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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
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Article

Competition between C−C and C−H Bond Fluorination: A Continuum of Electron Transfer and Hydrogen Atom Transfer Mechanisms

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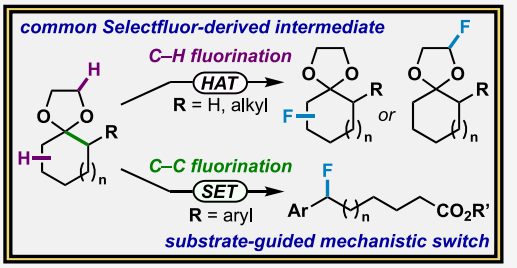
Cite This: J. Am. Chem. Soc. 2023, 145, 22442−22455

ABSTRACT: In 2015, we reported a photochemical method for directed C−C bond cleavage/radical fluorination of relatively unstrained cyclic acetals using Selectfluor and catalytic 9-fluorenone. Herein, we provide a detailed mechanistic study of this reaction, during which it was discovered that the key electron transfer step proceeds through substrate oxidation from a Selectfluor-derived *N*-centered radical intermediate (rather than through initially suspected photo-induced electron transfer). This finding led to proof of concept for two new methodologies, demonstrating that unstrained C−C bond fluorination can also be achieved under chemical and electrochemical conditions. Moreover, as C−C and C−H bond fluorination reactions are both theoretically possible on 2-aryl-cycloalkanone acetals and would involve the same reactive intermediate, we studied the competition between single-electron transfer (SET) and apparent hydrogen-atom transfer (HAT) pathways in acetal fluorination reactions using density functional theory. Finally, these analyses were applied more broadly to other classes of C−H and C−C bond fluorination reactions developed over the past decade, addressing the feasibility of SET processes masquerading as HAT in C−H fluorination literature.



INTRODUCTION

In the past decade, the evolution of mild C−H and C−C bond "radical" fluorination tactics has enabled late-stage, site-selective monofluorination of complex molecules and the synthesis of previously difficult-to-access building blocks.[1−3] From our vantage point, the apparent steady state of methodological advancements in this area since 2012[4−6] appears to be correlated to conscious efforts within the community to increase the level of mechanistic understanding.

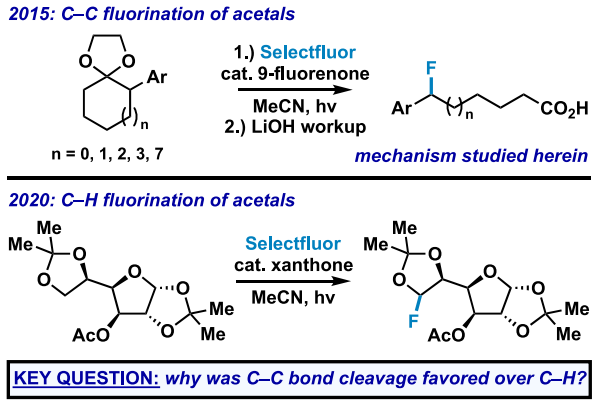
Several laboratories have undertaken in-depth mechanistic studies of mild radical fluorination reactions. For instance, our group communicated extensive studies on Cu(I)-promoted sp^3 C−H fluorination in 2014[7] and photoinitiated carbonyl-directed sp^3 C−H fluorination in 2020.[8] Additionally, Tan and co-workers reported transient absorption spectroscopy (TAS) data and density functional theory (DFT) calculations to investigate a photochemical sp^3 C−H fluorination initiated by anthraquinone in 2017.[9] Beyond the realm of C−H fluorination, Li and co-workers studied a Ag(I)-catalyzed decarboxylative fluorination (2012),[10] and our group studied an aminofluorination of arylcyclopropanes initiated by photo-induced electron transfer (PET) in 2016.[11] However, aside from decarboxylation and this boutique aminofluorination reaction, the mechanisms of C−C bond fluorination reactions have received considerably less attention (though several methods, primarily for fluorination of strained C−C bonds[11−18] with some noteworthy examples of relatively unstrained C−C bonds,[19−22] have been reported to date[23]).

In 2015, we reported a method for "unstrained" C−C bond cleavage/fluorination by leveraging substituent effects in 2-aryl-substituted (primarily cycloalkanone-based) acetals (Scheme 1, top).[19] Upon irradiating a mixture containing a suitable acetal substrate, Selectfluor, and a catalytic amount of 9-fluorenone (20 mol %) in MeCN, we demonstrated the ability to open 5-, 6-, 7-, 8-, and even 12-membered rings to achieve site-selective fluorination. We also showed that the product, an ethylene-glycol ester, can be readily converted to a carboxylic acid, an alcohol, or another ester simply by altering the workup, introducing an element of modularity to the transformation. While its utility in opening larger rings without evident assistance from a release in ring strain makes the reaction appealing from a methodological standpoint, it is arguably even more interesting from a mechanistic perspective. Why does C−

Received: June 19, 2023
Published: October 4, 2023

https://doi.org/10.1021/jacs.3c06477
J. Am. Chem. Soc. 2023, 145, 22442−22455

Scheme 1. Reported Conditions Demonstrating Circumstantial C−C or C−H Bond Fluorination of Acetals That Prompted This Study



C bond cleavage outcompete C−H bond cleavage? In 2020, we disclosed cases where the opposite was true−regioselective C−H bond fluorination in the α-ethereal position prevails over C−C bond fluorination on acetonide acetals under strikingly similar reaction conditions (Scheme 1, bottom).[24] This mechanistic switch between C−H and C−C bond fluorination seems heavily dependent on substituent effects, but neither the mechanism for C−C bond fluorination nor the reason for this switch has been studied in detail.

Herein, we present an extensive experimental study on the acetal C−C bond cleavage/fluorination reaction mechanism, in which we address the role and photochemistry of 9-fluorenone, the formation of an acetal radical cation intermediate, the mechanism for fluorination and propagation, and the surprising function of a Selectfluor-derived intermediate. Based on our findings, we provide proof of concept for two alternative approaches to acetal C−C bond fluorination, using both chemical and electrochemical initiation tactics, that support our mechanistic hypothesis and simultaneously exemplify how studying mechanisms can inform new reaction development. Finally, as we found the same Selectfluor-derived intermediate is known to be capable of either C−H or C−C bond fluorination (depending on the nature of the substrate), we examined the relative energetics of hydrogen atom transfer (HAT) vs single-electron transfer (SET) pathways using density functional theory (DFT) calculations. In a broader context, our study also suggests that some sp^3 C−H fluorination reactions that appear to proceed through a HAT mechanism may, in fact, proceed initially through SET. This finding not only sheds light on previously observed discrepancies in reactivity among substrates in C−H fluorination but also provides perspective for reaction development moving forward.

RESULTS AND DISCUSSION

Role of 9-Fluorenone in Reaction Initiation. We began our study by investigating the role of the chromophore—9 fluorenone (**1**)—under standard reaction conditions outlined in Scheme 1. To our fortune, the photochemistry and photophysics of 9-fluorenone and similar diaryl ketones are well documented.[25−27] In brief, photoexcited 9-fluorenone is known to undergo efficient intersystem crossing (ISC) to a long-lived triplet state, and this species has been reported to undergo chemical reactions, e.g., through triplet energy transfer[28] or through photoinduced electron transfer (PET)[29] whereby 9-fluoroenone acts as a mild photo-oxidant. In our case, UV−vis spectral analyses indicate that 9-fluorenone is the only chromophore present under standard reaction conditions, and we found that the reaction does not proceed in the absence of light. Thus, we explored the viability of either triplet energy transfer or PET processes playing a role in the acetal C−C bond cleavage/fluorination reaction.

