Protodefluorinated Selectfluor® Promotes Aggregative Activation of Selectfluor® for Efficient C(sp^3)−H Fluorination Reactions

Shahboz Yakubov,‡ Bastian Dauth,‡ Willibald J. Stockerl, Wagner M. da Silva, Ruth M. Gschwind,* Joshua P. Barham*

Institute of Organic Chemistry, University of Regensburg, Universitätsstr. 31, 93053 Regensburg (Germany)

*E-mail: Ruth.Gschwind@chemie.uni-regensburg.de ; Joshua-Philip.Barham@chemie.uni-regensburg.de

‡These authors contributed equally.

Abstract: We report herein a simple, yet unexpected approach to dramatically improve the efficiencies of radical fluorination reactions of C(sp^3)−H bonds. **H−TEDA(BF_4)$_2$** is readily generated as a byproduct during fluorination reactions with Selectfluor®, the world's most popular organic fluorination reagent. However, **H−TEDA(BF_4)$_2$** to date is overlooked and discarded as waste, despite comprising 95% of the M.W. of Selectfluor®. We demonstrate that the addition of **H−TEDA(BF_4)$_2$** at the start of fluorination reactions markedly increases their rates, outcompeting side reactions to access higher overall yields of fluorinated products. Showcasing the generality of the phenomenon, the performance additive enhances both photochemical/photocatalytic and thermal radical fluorination reactions by decreasing a discovered induction period in the former and by increasing the rate in the latter. Detailed mechanistic investigations reveal the key importance of aggregation changes in Selectfluor® and **H−TEDA(BF_4)$_2$** to fill gaps of understanding in how radical C(sp^3)−H fluorination reactions work. This study exemplifies how an overlooked reaction waste product can be upcycled for a high value-added application.

Introduction: Apart from well-defined complexes and single molecules, a particularly useful form of matter - that demonstrates modified or wholly new properties in comparison to its molecular components - is an aggregate (i.e., irregular clusters of many molecules). Among the many unique features only identified in aggregates are aggregation-caused quenching (ACQ) and aggregation-induced emission (AIE), which are among the top research fields in chemistry.[1] For example, porphyrins as single molecules in solution are highly emissive. However, their aggregates are non-emissive (ACQ).[1b] Conversely, tetraphenylethene is non-emissive as a single molecule in solution yet becomes highly emissive as an aggregate (AIE) (Scheme 1, A).[1a] Clearly, aggregation states influence photophysical behaviour of molecules and by extension will influence their photochemical behaviour as well. However, surprisingly, to date the field of synthetic photochemistry/photocatalysis has generally neglected aggregation states when considering reaction mechanisms. While the roles of electron-donor acceptor complexes (of reactants) and non-covalent assemblies of photocatalysts in the field have recently received attention,[2] the aggregation states of *reagents* are not considered, even

https://doi.org/10.26434/chemrxiv-2023-3t26g **ORCID:** https://orcid.org/0000-0003-1675-9399 Content not peer-reviewed by ChemRxiv. **License:** CC BY 4.0

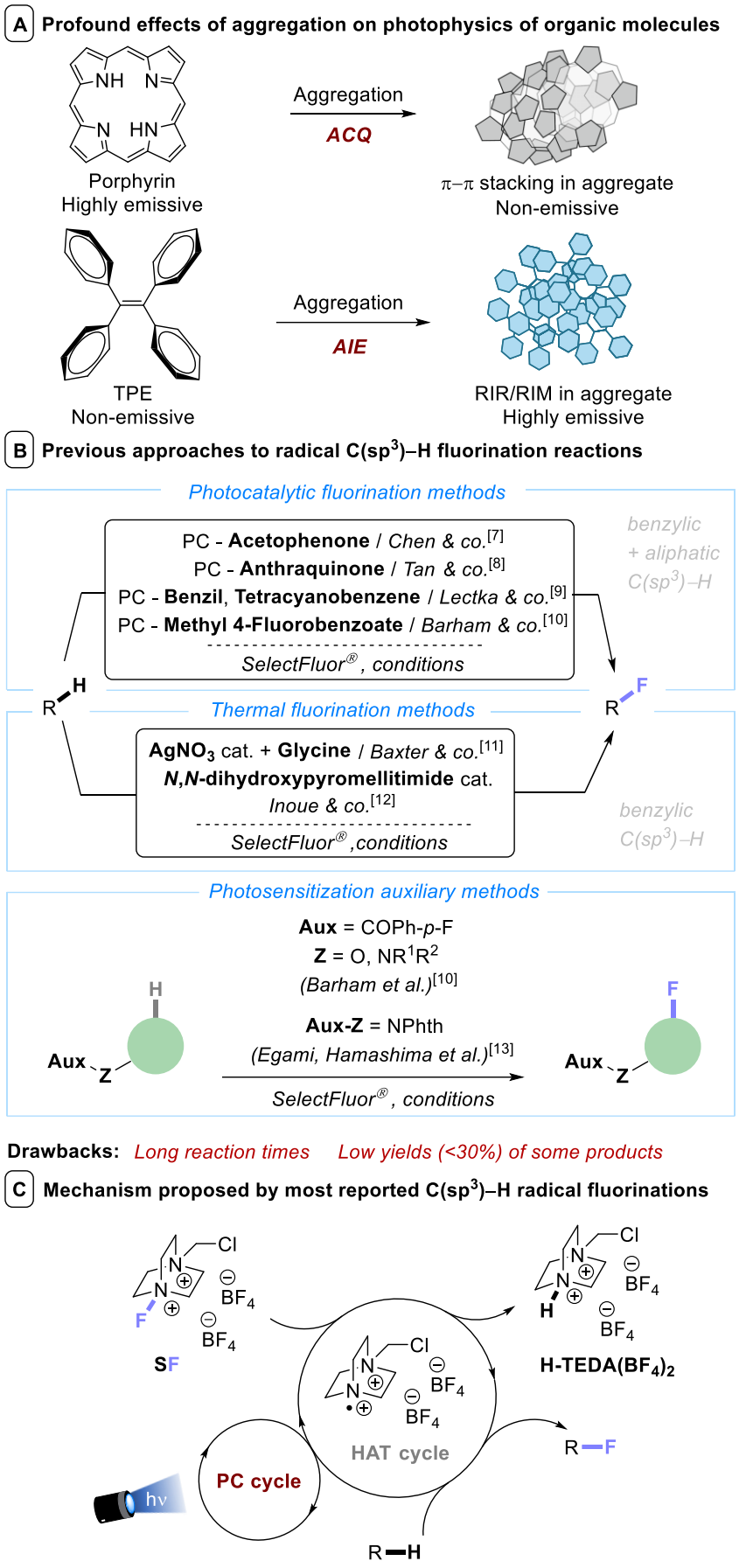
though aggregates can profoundly impact on solubility, reactivity, selectivity, and efficiency of their reactions. In this manuscript, we demonstrate the critical impact of aggregation changes of fluorinating reagents and their byproducts in inducing radical fluorination reactions of C(sp^3)−H bonds. by performing a series of DOSY experiments, and the efficiencies of those reactions.

Elsewhere, the importance of organofluorine compounds to all areas of chemistry has exploded over the past decades, including organic synthesis,[3] pharmaceutical science,[4] and materials development.[5] In this context, procedures for the direct conversion of unactivated C−H bonds to C−F bonds under mild conditions are highly prized. Among these, radical C(sp^3)−H fluorinations using Selectfluor® (**F−TEDA(BF_4)$_2$**, '**SF®**') are particularly attractive for their applicability in late-stage functionalization (LSF) of complex molecules, mild conditions, and (when photosensitized) the use of light as a sustainable source of energy.[6] Activation of **SF®** can be achieved by a photocatalyst, photosensitized auxiliary and thermal fluorination methods (Scheme 1, B).[7-13] Unfortunately, notably drawbacks of these methods are i) the variable yields - that good or excellent yields may result for some products but many products are achieved in unsatisfactory yields (<50%) and ii) the relatively long reaction times (typically >12 h for photochemical reactions).

The generally accepted mechanism that is proposed in most reported radical fluorination methods involves the radical of the substrate, resulting from HAT between the substrate and **TEDA$^{2+\bullet}$** (Scheme 1, C). In almost all previous reports, a chain mechanism is drawn and inferred, however, no evidence for a chain mechanism was actually provided. To the contrary, Lu, Soo, Tan and co-workers[8b] measured a very low quantum yield for their photocatalytic C(sp^3)−H fluorinations. Later, Baxter[11] also contested a possibility of radical chain mechanism after showing how stoichiometric (and not catalytic) amounts of glycine were necessary for product formation. Owing to on-line NMR irradiation capability, our team discovered an induction period for these reactions[10] – that is likely a general phenomenon for all photochemical C(sp^3)−H fluorination reactions. Obviously, the mechanistic situation is more complex than it was previously depicted.

Protodefluorinated Selectfluor® (**H−TEDA(BF_4)$_2$**) is the byproduct of any fluorination reactions using **SF®** as an electrophilic fluorine source (Scheme 2, A), and the former is always discarded as waste.[14] According to Research Excellence Framework 2014 report concerning the institution where **SF®** was discovered,[15] **SF®** is the world's most popular organic fluorination reagent in industrial processes - with annual worldwide production reaching ~25 tonnes (as of 2014). However, with 95% of its M.W. discarded in fluorination reactions, this could generate as much as ~24 tonnes of **H−TEDA(BF_4)$_2$** waste per year.[15] If the **H−TEDA(BF_4)$_2$** waste could be upcycled for useful synthetic applications, this would be a valuable endeavor.

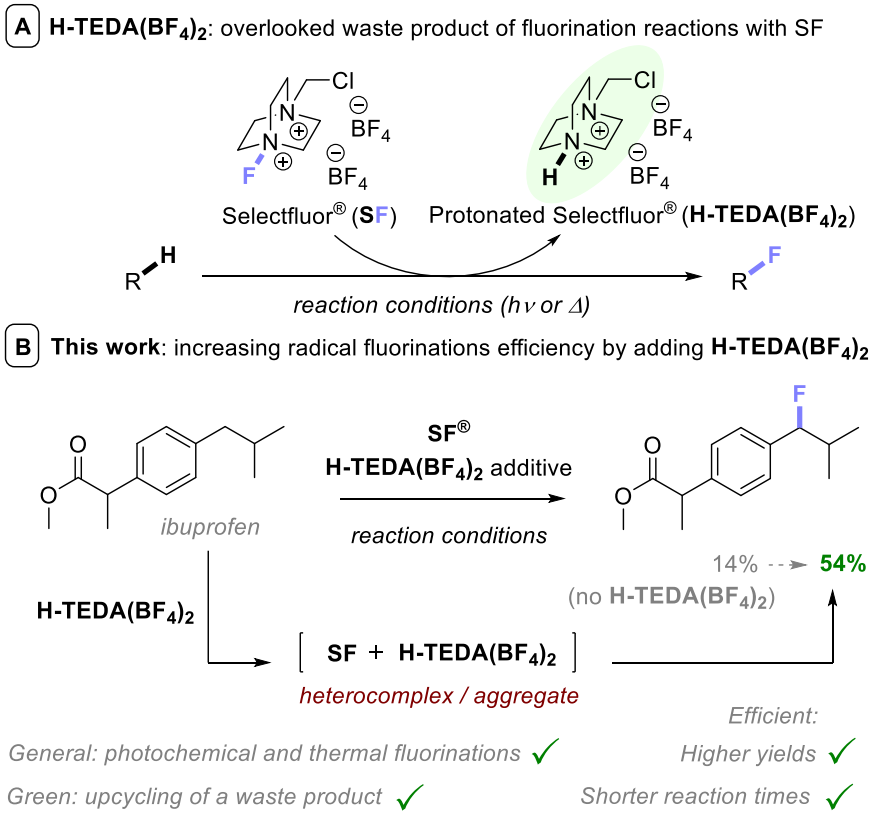
https://doi.org/10.26434/chemrxiv-2023-3t26g **ORCID:** https://orcid.org/0000-0003-1675-9399 Content not peer-reviewed by ChemRxiv. **License:** CC BY 4.0



Scheme 1. (A) Profound aggregation effects on organic chromophores. (B) Previous approaches to radical fluorination reactions. (C) General mechanism proposed in most reported radical fluorination methods.

https://doi.org/10.26434/chemrxiv-2023-3t26g **ORCID:** https://orcid.org/0000-0003-1675-9399 Content not peer-reviewed by ChemRxiv. **License:** CC BY 4.0

Herein, we report the discovery of **H−TEDA(BF$_4$)$_2$**'s hitherto unknown function as a cheap and recoverable performance additive that improves the efficiencies of a diversity of fluorination methods by altering the aggregation state of **SF**® (Scheme 2, B). We exemplify this for both thermal and photocatalytic fluorination studies where **H−TEDA(BF$_4$)$_2$** markedly increases the efficiency, rapidity, and practicality of C(sp^3)−H fluorination reactions. A highly attractive feature is that the **H−TEDA(BF$_4$)$_2$** can either be authentically synthesized from cheap DABCO or isolated as a 'waste' product from radical fluorination reactions, both approaches being feasible, high yielding and even tracelessly executed on a gram scale. The latter approach allows to upcycle a waste product that is until now discarded after radical fluorination reactions, to improve the efficiency of those very reactions.



