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Fluorofunctionalization of C═C Bonds with Selectfluor: Synthesis of *β*-Fluoropiperazines through a Substrate-Guided Reactivity Switch

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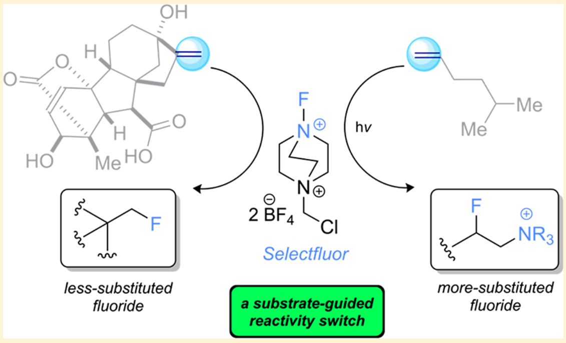
Supporting Information

ABSTRACT: The halofunctionalization of alkene substrates remains an essential tool for synthetic chemists. Herein, we report regioselective ammoniofluorination of unactivated alkenes through photochemical means. A one-pot transformation of the ammonium fluoride products into pharmaceutically relevant *β*-fluoropiperazines is highlighted. Furthermore, a substrate-guided reactivity switch is observed: certain alkenes are shown to react with the same fluorinating reagent to instead give the *less-substituted* fluoride. We hope that the ammoniofluorination reaction will be of utility in the area of medicinal chemistry, where nitrogen and fluorine are among the most important heteroatoms.



1. INTRODUCTION

The fluorofunctionalization of C═C bonds is an active and timely topic of study that complements the general renaissance in fluorination methodology. The goals are multifold and include the synthesis of biologically active fluorinated molecules,[1] chemical intermediates,[2] and pharmaceuticals.[3] From the standpoint of reactivity, mild and inexpensive conditions are desired.[4] The mechanistic aspects of fluorofunctionalization methods are significant as well, reactions involving an electrophilic fluorinating reagent are often expected to result in different regiochemical outcomes than reactions in which fluoride ion is the reagent.[5] Instead conceive of a situation in which the structure of the alkene substrate determines the regioselectivity of the reaction. This bespeaks a probable mechanistic "switch", in which the fluorinating agent plays a fundamentally different role. Such switch mechanisms have been of interest to our research group for a long time,[6] not least for the reason that they reveal basic reactivity patterns in fairly illuminating ways. Recently, we have employed Selectfluor (SF) in a variety of catalyzed and promoted fluorination reactions,[7] including a fluoroamination of arylcyclopropanes.[8] We discovered to our surprise that the DABCO moiety of Selectfluor itself was incorporated into the ring-opened products.

In this featured article, we report a fluorofunctionalization of alkenes that follows an unusual reactivity pattern. In the presence of UV light and a sensitizer, regioselective ammoniofluorination of monosubstituted alkenes is observed. The resulting products reveal the fluorine to be placed in the secondary position, and the ammonium substituent in the primary. In dramatic contrast, several di- and trisubstituted alkenes, especially those that can rearrange through carbocationic manifolds, afford the *less-substituted* fluoride instead with no incorporation of the DABCO moiety (Figure 1).

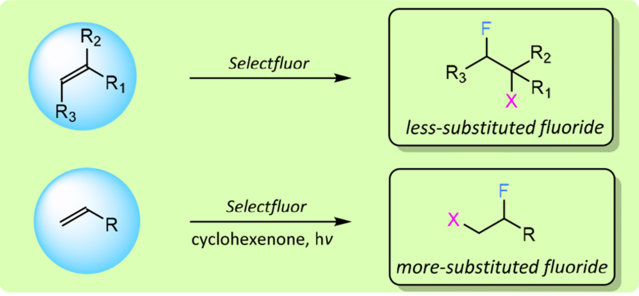


Figure 1. Switch in regioselectivity observed in the fluorination of alkenes.

The reaction of Selectfluor with alkenes was first reported shortly after the reagent was discovered.[9] Lal fluorinated styrene derivatives using Selectfluor in the presence of nucleophiles (no DABCO incorporation) and several reports have followed to describe the reaction of styrenyl alkenes in a similar manner.[10] Glycal enol ethers were also shown to react with Selectfluor to give fluorinated ammonium salts, which were then treated with various nucleophiles to displace the DABCO moiety.[11] In these two methods, regioselectivity arises due to the use of activated alkene substrates that form stabilized carbocations (i.e., a benzylic carbocation and an oxocarbenium ion). More recently, hydrofluorination,[12]

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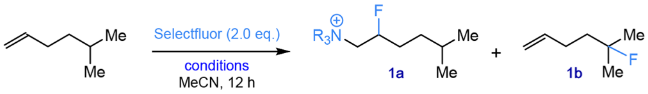
phosphonofluorination,[13] and azidofluorination[14] of unactivated alkenes using Selectfluor have been described, relying upon radical conditions to form the more substituted fluoride product.

On the other hand, direct aminofluorination of alkenes is less explored, and the few existing methods have limited substrate scope and are less suitable for diverse synthetic transformations.[15] Tosyl-protected pent-4-en-1-amine derivatives have been utilized under both metal and metal-free conditions to bring about an intramolecular aminofluorination using fluoride sources.[16] Several *N*-arylpent-4-enamides were also shown to participate in a similar intramolecular reaction using Selectfluor and $AgNO_3$.[17] Additionally, styrenes have been employed as activated olefin substrates in palladium (the amine derived from *N*-fluorobenzenesulfonimide traps the carbocation after the initial fluoride addition)[18] and copper[19] catalyzed intermolecular aminofluorinations leading to sulfonamide derivatives. This reaction requires the use of [*N*-(*p*-toluenesulfonyl)imino] phenyliodinane in addition to two catalysts and a fluorine source. A metal-free aminofluorination of styrenyl alkenes has been recently developed as well, utilizing azoles to trap a benzylic cation.[20] To the best of our knowledge, the only reported method for intermolecular aminofluorination of unactivated alkenes produces fluorinated carbamates rather than amines, requires two fluorine sources and a preformed catalyst, and has somewhat limited substrate scope with regards to unactivated olefins.[21]

2. RESULTS AND DISCUSSION

2.1. Optimization of Ammoniofluorination Conditions and Substrate Scope of the Reaction. Given our recent work in the area of photochemical sp^3 C−H fluorinations,[22] we were intrigued by the idea of an analogous sp^2 fluorination. Initial attempts of fluorinating 5-methyl-1-hexene with Selectfluor in MeCN under UV-irradiation (using 300 nm light sources) led to a mixture of two products, the *β*-ammoniofluoride (compound **1a**) and a tertiary fluoride that retained the olefin (compound **1b**, resulting from a photochemical sp^3 C−H fluorination at an activated tertiary site) in a ratio of approximately 1:1. In order to develop a regioselective fluorination protocol, we then screened different photosensitizers using 300 nm light sources (Table 1). As well, we briefly explored nonphotochemical conditions such as heat and BEt_3 (we have previously shown BEt_3 to effect the generation of the putative N-centered radical dication from Selectfluor that is important in electron transfer chemistry) to induce fluorination.[23] Gratifyingly, we found that the combination of cyclohexenone and 300 nm light to be the optimal conditions for a selective functionalization, resulting in the formation of the desired ammoniofluoride in excellent yield while affording only trace amounts of the tertiary fluoride byproduct.

Table 1. Screening for Reaction Conditions



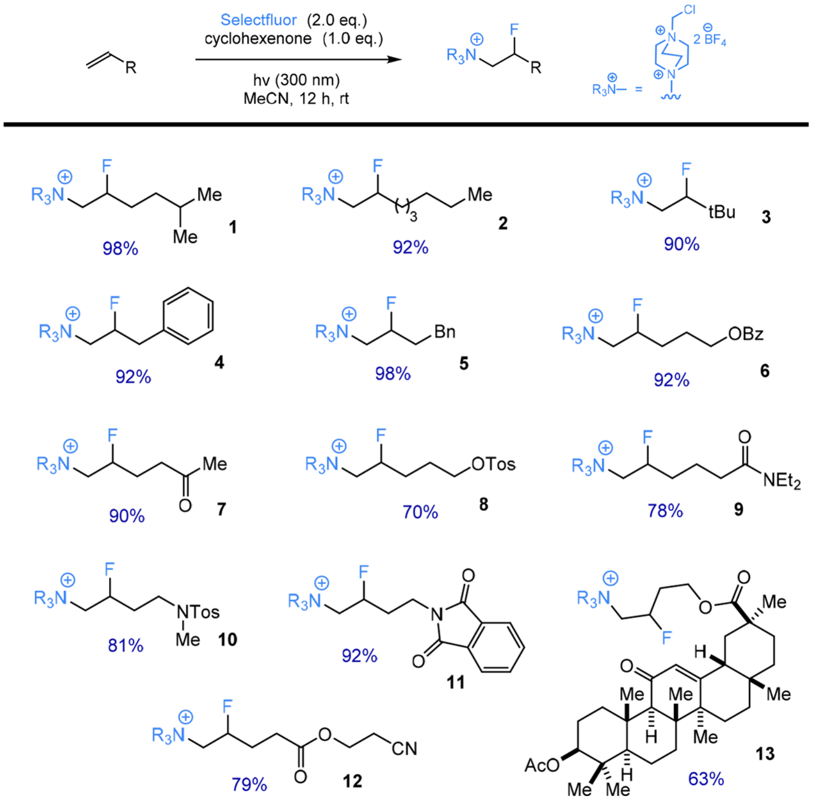
entry	conditions	% yields a	% yields b
1	*hν* (300 nm)	48	50
2	1,2,3,4,5-tetracyanobenzene, 0.1 equiv *hν* (300 nm)	79	15
3	80 °C (in dark)	80	18
4	rt (in dark)	<5	trace
5	2-cyclohexen-1-one, 1.0 equiv *hν* (300 nm)	**98**	<2
6	benzil, 0.1 equiv *hν* (LEDs)	70	12
7	5-dibenzosuberenone, 0.1 equiv *hν* (LEDs)	27	30
8	BEt_3, 0.2 equiv (in dark),	72	trace

Upon subjecting various alkenes to these optimized conditions, it became evident that monosubstituted alkenes work best (Table 2), whereas more substituted olefins tend to result in trace fluorination, a mixture of products, or both. We accordingly narrowed our focus to monosubstituted olefins and were pleased to observe that most perform well in the reaction, fluorinating regioselectively and in high yield.[24] Alkene substrates that include an alkyl or aryl substituent (compounds **1**−**5**) undergo ammoniofluorination in excellent yield. Oxygen-containing functional groups such as carbonyl, acetoxy, benzoyloxy, and sulfonyl were found to be compatible under our optimized reaction conditions (compounds **6**−**8**, **12**, and **13**). Moreover, several nitrogen-containing functional groups (namely, amido, phthalimido, sulfonamido, and cyano) were found to afford selectively ammoniofluorinated products in good yields (compounds **9**−**12**). Compound **13**, a derivative of the antiviral,[25] antifungal,[26] and antibacterial[27] drug enoxolone gives the desired ammoniofluoride product in good yield. This example demonstrates the reactivity of C=C bonds in the presence of many accessible sp^3 C−H bonds. It is worth noting that regioselectivity is not affected by the enone functional group at C11 even though it can direct fluorination to C1 under similar conditions.[28] Furthermore, compound **13** illustrates the potential to employ this method in a late-stage fluorination of a complex pharmaceutical target, making the reaction even more attractive to medicinal chemists.