First, we examined the feasibility of triplet energy transfer from excited 9-fluorenone to the reactants (Figure 1). It is well

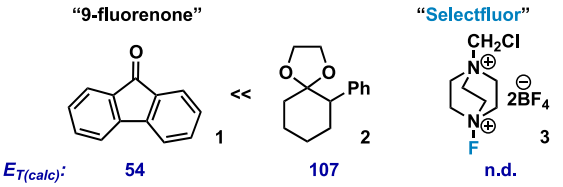


Figure 1. Singlet−triplet energy gaps (E_T) in kcal/mol calculated at UM06-2*X*/6-31+G(d,p)(SMD = MeCN) indicate that triplet energy transfer from excited 9-fluorenone is unfavorable.

established that the triplet energy of the donor (E_T^D) must be similar to or greater than the triplet energy of the acceptor (E_T^A) for energy transfer to be favorable.[30] That is, if E_T^D is more than a few kilocalories per mole less than E_T^A, then virtually no quenching occurs. Accordingly, we calculated triplet energies of the reactants by using density functional theory (DFT). For a calibration, the calculated singlet−triplet energy gap for 9-fluorenone at UM06-2*X*/6-31+G(d,p)(SMD = MeCN) is 54 kcal/mol, which is in accordance with the experimental value (54 kcal/mol). Using the same functional/basis set, the singlet−triplet energy gap for 6-phenyl-1,4-dioxaspiro[4.5]decane (**2**) is predicted to be much greater than 9-fluorenone (at 107 kcal/mol). Thus, the formation of the acetal triplet state does not appear viable. Lastly, we note that all attempts to calculate the triplet state of Selectfluor (**3**) resulted in convergency failures (i.e., E_T was not determined). This may be an indication of the unlikelihood of such an open shell intermediate, implying that triplet energy transfer from excited 9-fluorenone to Selectfluor may also be unlikely.

Previously, Tan and co-workers postulated the involvement of an anthraquinone:Selectfluor excited complex in a separate mechanistic study on photochemical C−H fluorination reactions.[9] Accordingly, we examined a 9-fluorenone:Selectfluor excited electron donor−acceptor (EDA) complex using DFT (Figure 2).[31] Contributing to the formation of this EDA complex were favorable noncovalent interactions (NCI) as witnessed by the green surface area of the complex shown in Figure 2, with a large degree of charge separation evident from the molecular electrostatic potential (MEP) surface plot. The HOMO and LUMO surfaces as well corroborate the charge

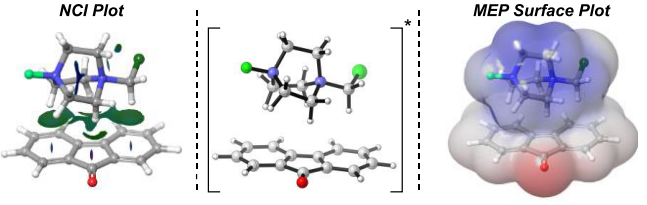


Figure 2. Calculated triplet state of a 9-fluorenone:Selectfluor excited EDA complex at UM06-2*X*/6-31+G(d,p) (SMD = MeCN).

https://doi.org/10.1021/jacs.3c06477
J. Am. Chem. Soc. 2023, 145, 22442−22455

transfer character of this complex (see the Supporting Information for details).

The calculated singlet−triplet energy gap ($E_{T(calc)}$) for this excited complex at UM06-2X/6-31+G(d,p)(SMD = MeCN) is 56 kcal/mol, which is similar to that of 9-fluorenone alone. In all, this indicates triplet energy transfer involving the excited state of 9-fluorenone or a 9-fluorenone:Selectfluor complex and the acetal substrate likely does not play an important role in the mechanism.

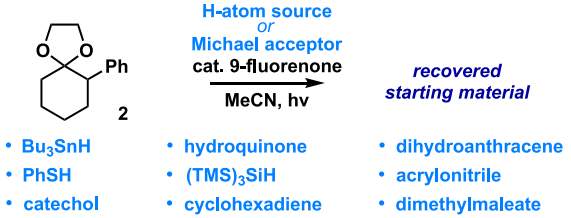
Alternatively, a photoinduced electron transfer (PET) pathway can be hypothesized, whereby the excited state of 9-fluorenone would be involved in substrate (acetal) oxidation. To assess the feasibility of PET, the Rehm−Weller equation (eq 1) is used to estimate Gibbs free energy based on experimental data (i.e., measured excited state energy and redox potentials).[32,33] The triplet energy and redox potential of 9-fluorenone,[11,34,35] as well as the redox potentials of Selectfluor[36,37] and acetal **2**,[38] have been reported and Gibbs free energies can be readily calculated. Intuitively, PET should not occur between the triplet state of 9-fluorenone and Selectfluor (this can also be confirmed by using eq 1). In addition, we determined that PET from the acetal substrate to triplet 9-fluorenone is endergonic, with ΔG°_{ET} = +24 kcal/mol, and is thus unfavorable.

$$\Delta G^{\circ}_{ET} = E^{\circ}_{(D^{+}/D)} - E^{\circ}_{(A/A^{-})} - E_{0,0} + w \quad (1)$$

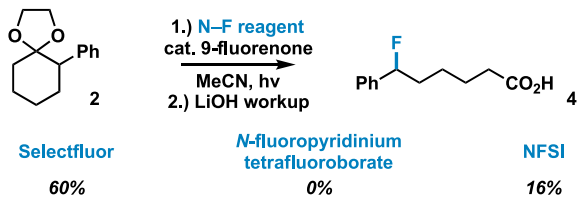
If PET from 9-fluorenone to the substrate were to occur in any case, then the resultant acetal radical cation would conceivably react with other "radical traps" in the absence of Selectfluor. Along these lines, Albini and co-workers demonstrated that 1,2,4,5-tetracyanobenzene (notably a much stronger photo-oxidant than 9-fluorenone) can oxidize similar acetals through PET, and they found that the resultant acetal radical cation can undergo ring-opening and radical arylation, hydrogenation, or Giese-type addition.[39,40] Accordingly, we ran several reactions: (1) in the absence of Selectfluor with various equiv of 9-fluorenone (0.2−1.0 equiv) and (2) whereby Selectfluor was replaced with known H atom donors (e.g., Bu_3SnH, PhSH, catechol, cyclohexadiene, dihydroanthracene, and *tris*(trimethylsilyl)silane) or Michael acceptors (e.g., acrylonitrile and dimethylmaleate). In each case, we recovered unreacted acetal starting material as determined by ^{1}H NMR analysis (Scheme 2). This also militates against PET under 9-fluorenone conditions and indicates that Selectfluor is somehow important beyond its putative role as an atomic fluorine source.

Along these lines, we also explored the replacement of Selectfluor with other common N−F reagents that could act as atomic fluorine sources.[41,42] While the product of C−C bond cleavage (**4**) was not observed using *N*-fluoropyridinium tetrafluoroborate (NFPY) on our test substrate, the product formed when using *N*-fluorobenzenesulfonimide (NFSI), albeit in only 16% yield by ^{19}F NMR analysis (Scheme 3).

Scheme 2. Products of C−C Bond Cleavage Not Observed upon Replacement of Selectfluor with Other Putative Radical Traps



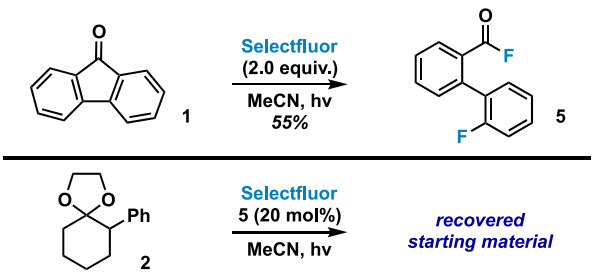
Scheme 3. Reaction Efficacy Across Common N−F Reagents



In a previous study, NFSI was shown to be a competent oxidant/fluorine source in a C−C bond aminofluorination reaction;[11] however, the reaction with Selectfluor was similarly more efficient and higher yielding in comparison. Note that NFPY is seldom competent in radical fluorination literature.[4]

Upon attempting to recover 9-fluorenone from the reaction mixture to ascertain whether it was acting as a true "catalyst", we discovered an important clue that suggests an alternative, less intuitive mechanism. That is, we found that 9-fluorenone undergoes a complete chemical transformation to a difluoride over the course of the reaction.[8] We confirmed that irradiation of 9-fluorenone in the presence of 2.0 equiv of Selectfluor leads to compound **5**, even in the absence of the substrate (Scheme 4, top). (Note that the use of NFSI instead of Selectfluor also

Scheme 4. (Top) Chemical Transformation of 9-Fluorenone to Compound 5 upon Irradiation in the Presence of Selectfluor.[8] (Bottom) Demonstrating That Compound 5 is Inactive toward Reaction Initiation



led to the formation of **5**, albeit in trace amounts.) Additionally, we determined that compound **5** is not a competent replacement for 9-fluorenone in effecting C−C bond fluorination (Scheme 4, bottom).