Scheme 2. A) **H−TEDA(BF$_4$)$_2$** Generated after Radical Fluorination Reactions. B) This Work: Increasing the Yield of the Fluorinated Ibuprofen Derivative by Addition of **H−TEDA(BF$_4$)$_2$** Promoter.

Results and Discussion:

Discovering radical fluorination promotor H−TEDA(BF$_4$)$_2$

In the first instance, we focused our efforts towards exploring the effect of **H−TEDA(BF$_4$)$_2$** on the kinetics of a photochemical fluorination reaction. The kinetic studies were performed by a photoirradiation probe that allows on-line LED irradiation within the NMR spectrometer (see Supporting Information (SI) for details).[16] Time-resolved ^{1}H{^{19}F} NMR was used to track consumption of all starting materials and formation of all products. To mimic the exact

https://doi.org/10.26434/chemrxiv-2023-3t26g **ORCID:** https://orcid.org/0000-0003-1675-9399 Content not peer-reviewed by ChemRxiv. **License:** CC BY 4.0

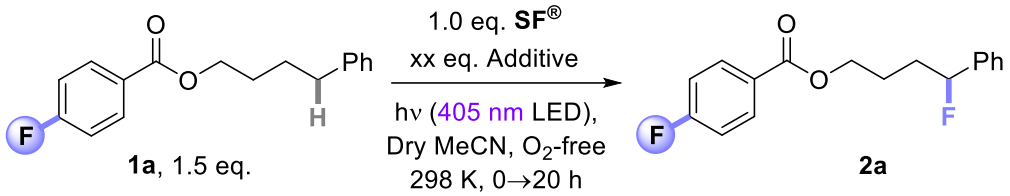
conditions of the batch reaction, the same concentration (0.31 M) was used for kinetic measurements. The reaction yield/time of the NMR reactions are not directly comparable to the stirred reactions in batch due to the following limitations such as i) the light intensity transmitted from the LED to the reaction is low (due to losses from using an optical fiber to transmit light inside the NMR spectrometer), ii) the lack of stirring (an unavoidable disadvantage of *in situ* NMR kinetics) and iii) **SF®** not being fully dissolved under these conditions. Reactions in NMR tubes do not reach as high yields/conversion rates as the batch reactions. Nevertheless, this approach was considered sufficient to interpret relative trends in reactions.

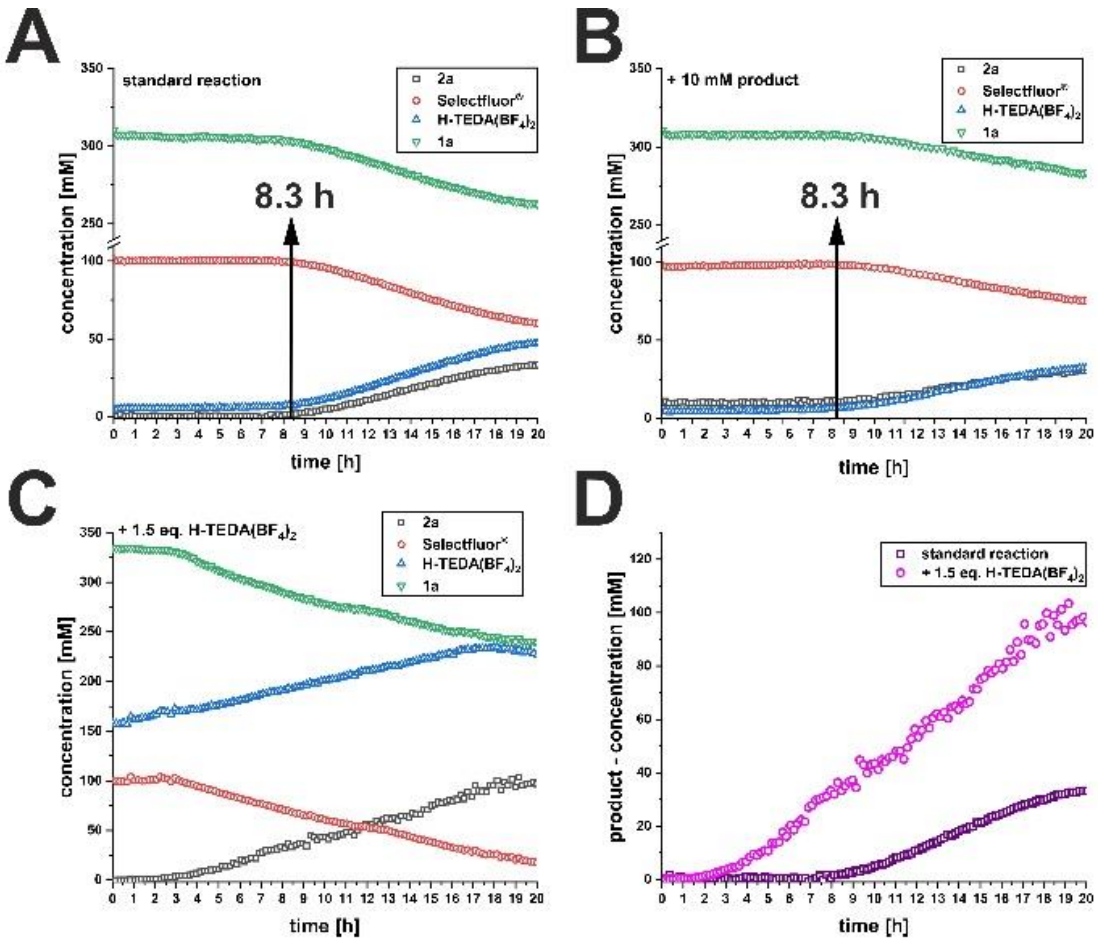
During the kinetic investigations of our previous study on photosensitized fluorination reactions,[10] we discovered an induction period where scarcely any product forms. Subsequently, we observed that increasing the loading of substrate (i.e. photoactive auxiliary) decreases this induction period. In this study, however, we took a different approach. We presumed that an active species was formed not at the beginning of the reaction but *during* the reaction that afterwards accelerates the product formation (Scheme 3, A). This prompted us to examine adding the two main reaction products - The two main product i) the fluorinated alkyl chain product **2a** and ii) **H−TEDA(BF$_4$)$_2$** - at the start of the reaction. Addition of **2a** to the reaction mixture did not influence the induction period of ~8.3 h (Scheme 3, B). However, when we added 1.5 eq. of **H−TEDA(BF$_4$)$_2$** to the reaction mixture prior to turning on the light, the reaction had a substantially shorter induction period of ~1.7 h and a profile typical of a first-order reaction (Scheme 3, C). Moreover, the rate of formation of **2a** and its overall yield was higher with the addition of **H−TEDA(BF$_4$)$_2$** (Scheme 3, D). Thus, it was highly encouraging to find that adding exogeneous **H−TEDA(BF$_4$)$_2$** not only minimizes the induction period, but also improves the efficiency of the reactions vs the presence of nascent **H−TEDA(BF$_4$)$_2$** generated in the reaction. In commercially supplied **SF®** samples, trace (2%) **H−TEDA(BF$_4$)$_2$** was present as an impurity; however, this is insufficient to observe any reaction promotion.

When substrate **1a** was fluorinated by **SF®** in the absence of **H−TEDA(BF$_4$)$_2$** in an *in situ* irradiation experiment within in an NMR tube in the NMR spectrometer, kinetic studies revealed a trace amount of nascent **H−TEDA(BF$_4$)$_2$** was formed after 5 h. As the concentration of nascent **H−TEDA(BF$_4$)$_2$** increased, a downfield shift of its N−CH_2−Cl ^{1}H NMR peak was observed (Scheme 4, A). This occurrence can be explained by aggregation of **H−TEDA(BF$_4$)$_2$** as its concentration increases. The average volume of **H−TEDA(BF$_4$)$_2$** in solution at different concentrations is shown *vide infra* (Table 2, entries 1-5), that increases with increasing its concentration, in line with aggregation. The induction period ended as soon as a certain aggregate/chemical shift of **H−TEDA(BF$_4$)$_2$** was reached (~5.275 ppm), and only then significant formation of the product started. This is an indication of **H−TEDA(BF$_4$)$_2$** being

https://doi.org/10.26434/chemrxiv-2023-3t26g **ORCID:** https://orcid.org/0000-0003-1675-9399 Content not peer-reviewed by ChemRxiv. **License:** CC BY 4.0

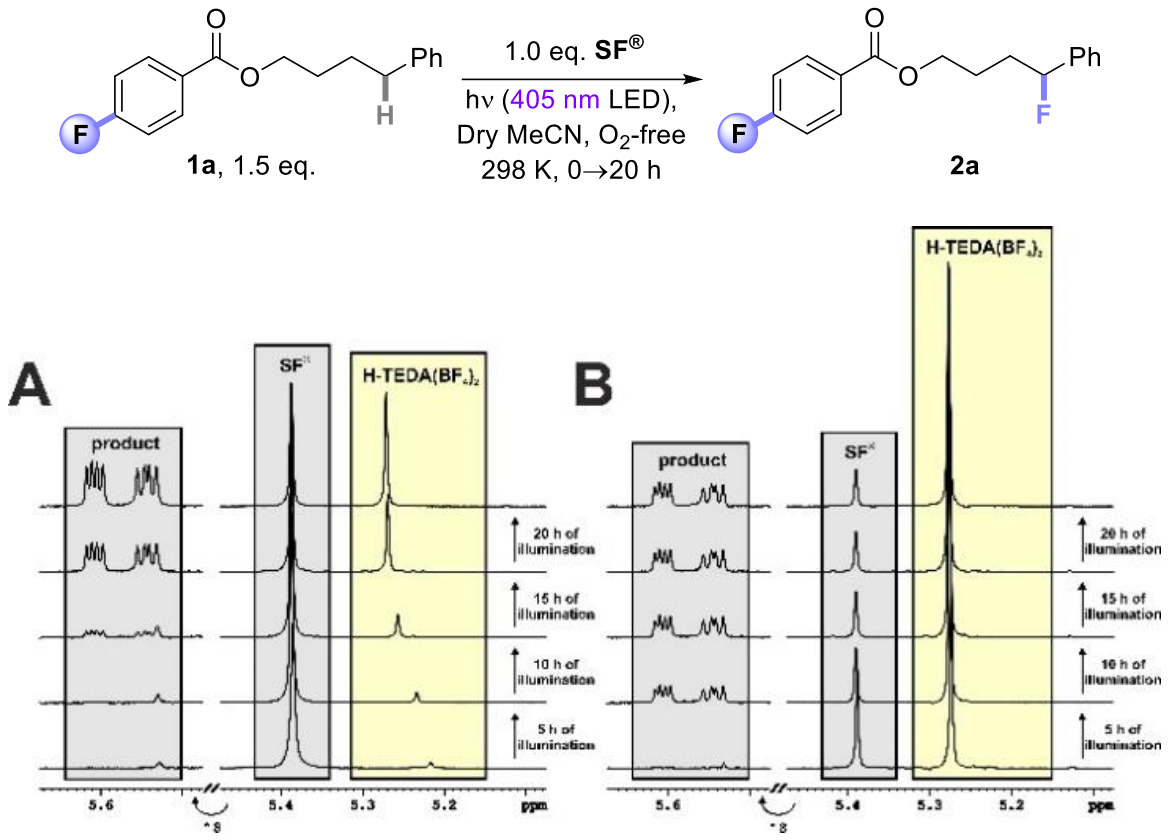
involved in a reactive species that drives the reaction towards the fluorinated product. When performing the same experiment with addition of 1.0 eq. exogeneous **H−TEDA(BF$_4$)$_2$**, the chemical shift observed was *already* ~5.275 ppm, and significant formation of the product started instantly (Scheme 4, B).





Scheme 3. $^{19}F\{^1H\}$ *in situ* illumination NMR reaction monitoring of the **H−TEDA(BF$_4$)$_2$** promotionary effect on the photosensitized auxiliary fluorination of **1a**. (A) Kinetic profiles of the photochemical reaction under standard conditions, (B) with 10 mM product at the start, (C) with 1.5 eq. **H−TEDA(BF$_4$)$_2$** at the start. **D**) Detailed comparison of the reaction profiles of product formation without and with 1.5 eq. of **H−TEDA(BF$_4$)$_2$**.

https://doi.org/10.26434/chemrxiv-2023-3t26g **ORCID:** https://orcid.org/0000-0003-1675-9399 Content not peer-reviewed by ChemRxiv. **License:** CC BY 4.0



Scheme 4. **A)** Stacking of ^{1}H-NMR spectra of photosensitized auxiliary C(sp^3)−H fluorination reaction of **1a** (without **H−TEDA(BF$_4$)$_2$**). **B)** Stacking of ^{1}H-NMR spectra of photosensitized auxiliary C(sp^3)−H fluorination reaction of **1a** (+ 1.0 eq. of **H−TEDA(BF$_4$)$_2$**). In all cases, NMR spectra were recorded periodically after 5 h of *in situ* illumination.

