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Aminofluorination of Cyclopropanes: A Multifold Approach through a Common, Catalytically Generated Intermediate

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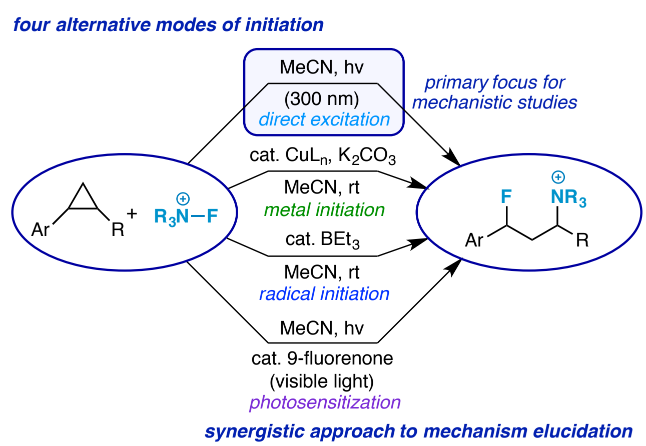
ABSTRACT: We have discovered a highly regioselective aminofluorination of cyclopropanes. Remarkably, four unique sets of conditions – two photochemical, two purely chemical – generated the same aminofluorinated adducts in good to excellent yields. The multiple, diverse ways in which the reaction could be initiated provided valuable clues that led to the proposal of a "unifying" chain propagation mechanism beyond initiation, tied by a common intermediate. In all, the proposed mechanism herein is substantiated by product distribution studies, kinetic analyses, LFER's, Rehm-Weller estimations of ΔG_{ET}, competition experiments, KIE's, fluorescence data, and DFT calculations. From a more physical standpoint, transient-absorption experiments have allowed *direct spectroscopic observation* of radical ion intermediates (previously only postulated or probed indirectly in photochemical fluorination systems) and, consequently, have provided kinetic support for chain propagation. Lastly, calculations suggest that solvent may play an important role in the cyclopropane ring-opening step.

Introduction. Organic methods are rarely *universal* - functional group and reagent compatibility can differ immensely from substrate to substrate, changing "the ideal synthetic method" from case to case. Accordingly, one of the greatest advantages a synthetic chemist can possess is a set of different methods to try - the ability to carry out a transformation under a variety of conditions. Along these lines, we have simultaneously discovered a cluster of reaction conditions – two photochemical, two purely chemical – for the direct, highly regioselective aminofluorination of cyclopropanes. In particular, we report the formation of 1,3-aminofluorinated products from arylcyclopropanes and N-F reagents through 1) direct photoexcitation, 2) metal initiation, 3) radical initiation, and 4) photosensitization (Scheme 1). Moreover, the multifold manner in which the reaction can be initiated allows us to propose a "unifying" chain propagation mechanism.

From a synthetic perspective, the development of diverse, direct aminofluorination reactions is of particular interest, given that nitrogen and fluorine represent two of the most important atoms in modern medicine[1] and agrochemistry.[2] Recently, geminal aminofluorination of diazo compounds[3] and direct 1,2-aminofluorination reactions of alkenes have emerged;[4] however, the 1,3-substitution of cyclopropanes reported herein accesses an entirely unique class of aminofluorinated adducts to serve as synthetic building blocks. From a mechanistic viewpoint, transition metal-promoted sp^3 C-H fluorination[5] and decarboxylative fluorination[6] methods have been studied in depth. Yet, *photochemical fluorination* tactics, despite their synthetic utility, are only ephemerally understood. Though discrete among existing fluorination reactions, the aminofluorination mechanism reported herein confirms the involvement of radical ions through direct spectroscopic observation, but also demonstrates that photochemical fluorination methods are more intricate than previously proposed in the literature. It is our hope that this study will promote further mechanistic investigation in the field to usher in new "photochemical fluorination" reaction development, optimization, and application.

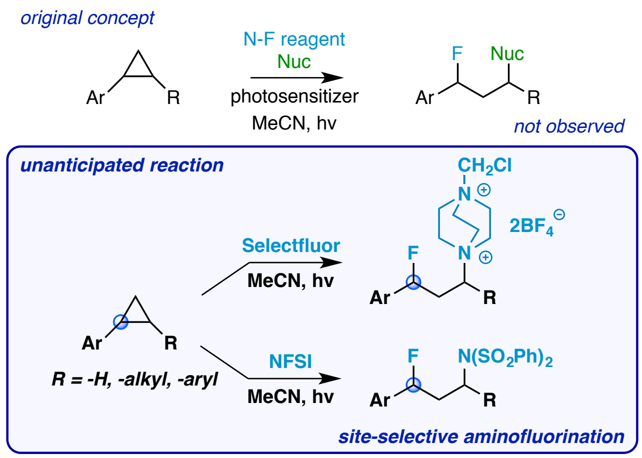
Reaction Discovery. Our aim was to merge photosensitized "three-electron" nucleophilic substitution reactions on arylcyclopropane compounds[7] with our longstanding interest in the fluorination of catalytically generated sp^3-carbon radicals.[8,9] Accordingly, we screened several combinations of photosensitizers, nucleophiles, and N-F reagents with 1,2-diphenylcyclopropane under irradiation in MeCN. The *same* signals were observed in the crude ^{19}F NMR spectra in nearly all instances – except with respect to the use of Selectfluor versus *N*-fluorobenzenesulfonimide (NFSI). Control reactions revealed that although irradiation proved essential, both the putative photosensitizers and external nucleophiles were unnecessary for product formation. Upon closer inspection, we determined that the irradiation of 1,2-diphenylcyclopropane in the presence of Selectfluor or NFSI in MeCN at 300 nm produces the ring-opened aminofluorinated adducts shown in Scheme 2 regioselectively.

Scheme 1. *Four unique aminofluorination tactics provide a synergistic approach to mechanism elucidation.*



We sought to understand the mechanism of this unusual aminofluorination reaction and, to our surprise, discovered three alternative modes of initiation along the way - using copper(I) salts, triethylborane, or a visible light photosensitizer. What is more, our data suggest that all four methods generate a common intermediate - a Selectfluor-derived radical dication (previously postulated by our laboratory)[5] - allowing us a synergistic approach to mechanism elucidation.

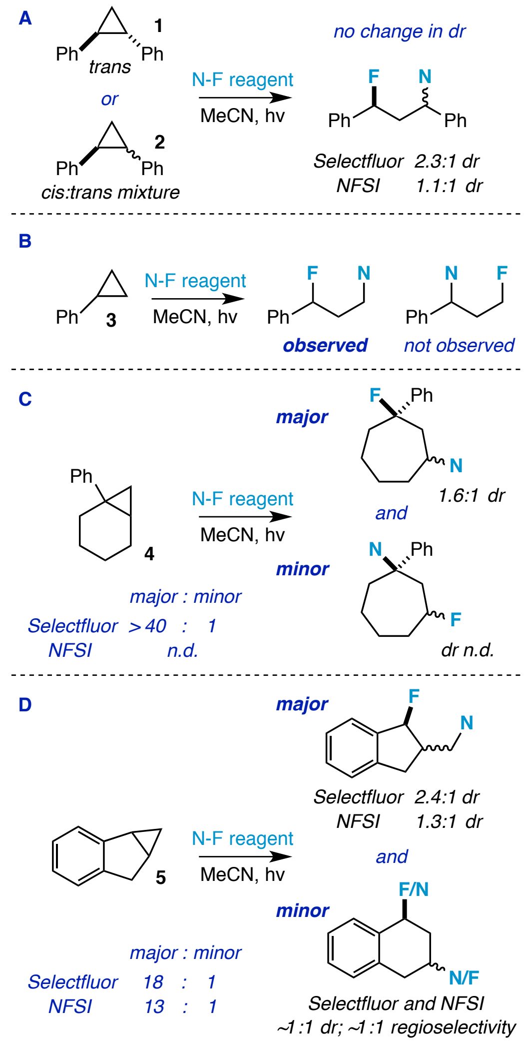
Scheme 2. *Discovered aminofluorination reaction.*



