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Carbonyl-Directed Aliphatic Fluorination: A Special Type of Hydrogen Atom Transfer Beats Out Norrish II

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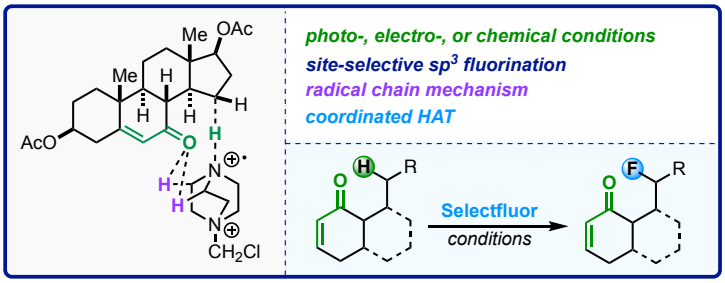
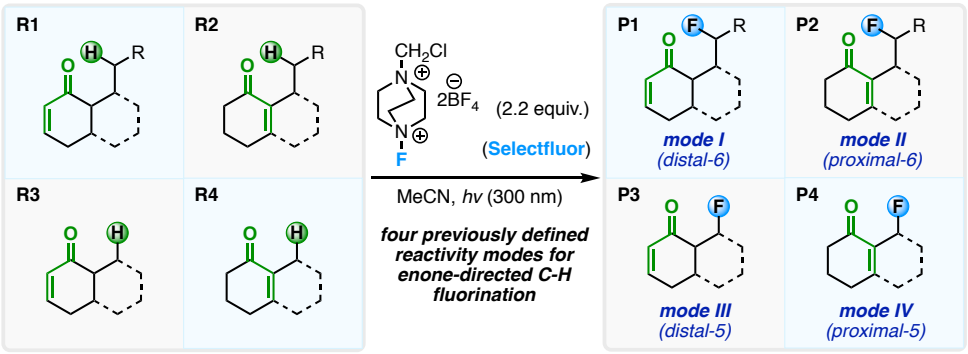
ABSTRACT: Recently, our group reported that enone and ketone functional groups, upon photoexcitation, can direct site-selective sp^3 C-H fluorination in terpenoid derivatives. How this transformation actually occurred remained mysterious, as a significant number of mechanistic possibilities came to mind. Herein, we report a comprehensive study describing the reaction mechanism through kinetic studies, isotope labeling experiments, ^{19}F NMR, electrochemical studies, synthetic probes, and computational experiments. To our surprise, the mechanism suggests intermolecular hydrogen atom transfer (HAT) chemistry at play, rather than classical Norrish hydrogen atom abstraction as initially conceived. What is more, we discovered a unique role for photopromoters such as benzil and related compounds that necessitates their chemical transformation through fluorination in order to be effective. Our findings provide documentation of an unusual form of directed HAT and are of crucial importance for defining the necessary parameters for the development of future methods.





Scheme 1. Initial discovery of enone-directed fluorination reactivity modes, classified based on 1) proximity of C=C bonds to the reactive site and 2) number of bonds between the carbonyl oxygen atom and the abstracted hydrogen atom.

Introduction. Putative single-electron transfer (SET) and hydrogen atom transfer (HAT) processes underpin much recent and remarkable synthetic chemistry.[1] The detailed mechanisms by which these reactions occur are generally much less well understood.[2] Under the umbrella of HAT, proton transfers play an additional role, giving rise to a spectrum of mechanistic scenarios: concerted proton-coupled electron transfer (CPET), sequential ET/PT, etc.[3] We recently reported that enone-containing rigid terpenoid derivatives, in which the carbonyl group is positioned to interact through potential 5- or 6-membered transition states with proximate C–H bonds, afforded alkyl fluorides regioselectively in moderate to high yields upon irradiation at 300 nm in the presence of Selectfluor (SF)(Scheme 1).[4]

We soon extended the scope of this work to include site-selective fluorination of substrates containing ketones, keto ethers, and benzylic positions activated by carbonyl groups (Figure 1).[5]

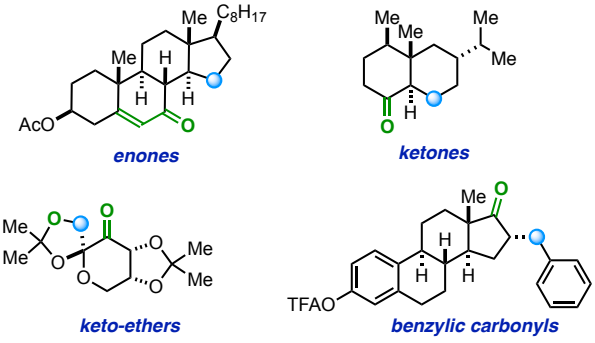


Figure 1. Expanded scope of study for carbonyl-directed fluorination in our recent work.

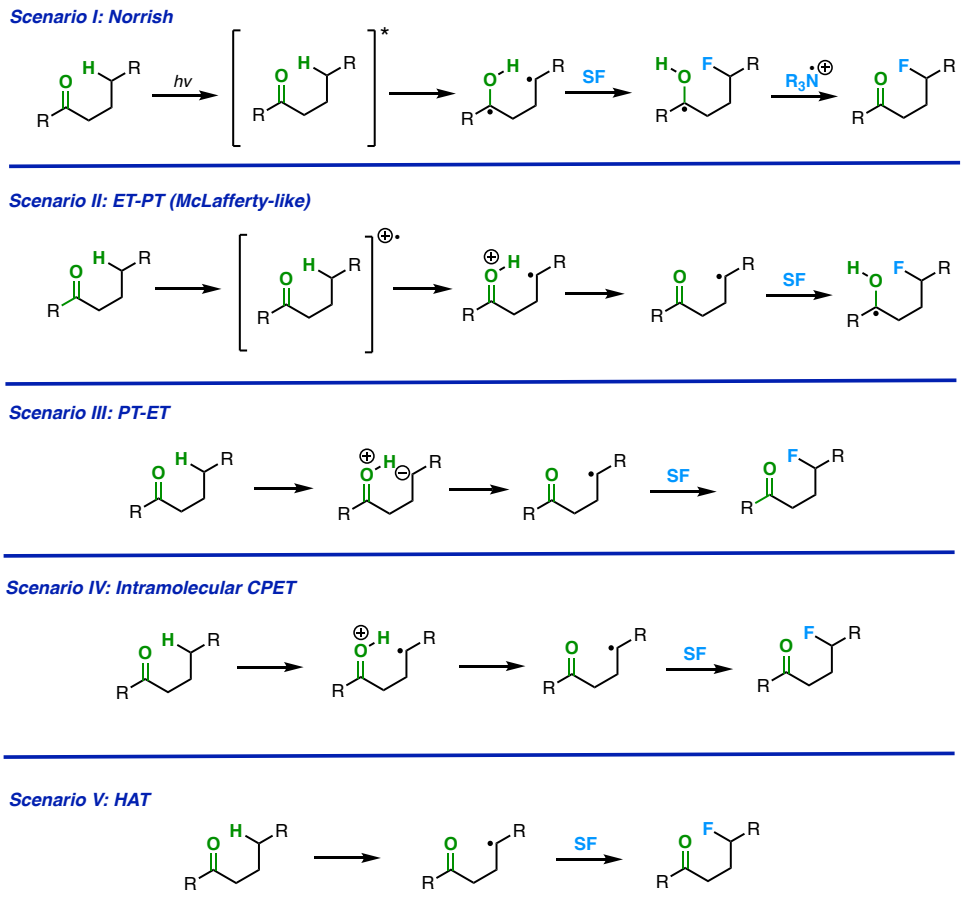


Figure 2. Five possible mechanistic hypotheses.

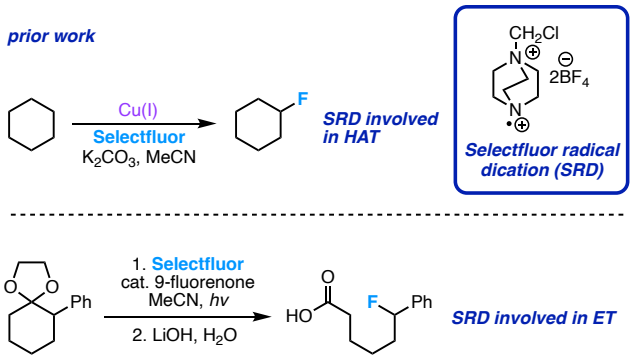
In each successive case, a proximate carbonyl group is poised to interact with a C-H bond through a 5- or 6-membered ring. On the other hand, how this remarkable transformation occurred was shrouded in mystery; aside from the fact that a proximate carbonyl group exerted a key directing effect, mechanistic details remained speculative.

We settled on five possible mechanistic hypotheses (Figure 2). Initially, our data seemed to comport with an interrupted Norrish II process involving intramolecular HAT (Scenario I). Electron transfer may play a pivotal role – in either sequential electron transfer-proton transfer (ET-PT, Scenario II) or PT-ET, which seems thermodynamically unreasonable but is included for the sake of completeness (Scenario III). Proton-coupled electron transfer, which may represent a point on the mechanistic continuum of HAT, must be considered a serious alternative (PCET, Scenario IV). On the other hand, direct, rate-determining HAT remained a possibility, although this scenario begs the question of what precise role the carbonyl group plays in directing the reaction (Scenario V).

