Catalyst-free photochemical fluorination of C-H bonds of aromatic carbonyl compounds

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ABSTRACT: A wide range of organic molecules can participate in hydrogen atom transfer (HAT) processes as both HAT-donors and photo-HAT-acceptors simultaneously. Therefore, it opens the possibilities to exclude catalysts for C-H functionalization in such cases. This is the underlying idea of the presented catalyst-free C-H bond fluorination approach. We demonstrated that broad range of aryl alkyl ketones can be efficiently fluorinated with Selectfluor-based reagents at benzylic position under UV-A irradiation without any added catalyst. The selectivity of mono- and difluorination can be controlled by controlling the excess of fluorinating reagent. Additionally, we propose an analog of Selectfluor reagent - F-TEDA-TFSI with much greater solubility in acetonitrile which makes our protocol solvent-economical. By the same manner benzaldehydes can be transformed to corresponding benzoyl fluorides with almost quantitative yields. The protocol was successfully applied in late-stage fluorination of complex molecules Tonalide and Tolperisone. Kinetic measurements demonstrated zero-order kinetics which indicates that light flux is the limiting factor. A tentative mechanism was proposed based on the selectivity of fluorination of primary, secondary, and tertiary benzylic C-H bonds.

Organofluorine chemistry has a wide range of applications in various fields, including pharmaceuticals, agrochemicals, and materials science. For example, fluorine-containing compounds are often used in pharmaceuticals due to their ability to increase drug efficacy and improve pharmacokinetic properties (~20% of FDA-approved pharmaceuticals).[1] In the agrochemical industry, organofluorine compounds are used as pesticides and herbicides owing to their high stability and reactivity (~25% of licensed agrochemicals).[2] High thermal and chemical stability of fluorinated organic materials make them ideal for use in electronic devices, such as OLEDs and solar cells.[3] Additionally, C-F bond activation is a valuable strategy in organic synthesis.[4] Overall, the unique properties of organofluorine compounds make the development of fluorination strategies an important subject of research and development. Numerous approaches to C-F bond formation have been developed. The most common are: deoxofluorination, electrophilic fluorination, Schiemann reaction and nucleophilic fluorination using fluoride sources.[5] Classical functional group transformations have obvious limitation: the need in preliminary functionalization of substrates.

One area of interest is the direct fluorination of C-H bonds. This approach allows introducing fluorine into molecules in step-economical manner without the need for preliminary functionalization, which is advantageous for late-stage diversification of target compounds. Several works have been published on the fluorination of unactivated aliphatic C-H bonds (Figure 1a). Among them were organocatalytic, transition metal (TM)-catalyzed (photochemical or thermal) or using radical initiators.[6] The "ionic" selectivity was reported; the fluorination takes place as far as possible from electronegative fragment. Benzylic and aldehyde C-H bond fluorination is more selective, since BDE of C-H bonds is lowered and radicals formed are more nucleophilic (Figure 1 b, c).[7,8] Lectka group made breakthrough research in the field of directed fluorination (Figure 1d).[9] They hypothesized that oxygen-containing groups coordinate F-TEDA-BF_4 (SelectFluor, SF); thereby, directing fluorination to the β- or γ-positions. Despite broad synthetic utility, catalytic approaches have some drawbacks: the requirements for additional catalysts and additives and often longer reaction times.

Catalyst-free synthesis is a promising area of research in organic chemistry.[10] By eliminating the need for expensive and potentially toxic catalysts, this approach can lead to more cost-effective and environmentally friendly processes. In 2017 Lectka Group have published enone-directed diastereoselective C-H fluorination (Figure 1e).[11] They used SF as fluorinating agent. This strategy was successfully applied to complex polycyclic terpenoid enones. Enone group was not only directing group, but also it was photosensitizating fragment. So, the same group performed beautiful fluorination approach without adding external catalysts. Later, Hamashima group published a catalyst-free approach to C-H bond fluorination of N-alkylphthalimides as photosensitizating auxilary (PSaux) using SF as fluorine source (Figure 1e).[12] This synthetic strategy is highly advantageous, since phthalimides are classical precursors to primary amines. In 2022 the same group published strategy, utilizing benzoyl group as PSaux in combination with SF, allowing catalyst-free fluorination.[13]

