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Protodefluorinated Selectfluor® heteroaggregate photoinduces direct C(sp³)−H fluorinations without photocatalyst†

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Herein, we uncover a hitherto hidden role of **H-TEDA(BF₄)₂** – a cheap, stable, recoverable by-product of radical C(sp³)−H fluorinations using Selectfluor®. This forms a photoactive, mixed heteroaggregate with Selectfluor® which underlies the reactivity of visible light photochemical fluorination reactions of unactivated C(sp³)−H bonds. Where previous reports claim to be 'photocatalytic', reactions work without photocatalyst when **H-TEDA(BF₄)₂** is dosed in at the start. Our results demonstrate that 'photocatalysts' are only necessary to generate a sufficient amount of nascent **H-TEDA(BF₄)₂**, whose heteroaggregate with Selectfluor® takes over as the main photoactive species. Mechanistic studies suggest the formation of a heteroaggregate between **H-TEDA(BF₄)₂** and Selectfluor® under photoirradiation, which generates **TEDA•²⁺**. A salient feature of our **H-TEDA(BF₄)₂**-promoted method is its flexibility to use the C(sp³)−H precursor substrate as the limiting reactant, simplifying product isolations.

Introduction

Considering the ubiquity of C–H bonds in molecules and the attractive properties that derive from a C–H to C–F replacement, methods for direct fluorinations of unactivated C(sp³)–H bonds are undoubtedly powerful additions to a synthetic chemist's arsenal.[1] Of these, remote photochemical C(sp³)–H fluorinations using Selectfluor® (**SF**) are particularly attractive for their mild reaction conditions. A whole host of reports emerged since 2014, employing various photosensitizers (typically, aryl ketones such as acetophenone, anthraquinone, benzil, *etc.*; but also, tetracyanobenzene and methyl 4-fluorobenzoate)[2] in catalytic loadings and **SF** typically as the limiting reactant, to fluorinate C(sp³)–H containing substrates under photoirradiation conditions. In recent years, cleavable photosensitizing auxiliaries (benzoyl, phthalimido)[2h,3] covalently tethered to the C(sp³)–H containing substrate have been successfully used to enhance efficiency and overcome shortcomings in the generality of prior methods. When 'photocatalysis' was invoked, proposed mechanisms varied from excited triplet

states participating directly in hydrogen atom transfer (HAT) with the target C(sp³)–H bond, to energy transfer (EnT) to **SF** to generate the **TEDA•²⁺** as the HAT agent. In any case, ultimately **SF** is the fluorine source and protodefluorinated **SF** (**H-TEDA(BF₄)₂**) is the endogenous byproduct of all such fluorination reactions (Scheme 1A). Recently, we reported that
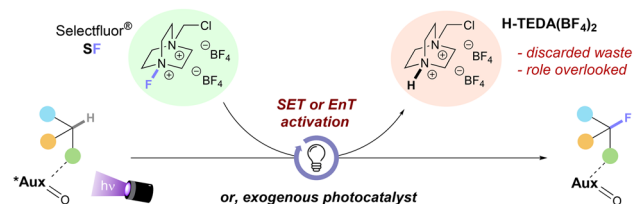
Scheme 1 (A) **H-TEDA(BF₄)₂** generated after photochemical (radical) C(sp³)−H fluorination reactions. (B) This work: **SF/H-TEDA(BF₄)₂** hetero-aggregate as an active species in fluorination reactions.
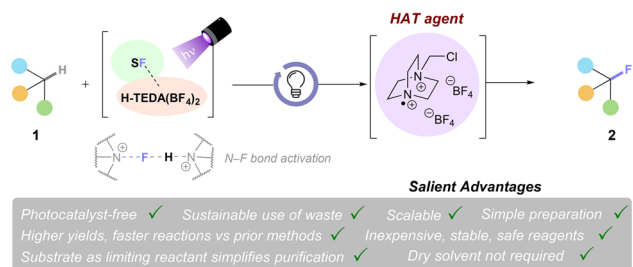
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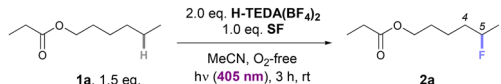*E-mail: Joshua-Philip.Barham@chemie.uni-regensburg.de*
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3156 | *Org. Chem. Front.*, 2025, **12**, 3156–3162

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adding exogenous **H-TEDA(BF₄)₂** deaggregates **SF**, forming a reactive heteroaggregate **H-TEDA(BF₄)₂···SF** (hereafter termed '**HA**') that promotes remote C(sp³)–H fluorinations to higher yields in shorter times.[4] However, it was yet unclear how **HA** enhances the reaction rate. In the case of photochemical/ photocatalytic methods, we observed an induction period that was dramatically shortened upon addition of exogenous H-TEDA(BF₄)₂. Thus, we postulated that (i) it is **HA** that is the actual major photoactive species, (ii) the 'photocatalyst' present in prior reports is merely an initiator, generating a small amount of **H-TEDA(BF₄)₂** in order for **HA** to carry the reaction forward, (iii) the 'photocatalyst' after its necessary role in generating **H-TEDA(BF₄)₂** then plays a disruptive role, screening light from **HA**. Were (i), (ii) and (iii) to be the case, one could add promotor **H-TEDA(BF₄)₂** at the start of the reaction without any 'photocatalyst', achieving comparable or higher efficiencies than prior 'photocatalyst'-present radical C(sp³)–H fluorinations. Herein, we disclose the photoactivity of HA and leverage it for a variety of C(sp³)–H fluorinations (Scheme 1B). Moreover, we show how other H-bond donating/ ion-pairing additives play similar roles, although **H-TEDA (BF₄)₂** is the most general promotor. We hypothesize that H-bond donating/ion-pairing additives: (1) activate the N⁺–F bond of **SF**, promoting (ii) fluorine atom transfer (FAT) to the incipient substrate-derived C-centered radical; (2) lead to a photoactive **HA** involving **SF**, that upon excitation forms an exciplex with **SF**. Where previous reports generally employ the C(sp³)–H substrate in excess (e.g. 1.5 equiv.), a salient feature of our discovery is its flexibility to use the C(sp³)–H substrate as the limiting reactant, which is particularly effective in cases involving few/a single inherent fluorination site/s (especially for complex molecule remote fluorinations). This increases utility, ease of work-up and product separation from unreacted precursor (otherwise needed in excess and left over).