Given that the only chromophore present in the reaction mixture absorbing in the 300 nm region was the enone moiety of the substrate, we originally surmised the main viable initiation pathway following its excitation could be a Norrish type II intramolecular process.[6] This initial supposition turned out to be overly simplistic, if not incorrect, and was surprisingly clarified by the subsequent use of longer wavelength absorbing photoinitiators such as benzil, thereby obviating Norrish chemistry. After wending our way down a tortuous path, we found that the mechanism instead indicates *intermolecular* HAT chemistry at play, rather than classical intramolecular Norrish hydrogen atom abstraction. This HAT can also be thought of potentially as a limiting PCET termed multi-site concerted proton-coupled electron transfer: MS-CPET.[7]

In this article, we wish to present our detailed mechanistic findings of this unusual and timely reaction. We also document the key role played by the remarkable chemical transformations of the photo*initiators* (affecting the paradigm or supposition that such compounds often act as photo*catalysts*). Mechanistic clues accumulated along the way were bolstered by alternative initiation of the reaction through chemical (BEt_3/O_2) and electrochemical means. Our findings provide an interesting case of "directed" HAT in a general synthetic method and hopefully will prove to be of crucial importance for defining parameters for the development of related methods.

Background. In earlier work, we developed a series of radical-based fluorination methods that highlight different potential mechanisms. For example, the Cu(I)-promoted fluorination of aliphatic substrates was shown (in at least some cases) most likely to proceed through a key HAT step.[8] Given the involvement of the putative Selectfluor radical dication (SRD) in published work and the present reaction, HAT became a logical mechanistic candidate, although we were quite skeptical as this pathway generally leads to "scattershot" fluorination at a large number of sites within a



Scheme 2. Examples where SRD has been shown to play a significant role in both hydrogen atom transfer (HAT) and electron transfer (ET).

complex molecule. On the other hand, the tandem C-C bond cleavage/fluorination of acetals (also involving SRD) *must proceed* through some sort of a SET process with no HAT involvement (Scheme 2).[9] The flexibility of the SRD/SF pair to play different roles warned us about jumping to conclusions.[10] In the present work, we were once again intrigued by the possibility that SRD may play an imperative role.

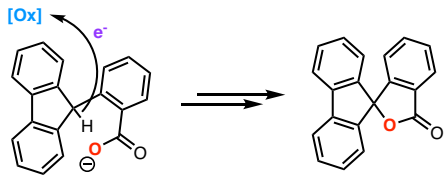
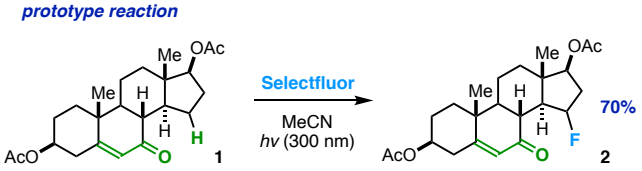


Figure 3. Mayer's multiple-site concerted proton-electron transfer (MS-CPET) system.

In regard to PCET, recent work by Knowles and coworkers demonstrates its viability for a number of unique synthetic transformations.[11] Additionally, variants of the basic PCET system should be noted. For example, the subclass "MS-CPET" (multiple-site concerted proton-electron transfer) has only recently been explored for C-H activation. To our knowledge, Mayer and coworkers described the first mechanistic account in 2019, whereby the carboxylate of fluorenyl-benzoate facilitates rapid cleavage of a benzylic C–H bond in the presence of a weak one-electron oxidant (Figure 3).[12] For our purposes, this precedent is important as it parallels, at least superficially, the present findings in several ways. In Mayer's case, a carboxylate acts as an internal base through a 6-membered ring transition state. The oxidant, in analogy to SRD, is an amine radical cation. We bear in mind what Mayer and coworkers have stated: "MS-CPET reactivity is increasingly proposed in biological and synthetic contexts, and some reactions typically described as HAT more resemble MS-CPET. Despite that HAT and MS-CPET reactions 'look different,' we argue here that these reactions lie on a reactivity continuum, and that they are governed by many of the same key parameters."[13] In our case as well, strict HAT or PCET may represent points on this reactivity continuum.



Scheme 3. Typical example of enone-directed fluorination through 300-nm irradiation.

Experiments: Results from Direct Photolysis. Our initial intuition for enone-directed fluorination led us to believe the observed selectivity was due to a Norrish-type pathway. As such, we proposed that intramolecular HAT may occur first, and the resulting carbon radical could then be intercepted through fluorination by Selectfluor (SF) before either cleavage or Yang cyclization could occur (Figure 2, Scenario I). For example, direct irradiation of compound **1** in acetonitrile with 300 nm light in the presence of SF produces the directed fluorinated product **2** in 70% yield (Scheme 3).[4] In the absence of SF, the above conditions produce a small quantity of unidentifiable products. Reactions conducted in the dark and under 400-nm irradiation (using blue LEDs) only result in recovered starting material. Additionally, the UV-vis spectra of Selectfluor in MeCN at various concentrations showed no absorption bands above 300 nm (Figure 4). These experiments *potentially* implicate a role for the Norrish reaction in initiation (albeit it has an even more questionable role in chain propagation/fluorination).

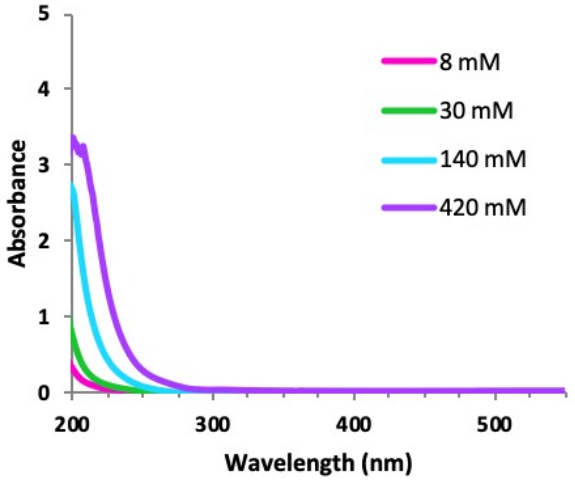
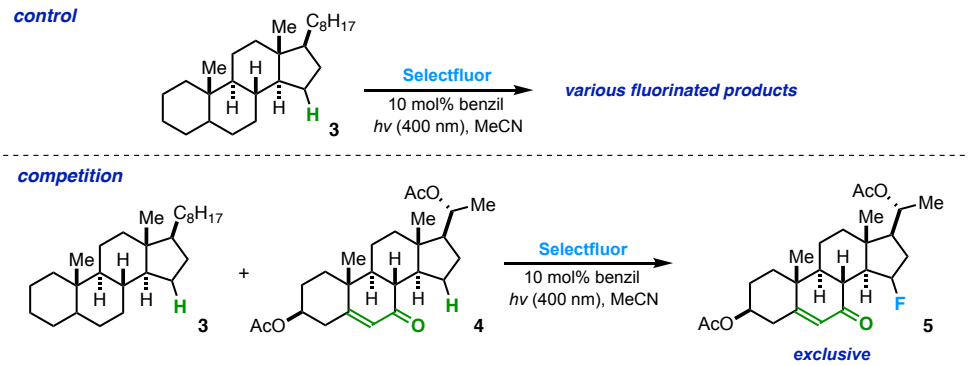


Figure 4. UV-vis spectra of Selectfluor in MeCN at various concentrations.

There are other conceivable pathways for initiation, such as triplet-triplet energy transfer from substrate to SF, or electron transfer from the excited substrate to SF that can generate SRD,[14] (although N-F bond activation in SF has been reported to occur at 400 nm with blue LEDs, as stated we see no absorption in the UV-vis spectrum in this range).[15] These alternatives are not mutually exclusive and may run parallel to each other; as all the hypotheses involve SRD, the

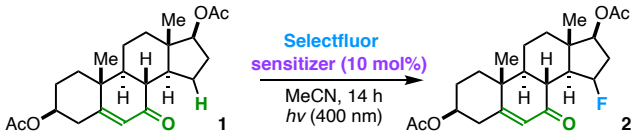


Scheme 4. Control and intermolecular competition experiments.

possibility of very complex hybrid mechanisms is possible. Thus direct photolysis, at least from a mechanistic standpoint, *appears to be anything but direct.* In contrast to enones, the direct photolysis of rigid, optimally configured ketones produces a generally lower yield of desired fluorinated products along with other non-directed fluorinated species. Decomposition of ketone substrates into a number of fluorinated products competes with the desired process. For example, α-cleavage of the O=C—C bond gives rise to evident acyl fluoride byproducts by ^{19}F NMR.[16] Enones do not seem to be quite as susceptible to these types of cleavage processes.

Photoinitiation. The unsuccessful utilization of ketones (and poor yields of certain products obtained from enones) prompted us to turn to visible light/near-UV photosensitization with the goal of increasing yields and improving conditions. Paradoxically, we also sought to clarify (or simplify) the mechanism through the addition of a photosensitizer. Table 1 shows a range of photosensitizers that we screened for both enones and ketones (reactivity was similar with both; steroid **1** is shown as a model substrate).

