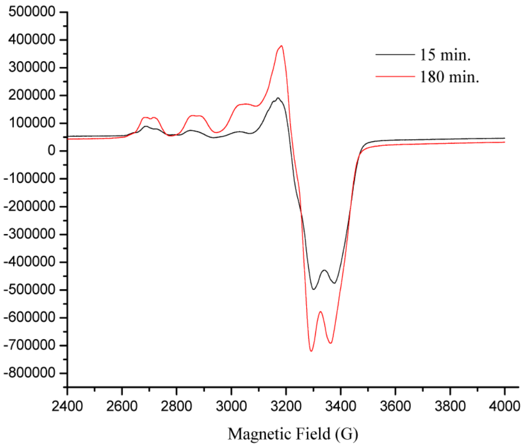


Figure 5. Solid-state spectra of copper(II) in the absence of a substrate at 8 K.

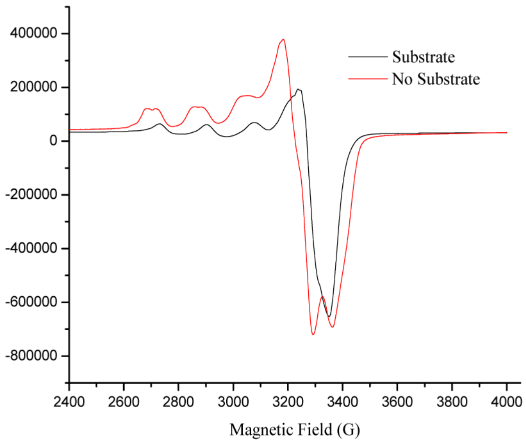
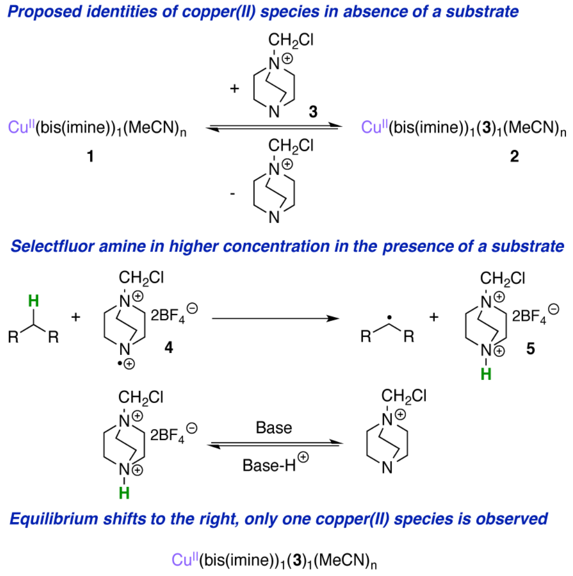


Figure 6. Solid-state spectra of copper(II) after 180 min with (C1) and without (C2) substrate present at 8 K.

Table 1. EPR Parameters for Complexes in Figures 5 and 6

complex	$g_{\parallel}$	$g_{\perp}$	$A_{\parallel}$ (G)	$A_{\perp}$ (G)	g_{iso}	A_{iso} (G)
C1	2.27	2.04	170	12.5	2.12	65
C2a	2.30	2.12	177	16.5	2.18	70
C2b	2.28	2.07	167	14.0	2.14	65

Scheme 3



definitively whether a direct Cu−F interaction is characteristic of the copper species at any point in the reaction.

Solid-state spectra of the reaction in the absence of a substrate display an interesting feature. An equilibrium of two copper(II) species is well resolved in a spectrum taken after 3 h (Figure 5). The signatures indicate that both species are monomeric, solely surrounded by nitrogen-containing ligands, and tetragonal in coordination geometry ($g_{\parallel} > g_{\perp} > g_e$; see Table 1).[22] Although it is tempting to mistake the separation of the hyperfine resonances for each species as "splitting", perhaps due to a Cu−F interaction, none is observed: these are two separate copper complexes that both lack coupling to fluorine. Regarding the implausibility of a Cu−F interaction, Weltner et al. reported a hyperfine coupling constant of $A(^{19}F) = 115$ G derived from EPR spectra of cupric fluoride at 4 K in argon and neon matrices, which is significantly higher than any supposed splitting observed in these complexes, but may not be the most appropriate comparison.[23] In another scenario, by exposing ceruloplasmin to 15 equiv of fluoride, Gray et al. reported $A(^{19}F) = 40$ G for a cupric fluoride,[24] which seems on par with the separation between our observed hyperfine resonances. Yet, the additional g_3 resonance that appears in our spectra shatters the appeal of perceiving this as Cu−F coupling and solidifies the notion of two separate copper(II) complexes.[25]

In the presence of substrate (under standard reaction conditions), something even more interesting is observed: the presence of only one of the two copper(II) species (Figure 6). This is likely an issue of dynamic ligand activity between the putative complexes **1** and **2** (Scheme 3). A higher concentration of an additional amine ligand **3** (Selectfluor minus F^+) is formed under reaction conditions, which shifts the equilibrium preferentially toward only one of the copper(II) species.