In prior work, we observed a similar phenomenon with benzil, which undergoes α-cleavage and benzoyl fluoride formation when irradiated in the presence of Selectfluor.[8] By analogy, we postulate that the excited state of 9-fluorenone is fluorinated by Selectfluor and promotes α-cleavage to form an acyl fluoride and a reactive aryl radical, and this radical is rapidly fluorinated in the presence of another Selectfluor molecule.

DFT calculations support this hypothesis (Figure 3). Fluorination of the triplet excited state of 9-fluorenone in the presence of Selectfluor to make **INT-1** and a Selectfluor-derived radical dication (SRD) was determined to be an exergonic process (ΔG° = −46 kcal/mol). The subsequent α-cleavage of **INT-1** to form aryl radical intermediate **INT-2** was found to be slightly endergonic (ΔG° = +9.4 kcal/mol from an

https://doi.org/10.1021/jacs.3c06477
J. Am. Chem. Soc. 2023, 145, 22442−22455

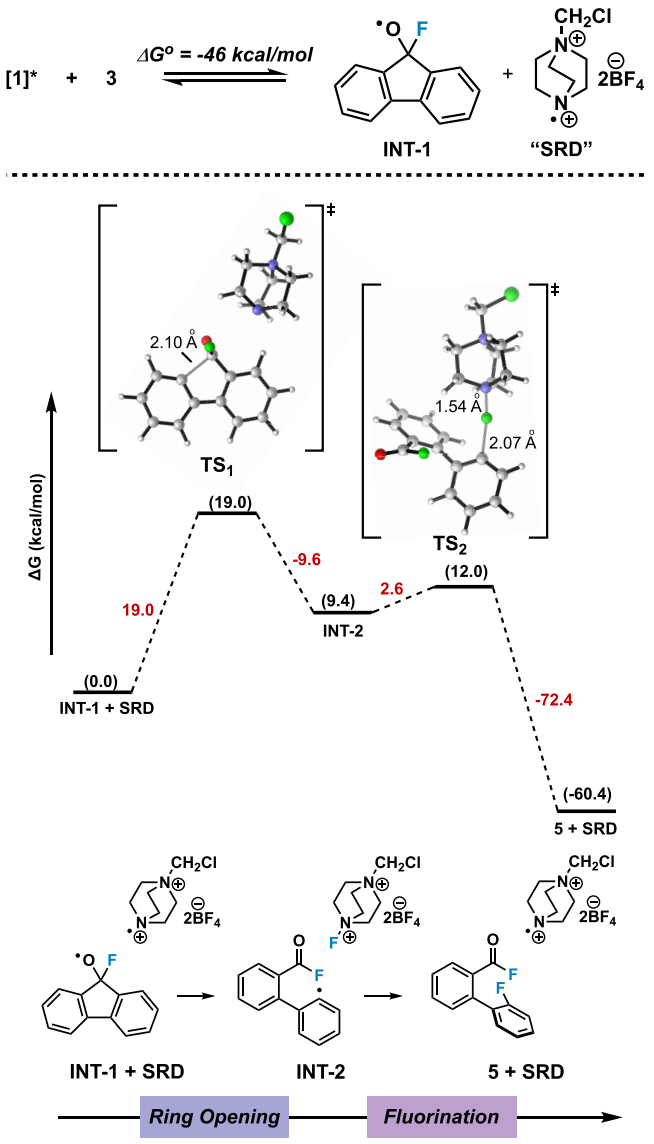


Figure 3. Energy profile for the photochemical difluorination of 9-fluorenone in the presence of Selectfluor calculated at the ωB97X-D/6-31+G(d,p) (SMD = MeCN) level of theory.

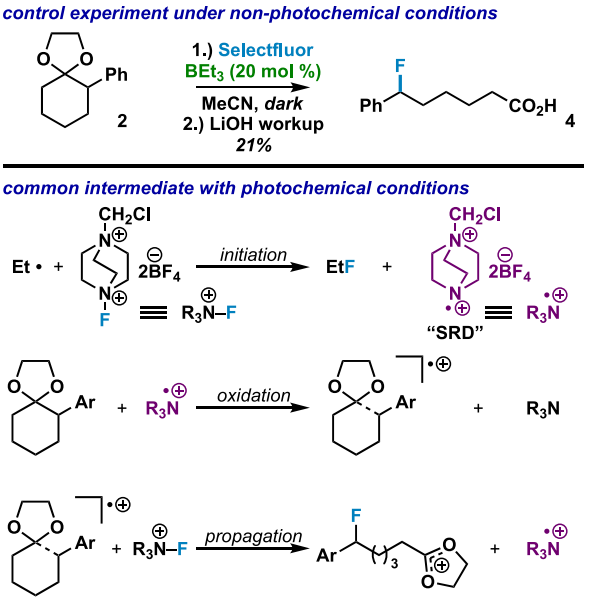
INT-1:SRD precomplex) and has an activation barrier ($\Delta G^{\ddagger}$) of 19 kcal/mol ($\mathbf{TS_1}$). This suggests α-cleavage of **INT-1** could be a rate-determining step in the formation of **5**. For the last step, we determined a low activation barrier for fluorination of **INT-2** by Selectfluor through $\mathbf{TS_2}$ ($\Delta G^{\ddagger}$ = 2.6 kcal/mol). Moreover, the aryl radical fluorination step is predicted to be highly exergonic (ΔG° = −70 kcal/mol). Thus, the overall process for the formal difluorination of 9-fluorenone to produce **5** is predicted to be energetically downhill and is consistent with our hypothesis.

Upon ruling out triplet energy transfer or PET pathways and obtaining evidence that 9-fluorenone is undergoing a chemical transformation, it seems that 9-fluorenone more likely plays the role of an initiator, as opposed to a true catalyst in the C−C bond fluorination reaction mechanism.

Acetal Radical Cation through Chemically Induced SET. Fluorination of 9-fluorenone by Selectfluor would lead to the formation of a Selectfluor-derived radical dication (SRD) intermediate. It stands to reason that if 9-fluorenone is not directly interacting with the acetal substrate in a productive manner under reaction conditions, the "versatile" SRD likely is.[43]

While SRD is a known actor in hydrogen atom abstraction, we have also demonstrated that this reactive intermediate is capable of oxidizing arylcyclopropanes and promoting strained C−C bond cleavage/aminofluorination.[11] To simultaneously support the notions that (1) 9-fluorenone may not be necessary beyond reaction initiation and (2) SRD can promote "unstrained" C−C cleavage of the acetal substrate via one-electron oxidation counterintuitively in lieu of abstracting a hydrogen atom, we sought to generate SRD in the presence of an acetal substrate but in the absence of 9-fluorenone and light. This can be achieved, for instance, by mixing the substrate with Selectfluor and catalytic amounts of BEt_3/O_2 (conditions for generation of ethyl radicals[44]) in the dark.[45] The so-called "triethylborane test"[8] was performed on compound **2**, and we observed the ring opened fluorinated product in 21% yield by ^{19}F NMR (Scheme 5, top). In addition to serving as an illuminating mechanistic experiment that allowed us to formulate a new hypothesis (Scheme 5, bottom), this represents proof-of-concept for the first nonphotochemical unstrained C−C bond cleavage/fluorination of 2-aryl-substituted acetals.