A trend stands out: carbonyl-containing sensitizers (such as benzil) work most effectively in the reaction. Benzil itself increases the yield considerably (from 70% to 94%) over direct photolysis. One other important fact related to the mechanism was immediately noted - a photosensitized approach utilizing 400 nm light (with a narrow 10 nm spectral dispersion) conclusively *rules out* a Norrish-type pathway at play in this case. Due to the ketone/enone absorbance below 350 nm and > 20 kcal/mol triplet energy gap between benzil and ketone/enone substrates, triplet sensitization is virtually prohibited.[17] In this case, it is not feasible to form the photoexcited substrate through direct excitation or triplet-triplet energy transfer. Thus, the photosensitizers are playing a very different initiation role. When a directing carbonyl group is not present (control **3**) fluorination still results, although it qualifies as "scattershot," resulting in a multitude of fluorinated products, none of which is produced in useful quantities. A mixture of a known substrate **4** plus hydrocarbon **3** produces product **5** exclusively, even though **4** is expected to have a higher ionization potential (Scheme 4; competition). Moreover, hydrocarbon **3** fails to fluorinate under 300-nm irradiation (Scheme 4; control). The chemical (and photochemical) behavior of benzil has been well documented over the past 150 years (e.g. as a hydrogen atom abstractor, oxygen scavenger, organic reagent, and a triplet-triplet energy transfer facilitator).[18]

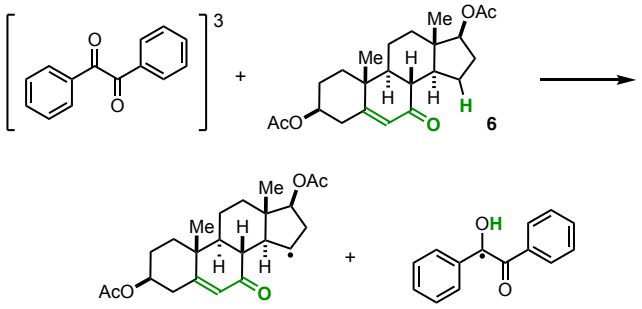


entry	*sensitizer*	*^{19}F NMR yield (%)*
1	-	0
2	2-bromo-9-fluorenone	43
3	9-fluorenone	47
4	dibenzosuberenone	55
5	9,10-phenanthrenequinone	64
6	4,4-difluorobenzil	67
7	2,7-dichloro-9-fluorenone	71
8	2-chlorothioxanthone	73
9	methylbenzoylformate	89
10	benzil	94

Table 1. Scope of sensitizers screened under 400-nm irradiation.

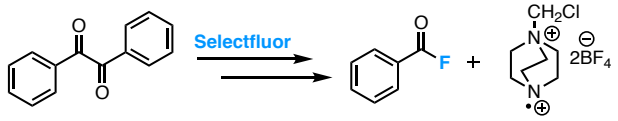
Our first thought turned to the possibility that photoexcited benzil acts through HAT (Scheme 5).[19] Photoexcited carbonyl-containing species are proposed to be competent hydrogen atom abstractors in a variety of settings.[20] In our case, this concept was unlikely for two reasons: 1) the energetics are not favorable (it would be a fairly endothermic process for the steroid substrates) and 2) benzil in any event is not expected to be a selective hydrogen atom abstractor. The calculated abstraction energy for steroid **1** is uphill by almost 12 kcal/mol (IEFPCM(CH_3CN)UωB97X-D/6-311++G(2d,2p)); in known cases where benzil engages in HAT, the hydrogen atom donor is fairly activated, as in cumene and isopropanol.[21] Furthermore, if the other photosensitizers of differing shapes, sizes, and electronic properties operate through HAT, it seems highly unlikely that they would afford the exact same site-selectivity as well. As can be seen in Table 1, along with direct photolysis, various

other carbonyl photosensitizers afford identical selectivity. On the other hand, Bunbury and Wang have irradiated benzil in cyclohexane solution, observing in the process both cleavage products and products resulting from H-abstraction.[18a,b] In our case, in a control experiment involving benzil irradiated with steroid **6** at 400 nm, we *do not observe* the cleavage byproducts consistent with benzil acting as an abstractor, which should include benzaldehyde.



Scheme 5. Concept of benzil acting through putative HAT.

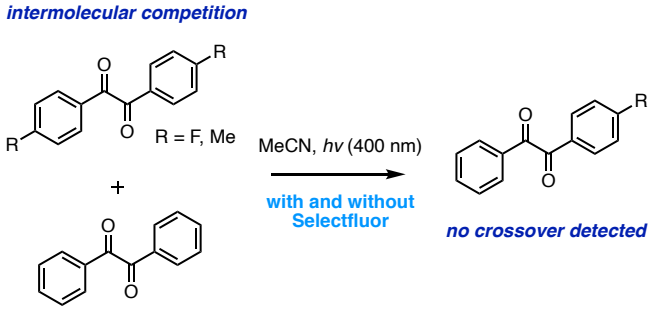
Appropriately, multifaceted benzil seems to take on yet another role in the present reaction. For example, we note the generation of significant quantities of *benzoyl fluoride* in all successful fluorination reaction mixtures with SF as reagent. As a control, a mixture of benzil and SF (no substrate) in MeCN was irradiated by a 400 nm LED lamp and generated benzoyl fluoride in 44% yield when performed in a glove box and 34% under normal reaction conditions. In contrast, benzoyl fluoride is not generated in the dark. As suggested in Scheme 6, the formation of benzoyl fluoride may logically be correlated to the generation of SRD. However, the question remains of how benzoyl fluoride is formed.



Scheme 6. Formation of benzoyl fluoride under irradiation.

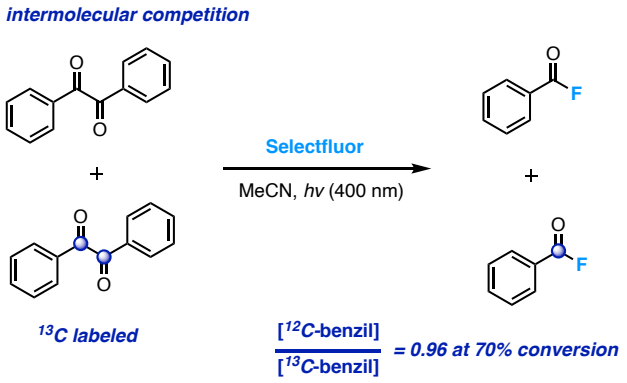
The α-cleavage of benzil is a conceivable pathway in which the reaction could be initiated. One can imagine the resultant benzoyl radicals reacting quickly with SF to produce PhCOF and SRD, thus initiating the reaction, as this process is predicted to be highly exothermic. The excitation and intersystem crossing of benzil to the T_n state may promote an energetically feasible homolysis – albeit one that has only been observed in laser pulse studies involving two-photon excitation.[18e,f] In fact, evidence for direct α-cleavage (Norrish I) of benzil under more normal chemical conditions is scant. Nevertheless, assuming that direct cleavage occurs under our conditions of photoexcitation, a simple synthetic probe to observe cross products would provide incontrovertible proof.

Accordingly, we irradiated a mixture of 4,4'-dimethylbenzil and benzil in acetonitrile with 400 nm light and found no detectable cross products (Scheme 7). The same result was obtained with 4,4'-difluorobenzil (both of these benzil derivatives work equally well in the reaction). In the presence of SF, recovered starting materials also showed no evidence of scrambling, suggesting that SF does not promote the process.



Scheme 7. Crossover experiment to probe possible direct α-cleavage of benzil derivatives in the presence and absence of Selectfluor.

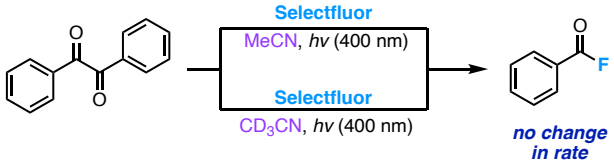
The results are consistent with *direct* cleavage not occurring to a significant extent, or else recombination of benzoyl radicals is happening faster than their diffusion. Even very prolonged irradiations produce no evidence of cross products, which along with precedent suggests that direct α-cleavage of benzil is simply not occurring under the usual fluorination conditions (400 nm irradiation). However, we conducted an intermolecular competitive kinetic isotope effect experiment and tracked the consumption of the benzil starting materials (due to the instability of benzoyl fluoride, we were not able to measure its formation with quantitative mass spectrometry). We found an enhancement of ^{13}C in the starting material as the reaction proceeds. This suggests that cleavage may be occurring through a different pathway (Scheme 8).



Scheme 8. Competitive kinetic isotope effect (KIE) experiment.

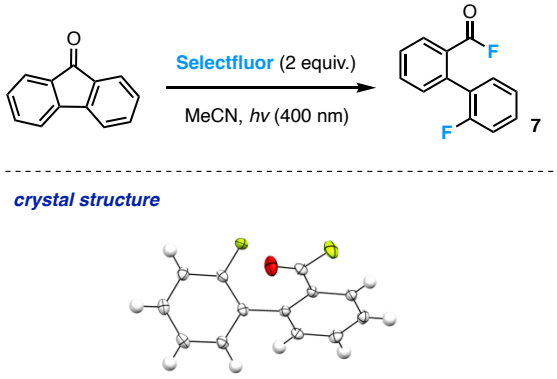
Another conceivable route involves excited-state benzil abstracting a hydrogen atom from acetonitrile and subsequently cleaving to generate a benzoyl radical.[22] Although energetically uphill by most measures, it was simple enough to test this hypothesis. We conducted a KIE experiment

employing acetonitrile-d_3; this experiment showed no change in rate when compared to acetonitrile (Scheme 9). Additionally, benzaldehyde is once again expected as a by-product, yet none was detected.



Scheme 9. KIE experiment probing role of solvent.