Results and discussion

To test our hypothesis, we initially examined hexyl propionate (**1a**) as a benchmark substrate. This does not contain any aryl-carbonyl group (eliminating the possibility of background self-fluorination[2c]). In the presence of 2.0 eq. of **H-TEDA(BF₄)₂** and 1.0 eq. of **SF**, under 405 nm LED light, the reaction of **1a** (1.5 eq.) proceeded successfully and provided an excellent yield of fluorinated product **2a** (91%) in only 3 h (Table 1, entry 1). This is higher than in the presence of 'photocatalyst' methyl 4-fluorobenzoate and absence of added **H-TEDA(BF₄)₂** (0% yield after 3 h) – which required 24 h to afford 73% yield (entry 2) – reflecting a dramatic rate enhancement effect resulting from the **HA**. We determined that inert atmosphere, light, and **H-TEDA(BF₄)₂** were all crucial for this 'photocatalyst'-free reaction to proceed successfully (see ESI† for full optimization details). By structural derivatization we found certain features of **H-TEDA(BF₄)₂** – such as its free N⁺–H, the BF₄ counterion and the Cl atom on the methylene substituent – were essential for reactivity (see ESI†). To investigate if the promotive effect of

Table 1 Fluorination of **1a** with different additives

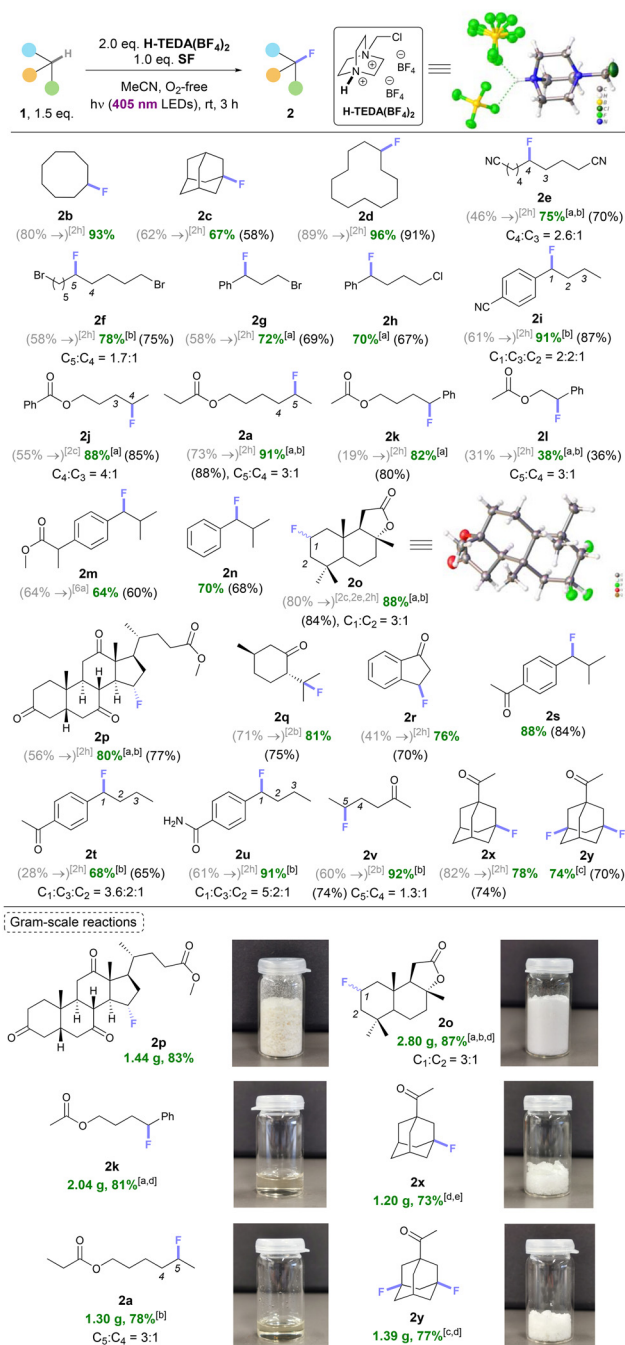| Entry	Deviation from **H-TEDA(BF₄)₂**/pK_aH[5]	Yield[a] (%)
1	None/2.3 [4]	91
2	No **H-TEDA(BF₄)₂**/with **MFB** (1 mol%)	0/73[b]
2	Py-H·BF₄/3.4 [4]	70
3	Boc-Val-OH/4.01 (predicted) [5a,b]	70
4	Imid-H·BF₄/6.4 [4]	62
5	TFA/3.4 [4]	63
6	Tartaric acid/2.98 [5c]	92

[a] Yield was determined by ¹⁹F NMR and pentafluorobenzene was used as an internal standard. **MFB**: methyl 4-fluorobenzoate. [b] Result from ref. 2h, after 24 h.