Scheme 5. (Top) Control Experiment under Conditions Known to Generate SRD in the Absence of 9-Fluorenone and Light; (Bottom) Proposed Role of SRD in C−C Bond Fluorination



Recent literature also indicates that the SRD intermediate can be accessed electrochemically through anodic oxidation of compound **6**.[8,46] Thus, we briefly explored the possibility of acetal fluorination under electrochemical conditions to complement the BEt_3/O_2 result (Scheme 6). To our satisfaction, we obtained preliminary evidence that C−C bond fluorination of 2-aryl-substituted acetals can, in fact, proceed under mediated electrolysis conditions (i.e., compound **7** was converted to **8** in 74% yield). This result represents proof-of-concept for the first electrochemical variation of this reaction and corroborates the notion that SRD is playing a critical role. (Note that exploring the full scope of this reaction will likely be the topic of future work.)

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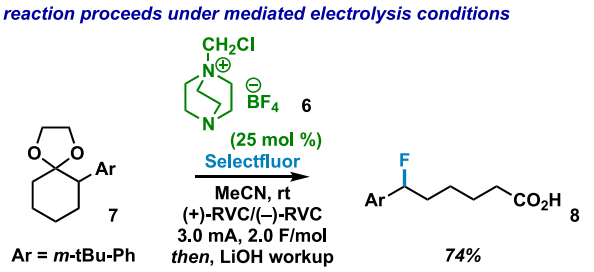
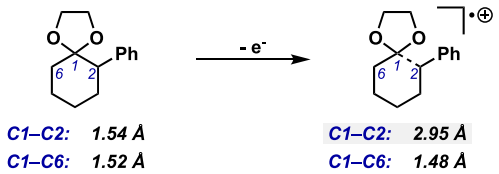
Scheme 6. Discovery That the Reaction Proceeds under Conditions Known to Generate the SRD Intermediate Electrochemically



Corroborated by both findings, the most plausible function of SRD is single-electron oxidation of the substrate, leading to an acetal radical cation intermediate (Scheme 5, bottom). DFT calculations performed at ωB97X-D/6-311++G(d,p) (IEPCM = MeCN) suggest that oxidation of compound 2 by SRD is thermodynamically favorable ($\Delta G^{\circ}_{ET} = -18$ kcal/mol). Moreover, the calculated ground-state structure of the acetal radical cation exhibits selective elongation of the C1−C2 bond to 2.95 Å from 1.54 Å in the neutral acetal, consistent with our observed selectivity (Scheme 7). For comparison, the radical cation C1−C6 distance is 1.48 Å vs 1.52 Å in the neutral acetal (**2**).

Scheme 7. C−C Bond Distances in Structures of Both Neutral and Oxidized Forms of Compound 2 Calculated at ωB97X-D/6-311++G(d,p) (IEPCM = MeCN)



As the reaction appears to proceed through acetal oxidation, the rate should be sensitive to aryl substituent effects, making this reaction a good candidate for linear free energy relationship (LFER) studies.[47,48] Thus, we synthesized a variety of para-substituted derivatives of compound **2** for the purpose of assembling a Hammett plot (Figure 4, top). For ease of analysis, the relative rates were equated to the product distributions ($[P_X]/[P_H]$) in intermolecular competition experiments whereby a 1:1 ratio of both substrates was used in excess of other reaction components. From these experiments, we determined a moderate negative ρ value of −1.44 ($R^2 = 0.96$) using Hammett σ_p values.[48] This indicates that there is a buildup of positive charge in the transition state of the rate-determining step, and the magnitude of the ρ value could be consistent with rate-determining single-electron oxidation of the acetal substrate to form a radical cation intermediate (or, e.g., formation of an encounter complex prior to SET).[49] From a theoretical standpoint, the HOMOs of the acetal substrates display significant coefficients in two ring C=C bonds on either side of the aromatic substituent across all levels of DFT, indicative of regions from which electron loss is most likely. The HOMO of an F-substituted acetal (**9**), for instance, is lower than that of the *t*-Bu-substituted substrate (**10**) by 0.6 eV (ωB97X-D/6-311+G(d,p)), consistent with more electron rich arenes being better candidates for electron transfer (Figure 5). Note that when the acetal contains two aryl substituents (one on each side, e.g., **11** and **12**) the HOMO coefficients are qualitatively and intuitively larger on the more electron rich arene and C−C bond cleavage seems to be preferred on this side experimentally. Similarly, computed nucleophilic Fukui function surfaces showed frontier orbital electron densities mirroring that of the HOMOs with the most reactive sites in these molecules localized to the aryl ring systems.[50−52] This is reflected in a Hammett plot constructed from intramolecular competition experiments, whereby a similar negative ρ value ($\rho = -1.45$; $R^2 = 0.98$) was observed (Figure 4, bottom).

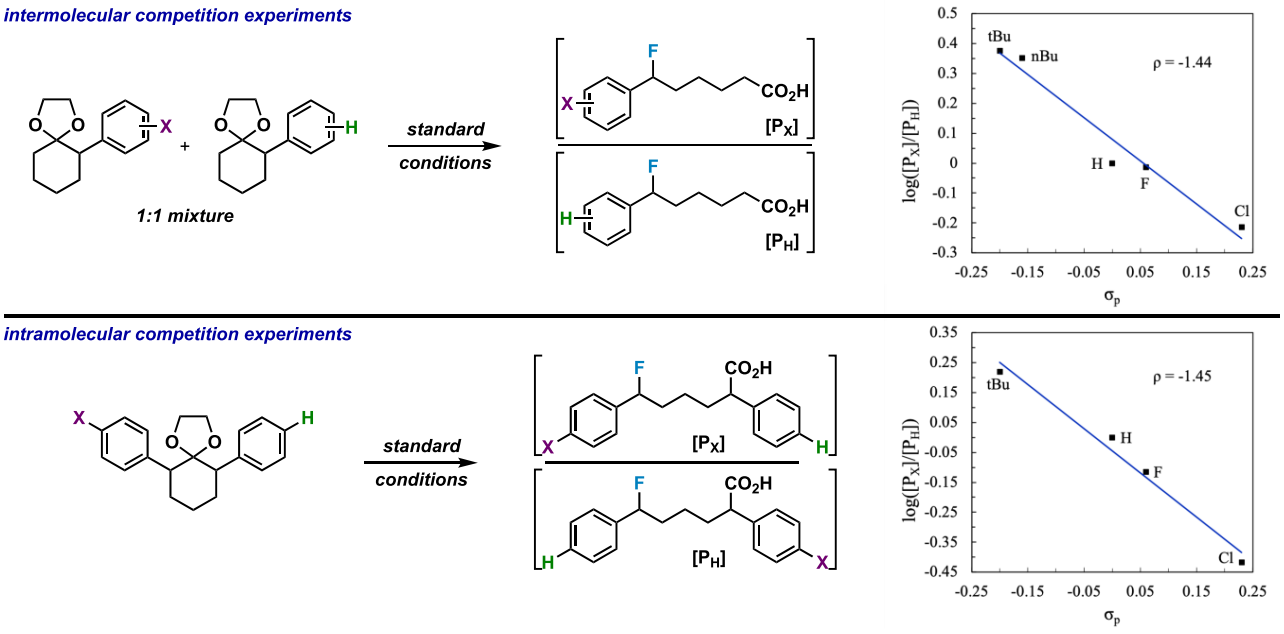


Figure 4. (Top) Intermolecular competition experiments and an associated Hammett plot ($\rho = -1.44$; $R^2 = 0.96$). (Bottom) Intramolecular competition experiments and associated Hammett plot ($\rho = -1.45$; $R^2 = 0.98$).