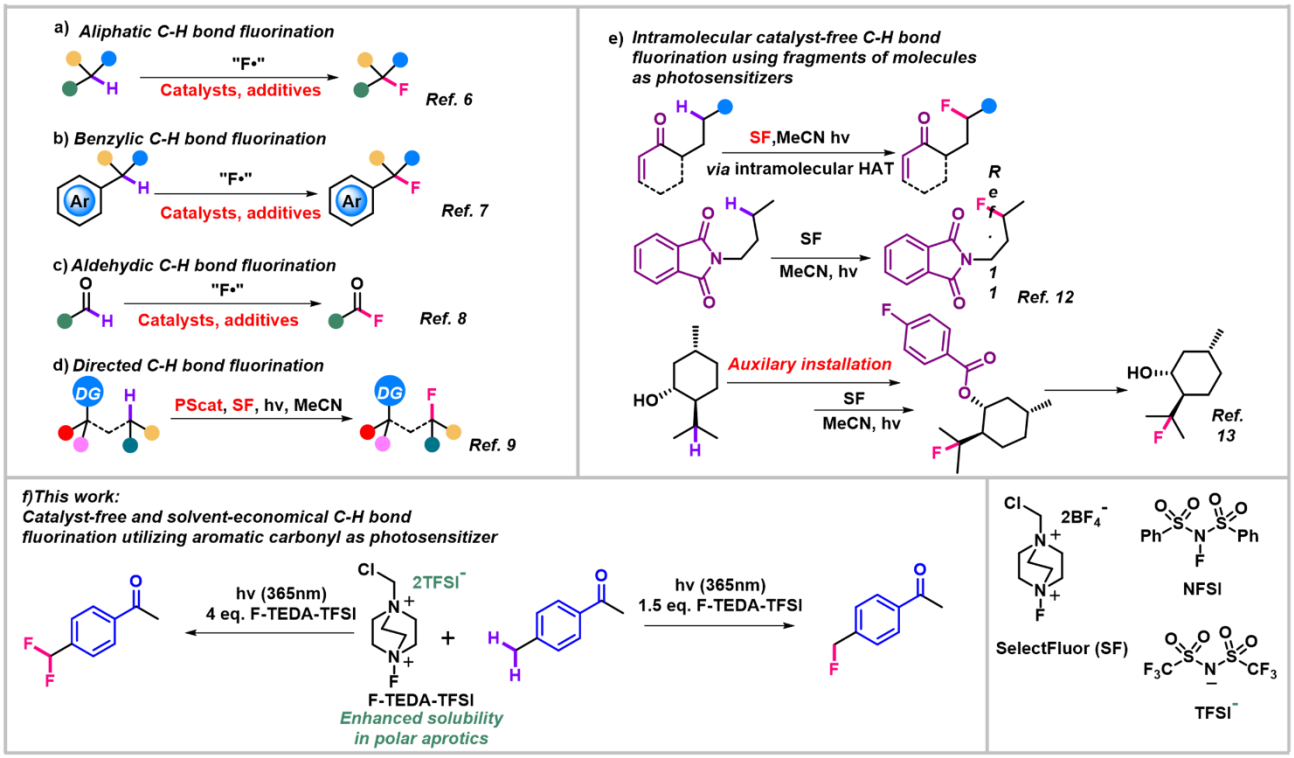


Figure 1. Approaches to C-H bond fluorination.

This is a great approach to fluorinated amines and alcohols. Amines without protecting groups are oxidized by SF, so the installation of benzoyl is not an additional step, but in case of alcohols installation of PSaux is a drawback. These PSaux-promoted fluorinations run faster than catalytic analogs. However, moderate solubility of SF in MeCN limits the scaling up due to use the large amount of solvent.