Product Distribution Studies. Initial mechanistic study involved probing the selectivity of the reaction with both Selectfluor and NFSI on a variety of substrate types (primarily accessed by a modified Simmons-Smith cyclopropanation).[10] Depending on the nature of the substrate, the resultant regio- and diastereoselectivity of a reaction can provide some valuable insight. For example, one may be able to ascertain whether functionalization occurs in a stepwise or concerted manner, obtain information about steric/electronic influence, and also monitor trends in the stabilities of putative intermediates.[11] Following up on our initial investigation of 1,2-diphenylcyclopropane, we studied the effect of the starting geometry on diastereoselectivity (as this reaction affords two spectroscopically distinct diastereomers by ^{19}F NMR). Although Selectfluor (2.3:1) and NFSI (1.1:1) provided products in slightly different diastereomeric ratios, an identical result is obtained when either pure *trans*-1,2-diphenylcyclopropane **1** or a *cis*:*trans* mixture **2** is employed (Scheme 3, A). This result, in tandem with the overall low diastereomeric ratios, suggests a stepwise mechanism over a concerted one; however, this alone may be insufficient evidence. The stereochemical integrity of the substrate is potentially compromised by photochemical isomerization (via formation of a biradical intermediate).[12] With this in mind, could the N-F reagent be fluorinating the biradical?

The notion of a radical fluorination followed by radical combination (to form the C-N bond) of a biradical intermediate prompted an investigation of a substrate that is not susceptible to isomerization – phenylcyclopropane **3** (Scheme 3, B). In all likelihood, if the biradical were fluorinated in this fashion, then the major product (or at least some product) would be the primary fluoride, as opposed to the benzylic fluoride, following conventional trends in radical reactivity. Yet, the primary fluoride was not observed under any circumstance. Thus, fluorination appears to occur at the most substituted/resonance-stabilized position. To investigate this claim further, the regioselectivity of the reactions with 1-phenylbicyclo[4.1.0]heptane **4** displays an overwhelming preference for fluorination in the tertiary benzylic position (Scheme 3, C). Note that aminofunctionalization also occurs in the more substituted position, affording only the ring-expanded products shown in low diastereomeric ratios (e.g. 1.6:1). These observations argue against the aforementioned biradical fluorination/combination pathway. On the other hand, they may be consistent with the ring opening of a radical cation intermediate (see below).[13]

Scheme 3. *Diastereoselectivity and regioselectivity probes.*



A seemingly anomalous result surfaced when we employed the rigid arylcyclopropane **5** derived from indene (Scheme 3, D). Consistent with previous substrates, fluorination occurred most favorably in the secondary benzylic position of the major product, and low diastereomeric ratios were obtained. Conversely, instead of favoring ring-expansion to form the tetralin derivative, the cyclopropane ring opened to provide the primary aminofunctionalized adduct. Such regioselectivity may be explained by involvement of a radical cation intermediate. In fact, this less-substituted ring-opening behavior has been previously observed from the indene-derived cyclopropane radi

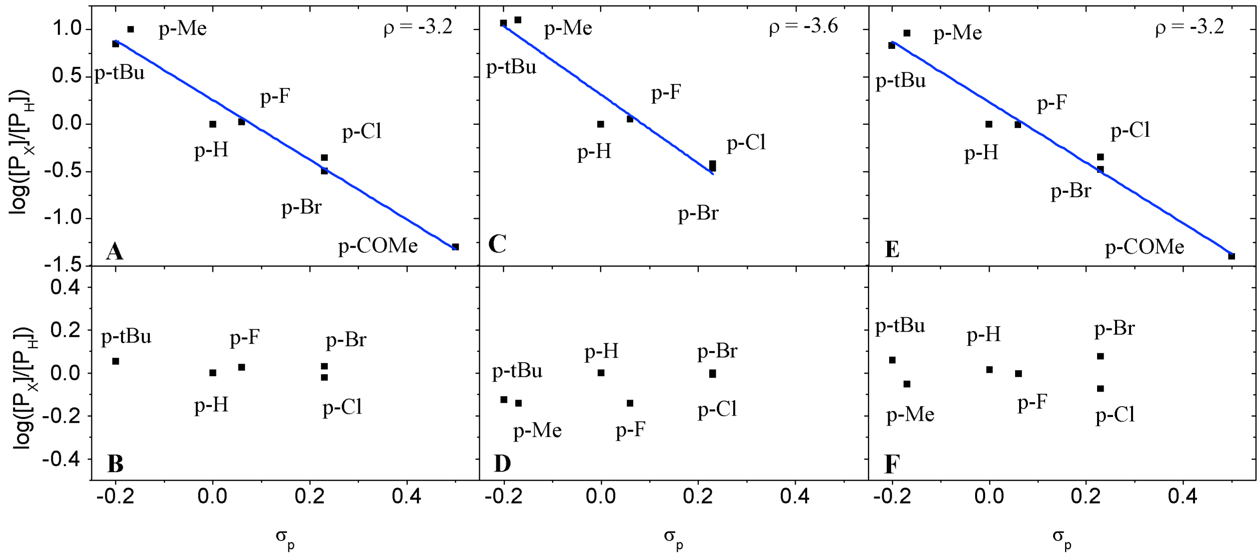


Figure 1. *Intermolecular (top row) and intramolecular (bottom row) Hammett plots. Conditions:* ***A***, ***B*** *= Selectfluor and 300 nm irradiation,* ***C***, ***D*** *= NFSI and 300 nm irradiation,* ***E***, ***F*** *= Selectfluor and catalytic* BEt_3*.*

cal cation; literature precedent suggests that the ring-opening step of this particular intermediate may be largely influenced by orbital overlap with the π-system (consistent with our observed regioselectivity).[14,15] Notably, the authors segregate the behavior of this compound from the "less rigid" arylcyclopropane radical cations that are often functionalized in the "more substituted" positions (consistent with all selectivity observed in Scheme 3).

In summation, for both Selectfluor and NFSI, these initial product distribution studies 1) hint at a stepwise mechanism, 2) reveal a preference for fluorination in the most substituted/resonance-stabilized position in all major products, and 3) prompt a search for evidence of arylcyclopropane radical cation intermediates.

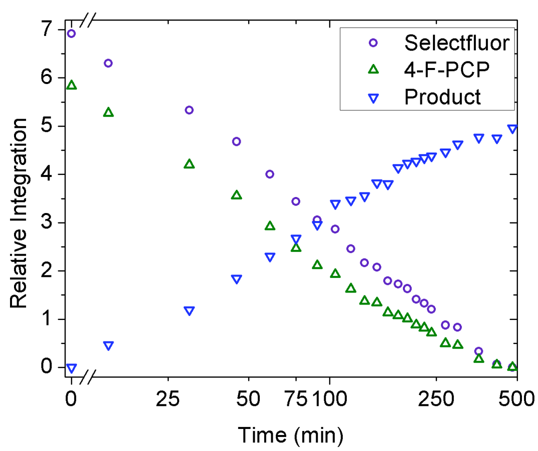
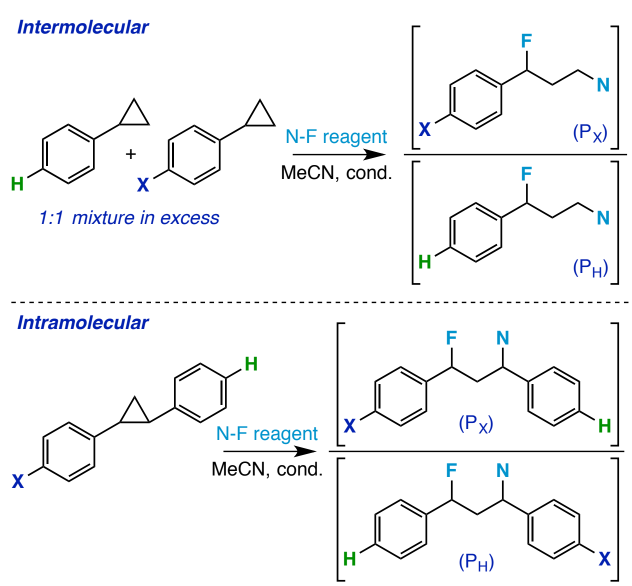