H-TEDA(BF₄)₂ was simply due to its Brønsted acidity, we examined whether other acids could serve as promoters and whether any trend existed with their pK_a(H) values (see ESI† for full details).[5] Pyridinium tetrafluoroborate (Py-H·BF₄) and Boc-Val-OH provided similar yields to each other (70%, Table 1, entries 3 and 4). Imidazolium tetrafluoroborate (Imid-H·BF₄) and TFA provided 62% and 63% yields, respectively (entries 5 and 6). Tartaric acid provided a comparable yield (92%) to **H-TEDA(BF₄)₂** (entry 7), however, its promotive effect was not general across different case studies unlike **H-TEDA (BF₄)₂** (see ESI†). In summary, no relation was found between the extent of promotion and Brønsted acidity.

Having demonstrated the effectiveness of the direct C(sp³)–H fluorination of **1a** using our **H-TEDA(BF₄)₂** system, we further explored the scope of this method by fluorinating numerous organic molecules with one or multiple unactivated C(sp³)–H bonds in their structures (Scheme 2). This method allowed us to fluorinate a variety of substrates with different functional groups, achieving higher yields than previously reported in 'photo-catalytic' reactions. Secondary and tertiary positions in alkanes were fluorinated, affording **2b**, **2c** and **2d** in good to excellent (67–96%) yields. Terminal halogens were well tolerated, affording **2f**, **2g** and **2h**, in yields of 78%, 72%, and 70%, respectively. Previously reported yields for 'photocatalytic' fluorinations of **2f** and **2g** were only 58%.[2h] Substrates **2g**, **2h**, **2k**, **2l**, **2m**, **2n**, **2r** and **2s** underwent only C(sp³)–H benzylic fluorination, while substrates **2i**, **2t** and **2u** provided several fluorinated isomers - those with benzylic fluorinated positions being the major products - in good to excellent yields (68–91%). To push the limits of utility of the 'photocatalyst'-free fluorination method, we applied it to the late-stage fluorination of complex molecules such as Sclareolide and a dehydrocholic acid derivative, achieving **2o** and **2p** in yields of 88% and 80%, respectively; higher than previously reported yields under 'photocatalyst'-present conditions (80% and 56%, respectively).[2c,h] Additionally, hexane-2-one was fluorinated to give **2v** in 92% yield, a marked improvement on the previously reported 60% under 'photocatalyst'-present conditions.[2b]

In previous 'photocatalytic' reports,[2] as well as our previous photosensitization auxiliary method,[2h] **SF** was consistently used
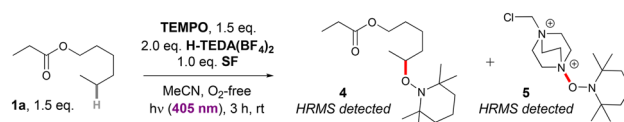
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Org. Chem. Front., 2025, **12**, 3156–3162 | **3157**

Scheme 2 Scope of H-TEDA(BF$_4$)$_2$–promoted photochemical C(sp^3)–H fluorination. NMR yields were determined by ^{19}F NMR with pentafluorobenzene as an internal standard (IS). Isolated yields are in parenthesis. Yields in grey: previously reported 'photocatalytic' methods. [a]1.0 eq. substrate and 2.0 eq. **SF**. [b]The major isomer is depicted, and the yield corresponds to the mixture of regioisomers. [c]1.0 eq. substrate and 3.0 eq. **SF**. [d]No purification was required. [e]1.0 eq. substrate and 1.2 eq. **SF**.

as the limiting reagent (1.0 eq. **SF** and 1.5 eq. C(sp^3)–H substrate), with reactions typically taking 24 h. In most previous reports, when deploying equimolar amounts of **SF** : C(sp^3)–H substrate or an excess of **SF**, reactions either proceeded in very low yields or not at all. A key advantage of the 'photocatalyst'-

free method is it can achieve high-yielding reactions with the C(sp^3)–H substrate as the limiting reagent. This increases utility of the reaction, especially for complex C(sp^3)–H precursors and increases isolated yields by simplifying purification (eliminating the need to separate the product from the remaining excess of starting material, which is often challenging for fluorinated products). For example, using **SF** as the limiting reactant and 1.5 eq. of **1p** gave product **2p** in a 63% yield. When **1p** was used as the limiting reactant (1.0 eq. substrate, 2.0 eq. **SF**), the yield increased to 80%. The same trend was observed in the formation of products **2e**, **2g**, **2h**, **2j**, **2a**, **2k**, **2l**, and **2o**, when using their C(sp^3)–H precursors as limiting reactants. However, for substrates with multiple potential fluorination sites, employing the substrate as the limiting reactant while using **SF** in excess often results in the formation of mixture of regioisomeric byproducts. Therefore, stoichiometric adjustments were made in such cases, with **SF** as the limiting reagent, to ensure selective product formation and ease of isolation.