Aromatic carbonyls are a common motif in organic synthesis. They include building blocks, biologically active compounds and pharmaceuticals (Figure 2).[14] The Ar-(CO)-fragment is widely used in various formal hydrogen atom transfer (HAT) reactions.[15] Thus, we proposed that these compounds can undergo hydrogen abstraction reactions without an addition of catalysts. In this work we aimed to develop an approach to catalyst-free fluorination of substrates simultaneously bearing a photoactive carbonyl group and a weak C-H bond suitable for radical fluorination.

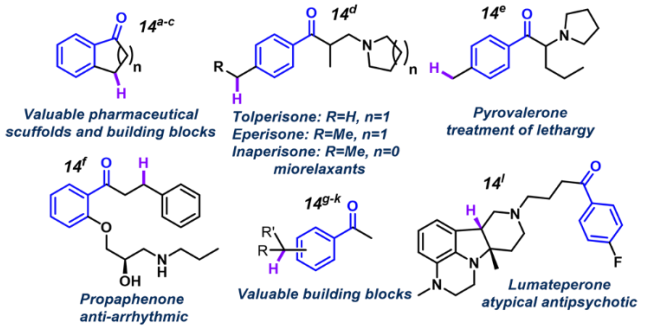
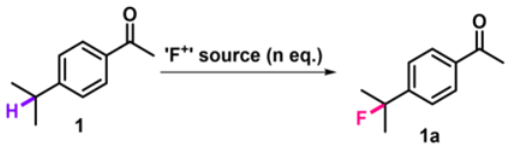


Figure 2. Benzylic C-H bond in aromatic carbonyl compounds suitable for functionalization.

Table 1. Optimization of reaction conditions.



Entry	F+ source	F+ eq.	n(F+)/V(MeCN), mmol/ml	time	yield
1	NFSI	2 eq.	1	4h	trace
2	SF	1.5 eq.	0.1	4h	41
3	SF	2 eq.	0.1	4h	47
4	SF	2.5 eq.	0.1	4h	53
5	SF	3 eq.	0.1	4h	55
6	F-TEDA-TFSI	1.5 eq.	1	2h	87
7	F-TEDA-TFSI	2 eq.	1	2h	94
8	F-TEDA-TFSI	2.5 eq.	1	2h	91
9	F-TEDA-TFSI	2.5 eq.	1	2h	92
10	F-TEDA-TFSI	3 eq.	1	2h	92