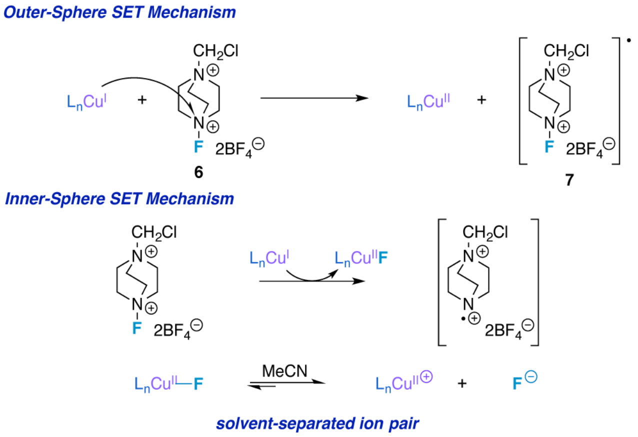
In the catalytic cycle we ultimately propose, radical dication **4** abstracts a hydrogen atom from an alkane to form ammonium salt **5**, which would easily be deprotonated in the presence of potassium carbonate (Scheme 3). The corresponding amine **3** would be a suitable ligand for copper(II). If an alkane substrate is not present, the formation of **5** is significantly slower, the concentration of the amine significantly lower, and thus, there is a mixture of amine-ligated copper(II) **2** and non-amine-ligated copper(II) **1**. This is consistent with the EPR parameters for the complexes (Table 1), which indicate that both copper species are surrounded solely by nitrogen-containing ligands. Under any circumstance, there is no observed Cu−F interaction, characteristic of a copper(II) bifluoride or otherwise. It is crucial to highlight that this by no means rules out the possibility of a solvent separated copper(II) fluoride being formed as a product of the reaction, which can be inferred reasonably from our NMR experiments.

Lastly, hoping for more clarification, several attempts were made to grow single crystals suitable for X-ray structure determination of the unoxidized copper(I)−bis(imine) complex and the oxidized copper(II) species observed by EPR. In the former scenario, an interesting polymeric structure was obtained exhibiting 2:1 cuprous iodide:bis(imine) ligand stoichiometry. However, this polymer is likely just a thermodynamic sink for the copper(I):bis(imine) ligand interaction and does not play an active role in the chemistry;

EPR signatures of the copper(II) species observed over the course of the reaction do not resemble those of dimeric or polymeric copper species.[26] In the latter scenario, any attempt to grow crystals of the oxidized copper species (in the presence of Selectfluor) only afforded the ammonium salt **5**, H-TEDA-BF_4, previously reported by the Baran group.[7]

Initiation by Single-Electron Transfer. Evidence of a rapid growth and persistence of copper(II) over the course of the reaction was observed in the liquid phase EPR studies, whereby copper(II) is formed rapidly over the first hour of the reaction (~85% conversion from copper(I)) and asymptotically approaches 100% conversion thereafter.[27] It is very possible that the copper species plays a laissez-faire role beyond initiating the reaction and generating an unstable Selectfluor derivative that serves as the H atom abstractor and propagator in the reaction mechanism. Taking into account previous observations by both our laboratory and the Baran laboratory, we explored the supposed SET chemistry between copper and Selectfluor. There are two potential scenarios to consider under the reaction conditions, resembling either an outer-sphere or inner-sphere electron transfer mechanism (Scheme 4).[28]

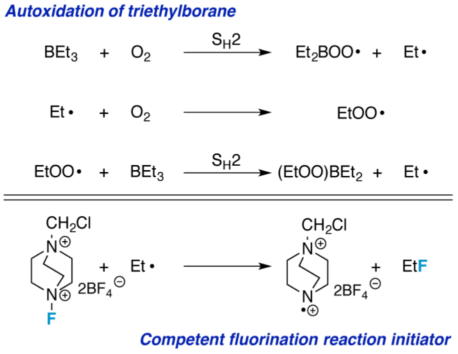
Scheme 4



Outer-Sphere SET. In the instance of an outer-sphere mechanism, the copper species and Selectfluor **6** would remain separate and otherwise unchanged throughout the course of an event where copper(I) transfers an electron to Selectfluor, generating copper(II) and Selectfluor radical cation **7**. One could draw out a mechanism where radical cation **7** performs H atom abstraction, forming HF and an alkyl radical, and the newly formed alkyl radical reacts with Selectfluor to generate a fluorinated product and a radical dication species (**4**) that would be responsible for subsequent H atom abstraction. However, a few experimental findings discount this possibility. First of all, if this outer-sphere mechanism holds true for initiating the reaction, other known, highly competent outer-sphere single-electron transfer reagents, such as ferrocene, should be able to produce similar results upon reaction with Selectfluor.[29] Running the reaction with ferrocene instead of cuprous iodide (despite the promising color change to dark green, indicating formation of the ferrocenium ion) gave very poor results, yielding only a trace amount of the desired fluorinated product. Tris(bypyridine)ruthenium(II) also proved incompetent in effecting the reaction. Second, a controlled potential electrolysis experiment was attempted in the presence of an electrolyte, Selectfluor, and cyclododecane, but was unsuccessful in reducing Selectfluor while producing any detectable fluorinated products. Third of all, in the absence of base (i.e., potassium carbonate), we should be able to detect an initial burst of HF by ^{19}F NMR at room temperature, but this was not observed. Lastly, a differential pulse voltammogram (DPV) of a 1:1 mixture of copper:bis(imine) ligand reveals an oxidation potential of +0.87 V vs SCE for the copper(II/I) transition; however, the reported reduction potential of Selectfluor, −0.296 V vs AgRE,[30] would suggest an unfavorable flow of electrons by an outer-sphere electron transfer mechanism and further aid in the nullification of this type of process. Thus, an inner-sphere mechanism whereby radical dication **4** is formed may be the more likely of the two.

Inner-Sphere SET. Still, a more convincing argument would be to show an example where the reaction *proceeds* through another inner-sphere electron transfer event. Thus, we examined an initiator that cannot fathomably form radical dication **4** through an "outer-sphere" process accompanied by loss of fluoride: a primary alkyl radical. The formation of ethyl radicals in situ is well established upon reaction of triethylborane with oxygen.[31] Applying this chemistry to our system, an ethyl radical could reasonably form **4** and fluoroethane upon interaction with Selectfluor (Scheme 5).