Among the various radical fluorination strategies reported,[6] several involve catalytic or metal-assisted approaches that typically require prolonged reaction times or high-energy irradiation. Although product **2m** (an ibuprofen derivative) was achieved in the same yield as a previous 'photocatalyst'-present report (64%),[6a] the previous conditions were more forcing (302 nm UV light for 24 h) than the milder conditions herein (405 nm, 3 h). Product **2x** was afforded in a slightly lower yield (78%) than our previous report (82%);[2h] however, by using substrate **1x** as the limiting reactant, we were able to obtain difluorinated product **2y** from substrate **1x** in a good yield (74%). Overall, Scheme 2's results demonstrate that conditions where **HA** is the only photoactive species facilitate reactions with moderate to good yield improvements and in shorter reaction times. Given the overall higher efficiency of the 'photocatalyst'-free C(sp^3)–H fluorination conditions, we wondered how amenable they were to scale-up. Pleasingly, gram-scale reactions of 6 substrates performed over 24 h achieved comparable (**2k**, **2a**, **2o**, **2x**) or even higher yields (**2p**, **2y**) than those obtained in small-scale (<0.5 mmol) reactions (Scheme 2). In every case, **H-TEDA(BF$_4$)$_2$** was recovered quantitatively and reused without any loss in reaction efficiency.

Consistent with previous 'photocatalyst'-present reports, the reaction of **1a** performed in the presence of 1.5 eq. TEMPO failed to afford any fluorinated product (**2a**). LC-MS analysis detected masses corresponding to TEMPO-trapped **1a** (= **4**) and **TEDA$^{•2+}$** (= **5**) (Scheme 3). This suggests that **TEDA$^{•2+}$** and the C(sp^3)–H derived radical from **1a** are competent intermediates. By extension, the initial mechanistic step involving the C(sp^3)–H activation of the substrate could be in common with

Scheme 3 Radical trapping reaction of **1a** with TEMPO.

3158 | *Org. Chem. Front.*, 2025, **12**, 3156–3162

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previous reports and not be altered by the presence of 2.0 eq. **H-TEDA(BF₄)₂**. Our focus turned to discerning the nature of the photoactive species and the fluorinating agent. The existence of **HA** was confirmed in our previous report,[4] but its photophysical properties and photochemical reactivity were not examined. If irradiation of **HA** gave rise to N⁺–F bond homolysis (of **SF** within **HA**, or by EnT to 'free' **SF**), then irradiating a mixture of **SF** and **H-TEDA(BF₄)₂** in absence of a C(sp³)–H substrate should afford **TEDA•²⁺** (**6**, Scheme 4A). Indeed, LC-MS of such a reaction in the presence of TEMPO (2.0 eq.) detected compound **5** (Scheme 4B). Moreover, in the presence of an established H-atom donor THF (10.0 eq.), full conversion of **SF** to **H-TEDA(BF₄)₂** occurred (2.0 eq. to 3.0 eq.).

UV-vis spectroscopy of the reaction mixture was performed using TFA as an active additive (Fig. 1) due to the limited solubility of **H-TEDA(BF₄)₂** in MeCN (see ESI for details†). The results revealed growth of a new absorption (λ_{max} = 358 nm) tailing into 400 nm, notably higher than any individual reaction component and which maximized at 2.0–5.0 eq. of TFA. This was attributed to **HA**. Luminescence spectroscopy was conducted on **SF** and **H-TEDA(BF₄)₂** separately, as well as on their mixtures in various ratios. Both **SF** and **H-TEDA(BF₄)₂** underwent marginal slow photodecomposition over successive excitations for 5–20 min (Fig. 2A and B; see ESI† for photodecomposition rates), with their peak intensities decreasing by ~10% after 20 min. The emission intensity of **H-TEDA(BF₄)₂**
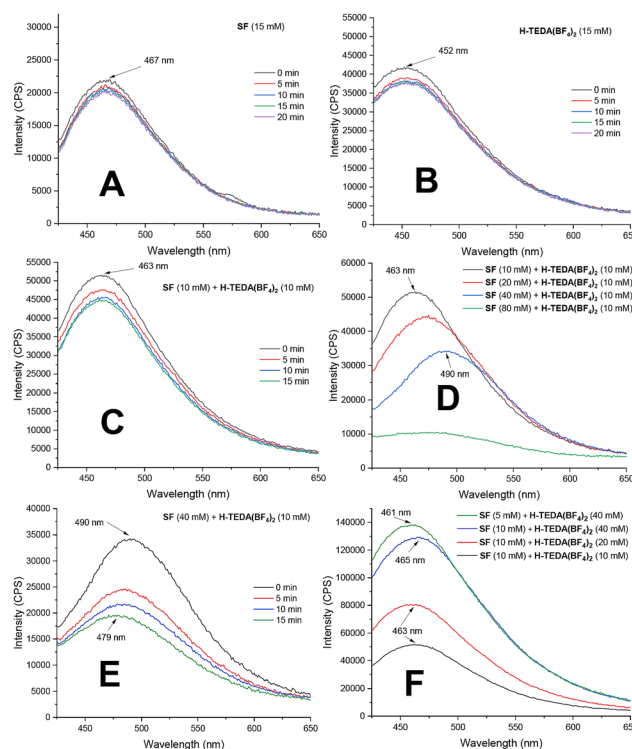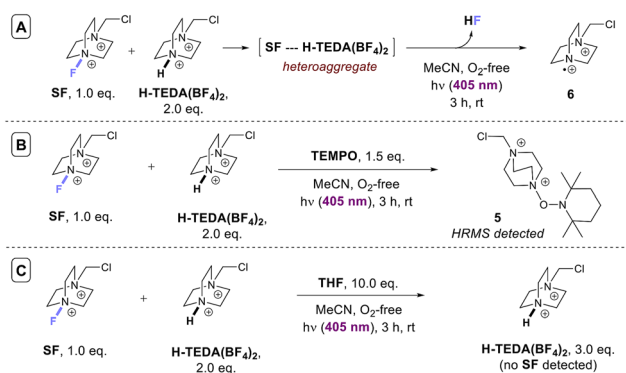