To evaluate the generality and synthetic efficiency benefit of additive **H−TEDA(BF$_4$)$_2$** on fluorination reactions using **SF®** we examined the impact of its presence on a number of reported photochemical/photocatalytic and thermal C(sp^3)−H fluorinations. We specifically selected substrates which afforded poor/moderate product yields (<20% or <55%) under the standard (unpromoted) reaction conditions. For all subsequent case studies, we evaluated the standard literature conditions without vs with 2.0 equiv. of **H−TEDA(BF$_4$)$_2$** additive present at the start of the reaction for the fixed reaction time period (see the SI file for results with different loadings).

Case Study 1: Photosensitized Auxiliary C(sp^3)−H Fluorinations

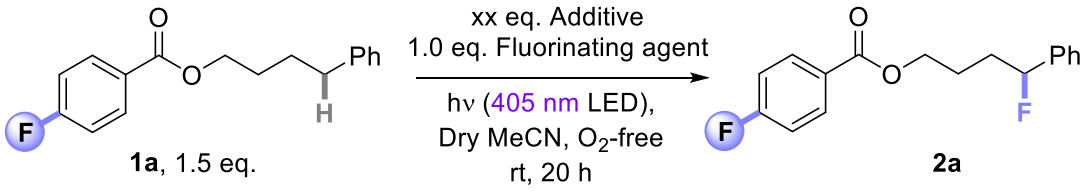
With standard conditions, substrate 4-phenylbutyl 4-fluorobenzoate (**1a**) provided 67% product yield (Table 1, entry 1). With the addition of 2.0 eq. of **H−TEDA(BF$_4$)$_2$** to the reaction mixture, an 85% yield of **2a** was obtained after the same time period (Table 1, entry 2). Although the presence of the 4-fluorobenzoyl auxiliary itself promotes the reaction by changing the aggregation state of **SF®**,[10] it was clear to us that **H−TEDA(BF$_4$)$_2$** further promoted this reaction. We decided to test the effect of different **H−TEDA(BF$_4$)$_2$** additive loadings on this reaction (See the SI file for the details). However, further increasing the **H−TEDA(BF$_4$)$_2$** loading led to lower

https://doi.org/10.26434/chemrxiv-2023-3t26g **ORCID:** https://orcid.org/0000-0003-1675-9399 Content not peer-reviewed by ChemRxiv. **License:** CC BY 4.0

product yields; e.g., 4.0 eq. and 8.0 eq. of **H−TEDA(BF$_4$)$_2$** provided 63% and 17% product yields respectively (Table 1, entries 3 and 4). Next, we tested if the **H−TEDA(BF$_4$)$_2$** additive promotes reactions of other fluorine sources. The standard reaction with SelectFluor II ('**SF II**' i.e., **SF®** where the Cl atom is replaced by H) instead of **SF®** provided only 36% of **2a** (Table 1, entry 6). However, the same reaction with addition of 2.0 eq. **H−TEDA(BF$_4$)$_2$** gave 64% of **2a** (Table 1, entry 7). The standard reaction with N-fluorobenzenesulfonimide (**NFSI**) instead of **SF®** did not afford **2a** (Table 1, entry 8). However, the same reaction with addition of 2.0 eq. **H−TEDA(BF$_4$)$_2$** provided 27% of **2a** (Table 1, entry 9). Thus, the promotionary effect of **H−TEDA(BF$_4$)$_2$** is not limited to **SF®** and is general to other fluorine sources.

We questioned if the promotionary role of **H−TEDA(BF$_4$)$_2$** came down to its Brønsted acidity and elected to examine whether other acids would serve as promotors(see the SI file for full details). Although the pK_a **H−TEDA(BF$_4$)$_2$** is not known, the pK_a of analogous protonated DABCO is 9.1 (in DMSO).[17] Thus, we examined additives with pK_as (in DMSO) that were higher, similar, and lower than 9. Brønsted acidic additives with markedly higher pK_as, such as water (pK_a 31.4),[18] 3-benzyl-1-methyl-1H-imidazol-3-ium hexafluorophosphate (BnMIM·PF$_6$) (pK_a 21.6)[19] and phenol (pK_a 18.0)[20] inhibited the reaction (Table 1, entries 9-11). Additives with similar pK_as - such as acetic acid (pK_a 12.3),[21] triethylammonium tetrafluoroborate (TEA−H·BF$_4$) (pK_a 9.1),[17] imidazolium tetrafluoroborate (Imid−H·BF$_4$) (pK_a 6.4) - gave similar results to the unpromoted reaction. Pyridinium tetrafluoroborate (Py−H·BF$_4$) (pK_a = 3.4)[22] gave a similar yield to the unpromoted reaction, while TFA (pK_a = 3.4)[21] gave an even higher (90%) product yield (Table 1, entry 11). Although the additional promoting benefit of the additives cannot easily be distinguished from the (already efficient reactivity promoting) 4-fluorobenzoyl auxiliary, it was nonetheless intriguing that other additives could be tolerated in the reaction providing their pK_a was sufficiently low.

Table 1. Initial investigations and optimization of conditions.

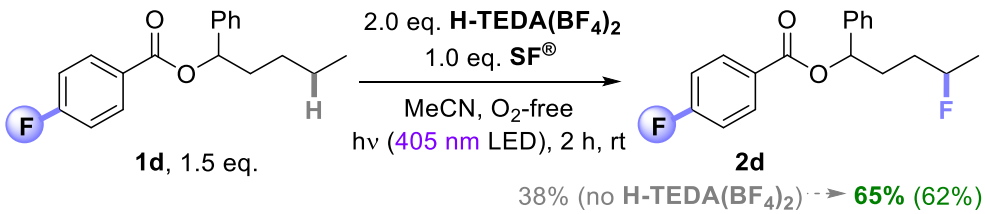


Entry	Fluorinating agent	Additive / pK_a / eq.	NMR yield (%)
1	SF®	-	67

https://doi.org/10.26434/chemrxiv-2023-3t26g **ORCID:** https://orcid.org/0000-0003-1675-9399 Content not peer-reviewed by ChemRxiv. **License:** CC BY 4.0

2	SF®	**H−TEDA(BF$_4$)$_2$** / ~9 / 2.0	85
3	SF®	**H−TEDA(BF$_4$)$_2$** / ~9 / 4.0	63
4	SF®	**H−TEDA(BF$_4$)$_2$** / ~9 / 8.0	17
5	SF II	-	36
6	SF II	**H−TEDA(BF$_4$)$_2$** / ~9 / 2.0	64
7	NFSI	-	0
8	NFSI	**H−TEDA(BF$_4$)$_2$** / ~9 / 2.0	27
9	SF®	H_2O / 31.4 / 2.0	0
10	SF®	BnMIM·PF_6 / 21.6 / 2.0	0
11	SF®	Phenol / 18.0 / 2.0	0
12	SF®	Acetic acid / 12.3 / 2.0	59
13	SF®	TEA−H·BF_4 / 9.1 / 2.0	65
14	SF®	Imid−H·BF_4 / 6.4 / 2.0	65
15	SF®	Py−H·BF_4 / 3.4 / 2.0	62
16	SF®	TFA / 3.4 / 2.0	90

Next, we examined the effect of **H−TEDA(BF$_4$)$_2$** on another substrate in the reported photocatalytic auxiliary fluorination method (Scheme 5).[10] Specifically, substrate **1d** when treated with **SF®** under 400 nm irradiation gave a low yield (38%) of fluorinated product **2d**. When the reaction was repeated with 2.0 eq. of **H−TEDA(BF$_4$)$_2$**, the yield increased from 38% to 65% (Figure 4). In this method, the auxiliary (4-fluorobenzoate) acts mainly as a photosensitizer and **H−TEDA(BF$_4$)$_2$** as a superior activating reagent of **SF®** via changing the aggregation state.



Scheme 5. Promoted vs Unpromoted Photosensitized auxiliary fluorination of **1d**. NMR yields were determined by ^{19}F NMR with pentafluorobenzene as the internal standard (IS). The yields are the average of triplicates (See the SI file for the details). Isolated yield is in parenthesis.

https://doi.org/10.26434/chemrxiv-2023-3t26g **ORCID:** https://orcid.org/0000-0003-1675-9399 Content not peer-reviewed by ChemRxiv. **License:** CC BY 4.0

To manifest aggregation trends of **SF®** and **H−TEDA(BF$_4$)$_2$**, we performed further diffusion ordered spectroscopy (DOSY) measurements for the pure components and for the reaction mixture and calculated the related volumes to determine aggregation trends (Table 2). At synthetic reaction concentrations (Table 2, entry 1) precipitation of **H-TEDA(BF$_4$)$_2$** occurs due to limited solubility in CD_3CN. For reliable aggregation studies, we used maximum concentrations of 90 mM for **SF®** and **H−TEDA(BF$_4$)$_2$**. The data in Table 2 (entries 2-5) show that the volume of **H−TEDA(BF$_4$)$_2$** nearly doubles from 1 mM to 90 mM (506 Å^3 and 934.9 Å^3, respectively). The volume of **H−TEDA(BF$_4$)$_2$** increases only slightly to 974 Å^3 at synthetic reaction concentrations (Table 2, entries 1 and 2). The monomeric volume of **H−TEDA(BF$_4$)$_2$** was calculated to be 321 Å^3 (see SI section 4.1.4). This indicates an average aggregation number of 3 for **H−TEDA(BF$_4$)$_2$** under synthetic conditions in MeCN as solvent.

SF® is significantly lower aggregated than **H−TEDA(BF$_4$)$_2$** at 90 mM (Table 2, entries 2 and 6). This offset in aggregation might be explained by pure ion pair aggregation of **SF®**, while **H−TEDA(BF$_4$)$_2$** can undergo ion pairing and hydrogen bonding.[10] Even more interesting, a further increase in volume for both **SF®** and **H−TEDA(BF$_4$)$_2$** was observed in the 1:1 component mixture at 90 mM (Table 2, entry 7). The volume of **SF** even increased by 47% (entries 6 and 7) while for **H−TEDA(BF$_4$)$_2$** a more moderate increase of 19% was observed (entries 2 and 7). These results clearly indicate a preferred complexation between **SF®** and **H−TEDA(BF$_4$)$_2$** over the homocomplexation of **SF®** or **H−TEDA(BF$_4$)$_2$**. Furthermore, similar ratios of diffusion coefficients for the $^-BF_4$ anion for the homo- and heterocomplexes indicate that different ion pair formations should be irrelevant (entries 12-14). Even though the overall ion concentration of the homocomplex situation is higher at 90 mM (entries 2 and 6), the volumes of **SF®** and **H−TEDA(BF$_4$)$_2$** increase at lower ion concentrations of 40 mM in their 1:1 component mixture (entry 8). Again, this corroborates heterocomplex formation of **SF®** and **H−TEDA(BF$_4$)$_2$**. Therefore, we suggest the additional $^+$N−H---F−N$^+$ interaction within the complex as a driving force for the preferred heterocomplex formation similar to the reported structures of Toste and co-workers (see Figure 6A, *vide infra*).[23] Subsequently, we determined the self-diffusion coefficients and volumes for **SF®** and **H−TEDA(BF$_4$)$_2$** with different **H−TEDA(BF$_4$)$_2$** loadings. It was found that enhancing the concentration of **H−TEDA(BF$_4$)$_2$** in the **SF®** / **H−TEDA(BF$_4$)$_2$** mixture markedly increases the volumes of both components (Table 2, entries 8-11). Thus, **H−TEDA(BF$_4$)$_2$** loading appears to enhance aggregation beyond heterodimer formation.