One other illuminating piece of data was obtained by the use of 9-fluorenone as a photoinitiator. The reaction provides a slightly lower yield of fluorinated ketone/enone in comparison to the benzil-initiated reaction, but still works moderately well. In the case of 9-fluorenone, hypothetical α-cleavage through a Norrish I fragmentation is expected to be less favorable than that of benzil as the resulting reactive intermediate consists of an aryl radical (Scheme 10). Nevertheless, purification of the reaction mixture led to the isolation of difluoride **7** (the structure was unambiguously assigned via single-crystal X-ray diffraction), evidently resulting from difluorination of an aryl-benzoyl radical, which should also be competent in generating SRD.



Scheme 10. α-Cleavage and difluorination of 9-fluorenone. Crystal structure of product shown (displacement ellipsoids at 50% probability with hydrogen atoms refined by a riding model).

An attractive pathway for the production of benzoyl fluoride is suggested by Saltiel's classic reaction of ground state triplet dioxygen with photoexcited benzil (Figure 5, left).[23] The resulting peroxyl radical intermediate (or perhaps transition state) cleaves to produce benzoyl radical and the daughter peroxy radical **8**. In order to determine whether dioxygen was involved in our reaction, we conducted our original experiments under strict atmospheric regulation, whereby a reaction mixture containing benzil, substrate **1**, and SF in dioxygen-free acetonitrile (freeze-pump-thaw cycled) was prepared in a glove box and then irradiated. The resultant crude mixture was found to have fluorinated in a comparable yield to the typical reaction conditions.

In addition, a fluorination reaction conducted under a pure dioxygen atmosphere failed to fluorinate either the steroid or benzil - suggesting that dioxygen was not only unnecessary for initiation, but that too much retards the initiation step by quenching the triplet-excited benzil either chemically or photochemically. Nevertheless, Saltiel's seminal experiments suggest a plausible analogy. In a more likely scenario, triplet benzil (drawn in a form emphasizing its diradical character) is trapped by Selectfluor (instead of dioxygen) and cleaves into benzoyl fluoride and benzoyl radical (Figure 5, right). This hypothesis is supported by DFT calculations (ΔE = -59.4 kcal mol^{-1} for the formation of products [UωB97XD/6-311+G**(MeCN)]). The calculated values for fluorination of triplet benzil are considerably more exothermic than those calculated for the triplet oxygen reaction (ΔE = -21.7 kcal mol^{-1}). Also in both cases, the presumed adducts (with $^3O_2$ and F•) are not stable minima and dissociate, suggesting a concerted route to products. Bear in mind that SF is an excellent radical trap and known to react extraordinarily rapidly with organic free radicals.[24]

A recent study by Tan and coworkers[25] addressed the interaction between photoexcited anthraquinone and Selectfluor using transient-absorption spectroscopy and DFT calculations. The authors propose that an anthraquinone-Selectfluor exciplex is responsible for initial HAT from their substrates, and this initiates a chain reaction. While we cannot rule out the formation of exciplexes in our system, it seems once again unlikely that HAT from excited state benzil would be selective in any form.

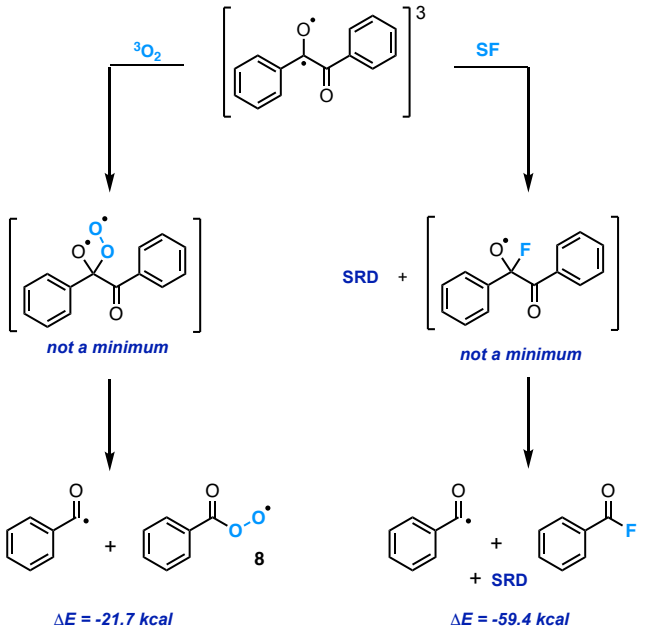
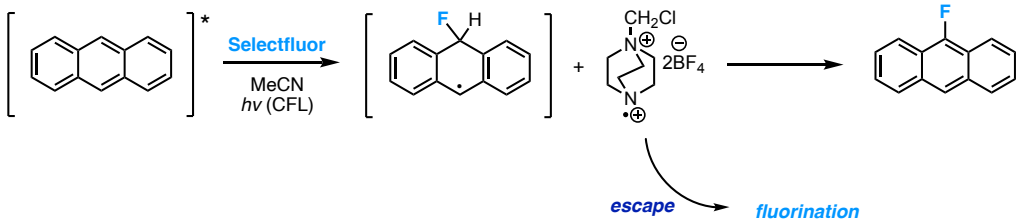


Figure 5. Analogy between Saltiel's experiments involving excited benzil and triplet dioxygen (left) and a plausible variant involving Selectfluor (right).

Photoinitiation with Other Promoters. Carbonyl-containing photopromoters that absorb in the region of irradiation are notable for their efficacy in the reaction, which we attribute to their propensity for α-cleavage in the presence of SF. Furthermore, a number of "non-carbonyl" photopromoters work as well. Anthracene produces a good yield of

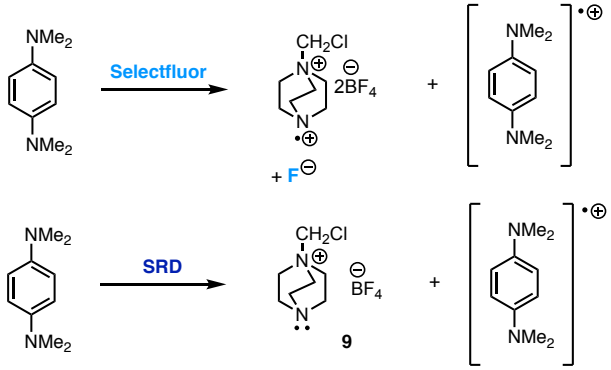


Scheme 11. Effecting the fluorination reaction with non-carbonylic photopromoters.

product **5** with a CFL bulb, whereas perylene produces no product. Note that the triplet energies of both anthracene ($E_T \approx 42$ kcal/mol) and perylene ($E_T \approx 35$ kcal/mol) are too low for sensitization to be viable, and that both anthracene[26] and perylene[27] absorb within the region of the light source emission.

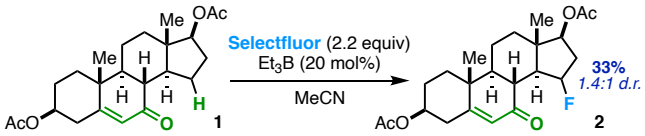
During the course of the reaction, anthracene is fluorinated (predominately in the 9-position) whereas perylene is not. One can imagine excited-state anthracene reacting with SF to liberate SRD and initiating a chain process (Scheme 11). A general rule of thumb is that *any photopromoter* that works well in the reaction is transformed itself by fluorination (presumably to produce SRD).

Alternative Methods to Generate SRD. To understand the intimate role that SRD plays within the mechanism, we sought methods for its generation by purely chemical means. *N,N,N′,N′*-Tetramethyl-*p*-phenylenediamine is an avid one-electron donor that generates the highly characteristic dye "Würster's Blue" in the process.[28] It reacts readily with SF, producing the colored dye immediately. Unfortunately, this reaction cannot be used to initiate a selective fluorination, as SRD itself is even more highly susceptible to one electron reduction. The result is almost clean conversion of SF to amine **9** (Scheme 12).



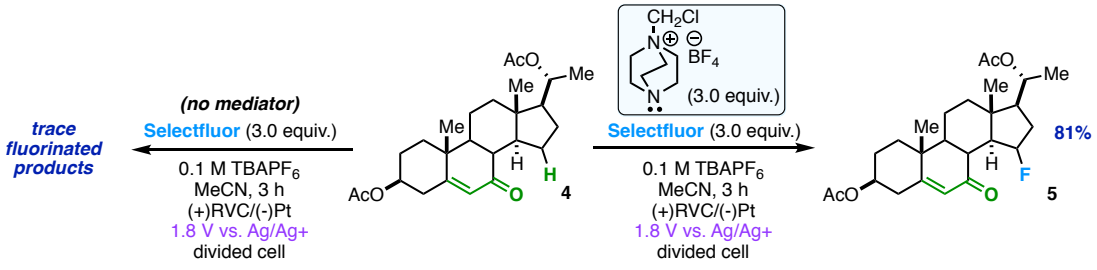
Scheme 12. Reactions of SF with *N,N,N′,N′*-tetramethyl-*p*-phenylenediamine.

The Triethylborane Method. We established in prior work that the production of ethyl radicals during the autoxidation[29] of triethylborane provides an adequate radical source to be fluorinated, thus generating SRD.[30] Under these strictly chemical conditions, fluorination of steroidal enones/ketones is possible (albeit in lower yields) with *identical* reactivity patterns to those derived from direct and benzil-catalyzed photolysis (example in Scheme 13). Moreover, the lower yields observed when using triethylborane are possibly attributed to maintaining a sufficient quantity of SRD at any one time, the necessary presence of dioxygen, and the vagaries of putative chain propagation in general. In particular, the reaction requires oxygen, but too much also inhibits the reaction.



Scheme 13. The triethylborane test in which SRD is generated under non-photochemical conditions.