Figure 2. *Kinetic profile of 4-fluorophenyl cyclopropane, Selectfluor, and aminofluorination product.*

Linear Free Energy Relationships. After these selectivity studies, a preliminary kinetic analysis was conducted. We monitored a reaction by ^{1}H and ^{19}F NMR and observed a kinetic profile characterized by a concomitant decrease of 4-fluorophenylcyclopropane and Selectfluor (Figure 2). Both display an apparent first-order decay, but note that the concept of "reaction order" becomes less straightforward in photochemical systems where the rate of light absorption may be a controlling factor.[16] Without knowing much about the mechanism at this juncture, we believed competition experiments would provide more useful information. Turning to linear free energy relationships, we uncovered additional support for radical cation intermediates.

The study of *para*- and *meta*-substituent effects on relative reaction rates can reveal potent information regarding charge development over the course of the rate-determining step.[17] As phenylcyclopropane and 1,2-diphenylcyclopropane provide rich opportunities for Hammett analyses, we prepared a variety of substituted phenyl- and 1,2-diphenylcyclopropanes. Analysis of the substituted 1,2-diphenylcyclopropanes was straightforward as a series of intramolecular comparisons (Scheme 4). Alternatively, the relative rates of reactions of substituted phenylcyclopropanes were obtained by assessment of relative product distributions in intermolecular competition experiments, whereby both substrates were run in the same reaction vessel in excess of the N-F reagents ($[P_X]/[P_H]$).

Scheme 4. *Hammett plot competition experiments.*



In the instance of *para*-substituted phenylcyclopropanes, fairly large, negative ρ values were measured for both Selectfluor (-3.2) and NFSI (-3.6) with good correlation using Hammett σ_p values (Figure 1, **A** and **C**).[18] Additionally, *meta*-substituent plots provided ρ values of -4.2 and -4.6, respectively (see Supporting Information). This denotes 1) a buildup of a positive charge during the rate-determining step and 2) reaction sensitivity to both resonance and inductive effects. Although ρ values for formal cationic intermediates are typically greater in magnitude,[19] these values could suggest the involvement of arylcyclopropane radical cation intermediates.[20]

For another perspective, we examined the results of intramolecular competition experiments with *para*-substituted 1,2-diphenylcyclopropanes. The structures of an array of arylcyclopropane radical cations have been studied extensively both computationally[21] and spectroscopically;[22,26] although some arylcyclopropanes exhibit closed radical cation geometries, diarylcyclopropanes have been determined to be *open*.[28] Our idea was that substituted diarylcyclopropanes, with the possibility of open geometries, could display divergent behavior in a Hammett plot. In fact, whereas the intermolecular competitions showed good correlation, these intramolecular competitions provided little to no correlation with Hammett σ_p or σ^+ values (Figure 1, **B** and **D**).[23]

This largely diminished substituent effect in the intramolecular competitions now opens up possible interpretations of either rate-determining oxidation or ring opening. The former scenario seems more likely *prima facie*, but equilibrium isotope effect (EIE) calculations on arylcyclopropane oxidation suggest upper bounds for kinetic isotope effects (KIE's) that are well below the observed KIE's in Table 3 (1.05 for phenylcyclopropane and 1.18 for 1,2-diphenylcyclopropane at wB97XD/6-311++G** [MeCN]). Therefore, oxidation is unlikely rate-determining; on the other hand, additional KIE calculations (below) suggest that rate-determining ring opening of the radical cation intermediate is plausible. In this light, there is evidently minimal impact of the substituents on the ring opening transition states of the two competing sites, each of which is part radical and part cation being attacked by a weak solvent nucleophile.

Together, the results of the Hammett plots begin to build a strong case for arylcyclopropane radical cation intermediates, leading to another important question: how are these radical ions being generated?

On Photoinduced Electron Transfer. Arylcyclopropane radical cation intermediates have been accessed and studied by electron transfer quenching of the excited states of various singlet or triplet acceptors (e.g. 1,4-dicyanonaphthalene,[13] 1-cyanonaphthalene,[24] 1,4-dicyanobenzene,[25] 1,2,4,5-tetracyanobenzene,[26] 9-cyanophenanthrene,[27] chloranil,[28] and 3,3',4,4'-benzophenonetetracarboxylic anhydride[26]).[29] The formation of radical ion pairs between arylcyclopropanes and these photosensitizers by photoinduced electron transfer (PET) is typically guided by the excited state of the electron acceptor, which makes this aminofluorination reaction unique. In a reaction with Selectfluor, the arylcyclopropane is the only chromophore present using 300 nm irradiation.[30] Thus, if a radical ion pair is being formed from PET, the *excited* arylcyclopropane, as opposed to the ground state, must be acting as the electron donor.

Table 1. *Rehm-Weller estimation of PET free energies.*[31]

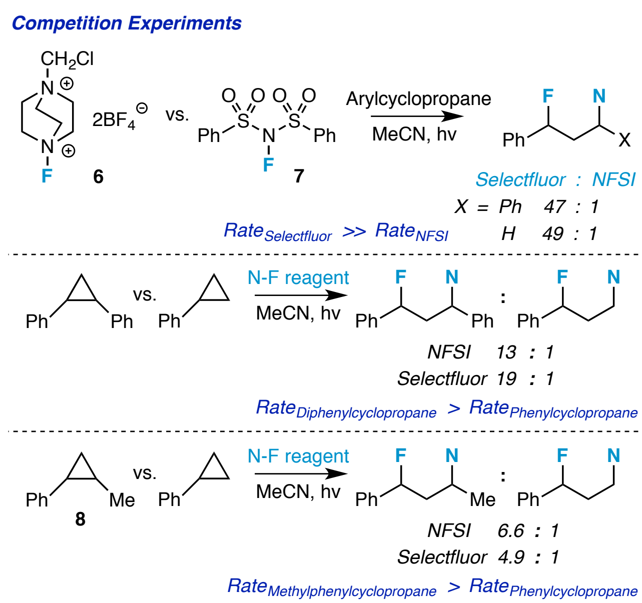
$$\Delta G^0_{ET} = E^0_{(D+/D)} - E^0_{(A/A-)} - E_{0,0} + w^a$$

Donor	Acceptor	$E^0_{(D+/D)}$	$E^0_{(A/A-)}$	$E_{0,0}$	ΔG^0_{ET}
1,2-diphenylcyclopropane*	Selectfluor	1.62[b]	-0.04[d]	2.3[f]	-13
1,2-diphenylcyclopropane*	NFSI	1.62[b]	-0.78[d]	2.3[f]	+3.7
1,2-diphenylcyclopropane	9-fluorenone*	1.62[b]	-1.29[e]	2.4[g]	+13
1,2-diphenylcyclopropane*	9-fluorenone	1.62[b]	-1.29[e]	2.3[f]	+15
phenylcyclopropane*	Selectfluor	1.87[c]	-0.04[d]	3.5[h]	-35
phenylcyclopropane*	NFSI	1.87[c]	-0.78[d]	3.5[h]	-18
phenylcyclopropane	9-fluorenone*	1.87[c]	-1.29[e]	2.4[g]	+19
phenylcyclopropane*	9-fluorenone	1.87[c]	-1.29[e]	3.5[h]	-6.0

[a]ΔG^0_{ET} = free energy of electron transfer (kcal/mol); $E^0_{(D+/D)}$ = oxidation potential of electron donor (V vs. SCE); $E^0_{(A/A-)}$ = reduction potential of electron acceptor (V vs. SCE); $E_{0,0}$ = excitation energy (eV); w = Coulomb term (estimated 0.06 eV in MeCN). [b]Ref. 31a. [c]Ref. 31b. [d]Ref. 31c. [e]Ref. 31d. [f]Ref. 31e. [g]Ref. 31f. [h]Ref. 31g.