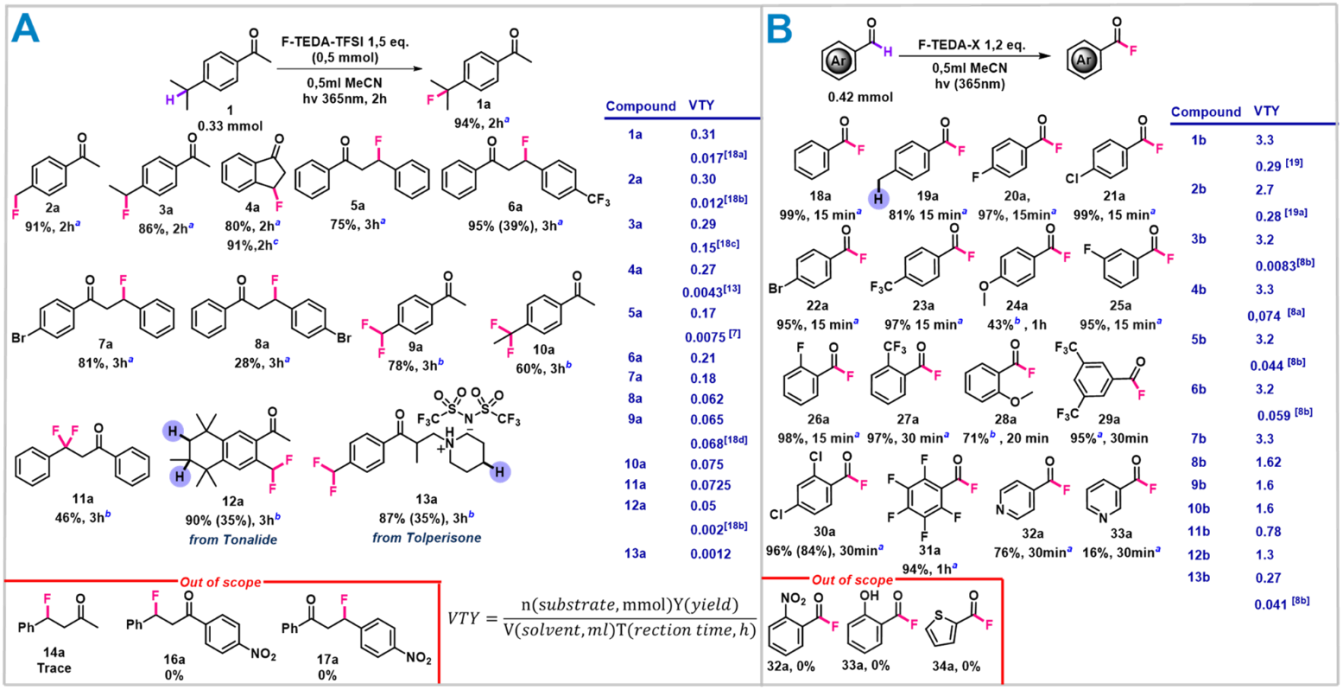


Figure 3. Substrate scope: A – aromatic ketones; B – aromatic aldehydes. NMR yields are reported, isolated yields are given in brackets. **A:** [a]0.75 ml MeCN, 0.5 mmol substrate and 556 mg (0.75 mmol, 1.5 eq.) F-TEDA-TFSI, the reaction mixture was irradiated in a photoreactor for 2-3 hours. [b]0.188 mmol of substrate and 556 mg (0.75 mmol, 4 eq.) of F-TEDA-TFSI, the reaction mixture was irradiated in a photoreactor for 3 hours. [c]performed analogously, 0.25 mmol of substrate (3 eq. of F-TEDA-TFSI); **B:** [a]0.75 ml MeCN, 0.625 mmol substrate and 556 mg (0.75 mmol, 1.2 eq.) F-TEDA-TFSI, the reaction mixture was irradiated in a photoreactor for 15-60 min. [b]4 ml MeCN, 141.7 mg (0.4 mmol) SelectFluor (SF) and 0.33 mmol aldehyde, the reaction mixture was irradiated for 1 hour.

We began our investigations by optimizing the fluorination of 4-isopropylacetophenone **1** with common fluorinating reagents N-fluorobenzenesulfonimide (NFSI) and Selectfluor (SF) under the UV-A (365 nm) irradiation from black-light bulb (BLB) (Table 1).

We started from NFSI reagent, since it was successfully utilized in decatungstate-catalyzed benzylic fluorination.[7b] Surprisingly, NFSI reagent was found to be completely ineffective, and no fluorination products was observed. The reaction between **1** and 1,5 equivalents of SF produced reasonable yield of compound **1a**. The increase of SF loadings had only a little effect on product yield, but the stoichiometry variation was very limited due to moderate solubility of SF in MeCN.

To overcome the solubility limitations, we prepared a Selectfluor analogue by the anion exchange from BF_4^- to trifluoromethylsulfonimide (TFSI). The new reagent obtained (F-TEDA-TFSI) has tremendously higher solubility in MeCN, as 1 ml of MeCN can dissolve 1 mmol of F-TEDA-TFSI. The use of F-TEDA-TFSI led to higher yields and shorter reaction times. Also, the volume of solvent was reduced, which made it easier to scale up the reaction.