Fig. 2 Luminescence of **SF** and **H-TEDA(BF₄)₂**. (A) **SF** only (15 mM). (B) **H-TEDA(BF₄)₂** only (15 mM). (C) **SF** and **H-TEDA(BF₄)₂** in 1:1 ratio. (D) **H-TEDA(BF₄)₂** (10 mM) with increasing concentrations of **SF**. (E) **SF** and **H-TEDA(BF₄)₂** in a 4:1 ratio. (F) **SF** (10 mM) with increasing concentrations of **H-TEDA(BF₄)₂**.

Scheme 4 (A) Formation of **TEDA•²⁺**. (B) Radical trapping of **SF** and **H-TEDA(BF₄)₂** with TEMPO. (C) Reaction of **SF** and **H-TEDA(BF₄)₂** with THF as a hydrogen donor.
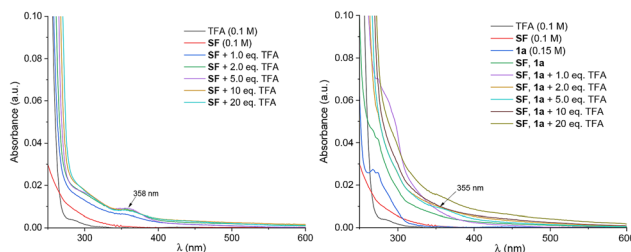

Fig. 1 UV-visible spectroscopy of TFA, **SF** and their mixtures (left). UV-visible spectroscopy of TFA, **1a**, **SF** and their mixtures (right).

(λ_{max} = 452 nm) was twice as high as that of **SF** (λ_{max} = 467 nm) at isoconcentration. Mixing **SF** with **H-TEDA(BF₄)₂** in a 1:1 ratio to afford the **HA** gave rise to a single peak (λ = 463 nm), resembling the emission wavelength of **SF** alone (Fig. 2A and C) but also resembling the higher emission intensity (2.4× vs. **SF** alone) of **H-TEDA(BF₄)₂**. The intensity of **HA** decreased by ~15% over a 15 min period of successive excitations, which was a faster decay than either of its constituent molecules alone. When **H-TEDA(BF₄)₂** was mixed with excesses of **SF** (1:1 → 1:4 ratio) (Fig. 2D), this led to a strong bathochromic shift in the emission peak (λ_{max} = 463 → 490 nm) together with a marked decrease in emission intensity. At a 1:4 ratio, the peak at λ_{max} = 490 nm is attributed to an exciplex of **HA** with **SF**. Exciplexes between arylketone reagents and **SF** were previously reported.[2c,d] This exhibited a pronounced decrease in intensity upon repeated excitations (Fig. 2E), with the peak wavelength shifting back to values more closely resembling **SF**, which is of course present in excess. This suggests quenching of **HA** by 'free' **SF**, presumably by EnT, leading to N⁺–F homolysis. Conversely, mixing **SF** (10 mM) with increasing concentrations of **H-TEDA(BF₄)₂** (10 → 40 mM) did not alter the wavelength but did increase emission intensity up to 2.7× (Fig. 2F), corresponding simply to the higher emission intensity of 'free' **H-TEDA(BF₄)₂**. Clearly, all **SF** is constrained within **HA**; no **SF** is available to form the exciplex.

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Org. Chem. Front., 2025, **12**, 3156–3162 | **3159**

Based on our observations and consolidating knowledge from previous literature reports, we propose two mechanisms (Scheme 5), one involving a radical chain and one not.