Scheme 5



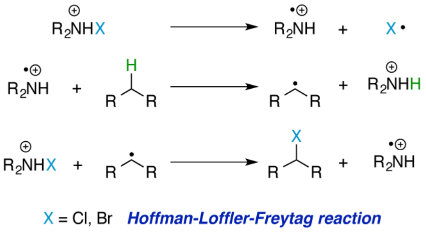
To our satisfaction, adding a catalytic amount of triethylborane to a solution of Selectfluor and cyclododecane in MeCN, with no measures taken to remove O_2, resulted in the formation of 1-fluorocyclododecane in 50% yield after 4 h. The involvement of ethyl radicals in initiating the reaction is supported by detection of fluoroethane by ^{19}F NMR. Furthermore, a few other synthetic methods have been published since our original copper system that effect an analogous fluorination reaction using catalytic amounts of iron,[10] vanadium,[32] and organic-based reagents[33] that conceivably participate in inner-sphere electron transfer chemistry with Selectfluor. (Note that other methods have also been published recently using photocatalysts that likely operate under much different initiation mechanisms.[34])

Additional efforts were made to probe the role of copper as an initiator by attempting to remove or sequester copper during the course of the reaction and also suggest that the reaction does not need copper to proceed beyond initiation (see Supporting Information for details). Lastly, an experiment probing the potential for asymmetric induction—using a chiral variant of our bis(imine) ligand (derived from *trans*-1,2-cyclohexanediamine)[35] and the Mosher ester of 3-phenylpropanol[36] (as benzylic fluorination of this substrate establishes spectroscopically distinct diastereomers by ^{19}F NMR)[37]—

resulted in a distribution of fluorinated products that was identical to the distribution when an achiral ligand was employed. In a small way, this helps support the notion that fluorine may not be transferred from a copper catalyst. All things considered, the evidence overwhelmingly insinuates that copper(I) is, in fact, an initiator in our system that operates through an inner-sphere electron transfer mechanism with Selectfluor, as opposed to being necessary throughout the catalytic cycle.

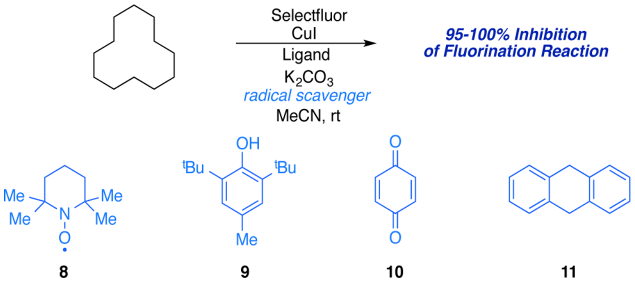
As suggested in Scheme 4, copper(I) is used to generate what we propose to be the true "catalyst" from Selectfluor: a radical dication (**4**).[38] Conceptually, if this radical dication acts as an H atom abstractor, an alkyl radical would be generated that could feasibly react with Selectfluor to form the fluorinated product and regenerate the radical dication. This idea is akin to the mechanism established by Corey and co-workers for the Hoffman–Löffler–Freytag reaction (Scheme 6).[39] Correspondingly, the next set of experiments discussed focus on probing the involvement of radicals.

Scheme 6



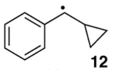
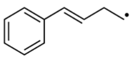
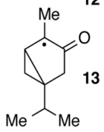
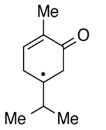
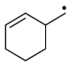
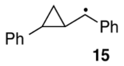
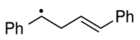
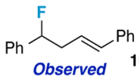
Involvement of Alkyl Radicals. The reaction was run in the presence of four radical scavengers to explore the involvement of radical intermediates: 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) **8**, 2,6-di-*tert*-butyl-4-methylphenol (BHT) **9**, *p*-quinone **10**, and dihydroanthracene **11** (Scheme 7).[40] Subjecting cyclododecane to normal reaction conditions with an added 1.2 equiv of each radical scavenger, the formation of fluorocyclododecane was inhibited by 95% in the presence of *p*-quinone, 97% with BHT, and completely in the presence of either TEMPO or dihydroanthracene. One potential criticism of these experiments may be that some of these compounds do not solely act as radical scavengers; rather, some will likely also be fluorinated or oxidized, consuming a significant amount of Selectfluor, and thus inhibiting fluorination through another venue. To elucidate the primary role of these compounds as radical inhibitors, we also found that (1) merely 0.15 equiv of TEMPO and dihydroanthracene—leaving a 15-fold excess of Selectfluor—also resulted in significant reaction inhibition (85% with TEMPO and 70% with dihydroanthracene) without any substantial amount of fluorinated variants of the scavengers detected and (2) if dihydroanthracene is added at any point after fluorinated products start to appear by ^{19}F NMR, the fluorination reaction stops. These experiments strongly infer the shutting down of a radical pathway. Note that oxygen also quenches the reaction, typical of many radical chain reactions.

Scheme 7



Although we have shown the ability to interrupt the proposed radical pathway, these experiments do not necessarily allude to the scavenging of *alkyl* radicals. In fact, the aforementioned compounds and oxygen are likely to inhibit the reaction via cessation of the radical dication. The best way to probe the involvement of alkyl radicals is to run the reaction with substrates that notoriously rearrange to provide more stable radicals or release ring strain, such as those containing a cyclopropyl moiety. The rates of rearrangement have been studied for several "radical clocks" and, under certain circumstances, allow the possibility of extrapolating rate information from the reaction. We studied a small family of cyclopropane-based radical clocks, spanning rearrangement rates over a few orders of magnitude (Table 2).