Bulk Electrolysis. Using cyclic voltammetry (CV), peak oxidation potentials of amine **9** (a direct precursor to SRD) and substrates **6** and **4** were found to lie between 1.9 and 2.4 V vs. Ag/Ag+ (Figure 6). Unsurprisingly, the oxidations are irreversible at all scan rates probed, although peak shapes change. We bore in mind that these outcomes are dependent on the electrochemical solution concentrations, but they provided a rough guide to voltage tuning for the performance of a bulk electrolysis.[31] Irreversible peak reduction of SF was also observed at –0.3 V; the presumably liberated SRD is quickly reduced itself (dry and de-oxygenated MeCN with 0.1 M $TBAPF_6$ and a potential sweep rate of 100 mV/s (vs Fc/Fc+)). We chose to conduct a bulk electrolysis experiment whereby substrate **4** and SF were mixed in MeCN, and a potential of 1.8 V (approximate anodic potential of amine



Scheme 14. Bulk electrolysis experiment supporting involvement of SRD.

9, and out of range to oxidize compound **4**) was applied to the cell for 3 h (Scheme 14, left). Under these conditions, product yields were very low (< 3%). On the other hand, electrolysis in the presence of amine **9** resulted in an 81% yield of product, and once again, the exact *same product distribution* was observed as compared to the photolytic approach (Scheme 14, right). Amine promotor **9** proved absolutely necessary as a mediator – the optimal voltage for the reaction corresponds very roughly to its oxidation, suggesting that SRD is once again the indispensable actor. Direct oxidation of the steroid itself produced product (E = 2.3 V), albeit in only 10% yield, suggesting that a critical threshold of SRD as a chain carrier was not attained. Use of other fluorinating agents such as NFSI produced small amounts of various unselective fluorinated products. This experiment, besides its innate utility, cleared away a number of mechanistic ambiguities.

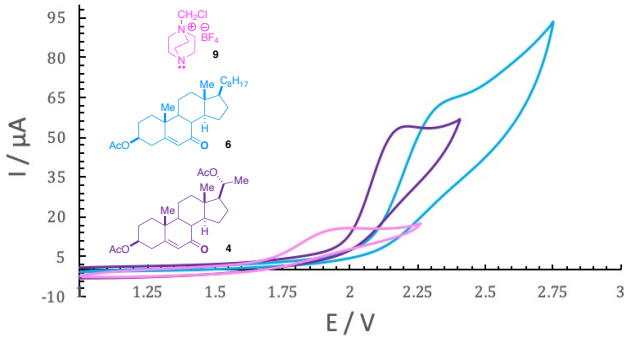
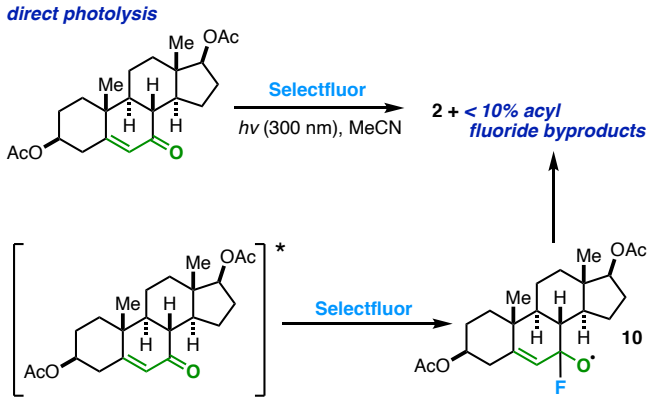


Figure 6. Cyclic voltammograms of compounds **9**, **6**, and **4** in dry and de-oxygenated MeCN with 0.1 M $TBAPF_6$ and a potential sweep rate of 100 mV/s (vs Fc/Fc^+).

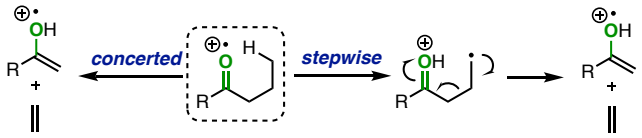
Direct Reprise. Reprising briefly the topic of direct photolysis, Scheme 15 provides one clue as to the lower yields observed; the substrate itself likely serves as the initiator. As mentioned, every successful photopromotor is itself fluorinated in order to liberate SRD. This may apply to direct photolysis as well - the minor acyl fluoride byproducts (highly characteristic by ^{19}F NMR in the vicinity of +17 ppm) likely result from the cleavage of putative radical intermediate **10** (Scheme 15).



Scheme 15. Under 300-nm irradiation in the absence of a sensitizer.

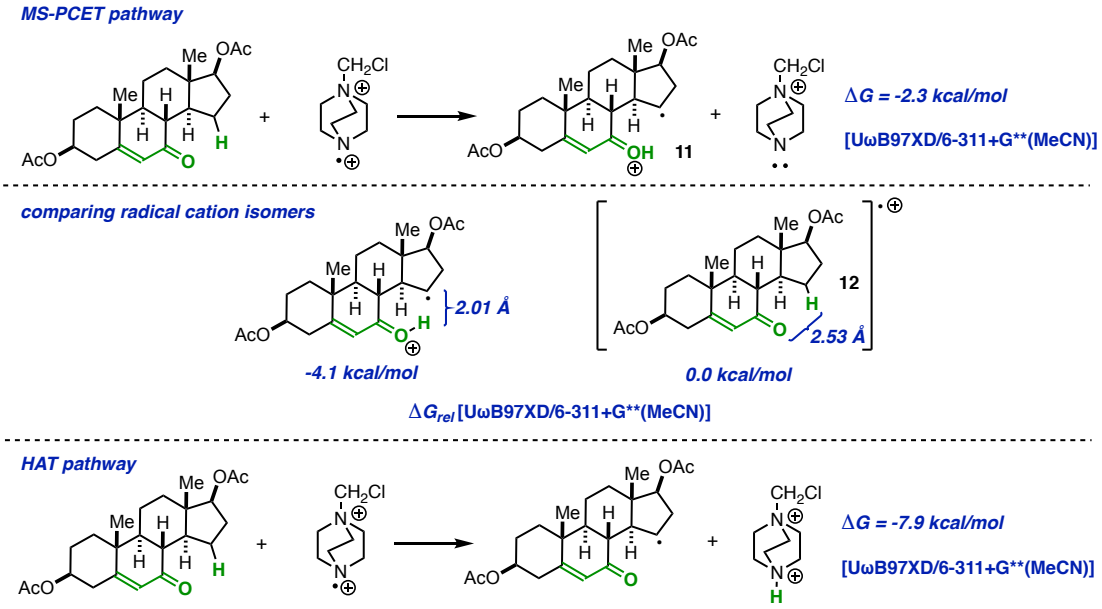
In the absence of SF, unidentifiable products form, but at a *much* lower rate than fluorinated byproducts when SF is present, suggesting that another pathway is at work. Consequently, yields are naturally lower as a bit of the substrate is sacrificed. The situation is most dramatic for ketones, whose propensity to fragment seems to be greater than that for enones.

ET/PT. Benzil, photoinitiation, borane initiation and bulk electrolysis conclusively rule out Norrish II chemistry, as well as any other chemistry involving photoexcitation of the enone chromophore with the exception of direct excitation. If ET/PT were operative, the carbonyl lone pairs must act as an internal base to deprotonate intramolecularly an optimally poised C-H bond, yielding a protonated carbonyl and a secondary carbon radical. This step (proton transfer) can happen sequentially or simultaneously with an electron transfer; consequently, there exist two reasonable pathways: electron transfer followed by proton transfer (ET-PT) or concerted transfer of the two particles (CPET). One other pathway (PT-ET) is high energy by any estimation and should be discounted.[32]



Scheme 16. Gas-Phase McLafferty rearrangement.

The Relationship of CPET and ET/PT to the Gas-Phase McLafferty Rearrangement. The enone activation process bears a resemblance to the gas-phase McLafferty rearrangement (Scheme 16). This venerable gas-phase reaction involves carbonyl-containing compounds possessing γ-hydrogens, similar to many of our substrates.[33] The (somewhat limited) mechanistic consensus advocates electron abstraction, followed by intramolecular HAT and then fragmentation (the present work could thus be considered a formal "interrupted" McLafferty reaction). Intramolecular isotope effects for these rearrangements are documented; these range over a wide spectrum of values.[34] However, intermolecular isotope effects for McLafferty reactions are not widely known. The McLafferty rearrangement would seem to be a candidate for PCET, but not much if anything is reported about this option. Djerassi and coworkers[35] have examined potential McLafferty rearrangements in keto steroids and found that only when the interacting carbonyl and C-H bonds can approach to within 1.5 Å is the rearrangement feasible (Figure 7). In more rigid steroidal ketones it does not occur, in contrast to the present chemistry. This is an interesting fact that begs the question whether CPET or ET is involved in our system at all, as our geometric requirements are so different than typical McLafferty substrates. Granted, McLafferty chemistry is all gas phase, so the lack of correlation may not be taken as definitive.



Scheme 17. Comparing calculations of MS-PCET and HAT mechanisms.