Proposed mechanism 1

'*Photoactive HA-initiated HA-promoted-propagation chain*' – In this proposed mechanism (Scheme 5A), **HA** plays two roles, (1) a photoactive radical chain initiator; (2) a fluorine atom donor *via* a more reactive N⁺–F bond (*vs.* **SF**). Firstly, photoactive **HA** is formed immediately upon mixing of **H-TEDA(BF₄)₂** with **SF**. Photoexcitation of **HA** affords ***HA**, which either (i) extrudes HF and forms two molecules of chain carrier **TEDA·²⁺**, or (ii) forms an exciplex with **SF**, which reacts to regenerate **HA** and generate one molecule of **TEDA·²⁺**. In the propagation cycle, **TEDA·²⁺** engages the C(sp³)–H substrate (**1**) in intermolecular HAT, affording an alkyl radical **1′** and regenerating **H-TEDA (BF₄)₂**. Then, the key role of **HA** comes into play as a more active F atom donor than **SF** in the FAT step. Owing to its more activated N⁺–F bond, **1′** reacts rapidly with **HA** in FAT, affording the fluorinated product **2**. This enhanced reactivity minimizes opportunities for putative side reactions involving the alkyl radical (*e.g.* dimerization, disproportionation, HAT with substrate molecules, that would compromise the overall fluorinated product yield), leading to a more efficient and cleaner reaction when **HA** is present from the start. This could be one reason underlying enhanced reaction rates and overall yields in our HA-present 'photocatalyst'-free protocol, compared to previous 'photocatalytic' C(sp³)–H fluorinations. This mechanism is supported by emission spectroscopic detection of an exciplex (Fig. 2) and the detection of **5** upon irradiation of **HA** with TEMPO (Scheme 4B). Although this is inconsistent with the previously reported quantum yields of <0.15,[2d,4] and the non-detection of HF/(F⁻) proposed to be generated in the initiation step, (i) a chain mechanism cannot be conclusively ruled out by low quantum yields, and (ii) formation of traces of HF that react with the glass vial cannot be ruled out.
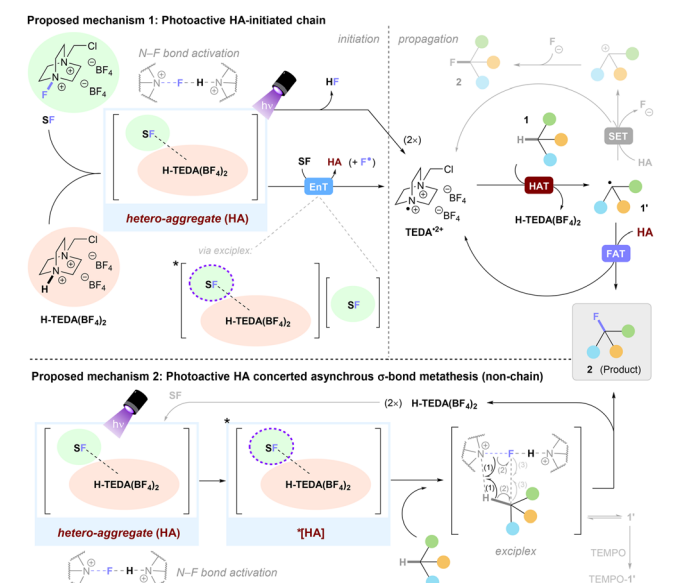
We deem a radical polar crossover-type SET between **1′** and **HA/SF** to be unlikely, as this would imply unstabilized 2° carbocationic intermediates, prone to Ritter-type reactivity[7] with MeCN solvent (or with certain starting materials as Ritter-type nucleophiles). This is inconsistent with the observed efficiency and selectivity of the reaction (*e.g.* an excellent yield of **2u** and the absence of Ritter-type products that we detected in studies of other reactions in our group[7b,c]).

Proposed mechanism 2

'*Photoactive HA asynchronous concerted σ-bond metathesis (non-chain)*' – In this proposed mechanism, photoactive **HA** is formed immediately upon mixing of **H-TEDA(BF₄)₂** with **SF**. Photoexcitation of **HA** affords ***HA**, which acts like a previously reported EnT photosensitizer, forming an exciplex with the C(sp³)–H substrate.[2c,d] This undergoes asynchronous concerted σ-bond metathesis, initially forming **1′** and a non-free (stabilized) F·, which rapidly combine within the aggregate/solvent cage to afford fluorinated product **2**. Although F· is among the most reactive free radicals known, in this mechanism, **1′** and F· are generated in close proximity and the latter is still stabilized within **HA** so is not a 'free' radical. If **1′** was to diffuse away (**TEMPO-1′** was detected), F· could engage the **H-TEDA(BF₄)₂** – to which it is proximally formed – indiscriminately in HAT (at the N⁺–H bond, providing **6**), shielding fresh molecules of **1**. This non-chain mechanism would consist with previously reported quantum yields of <0.15,[2d,4] and the photodecomposition of **HA** (Fig. 2C) upon successive excitations. The σ-bond metathesis being asynchronous (rather than synchronous concerted) is consistent with the TEMPO trapping experiment detecting both **4** and **5**, implying a degree of escape of **1'** from the aggregate/solvent cage.

Conclusion

We report the discovery of a straightforward, scalable 'photocatalyst'-free direct photochemical fluorination of unactivated C(sp³)–H bonds, which employs the natural reaction by-product **H-TEDA(BF₄)₂** at the start of reactions to afford a photoactive species *in situ*. This results in moderate to good yield improvements over previous 'photocatalyst'-present methods, dramatically increases reaction rates, and is conducive to scale-up (gram-scale). Importantly, it offers the flexibility to use the C(sp³)–H substrate as the limiting reactant, thereby increasing utility for complex molecule fluorinations under visible light irradiation, and simplifying work-up and purification. Mechanistic studies indicate the formation of a photoactive **SF/H-TEDA(BF₄)₂** heteroaggregate (**HA**) that obviates the need for any exogenous photocatalyst. This rationalizes the common role of exogeneous 'photocatalysts' in previous studies: they are merely initiators needed to form **HA**, which is likely to be the primary photoactive species responsible for executing efficient photochemical radical C(sp³)–H fluorinations involving **SF**.

Scheme 5 Proposed reaction mechanisms.