Table 2. Radical Clocks

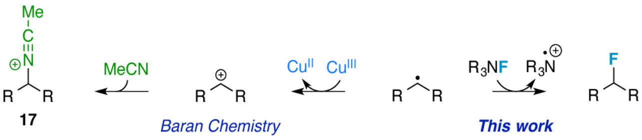
Rearrangement			*Rearranged Fluorinated Product*
 **12**	$k_r < 2.0 \times 10^5$ s^{-1}		*Not observed*
 **13**	$k_r \sim 1.0 \times 10^8$ s^{-1}		*Not observed*
 **14**	$k_r = 2.0 \times 10^8$ s^{-1}		*Not observed*
 **15**	$k_r = 3.6 \times 10^8$ s^{-1}		 **16** *Observed*

The first three radical clocks studied—benzylcyclopropane, thujone, and norcarane[41]—showed evidence of fluorinated product mixtures by ^{19}F NMR, but no detectable amount of the expected "rearranged" fluorinated products following the putative formation of radicals **12**, **13**, and **14**, respectively.[42] However, the rate of fluorination may be significantly faster than their rates of rearrangement, and the latter two clocks have multiple competing sites for H atom abstraction that would not allow for a rearranged product anyway. Accordingly, we examined another slightly faster clock with one favorable benzylic site for H atom abstraction under our reaction conditions: 2-phenylbenzylcyclopropane (to form radical **15**).[43] A ^{19}F NMR analysis revealed that the reaction yielded four fluorinated products in a total yield of 18.2%: one of these signals corresponds to the (*E*)-isomer of rearranged product **16** ($\delta = -172.53$ ppm, ddd, $J = 47.4, 24.8, 16.5$ Hz), and another signal also has the characteristics of an "opened" fluorinated clock ($\delta = -178.69$ ppm, ddd, $J = 48.5, 39.2, 14.4$ Hz).[44] The two additional signals have slightly more difficult splitting to decipher, but have chemical shifts that reasonably match up with two benzylic fluorinated isomers that contain an intact cyclopropane ring ($\delta = -179.81$ ppm, m and $\delta = -185.33$ ppm, m). The identification of these compounds is also supported by a crude GC/MS analysis where four similar fragmentation patterns were found with m/z = 226.3. The ratio of total rearranged products to intact cyclopropane products is ca. 1:1.09. This rearrangement is strong evidence for a stepwise fluorination mechanistic pathway and for the involvement of short-lived alkyl radicals.

As an aside, the fact that the reported rates of rearrangement for norcarane and 2-phenylbenzylcyclopropane are very similar, yet we found no rearranged norcarane products, is a noteworthy result. As either rearrangement or fluorination of the radical happens *after* the rate-determining step (vide infra), this observation indicates that secondary alkyl radicals fluorinate faster than the more delocalized secondary benzylic radicals in this reaction.

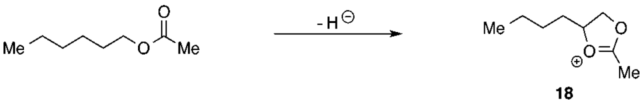
Thus far, these experiments paint a reasonably convincing picture where radical dication **4** generates an alkyl radical, which may react homolytically with Selectfluor to yield a fluorinated product and regenerate **4**. One alternative to consider is the role that carbocations may play in the mechanism, as cationic intermediates may also result in the opening of the cyclopropane ring. For example, can an alkyl radical sacrifice another electron to a suitable acceptor and then trap fluoride? There are a number of factors from theoretical and experimental standpoints that militate against this possibility. Most of all, we would be considering secondary cations, whose free existence in solution is at the very least unfavorable, and somewhat debatable.[45] In any case, a secondary cation in MeCN solvent would rapidly collapse to the nitrilium as opposed to trapping fluoride. Nitrilium adducts **17**—rather, acetamides upon aqueous workup—were observed by Baran and co-workers in a copper(II)−Selectfluor based system.[7] However, their postulated mechanism, involving a copper(II) reagent that is subjected to harsher conditions in the presence of Selectfluor, invokes formation of a precedented copper(III) species that is much more likely to be reduced by an alkyl radical than our observed copper(II) species (Scheme 8). The fact that nitrilium derived products are minimal in our system (aside from ex post facto solvolysis) would seem to indicate that cations play a minor role.

Scheme 8



What about direct formation of cations through hydride transfer? Take the well-behaved substrate 1-hexyl acetate, which fluorinates predominately in the 5-position, as a model. Hexyl acetate should donate hydride preferentially from the 2-position, as this would form, after anchimeric assistance, a stable cyclic oxonium **18** that could trap fluoride (Scheme 9). This product is not observed to any significant extent.

Scheme 9



Induction Period. A mechanistic study would not be complete without an analysis of reaction kinetics. A preliminary kinetic study to monitor the rate of appearance of the fluorinated product of 3-phenylpropyl acetate by ^{19}F NMR under standard reaction conditions revealed a significant induction period before the desired 3-fluoro-3-phenylpropyl acetate began to form. Over the course of our studies, we have noted induction periods for this same compound varying anywhere from 20 min to 2.5 h. We also found that the length of this induction period can vary greatly among all substrates; for instance, the induction periods for monitored reactions with cyclodecane or cyclohexane have varied in length on the orders of minutes to hours, just as 3-phenylpropyl acetate has. (A sample plot of the rate of fluorination of cyclodecane is provided in Figure 7, illustrating the induction period.)

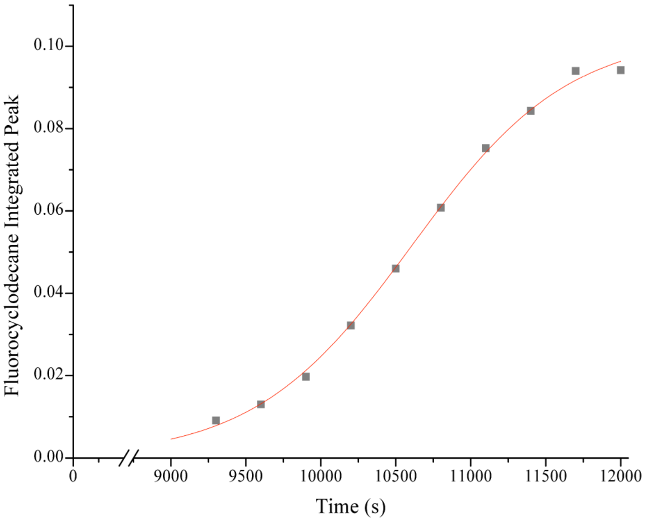


Figure 7. Sample rate of fluorination plot displaying induction period.