The energetics of PET reactions can be studied using the Rehm-Weller relationship (Table 1).[32] The free energy of electron transfer (ΔG^0_{ET}) is estimated from consideration of both donor and acceptor one-electron redox potentials ($E^0_{(D+/D)}$ and $E^0_{(A/A-)}$), the excited state energy of the molecule of interest ($E^*_{(0,0)}$), and a solvent-dependent work function (w) accounting for ion pairing.[33] Assessing the excited states of both phenyl- and 1,2-diphenylcyclopropane in a reaction with Selectfluor, we calculate a thermodynamic preference for electron transfer quenching to form the radical ion pair (-35 and -13 kcal/mol, respectively). Using NFSI, we calculate favorable radical ion formation with phenylcyclopropane at -18 kcal/mol and a small barrier with 1,2-diphenylcyclopropane at +3.7 kcal/mol.

Scheme 5. *Relative rates via competition experiments.*



The higher oxidation potential of Selectfluor lends itself to more thermodynamically favorable electron transfer than NFSI in both instances. Unsurprisingly, competition experiments between Selectfluor **6** and NFSI **7** display an overwhelming preference for the Selectfluor-substituted product (Scheme 5). On the other hand, PET is predicted to be more thermodynamically favorable for phenylcyclopropane over 1,2-diphenylcyclopropane (and presumably 1-methyl-2-phenylcyclopropane **8**, as well), yet competition experiments reveal a preference for the disubstituted cyclopropanes in both instances (Scheme 5). These discrepancies may suggest that photoinduced electron transfer is not a rate-determining step.

Fluorescence and Time-Resolved Spectroscopy. To confirm whether the excited state of the arylcyclopropane is quenched by the N-F reagent via PET, we turned to steady-state fluorescence and transient-absorption spectroscopies. All spectroscopic measurements were conducted with Selectfluor rather than NFSI in order to eliminate overlap in absorption of phenylcyclopropane and the N-F reagent at accessible excitation wavelengths (Figure S1); however, the photochemistry of NFSI and phenylcyclopropane mixtures were examined under identical conditions.[34]

If the excited state of the arylcyclopropane reacts with Selectfluor by PET one would expect quenching of its fluorescence according to the Stern-Volmer relationship (Eq. 1).[35]

$$\frac{F_0}{F} = 1 + k_q \tau_0 [Q] \qquad (1)$$

Here, F_0 is the fluorescence intensity measured in the absence of quencher Q, F is the fluorescence intensity in the presence of quencher Q, k_q is the quenching rate constant, and τ_0 is the innate lifetime of the excited state. Figure 3 shows that the fluorescence ratios (F_0/F) of several arylcyclopropanes increase linearly with concentration of Selectfluor (Q) with excellent coefficients of determination ($R^2 \approx 1$). The excited-state lifetimes (τ_0) of various arylcyclopropanes were measured by nanosecond transient absorption spectroscopy (Figure S2) in order to explore isotope and substituent effects on quenching rates; values obtained for τ_0 and k_q are given in Table 2.

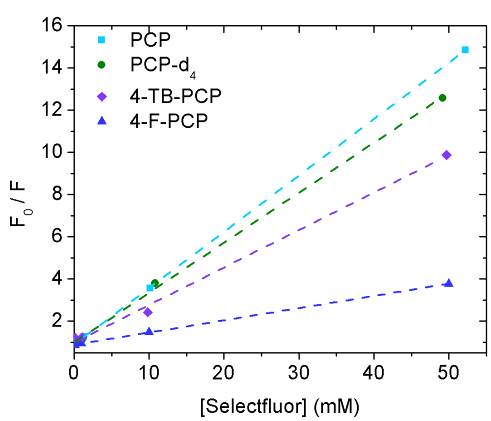


Figure 3. *Stern-Volmer plots for fluorescence quenching of arylcyclopropanes by Selectfluor.*

Table 2. *Excited-state lifetimes (τ_0) measured by nanosecond transient absorption spectroscopy and quenching constants (k_q) from Stern-Volmer analysis.*

Arylcyclopropane	τ_0 *(ns)*	k_q *(ns M)$^{-1}$*
phenylcyclopropane (PCP)	13.8	19.3
phenylcyclopropane-d_4 (PCP-d_4)	9.9	23.9
4-fluorophenylcyclopropane (4-F-PCP)	5.9	30.0
4-*tert*-butylphenylcyclopropane (4-TB-PCP)	13.8	4.1

Although these observations verify quenching of excited arylcyclopropanes by Selectfluor, fluorescence spectroscopy alone does not provide conclusive details about the quenching mechanism. If our hypothesis regarding quenching through PET is correct, then transient-absorption spectroscopy could help identify one or more of the putative radical ion intermediates. For instance, arylcyclopropane radical cation transients are reported to have a strong, distinct absorption feature in the visible range.[36] Figure 4 presents transient absorption spectra obtained over delays ranging 10 ps to 2 μs after 266-nm excitation of phenylcyclopropane in the presence of Selectfluor, 5:50 mM respectively. Under these conditions the spectrum of the radical cation ($PCP^{\bullet+}$, λ_{max} = 545 nm[37]) is observed to appear with the decay of excited state absorption of phenylcyclopropane. The radical cation spectrum is consistent with literature precedent and was reproduced under similar experimental conditions for comparison (Figure S3).[7,37,38] In contrast, no signature of the radical cation appears in absence of Selectfluor; ultrafast transient spectroscopy of the excited state in absence of Selectfluor is shown in Figure S4. Hence, transient spectroscopy provides direct evidence for the proposed PET quenching mechanism.

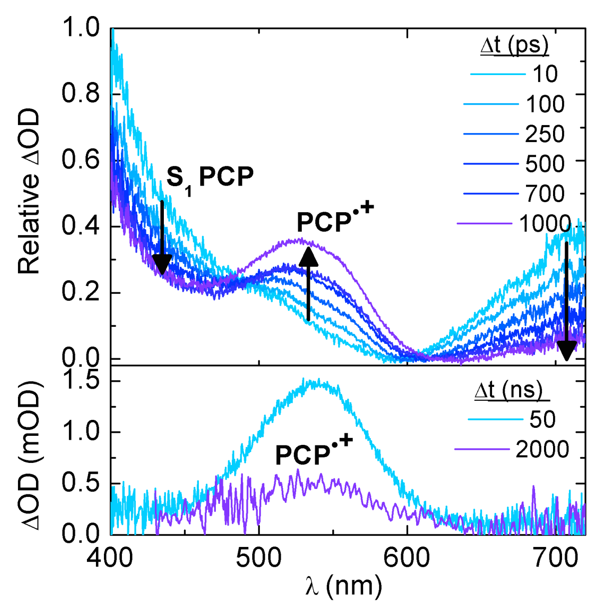


Figure 4. *Time-resolved transient absorption spectroscopy of phenylcyclopropane following 266-nm excitation; radical cation ($PCP^{\bullet+}$, λ_{max} = 545 nm[37]) is generated in the presence of Selectfluor. The upper panel has been referenced to a ΔOD of 0 to highlight the spectral evolution.*