3160 | *Org. Chem. Front.,* 2025, **12**, 3156–3162

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Data availability

On behalf of all authors, I confirm that all the data pertaining to this article are available within the ESI† (experimental procedures, listed data, NMR spectra). No code or public datasets are relevant in this case. CCDC deposition numbers have been provided for the two X-ray diffraction (XRD) structures relating to this manuscript (see ESI†). Both CIF files and checkcif.pdf reports are provided for the XRD data.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

References

1 (*a*) T. Liang, C. N. Neumann and T. Ritter, Introduction of Fluorine and Fluorine-Containing Functional Groups, *Angew. Chem., Int. Ed.*, 2013, **52**, 8214, (*Angew. Chem.*, 2013, **125**, 8372); (*b*) A. Lin, C. B. Huehls and J. Yang, Recent advances in C–H fluorination, *Org. Chem. Front.*, 2014, **1**, 434; (*c*) P. A. Champagne, J. Desroches, J.-D. Hemel, M. Vandamme and J.-F. Paquin, Monofluorination of Organic Compounds: 10 Years of Innovation, *Chem. Rev.*, 2015, **115**, 9073; (*d*) B. Lantaño and A. Postigo, Radical fluorination reactions by thermal and photoinduced methods, *Org. Biomol. Chem.*, 2017, **15**, 9954; (*e*) R. Szpera, D. F. Moseley, L. B. Smith, A. J. Sterling and V. Gouverneur, The Fluorination of C–H Bonds: Developments and Perspectives, *Angew. Chem., Int. Ed.*, 2019, **58**, 14824; (*f*) S. Yakubov and J. P. Barham, Photosensitized direct C–H fluorination and trifluoromethylation in organic synthesis, *Beilstein J. Org. Chem.*, 2020, **16**, 2151; (*g*) R.-B. Montserrat, C. C. Sazepin, J. C. Leung, T. Okbinoglu, P. Kennepohl, J. Paquin and G. M. Sammis, Fluorine Transfer to Alkyl Radicals, *J. Am. Chem. Soc.*, 2012, **134**, 4026; (*h*) F. Yin, Z. Wang, Z. Li and C. Li, Silver-Catalyzed Decarboxylative Fluorination of Aliphatic Carboxylic Acids in Aqueous Solution, *J. Am. Chem. Soc.*, 2012, **134**, 10401; (*i*) A. M. Hua, D. N. Mai, R. Martinez and R. D. Baxter, Radical C–H Fluorination Using Unprotected Amino Acids as Radical

Precursors, *Org. Lett.*, 2017, **19**, 2949; (*j*) A. M. Hua, S. L. Bidwell, S. I. Baker, H. P. Hratchian and R. D. Baxter, Experimental and Theoretical Evidence for Nitrogen–Fluorine Halogen Bonding in Silver-Initiated Radical Fluorinations, *ACS Catal.*, 2019, **9**, 3322.

2 (*a*) J. B. Xia, C. Zhu and C. Chen, Visible Light-Promoted Metal-Free C–H Activation: Diarylketone-Catalyzed Selective Benzylic Mono- and Difluorination, *J. Am. Chem. Soc.*, 2013, **135**, 17494; (*b*) J. B. Xia, C. Zhu and C. Chen, Visible light-promoted metal-free sp³-C–H fluorination, *Chem. Commun.*, 2014, **50**, 11701; (*c*) C. W. Kee, K. F. Chin, M. W. Wong and C. H. Tan, Selective fluorination of alkyl C–H bonds *via* photocatalysis, *Chem. Commun.*, 2014, **5**, 8211; (*d*) J. W. Kee, H. Shao, C. W. Kee, Y. Lu, H. S. Soo and C. H. Tan, Mechanistic insights for the photoredox organocatalytic fluorination of aliphatic carbons by anthraquinone using time-resolved and DFT studies, *Catal. Sci. Technol.*, 2017, **7**, 848; (*e*) S. Bloom, J. L. Knippel and T. Lectka, Direct monofluoromethylation of *O*-, *S*-, *N*-, and *P*-nucleophiles with PhSO(NTs)CH₂F: the accelerating effect of α-fluorine substitution, *Chem. Sci.*, 2014, **5**, 1175; (*f*) D. D. Bume, C. R. Pitts, F. Ghorbani, S. A. Harry, J. N. Capilato, M. A. Siegler and T. Lectka, Ketones as directing groups in photocatalytic sp³ C–H fluorination, *Chem. Sci.*, 2017, **8**, 6918; (*g*) F. Ghorbani, S. A. Harry, J. N. Capilato, C. R. Pitts, J. Joram, G. N. Peters, J. D. Tovar, I. Smajlagic, M. A. Siegler, T. Dudding and T. Lectka, Carbonyl-Directed Aliphatic Fluorination: A Special Type of Hydrogen Atom Transfer Beats Out Norrish II, *J. Am. Chem. Soc.*, 2020, **142**, 14710; (*h*) S. Yakubov, W. J. Stockerl, X. Tian, A. Shahin, M. J. P. Mandigma, R. M. Gschwind and J. P. Barham, Benzoates as photosensitization catalysts and auxiliaries in efficient, practical, light-powered direct C(sp³)–H fluorinations, *Chem. Sci.*, 2022, **13**, 14041; (*i*) C. R. Pitts, S. Bloom, R. Woltornist, D. J. Auvenshine, L. R. Ryzhkov, M. A. Siegler and T. Lectka, Direct, Catalytic Monofluorination of sp³ C–H Bonds: A Radical-Based Mechanism with Ionic Selectivity, *J. Am. Chem. Soc.*, 2014, **136**, 9780.

3 H. Egami, S. Masuda, Y. Kawato and Y. Hamashima, Photofluorination of Aliphatic C–H Bonds Promoted by the Phthalimide Group, *Org. Lett.*, 2018, **20**, 1367.