2.2. Application of the Ammoniofluorination to the Synthesis of Fluoropiperazines. We found that it is simple to isolate the Selectfluor-adducts after the ammoniofluorination but challenging to separate them from the unreacted Selectfluor and derived impurities, as has been previously shown in similar compounds.[26] Given that the Selectfluor moiety is not particularly useful or interesting as a substituent, we next turned our focus toward ways to derivatize the ammonium fluoride compounds. Adopting a previously reported procedure from the Ritter group,[29] the DABCO moiety of the Selectfluor-adduct was efficiently reduced with aqueous $Na_2S_2O_3$, providing easy access to *β*-fluoropiperazine derivatives (Table 3). Importantly, the Selectfluor impurities can now be very easily separated from the desired product in an aqueous workup. The reduction can be performed in a one-pot fashion following the fluorination step; it works equally well on the isolated ammonium salts. For example, we demonstrated this approach on four alkenes and obtained the reduced products in good yields. We anticipate that a one-pot strategy to synthesize fluoropiperazines will be of great use to medicinal chemists, given the ubiquity of both piperazines and fluorine in pharmaceuticals.[30] The fluoropiperazine products were transformed into Cbz derivatives to facilitate chromatography (compounds **14**−**17**); however, they could also be isolated as the free secondary amines or instead alkylated or acylated with any appropriate electrophile.

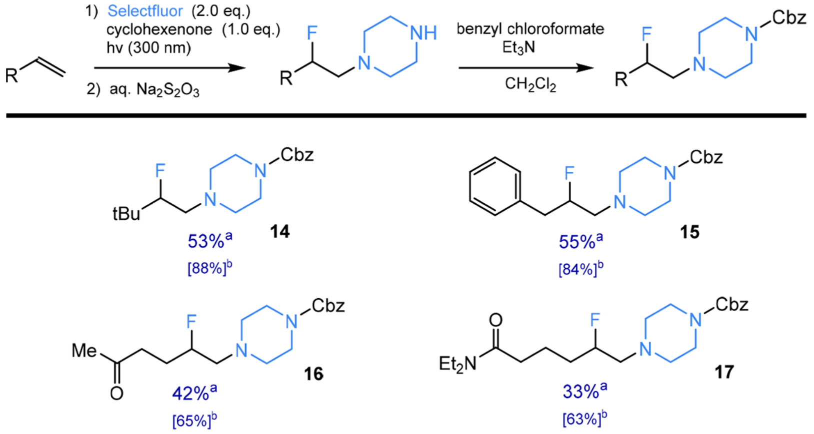
On another front, we briefly explored nucleophilic displacement of the DABCO-adducts by treating the ammonium fluoride salts with various nucleophiles. Unfortunately, we found this to be a surprisingly reluctant reaction. Nucleophiles such as sodium thiophenolate, sodium azide, potassium thiocyanate, sodium hydroxide, and several others were

Table 2. Substrate Scope of Monosubstituted Alkenes[a]



[a]Yields were determined by integration of ^{19}F NMR signals relative to an internal standard.

Table 3. One-Pot Synthesis of Fluoropiperazines from Alkenes



[a]Isolated yield over three steps. [b]Isolated yield over two steps.

observed to give a mixture of products in low yield. Although we have previously reported the displacement of a Selectfluor-adduct with potassium thiocyanate, the ammonium group was on a secondary benzylic carbon and likely was displaced through a different mechanism (S_N1).[8] While we remain interested in the potential utility of this substitution reaction, further exploration in this area is beyond the scope of this work.

2.3. Reactivity Switch Observed in the Fluorination of Other Alkenes with Selectfluor. In contrast to the reactivity of unactivated monosubstituted alkenes, we also report several new examples of alkenes reacting with SF to give the *less substituted* fluoride (Table 4). These products arise from a reactivity switch in which Selectfluor is reacting in a two-electron fashion with the olefin or instead via single electron transfer followed by rearrangement. Gibberellic acid, a plant hormone that is used in the agricultural industry,[31] undergoes a remarkably clean reaction with SF in high yield. The fluorogibberellin product (compound **18**) contains a $-CH_2F$ group as well as a ketone, which is the result of a Wagner-Meerwein rearrangement. A similar rearrangement has been reported on gibberellic acid using HCl;[32] however, under these conditions, the cyclohexene ring first aromatizes before the alkene reacts with the acid and ultimately rearranges. Therefore, this procedure is noteworthy as it allows modification of the 1,1-disubstituted alkene without disrupting

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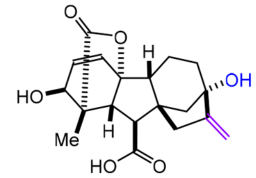
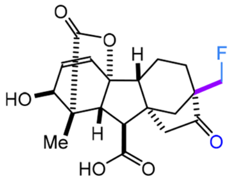
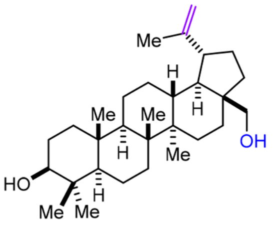
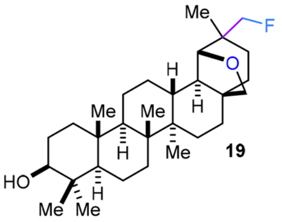
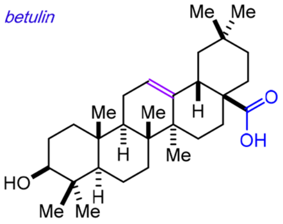
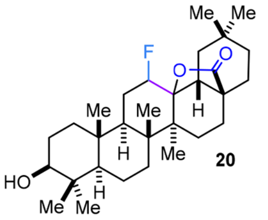
Table 4. Examples of an Alkene Reacting Nonphotochemically with Selecfluor to Give the *Less-Substituted* Fluoride[a]

substrate	*product*	*% yield*	*d.r.*
 *gibberellic acid*	 **18**	86^b	n/a
 *betulin*	 **19**	51^c	6.7 : 1
 *oleanolic acid*	 **20**	79^c	9 : 1

[a] Yields include both diastereomers and were determined by integration of ^{19}F NMR signals relative to an internal standard and confirmed by isolation of products through column chromatography on silica gel. [b] A mixture of Selectfluor and substrate was stirred at r.t. for 12 h. [c] A mixture of Selectfluor and subtrate was heated to 80 °C for 12 h (heat was necessary to dissolve the substrate).

the cyclohexene and lactone rings. Betulin, an abundant triterpene commonly extracted from birch bark,[33] is also known to undergo a Wagner-Meerwein rearrangement in the presence of strong acid[34] to form allobetulin. Upon treating betulin with SF, fluoroallobetulin (compound **19**) was obtained in good yield, possessing a $-CH_2F$ group consistent with SF behaving as a two-electron electrophilic source of fluorine. Because many betulin derivatives are known to be biologically active (for example, possessing anticancer and anti-HIV activity), a fluorinated analogue could be of interest as well.[35] Oleanolic acid, another anticancer terpenoid,[36] provides an additional example of an alkene that reacts with SF to give the less substituted fluoride. This substrate, however, is unique due to the fact that it contains a trisubstituted C═C bond (the previous two examples being 1,1-disubstituted alkenes) that undergoes a lactonization (rather than a Wagner-Meerwein rearrangement) when treated with strong acid.[37] In the presence of Selectfluor, a fluorolactonization occurs in high yield to afford compound **20**. A common trait of these three substrates is that the reactive alkene can be thought of as "activated." Each molecule contains some feature that stabilizes the carbocation resulting after fluorination (e.g., a potential to rearrange, an intramolecular nucleophile, etc.). This seems to be a pivotal factor that determines if Selectfluor by itself will react with an alkene and if it will do so regioselectively. Ultimately, these counterexamples provide evidence that the simple reaction between SF and a C═C bond is limited in scope, and therefore, methods involving fluorofunctionalization of unactivated alkenes are necessary.

2.4. Mechanistic Studies and Considerations.

Although gibberellic acid reacts with Selectfluor in the absence of light or additives, we subjected this substrate to a reaction with SF under the ammoniofluorination conditions ($h\nu$ 300 nm, cyclohexenone, ACN) as a control experiment. To our surprise, the primary fluoride still formed in high yield whereas no ammoniofluoride was observed. We also treated several unactivated alkenes with SF in the dark and observed only trace or no fluorination. The results of these controls are consistent with the notion that the structure of the alkene governs the mechanism by which it reacts with SF, and the reaction conditions are therefore of lesser importance.

We next performed a series of intermolecular competition experiments in which both types of alkenes (i.e., unactivated and activated) were present in the same vial and were subjected to the ammoniofluorination conditions. While the overall selectivity was consistent with our prediction, (the activated alkene fluorinates preferentially), the degree of selectivity was a bit surprising. In an initial reaction containing 1 equiv of gibberellic acid, 1 equiv of allyl benzene, 1 equiv cyclohexenone, and 1.5 equiv of Selectfluor, we observed a 95% yield of the primary fluoride derived from gibberellic acid and an 11% yield of the secondary ammoniofluoride of allyl benzene after 12 h. Peculiarly, the yield for the fluorination of gibberellic acid increased in the presence of light; however, some minor byproducts were observed. By changing the conditions (1.2 equiv of Selectfluor, 9 h) we noted a 75% yield of fluorinated gibberellic acid and only 4% of the allyl benzene fluoroammonium salt. Similarly, we looked at the analogous competition experiment with oleanolic acid and allyl benzene, which gave the fluorolactone of oleanolic acid in 30% yield (due to low solubility in ACN at room temperature) but only trace amounts of the ammoniofluoride of allyl benzene. These results suggest that a putative two-electron reaction of Selectfluor with activated alkenes can be significantly faster than the one-electron reaction of Selectfluor with unactivated olefins, even if the activated substrates are more sterically hindered.