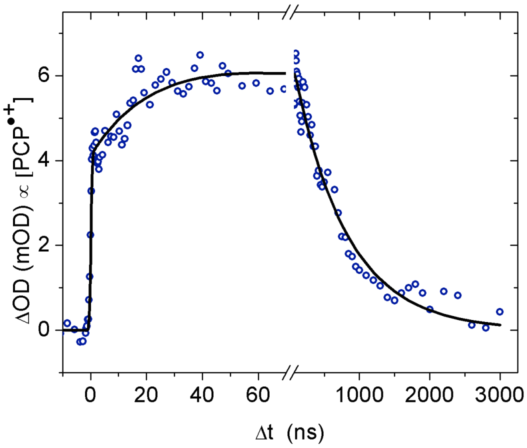


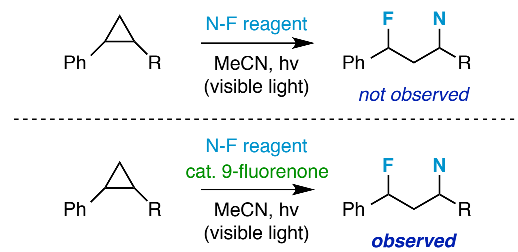
Figure 5. *Kinetics of the phenylcyclopropane radical cation (PCP•+) generated in presence of Selectfluor according to nanosecond-resolved transient absorption at 520 nm.*

The kinetics of the phenylcyclopropane radical cation were monitored by transient absorption at 520 nm following 266-nm excitation and is characterized by an exponential rise and decay of 47.2 ns and 816 ns, respectively. While a lifetime of ~1 μs has been reported for the decay of phenylcyclopropane radical cation under sensitized reaction conditions, the exponential rise was not reported previously, most likely due to lower instrument time resolution.[24] The broadband transient absorption spectrum recorded at 2 μs (Figures 4 and S5) indicates that the phenylcyclopropane radical cation does not result in any other spectroscopically detectable reaction products in the range of 430-750 nm.

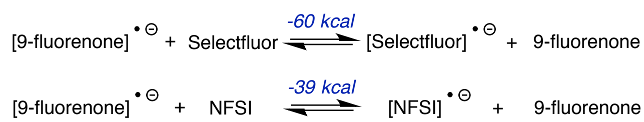
A small, inverse isotope effect is observed in the quenching rate constants of phenylcyclopropane (PCP) and phenylcyclopropane-d_4 (PCP-d_4); this differs from the competitive KIE (below). Additionally, quencher rate constants of different *para*-substituted phenylcyclopropanes (4-*tert*-butyl- and 4-fluorophenylcyclopropane; 4-TB-PCP and 4-F-PCP) do not follow the exact same trend observed in the competition experiments used to generate the Hammett plots. This is not particularly alarming; on the contrary, it supports the claim that the photoinduced electron transfer event has minimal impact on the overall rate equation.

Alternative Photosensitized Initiation. The spectroscopic observations *vide supra* inspired us to seek out the result of generating an arylcyclopropane radical cation with a visible light photosensitizer. Although we observed no aminofluorination using visible light (14-Watt CFL) with phenylcyclopropane and the N-F reagents alone, we did observe product formation in the presence of 9-fluorenone – an established visible light photosensitizer[39] – albeit in consistently lower yields (Scheme 6). Considering that only the excited state of 9-fluorenone is accessible under visible light conditions, electron transfer quenching events by ground state phenyl- and 1,2-diphenylcyclopropane are predicted to be more endergonic at +19 and +13 kcal/mol (Table 1). Perhaps lower product yields are a reflection of inefficient PET in these particular cases. However, this newly discovered mode of initiation prompts us to entertain the probability of a reaction between arylcyclopropane radical cations and N-F reagents directly (unlikely, due to charge repulsion) and also the possibility of an electron relay from the 9-fluorenone radical anion to the N-F reagent (thereafter, providing the same intermediates as direct photoexcitation). Calculations at B3PW91/6-311++G** employing the default MeCN continuum (Scheme 7) suggest very favorable electron transfer from the 9-fluorenone radical anion to both Selectfluor (ΔG_{calc} = -60 kcal/mol) and NFSI (ΔG_{calc} = -39 kcal/mol).[40] As such, the consequences of one-electron reduction of the N-F reagents were explored in more detail.

Scheme 6. *Alternative photochemical initiation.*



Scheme 7. *Electron relay at B3PW91/6-311++G** (MeCN).*

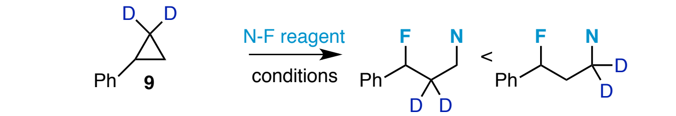
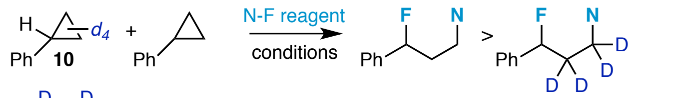
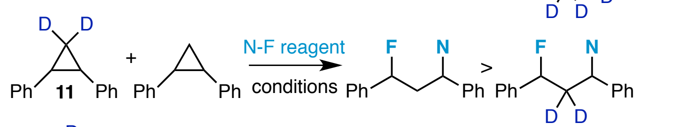
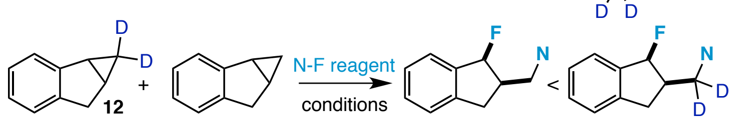


Alternative Chemical Initiation. From studying the copper(I)/Selectfluor aliphatic fluorination system,[5] we determined that an inner-sphere electron transfer event also results in one-electron reduction of Selectfluor, concomitant with loss of fluoride. This process generates the elusive Selectfluor "radical dication" that is responsible for H-atom abstraction in the copper system[5] (and likely the triethylborane variant[41]). The calculated geometry of the one-electron reduced structure of Selectfluor (and NFSI) that would result from PET shows significant elongation of the N-F bond (Scheme 8). It is likely that this structure would rapidly expel fluoride to give the same radical dication species, but the question is whether or not this species is responsible for any of the observed chemistry in this aminofluorination system. In an effort to probe the role of the Selectfluor radical dication intermediate, we submitted phenylcyclopropane and 1,2-diphenylcyclopropane to the copper(I) and triethylborane reactions *vide infra* in the absence of light and obtained a surprising result – the same aminofluorination reaction (Scheme 9).

The ability to reproduce the reaction in the absence of light offers a crucial new perspective to understanding the reaction mechanism beyond photoexcitation. However, one must first rule out the possibility of the non-photochemical systems operating by an entirely different mechanism. By repeating the product distribution studies, Hammett analyses, and kinetic isotope effects (see below), we discovered very similar behavior of the triethylborane and copper(I) systems[42] to the direct photoexcitation of arylcyclopropanes and Selectfluor (note that these methods are incompatible with NFSI).