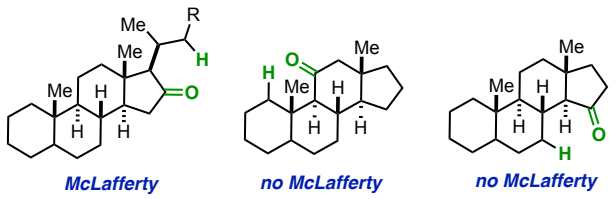
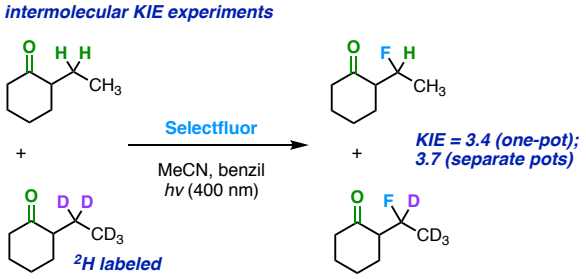


Figure 7. Examples of steroid cores that were or were not observed to undergo McLafferty rearrangements in gas-phase experiments.

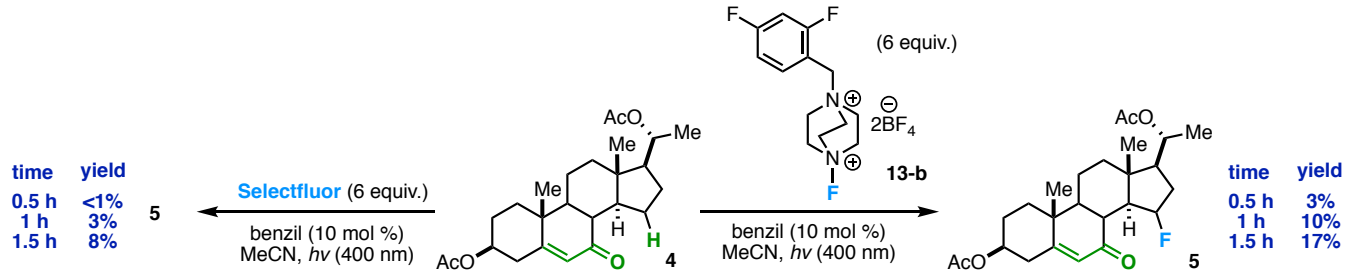


Scheme 18. Competitive intermolecular kinetic isotope effect experiment. The reaction gives rise to minor amounts of ring-fluorinated byproducts that do not affect the analysis.

One insightful calculation shows that CPET (to be more accurate: MS-PCET) is modestly exothermic for a typical steroidal substrate (Scheme 17). The precise number, of course, is to be best viewed as a ballpark figure. More interesting is the comparative energy of radical cation isomers that favors **11** by 2.3 kcal/mol. The structure of **11** reveals what could be characterized as a hydrogen bonding contact between the radical center and the OH proton (2.01 Å).[36] A weaker interaction exists in computed radical cation **12** of 2.37 Å between C and O (Scheme 17). On the other hand, a straightforward HAT is exothermic by more than 7.9 kcal/mol.

Our efforts to discern between the two viable possibilities led us to use a mechanistic probe: an isotope effect experiment between 2-(pentadeuteroethyl)cyclo-hexanone and 2-ethylcyclohexanone). We observed a phenomenological kinetic isotope effect in a one-pot intermolecular competition reaction (KIE = 3.4) and also when comparing initial rates of reaction of each isotopomer separately (KIE = 3.7). Both results are large enough to encompass a primary effect (cleavage of the C-H bond) along with superimposing secondary effects (Scheme 18).[37] *These numbers rule out an initial rate-limiting ET in ET-PT and argue against pre-equilibrium PT in PT-ET.*

Although we observed a primary KIE, PT-ET (rate-limiting PT) is unreasonable; the rate determining PT would be highly thermodynamically unfavorable due to the low acidity of the targeted C-H bond and the resulting instability of the zwitterion intermediate. One important experiment designed to distinguish MS-PCET and HAT from pre-equilibrium ET in ET/PT involves the use of SF derivatives possessing different oxidizing power. SF derivative **13-a** has a more positive anodic peak potential (E_a = 2.14 V) and inflection-point potential (E_i = 1.88 V) compared to compound **9** (E_a = 1.99 V amd E_i = 1.77 V) (Figure 8), and leads to a faster reaction (Scheme 19), which could be due to HAT, an enhanced electron transfer rate or else fluorination. However, the observation of a KIE for proton transfer in the reaction militates against the fluorination step being rate-determining; thus, this result supports the involvement of HAT or electron transfer in the rate-determining step. Congruent with this conclusion is our prior work that established a very fast rate for the reaction of SF with free radicals.[24a]



Scheme 19. Rate comparative studies for compound **13-b** vs. SF; monitored initial rate with excess fluorinating reagent present.

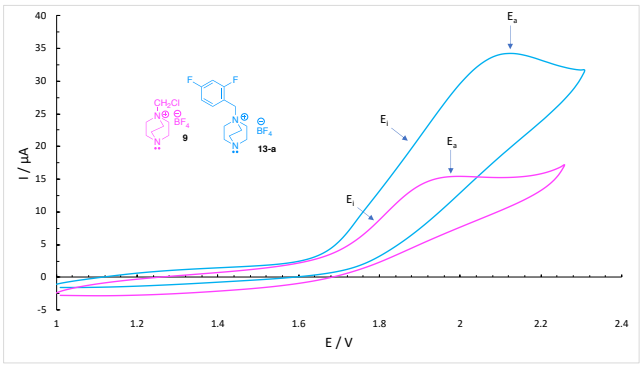


Figure 8. Cyclic voltammograms of compounds **9** and **13-a** in dry and de-oxygenated MeCN with 0.1 M $TBAPF_6$ and a potential sweep rate of 100 mV/s (vs Fc/Fc+).

Carbonyl-coordinated HAT. Considering the aforementioned results, we are left with viable pathways in the form of HAT and MS-PCET. The former, HAT through SRD, would seem to be disfavored based on calculated C-H bond dissociation energies (a factor of HAT capability).[38] DFT calculations on steroid **6** (ωB97XD/6-311++G** in MeCN) show numerous weaker C-H bonds in the presence of the targeted C-H bond in substrate **6** (Figure 9). However, this analysis is naïve as it takes no account of steric and electronic factors. It is the transition state energies that dictate the selectivity of HAT, not merely BDEs. *Is it possible that SRD interacts with a proximate carbonyl group in a way to organize a lower energy transition state?*

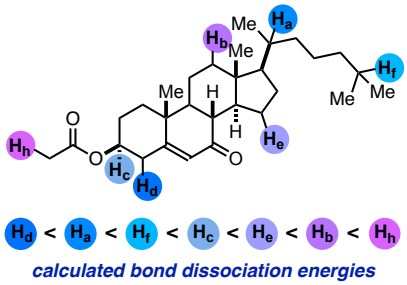
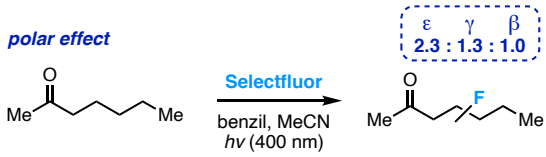


Figure 9. Relative calculated C-H bond dissociation energies (weakest to strongest from left to right).

In order to address this issue, we undertook transition state calculations on a model substrate. In less rigid systems (for example, entities containing a floppy side chain), the carbonyl is not adequately locked, and activation may occur at several sites simultaneously. In a simple probe, we observe product distribution in accordance with the "polar effect," a known HAT pathway (Scheme 20).[39]



Scheme 20. Distribution of fluorinated products from reactions employing non-rigid carbonyl-containing substrates are characteristic of the established "polar effect."

In more rigid systems however, if the carbonyl is indeed templating the approach of SRD to the targeted C-H bond, then it stands to reason that other HAT agents that do not possess this ability would afford "scattershot" fluorination if they were to afford anything at all. A good example would be the free radical derived from NFSI; it is a known HAT agent,[40] and contains no functional groups with particular affinity for carbonyl coordination. Scattershot fluorination is in fact the case; a variety of fluorinated products in low yield is observed in the reaction of NFSI and a model substrate. A similar result is obtained when *N*-fluoropyridinium triflate is used – small amounts of unselectively fluorinated products are observed (Figure 10).

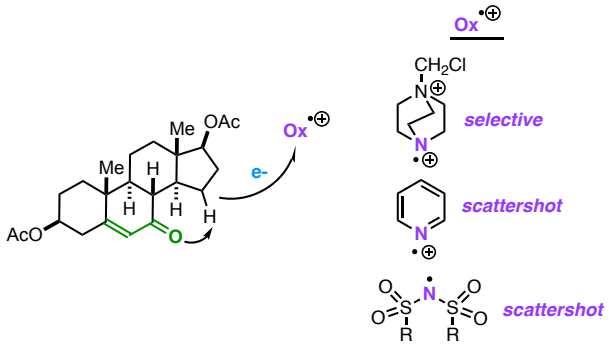
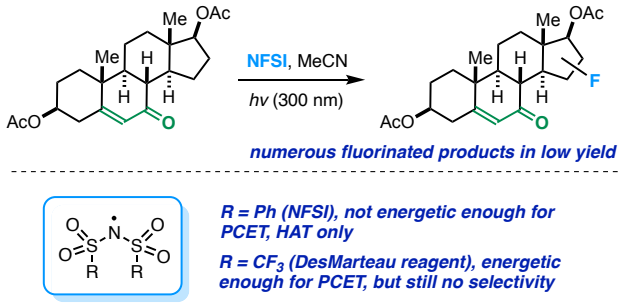


Figure 10. Product distribution classified as "selective" or "scattershot" in reactions involving presumed *N*-centered radical intermediates.