High conversions were achieved even with 1.2-2.5 eq. of F-TEDA-TFSI, giving almost quantitative yields. 1.5 mol excess was shown to be optimal balance between F-TEDA-TFSI loadings and yield.

Using optimized conditions, we proceeded to explore substrate tolerance. 4-Alkylacetophenones gave monofluorides **2a** and **3a** in high yields (Figure 3). Then we tried fluorination of indanone, a precursor of rasagiline and a valuable moiety in medicinal chemistry.[14b,16] Fluorination of indanone gave corresponding monofluoride **4a** in 80% yield.

The decreased reactivity of indanone can be attributed to the higher stress in the planar radical of the 5-membered ring. Dihydrochalcones (DHC) have a number of interesting biological properties.[17] We have successfully applied these conditions to fluorination of substituted DHC. Compounds **5a** and **7a** were obtained in high yields. Compound **6a** was formed almost quantitatively (Figure 3). This can be explained by the fact that the trifluoromethyl group deactivates the benzylic radical, preventing the formation of impurity difluoride. In contrast, fluorination of bromo-substituted DHC **8** to corresponding **8a** resulting in 28% yield.

Tonalide turned out to be very reactive: it was impossible to obtain monofluoride selectively, a significant amount of difluoride was formed. This reactivity can be explained by intramolecular [1,5]-HAT. This example shows high tolerance towards aliphatic C-H bonds. By increasing the number of equivalents of the fluorinating reagent, the difluoride **12a** was obtained selectively (Figure 3). Then we applied these conditions to obtain several benzylidene difluorides.

Compound **13a,** obtained by late-stage C-H bond fluorination of TFSI salt of tolperisone, is another representative example. No fluorination in piperidine cycle have been observed. TFSI salt of Tolperisone was used to protect of amine fragment from oxidation.

To evaluate the efficiency of the presented approach and compare it with similar protocols of benzylic fluorination published in literature, we introduced and calculated the Volume Time Yield (VTY) metric for selected products (Figure 3).[18]