The involvement of an arylcyclopropane radical cation intermediate in the non-photochemical systems is still supported by the negative ρ values in the intermolecular competition experiments (-3.2 for triethylborane shown; -2.9 for copper(I) in

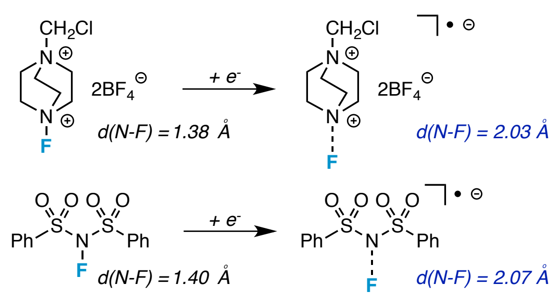
Table 3. *Intramolecular and intermolecular competitive KIE's.*

Entry	Competition Experiment	$KIE_{Selectfluor}$ (300 nm)	KIE_{NFSI} (300 nm)	$KIE_{Selectfluor}$ (cat. BEt_3)
1		0.88	0.89	n.d.
2		1.4(3)	1.4(5)	1.4(3)
3		1.4(9)[a]	1.4(6)[a]	1.4(7)[a]
4		0.89[b]	0.86[b]	0.94[b]

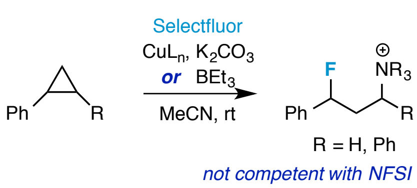
[a]Average KIE (considering both diastereomers). [b]KIE only determined for cis diastereomer.

Supporting Information) and similar distributions in the intramolecular experiments (Figure 1, **E** and **F**). In this light, another proposal for the formation of arylcyclopropane radical cations that applies to all systems is chemical oxidation by the Selectfluor-derived radical dication. Through this pathway, the arylcyclopropane radical cation could be generated along with a neutral Selectfluor-derived amine that can conceivably participate in a three-electron nucleophilic substitution reaction. The result would be a ring-opened intermediate containing a benzylic radical; we have shown that such radicals are readily fluorinated in the presence of Selectfluor, yielding the fluorinated product and regenerating the radical dication.[5]

Scheme 8. *Elongation/cleavage of N-F bond upon reduction at B3PW91/6-311++G** (MeCN).*



Scheme 9. *Alternative chemical initiation.*



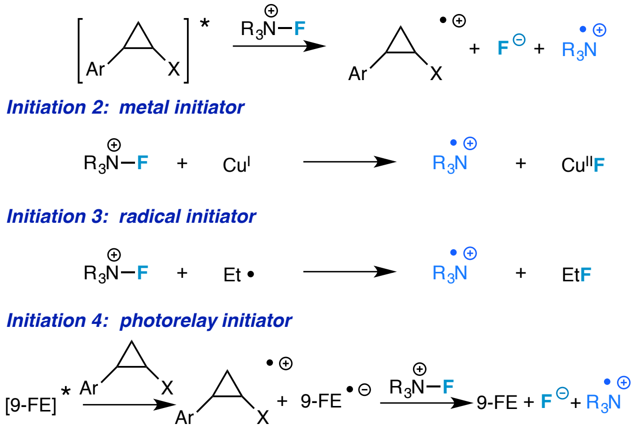
Qualitatively, a radical chain mechanism after photoexcitation presents an explanation for anomalous behavior of the phenylcyclopropane radical cation kinetics observed during time-resolved experiments (Figure 5). After photoexcitation, the single-wavelength trace at 520 nm, which is proportional to the phenylcyclopropane radical cation concentration, exhibits approximately a 50 ns rise. Given the experimental conditions (50 mM Selectfluor) and the determined k_q from the Stern-Volmer analysis, the phenylcyclopropane excited-state should be quenched on a timescale of ~0.8 ns; indeed, ultrafast measurements reflect such a quenching rate under these conditions (Figure S6). Therefore, the observed absorption must be *solely due to the radical cation*. In light of the proposed mechanism, this increase in concentration reflects propagated chemical oxidation of phenylcyclopropane by the Selectfluor-derived radical dication. Furthermore, it is important to note that the lifetimes of radical chain propagations are typically less than one second[43] and require a continuous source of initiation.[44]

Kinetic Isotope Effects. We further assessed the viability of this pathway with competitive kinetic isotope effect experiments (Table 3). Phenylcyclopropane-d_2 **9** was synthesized by standard Wittig chemistry with benzaldehyde and iodomethane-d_3,[45] followed by a modified Simmons-Smith cyclopropanation, to be used as an intramolecular KIE probe. The observed intramolecular KIE's for Selectfluor (0.88) and NFSI (0.87) represent inverse secondary effects. Following the notion that the ring-opening step is rate determining, the inverse secondary effect is consistent with 1) less-hindered nucleophilic attack on the cyclopropane ring[7] and 2) the change in geometry accompanied with ring opening. That is, a consequence of ring strain in cyclopropane compounds is the virtual sp^2 hybridization of the C-H(D) bonds; nucleophilic ring opening thus resembles a change in hybridization from sp^2 to sp^3.

For another vantage point, phenylcyclopropane-d_4 **10** and 1,2-diphenylcyclopropane-d_2 **11** were synthesized in a similar fashion (using diiodomethane-d_2 in the cyclopropanation step) as intermolecular KIE probes. The observed intermolecular KIE's for Selectfluor and NFSI are ca. 1.4 in all instances. These fairly large, normal secondary effects are consistent with rate-determining cyclopropane ring opening if one considers β-H-stabilization (over β-D-stabilization) of the charges in the transition state. To support this claim, a dideuterated indene-derived arylcyclopropane **12** was synthesized as an intermolecular KIE probe lacking β-isotopic substitution. As anticipated, the normal secondary effect that may result from β-H(D)-stabilization was not observed. Instead, an inverse secondary effect was observed that is consistent with nucleophilic ring opening.

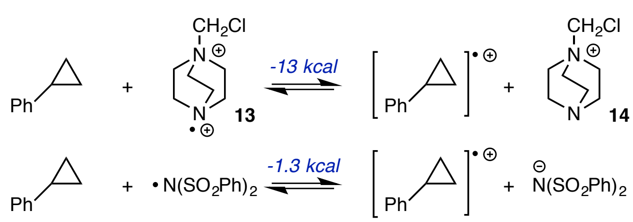
Drawing a Unified Mechanism. At this point, reasonable mechanisms can be drawn for the four methods of initiation and the common chain propagation. Given that the non-photochemical reactions are not competent with NFSI, we focus the discussion in this section to reactions with Selectfluor.

Scheme 10. *Proposed initiation mechanisms.*



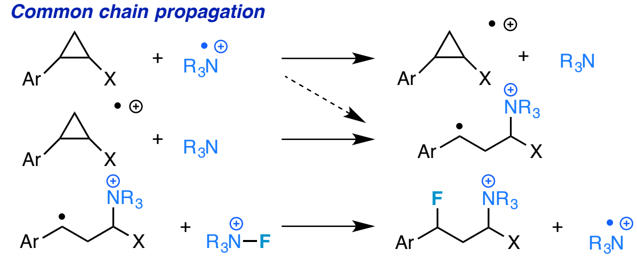
The nearly identical behavior of all photochemical and non-photochemical systems in our mechanistic studies strongly suggests a common mechanism beyond initiation. From precedent, we conclude that the key player is a Selectfluor-derived radical dication.[5] This putative intermediate may be generated in several ways: 1) direct photoexcitation of an arylcyclopropane, followed by photoinduced electron transfer to an N-F reagent that, in its reduced form, is predicted to lose fluoride, 2) inner-sphere electron transfer with copper(I) concomitant with loss of fluoride, 3) direct F-atom abstraction with an ethyl radical generated from BEt_3, and 4) photosensitized oxidation of the arylcyclopropane, followed by a "relay" of the electron to the N-F reagent, which decomposes to the radical dication as mentioned (Scheme 10).