What about an outer-sphere PCET (MS-PCET)? Although the NFSI-derived free radical may not be sufficiently energetic to engage in PCET, using more reactive analogues of NFSI (e. g. the DesMarteau reagent)[41] produces a similar pattern of scattershot fluorination (Scheme 21). This is notable as the DesMarteau reagent *should be* energetically capable

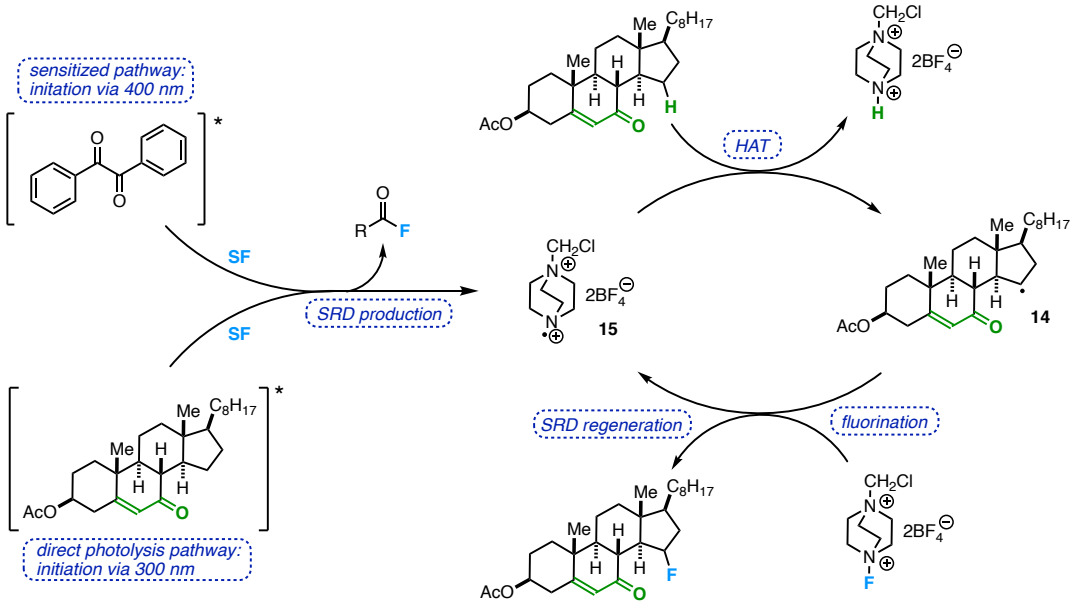
of engaging in MS-PCET. Once again, this consideration applies to *N*-fluoropyridinium. On the other hand, in a true MS-PCET system such as that of Mayer and coworkers, the desired event occurred in the presence of a wide variety of one-electron oxidants as long as they possessed the correct potentials. In our case, it is clear that the nature of the reaction is not dependent on oxidation potential, but on chemical structure. *This would seem to be strong evidence for a very selective and special version of HAT or inner-sphere PCET.*



Scheme 21. Reactivity of NFSI derivatives differs from that of Selectfluor.

Evidence for a Chain Reaction. After the critical HAT step, the substrate is left with a free radical (Scheme 22, compound **14**). The final step of the chain propagation is well established through prior studies: reaction between the resultant radical and Selectfluor to yield an alkyl fluoride and to regenerate SRD (Scheme 22, compound **15**).[29] To verify a chain process, we calibrated the quantum yield Φ of the standard reaction (SF, benzil, 400 nm LED, MeCN) against the photodecomposition of lime green potassium ferrioxalate, a well-established chemical actinometer, and found Φ = 18.

Calculations. In the mechanistic study of the carbonyl-directed reaction, quantum calculations were always destined to play an important role. If our hypothesis of carbonyl-directed HAT is true, then the corresponding HAT transition states should be the lowest energy of all reasonable sites in the molecule. Sampling all chemically distinct hydrogen atoms at a sufficient level of theory is a tall order; however, we strove to be as comprehensive as possible. Additionally, each carbonyl-activated site is a methylene unit containing diastereotopic protons; it is quite possible that only one of whose abstractions would be favored. Take, for example, model substrate **1** (Figure 11). Abstraction of the α proton is favored by 2.9 kcal/mol over the β proton. Abstractions of protons from other logical sites are relatively disfavored (see SI for structures). The reason is evident from both the geometry and energetics of the transition states – two key C–H···O=C hydrogen bonds anchor and stabilize the assembly in the correct orientation. This deduction was supported by second order perturbation theory analysis of Fock matrix in natural bond orbital (NBO) basis for alpha and beta manifolds. These hydrogen bonds, involving slightly acidified protons on SRD, are calculated to be worth 4–5 kcal/mol — more than enough to torque the system toward directed abstraction. The other stabilizing interaction exists between the transferring hydrogen atom and the carbonyl group. This is a weak H-bond in its own right and a contributing factor to the transition state stability as well. In the case of the lowest energy transition state, all three interactions are a bit tighter. The transferring hydrogen carries a calculated partial positive charge of 0.41, which is not unusual for HAT.[42] As for potential inner-sphere PCET, the theoretical criteria of Mayer and coworkers would seem to disfavor this possibility.[43]



Scheme 22. Chain propagation mechanism at play.

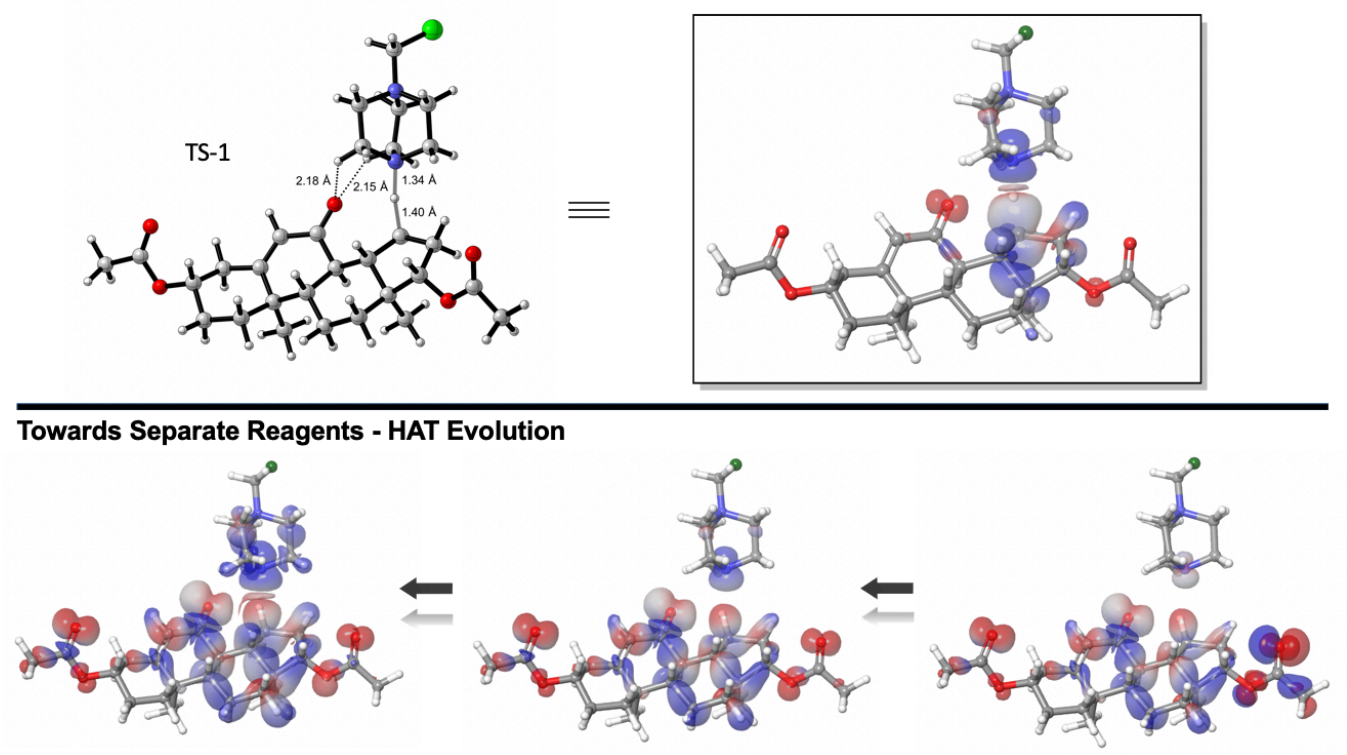


Figure 12. HAT transition state (top) and intrinsic reaction coordinate (IRC) derived evolution of HAT reaction coordinate (bottom) with molecular electrostatic potential (MEP) surfaces (isovalue = 0.001, min = 50.0 and max = 110.0) superimposed on spin orbital densities (isovalue = -0.0045). The transition state optimization and IRC computed at UB3LYP/6-31G(d). The MEP surfaces and spin orbital densities computed by single point calculations at the UB3LYP-D3/6-311++G(2d,2p).