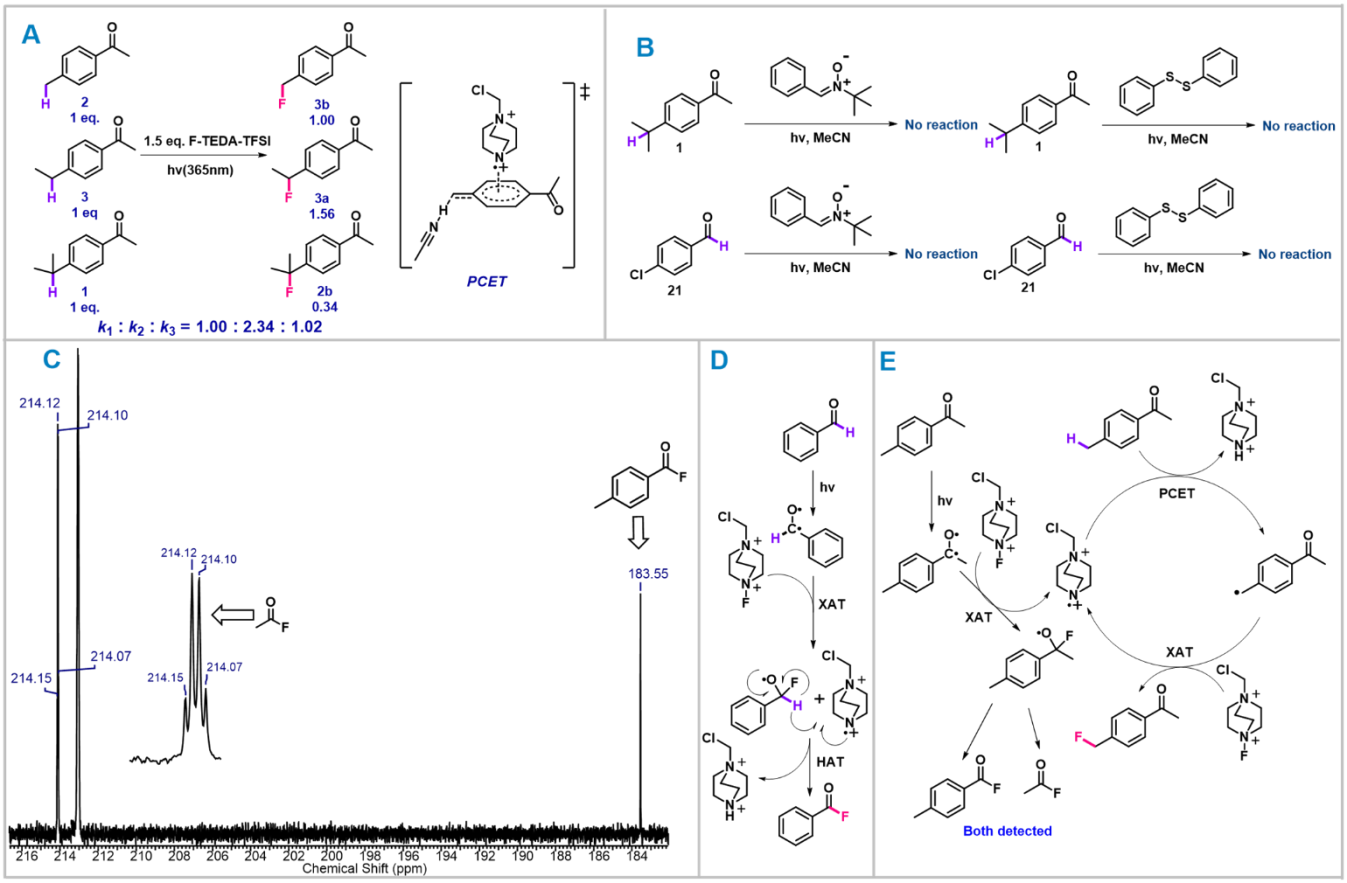


Figure 4. Mechanism elucidation: A – competitive kinetics; B – Spin trapping experiments; C – presence of acid fluorides in crude rection mixture of compound **2** fluorination (C_6F_6 is an internal standard); D – proposed mechanism for aldehyde fluorination; E – proposed mechanism of benzylic fluorination.

The introduced metric reflects the specific efficiency of the particular protocol equal to molar amount of product that may be obtained from the unit of solvent per hour. See SI for more detailed comparison.

Fluorination of benzylacetone was unsuccessful and only traces of monofluorinated product **14a** were observed under standard conditions.

The reason was probably the lower extinction of dialkylketone fragment to initiate reaction with appreciable rate. By the way, under much longer irradiation time (40h) the corresponding product formed with moderate conversion. Introduction of nitro-group inhibits fluorination, no **16a** or **17a** were observed.

Aromatic aldehydes possess a similar π-system and aldehyde C-H bond with low BDE. Following this synthetic logic, we decided to carry out the transformation of benzaldehydes into corresponding benzoyl fluorides. The reaction proceeds almost quantitively and much faster (mostly in 15-30 min) and requires less fluorinating reagent (1,2 eq.) (Figure 3).

Fluorination of compound **19a** demonstrated higher selectivity towards aldehyde than benzylic C-H bonds. p-Methoxybenzaldehyde gave higher yields of **24a** when SF was used rather than F-TEDA-TFSI due to competitive thermal electrophilic fluorination in aromatic core at higher concentrations of the reaction solution. Analogous reaction using sodium decatungstate (NaDT) as external photocatalyst is less effective and takes longer times.[7b] o-Methoxybenzaldehyde gives a higher yield of compound **28a**.The conversion efficiency did not depend on the presence of heavy atoms, weak π-donor or strong σ-acceptor substituents and decreases if the benzene ring is replaced by a pyridine ring: in the case of compound **32a** the yield achieved is 76%, while for **33a** the yield is only 16%.