Scheme 11. *Calculated phenylcyclopropane oxidations (ΔG_{calc}) at B3PW91/6-311++G** (MeCN).*



Upon formation, the Selectfluor-derived radical dication **13** is predicted to oxidize arylcyclopropanes very efficiently (Scheme 11).[46] This oxidation step could 1) result in an arylcyclopropane radical cation and amine **14** that subsequently undergo three-electron nucleophilic substitution (stepwise) or 2) occur simultaneously with ring opening (concerted). In either case, a radical is generated on the newly aminofunctionalized substrate that is fluorinated in the presence of Selectfluor. Thus, the Selectfluor-derived radical dication is regenerated and the chain propagates (Scheme 12).

Scheme 12. *Oxidation, aminofunctionalization, fluorination, and propagation.*



Though NFSI was not studied as thoroughly as Selectfluor in this work, many observations and computations suggest it is operating by a similar mechanism under photochemical conditions. It is surprising how alike the LFER's and KIE's are for reactions with Selectfluor and NFSI. These parallels prompted us to entertain the possibility of a common solvent-assisted ring-opening mechanism (Scheme 13). We argue the plausibility of ring opening by acetonitrile for the following reasons: 1) if ring opening is rate-determining, one might expect the amine nucleophiles derived from Selectfluor and NFSI to have different transition state structures (thus having an impact on isotope effect magnitudes), 2) arylcyclopropanes are known to have irreversible one-electron oxidation potentials in MeCN due to irreversible ring opening,[36,47] and 3) transition state structures have been calculated that are in accord with some of the observed isotope effects above. For instance, using the Bigeleisen-Mayer method of calculating KIE's,[48] we have determined an isotope effect of 0.95 for phenylcyclopropane-d_2 (intramolecular KIE) and 1.30 for phenylcyclopropane-d_4 (intermolecular KIE) using the transition state structure in Figure 6 (consider aforementioned EIE's and Table 3, Entry 1 and 2).

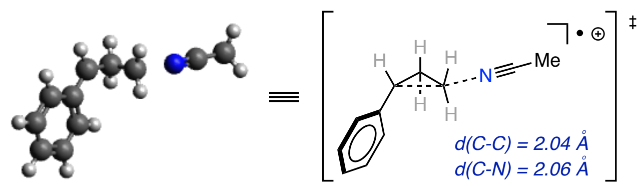
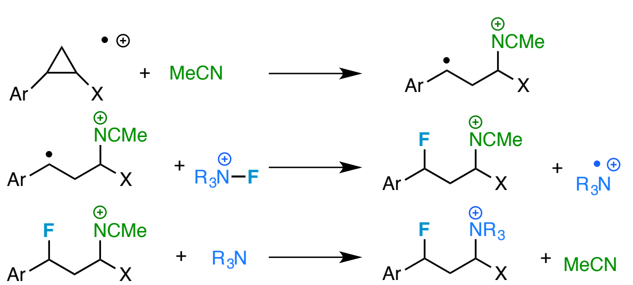


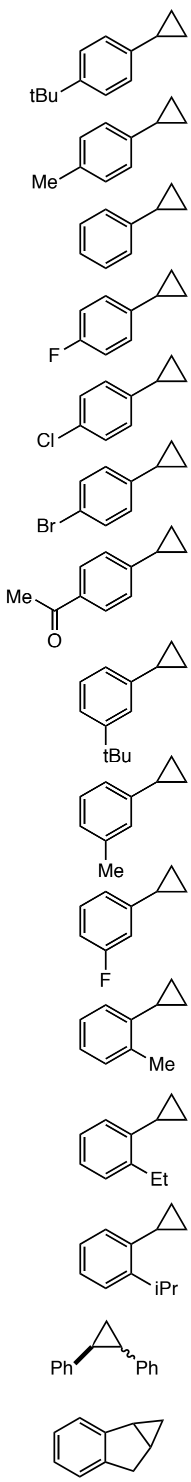
Figure 6. *Solvent-assisted ring opening transition state at wB97XD/6-311++G** (MeCN).*[49]

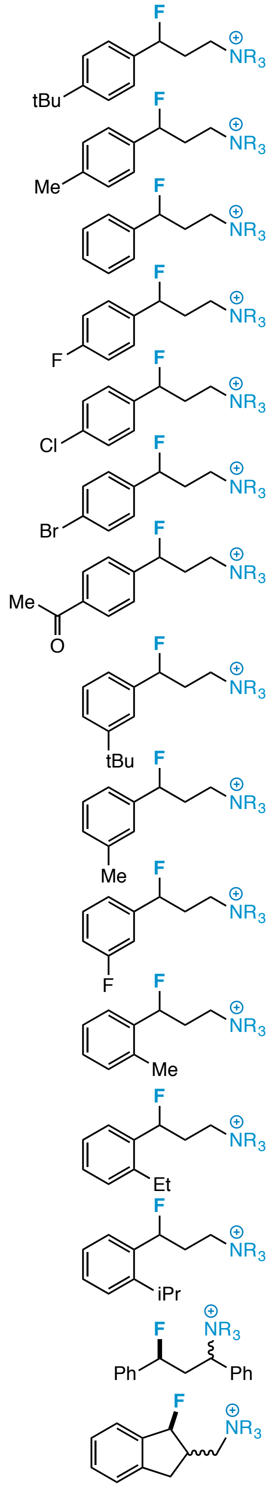
Scheme 13. *Acetonitrile-assisted ring opening.*

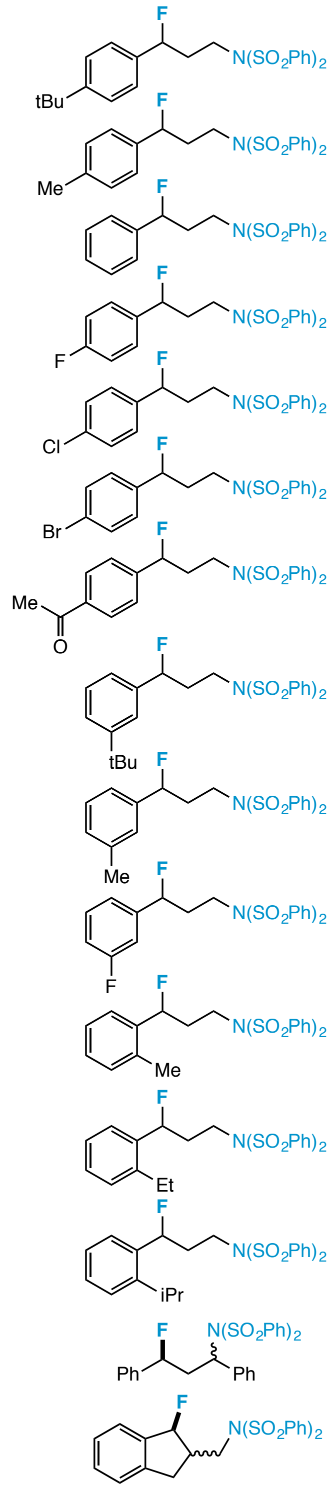


One might expect to obtain a small amount of the 1,3-fluoroacetamide upon workup if this solvent-assisted mechanism is at play, but none was observed. However, we have made a noteworthy observation. While monitoring the kinetic profile of a reaction with 4-fluorophenylcyclopropane and Selectfluor, we noticed a trace amount of another fluorinated product appear and disappear in the ^{19}F NMR spectra over the

Table 4. *Scope of aminofluorination reaction for Selectfluor and NFSI under 300 nm irradiation.*