To determine whether the substrate itself plays a significant role in the induction period of the reaction, we looked at the consequences of "aging" the catalyst in six reactions set up in parallel. In this experiment, 3-phenylpropyl acetate was added at six different time intervals (t = 0, 15 min, 30 min, 1 h, 2 h, and 4 h) into six different reaction flasks, and an aliquot was taken from each flask at the 4.5 h mark. In every instance where the starting material was added at/prior to 2 h, the percent yields of the fluorinated products by ^{19}F NMR relative to an internal standard were virtually identical. However, in the reaction where the starting material was added at 4 h, well past any previously observed induction period, the fluorinated product had already appeared after only 30 min of stirring, and in half the percent yield of the other reactions. Thus, the induction period does not appear to be substrate dependent.

We noticed shorter induction periods as technique improved, presumably with respect to excluding oxygen from the system. In fact, suspecting the involvement of radical species, we noted that the reaction is greatly hindered in the presence of an O_2 atmosphere and also found that the induction period is typically shorter using degassed anhydrous MeCN (with N_2) over simply anhydrous MeCN (with no measures taken to remove dissolved oxygen).[46] If oxygen is quenching **4**, then the origin of the induction period is likely attributed to a slower buildup in concentration of **4**, the effective catalyst, in situ.[47] Even after rigorous efforts to exclude oxygen, a small concentration was present in each reaction: the induction periods shortened significantly, but never disappeared.

Rate Dependence. We next sought to determine the overall order of the reaction using the method of initial rates; however, it is very challenging if not impossible to obtain quantitative rate dependencies for this reaction, given its induction period and the limited solubility of several components.

Our model thus far involves three steps: (1) an inner-sphere SET event between Selectfluor and copper(I) generates copper(II) and a radical dication; (2) this radical dication performs H atom abstraction on an alkane, which generates an ammonium salt and an alkyl radical; and (3) the resultant alkyl radical abstracts a fluorine atom from Selectfluor, which regenerates the radical dication to enter the catalytic cycle. Since the radical dication is believed to be the true catalyst (or chain carrier), then if H atom abstraction is the rate-limiting step, the rate of product formation (studied by ^{19}F NMR) would likely have a first-order dependence on both the alkane and the radical dication. Our data show that the rate of product formation is, in fact, strictly first-order with respect to the substrate.

The rate of radical cation formation is dependent on the concentrations of copper(I) and Selectfluor, but the observed induction period seriously complicates the picture. Qualitatively, the length of the induction period is inversely proportional to the concentration of copper and proportional to the concentration of oxygen. We also observed that copper(I) is not entirely expended as the reaction rate accelerates. The total concentration of radical cation, and thus product, is dependent on a first-order term in Selectfluor and a reciprocal first-order term (reflecting the production of the radical dication). An accurate mathematical analysis of the rate dependencies of Selectfluor and copper(I) is less feasible under these circumstances, but qualitatively they should both be <1 (depending on the relative contributions of the two terms), which proved to be the case. The proposed rate equation is illustrated in eq 1.

$$\frac{\mathrm{d[fluoroalkane]}}{\mathrm{d[t]}} = \mathrm{k[alkane][radical\ dication]}$$
$$\frac{\mathrm{d[radical\ dication]}}{\mathrm{d[t]}} = \mathrm{k_1[Selectfluor][Cu] - k_2[Selectfluor][Cu][quencher]} \quad (1)$$

KIE. Kinetic isotope effect (KIE) experiments are also capable of providing a wealth of knowledge about a reaction mechanism, from information about the rate-determining step to intimate details about the nature of the transition state.[48] An appropriate benzylic substrate for this experiment would be 3-phenylpropyl acetate, as it yields only one fluorinated product (in the benzylic position) and the corresponding mono/dideuterio species **19** is easily accessible.[49] The appearance of fluorinated products **20** was monitored by ^{19}F NMR in a competitive KIE experiment, as the deuterium-induced ^{19}F isotopic shift is significant enough to allow independent observation of the geminal protio and deuterio products ($\Delta\delta$ = 0.59 ppm; Figure 8).[50] This method also obviates misleading results from potential inconsistencies in induction periods.

Comparison of the initial rates revealed an average kinetic isotope effect of 2.3, which is a superposition of a moderate primary KIE and a secondary effect from the dideuterio species (Scheme 10). This diminished putative primary KIE value appears to be consistent with an early or bent transition state if the rate-limiting step is, in fact, H atom abstraction.[51] A transition state calculation of the radical dication **4** engaging in H atom abstraction at B3LYP/6-311++G** supports this notion (d(C−H) = 1.17 Å, d(N−H) = 1.69 Å)). (In order to simplify the calculation, the aliphatic substrate used was propane. Counterions were included in an MeCN dielectric, as otherwise without counterions present the barrier to H atom transfer diminished to zero.)