Nitro-substituted benzaldehyde is out of scope, presumably for the same reasons as nitro-substituted DHC. The hydroxy group in the benzene ring blocks fluorination, presumably due to oxidation to an intensely absorbing phenoxy radical.

Kinetic measurements showed that up to 70% conversion, the benzylic fluorination reaction has zero order (SI). Further, the rate decreases, probably due to decrease in the efficiency of UV absorption by the reactive chromophore because of accumulation of highly absorbing polymeric impurities. The reaction does not proceed in the absence of light in appreciable amounts. Zero-order kinetics indicates that excitation is the limiting factor; therefore, the formation of reactive excited triplet carbonyl is a crucial step.

Difference between experiments with NFSI and SF indicates that fluorinating reagent somehow takes part in initiation or first propagation steps of reaction.

To shed light to the mechanism of fluorination we performed competitive kinetics experiments of fluorination of primary, secondary and tertiary C-H bonds of isoelectronic acetophenones (Figure 4A). We obtained the following ratio

between constants $k_1 : k_2 : k_3 = 1.00 : 2.34 : 1.02$. This ratio is not typical for the hydrogen atom transfer (HAT) mechanism, in which the ratio of rate constants $k_1 < k_2 < k_3$ is strictly fulfilled and dictated by the relative BDE values. The obtained distribution is characteristic for various electron transfer reaction, particularly proton-conjugate electron transfer (PCET) reactions.[20] PCET mechanism also provides explanation of high efficiency of the transformation in the presence of EWG groups, as in the case of compound **6a**, since in the case of PCET the increase in the acidity of the abstracted proton may lower the activation energy.

In the absence of the fluorinating agent, substrates did not react with spin traps under the reaction conditions (Figure 4B). Thus, the fluorinating agent is directly involved in the initiation of the reaction.

For a similar system in which benzyl was the photoinitiator, Lectka group proposed a mechanism of initiation of C-H fluorination consisting in the transfer of a fluorine atom from SF to an excited benzyl molecule.[11b] We can assume that a similar mechanism of initiation is observed in our process: the excited carbonyl triplet is fluorinated with SF or F-TEDA-TFSI with the formation of alpha-fluoroalkoxyl radical. This hypothesis is supported by the presence of acyl fluorides in trace amounts in the reaction mixture during fluorination of aromatic ketones (Figure 4C). Also, this hypothesis is consistent with the high increase in the reaction rate in the case of benzaldehydes: in such a case, the reaction may proceed in a solvent cage, unlike in the case of ketones.

Thus, we can formulate the tentative mechanism of these transformations (Figure 4D,E). For both types of substrates, the reaction starts with photoexcitation of the aromatic carbonyl compound followed by the fluorine atom transfer (XAT) to the excited triplet, with the generation of the $NR_3^{+\cdot}$ Selectfluor radical dication (SRD) (Figure 4D). In case of aldehydes, subsequent hydrogen transfer from the substrate to the SRD (HAT) leads to the product (Figure 4E). In the case of ketones, the formed SRD performs a formal hydrogen atom transfer reaction by the proton-conjugated hydrogen transfer (PCET) mechanism to form a benzyl radical. The benzyl radical further reacts with SF by the XAT mechanism leading to products and regeneration of the SRD.

In summary, we have developed fast and efficient photochemical catalyst-free C-H bond fluorination approach to benzyl fluorides, benzylidene difluorides and benzoyl fluorides. Solvent economy was achieved by using fluorinating reagent F-TEDA-TFSI, which has higher solubility in polar aprotic solvents, than traditionally used SelectFluor. This protocol was successfully applied in late-stage fluorination of complex molecules Tonalide and Tolperisone. Proposingly, reaction undergoes via sequential XAT and PCET mechanisms.

ASSOCIATED CONTENT

The Supporting Information is available free of charge via the Internet at http://pubs.acs.org
Experimental procedures, characterization data, and VTI discussion. (PDF)

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Author Contributions

Both authors contributed equally.

Notes

The authors declare no competing financial interest.

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