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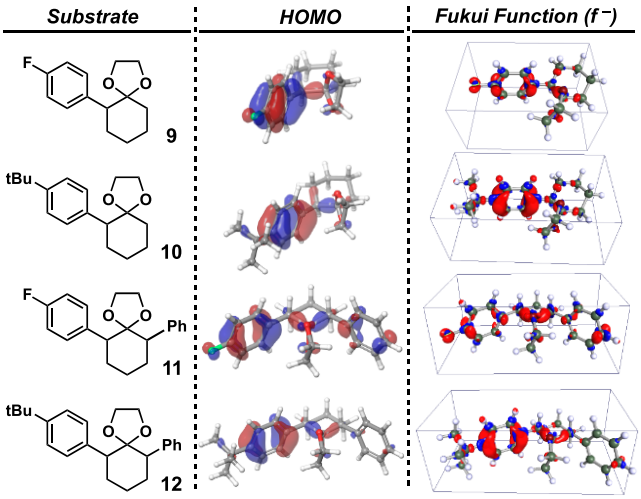
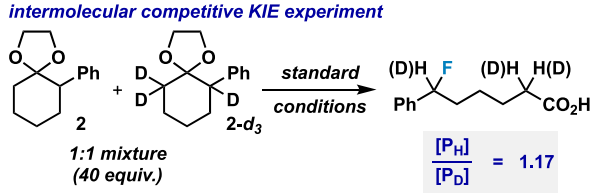


Figure 5. Computed HOMO structures (acetals using ωB97X-D/6-311+G(d,p) level of theory) and Fukui function of spin density (using M06-2X/def2SV(P) level of theory) of substituted mono- and diaryl acetals.

An intermolecular kinetic isotope effect (KIE) experiment was also conducted using compound **2** and compound **2**-d_3; we measured an average $[P_H]/[P_D]$ ratio of 1.17 over two runs, indicative of a small, normal isotope effect (Scheme 8).[53] One

Scheme 8. Observed Kinetic Isotope Effect (KIE) from a Competition Experiment

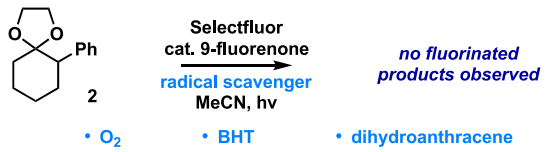


possible explanation for this observation is rate-determining SET to form an acetal radical cation, especially as the contribution of solvent reorganization to SET is suspected to be large.[54] It is important to note that the magnitude of deuterium KIEs in electron transfer reactions can vary greatly depending on the distance between donor and acceptor prior to SET (qualitatively, lower KIE values are believed to be indicative of greater distance between the donor and acceptor in the encounter complex).[54−58]

Mesolytic Cleavage and Benzylic Radical Fluorination. Upon mesolytic cleavage and dissociation of the acetal radical cation, one can think of the intermediate structure simplistically as a separated cation resonance-stabilized as an oxonium ion and a resonance-stabilized benzylic radical (i.e., a distonic radical cation[59]). Thereafter, fluorination of the benzylic radical with Selectfluor would lead to the desired product and form another equivalent of SRD to propagate a single-electron-transfer-based chain mechanism (consistent with the need for only a catalytic amount of 9-fluorenone).

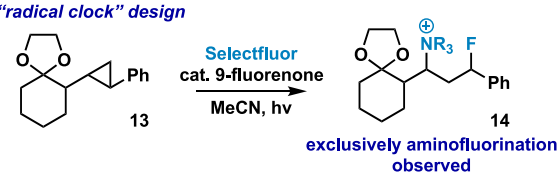
Sammis, Paquin, and co-workers reported that N−F reagents could serve as atomic sources of fluorine in the presence of alkyl radicals in 2012.[4] Since this report, our laboratory and several others have substantiated this finding.[2] In addition, we have shown that similar types of radical fluorination reactions involving Selectfluor tend to shut down entirely in the presence of radical scavengers.[7] Accordingly, we ran reactions under standard conditions in the presence of 0.2−1.0 equiv of dihydroanthracene (DHA) and butylated hydroxytoluene (BHT). In each instance, no fluorinated products were observed by ^{19}F NMR (Scheme 9). We also noted the same result when the reaction is run open to air or under an O_2 atmosphere.

Scheme 9. Reaction Does Not Proceed in the Presence of Known Radical Scavengers



Complementary evidence for the formation of radicals may also come from observed rearrangement of a cyclopropane-based radical clock, in principle.[60] Though it is known that radical ion rearrangements cannot necessarily be equated to trends in rearrangements of neutral radicals.[61] Nonetheless, one "radical clock" design for our system involves inserting a cyclopropane ring between the core acetal structure and the phenyl ring (i.e., to make compound **13**, accessible in a three-step synthetic sequence). Similar arylcyclopropanes are known to rearrange at near-diffusion controlled rates to produce a benzylic radical.[62] Interestingly, under standard reaction conditions, we observed exclusively cyclopropane ring opening/aminofluorination to make compound **14** in lieu of unstrained C−C bond cleavage/fluorination (Scheme 10).[11]

Scheme 10. Radical Clock-Type Experiment Results in Aminofluorination of the Strained C−C Bond of the Arylcyclopropane Moiety



The structure of the radical cation of **13** calculated at ωB97X-D/6-311++G(d,p) (SMD = MeCN) provides some insight. Upon oxidation of **13**, the cyclopropane C−C bond selectively elongates (from 1.51 Å in the neutral structure to 1.70 Å in its oxidized form). Elongation of the relatively "unstrained" C−C bond adjacent to the acetal is not observed. Accordingly, compound **13** does not seem to provide any service as a conventional radical clock; however, the experiment illuminates the importance of having the arene substituent in the 2-position for unstrained C−C bond cleavage to occur.

An alternative "radical clock" design can be envisioned with a norcarane-type core that maintains this requisite 2-aryl substitution pattern.[63] Compound **15** was thus synthesized as a mixture of *cis* and *trans* isomers and subjected to standard C−C bond fluorination reaction conditions (Scheme 11). Subsequently, ^{19}F NMR analysis of the crude reaction mixture unveiled an extremely complex (and later proved to be inseparable) mixture of fluorinated products. The ^{1}H NMR spectrum of the crude reaction mixture was consistent with the

https://doi.org/10.1021/jacs.3c06477
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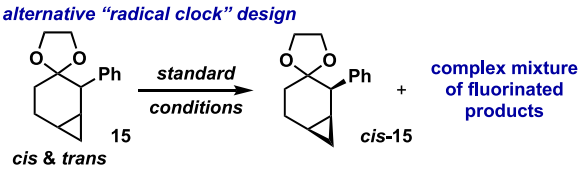
Scheme 11. Alternative Radical Clock-Type Experiment with Compound 15 Results in Kinetic Resolution of Cis Isomer and a Complicated Mixture of Fluorinated Products



formation of multiple secondary and some primary fluorinated products (see the Supporting Information for details). Additionally, signals in the alkene region were observed that suggest cyclopropane ring opening likely occurred to some extent, although we were unable to isolate these compounds from the complex product mixture to confirm identity.

Interestingly, analysis of the ^{1}H NMR spectrum of the crude reaction mixture also revealed something unexpected: kinetic resolution of the starting material (Scheme 11). That is, we found the *cis* isomer of **15** to be significantly less reactive (or unreactive) under standard conditions relative to the *trans* isomer. This indicates that *trans*-**15** is more readily oxidized by SRD than *cis*-**15**. Ultimately, both radical clock designs support the involvement of radical cation intermediates and provide some insight into how both arene position and conformational effects can dramatically influence C−C fluorination.

Proposed Mechanism. Based on the results of the experiments provided above, we can propose a reasonable mechanism (Figure 6). Chemical transformation of 9-fluorenone in the presence of Selectfluor suggests that 9-fluorenone is playing the role of a *photoinitiator*, assisting in generation of the key SRD intermediate. Then, the SRD and the acetal substrate undergo an SET reaction whereby an acetal radical cation is formed. Upon dissociation of this radical cation, the resultant benzylic radical is rapidly fluorinated in the presence of Selectfluor to provide the product of C−C cleavage/fluorination (which is then transformed to a carboxylic acid during LiOH workup). Finally, the SRD is formed once more and propagates an SET-based radical chain mechanism.

Competition between C−H and C−C Fluorination. The most remarkable aspect is that the proposed SRD intermediate is theoretically capable of either HAT (C−H fluorination) or SET (C−C fluorination) on these 2-aryl-substituted acetal substrates, yet SET tends to be the preferred pathway. In contrast, we previously showed that other classes of acetals (e.g., acetonide or certain spiro acetals[64]) favor α-ethereal C−H fluorination through HAT.[24] Could a HAT-type pathway also be operative in fluorination of 2-aryl-substituted acetal substrates to some extent?