Entry	*Substrate*	*Selectfluor Adduct % Yield*	*NFSI Adduct % Yield*
1	**15**	96	67 (67)
2	**16**	90[a]	41 (43)
3	**3**	85	43 (42)
4	**17**	95	n.d.
5	**18**	87	n.d.
6	**19**	92	n.d.
7	**20**	54	n.d.
8	**21**	72	50 (48)
9	**22**	83[a]	41 (38)
10	**23**	74	n.d.
11	**24**	93[a]	60
12	**25**	96[a]	57 (53)
13	**26**	93	66 (60)
14	**2**	97[b]	60 (54)[b]
15	**5**	78[b]	66[b]

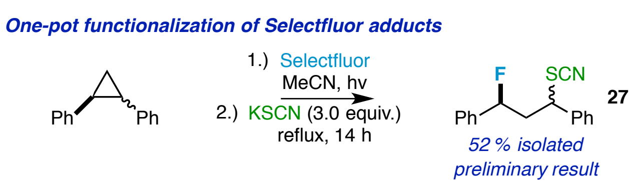
Unless otherwise specified, substrates were stirred with 2.2 equiv. N-F reagent in MeCN and irradiated at 300 nm in Pyrex microwave vials for 14 h. ^{19}F NMR yields are reported; isolated yields for NFSI adducts appear in parentheses. *N*-chloromethyl-DABCO substituents on Selectfluor-arylcyclopropane adducts are abbreviated as NR_3. [a]Only 1.0 equiv. of N-F reagent used (to minimize additional methyl fluorination). [b]Mixture of diastereomers.

course of the reaction that is an apparent ddd with the correct shift/coupling constants to be a benzylic fluoride. This signal was never observed in any NMR spectra of completed reactions, but unveils another benzylic fluoride intermediate - possibly the fluorinated acetonitrile adduct.[50] The acetonitrile molecule is conceivably displaced from the fluorinated product by the more nucleophilic amine derived from either Selectfluor or NFSI, thus accounting for a lack of substantial 1,3-

fluoroacetamide in the final product mixture. To provide additional support for solvent involvement, we conducted a few reactions in 1:1 acetonitrile:pivalonitrile and found that new benzylic fluoride peaks evolve in each instance that we have assigned as the pivalonitrile-trapped nitrilium adducts. Likely, the pivalonitrile adducts are less easily displaced than the corresponding acetonitrile adducts; thus, small amounts (≤ 3 %) persist upon reaction completion. Although solvent-assisted ring opening cannot be unequivocally determined as the *sole* ring opening mechanism at play, the above observations provide evidence for its viability.

As a Synthetic Method. Thus far, the primary focus of this article has been elucidation of reaction mechanism. As synthetic methods, our findings also add a very efficient and regioselective aminofluorination reaction to the toolbox of the synthetic chemist. The reactions with Selectfluor, in many instances, approach quantitative yields; but note that the products are difficult to separate from the chloromethyl DABCO byproduct via chromatography, extraction, or crystallization techniques (thus, spectra of the crude reaction mixtures are reported in the Supporting Information). However, the products (even with the quaternary ammonium substitution) are quite stable and may be separated from other non-ionic byproducts by column chromatography on C18 or diol media, eluting with MeCN/H_2O.

From a more practical standpoint, we found that the 1,3-aminofluorinated products from reactions with NFSI are easily isolated by column chromatography on silica gel or Florisil (more extensive characterization data is reported for these compounds in the Supporting Information). To access more synthetically useful, isolable compounds from the Selectfluor adducts, we imagined the ammonium substituent could be displaced by a nucleophile under proper reaction conditions. Accordingly, we discovered that, following irradiation, the addition of potassium thiocyanate to the reaction mixture under reflux for 14 h provides the 1,3-fluorothiocyanate **27** from 1,2-diphenylcyclopropane in a 52 % isolated yield (Scheme 14). Although reaction optimization/examination of the competency of various nucleophiles is beyond the scope of this study, this showcases potential synthetic utility of this method as a one-pot aminofluorination/nucleophilic displacement reaction.[51]



Scheme 14. *Potential synthetic utility of Selectfluor adducts.*

Over the course of our studies, we have noted several features about the substrate scope (Table 4). First of all, reactions with Selectfluor tend to be higher yielding than reactions with NFSI. This is consistent with our studies thus far that highlight several ways in which Selectfluor was determined to be more reactive. Note that the majority (if not entirety) of the remaining mass balance from reactions with NFSI can be assigned to unreacted starting material; longer reaction times and larger quantities of NFSI did not result in higher yields. When employing either N-F reagent, substrates adorned with electron donating groups (e.g. Me, Et, iPr, tBu) tend to provide higher product yields than those with electron withdrawing groups (e.g. F, Cl, Br, OAc). Note that stronger donating groups suffer from competitive aryl ring fluorination and more extreme withdrawing groups (for instance, NO_2) are not competent in the reaction. Additionally, aryl rings substituted in the *ortho*, *meta*, or *para* positions are competent in the reaction; steric bulk in the *ortho* position has minimal impact on reactivity,[52] though the reaction is sensitive to electronic effects (as demonstrated in the Hammett analyses of *meta* and *para* substitutions). Beyond ring-substituted phenylcyclopropanes, other substituents on the ring (i.e. Me and Ph) guide regioselective aminofunctionalization (in addition to selective benzylic fluorination). More rigid cyclopropanes, e.g. the indene-derived cyclopropane, undergo regioselective substitution, as well. Lastly, primary, secondary, and secondary benzylic amination is shown to be viable, as is secondary and tertiary benzylic fluorination. Note that our example of a tertiary benzylic fluoride was excluded from the table due to its strong tendency to dehydrofluorinate upon workup (presumably to make the allylic or homoallylic amine).

Conclusions. In exhibition of a "multifold approach" to method development and mechanistic studies, we report four sets of reaction conditions – linked by a common intermediate – that effect a unique, regioselective fluorination of arylcyclopropanes with N-F reagents. We propose a detailed mechanism based on extensive experimental and computational studies; specifically, we propose photochemical initiation (by PET, in the direct excitation method) of a radical chain mechanism that is corroborated by three alternative initiation methods, two of which are non-photochemical. Linear free energy relationships, estimations of free energies of electron transfer (via Rehm-Weller relationships), competition experiments, fluorescence, and transient-absorption spectroscopy all support direct photoexcitation of the arylcyclopropane and subsequent quenching of the excited state via PET in the presence of an N-F reagent. This is solidified by direct observation of the arylcyclopropane radical cation intermediate under reaction conditions. Alternative methods that we have shown to effect the same reaction (using Selectfluor) suggest that the observed PET only initiates the reaction, and it is followed by a radical chain mechanism propagated by a previously postulated Selectfluor-derived radical dication. Further evidence for this radical chain mechanism, characterized by rate-determining cyclopropane ring opening and subsequent radical fluorination, is provided through product distribution studies, kinetic analyses, a table of kinetic isotope effects, literature precedent, and DFT calculations. Additionally, we examined the plausibility of a solvent-assisted cyclopropane ring opening mechanism instead of/in addition to the amine that ultimately functionalizes the molecule. Lastly, as a synthetic method, the reaction cleanly and regioselectively produces unusual aminofluorinated products in good to excellent yields that may serve as building blocks toward the synthesis of both fluoro- and aminofunctionalized complex molecules.

ASSOCIATED CONTENT

Supporting Information

General experimental procedures, kinetic data, characterization data, spectral data, computational files, and optical spectroscopy equipment/procedures. The Supporting Information is available free of charge on the ACS Publications website.

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[46] As shown in Scheme 11, the putative *N*-centered radical generated from one-electron reduction of NFSI/loss of fluoride is also predicted to oxidize phenylcyclopropane, though much less efficiently than the Selectfluor-derived radical dication.

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SYNOPSIS TOC (Word Style "SN_Synopsis_TOC").