Table 2. Volumes of **SF®** and **H−TEDA(BF$_4$)$_2$**, pure and with different **H−TEDA(BF$_4$)$_2$** loadings in anhydrous and degassed CD_3CN at 308 K, measured by DOSY NMR experiments (for details, see SI section 4.1.4).

https://doi.org/10.26434/chemrxiv-2023-3t26g **ORCID:** https://orcid.org/0000-0003-1675-9399 Content not peer-reviewed by ChemRxiv. **License:** CC BY 4.0

Entry	Compounds	C [mM]	Average volume [Å^3]
1	**H−TEDA(BF$_4$)$_2$** (precipitation)	209	974
2	H−TEDA(BF$_4$)$_2$	90	935
3	H−TEDA(BF$_4$)$_2$	50	878
4	H−TEDA(BF$_4$)$_2$	20	797
5	H−TEDA(BF$_4$)$_2$	1.0	506
6	SF®	90	718
7	SF® / H−TEDA(BF$_4$)$_2$	90 / 90	**SF®**: 1055 H−TEDA(BF$_4$)$_2$: 1111
8	SF® / H−TEDA(BF$_4$)$_2$	40 / 40	**SF®**: 1045 H−TEDA(BF$_4$)$_2$: 1040
9	SF® / H−TEDA(BF$_4$)$_2$	40 / 30	**SF®**: 813 H−TEDA(BF$_4$)$_2$: 792
10	SF® / H−TEDA(BF$_4$)$_2$	40 / 20	**SF®**: 763 H−TEDA(BF$_4$)$_2$: 710
11	SF® / H−TEDA(BF$_4$)$_2$	40 / 10	**SF®**: 766 H−TEDA(BF$_4$)$_2$: 696
12	BF$_4$ of **SF®**	90	461
13	BF$_4$ of H−TEDA(BF$_4$)$_2$	90	504
14	BF$_4$ of SF® / H−TEDA(BF$_4$)$_2$	90	620

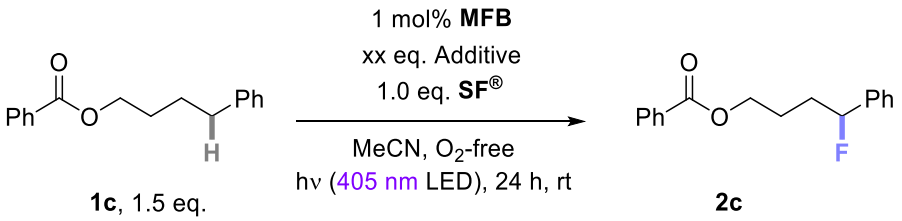
Case Study 2: Photocatalytic C(sp^3)−H Radical Fluorinations

In our previous study,[10] we demonstrated methyl 4-fluorobenzoate as a non-ketone photosensitization catalyst for C(sp^3)−H fluorinations. Although a variety of small molecules with different functional groups were tolerated, yields were variable (31 – 94%) and some substrates required a 4-fluorobenzoyl auxiliary to achieve satisfactory (>50%) yields. One of the poorly reactive substrates under photocatalytic conditions was 4-phenylbutyl benzoate (**1c**), which afforded only 10% of **2c** when treated with 1 mol% photocatalyst (**MFB**) under 400 nm irradiation for 24 h (Table 3, entry 1) (see the SI file for the details). In the absence of any photocatalyst, the reaction proceeds in a similar yield showing that the benzoyl group can serve as a photosensitizing auxiliary, however it is very inefficient compared to 4-fluorobenzoyl

https://doi.org/10.26434/chemrxiv-2023-3t26g **ORCID:** https://orcid.org/0000-0003-1675-9399 Content not peer-reviewed by ChemRxiv. **License:** CC BY 4.0

as we previously reported.[10] Under the standard reaction conditions (with 1 mol% **MFB**) but with 2.0 eq. of **H−TEDA(BF$_4$)$_2$** present at the start of the reaction, the yield of **2c** increased dramatically to 68% (Table 3, entry 2). Using 6.0 eq. **H−TEDA(BF$_4$)$_2$** provided an even higher yield of **2c** (81%) (Table 3, entry 3), while 10.0 eq. **H−TEDA(BF$_4$)$_2$** provided only 57%, presumably due to substantial light occlusion under these low solubility conditions. TEA−H·BF$_4$ - as an additive that has a similar pK_a (9.1) to **H−TEDA(BF$_4$)$_2$** (~9) - provided **2c** in 63% yield. Next, we tested the effect of TFA in this photocatalytic fluorination reaction, since it promoted fluorination of **1a** (Table 1, entry 11). Adding 2.0 eq. TFA at the start of the fluorination reaction of **1c**, promoted the reaction only to 45% yield of **2c** and 4.0 eq. TFA gave **2c** in a worse (24%) yield. Although TFA was a superior promotor for **1a**'s fluorination it was an inferior promoter for **1c**'s fluorination.

Table 3. Photocatalytic fluorination of **1c** using MFB catalyst with different amounts of additives.

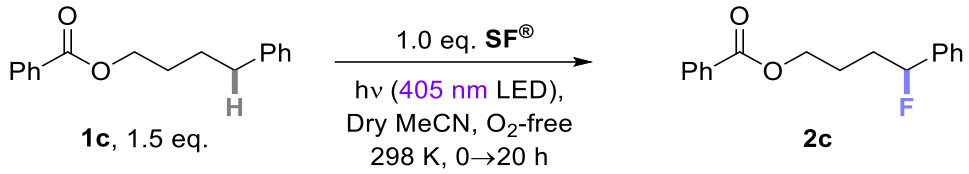


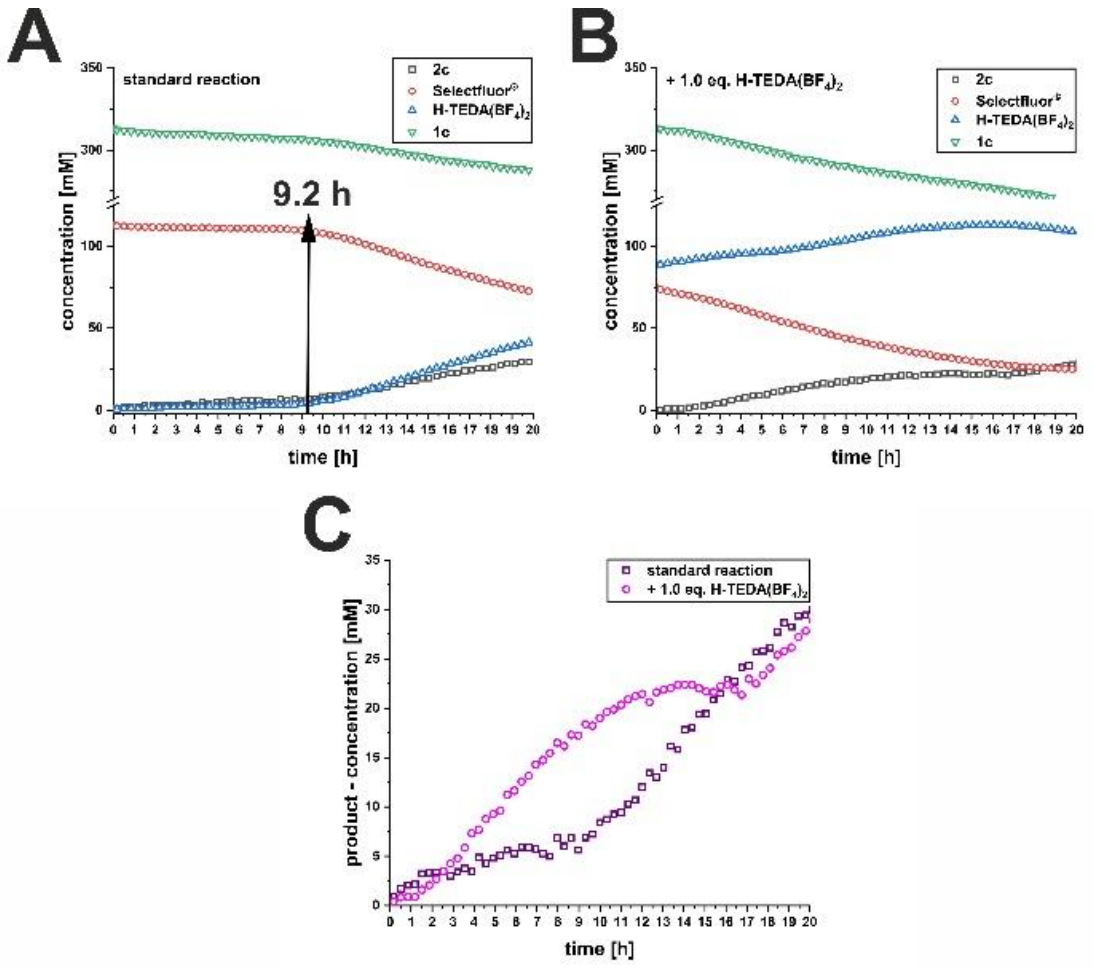
Entry	Additive / pK_a / eq.	NMR yield (%)
1	-	10
2	H−TEDA(BF$_4$)$_2$ / ~9 / 2.0	68
3	H−TEDA(BF$_4$)$_2$ / ~9 / 6.0	81
4	**H−TEDA(BF$_4$)$_2$** / ~9 / 10.0	57
5	TEA−H·BF$_4$ / 9.1 / 2.0	63
6	TFA / 3.4 / 2.0	45
7	TFA / 3.4 / 4.0	24

The on-line NMR irradiation kinetic experiment (Scheme 6) revealed a long induction period (9.2 h) where scarcely any product is formed (Scheme 6, A). In the presence of 1.0 eq. of **H−TEDA(BF$_4$)$_2$**, the induction period shortened from 9.2 h to 1.4 h (Scheme 6, B). To put in perspective, after 9.2 h of *in situ* illumination, only 5 mM of product was formed in the standard reaction whereas 16 mM of product was generated by addition of 1.0 eq. **H−TEDA(BF$_4$)$_2$** in the

https://doi.org/10.26434/chemrxiv-2023-3t26g **ORCID:** https://orcid.org/0000-0003-1675-9399 Content not peer-reviewed by ChemRxiv. **License:** CC BY 4.0

beginning of the reaction. Overall, by addition of 1.0 eq. of **H−TEDA(BF$_4$)$_2$** the induction phase was shortened, and product formation was increased (Scheme 6, C).





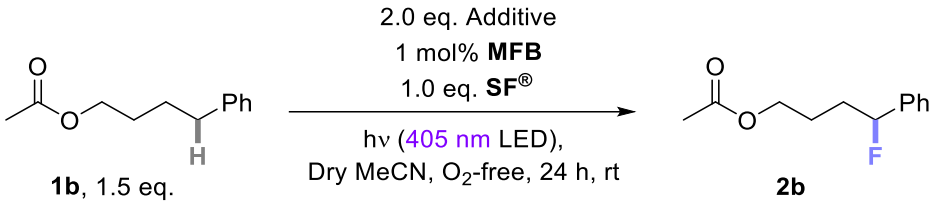
Scheme 6. $^{19}F\{^1H\}$ In situ illumination NMR reaction monitoring of **H−TEDA(BF$_4$)$_2$**'s promotionary effect on the photochemical fluorination of **1c**. Kinetic profiles of (**A**) the photochemical reaction under standard conditions and (**B**) with 1.0 eq. **H−TEDA(BF$_4$)$_2$**. (**C**) Comparison of the reaction profiles of product formation without vs with 1.0 eq. **H−TEDA(BF$_4$)$_2$**.

Another substrate from the same study was 4-phenylbutyl acetate (**1b**).[10] The key difference from **1a** and **1c** is that **1b** does not contain any attached (benzoyl) photosensitizer, thus eliminating the possibility of background self-fluorination. Substrate **1b** was reported to afford only 19% yield of **2b** when treated with 1 mol% photocatalyst (**MFB**) under 400 nm irradiation

https://doi.org/10.26434/chemrxiv-2023-3t26g **ORCID:** https://orcid.org/0000-0003-1675-9399 Content not peer-reviewed by ChemRxiv. **License:** CC BY 4.0

for 24 h (Table 4, entry 1) (see the SI file for the details). Adding 2.0 eq. of promoter **H−TEDA(BF$_4$)$_2$** to the reaction mixture increased the yield of **2b** dramatically to 64% (entry 4). The reaction efficiency of **1b** was then comparable to that achieved with its 4-fluorobenzoyl derivative (**1a→2a** (67%)), showing how the benefit of exogenous promotor **H−TEDA(BF$_4$)$_2$** is at least comparable to the endogenous promoting photosensitization auxiliary. Clearly, the exogenous promotor is a more generally applicable and useful strategy. Regarding other Brønsted acidic additives, interestingly, those with a pK_a ~9 were most effective promotors (entries 3,4), while AcOH with a higher pK_a (entry 2) and those with lower pK_as (entries 5-7) were less effective. The comparison of **H−TEDA(BF$_4$)$_2$** and TFA here tracks well with Table 3.

Table 4. Photocatalytic fluorination of **1b** with MFB catalyst in presence of different additives and different loadings.