4 S. Yakubov, B. Dauth, W. J. Stockerl, W. M. da Silva, R. M. Gschwind and J. P. Barham, Protodefluorinated Selectfluor® Aggregatively Activates Selectfluor® for Efficient Radical C(sp³)−H Fluorination Reactions, *ChemSusChem*, 2024, **17**, e202401057.

5 The p*K*ₐ value of valine is known to be 2.32 according to this literature: (*a*) R. M. C. Dawson and W. H. Elliott, in *Data for biochemical research*, Oxford University Press, Oxford, 1959, pp. 200–205. Only a predicted p*K*ₐ value was found (4.01) for Boc-Val-OH: (*b*) Predicted NMR data calculated using Advanced Chemistry Development, Inc. (ACD/Labs) Software (© 1994–2024 ACD/Labs); (*c*) T. L. Edwards, V. L. Singleton and R. Boulton, Formation of Ethyl Esters of Tartaric Acid During Wine Aging: Chemical and Sensory Effects, *Am. J. Enol. Vitic.*, 1985, **36**, 118.

This journal is © the Partner Organisations 2025

Org. Chem. Front., 2025, **12**, 3156–3162 | **3161**

6 (*a*) S. Bloom, M. McCann and T. Lectka, Photocatalyzed Benzylic Fluorination: Shedding "Light" on the Involvement of Electron Transfer, *Org. Lett.*, 2014, **16**, 6338; (*b*) Y. Amaoka, M. Nagatomo and M. Inoue, Metal-Free Fluorination of C(sp^3)–H Bonds Using a Catalytic *N*-Oxyl Radical, *Org. Lett.*, 2013, **15**, 2160; (*c*) Z. Li, L. Song and C. Li, Silver-Catalyzed Radical Aminofluorination of Unactivated Alkenes in Aqueous Media, *J. Am. Chem. Soc.*, 2013, **135**, 4640; (*d*) S. Bloom, C. R. Pitts, D. C. Miller, N. Haselton, M. G. Holl, E. Urheim and T. Lectka, A Polycomponent Metal-Catalyzed Aliphatic, Allylic, and Benzylic Fluorination, *Angew. Chem., Int. Ed.*, 2012, **51**, 10580, (*Angew. Chem.*, 2012, **124**, 10732); (*e*) D. D. Bume, S. A. Harry, C. R. Pitts and T. Lectka, Sensitized Aliphatic Fluorination Directed by Terpenoidal Enones: A "Visible Light" Approach, *J. Org. Chem.*, 2018, **83**, 1565; (*f*) D. D. Bume, C. R. Pitts, R. T. Jokhai and T. Lectka, Direct, visible light-sensitized benzylic C–H fluorination of peptides using dibenzosuberenone: selectivity for phenylalanine-like residues, *Tetrahedron*, 2016, **72**, 6031; (*g*) C. R. Pitts, D. D. Bume, S. A. Harry, M. A. Siegler and T. Lectka, Multiple Enone-Directed Reactivity Modes Lead to the Selective Photochemical Fluorination of Polycyclic Terpenoid Derivatives, *J. Am. Chem. Soc.*, 2017, **139**, 2208; (*h*) J. N. Capilato, C. R. Pitts, R. Rowshanpour, T. Dudding and T. Lectka, Site-Selective Photochemical Fluorination of Ketals: Unanticipated Outcomes in Selectivity and Stability, *J. Org. Chem.*, 2020, **85**, 2855; (*i*) A. Vasilopoulos, D. L. Golden, J. A. Buss and S. S. Stahl, Copper-Catalyzed C–H Fluorination/Functionalization Sequence Enabling Benzylic C–H Cross Coupling with Diverse Nucleophiles, *Org. Lett.*, 2020, **22**, 5753; (*j*) W. Liu, X. Huang, M.-J. Cheng, R. J. Nielsen, W. A. Goddard III and J. T. Groves, Oxidative aliphatic C-H fluorination with fluoride ion catalyzed by a manganese porphyrin, *Science*, 2012, **337**, 1322; (*k*) Y. Zhang, N. A. Fitzpatrick, M. Das, I. P. Bedre, H. G. Yayla, M. S. Lall and P. Z. Musacchio, A photoredox-catalyzed approach for formal hydride abstraction to enable C$_{sp^3}$–H functionalization with nucleophilic partners (F, C, O, N, and Br/Cl), *Chem Catal.*, 2022, **2**, 292.

7 (*a*) M. Lepori, I. Dey, C. Pratley and J. P. Barham, Merging New and Old Concepts: Tandem Oxidative Radical-Polar Crossover Ritter Amidation via Multicomponent Photo- and Electrochemical Processes, *Eur. J. Org. Chem.*, 2024, **27**, e202400840; (*b*) S. Schmid, S. Wu, I. Dey, M. Domański, X. Tian and J. P. Barham, Photoelectrochemical Heterodifunctionalization of Olefins: Carboamidation Using Unactivated Hydrocarbons, *ACS Catal.*, 2024, **14**, 9648; (*c*) M. Lepori, C. Pratley, I. Dey, V. Butera, V. Roider and J. P. Barham, Photocatalysis Enables Chemodivergent Radical Polar Crossover: Ritter-Type Amidation vs Heck-Type Olefin Carbofunctionalizations, *ChemRxiv*, 2025, preprint, DOI: **10.26434/chemrxiv-2025-cjjxv.**

3162 | *Org. Chem. Front.*, 2025, **12**, 3156–3162

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