Upon careful investigation of the ^{19}F NMR spectra of the crude mixtures following reactions with compounds **2**, **7**, **9**, **10**, and **16**−**19**, we discovered that C−H fluorination byproducts account for a significant amount of the material balance under C−C fluorination reaction conditions (Table 1). (This was originally overlooked as many of the C−H fluorination products are evidently unstable toward column chromatography.) The apparent competition between C−C and C−H fluorination pathways on the same substrate class is notable in and of itself, but what is more striking is the observed selectivity in the HAT pathway. Most often, either 1 or 2 major HAT byproducts were observed (relative to other HAT byproducts). Based on ^{19}F NMR chemical shifts (δ), it is evident in most cases that C−H fluorination occurred preferentially on the cyclohexane ring, as opposed to in the more intuitive α-ethereal position.[66] Products of arene C−H amination by SRD, as previously observed by Ritter and co-workers, were also not formed to any major extent, if at all.[65]

Closer inspection of the ^{19}F NMR data following fluorination of our prototypical substrate (compound **2**) reveals a dddd (J = 48.4, 29.2, 23.4, and 10.9 Hz) centered at −193 ppm. The splitting pattern is consistent with C−H fluorination occurring at the C3 site, and both the chemical shift and J-values suggest the C−F bond is in the axial position, cis to the phenyl ring (Figure 7).[66] The ^{19}F NMR spectra of other substrates in Table 1 also indicate that another HAT

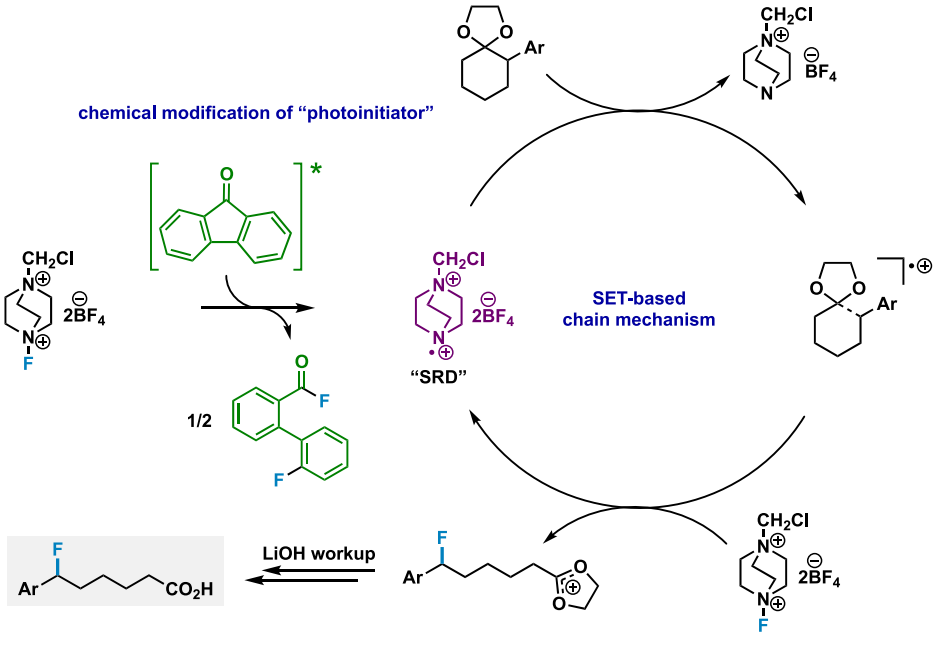


Figure 6. Proposed mechanism for 2-aryl-substituted acetal C−C bond fluorination based on experimental evidence.

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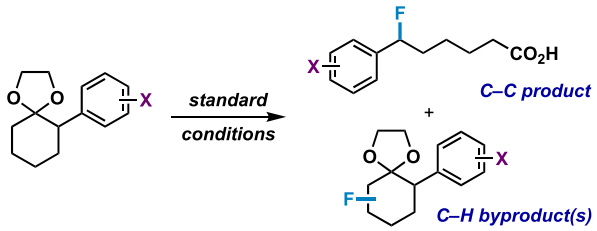
Table 1. Competitive Formation of C−H Fluorination Byproducts Observed under C−C Bond Fluorination (SET) Conditions



compound	X	C–C	C–$H_{cyclohexane}$[a]	C–$H_{\alpha\text{-ethereal}}$[a]
10	*p*-^{t}Bu	64%	30%[b]	–
16	*p*-^{n}Bu	47%	24%[b]	–
7	*m*-^{t}Bu	58%	38%[b]	–
2	H	60%	29%[c]	–
9	*p*-F	70%	18%[b]	–
17	*p*-Cl	54%	18%[b]	–
18	*m*-F	35%	15%[b]	47%
19	*m*-Cl	20%	8%[c]	16%

Yields were determined by ^{19}F NMR analysis of the crude reaction mixture. [a]Combined yields of all C−H fluorination products observed. [b]Two major C−H fluorination products observed. [c]One major C−H fluorination product observed.

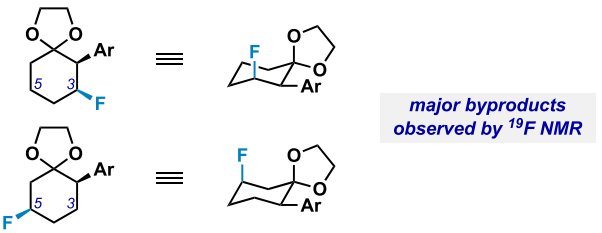


Figure 7. C−H fluorination byproducts formed upon submitting compounds in Table 1 to standard C−C fluorination conditions.

byproduct forms with the C−F bond in the axial position; we have attributed this to fluorination at C5 (see the Supporting Information for details).

Transition State Study: C−H Fluorination. This prompted an extensive transition state (TS) study on the feasibility of HAT from **2** by SRD at various sites computed using the ωB97X-D/6-31+G(d,p) (SMD = MeCN) level of theory and Gaussian 16 software package.[67] Consistent with our observed selectivity trends, the lowest energy TS structures were associated with abstraction of the C−H bonds at C3 and C5 to form **INT-C3** and **INT-C5**, as well as **20** (Figure 8). The activation energy barriers ($\Delta G^{\ddagger}$) for HAT were determined to be 7.5 kcal/mol for the C5 hydrogen atom vs 6.5 kcal/mol for the hydrogen atom at C3, respectively. Note that these HAT steps are also predicted to be exergonic (ΔG° = −13.5 kcal/mol for C5 and −10.8 kcal/mol for C3). Notably, among these structures, equatorial hydrogen atom abstraction at C3 via $\mathbf{TS_{C3}}$ was preferred by 1.0 kcal/mol. To contextualize these findings, our previous TS study on HAT from galactose diacetonide (a substrate in which only HAT-type fluorination occurred) determined an activation energy barrier of 7.4 kcal/mol, which is in reasonable accord.[24] These values are also lower than activation energy barriers reported for HAT reaction mechanisms involving quinuclidine-based *N*-centered radical cations by several kcal/mol.[68]

In terms of $\mathbf{TS_{C3}}$, attack of radical dication SRD at the cyclohexyl ring equatorial C−H bond located at carbon atom C3 occurs with bond breaking and bond making distances of 1.64 and 1.15 Å. These bond breaking and making events are consistent with the HOMO−2 of the HAT manifold and neighboring ring systems (Figure 8, top right-hand side). In this case, the transferring hydrogen carries a calculated partial positive charge of 0.2, which is not unusual for HAT.[69] As for potential inner-sphere PCET involving the nearby phenyl group, the theoretical criteria of Mayer and co-workers would seem to disfavor this possibility.[70] (Though we note that stepwise electron transfer/proton transfer (ET/PT) processes involving SRD instead of or in addition to HAT cannot be ruled out.[71]) Also present were stabilizing noncovalent interactions, largely between SRD and the proximal phenyl group−clearly visible from the NCI plot (see the Supporting Information for details). Moreover, steric interactions were minimal. It is perhaps interesting that in the present case, favorable cation-aryl group interactions outcompete the directing-group-type effect offered by the acetal motif for HAT, as seen in the transition states for C3 and C5 hydrogen atom abstraction. This favored HAT reactivity at carbon atom C3 is fully consistent with experimental results, providing rapid stereoinversion and fluorination of the resulting carbon-based radical by Selectfluor.