Entry	Additive (2.0 eq.) / pK_a	NMR yield (%)
1	-	19
2	Acetic acid / 12.3	59
3	TEA−H·BF$_4$ / 9.1	62
4	**H−TEDA(BF$_4$)$_2$ / ~9**	64
5	Imid−H·BF$_4$ / 6.4	60
6	Py−H·BF$_4$ / 3.4	36
7	TFA / 3.4	43

We hypothesize that intermolecular interactions between **SF®** and **H−TEDA(BF$_4$)$_2$** potentially *via* higher aggregation leads to activation of **SF®** in the reaction mixture. To manifest the effects of **H−TEDA(BF$_4$)$_2$** loading during the reaction, DOSY experiments and simultaneous ^{1}H NMR kinetic measurements were performed during *in situ* illumination (see SI section 4.1.5). To prevent precipitation of any component, concentrations of 30 mM were used for **SF®** and **H−TEDA(BF$_4$)$_2$**. As evident from the consumption of **SF®**, the reaction starts directly for the **H−TEDA(BF$_4$)$_2$** promoted experiment, while under the standard reaction conditions no

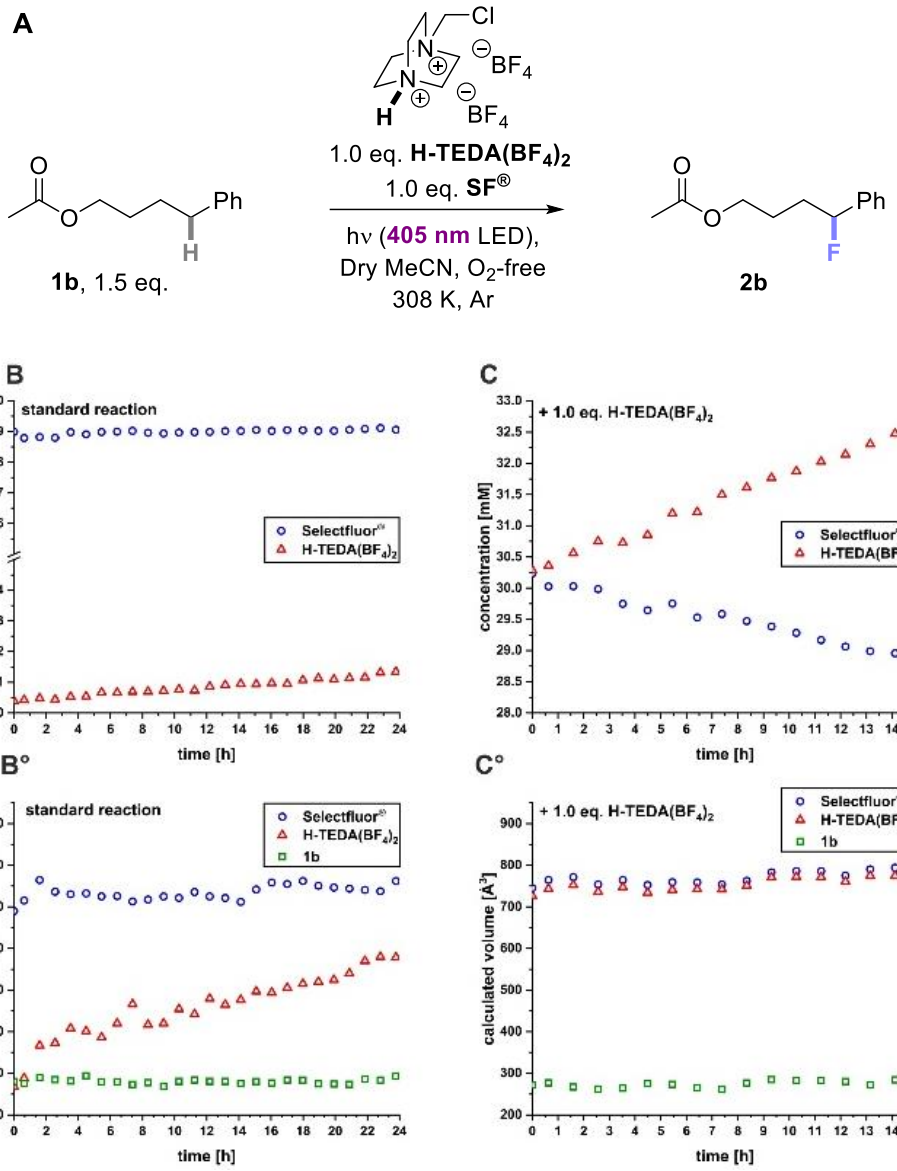
https://doi.org/10.26434/chemrxiv-2023-3t26g **ORCID:** https://orcid.org/0000-0003-1675-9399 Content not peer-reviewed by ChemRxiv. **License:** CC BY 4.0

conversion can be detected (see Scheme 7, B/C). For the **H−TEDA(BF$_4$)$_2$** promoted experiment, the volumes of **SF®** and **H−TEDA(BF$_4$)$_2$** hardly change during *in situ* illumination (Scheme 7, C°). Thus, an aggregation state of **SF®** and **H−TEDA(BF$_4$)$_2$** of approx. 700 Å^3 each allows high reactivity. In contrast, for the unpromoted reaction, the aggregation state of **H−TEDA(BF$_4$)$_2$** increases during the reaction (Scheme 7, B°). The DOSY data for both **SF®** and **H−TEDA(BF$_4$)$_2$** clearly show that the nascent **H−TEDA(BF$_4$)$_2$** is initially not included in the **H−TEDA(BF$_4$)$_2$** / **SF®** heterocomplex. Of course, its gradual inclusion in the reactive **H−TEDA(BF$_4$)$_2$** / **SF®** aggregate can explain the induction period observed in the previous reaction studies (Scheme 3, 4 and 6). This nicely explains the experimental observation that nascent **H−TEDA(BF$_4$)$_2$** formed during the reaction *does not substitute the higher reactive **H−TEDA(BF$_4$)$_2$ / SF®** aggregate formed by adding **H−TEDA(BF$_4$)$_2$** at the start of the reaction*. Taken together, aggregation and concentration monitoring during the reaction indicated that formation of the reactive heterocomplex requires certain **H−TEDA(BF$_4$)$_2$** concentrations in solution. Consequently, loading **H−TEDA(BF$_4$)$_2$** loading prior to the reaction allows immediate aggregation of the components and thus activates **SF®** at the beginning of the reaction, eliminating induction phases in which the concentration of nascent **H−TEDA(BF$_4$)$_2$** is required to increase.

Next, more information about the structure and interactions within the **H−TEDA(BF$_4$)$_2$** / **SF®** aggregate was gathered. As per the aforementioned model system, a 1:1 mixture with concentrations of 90 mM of both components was studied in CD_3CN. The acidic $^+$N−H proton signal of pure **H−TEDA(BF$_4$)$_2$** - a broad singlet at 7.11 ppm - shifts to 7.45 ppm in this 1:1 mixture, while no other signals of **H−TEDA(BF$_4$)$_2$** show any change. This $^+$N−H shift is typical for the formation of a hydrogen bond involving the acidic proton of **H−TEDA(BF$_4$)$_2$** and correlates directly with the amount of **SF®**. In contrast, ion pair aggregation can occur without chemical shift changes as observed in previous investigations.[16] To verify whether there are specific intermolecular interactions between the components, we performed ^{1}H ^{1}H NOESY, ^{1}H ^{1}H ROESY and ^{1}H ^{19}F HOESY experiments at lower temperatures (230 K). These low temperatures are applied to inhibit exchange processes and promote preferred conformations. Cross peaks of the remaining signals in the ^{1}H ^{1}H NOESY and ^{1}H ^{1}H ROESY experiments showed multiple intermolecular NOE contacts between the cations of **SF®** and **H−TEDA(BF$_4$)$_2$**, confirming heterocomplexation (see Figure 6A and SI chapter 5.1). The ^{1}H ^{19}F HOESY experiment could not reveal any N$^+$-H···F-$^+$N interactions due to fast exchange processes. However, the overall NOE pattern at 230 K clearly reflects the overall aggregated ion pair structure and indicates that there is not a single complex structure formed but that multiple complexes are present, and potential both chlorine and fluorine act as hydrogen bond acceptors in the **H−TEDA(BF$_4$)$_2$** / **SF®** complex (see Figure 6A and SI, Figure S13). The general downstream mechanism of the **H−TEDA(BF$_4$)$_2$** - induced fluorination reactions resembles that

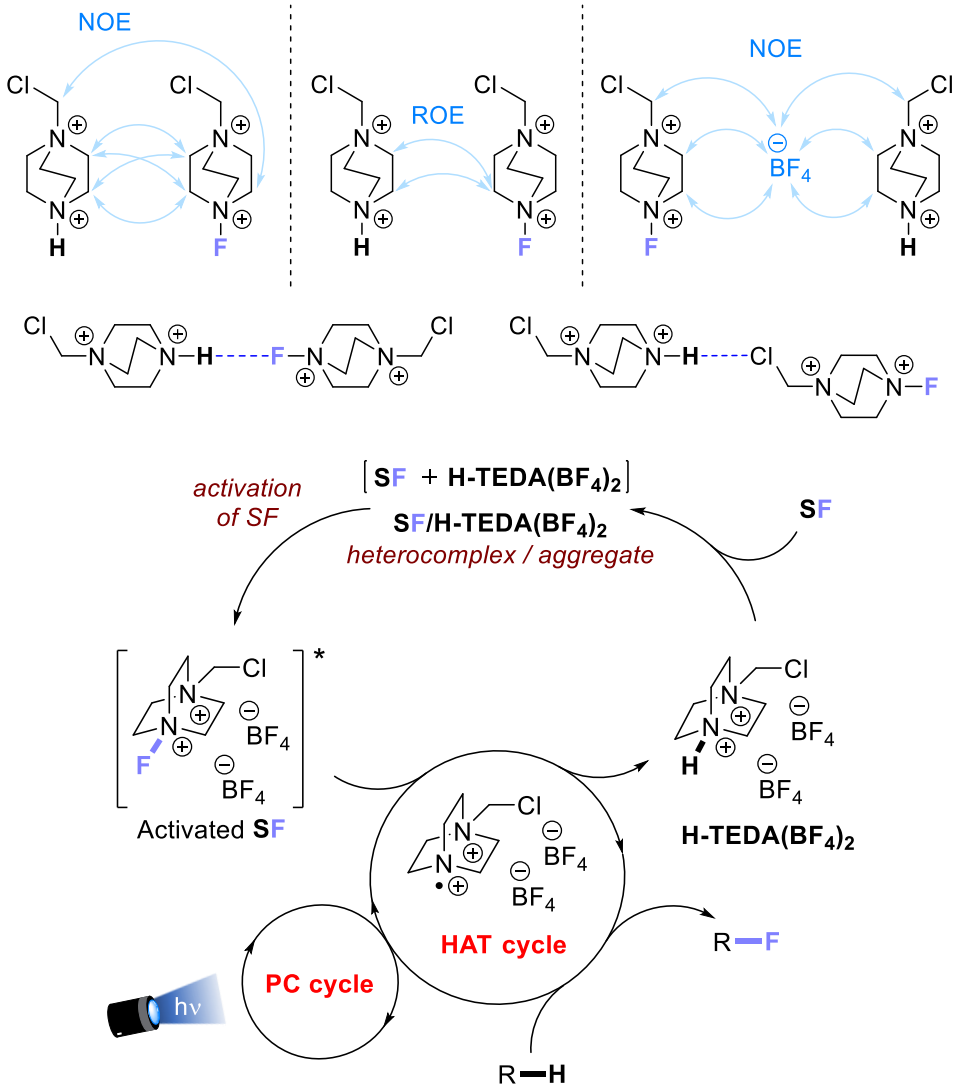
https://doi.org/10.26434/chemrxiv-2023-3t26g **ORCID:** https://orcid.org/0000-0003-1675-9399 Content not peer-reviewed by ChemRxiv. **License:** CC BY 4.0

proposed in the literature,[7-10] however we propose initial steps of the aggregation that are essential for activation of **SF®** (Scheme 8, B).



Scheme 7. (A) Change in concentration of **SF®** and (B) **H−TEDA(BF$_4$)$_2$** during *in situ* illumination of the photochemical C(sp^3)−H fluorination of **1b** under standard conditions and (C) with 1.0 eq. **H−TEDA(BF$_4$)$_2$** loading. (B°) Simultaneous ^{1}H-NMR aggregation monitoring by *in situ* illumination 1D-DSTE DOSY experiments under standard conditions and (C°) with 1.0 eq. **H−TEDA(BF$_4$)$_2$** loading.

https://doi.org/10.26434/chemrxiv-2023-3t26g **ORCID:** https://orcid.org/0000-0003-1675-9399 Content not peer-reviewed by ChemRxiv. **License:** CC BY 4.0

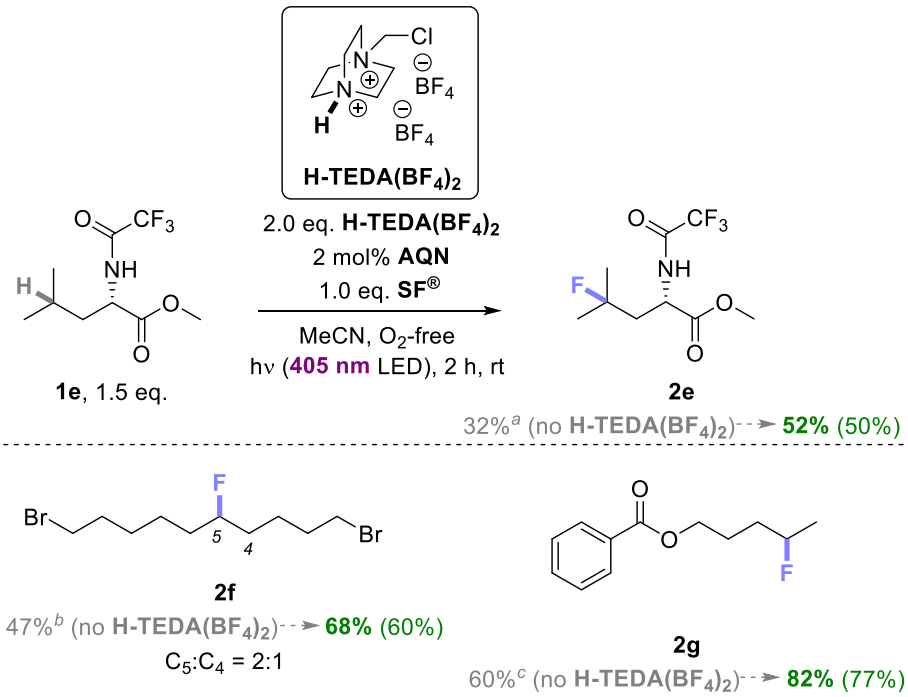


Scheme 8. (A) Possible interaction modes of aggregate formation based on 2D NMR experiments. (B) Proposed general reaction mechanism of the radical fluorination reactions promoted by **H−TEDA(BF$_4$)$_2$**.