The reaction between SF and monsubstituted alkenes proceeds thermally, although the yields of desired products are often low and other fluorinated byproducts are observed as well. On the other hand, in the presence of cyclohexenone and 300 nm irradiation, the reaction is high yielding and very selective. These are conditions in which the Selectfluor radical dication (SRD) is expected to form. Attack of the SRD at the primary carbon of the alkene produces free radical **21**, which is fluorinated by SF, thus regenerating the SRD to carry forward the chain (Figure 2a). In the case of the more electron rich di- and trisubstituted alkenes, a different scenario pertains. For example, fluorine can transfer to the primary carbon from SF as formal F^+, resulting in a carbocation that rearranges. Alternatively, single electron transfer (SET) from the alkene to SF results in the SRD and the substrate radical cation, which can rearrange through a carbocationic process before reacting with SF at the primary radical position (Figure 2b). As SF so commonly plays through SET chemistry,[38] this alternative must be taken seriously.

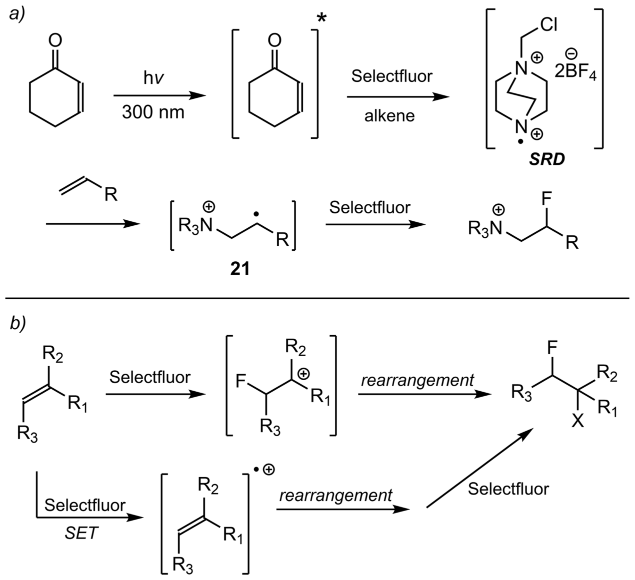


Figure 2. Mechanistic considerations for the reaction of Selectfluor with C=C bonds.

While the Selectfluor radical dication is known as an intermediate which typically reacts with sp^3 bonds,[39] it has been recently reported to engage in charge-transfer with arenes.[26] Even more recently, the SRD has been postulated in a proposed mechanism to undergo an addition to an olefin to give a radical similar to **21**, which could go on to get trapped by a Cu(II)-CN species.[40] These works provide support for our proposed mechanism, but at this time we cannot definitively confirm any details without a more in-depth mechanistic study.

It is currently unclear what the exact role of cyclohexenone is in the ammoniofluorination; however, the enone triplet excited state is potentially involved. Extant photochemistry involving the reaction of cyclic enones with alkenes is centered on the well-studied [2 + 2] photocycloaddition.[41] The original hypothesis for this reaction, which invoked the (n, π^*) enone excited state as well as exciplex formation, is now understood to be inaccurate. Rather, it is the (π, π^*) state of the enone that is involved in the cycloaddition and exciplexes are no longer described in the mechanism, as evidence for their involvement never materialized. Given the fact that this ammoniofluorination is generally high yielding (with respect to the alkene), we were surprised to observe a yield of only 35% recovered cyclohexenone after the reaction. Even less cyclohexenone is recovered (11%) when the enone is treated under the ammoniofluorination conditions without the alkene present. These findings prompted us to examine the byproducts formed during the reaction, and accordingly, we have observed evidence for the formation of [2 + 2] photocycloaddition products. Adducts of cyclohexenone and neohexene were detected in small quantities by ^1H NMR in addition to the photodimer of cyclohexenone, which has been previously reported to form in the presence of UV light.[42] On the other hand, we observed no trapped (fluorinated) 1,4-biradicals, intermediates that are known to be involved in [2 + 2] photocycloadditions. While [2 + 2] cycloadditions represent a minor competing reaction pathway cyclohexenone can participate in, the molecule must be playing a slightly different role in the ammoniofluorination mechanism. For instance, the enone could be acting as a photosensitizer, exciting the alkene which could then be oxidized by SF and ultimately give the SRD after loss of fluoride.[8] Another scenario that we envisioned involves the triplet excited enone directly oxidizing the alkene to form a radical anion/radical cation pair that could react with SF to give the SRD. Calculated energies of the involved species suggest that the sensitization route is considerably more favorable, having a ΔG_{calc} value of −5.5 kcal while the other proposed path is significantly uphill (Figure 3a). Furthermore, the subsequent step to form the SRD from the excited alkene was likewise found to be energetically favorable (Figure 3b), providing a plausible means of initiation. Nevertheless, these energies should be viewed strictly qualitatively given the nature of charged open-shell species. It is of course still possible that cyclohexenone is playing a role other than sensitizer in this reaction, and for that reason we plan to explore this intriguing mechanism in future research efforts.

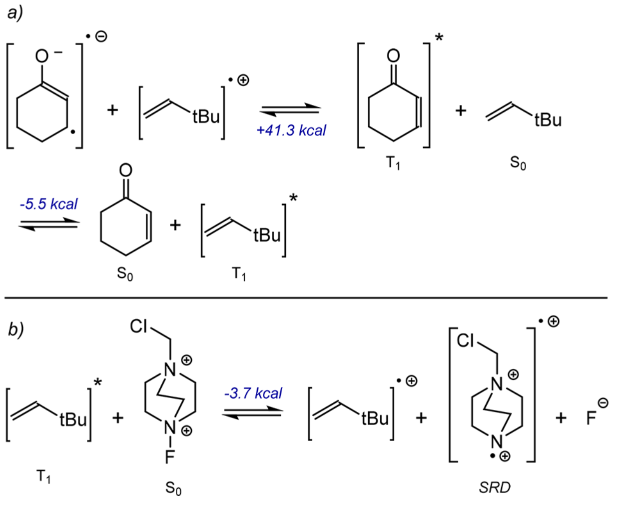


Figure 3. Calculated energies of intermediates at ωB97XD/6-311+G** (MeCN).

3. CONCLUSION

A one-pot method involving a novel photochemical ammoniofluorination furnishes β-fluoropiperazines from monosubstituted alkenes. In addition to being operationally simple and cost-effective, the reaction is highly regioselective for the formation of the *more substituted* (secondary) fluoride. We contrasted this reactivity to several alkene-containing natural products which react with the same fluorinating reagent, Selectfluor, to give the *less substituted* fluoride. Further studies are required to complete our understanding of this reactivity switch, but the structure of the alkene and the overall compound seems to play a paramount role that outweighs the reaction conditions. We anticipate that the ammoniofluorination reaction will be of immediate use in the medicinal chemistry community and aim to further elucidate mechanistic details in future projects.

4. EXPERIMENTAL SECTION

General Methods. Unless otherwise stated, all reactions were carried out under strictly anhydrous conditions and N_2 atmosphere. All solvents were dried and distilled by standard methods. All ^1H spectra were acquired on a 400 MHz NMR spectrometer in CD_3CN or $CDCl_3$, ^{19}F spectra were acquired on a 300 MHz NMR spectrometer in CD_3CN or $CDCl_3$, and ^{13}C NMR spectra were acquired on a 400 MHz NMR spectrometer in CD_3CN or $CDCl_3$. The ^1H, ^{13}C, and ^{19}F NMR chemical shifts are given in parts per million (δ) with respect to an internal tetramethylsilane (TMS, δ = 0.00 ppm) standard and/or 3-chlorobenzotrifluoride (δ = −64.2 ppm relative to $CFCl_3$). ^1H NMR data are reported in the following format: chemical shift (integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz)). Spectral data were processed with Bruker software. Photochemical reactions were run in a Rayonet photochemical reactor with 300 nm bulbs. The Gaussian '09 package was used for all calculations.

General Ammoniofluorination Procedure. Selectfluor (354 mg, 1.0 mmol) was added to an oven-dried microwave vial equipped with a stir bar; the vial was then sealed with a cap with Teflon septum using a crimper and evacuated/refilled with N_2 multiple times. Anhydrous CH_3CN (8 mL) was added, followed by the alkene substrate (0.50 mmol) (if the substrate is a solid, it is added along with Selectfluor before sealing the vial) and then cyclohexenone (0.048 mL, 0.50 mmol). The reaction mixture was irradiated with 300 nm light while stirring. After 12 h, a 0.3 mL aliquot was taken for ^{19}F NMR yield determination. The rest of the reaction mixture was either subjected to the reduction (see below) or triturated with solvent to isolate the ammonium salt product. Note: We found it difficult to separate the Selectfluor-adduct products from the excess Selectfluor and Selectfluor byproducts, which are all cationic species. This is not a significant issue, as the Selectfluor-adducts are more typically reduced to piperazines before isolation, at which point separation from the Selectfluor byproducts is straightforward. However, if there is a desire to isolate the fluorinated Selectfluor-adduct, a typical procedure is as follows: The reaction mixture was diluted with a mixture of 1:1 hexanes/EtOAc (25 mL), causing the product to precipitate out of solution along with the Selectfluor byproducts. The solid precipitate/oil was collected and washed with diethyl ether (25 mL × 3) to remove the nonpolar impurities (cyclohexenone and alkene starting material). The product can then be further purified by recrystallization from EtOH and/or trituration (the adduct is dissolved using a 40:60 mixture of ACN−DCM (25 mL × 2), filtered, and concentrated to dryness. Figure S25 provides a labeled ^1H NMR to point out peaks derived from Selectfluor impurities.

General Procedure for the One-Pot Reduction of Selectfluor-Adducts. The following procedure was adopted from a previously reported method.[26] After the aminofluorination reaction has completed (0.50 mmol scale, see above), a solution of saturated aq $Na_2S_2O_3$ (5.0 mL) was added to the microwave vial, followed by H_2O (5.0 mL) (for larger scale reactions, the reaction mixture was transferred to a pressure tube to accommodate the larger volume). The mixture was stirred in the sealed vial at 100 °C for 12−24 h. Upon cooling to room temperature, the reaction mixture was transferred to a separatory funnel and diluted with DCM (10 mL). Ethylene diamine (0.9 mL) was added, followed by 6 M NaOH (2.9 mL), and the mixture was shaken. The resulting emulsion was treated with brine (50 mL), and after shaking, the organic layer was separated. The aqueous layer was re-extracted with DCM (2 × 10 mL), and then the combined organic layers were extracted with 1 M HCl (2 × 10 mL). Ethylene diamine (2.9 mL) was added to the combined HCl extracts, followed by 6 M NaOH (4.7 mL). The basicified aqueous mixture was then extracted with DCM (3 × 10 mL), and the combined organic layers were dried with $MgSO_4$, filtered, and concentrated. The crude residue was used directly in the next step or purified on basic alumina, eluting with EtOAc/hexanes.