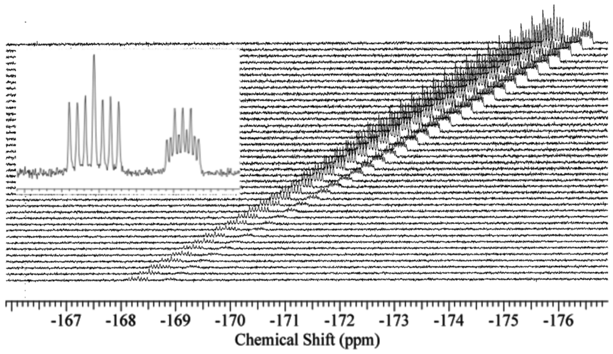
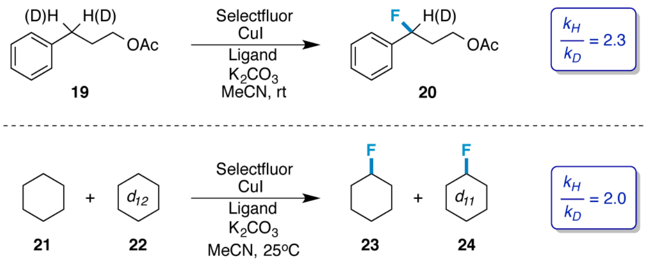


Figure 8. Competitive KIE ^{19}F NMR overlay of the formation of 3-fluoro-3-phenylpropyl acetate (left, ddd, J = 47.4, 30.9, 14.4 Hz) and 3-fluoro-3-phenylpropyl-3-d acetate (right, ddt, J = 30.9, 14.4, 7.2 Hz).

Scheme 10



A second competitive KIE experiment was also conducted using a purely aliphatic substrate, viz., a 1:1 mixture of cyclohexane (**21**):cyclohexane-d_{12} (**22**) to provide **23** and **24**, which provided a slightly smaller average value of 2.0 (Scheme 10). Similar to the 3-phenylpropyl acetate result, there is a moderate primary isotope effect and small secondary effect from the geminal deuterium atom. On the other hand, cyclohexane-d_{12} has four vicinal deuterium atoms that have an inverse secondary effect on the rate that accounts for a notable diminution of the phenomenological KIE value.[48]

Proposed Mechanism. Based on experimental observations thus far, we can propose a reasonable mechanism. EPR, UV−vis, ^{19}F NMR, and several synthetic experiments point to an inner-sphere SET reaction between copper and Selectfluor whereby copper(I) is oxidized to copper(II) accompanying a loss in fluoride from Selectfluor. As determined by the aforementioned KIE experiments and transition state calculation, the resultant radical dication species from the SET reaction **4** is a reasonable actor in H atom abstraction that occurs through an early transition state and is postulated to be rate-determining. Radical scavenger and radical clock experiments confirm the involvement of alkyl radicals that would be formed along with ammonium salt **5** (observed) upon H atom abstraction. Furthermore, the notion that fluorine is being transferred directly from Selectfluor is logical, as this would regenerate the radical dication and complete a catalytic cycle/radical chain reaction similar to the Hoffman−Löffler−Freytag

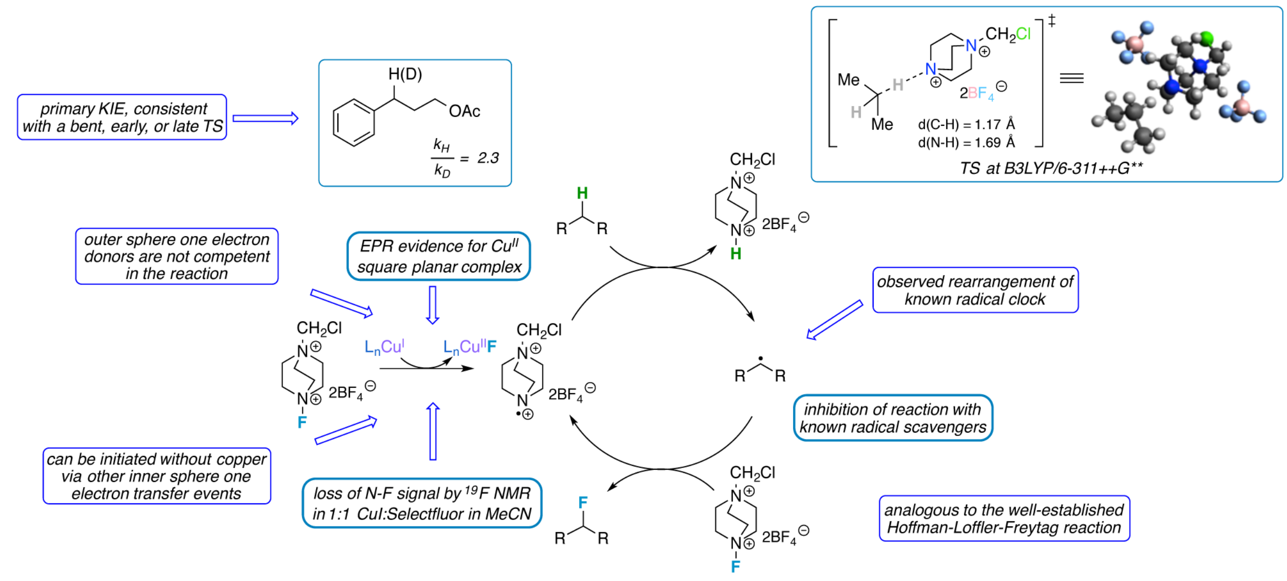


Figure 9. Mechanistic hypothesis based on experimental results.

reaction (Figure 9). We have also provided an energetic profile of the reaction intermediates in the catalytic cycle that illustrates a largely exothermic reaction pathway (Figure 10).