Tan and co-workers developed a photocatalytic energy transfer method for direct fluorination of unactivated C-H bonds employing **SF®** as an electrophilic fluorine source and anthraquinone (AQN) as a photocatalyst.[8a] A variety of different compounds containing multiple C(sp^3)–H bonds and different functional groups were successfully fluorinated in moderate to good yields (34 - 77%). In our hands, their standard conditions (1.0 eq. **SF®** and 2 mol% AQN), gave **2e** in a yield (32%) comparable to the literature (34%),[8a] giving us confidence over our literature reproducibility (Scheme 9). Under the same conditions but with 2.0 eq. of **H−TEDA(BF$_4$)$_2$** present at the start of the reaction, the yield of **2e** increased dramatically to 55%. We also examined 1,10-dibromodecane (**1f**) and amyl benzoate (**1g**), whose literature yields (41% and 55%, respectively)[8a] were also successfully reproduced in our hands (47% and 60%, respectively). By adding 2.0 eq. of **H−TEDA(BF$_4$)$_2$**, the fluorinated product yields increased by

https://doi.org/10.26434/chemrxiv-2023-3t26g **ORCID:** https://orcid.org/0000-0003-1675-9399 Content not peer-reviewed by ChemRxiv. **License:** CC BY 4.0

~20% in both cases (68% of **2f** and 82% of **2g**), showing the generality of the promoting **H−TEDA(BF$_4$)$_2$** additive. Chen and co-workers reported acetophenone as a photocatalyst for the direct C–H fluorination of unactivated C(sp^3)–H bonds under near-UV light (375–400 nm).[7b] A variety of substrates containing unactivated C(sp^3)–H groups were monofluorinated in good to excellent yields (55 - 85%).



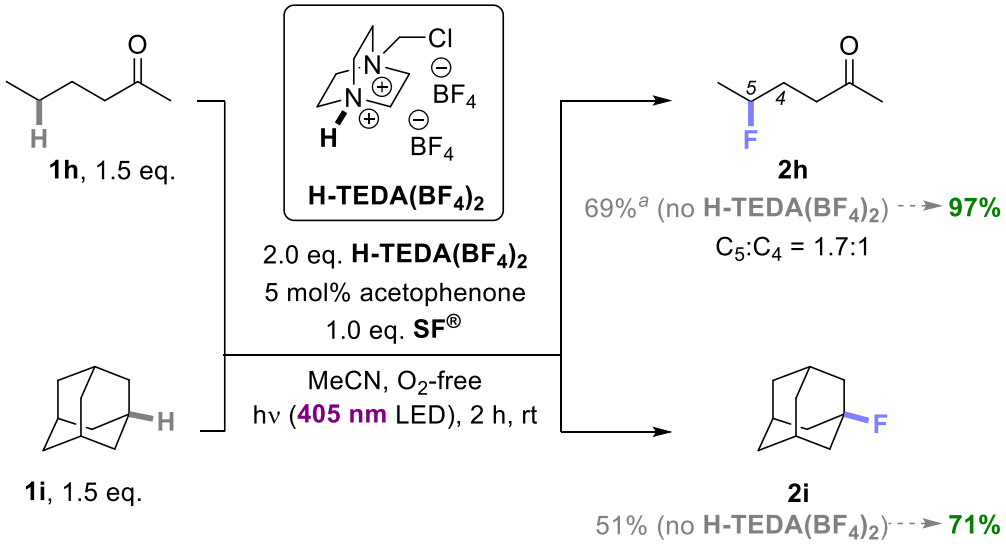
Scheme 9. Promoted vs Unpromoted Photocatalytic Fluorinations of **1e**, **1f**, and **1g** with AQN Catalyst. NMR yields were determined by ^{19}F NMR with pentafluorobenzene as the internal standard (IS). The yields are the average of triplicates (see the SI file for the details). Isolated yields are in parenthesis. [a] Literature yield of **2e** is 34%. [b] Literature yield of **2f** is 41%. [c] Literature yield of **2g** is 55%. All literature yields were obtained after 11 W CFL bulb irradiation for 24 h.[8a]

Chen and co-workers proposed that the reaction proceeded via HAT between the excited-state of acetophenone and the unactivated C(sp^3)–H group of the substrate forming substrate radical. **SF®** fluorinates substrate radical producing radical dication of **SF®** which then undergoes HAT with catalyst derivative to form **H−TEDA(BF$_4$)$_2$**. We believed that the addition of **H−TEDA(BF$_4$)$_2$** in the beginning of this reaction would activate **SF®** by the way of aggregation thus accelerating the reaction to provide higher yields. In our hands, their standard conditions (1.0 eq. **SF®** and 5 mol% acetophenone), gave **2h** in a yield comparable (69%) to the literature (60%) (Scheme 10).[7b] Under the same conditions but with 2.0 eq. of **H−TEDA(BF$_4$)$_2$** additive, the yield of **2h** increased dramatically from 69% to 97%, once again proving the efficiency of our method (Scheme 10). The yield of the fluorinated adamantane (**2i**) increased from 51% to 71% as well.

For an insight into the reaction kinetics of the C-H fluorination reaction using acetophenone as a photocatalyst, the model reaction of **1h** without, and with different loadings of **H−TEDA(BF$_4$)$_2$**

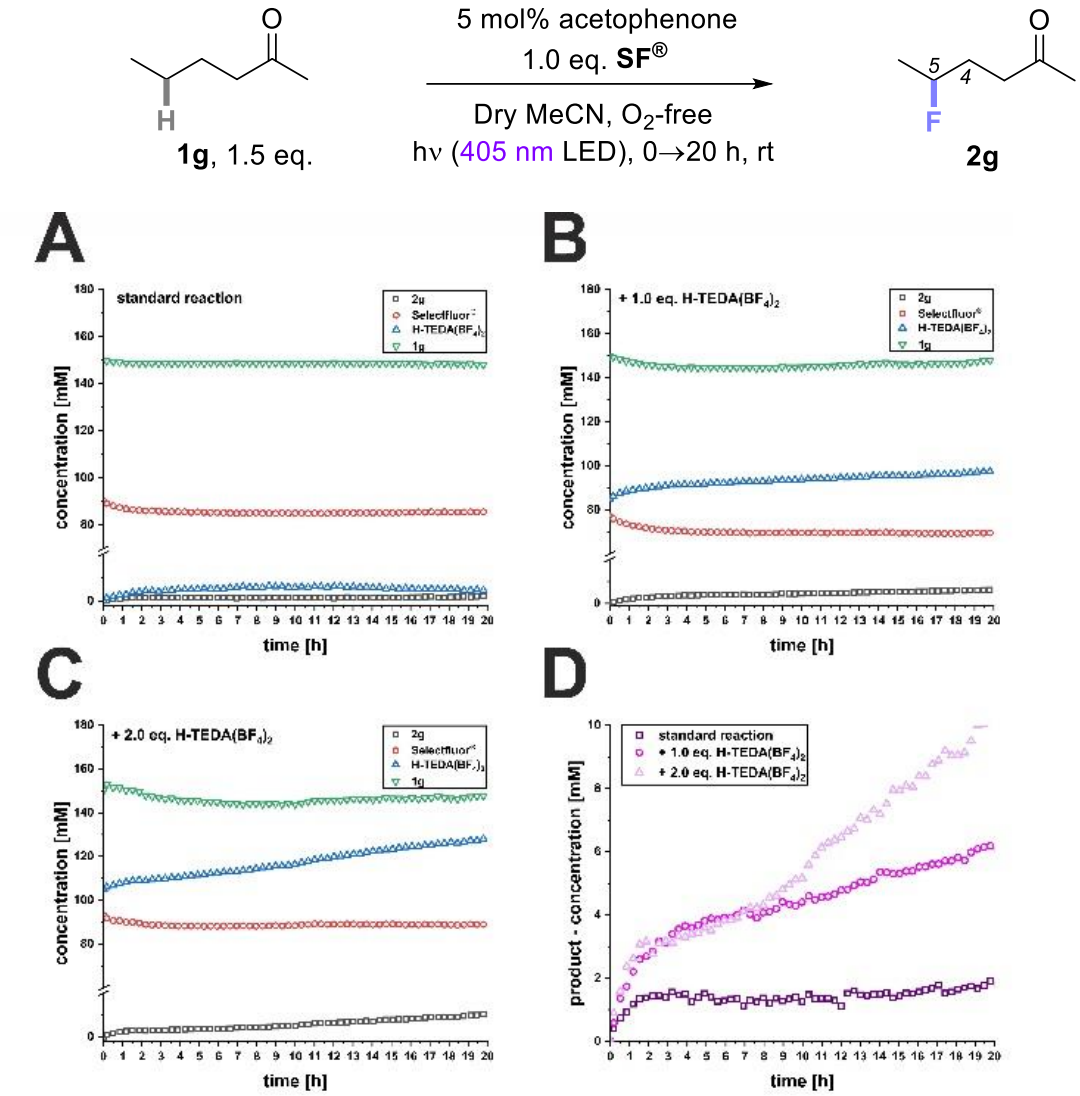
https://doi.org/10.26434/chemrxiv-2023-3t26g **ORCID:** https://orcid.org/0000-0003-1675-9399 Content not peer-reviewed by ChemRxiv. **License:** CC BY 4.0

was investigated (Scheme 11). While the standard reaction (without **H−TEDA(BF$_4$)$_2$**) shows product formation at a rate of 1.90 × 10^{-4} mM/s (Scheme 11, A), the product formation rate was doubled to 3.99 × 10^{-4} mM/s by addition of 1.0 eq. of **H−TEDA(BF$_4$)$_2$** (Scheme 11, B). An even higher product formation rate (4.42 × 10^{-4} mM/s) was obtained by addition of 2.0 eq. of **H−TEDA(BF$_4$)$_2$** (Scheme 11, C). Furthermore, in contrast to the standard reaction where only 1 mM of product is generated after 20 h of *in situ* illumination, 1.0 eq. and 2.0 eq. of **H−TEDA(BF$_4$)$_2$** loading increased the product formation up to 6 mM and 10 mM respectively (Scheme 11, D). When using 1.0 eq. and 2.0 eq. of **H−TEDA(BF$_4$)$_2$** loading, not only the induction period is cut, but also the later stages of the reaction are promoted in terms of rates. That means that the more nascent **H−TEDA(BF$_4$)$_2$** is generated, increasing the overall rate further. Moreover, one would expect that as the **H−TEDA(BF$_4$)$_2$** concentration is higher at the start, this would inhibit a radical chain mechanism as the substrate derived radical undergoes “back HAT" with the **H−TEDA(BF$_4$)$_2$** in competition with an F atom of **SF®**. Both steps generate the **TEDA$^{2+\bullet}$**, but the former also regenerates the starting material. Furthermore, the aggregation of **SF®** with **H−TEDA(BF$_4$)$_2$** should decrease its accessibility in a propagation step. Overall, the kinetics of the photocatalytic C(sp^3)−H fluorination reaction indicated that **H−TEDA(BF$_4$)$_2$** loading enhances the reaction rate, and this refutes a radical chain mechanism. Our conclusion is consistent with the fact that previous studies reported very low quantum yields <0.15 for such reactions.[8b,10]



Scheme 10. Promoted vs Unpromoted Photocatalytic Fluorinations of **1h** and **1i** with Acetophenone Catalyst. NMR yield is determined by ^{19}F NMR with pentafluorobenzene as the internal standard (IS). The yields are the average of triplicates (See the SI file for the details). [a] Literature yield of **2h** is 60% (under CFL-irradiation for 48 h).[7b]

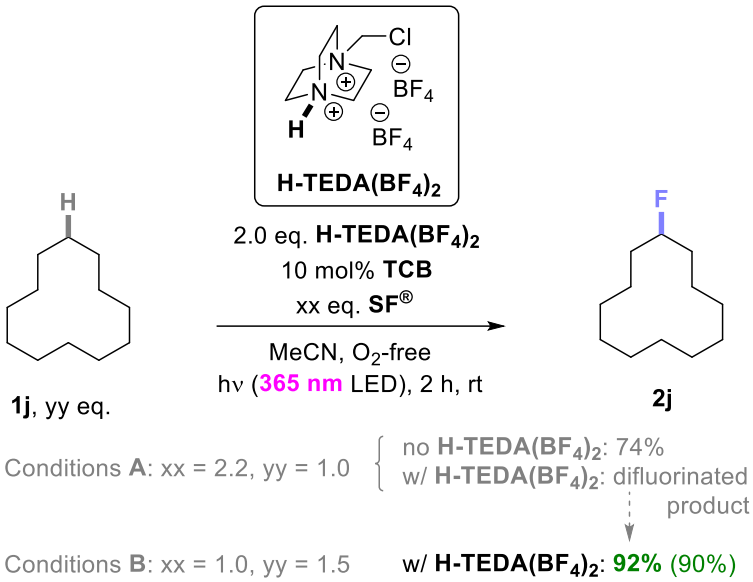
https://doi.org/10.26434/chemrxiv-2023-3t26g **ORCID:** https://orcid.org/0000-0003-1675-9399 Content not peer-reviewed by ChemRxiv. **License:** CC BY 4.0



Scheme 11. $^{19}F\{^{1}H\}$ *in situ* illumination NMR reaction monitoring of **H−TEDA(BF$_4$)$_2$**'s promotionary effect on the photocatalytic fluorination of **1g** with acetophenone catalyst. Kinetic profiles of the photocatalytic reaction under standard conditions (**A**), with 1.0 eq. (**B**) and 2.0 eq. (**C**) of **H−TEDA(BF$_4$)$_2$**. **D**) Detailed comparison of the reaction profiles of product formation with different equivalents of **H−TEDA(BF$_4$)$_2$**.