General Procedure for the Acylation of Fluoropiperazines. The piperazine (0.50 mmol) was dissolved in dichloromethane (5.0 mL) in a round-bottom flask equipped with a stir bar under N_2. The reaction mixture was cooled to 0 °C and treated with triethylamine (0.14 mL, 1.0 mmol) followed by benzyl chloroformate (0.108 mL, 0.75 mmol). The reaction was stirred overnight at room temperature under N_2 and then was diluted with DCM (50 mL) and transferred to a separatory funnel. The organic mixture was washed with saturated sodium bicarbonate (25 mL), then brine (25 mL), and then dried with $MgSO_4$ and concentrated. The crude residue was purified via column chromatography on basic alumina with EtOAc/hexanes to provide the Cbz-piperazine.

General Fluorination Procedure for Compounds 18−20. Selectfluor (354 mg, 1.0 mmol) and the alkene substrate (0.50 mmol) were added to an oven-dried microwave vial equipped with a stir bar. The vial was then sealed with a cap with a Teflon septum using a crimper and evacuated/refilled with N_2 multiple times. Anhydrous CH_3CN (8 mL) was added, and the reaction mixture was stirred at either room temperature (compound **18**) or at 80 °C (compounds **19** and **20**). After 12 h, a 0.3 mL aliquot was taken for ^{19}F NMR yield determination. The reaction mixture was transferred to a separatory funnel, diluted with water (50 mL), and extracted with DCM (3 × 25 mL). The combined organic layers were washed with brine, dried with $MgSO_4$, and concentrated. The crude residue was purified via column chromatography on silica gel with EtOAc/hexanes.

Characterization of Fluorinated Compounds. *Benzyl 4-(2-Fluoro-3,3-dimethylbutyl)piperazine-1-carboxylate (**14**).* Fluorination was run according to the general aminofluorination procedure, and the product was isolated via gradient column chromatography on basic alumina gel eluting with 15% EtOAc/hexanes. Yellow oil (85 mg, 53% over 3 steps). ^1H NMR (400 MHz, $CDCl_3$): δ 7.39−7.29 (5H, m), 5.13 (2H, s), 4.37−4.22 (1H, m), 3.55−3.53 (4H, m), 2.63−2.48 (6H, m), 0.94 (9H, d, J = 1.27 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 155.2, 136.7, 128.5, 128.0, 127.9, 98.6 (d, J = 175.81 Hz), 67.1, 58.7 (d, J = 21.75 Hz), 53.3, 43.8−43.6 (m), 34.1 (d, J = 19.53 Hz), 25.3 (d, J = 4.79 Hz); ^{19}F NMR (282 MHz, $CDCl_3$): δ −184.0 to (−184.4) (1F, m); HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ Calcd for $C_{18}H_{28}O_2N_2F^+$323.2134; Found 323.2123.

*Benzyl 4-(2-Fluoro-3-phenylpropyl)piperazine-1-carboxylate (**15**).* Fluorination was run according to the general aminofluorination procedure, and the product was isolated via gradient column chromatography on basic alumina gel eluting with 15% EtOAc/hexanes. Yellow oil (98 mg, 55% over 3 steps). ^1H NMR (400 MHz, $CDCl_3$): δ 7.37−7.29 (8H, m), 7.24−7.21 (2H, m), 5.13 (2H, s), 5.02−4.84 (1H, m), 3.56−3.54 (4H, m), 3.01−2.93 (2H, m), 2.65−2.49 (6H, m); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 155.1, 136.6, 136.6−136.5 (m), 129.3, 128.5, 128.5, 128.0, 127.9, 126.7, 92.4 (d, J = 173.13 Hz), 67.1, 61.1 (d, J = 21.27 Hz), 53.3, 43.6−43.4 (m), 39.6 (d, J = 21.27 Hz); ^{19}F NMR (282 MHz, $CDCl_3$): δ −177.4 to (−177.9) (1F, m); HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ Calcd for $C_{21}H_{26}O_2N_2F^+$ 357.1978; Found 357.1964.

*1-(2-Fluoro-3-phenylpropyl)piperazine (**15b**).* Fluorination was run according to the general aminofluorination procedure, and the product was isolated via gradient column chromatography on basic

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alumina gel eluting with 60% EtOAc/hexanes. Yellow oil (93 mg, 84% over 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32−7.28 (2H, m), 7.25−7.21 (3H, m), 4.97−4.79 (1H, m), 3.00−2.97 (1H, m), 2.95−2.89 (4H, m), 2.64−2.45 (7H, m); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 136.9 (d, J = 4.77 Hz), 129.3, 128.4, 126.5, 92.6 (d, J = 173.13 Hz), 61.9 (d, J = 21.27 Hz), 54.6 (d, J = 1.10 Hz), 45.8, 39.7 (d, J = 21.27 Hz); ^{19}F NMR (282 MHz, $CDCl_3$): δ −177.6 to (−178.1) (1F, m); HRMS (ESI-Orbitrap) *m*/*z*: [M + H]$^+$ Calcd for $C_{13}H_{20}N_2F^+$ 223.1610; Found 223.1595.

*Benzyl 4-(2-Fluoro-5-oxohexyl)piperazine-1-carboxylate (**16**).* Fluorination was run according to the general aminofluorination procedure, and the product was isolated via gradient column chromatography on basic alumina gel eluting with 20% EtOAc/hexanes. Yellow oil (71 mg, 42% over 3 steps). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38−7.30 (5H, m), 5.13 (2H, s), 4.77−4.59 (1H, m), 3.54−3.52 (4H, m), 2.68−2.49 (8H, m), 2.16 (3H, s), 2.01−1.77 (2H, m); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 207.7, 155.2, 136.7, 128.5, 128.0, 127.9, 91.4 (d, J = 169.83 Hz), 67.1, 62.2 (d, J = 21.27 Hz), 53.4, 43.7−43.6 (m), 38.6 (d, J = 3.67 Hz), 30.0, 27.2 (d, J = 20.91 Hz); ^{19}F NMR (282 MHz, $CDCl_3$): δ −182.5 to (−183.1) (1F, m); HRMS (ESI-Orbitrap) *m*/*z*: [M + H]$^+$ Calcd for $C_{18}H_{26}O_3N_2F^+$ 337.1927; Found 337.1914.

*Benzyl 4-(6-(Diethylamino)-2-fluoro-6-oxohexyl)piperazine-1-carboxylate (**17**).* Fluorination was run according to the general aminofluorination procedure, and the product was isolated via gradient column chromatography on basic alumina gel eluting with 30% EtOAc/hexanes. Yellow oil (67 mg, 33% over steps). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36−7.30 (5H, m), 5.12 (2H, s), 4.79−4.61 (1H, m), 3.54−3.51 (4H, m), 3.38−3.26 (4H, m), 2.69−2.45 (6H, m), 2.33 (2H, t, J = 7.04 Hz), 1.82−1.61 (4H, m), 1.18−1.08 (6H, m); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 171.4, 155.1, 136.6, 128.4, 128.0, 127.8, 92.2 (d, J = 169.46 Hz), 67.1, 62.2 (d, J = 20.54 Hz), 53.3, 43.7−43.6 (m), 41.8, 40.1, 33.0 (d, J = 20.91 Hz), 32.4, 20.8 (d, J = 4.77 Hz), 14.3, 13.1; ^{19}F NMR (282 MHz, $CDCl_3$): δ −179.7 to (−180.2) (1F, m); HRMS (ESI-Orbitrap) *m*/*z*: [M + H]$^+$ Calcd for $C_{22}H_{35}O_3N_3F^+$ 408.2662; Found 408.2652.

*Fluoride **18**.* Fluorination was run according to the general fluorination procedure for compounds **18**−**20**, and the product was isolated via gradient column chromatography on silica gel eluting with a 96:2.5:1.5 mixture of DCM−MeOH−AcOH. White solid (157 mg, 86%). Mp = 242−243 °C. ^{1}H NMR (400 MHz, CD_3CN): δ 6.43−6.40 (1H, m), 5.88−5.85 (1H, m), 4.62−4.07 (2H, m), 4.06 (1H, d, J = 3.52 Hz), 3.19 (1H, d, J = 7.24 Hz), 2.79 (1H, d, J = 7.24 Hz), 2.75−2.69 (1H, m), 2.28−2.21 (4H, m), 1.83−1.78 (1H, m), 1.53−1.44 (3H, m), 1.23 (3H, s); ^{13}C{^{1}H} NMR (100 MHz, CD_3CN): δ 215.5 (d, J = 3.32 Hz), 179.6, 174.0, 134.4, 131.4, 90.3, 84.6 (d, J = 167.33 Hz), 71.0, 56.4, 56.1, 53.4, 51.8, 51.1 (d, J = 1.11 Hz), 49.9, 49.7, 42.4 (d, J = 2.95 Hz), 29.8 (d, J = 6.27 Hz), 19.1 (d, J = 1.11 Hz), 14.7; ^{19}F NMR (282 MHz, CD_3CN): δ −229.7 (1F, t, J = 47.61 Hz); HRMS (ESI-Orbitrap) *m*/*z*: [M + H]$^+$ Calcd for $C_{19}H_{22}O_6F$ 365.1400; Found 365.1389.

*Fluoride **19** (Major Diastereomer).* Fluorination was run according to the general fluorination procedure for compounds **18**−**20**, and the product was isolated via gradient column chromatography on silica gel eluting with 10−15% EtOAc/hexanes. White solid (117 mg, 51%). Mp = 257−258 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.45−3.92 (2H, m), 3.84−3.78 (2H, m), 3.43 (1H, d, J = 7.92 Hz), 3.23−3.17 (1H, m), 1.75−1.69 (1H, m), 1.67−1.09 (23H, m), 0.97 (6H, s), 0.92 (6H, s), 0.84 (3H, s), 0.76 (3H, s), 0.72−0.68 (1H, m); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 89.7 (d, J = 171.29 Hz), 82.0 (d, J = 3.67 Hz), 78.9, 71.4, 55.5, 51.1, 46.6, 41.7, 40.7, 40.6, 40.5, 38.9, 38.8, 37.3, 35.8, (d, J = 1.47 Hz), 34.1, 33.9, 28.0, 27.4, 26.5, 26.4, 26.3, 26.2, 20.9, 19.2 (d, J = 4.40 Hz), 18.2, 16.5, 15.7, 15.4, 13.5; ^{19}F NMR (282 MHz, $CDCl_3$): δ −229.6 (1F, t, J = 48.18 Hz); HRMS (ESI-Orbitrap) *m*/*z*: [M + H]$^+$ Calcd for $C_{30}H_{50}O_2F^+$ 461.3794; Found 461.3785.