SET vs HAT with SRD in Broader Context. Over the past decade, we have developed several fluorination reactions wherein the Selectfluor-derived radical dication (SRD) is a proposed intermediate.[2] Among various substrate classes, we have detailed observations suggesting HAT selectivity can be guided by innate polar effects[72] or, alternatively, various substituent directing effects. We have also reported SRD playing the role of an oxidant in SET reactions with strained-ring-containing substrates (e.g., cyclopropyl alcohols and arylcyclopropanes). The 2-aryl-substituted acetal substrate class is relatively unique in the sense that products are observed that suggest seemingly both SET and directed HAT-type mechanistic pathways could be operative, with C−C fluorination being favored (discussed above). In the final stage of our study, we examined the energetics of SET across various substrate classes studied by our group and others over the years, many of which were assumed to proceed through a HAT-type mechanism (Table 2).

In a hypothetical SET reaction between the SRD and a substrate, the Gibbs free energy of activation may be described and predicted by Marcus−Hush theory.[73−82] Using a DFT-based approach (calculations performed at ωB97X-D/6-311++G(d,p) (IEPCM = MeCN)), the activation energy barriers ($\Delta G^{\ddagger}$) of electron transfer can be calculated using eq 2:[83]

$$\Delta G^{\ddagger} = \frac{(\Delta G^{0}_{ET} + \lambda_{tot})^2}{4\lambda_{tot}} \quad (2)$$

Here, the Gibbs free energy of the electron-transfer reaction (ΔG°_{ET}) is readily determined by $\sum G_{products} - \sum G_{reactants}$ following straightforward geometry optimizations, and the total reorganization energy (λ_{tot}) accounts for both inner-sphere (λ_{in}) and outer-sphere (λ_{out}) reorganization energy components, as per eq 3:[84]

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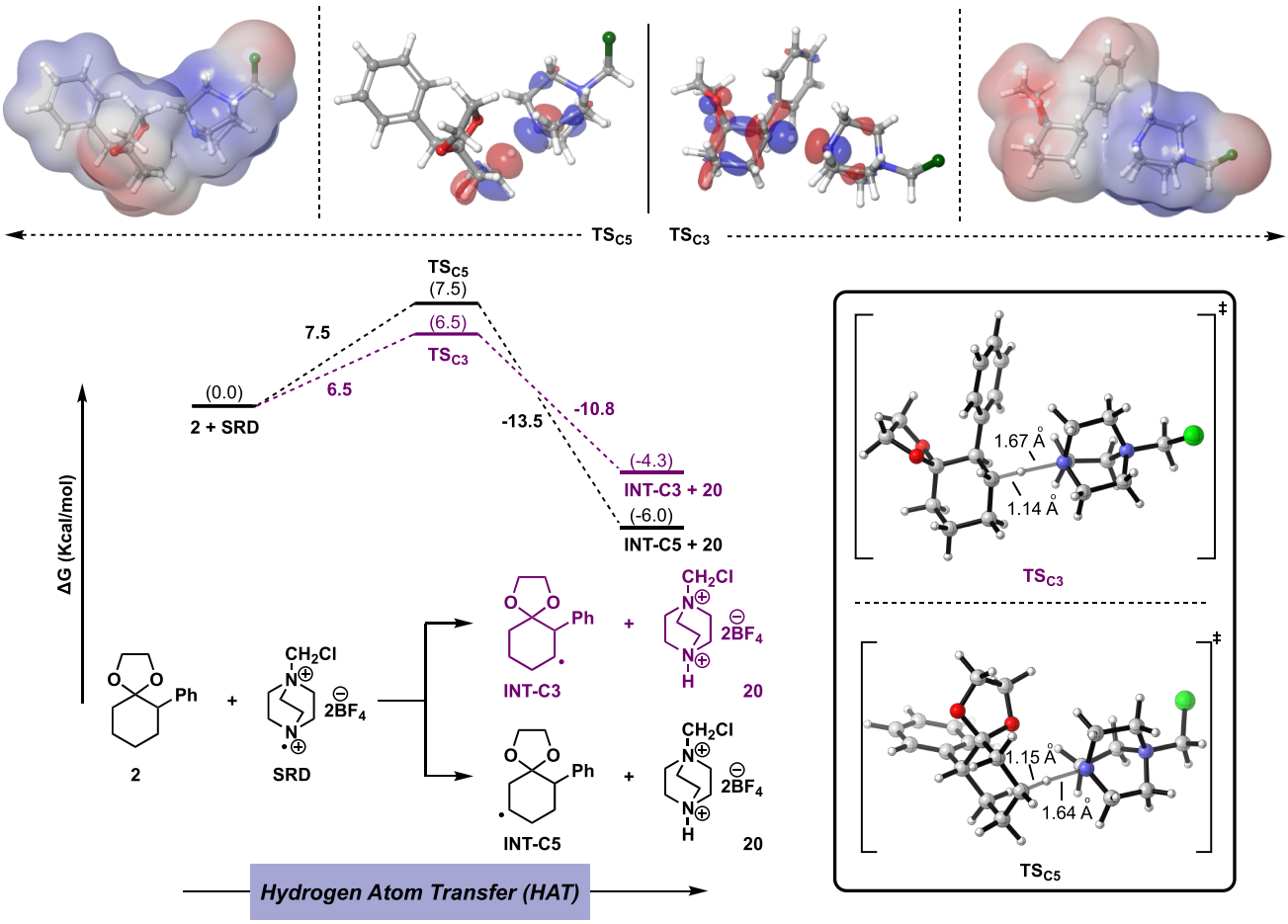

Figure 8. Energy profiles of HAT of axial C−H bonds at C3 and C5 calculated at the ωB97X-D/6-31+G(d,p) (SMD = MeCN) level of theory. The figure includes the molecular electrostatic potential (MEP) and HOMOs for both **TS$_{C5}$** and **TS$_{C3}$**.

$$\lambda_{tot} = \frac{\lambda_{in} + \lambda_{out}}{2} \quad (3)$$

The inner-sphere reorganization energy term (λ_{in}) is associated with molecular structural distortions that occur following SET to reach the lowest energy ground states of the products. It can be calculated using Nelsen's four-point method, as per eq 4:[84]

$$\lambda_{in} = \Delta E^{react}_{aq,ET} - \Delta E^{react}_{aq,calc,ET} \quad (4)$$

Lastly, the outer-sphere reorganization energy term (λ_{out}) is associated with changes in the solvent environment that accompany SET. It can be calculated using a modified two-sphere model, as per eq 5:[84,85]

$$\lambda_{out} = \Delta e^2 N_A \left(\frac{1}{2r_D} + \frac{1}{2r_A} - \frac{1}{R}\right)\left(\frac{1}{\varepsilon_o} - \frac{1}{\varepsilon_s}\right) \quad (5)$$

Here, Δe is the total number of charge transferred, N_A is the Avogadro's number, r_D is the ionic radii of the donor molecule (substrate), r_A is the ionic radii of the acceptor molecule (SRD), R is the sum of r_D and r_A, ε_o is the optical dielectric constant of the solvent (1.34 for MeCN), and ε_s is the dielectric constant of the solvent (37.5 for MeCN).[86] See the Supporting Information for additional details regarding these calculations.

While this type of DFT-based approach has predicted activation energy barriers in good agreement with experimental results in many instances,[87−89] there are also several notable limitations worth mentioning. For instance, this approach does not consider the nature and significance of encounter complexes, outer-sphere reorganization energy is estimated using a classical dynamic method as opposed to a quantum mechanical analysis of explicit solvent-molecule interactions, and hard assumptions are made about the curvatures of the parabolas that may affect the accuracy of the inner-sphere reorganization energy term.[90,91] In this light, we suggest that a more prudent interpretation of the following results across a subset of theoretical SET reactions in our system (Table 2) considers general (qualitative) trends and relative differences on the order of several kcal/mol rather than absolute (quantitative) values of calculated λ_{tot} and $\Delta G^{\ddagger}$.