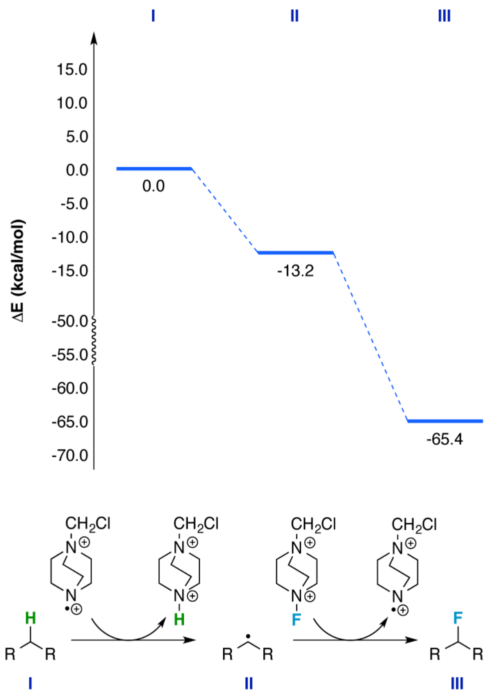


Figure 10. Free-energy profile for the monofluorination of cyclodecane through our proposed catalytic cycle.

Overall, this picture appears to be a reasonable mechanism for this system. However, perhaps the most difficult question to answer pertaining to the selectivity of the reaction still remains: *why is monofluorination preferred?* Finally, we turned our attention to a more in-depth theoretical analysis to try to complete the puzzle.

Role of Valence Bond "Ionicity" in Reaction Selectivity. One of the most enlightening features regarding the selectivity of this reaction is in the highly reproducible product distribution of 1-hexyl acetate. Fluorination of this substrate predominates in the 5-position, yields of the other monofluorinated isomers largely decrease moving down the chain, and there are trace (if any) monofluorinated products in the 1-position, 6-position, and α-position to the carbonyl. Compare this to the outcome of a reaction using *n*-dodecane, where an almost equal distribution of monofluorinated products on the methylene sites is observed. It is clear that the reaction is sensitive to substituent effects that will provide some potent clues.

From one vantage point, as we propose a mechanism involving a radical chain process, we conducted a computational experiment early on that interestingly suggested that the observed distribution of *n*-fluoro-1-hexyl acetate isomers correlates with the calculated relative stabilities of the corresponding hexyl acetate radicals. If the selectivity of the reaction is based solely on radical stability though, which is characteristic of a purely covalent valence bond model for the rate-determining H atom abstraction transition state,[52] then geminal difluorination should be favored. Also consider the isodesmic analyses of cyclohexane and cyclodecane (Table 3) that indicate favorable formations of 1,1-difluorocyclohexane and 1,1-difluorocyclodecane over monofluorination based on thermodynamic considerations; yet, *geminal difluorinated products are not observed experimentally,* except to a minor extent when we apply forcing conditions (but even then, ionization/trapping of acetonitrile is a more competitive

Table 3. Isodesmic Reactions[a]

Isodesmic Reaction	ΔE (kcal/mol)
	0.8
	0.2

[a] All geometry optimizations were performed at B3PW91/6-311+G**-(MeCN).

process). The desire to analyze this reaction in terms of generating the most stable radical, a bond dissociation energy argument, is thus a misguided instinct.

Instead, if we revisit the substituent effect observed in 1-hexyl acetate as an effect resembling that of a radical reaction with *ionic* character in the transition state, then we can begin to rationalize the selectivity. In this light, the deactivation of sp^3 C−H sites proximal to an electron-withdrawing group toward fluorination agrees nicely with our proposed mechanism. The species that we suggest is responsible for H atom abstraction, radical dication **4**, is an electron deficient radical that would much prefer interaction with the more electron rich C−H sites (hence the starting material over the newly formed fluorinated products).

Polar Effect. Ionic-like selectivity is not unheard of in radical reactions; there are several accounts of this phenomenon in the literature, first noted by Walling and Mayo[53] in free radical polymerization reactions and since referred to as "the polar effect". By analogy of our reaction to the Hoffman−Löffler−Freytag reaction, reports demonstrating that this polar effect, putatively at play in our fluorination reaction, is similarly observed in free radical chlorination[54] and bromination[55] reactions involving intermolecular H atom abstraction also by amine radical cations make an extremely convincing argument for our case. These reports also indicate an overwhelming preference for the penultimate sp^3 C−H site on *n*-alkyl esters, which they attribute to such polar (and also minor steric) effects.

The last piece of the puzzle lies in further examining the effect of ionicity on the H atom abstraction transition states of the alkane versus the monofluorinated product. Postulating the role of the ionic potential energy surface on dictating selectivity and given the complexity of transition state calculations, we first turned to Donahue's seminal ionic curve crossing theory as a way to study the nature of the transition states: only geometry optimization calculations are necessary by this analysis.[56] This theory indicates that the lowering in energy of the saddle point on the ground state potential energy surface results from an avoided curve crossing with the ionic potential energy surface. Succinctly stated, lower ionic state energies correlate with lower transition state energies. Boundary conditions for an avoided curve crossing are derived from plotting the evolution of the ground and ionic state energies as reactants approach each other (bear in mind that, for radical cation abstraction reactions, the ground state is ionic, as well). In our system, ΔE_1 is the calculated difference between ground and "ionic" states of the reactants, ΔE_2 is the same for the products, ΔE_a is the activation energy, $\Delta H_{\mathrm{REACT}}$ is the reaction enthalpy, and CP is the potential energy surface crossing point (eq 2).

$$\mathrm{CP} = \frac{\Delta E_1(\Delta E_1 + \Delta H_{\mathrm{REACT}})}{\Delta E_1 + \Delta E_2} \qquad (2)$$

For cyclodecane, CP is calculated to be 4.6 kcal, whereas fluorocyclodecane, as a precursor to the more stable 1-fluorocyclodecyl radical, leads to CP = 5.4 kcal (B3PW91/6-311++G**/MeCN), implying a higher activation energy for its formation, consistently accounting for the observed selectivity from this reaction (Figure 11).