*Fluoride **20** (Major Diastereomer).* Fluorination was run according to the general fluorination procedure for compounds **18**−**20**, and the product was isolated via gradient column chromatography on silica gel eluting with 10−15% EtOAc/hexanes. White solid (187 mg, 79%). Mp = 215−217 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.63−4.50(1H, m), 3.24−3.20 (1H, m), 2.18−2.06 (2H, m), 2.02−1.80 (4H, m), 1.75−1.53 (10H, m), 1.44−1.19 (10H, m), 1.11 (3H, s), 0.99 (6H, s), 0.90 (3H, s), 0.87 (3H, s), 0.78 (3H, s), 0.75−0.72 (1H, m); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 179.3, 96.7 (d, J = 171.38 Hz), 88.0 (d, J = 25.80 Hz), 78.7, 55.0, 50.9, 44.6, 44.3, 41.9, 41.7, 38.9, 38.5, 36.4, 34.1, 33.5, 33.2, 31.5, 27.9, 27.4 (d, J = 10.32 Hz), 27.1, 25.8, 25.6, 23.7, 21.0, 18.3, 17.9 (d, J = 8.11 Hz), 17.6, 16.0, 15.3; ^{19}F NMR (282 MHz, $CDCl_3$): δ −179.3 to (−179.7) (1F, m); HRMS (ESI-Orbitrap) *m*/*z*: [M + H]$^+$ Calcd for $C_{30}H_{48}O_3F^+$ 475.3587; Found 475.3578.

Characterization of Selectfluor-Adducts. *Fluoride **1**.* Off-white solid (hygroscopic, quickly turning into an oil) (222 mg, 98%). ^{1}H NMR (400 MHz, CD_3CN): δ 5.06−4.83 (3H, m), 3.80−3.67 (14H, m), 1.47−1.34 (2H, m), 1.22−1.05 (3H, m), 0.72−0.67 (6H, m); ^{13}C{^{1}H} NMR (100 MHz, CD_3CN): δ 88.3 (d, J = 171.66 Hz), 69.6, 68.4−68.1 (m), 52.5−52.4 (m), 51.0, 33.4−33.3 (d, J = 4.03 Hz), 30.7−30.5 (m), 28.1, 22.4−22.2 (d, J = 15.41 Hz); ^{19}F NMR (282 MHz, CD_3CN): δ −181.2 to (−181.8) (1F, m); HRMS (ESI-Orbitrap) *m*/*z*: [M − BF_4^-]$^+$ Calcd for $C_{14}H_{28}N_2BClF_5^+$ 365.1954; Found 365.1940.

*Fluoride **2**.* Off-white solid (214 mg, 92%). ^{1}H NMR (400 MHz, CD_3CN): δ 5.29−5.07 (3H, m), 4.06−3.80 (14H, m), 1.80−1.51 (3H, m), 1.43−1.26 (7H, m), 0.91 (3H, t, J = 6.85 Hz); ^{13}C{^{1}H} NMR (100 MHz, CD_3CN): δ 88.2 (d, J = 171.02 Hz), 69.8, 68.5−68.3 (m), 52.7−52.6 (m), 51.1, 32.9−32.6 (m), 32.0, 29.2, 24.6 (d, J = 4.05 Hz), 23.0, 14.1; ^{19}F NMR (282 MHz, CD_3CN): δ −181.3 to (−181.9) (1F, m); HRMS (ESI-Orbitrap) *m*/*z*: [M − BF_4^-]$^+$ Calcd for $C_{15}H_{30}N_2BClF_5^+$ 379.2110; Found 379.2096.

*Fluoride **3**.* Off-white solid (197 mg, 90%). ^{1}H NMR (400 MHz, CD_3CN): δ 5.26 (2H, s), 4.94−4.73 (1 H, m), 4.11−3.90 (14H, m), 0.95 (9H, s); ^{13}C{^{1}H} NMR (100 MHz, CD_3CN): δ 93.5 (d, J = 176.80 Hz), 69.5, 66.4−66.1 (m), 52.3−52.2 (m), 50.9, 35.2−35.0 (m), 24.5 (d, J = 4.77 Hz); ^{19}F NMR (282 MHz, CD_3CN): δ −184.8 to (−185.1) (1F, m); HRMS (ESI-Orbitrap) *m*/*z*: [M − BF_4^-]$^+$ Calcd for $C_{13}H_{26}N_2BClF_5^+$ 351.1797; Found 351.1784.

*Fluoride **4**.* Off-white solid (217 mg, 92%). ^{1}H NMR (400 MHz, CD_3CN): δ 7.40−7.28 (5H, m), 5.49−5.29 (1H, m), 5.24 (2H, s), 4.00−3.88 (14H, m), 3.13−2.93 (2H, m); ^{13}C{^{1}H} NMR (100 MHz, CD_3CN): δ 135.7 (d, J = 2.94 Hz), 130.5, 129.6, 128.2, 88.4 (d, J = 174.23 Hz), 69.9, 68.1−67.9 (m), 52.8−52.7 (m), 51.2, 38.8−38.6 (m); ^{19}F NMR (282 MHz, CD_3CN): δ −180.6 to (−181.1) (1F, m); HRMS (ESI-Orbitrap) *m*/*z*: [M − BF_4^-]$^+$ Calcd for $C_{16}H_{24}N_2BClF_5^+$ 385.1641; Found 385.1625.

*Fluoride **5**.* Off-white solid (238 mg, 98%). ^{1}H NMR (400 MHz, CD_3CN): δ 7.35−7.28 (2H, m), 7.27−7.18 (3H, m), 5.29−5.09 (3H, m), 4.05−3.81 (14H, m), 2.87−2.65 (2H, m), 2.06−1.95 (2H, m); ^{13}C{^{1}H} NMR (100 MHz, CD_3CN): δ 141.4, 129.5, 129.3, 127.2, 87.8 (d, J = 172.49 Hz), 69.9, 68.4−68.2 (m), 52.8−52.7 (m), 51.2, 34.7−34.5 (m), 30.8 (d, J = 4.42 Hz); ^{19}F NMR (282 MHz, CD_3CN): δ −182.1 to (−182.7) (1F, m); HRMS (ESI-Orbitrap) *m*/*z*: [M − BF_4^-]$^+$ Calcd for $C_{17}H_{26}N_2BClF_5^+$ 399.1797; Found 399.1781.

*Fluoride **6**.* Off-white solid (250 mg, 92%). ^{1}H NMR (400 MHz, CD_3CN): δ 8.04−8.01 (2H, m), 7.65−7.60 (1H, m), 7.52−7.47 (2H, m), 5.37−5.16 (3H, m), 4.39−4.26 (2H, m), 4.04−3.80 (14H, m), 1.92−1.73 (4H, m); ^{13}C{^{1}H} NMR (100 MHz, CD_3CN): δ 167.1, 134.0, 131.2, 130.1, 129.5, 88.0 (d, J = 172.40 Hz), 69.9, 68.4−68.2 (m), 64.6, 52.7−52.6 (m), 51.5, 29.6−29.4 (m), 24.3 (d, J = 4.03 Hz); ^{19}F NMR (282 MHz, CD_3CN): δ −182.4 to (−183.0) (1F, m); HRMS (ESI-Orbitrap) *m*/*z*: [M − BF_4^-]$^+$ Calcd for $C_{19}H_{28}O_2N_2BClF_5^+$ 457.1852; Found 457.1839.

*Fluoride **7**.* Off-white solid (203 mg, 90%). ^{1}H NMR (400 MHz, CD_3CN): δ 5.30−5.07 (3H, m), 4.08−3.84 (14H, m), 2.70−2.58 (2H, m), 2.54−2.19 (2H, m), 2.11 (3H, s); ^{13}C{^{1}H} NMR (100 MHz, CD_3CN): δ 207.9, 87.7 (d, J = 171.66 Hz), 69.9, 68.3−68.1 (m), 52.8−52.7 (m), 51.2, 37.9 (d, J = 4.03 Hz), 29.9, 27.0−26.8 (m); ^{19}F NMR (282 MHz, CD_3CN): δ −181.8 to (−182.4) (1F, m); HRMS (ESI-Orbitrap) *m*/*z*: [M − BF_4^-]$^+$ Calcd for $C_{13}H_{24}ON_2BClF_5^+$ 365.1590; Found 365.1579.

*Fluoride **8***. Off-white solid (208 mg, 70%). ^{1}H NMR (400 MHz, CD_3CN): δ 7.78−7.76 (2H, m), 7.45−7.43 (2H, m), 5.30−5.09 (3H, m), 4.07−3.79 (16H, m), 2.43 (3H, s), 1.81−1.62 (4H, m); ^{13}C{^{1}H} NMR (100 MHz, CD_3CN): δ 146.2, 133.3, 130.8, 128.4, 87.6 (d, J = 171.66 Hz), 70.8, 69.6, 68.0−67.8 (m), 52.6−52.5 (m), 51.0, 28.9−28.7 (m), 24.4 (d, J = 4.03 Hz), 21.4; ^{19}F NMR (282 MHz, CD_3CN): δ −182.2 to (−182.7) (1F, m); HRMS (ESI-Orbitrap) m/z: $[M - BF_4^-]^+$ Calcd for $C_{19}H_{30}O_3N_2BClF_5S^+$ 507.1678; Found 507.1663.

*Fluoride **9***. Off-white solid (204 mg, 78%). ^{1}H NMR (400 MHz, CD_3CN): δ 5.31−5.16 (3H, m), 4.05−3.90 (14H, m), 3.34−3.28 (4H, m), 2.39−2.30 (2H, m), 1.78−1.57 (4H, m), 1.15−1.02 (6H, m); ^{13}C{^{1}H} NMR (100 MHz, CD_3CN): δ 172.4, 88.0 (d, J = 170.93 Hz), 69.5, 68.2−68.0 (m), 52.5−52.4 (m), 51.0, 44.8, 32.3, 20.6 (d, J = 4.40 Hz), 14.2, 13.1; ^{19}F NMR (282 MHz, CD_3CN): δ −181.1 to (−181.7) (1F, m); HRMS (ESI-Orbitrap) m/z: $[M - BF_4^-]^+$ Calcd for $C_{17}H_{33}BClF_5N_3O^+$ 436.2325; Found 436.2297.