Consistent with a favorable SET reaction between SRD and our model substrate (**2**), the DFT-based Marcus−Hush theory analysis predicts a low activation energy barrier and an overall exergonic process (ΔG°_{ET} = −18 kcal/mol). In contrast, upon removal of the 2-aryl substituent from the substrate (i.e., to make **21**), the SET reaction with SRD is predicted to be nearly thermoneutral. Note that C−C bond cleavage/fluorination is not observed when subjecting **21** to standard reaction conditions. In this case, one interpretation is that back-electron transfer effectively may stifle productive fluorination.

Next, we applied this analysis to a hypothetical SET reaction with compound **22**—an acetal that undergoes exclusively HAT-type fluorination in the presence of SRD.[24] The results are consistent with SET being less favorable, as the overall

https://doi.org/10.1021/jacs.3c06477
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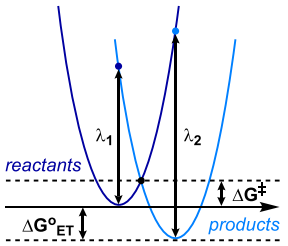
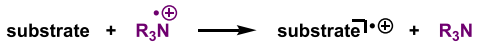
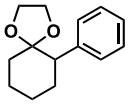
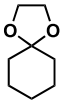
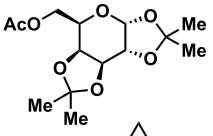
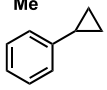
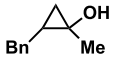
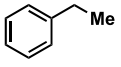
Table 2. Free Energies of Electron Transfer ($\Delta G°_{ET}$) and free energies of activation ($\Delta G^{‡}$) were calculated for various substrates in the presence of SRD using ωB97X-D/6-311++G(d,p) (IEPCM = MeCN)





compound	substrate	$\Delta G°_{ET}$	$\Delta G^{‡}$
2		-18	1.0
21		-1.7	1.6
22		4.0	4.8
23		-12	0.6
24		-25	2.7
25		16	16
26		6.7	6.9
27		-5.3	0.6
28		-5.5	0.3

process is predicted to be endergonic ($\Delta G°_{ET}$ = +4.0 kcal/mol). Additionally, the activation energy barrier was determined to be several kcal/mol higher than that for the SET reaction with **2**.

To extend our analysis beyond acetal substrates, we examined compounds with strained cyclopropane rings (**23** and **24**) that are known to undergo C−C bond fluorination under similar reaction conditions.[11,12] As anticipated, SET processes between SRD and both substrates are predicted to be exergonic (−12 and −25 kcal/mol) and have relatively low activation barriers. Note that a previous study provided experimental support for one-electron oxidation of **23** by SRD,[11] but the feasibility of SET between **24** and SRD was not initially considered.[12]

On the opposite end of the spectrum, we examined alkanes such as cyclohexane (**25**) and adamantane (**26**) that are known to undergo C−H fluorination in the presence of SRD, most likely through a HAT-type process based on previous studies.[6,7,9] In both cases, hypothetical SET reactions with SRD are predicted to be thermodynamically unfavorable ($\Delta G°_{ET}$ = +16 and +6.7 kcal/mol). Moreover, the activation energy barriers are predicted to be significantly higher (in some cases by over an order of magnitude) than other entries in Table 2. The energetics are consistent with previous studies that have concluded a HAT-type mechanism is more likely operative than a stepwise electron-transfer proton-transfer (ET/PT) for this substrate class.

Lastly, we assessed the feasibility of SET between SRD and both toluene (**27**) and ethylbenzene (**28**). These substrates are known to undergo C−H fluorination in the benzylic position.[6,7,92,93] While a HAT mechanism has been assumed previously by analogy to alkane fluorination, our analysis of the reaction energetics reveals that SET to SRD could indeed play an important role in benzylic C−H fluorination mechanisms. Not only are the overall SET processes predicted to be energetically downhill in each case (−5.3 and −5.5 kcal/mol), but the activation energy barriers are also on the order of those predicted for other SET reactions that result in radical fluorination (i.e., involving substrates **2**, **23**, and **24**).

These results suggest that benzylic C−H fluorination reactions involving the SRD intermediate could proceed through an ET/PT pathway rather than HAT, though this must be considered on a case-by-case basis. The ET/PT pathway ultimately leads to the same benzylic radical intermediate that would be proposed for HAT; however, this subtle switch in mechanisms may be responsible for differences in reactivity/selectivity patterns we observed, for instance, in the original Cu-initiated C−H fluorination reactions we studied in 2014 that remained unclear.[7] Additionally, while ET/PT pathways in photochemical benzylic fluorination reactions have been proposed involving strong photo-oxidants such as 1,2,4,5-tetracyanobenzene, the notion of SRD playing a key role in ET/PT in benzylic fluorination was not originally contemplated.[94,95] Furthermore, the putative involvement of arene oxidation in benzylic C−H fluorination illuminates the stipulation of having an aryl substituent in the 2-position of the acetal for C−C bond fluorination to be favored over C−H fluorination.

CONCLUSION

At the outset, we aimed to elucidate the mechanism of photoinduced "unstrained" C−C bond cleavage and fluorination of 2-aryl-substituted acetals in the presence of Selectfluor and catalytic 9-fluorenone. To our surprise, 9-fluorenone was found to undergo a chemical transformation and serve as an *initiator* (as opposed to participating in triplet energy transfer or PET) whose primary role is to access a key Selectfluor-derived radical dication (SRD) intermediate. The SRD appears to engage in a SET event with the acetal substrate to form an acetal radical cation (supported by, e.g., LFER, KIE, and DFT studies). Finally, substituent-directed mesolytic cleavage/dissociation of the acetal radical cation leads to a benzylic radical intermediate that is fluorinated rapidly in the presence of Selectfluor. This step reforms the SRD and propagates an SET-based chain propagation mechanism, in contrast to our

https://doi.org/10.1021/jacs.3c06477
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original thought that 9-fluorenone played a role in the catalytic cycle. During two separate attempts to corroborate the role of 9-fluorenone as merely an initiator, we also demonstrated proof of concept for two new methods for acetal C−C cleavage fluorination. That is, we provide evidence that the same transformation can be accomplished either chemically (using BEt_3/O_2) or electrochemically, underscoring the value of mechanistic elucidation as a guide for method development.

Considering that the same SRD intermediate has been proposed to fluorinate α-ethereal C−H bonds in other classes of acetals, we also sought to better understand the subtleties surrounding the mechanistic switch between apparent HAT and SET pathways. Careful ^{19}F NMR analyses of the C−C fluorination reactions on the 2-aryl-substituted acetal substrate class revealed C−H fluorination byproducts that are formed with some degree of selectivity, not through α-ethereal fluorination, but in a manner that suggests a directing effect from the aryl group (or, in some substrates, possibly also a directing effect from an oxygen atom on the acetal[96]) through space. Detailed transition state studies and the examination of energetic profiles seem consistent with this idea. We then extended our study further to examine the feasibility of SET within other substrate classes known to undergo either C−H or C−C bond fluorination under similar conditions using a DFT-based Marcus−Hush theory analysis. Interestingly, we posit that some previously reported transformations that look like HAT (e.g., benzylic C−H fluorination reactions involving Selectfluor) are arguably ET/PT processes. Effectively, this alters the way one might think about the development of new fluorination methods using Selectfluor and provides overdue insight regarding previously observed discrepancies between aliphatic and benzylic C−H fluorination reactions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.3c06477.

Experimental procedures, characterization data, NMR spectra, and computational details (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

T.L. thanks the NSF (2102116) for support. T.D. thanks the Natural Sciences and Engineering Research Council of Canada for Discovery Grants (RGPIN-2019-04205). This research was enabled in part by the support provided by SHARCNET (Shared Hierarchical Academic Research Computing Network) and Compute/Calcul Canada and the Digital Research Alliance of Canada. C.R.P. thanks the University of California, Davis, for financial support, as well as the UC Davis core NMR facility.

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