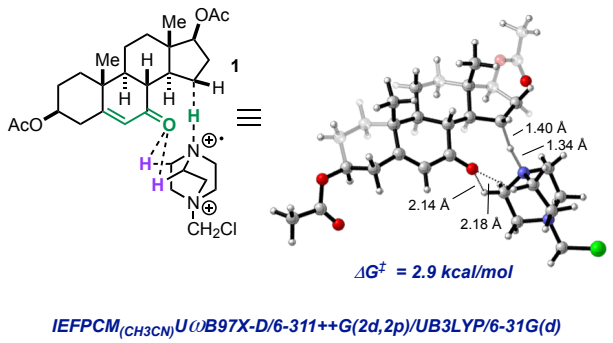
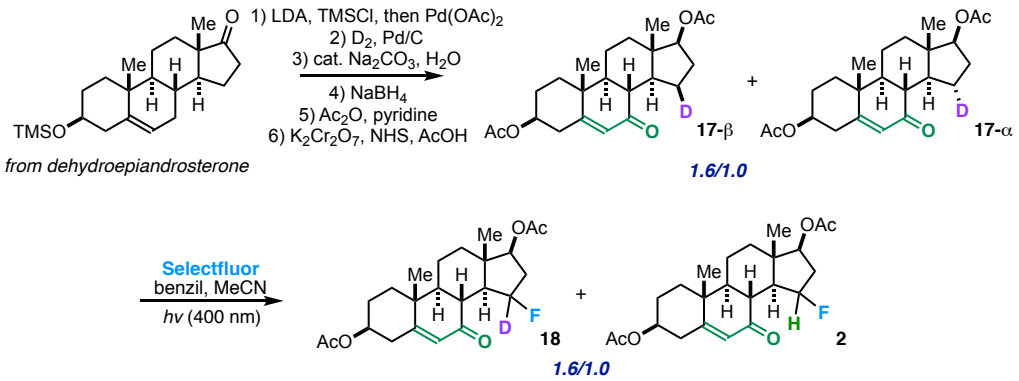


Figure 11. Comparing transition state energies involving HAT from each of the diastereotopic protons at C15 of a prototypical enone-containing substrate.

Figure 12 shows an image of the computed spin orbital density of TS assembly **TS-1** with its electrostatic potential superimposed. This distribution of spin tells an interesting story - namely, in this transition state, the cationic-radical nitrogen atom to which the hydrogen is being donated significantly lacks electron density — indicative of partial positive charge — while there is a larger degree of electron density at the transferring hydrogen atom, thus, suggestive of negative charge build-up. The developing carbon-centered radical, on the other hand, is essentially neutral. This spin orbital density and imbedded charge distribution are indicative of a three-electron, three-center transition state. Recollect that the lone pair of the distal carbonyl oxygen is directly pointed at the C–H bond undergoing homolytic cleavage; associated with this interaction is favorable Coulombic attraction between the cationic SRD species and the negatively charged carbonyl oxygen. Conversely, if this were a PCET mechanism, it would require the transferring hydrogen to be a part of a four-electron, three-center array more consistent with hydrogen bonding.[44] In this instance the carbonyl oxygen would need to have significant radical cationic character, or at least positive charge build-up relative to the substrate.

Figure 12 also depicts the evolution of the HAT reaction coordinate, with images of the spin orbital density with the electrostatic potential (blue positive, red negative) superimposed. Beginning at the bottom right is a precomplex wherein, there is no orbital density indicative of HAT; instead it looks to be a scenario primed for PCET or at the least intramolecular hydrogen abstraction by the carbonyl oxygen (NBO analysis shows a very small donation of carbonyl oxygen lone pair electron density to the C–H bond involved in hydrogen abstraction of 2.3 kcal/mol). As one moves along the bottom of the figure toward the left-hand side, HAT orbital density emerges and at the transition state (top of Figure 12) HAT type bonding is clearly visible, respectively.



Scheme 23. Isotopic-labeling experiment confirming preferential abstraction of the α-hydrogen and deuterium atoms, consistent with DFT-predicted HAT hypothesis.

The overall analysis holds for rigid ketones as well (Figure 13). Selective abstraction from ketone **16** is unusual in that the calculated energies between diastereotopic transition states is sizeable (3.6 kcal/mol). In the high energy transition state, the anchoring effect of the two acidic C–H bonds on SRD is greatly attenuated; one of the contacts is severed completely.

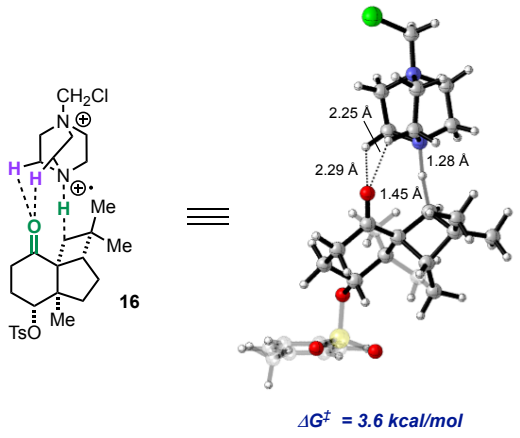


Figure 13. Comparing transition state energies involving HAT from each of the diastereotopic protons of a rigid, non-steroidal ketone-containing substrate.

Although the magnitude of the KIE in deuterated 2-ethylcyclohexanone indicates a primary isotope effect (Scheme 18), it occurred to us that substrate **1** would provide a way to affirm our computational predictions based on selective isotopic labeling. For a more compelling and less ambiguous case, we sought to make a specifically deuterated steroidal substrate optimally poised for fluorination (Scheme 23). For example, the unlabeled variant of **1** is predicted to fluorinate through preferential abstraction of the β-C15 hydrogen atom. This prediction could be verified by a simple labeling experiment. In the event, we began the synthesis with dehydroepiandrosterone (DHEA). Enolization was followed by Pd(II)-catalyzed oxidation to form the enone. Reduction with D_2, followed by base-catalyzed exchange of the C16 hydrogen atoms, produced a mixture of isotopomers in a 1.6/1 ratio. The synthesis is completed by stereospecific reduction of the ketone carbonyl, acetylation, and standard allylic oxidation with potassium dichromate, N-hydroxysuccinimide (NHS), and AcOH to produce the product as a mixture of βD/αD isomers of 1.6/1 (compound **17**). The assignment of isotopomers was made by ^{2}H NMR, with confirmation by ^{1}H NMR (see SI). The use of benzene-d_6 as solvent greatly aids the assignment of diagnostic signals.

Upon standard reaction conditions, remarkably, substrate **17** is converted to a 1.6/1 ratio of labeled isomeric products (compounds **18** and **2**). The result is exactly in line with what we would expect for preferential abstraction of the α-hydrogen and deuterium atoms. Preferential β-abstraction, on the other hand, would have yielded the opposite result.

Conclusion: We have explored the mechanistic possibilities of our previously reported enone/ketone-directed site-selective sp^3 C-H fluorination of terpenoid derivatives. Our findings suggest intermolecular hydrogen atom transfer (HAT) chemistry is at play, rather than classical Norrish hydrogen atom abstraction as initially conceived. Isotope effect studies, detailed quantum computations, thermochemical experiments, and reactions with one-electron oxidants all point conclusively toward a special type of HAT mechanism in which SRD approaches the targeted C-H bond by coordinating to the proximate carbonyl group. This interesting form of HAT may mimic such venerable reactions as the Norrish II cleavage and the McLafferty reaction but in actuality is quite different. Finally, this principle of selective, directed HAT may be leveraged in the interaction of SRD and related radical cations with other functional groups in works to follow.

ASSOCIATED CONTENT

Supporting Information. The Supporting Information containing experimental procedures, spectra, computational data, and crystallographic data for compound **7** is available free of charge on the ACS Publications website at DOI:

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Notes

The authors declare no competing financial interest.

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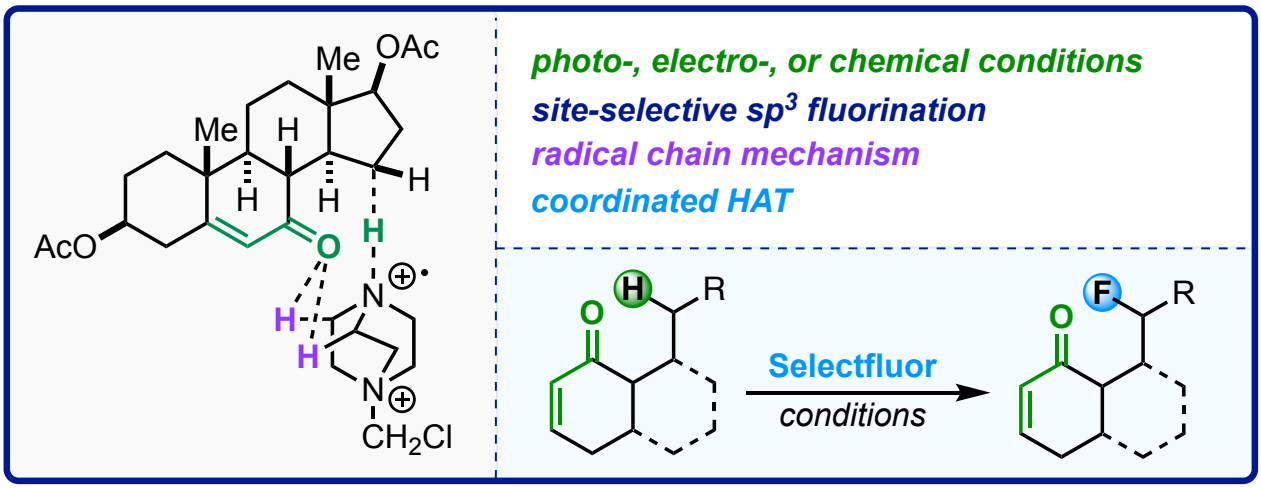
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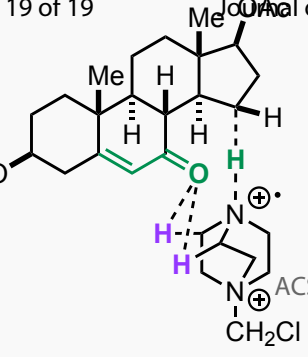

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