*Fluoride **10***. Off-white solid (240 mg, 81%). ^{1}H NMR (400 MHz, CD_3CN): δ 7.68−7.66 (2H, m), 7.42−7.40 (2H, m), 5.43−5.21 (3H, m), 4.11−3.71 (16H, m), 3.22−2.96 (2H, m), 2.68 (3H, s), 2.41 (3H, s); ^{13}C{^{1}H} NMR (100 MHz, CD_3CN): δ 144.8, 134.4, 130.6, 128.1, 86.0 (d, J = 172.03 Hz), 69.6, 68.0−67.7 (m), 52.6−52.5 (m), 51.0, 46.1 (d, J = 5.50 Hz), 35.5, 31.0−30.8 (m), 21.2; ^{19}F NMR (282 MHz, CD_3CN): δ −182.4 to (−182.9) (1F, m); HRMS (ESI-Orbitrap) m/z: $[M - BF_4^-]^+$ Calcd for $C_{19}H_{31}O_2N_3BClF_5S^+$ 506.1838; Found 506.1820.

*Fluoride **11***. Off-white solid (255 mg, 92%). ^{1}H NMR (400 MHz, CD_3CN): δ 7.86−7.79 (4H, m), 5.31−5.12 (3H, m), 4.02−3.69 (16H, m), 2.14−1.98 (2H, m); ^{13}C{^{1}H} NMR (100 MHz, CD_3CN): δ 169.2, 135.2, 133.1, 123.8, 86.5 (d, J = 172.03 Hz), 69.9, 68.0−67.8 (m), 52.8−51.2 (m), 45.2−45.1 (m), 33.9−33.8 (d, J = 5.14 Hz), 31.9−31.6 (m); ^{19}F NMR (282 MHz, CD_3CN): δ −183.4 to (−184.0) (1F, m); HRMS (ESI-Orbitrap) m/z: $[M - BF_4^-]^+$ Calcd for $C_{19}H_{25}O_2N_3BClF_5^+$ 468.1648; Found 468.1626.

*Fluoride **12***. Off-white solid (200 mg, 79%). ^{1}H NMR (400 MHz, CD_3CN): δ 5.37−5.31 (0.5H, m), 5.28−5.19 (2.5H, m), 4.33−4.19 (3H, m), 4.15−3.80 (13H), 2.75 (2H, t, J = 6.02 Hz), 2.58−2.42 (4H, m); ^{13}C{^{1}H} NMR (100 MHz, CD_3CN): δ 172.5, 118.9, 87.4 (d, J = 172.39 Hz), 69.9, 68.2−68.0 (m), 60.1, 52.8−52.7 (m), 51.2, 29.2 (d, J = 4.77 Hz), 28.2−28.0 (m), 18.4; ^{19}F NMR (282 MHz, CD_3CN): δ −183.2 to (−183.7) (1F, m); HRMS (ESI-Orbitrap) m/z: $[M - BF_4^-]^+$ Calcd for $C_{15}H_{25}O_2N_3BClF_5^+$ 420.1648; Found 420.1625.

*Fluoride **13** (Mixture of Diastereomers)*. White solid (290 mg, 63%). ^{1}H NMR (400 MHz, CD_3CN): δ 5.51−5.44 (1H, m), 5.32−5.21 (3H, m), 4.48−4.40 (1H, m), 4.11−3.90 (16H, m), 2.76−2.64 (1H, m), 2.49−2.28 (3H, m), 2.11−2.03 (3H, m), 1.98 (3H, s), 1.802−1.53 (9H, m), 1.44−1.35 (7H, m), 1.19−1.07 (12H, m), 0.86 (6H, s), 0.79 (3H, s); ^{13}C{^{1}H} NMR (100 MHz, CD_3CN): δ 201.6, 201.1, 176.9, 176.7, 171.5, 171.2, 128.4, 128.2, 86.7 (d, J = 59.05 Hz), 84.9 (d, J = 58.32 Hz), 80.9, 69.8, 69.7, 69.6, 69.4, 62.1, 62.0, 54.9, 52.8, 52.7, 52.6, 51.6, 51.1, 51.0, 49.6, 49.1, 46.0, 45.9, 44.6, 44.6, 44.5, 44.5, 44.0, 44.0, 43.9, 41.6, 39.1, 39.1, 38.5, 38.3, 38.1, 38.0, 37.6, 37.6, 37.5, 32.9, 32.4, 32.4, 31.2, 28.7, 28.6, 28.2, 28.1, 28.0 ; ^{19}F NMR (282 MHz, CD_3CN): δ −182.9-(−183.5) (1F, m), −186.8 to (−187.4)(1F, m); HRMS (ESI-Orbitrap) m/z: $[M - BF_4^-]^+$ Calcd for $C_{43}H_{68}O_5N_2BClF_5^+$ 833.4830; Found 833.4813.

Syntheses and Characterization of Starting Materials. *Pent-4-en-1-yl Benzoate (Starting Material for Compound **6**).* 4-Penten-1-ol (0.5 mL, 4.85 mmol) was dissolved in dichloromethane (25 mL) in a round-bottom flask equipped with a stir bar under N_2. The reaction mixture was treated with triethylamine (1.4 mL, 9.7 mmol) and DMAP (60 mg, 0.485 mmol), followed by benzoic anhydride (2.19 g, 9.7 mmol). The reaction was stirred overnight at room temperature under N_2 and then was diluted with DCM (50 mL) and transferred to a separatory funnel. The organic mixture was washed with 1 M HCl (25 mL), saturated sodium bicarbonate (50 mL) then brine (50 mL), and then dried with $MgSO_4$ and concentrated. The crude residue was purified via column chromatography on silica gel, eluting with 10% EtOAc/hexanes to provide pent-4-en-1-yl benzoate (0.84 g, 91%). NMR data matches previously reported spectra.[43]

*Pent-4-en-1-yl 4-Methylbenzenesulfonate (Starting Material for Compound **8**).* 4-Penten-1-ol (1.0 mL, 9.68 mmol) and DMAP (0.118 g, 0.968 mmol) were dissolved in dichloromethane (42 mL) in a round-bottom flask equipped with a stir bar under N_2. The reaction mixture was treated with TsCl (2.03 g, 10.6 mmol) and then triethylamine (1.48 mL, 10.6 mmol). The reaction stirred overnight at room temperature under N_2 and then was diluted with DCM (50 mL) and transferred to a separatory funnel. The organic mixture was washed with 1 M HCl (25 mL), saturated sodium bicarbonate (50 mL), then brine (50 mL), and then dried with $MgSO_4$ and concentrated. The crude residue was purified via column chromatography on silica gel, eluting with 10% EtOAc/hexanes to provide pent-4-en-1-yl 4-methylbenzenesulfonate (2.16 g, 93%). NMR data matches previously reported spectra.[44]

*N,N-Diethylpent-4-enamide (Starting Material for Compound **9**).* 4-Pentenoic acid (0.817 g, 7.16 mmol) and diethylamine (1.48 mL, 14.32 mmol) were dissolved in dichloromethane (57 mL) in a round-bottom flask equipped with a stir bar under N_2. EDC-HCl (1.51 g, 7.87 mmol), HOBt (1.21 g, 7.87 mmol), and triethylamine (2.19 mL, 15.74 mmol) were added and the reaction and stirred overnight at room temperature under N_2. The reaction mixture was diluted with DCM (50 mL) and transferred to a separatory funnel. After washing with 1 M HCl (50 mL), saturated sodium bicarbonate (50 mL), and then brine (50 mL), the organic layer was dried with $MgSO_4$ and concentrated. The crude residue was purified via column chromatography on silica gel, eluting with 30% EtOAc/hexanes to provide *N*,*N*-diethylpent-4-enamide (1.07g, 88%). NMR data matches previously reported spectra.[45]

*N-3-butenyl-N-methyl-p-toluenesulfonamide (Starting Material for Compound **10**).* 4-Bromo-1-butene (0.752 mL, 7.41 mmol) and *p*-toluenesulfonamide (2.53 g, 14.82 mmol) were dissolved in dry acetonitrile (22 mL) in a round-bottom flask equipped with a stir bar and a reflux condenser under N_2. The reaction mixture was treated with KI (0.123 g, 0.741 mmol) and K_2CO_3 (2.05 g, 14.82 mmol) and then stirred at reflux under N_2 overnight. The solvent was concentrated to dryness, redissolved in dichloromethane, washed with brine (100 mL), and then dried with $MgSO_4$ and concentrated. The crude material was purified via column chromatography on silica gel with EtOAc/hexanes to provide *N*-(but-3-en-1-yl)-4-methylbenzenesulfonamide (1.05 g, 63%). NaH (0.181 g, 4.52 mmol, 60%) was added to dry DMF (19 mL) in a round-bottom flask equipped with a stir bar under N_2 and the mixture was cooled to 0 °C. *N*-(But-3-en-1-yl)-4-methylbenzenesulfonamide (1.05 g, 4.66 mmol) in DMF (5 mL) was added dropwise at 0 °C and the mixture stirred for 30 min and warmed to room temperature. After cooling back down to 0 °C, MeI (0.352 mL, 5.66 mmol) was added dropwise and then the reaction was stirred overnight at room temperature under N_2. The reaction mixture was transferred to a separatory funnel, diluted with water (200 mL) and extracted with diethyl ether (50 mL × 3). The combined organic layers were washed with brine (100 mL × 3) and then dried with $MgSO_4$ and concentrated. The crude residue was purified via column chromatography on silica gel, eluting with 20% EtOAc/hexanes to provide *N*-3-butenyl-*N*-methyl-*p*-toluenesulfonamide (0.892 g, 80%). NMR data matches previously reported spectra.[46]

*2-(But-3-en-1-yl)isoindoline-1,3-dione (Starting Material for Compound **11**).* Phthalimide potassium salt (1.46 g, 7.88 mmol) was dissolved in acetone (32 mL) in a round-bottom flask equipped with a stir bar and reflux condenser under N_2. 4-Bromo-1-butene (1.0 mL, 9.85 mmol) was added dropwise, and the reaction was stirred overnight at reflux. After cooling to room temperature, the solvent was removed in vacuo. The crude residue was dissolved in EtOAc (100 mL) and washed with water (50 mL), 1 M NaOH (50 mL), and then brine (50 mL). The organic layer was dried with $MgSO_4$ and concentrated, providing 2-(but-3-en-1-yl)isoindoline-1,3-dione, which was used without further purification (1.14 g, 72%). NMR data matches previously reported spectra.[47]

*2-Cyanoethyl Pent-4-enoate (Starting Material for Compound **12**).* 2-Cyanoethanol (0.372 mL, 5.44 mmol) was dissolved in dichloromethane (23 mL) in a round-bottom flask equipped with a stir bar under N_2. The reaction mixture was treated with triethylamine (0.95 mL, 6.80 mmol) and DMAP (55 mg, 0.453 mmol), and then 4-pentenoyl chloride (0.50 mL, 4.53 mmol) was added dropwise. The reaction stirred at room temperature under N_2 for 3 h, at which point the reaction was shown to be complete by TLC. The reaction mixture was diluted with DCM (50 mL) and transferred to a separatory funnel. The solvent was washed with 1 M HCl (25 mL), saturated sodium bicarbonate (50 mL), and then brine (50 mL) and then dried with $MgSO_4$ and concentrated. The crude residue was purified via column chromatography on silica gel using a gradient of 0−40% EtOAc/hexanes to provide 2-cyanoethyl pent-4-enoate (0.583 g, 84%). Colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 5.37−5.73 (1H, m), 5.07−4.97 (2H, m), 4.25 (2H, t, J = 6.26 Hz), 2.67 (2H, t, J = 6.36 Hz), 2.47−2.41 (2H, m), 2.39−2.32 (2H, m); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 172.3, 136.1, 116.7, 115.7, 58.5, 32.3, 28.5, 17.9; HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ Calcd for $C_8H_{12}O_2N^+$ 154.0868; Found 154.0856.