Lectka and co-workers discovered another fluorination method using 1,2,4,5-tetracyanobenzene (TCB) as a photosensitizer under UV-light.[9a] They demonstrated the utility of their method on a variety of substrates, from simple hydrocarbons to complex natural products in moderate to very good yields (45% - 77%). According to their proposed mechanism, the reaction undergoes via photosensitization of TCB followed by fluorination step. Although the authors were not able to trap any radical by TEMPO, they proposed formation of the substrate-derived radical from HAT with **TEDA$^{2+\bullet}$**. Their standard conditions (2.2 eq. **SF®** and 10 mol% TCB; 63% of **2j**),[9a] in our hands gave **2j** in a comparable yield of 74% (Scheme 12).

https://doi.org/10.26434/chemrxiv-2023-3t26g **ORCID:** https://orcid.org/0000-0003-1675-9399 Content not peer-reviewed by ChemRxiv. **License:** CC BY 4.0



Scheme 12. Promoted vs Unpromoted Photocatalytic Fluorination of **1j** with TCB Catalyst. NMR yield is determined by ^{19}F NMR with pentafluorobenzene as the internal standard (IS). The yields are the average of triplicates (See the SI file for the details). Isolated yield is in parenthesis. [a] Literature yield of **2j** is 63% (under 302 nm UV Lamp for 16 h).[9a]

However, with addition of 2.0 eq. of **H−TEDA(BF$_4$)$_2$**, we observed mainly difluorinated products of **1j**, due to the excess and high reactivity of **SF®** in the presence of **H−TEDA(BF$_4$)$_2$** (Scheme 12). We repeated this experiment with 1.0 eq. **SF®** (i.e. as the limiting reagent) and 2.0 eq. **H−TEDA(BF$_4$)$_2$** and obtained the product **2j** in 92% yield.

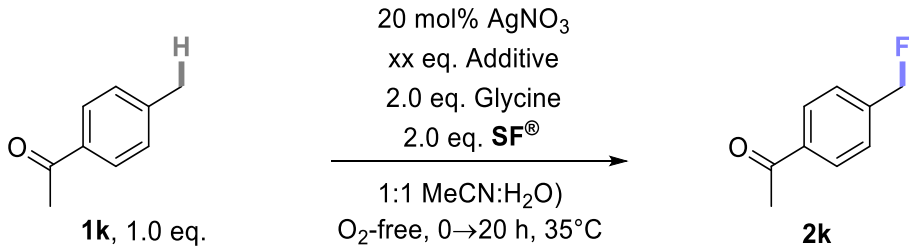
Case Study 3: Thermal C(sp^3)−H Radical Fluorinations

Having demonstrated the generality of **H−TEDA(BF$_4$)$_2$** as a promoter for photochemical fluorinations, we sought to assess its promotionary impact on thermal fluorination reactions. Baxter and co-workers reported a radical C(sp^3)−H fluorination method[11] using **SF®**, a catalytic amount of silver nitrate and an unprotected amino acid - glycine - as a radical precursor. Here, **SF®** serves both as a mild oxidant and as an electrophilic fluorine source. According to their mechanistic studies, Ag(I) is precoordinated by one or more glycines generating an electron-rich silver species that can undergo single-electron oxidation by **SF®**, resulting in formation of Ag(II), **TEDA$^{2+\bullet}$** and fluoride anion. Glycine undergoes rapid decarboxylation with Ag(II) regenerating Ag(I) and liberating an α-aminoalkyl radical. HAT between the α-aminoalkyl radical and a benzylic C-H bond generates a benzylic radical and methylamine. The benzylic radical then reacts with **SF®** to provide the desired fluorinated product. They also mentioned a possibility of chain radical process initiated by glycine that involves **TEDA$^{2+\bullet}$** as an active HAT agent. However, employing a catalytic amount of glycine produced only traces of the product, contradicting this possibility.

https://doi.org/10.26434/chemrxiv-2023-3t26g **ORCID:** https://orcid.org/0000-0003-1675-9399 Content not peer-reviewed by ChemRxiv. **License:** CC BY 4.0

Under their optimized conditions, Baxter and co-workers were able to achieve fluorination of variety of benzylic substrates in moderate to excellent yields (30 - 89%).[11] One substrate for which the method was inefficient was 4-methyl acetophenone (**1k**). The standard conditions - in our hands - provided only 8% of fluorinated product **2k** (Table 5, entry 1), and a catalytic quantity of **H−TEDA(BF$_4$)$_2$** (0.1 eq.) made no difference (entry 2). By adding 2.0 eq. of **H−TEDA(BF$_4$)$_2$** to the reaction mixture (entry 3), the yield of **2k** more than doubled (20%). Interestingly, presence of 2.0 eq. **H−TEDA(BF$_4$)$_2$** *in the absence of glycine* led to a 37% yield of **2k** (entry 3) which ~doubled to 66% with a longer reaction time of 48 h (entry 4). Increasing the loading of **H−TEDA(BF$_4$)$_2$** further to 6.0 eq. or 10.0 eq. increased the yield further, giving a clear trend both in the presence and absence of glycine (entries 5-9). Other Brønsted acidic additives with lower pK_as (Py−H·BF$_4$ and TFA, see SI file) halted reactivity in the presence of glycine (presumably deactivating glycine by protonation) but increased the yield in the absence of glycine (entries 10-11).

Table 5. Thermal Ag-catalyzed Fluorination of **1k** with Different Additives and Additive Loadings.



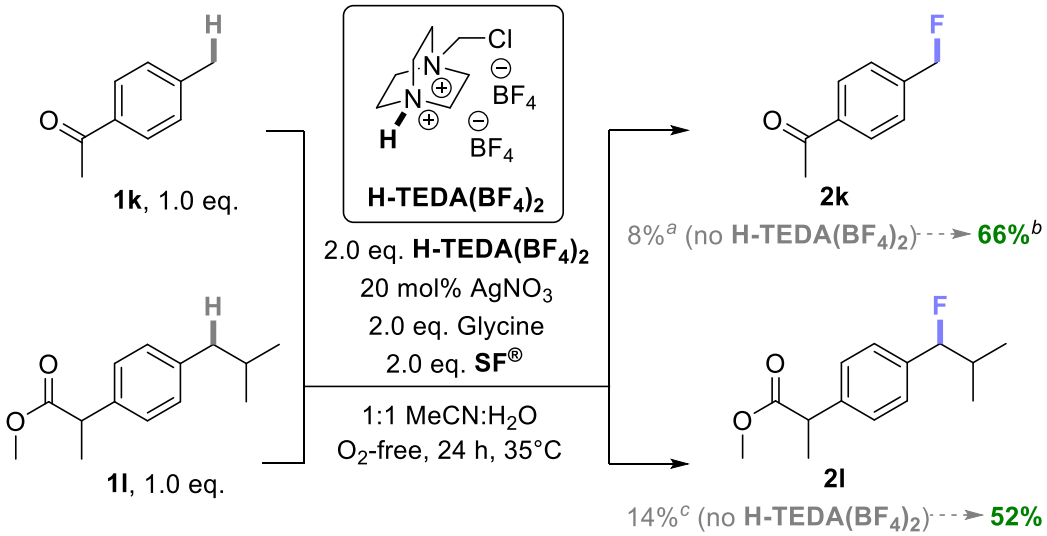
1k, 1.0 eq. **2k**

Entry	Additive / pK_a / eq.	NMR yield (%)
1	-[a]	8
2	**H−TEDA(BF$_4$)$_2$** / ~9 / 0.1	3
3	**H−TEDA(BF$_4$)$_2$** / ~9 / 2.0	20
4	**H−TEDA(BF$_4$)$_2$**[b] / ~9 / 2.0	37
5	**H−TEDA(BF$_4$)$_2$**[a,b] / ~9 / 2.0	66
6	**H−TEDA(BF$_4$)$_2$** / ~9 / 6.0	41
7	**H−TEDA(BF$_4$)$_2$**[a,b] / ~9 / 6.0	68
8	**H−TEDA(BF$_4$)$_2$** / ~9 / 10.0	58
9	**H−TEDA(BF$_4$)$_2$**[a,b] / ~9 / 10.0	77
10	Py−H·BF$_4$ / 3.4 / 2.0	Traces
11	Py−H·BF$_4$[b] / 3.4 / 2.0	18

[a] Reaction time 48 h. [b] Without glycine.

https://doi.org/10.26434/chemrxiv-2023-3t26g **ORCID:** https://orcid.org/0000-0003-1675-9399 Content not peer-reviewed by ChemRxiv. **License:** CC BY 4.0

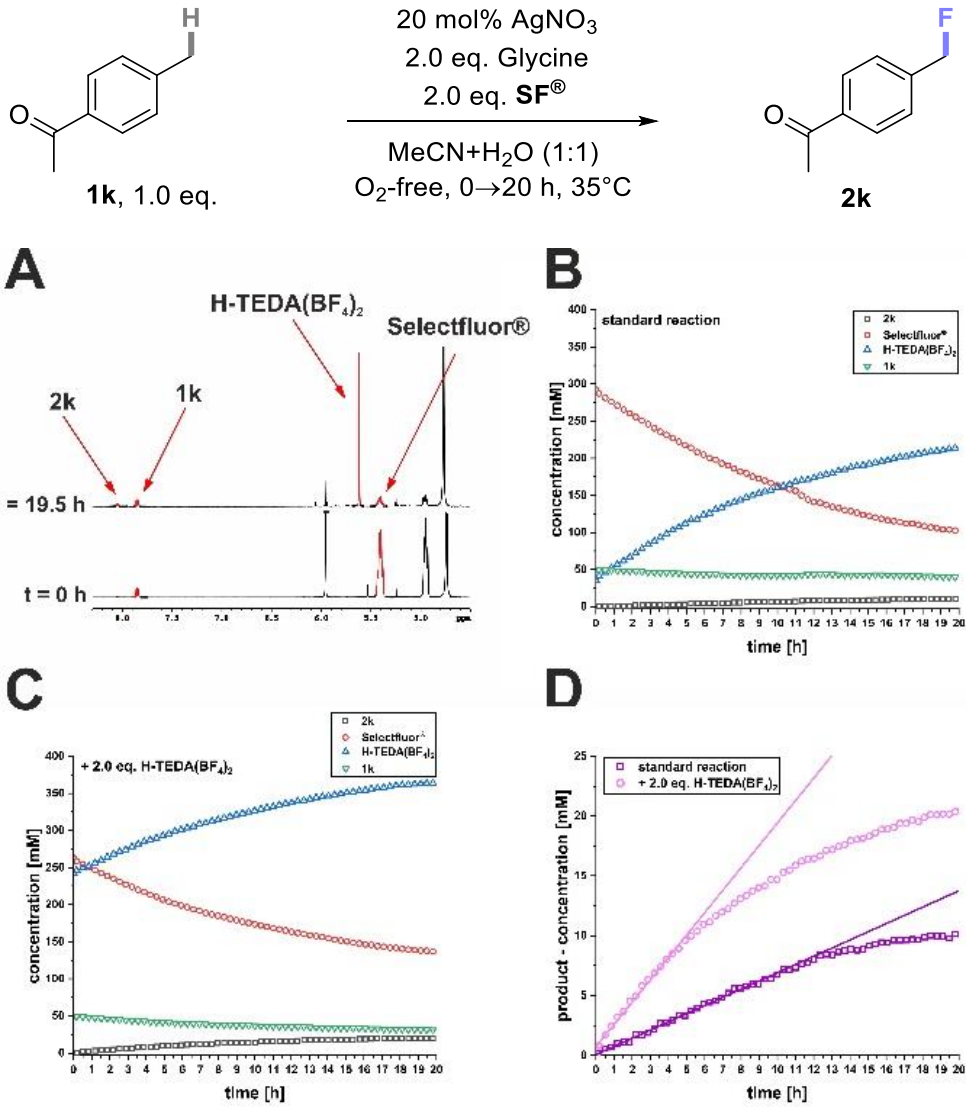
Elsewhere, Baxter and co-workers fluorinated the more electron-rich benzylic position of ibuprofen methyl ester (**1l**),[11] using 5.0 eq. of both glycine and **SF®** for this particular substrate (46% literature yield of **2l**).[11] In our hands, when using 2.0 eq. of both glycine and **SF®**, only 14% of **2l** was obtained (Scheme 13). By adding 2.0 eq. of **H−TEDA(BF$_4$)$_2$** to the reaction, the yield of **2l** increased to 54%. In summary, addition of the **H−TEDA(BF$_4$)$_2$** promoter provided an even higher yield than the literature and allowed us to employ far less (2.5×) **SF®** and glycine. Since **SF®** is substantially more expensive to prepare than **H−TEDA(BF$_4$)$_2$**, this demonstrates the cost and sustainability benefits of our discovery.