The calculations in Figure 11 include optimized geometries of the 1-fluorocyclodecyl and cyclodecyl cations, both of which are found to be hydrido-bridged employing the MeCN continuum. This model is consistent in predicting the observed preference for monofluorination of cyclohexane, as well. For cyclohexane, CP is calculated to be 3.4 kcal, which is a lower barrier than that of fluorocyclohexane at 5.5 kcal.

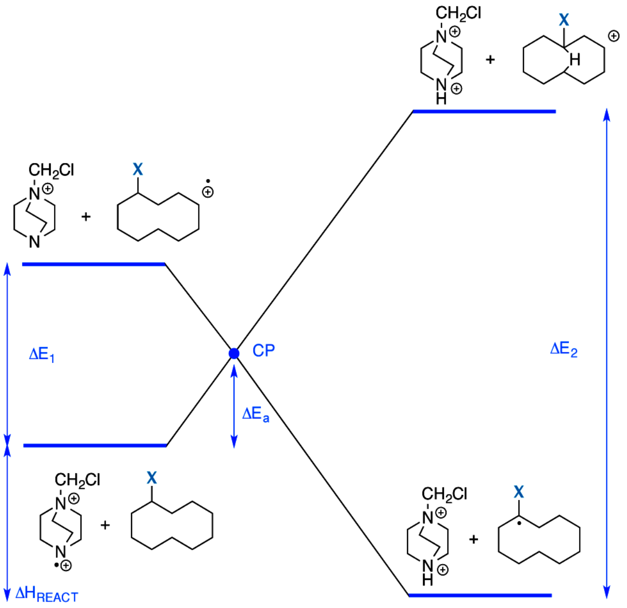


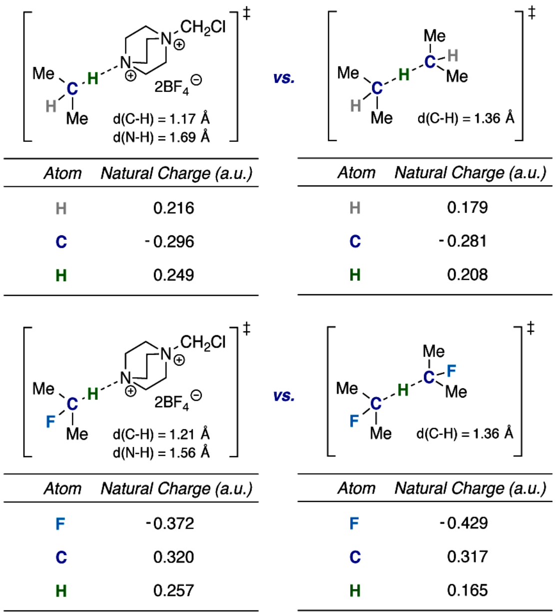
Figure 11. Application of Donahue's theory.

Additionally, we calculated the transition states for formation of the isopropyl radical and the 2-fluoroisopropyl radical, representing pruned substrates for ease of calculation. The result is in excellent agreement with the curve crossing analysis, vide supra, as the transition state for the formation of the isopropyl radical is earlier and calculated to be 2.2 kcal lower than for the formation of the 2-fluoroisopropyl radical at B3LYP/6-311++G**. An NBO analysis also confirms that a positive charge has developed in the transition state (relative to an isoenergetic H atom abstraction) that is accentuated on the hydrogen atom. A strong electron-withdrawing group such as fluorine would destabilize this positive charge, advocating again for H atom abstraction of an alkane over a fluoroalkane (Figure 12).

Finally, note that all attempts to calculate the transition state whereby Selectfluor fluorinates the isopropyl radical repeatedly collapsed to the products, potentially signifying a barrier-less reaction.

■ CONCLUSIONS

Through in-depth analysis of experimental and theoretical data, we are able to propose a mechanistic scenario of the copper-initiated sp^3 C−H fluorination methodology. Spectroscopic evidence and synthetic experiments confirm a radical chain mechanism initiated by an inner-sphere SET from copper(I) to Selectfluor (as opposed to a mechanism where copper plays a role in the catalytic cycle), but this alone does not explain the observed preference for monofluorination. Analyzing the influence of the ionic potential energy surface and applying Donahue's ionic curve crossing theory has allowed us to offer a reasonable explanation for the energetics and selectivity of the reaction.



Atom	Natural Charge (a.u.)
H	0.216
C	-0.296
H	0.249

Atom	Natural Charge (a.u.)
H	0.179
C	-0.281
H	0.208

Atom	Natural Charge (a.u.)
F	-0.372
C	0.320
H	0.257

Atom	Natural Charge (a.u.)
F	-0.429
C	0.317
H	0.165

Figure 12. Transition state calculations and charge distributions alongside isoenergetic scenarios.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

General experimental procedures, kinetic data, spectral data, crystallographic information, and computational files. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*lectka@jhu.edu

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

T.L. thanks the NSF (CHE 1152996) for support. C.R.P. thanks Johns Hopkins for a Gary H. Posner Fellowship.

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(16) Another control experiment was also designed to probe the involvement of a copper(III) fluoride by applying a (2-pyridyl) methylamine ligand to the system, which has been shown to promote two-electron chemistry in copper(I) complexes, but no positive ligand effects were observed. See: Osaka, T.; Karlin, K. D.; Itoh, S. *Inorg. Chem.* **2005**, *44*, 410−415.

(17) Another control experiment conducted was a thermolysis of *tert*-butyl 2-phenylpropaneperoxoate in the presence of cupric fluoride under Sammis's conditions (ref 6) that could conceivably illuminate how an alkyl radical reacts with a copper(II) fluoride. No 1-fluoroethylbenzene was observed; however, these conditions do not directly mimic the reaction conditions.

(18) Note that the reaction does not produce fluorinated products under the reaction conditions with Selectfluor in the absence of copper either; this control reaction was conducted.

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