*Starting Material for Enone **13**.* 18β-Glycyrrhetinic acid (0.750 g, 1.59 mmol) was dissolved in pyridine (11 mL) in a round-bottom flask equipped with a stir bar under N_2. The reaction mixture was cooled to 0 °C and treated with acetic anhydride (7.5 mL) dropwise. The reaction stirred overnight at room temperature and then was poured into cold water (200 mL). The solid was washed with water (100 mL), then dissolved in dichloromethane, and dried with $MgSO_4$ and concentrated. Glycyrrhetinyl acetate (0.748 g, 1.46 mmol) was dissolved in dry DMF (15 mL), and then K_2CO_3 (0.243 g, 1.76 mmol) was added. 4-Bromo-1-butene (0.179 mL, 1.76 mmol) was added and the reaction stirred at room temperature for 4.5 h. The reaction mixture was poured into water (200 mL), filtered, and washed with water (100 mL). The solid was dissolved in dichloromethane, dried with $MgSO_4$, and concentrated. The crude residue was purified via column chromatography on silica gel, eluting with 10−15% EtOAc/hexanes to provide the desired product (0.457 g, 56% over two steps). White solid. Mp = 185−186 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 5.80−5.68 (1H, m), 5.60 (1H, s), 5.11−5.02 (2H, m), 4.49−4.44 (1H, m), 4.17−4.05 (2H, m), 2.79−2.71 (1H, m), 2.39−2.29 (3H, m), 2.10−1.78 (8H, m), 1.68−1.51 (5H, m), 1.40−1.21 (8H, m), 1.17−0.90 (13H, m), 0.83 (6H, s), 0.75 (3H, s); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 199.9, 176.2, 170.8, 169.1, 133.9, 128.3, 117.3, 80.4, 63.2, 61.6, 54.9, 48.1, 45.2, 43.9, 43.1, 40.9, 38.6, 37.9, 37.6, 36.8, 33.1, 32.6, 31.7, 30.9, 28.4, 28.3, 27.9, 26.3, 26.3, 23.4, 23.2, 21.2, 18.5, 17.2, 16.6, 16.3; HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ Calcd for $C_{36}H_{55}O_5^+$ 567.4049; Found 567.4016.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

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NMR spectra, HRMS data, and computational information (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Shah, P.; Westwell, A. D. The role of fluorine in medicinal chemistry. *J. Enzyme Inhib. Med. Chem.* **2007**, *22*, 527−540. (b) Hiyama, T.; Yamamoto, H. Biologically Active Organofluorine Compounds. *Organofluorine Compounds* **2000**, *1*, 137−182.

(2) (a) Gloria, C. Organic fluorinated intermediates: Production and Industrial Uses. *J. Fluorine Chem.* **1992**, *58*, 128. (b) Pathak, V. N.; Sareen, V.; Joshi, K. C. Fluorinated 1,3-diketones as reaction intermediates for synthesis of biologically active heterocycles. *J. Fluorine Chem.* **1985**, *29*, 202.

(3) (a) O'Hagan, D. Fluorine in health care: Organofluorine containing blockbuster drugs. *J. Fluorine Chem.* **2010**, *131*, 1071−1081. (b) Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. Fluorine in Pharmaceutical Industry: Fluorine-Containing Drugs Introduced to the Market in the Last Decade (2001−2011). *Chem. Rev.* **2014**, *114*, 2432−2506.

(4) (a) Campbell, M. G.; Ritter, T. Late-Stage Fluorination: From Fundamentals to Application. *Org. Process Res. Dev.* **2014**, *18*, 474−480. (b) Champagne, P. A.; Desroches, J.; Hamel, J.; Vandamme, M.; Paquin, J. Monofluorination of Organic Compounds: 10 Years of Innovation. *Chem. Rev.* **2015**, *115*, 9073−9174. (c) Chatalova-Sazepin, C.; Hemelaere, R.; Paquin, J.; Sammis, G. M. Recent Advances in Radical Fluorination. *Synthesis* **2015**, *47*, 2554−2569.

(5) (a) Zhao, H.; Gabbaï, F. P. Nucleophilic Fluorination Reactions Starting from Aqueous Fluoride Ion Solutions. *Org. Lett.* **2011**, *13*, 1444−1446. (b) Shamma, T.; Buchholz, H.; Prakash, G. K.; Olah, G. A. Electrophilic Fluorination of Aromatics with Selectfluor and Trifluoromethanesulfonic Acid. *Isr. J. Chem.* **1999**, *39*, 207−210.

(6) (a) Abraham, C. J.; Paull, D. H.; Bekele, T.; Scerba, M. T.; Dudding, T.; Lectka, T. A Surprising Mechanistic "Switch" in Lewis Acid Activation: A Bifunctional, Asymmetric Approach to α-Hydroxy Acid Derivatives. *J. Am. Chem. Soc.* **2008**, *130*, 17085−17094. (b) Wack, H.; Drury, W. J.; Taggi, A. E.; Ferraris, D.; Lectka, T. Nucleophilic Metal Complexes as Acylation Catalysts: Solvent-Dependent "Switch" Mechanisms Leading to the First Catalyzed Staudinger Reaction. *Org. Lett.* **1999**, *1*, 1985−1988.

(7) (a) Bume, D. D.; Harry, S. A.; Lectka, T.; Pitts, C. R. Catalyzed and Promoted Aliphatic Fluorination. *J. Org. Chem.* **2018**, *83*, 8803−8814. (b) Bume, D. D.; Pitts, C. R.; Ghorbani, F.; Harry, S. A.; Capilato, J. N.; Siegler, M. A.; Lectka, T. Ketones as directing groups in photocatalytic sp3 C−H fluorination. *Chem. Sci.* **2017**, *8*, 6918−6923. (c) Bloom, S.; Pitts, C. R.; Miller, D. C.; Haselton, N.; Holl, M. G.; Urheim, E.; Lectka, T. A Polycomponent Metal-Catalyzed Aliphatic, Allylic, and Benzylic Fluorination. *Angew. Chem., Int. Ed.* **2012**, *51*, 10580−10583.

(8) Pitts, C. R.; Ling, B.; Snyder, J. A.; Bragg, A. E.; Lectka, T. Aminofluorination of Cyclopropanes: A Multifold Approach through a Common, Catalytically Generated Intermediate. *J. Am. Chem. Soc.* **2016**, *138*, 6598−6609.

(9) Lal, G. S. Site-Selective Fluorination of Organic Compounds Using l-Alkyl-4-fluoro-l,4-diazabicyclo[2.2.2]octane Salts (Selectfluor Reagents). *J. Org. Chem.* **1993**, *58*, 2791−2796.

(10) (a) Luo, H.; Loh, T. Synthesis of aryl allylic fluorides by direct electrophilic fluorination of alkenes. *Tetrahedron Lett.* **2009**, *50*, 1554−1556. (b) Kumar, A.; Singh, T. V.; Venugopalan, P. Microwave assisted fluorofunctionalization of phenyl substituted alkenes using selectfluor. *J. Fluorine Chem.* **2013**, *150*, 72−77. (c) Yang, Q.; Mao, L.; Yang, B.; Yang, S. Metal-Free, Efficient Oxyfluorination of Olefins for the Synthesis of α-Fluoroketones. *Org. Lett.* **2014**, *16*, 3460−3463.

(11) Albert, M.; Dax, K.; Ortner, J. A novel direct route to 2-deoxy-2-fluoro-aldoses and their corresponding derivatives. *Tetrahedron* **1998**, *54*, 4839−4848.

(12) Barker, T. J.; Boger, D. L. Fe(III)/$NaBH_4$-Mediated Free Radical Hydrofluorination of Unactivated Alkenes. *J. Am. Chem. Soc.* **2012**, *134*, 13588−13591.

(13) Zhang, C.; Li, Z.; Zhu, L.; Yu, L.; Wang, Z.; Li, C. Silver-Catalyzed Radical Phosphonofluorination of Unactivated Alkenes. *J. Am. Chem. Soc.* **2013**, *135*, 14082−14085.

(14) Li, Z.; Zhang, C.; Zhu, L.; Liu, C.; Li, C. Transition-metal-free, room-temperature radical azidofluorination of unactivated alkenes in aqueous solution. *Org. Chem. Front.* **2014**, *1*, 100−104.

(15) Kong, W.; Merino, E.; Nevado, C. Divergent Reaction Mechanisms in the Aminofluorination of Alkenes. *Chimia* **2014**, *68*, 430−435.

(16) (a) Wang, Q.; Zhong, W.; Wei, X.; Ning, M.; Meng, X.; Li, Z. Metal-free intramolecular aminofluorination of alkenes mediated by PhI(OPiv)$_2$/hydrogen fluoride−pyridine system. *Org. Biomol. Chem.* **2012**, *10*, 8566−8569. (b) Wu, T.; Yin, G.; Liu, G. Palladium-Catalyzed Intramolecular Aminofluorination of Unactivated Alkenes. *J. Am. Chem. Soc.* **2009**, *131*, 16354−16355.

(17) Li, Z.; Song, L.; Li, C. Silver-Catalyzed Radical Aminofluorination of Unactivated Alkenes in Aqueous Media. *J. Am. Chem. Soc.* **2013**, *135*, 4640−4643.

(18) Qiu, S.; Xu, T.; Zhou, J.; Guo, Y.; Liu, G. Palladium-Catalyzed Intermolecular Aminofluorination of Styrenes. *J. Am. Chem. Soc.* **2010**, *132*, 2856−2857.

(19) Saavedra-Olavarria, J.; Arteaga, G. C.; Lopez, J. J.; Perez, E. G. Copper-catalyzed intermolecular and regioselective aminofluorination of styrenes: facile access to *β*-fluoro-N-protected phenethylamines. *Chem. Commun.* **2015**, *51*, 3379−3382.

(20) Zhang, Q.; Zheng, G.; Zhang, Q.; Li, Y.; Zhang, Q. Metal-Free Three-Component Regioselective Aminofluorination of Styrene Derivatives. *J. Org. Chem.* **2017**, *82*, 8258−8266.