Scheme 13. Promoted vs Unpromoted Thermal Ag-catalyzed fluorinations of **1k** and **1l**. NMR yields were determined by ^{19}F NMR with pentafluorobenzene as the internal standard (I.S.). The yields are the average of triplicates (see the SI file for the details). [a] Literature yield of 2k is 30%.[11] [b] 2.0 eq. H-TEDA(BF$_4$)$_2$ without glycine after 48 h. [c] Literature yield of 2l is 46% (5.0 eq. SF® and Glycine, instead of 2.0 eq.).[11]

To explore further the promotionary effect of **H−TEDA(BF$_4$)$_2$** on thermal radical fluorinations, the reaction kinetics of a model reaction with and without **H−TEDA(BF$_4$)$_2$** were followed by *in situ* monitoring within a variable temperature NMR probe (Scheme 14). The result of the standard reaction conditions (without **H−TEDA(BF$_4$)$_2$**) revealed that approximately 10 mM product is generated after 19.5 h of irradiation (Scheme 14, B) while in the presence of 2.0 eq. of **H−TEDA(BF$_4$)$_2$** approximately 20 mM product is generated after the same time period (Scheme 14, C). Calculated initial rates revealed that 2.0 eq. of **H−TEDA(BF$_4$)$_2$** loading increased the product formation rate by a factor of 3 (from 0.7 to 2.1) (Scheme 14, D). So, not only the initial rate of the reaction was faster in the presence of **H−TEDA(BF$_4$)$_2$**, the final yield upon which the reaction converged was almost doubled.

https://doi.org/10.26434/chemrxiv-2023-3t26g **ORCID:** https://orcid.org/0000-0003-1675-9399 Content not peer-reviewed by ChemRxiv. **License:** CC BY 4.0



Scheme 14. $^{19}F\{^{1}H\}$ *in situ* illumination NMR reaction monitoring of **H−TEDA(BF$_4$)$_2$**'s promotionary effect. (A) ^{1}H spectra of the standard reaction before (t = 0 h) and after illumination for 19.5 h. The integrated and plotted signal regions for each compound is highlighted in red. (B) Kinetic profile of the standard reaction (without **H−TEDA(BF$_4$)$_2$**). (C) Kinetic profile of the standard reaction with 2.0 eq. of **H−TEDA(BF$_4$)$_2$**. (D) Detailed comparison of the product build-up curves for the standard reaction without and with 2.0 eq. of **H−TEDA(BF$_4$)$_2$**.

Conclusion

In conclusion, we report the discovery of **H−TEDA(BF$_4$)$_2$** as a highly efficient, cheap, performance-enhancing additive repurposed from chemical waste that increases the rates and final reaction yields for various direct C(sp^3)−H fluorination reactions, including those under photochemical and thermal conditions. When employing the additive, reaction yields were increased as much as triple, and the duration of reactions could be shortened as dramatically as from 48 h to 2 h. This study also highlights an overlooked but increasingly important mechanistic aspect of reagent aggregation in radical reactions. In this case SelectFluor®'s aggregation state profoundly influences various radical fluorination reactions, and may well be - beyond temperature, catalyst, or light intensity - the *key* reactivity-determining influence.

https://doi.org/10.26434/chemrxiv-2023-3t26g **ORCID:** https://orcid.org/0000-0003-1675-9399 Content not peer-reviewed by ChemRxiv. **License:** CC BY 4.0

Thorough DOSY investigations of **SF®** and **H−TEDA(BF$_4$)$_2$** we confirmed enhanced aggregation of both components by increased **H−TEDA(BF$_4$)$_2$** concentrations. **H−TEDA(BF$_4$)$_2$** loading thereby enhances the formation of intermolecular interactions resulting in the activation of **SF®**. 2D NMR experiments confirmed the formation of **H−TEDA(BF$_4$)$_2$** / **SF®** complexes where NOE contacts between cations of **SF®** and **H−TEDA(BF$_4$)$_2$** could be detected. Finally - showing the generality of the phenomenon - other Brønsted acidic additives can also serve as promoters, although **H−TEDA(BF$_4$)$_2$** is the most robust. Additives with a pK_a ~9 are most suitable for the majority of reaction case studies.

Acknowledgements

S. Y. and J. P. B. thank the Alexander von Humboldt Foundation for funding, provided within the framework of the Sofja Kovalevskaja Award endowed by the German Federal Ministry of Education and Research. S. Y. is grateful for funding provided by the SynCat programme of the Elite Network of Bavaria. R. M. G. and W. J. S. acknowledge financial support by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) - GS 13.4-2 – Organokatalyse II. S. Y., R. M. G. and J. P. B. are members of RTG 2620 ‘Ion Pair Effects in Molecular Reactivity (426795949). R. M. G. and J. P. B. are members of DFG TRR 325 ‘Assembly Controlled Chemical Photocatalysis’ (444632635). We thank other members of the RTG and TRR for helpful discussions.

Conflict of Interest

A provisional patent has been filed by the authors based on part on this work:
EP 23 205 559 0.

Keywords: fluorination • aggregation • radical reactions • photocatalysis • protodefluorinated Selectfluor®

References

1. (a) J. Mei, N. L. Leung, R. T. Kwok, J. W. Lam, B. Z. Tang, *Chem. Rev.* **2015**, *115*, 11718; (b) G. B. Bodedla, X. Zhu, W.-Y. Wong, *Aggregate* **2023**, *4*, e330; Y. Hong, J. W. Y. Lam, B. Z. Tang, *Chem. Soc. Rev.* **2011**, *40*, 5361; (c) H. Zhang, Z. Zhao, A. T. Turley, L. Wang, P. R. McGonigal, Y. Tu, Y. Li, Z. Wang, R. T. K. Kwok, J. W. Y. Lam, B. Z. Tang, *Adv. Mater*. **2020**, *32*, 2001457.
2. (a) G. E. M. Crisenza, D. Mazzarella, P. Melchiorre, *J. Am. Chem. Soc.* **2020**, *142*, 5461; (b) A. Bhattacharyya, S. De Sarkar, A. Das, *ACS Catal.* **2021**, *11*, 710; (c) Y. Sempere, M. Morgenstern, T. Bach, M. Plaza, *Photochem. Photobiol. Sci.* **2022**, *21*, 719; (d) M. J. P. Mandigma, J. Kaur, J. P. Barham, *ChemCatChem* **2023**, *15*, e202201542.
3. (a) M. Shimizu, T. Hiyama, *Angew. Chem., Int. Ed.* **2005**, *44*, 214; (b) E. Lee, A. S. Kamlet, D. C. Powers, C. N. Neumann, G. B. Boursalian, T. Furuya, D. C. Choi, J. M. Hooker, T. Ritter, *Science* **2011**, *334*, 639;

https://doi.org/10.26434/chemrxiv-2023-3t26g **ORCID:** https://orcid.org/0000-0003-1675-9399 Content not peer-reviewed by ChemRxiv. **License:** CC BY 4.0

(c) C. Hollingworth, V. Gouverneur, *Chem. Commun.* **2012**, *48*, 2929; (d) T. Liang, C. N. Neumann, T. Ritter, *Angew. Chem., Int. Ed.* **2013**, *52*, 8214; (e) M. G. Campbell, T. Ritter, *Chem. Rev.* **2015**, *115*, 612.

4. (a) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320; (b) R. Filler, R. Saha, *Future Med. Chem.* **2009**, *1*, 777; (c) D. O'Hagan, *J. Fluor. Chem.* **2010**, *131*, 1071; (d) H. Mei, J. Han, S. Fustero, M. Medio-Simon, D. M. Sedgwick, C. Santi, R. Ruzziconi, V. A. Soloshonok, *Chem. – Eur. J.* **2019**, *25*, 11797.
5. (a) P. Maienfisch, R. G. Hall, *Chimia* **2004**, *58*, 93; (b) M. Hird, *Chem. Soc. Rev.* **2007**, *36*, 2070; (c) R. Berger, G. Resnati, P. Metrangolo, E. Weber, J. Hulliger, *Chem. Soc. Rev.* **2011**, *40*, 3496.
6. (a) B. Lantaño, A. Postigo, *Org. Biomol. Chem.* **2017**, *15*, 9954; (b) S. Yakubov, J. P. Barham, *Beilstein J. Org. Chem.* **2020**, *16*, 2151.
7. (a) J. B. Xia, C. Zhu, C. Chen, *J. Am. Chem. Soc.* **2013**, *135*, 17494; (b) J. B. Xia, C. Zhu, C. Chen, *Chem. Commun.* **2014**, *50*, 11701.
8. (a) C. W. Kee, K. F. Chin, M. W. Wong, C. H. Tan, *Chem. Commun.* **2014**, *50*, 8211; (b) J. W. Kee, H. Shao, C. W. Kee, Y. Lu, H. S. Soo, C. H. Tan, *Catal. Sci. Technol.* **2017**, *7*, 848.
9. (a) S. Bloom, J. L. Knippel, T. Lectka, *Chem. Sci.* **2014**, *5*, 1175; (b) S. Bloom, M. McCann, T. Lectka, *Org. Lett.* **2014**, *16*, 6338; (c) D. D. Bume, C. R. Pitts, F. Ghorbani, S. A. Harry, J. N. Capilato, M. A. Siegler, T. Lectka, *Chem. Sci.* **2017**, *8*, 6918.
10. S. Yakubov, W. J. Stockerl, X. Tian, A. Shahin, M. J. P. Mandigma, R. M. Gschwind, J. P. Barham, *Chem. Sci.* **2022**, *13*, 14041.
11. A. M. Hua, D. N. Mai, R. Martinez, R. D. Baxter, *Org. Lett.* **2017**, *19*, 2949.
12. Y. Amaoka, M. Nagatomo, M. Inoue, *Org. Lett.* **2013**, *15*, 2160.
13. H. Egami, S. Masuda, Y. Kawato, Y. Hamashima, *Org. Lett.* **2018**, *20*, 1367.
14. (a) F. J. A. Troyano, K. Merkens, A. Gómez-Suárez, *Asian J. Org. Chem.* **2020**, *9*, 992; (b) D. E. Yerien, S. Bonesi, A. Postigo, *Org. Biomol. Chem.* **2016**, *14*, 8398.
15. University of Manchester, The development of Selectfluor® as a commercial electrophilic fluorinating agent. *Research Excellence Framework 2014 Impact Case Studies*. REF3b. https://impact.ref.ac.uk/casestudies/CaseStudy.aspx?Id=28087 (accessed 29.10.2023)
16. Previous examples of photochemical reaction kinetics using an on-line NMR irradiation experiment in an NMR tube: (a) S. Wang, N. Lokesh, J. Hioe, R. M. Gschwind, B. König, *Chem. Sci.* **2019**, *10*, 4580; (b) C. Feldmeier, H. Bartling, E. Riedle, R. M. Gschwind, *J. Magn. Reson.* **2013**, *232*, 39; (c) K. Chen, N. Berg, R. Gschwind, B. König, *J. Am. Chem. Soc.* **2017**, *139*, 18444; (d) H. Bartling, A. Eisenhofer, B. König, R. M. Gschwind, *J. Am. Chem. Soc.* **2016**, *138*, 11860.
17. M. R. Crampton, I. A. Robotham, *J. Chem. Res.* **1997**, 22.
18. W. N. Olmstead, Z. Margolin, F. G. Bordwell, *J. Org. Chem.* **1980**, *45*, 3295.
19. Y. Chu, H. Deng, J. P. Cheng, *J. Org. Chem.* **2007**, *72*, 7790.
20. F. G. Bordwell, R. J. McCallum, W. N. Olmstead, *J. Org. Chem.* **1984**, *49*, 1424.
21. G. I. Almerindo, D. W. Tondo, J. R. Pliego, *J. Phys. Chem. A* **2004**, *108*, 166.
22. F. G. Bordwell, *Acc. Chem. Res.* **1988**, *21*, 456-463.
23. Y. M. Wang, J. Wu, C. Hoong, V. Rauniyar, F. D. Toste, *J. Am. Chem. Soc.* **2012**, *134*, 12928.

https://doi.org/10.26434/chemrxiv-2023-3t26g **ORCID:** https://orcid.org/0000-0003-1675-9399 Content not peer-reviewed by ChemRxiv. **License:** CC BY 4.0