(21) Lu, D.; Zhu, C.; Sears, J.; Xu, H. Iron(II)-Catalyzed Intermolecular Aminofluorination of Unfunctionalized Olefins Using Fluoride Ion. *J. Am. Chem. Soc.* **2016**, *138*, 11360−11367.

(22) (a) Bloom, S.; McCann, M.; Lectka, T. Photocatalyzed Benzylic Fluorination: Shedding "Light" on the Involvement of Electron Transfer. *Org. Lett.* **2014**, *16*, 6338−6341. (b) Pitts, C. R.; Bloom, M. S.; Bume, D. D.; Zhang, Q. A.; Lectka, T. Unstrained C−C bond activation and directed fluorination through photocatalytically-generated radical cations. *Chem. Sci.* **2015**, *6*, 5225−5229.

(23) Pitts, C. R.; Ling, B.; Woltornist, R.; Liu, R.; Lectka, T. Triethylborane-Initiated Radical Chain Fluorination: A Synthetic Method Derived from Mechanistic Insight. *J. Org. Chem.* **2014**, *79*, 8895−8899.

(24) We found that styrene did not fluorinate regioselectively under the ammoniofluorination conditions, likely because it contains an activated olefin (a benzylic carbocation results after Selectfluor reacts with the alkene at the primary position.

(25) Badam, L.; Amagaya, S.; Pollard, B. In vitro antiviral activity of indigenous glycyrrhizin, licorice and glycyrrhizic acid (Sigma) on Japanese encephalitis virus. *J. Community Dis.* **1997**, *29*, 91−99.

(26) Guo, N.; Takechi, M.; Uno, C. Protective effect of glycyrrhizine in mice with systemic Candida albicans infection and its mechanism. *J. Pharm. Pharmacol.* **1991**, *13*, 380−383.

(27) (a) Fuji, H. Y.; Tian, J.; Luka, C. Effect of glycyrrhetinic acid on influenza virus and pathogenic bacteria. *Bull. Chin. Mater. Med.* **1986**, *11*, 238−241. (b) Salari, M. H.; Sohrabi, N.; Kadkhoda, Z.; Khalili, M. Antibacterial effects of enoxolone on periodontopathogenic and capnophilic bacteria isolated from specimens of periodontitis patients. *Iran. Biomed. J.* **2003**, *7*, 39−42.

(28) (a) Pitts, C. R.; Bume, D. D.; Harry, S. A.; Siegler, M. A.; Lectka, T. Multiple enone-directed reactivity modes lead to the selective photochemical fluorination of polycyclic terpenoid derivatives. *J. Am. Chem. Soc.* **2017**, *139*, 2208−2211. (b) Bume, D. D.; Harry, S. A.; Pitts, C. R.; Lectka, T. Sensitized Aliphatic Fluorination Directed by Terpenoidal Enones: A "Visible Light" Approach. *J. Org. Chem.* **2018**, *83*, 1565−1575.

(29) Boursalian, G. B.; Ham, W. S.; Mazzotti, A. R.; Ritter, T. Charge-transfer-directed radical substitution enables para-selective C−H functionalization. *Nat. Chem.* **2016**, *8*, 810−815.

(30) (a) Edgar, S. A.; Davis, D. C.; Frazier, J. A. The efficacy of some piperazine compounds in the elimination of helminths from experimentally-and naturally-infected poultry. *Poult. Sci.* **1957**, *36*, 495−510. (b) Ban, T. A.; Fujimori, M.; Petrie, W. M.; Ragheb, M.; Wilson, W. Systematic studies with amoxapine, a new antidepressant. *Int. Pharmacopsychiatry* **2017**, *17*, 18−27. (c) Nicholson, A. N.; Stone, B. M.; Turner, C.; Mills, S. L. Central effects of cinnarizine: restricted use in aircrew. *Aviat. Space Environ. Med.* **2002**, *73*, 570−574. (d) Boolell, M.; Allen, M. J.; Ballard, S. A.; Gepi-Attee, S.; Muirhead, G. J.; Naylor, A. M.; Osterloh, I. H.; Gingell, C. Sildenafil: an orally active type 5 cyclic GMP-specific phosphodiesterase inhibitor for the treatment of penile erectile dysfunction. *Int. J. Impot. Res.* **1996**, *8*, 47−52.

(31) (a) Pharis, R. P.; King, R. W. Gibberellins and reproductive development in seed plants. *Annu. Rev. Plant Physiol.* **1985**, *36*, 517−568. (b) Brian, P. W.; Elson, G. W.; Hemming, H. G.; Radley, M. J. The plant growth promoting properties of gibberellic acid, a metabolic product of the fungus Gibberella fugikuroi. *J. Sci. Food Agric.* **1954**, *5*, 602−612.

(32) (a) Huigens, R. W., III; Morrison, K. C.; Hicklin, R. W.; Flood, T. A.; Richter, M. F.; Hergenrother, P. J. A ring-distortion strategy to construct stereochemically complex and structurally diverse compounds from natural products. *Nat. Chem.* **2013**, *5*, 195−202. (b) Cross, B. E. Gibberellic Acid. Part I. *J. Chem. Soc.* **1954**, *0*, 4670−4676.

(33) Hayek, E. W. H.; Jordis, U.; Moche, W.; Sauter, F. A Bicentennial of Betulin. *Phytochemistry* **1989**, *28*, 2229−2242.

(34) Li, T.; Wang, J.; Zheng, X. Simple synthesis of allobetulin, 28-oxyallobetulin and related biomarkers from betulin and betulinic acid catalysed by solid acids. *J. Chem. Soc., Perkin Trans. 1* **1998**, *0*, 3957−3966.

(35) (a) Jonnalagadda, S. C.; Suman, P.; Morgan, D. C.; Seay, J. N. Recent Developments on the Synthesis and Applications of Betulin and Betulinic Acid Derivatives as Therapeutic Agents. *Stud. Nat. Prod. Chem.* **2017**, *53*, 45−84. (b) Dehelean, C. A.; Soica, C.; Ledeti, I.; Aluas, M.; Zupko, I.; Galuscan, A.; Cinta-Pinzaru, S.; Munteanu, M. Study of the betulin enriched birch bark extracts effects on human carcinoma cells and ear inflammation. *Chem. Cent. J.* **2012**, *6*, 137.

(36) Ziberna, L.; Samec, D.; Mocan, A.; Nabavi, S. F.; Bishayee, A.; Farooqi, A. A.; Sureda, A.; Nabavi, S. M. Oleanolic Acid Alters Multiple Cell Signaling Pathways: Implication in Cancer Prevention and Therapy. *Int. J. Mol. Sci.* **2017**, *18*, 643−659.

(37) Pattnaik, B.; Lakshma Nayak, V.; Ramakrishna, S.; Venkata Mallavadhani, U. Synthesis of ring-C modified oleanolic acid derivatives and their cytotoxic evaluation. *Bioorg. Chem.* **2016**, *68*, 152−158.

(38) Nyffeler, P. T.; Duron, S. G.; Burkart, M. D.; Vincent, S. P.; Wong, C. Selectfluor: Mechanistic Insight and Applications. *Angew. Chem., Int. Ed.* **2005**, *44*, 192−212.

(39) (a) Kee, C. W.; Chin, K. F.; Wong, M. W.; Tan, C. Selective fluorination of alkyl C−H bonds via photocatalysis. *Chem. Commun.* **2014**, *50*, 8211−8214. (b) Michaudel, Q.; Thevenet, D.; Baran, P. S. Intermolecular Ritter-Type C−H Amination of Unactivated sp3 Carbons. *J. Am. Chem. Soc.* **2012**, *134*, 2547−2550.

(40) Gao, D.; Vinogradova, E. V.; Nimmagadda, S. K.; Medina, J. M.; Xiao, Y.; Suciu, R. M.; Cravatt, B. F.; Engle, K. M. Direct Access to Versatile Electrophiles via Catalytic Oxidative Cyanation of Alkenes. *J. Am. Chem. Soc.* **2018**, *140*, 8069−8073.

(41) (a) Schuster, D. I.; Lem, G.; Kaprinidis, N. A. New insights into an old mechanism:[2+ 2] photocycloaddition of enones to alkenes. *Chem. Rev.* **1993**, *93*, 3−22. (b) Maradyn, D. J.; Weedon, A. C. The photochemical cycloaddition reaction of 2-cyclohexenone with alkenes: trapping of triplet 1, 4-biradical intermediates with hydrogen selenide. *Tetrahedron Lett.* **1994**, *35*, 8107−8110.

(42) (a) Yang, J.; Dewal, M. B.; Shimizu, L. S. Self-assembling bisurea macrocycles used as an organic zeolite for a highly stereoselective photodimerization of 2-cyclohexenone. *J. Am. Chem. Soc.* **2006**, *128*, 8122−8123. (b) Cecil, J. C.; Dyer, C. W.; Fleming, S. A.; Jessop, T. C. Structural elucidation of a photocycloaddition dimer of cyclohexenone. *Anal. Sci.* **1999**, *15*, 895−897.

(43) Ginotra, S. K.; Friest, J. A.; Berkowitz, D. B. Halocarbocyclization entry into the oxabicyclo [4.3. 1] decyl exomethylene-*δ*-lactone cores of linearifolin and zaluzanin A: exploiting combinatorial catalysis. *Org. Lett.* **2012**, *14*, 968−971.

(44) Stokes, B. J.; Opra, S. M.; Sigman, M. S. Palladium-catalyzed allylic cross-coupling reactions of primary and secondary homoallylic electrophiles. *J. Am. Chem. Soc.* **2012**, *134*, 11408.

(45) Fukuyama, T.; Nishitani, S.; Inouye, T.; Morimoto, K.; Ryu, I. Effective Acceleration of Atom Transfer Carbonylation of Alkyl Iodides by Metal Complexes. Application to the Synthesis of the Hinokinin Precursor and Dihydrocapsaicin. *Org. Lett.* **2006**, *8*, 1383−1386.

(46) Lu, Z.; Zeng, X.; Hammond, G. B.; Xu, B. Widely Applicable Hydrofluorination of Alkenes via Bifunctional Activation of Hydrogen Fluoride. *J. Am. Chem. Soc.* **2017**, *139*, 18202−18205.

(47) Alamillo-Ferrer, C.; Curle, J. M.; Davidson, S. C.; Lucas, S. C. C.; Atkinson, S. J.; Campbell, M.; Kennedy, A. R.; Tomkinson, N. C. O. Alkene Oxyamination Using Malonoyl Peroxides: Preparation of Pyrrolidines and Isoxazolidines. *J. Org. Chem.* **2018**, *83*, 6728−6740.

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