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Electrophotochemical Synthesis Facilitated Trifluoromethylation of Arenes Using Trifluoroacetic Acid

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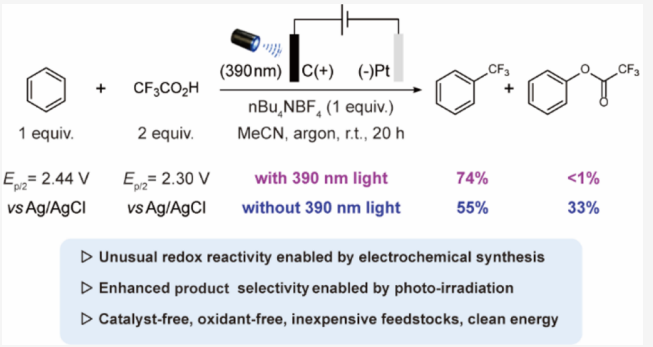
ABSTRACT: The trifluoromethyl (CF_3) group is an essential moiety in medicinal chemistry due to its unique physicochemical properties. While trifluoroacetic acid (TFA) is an inexpensive and easily accessible reagent, its use as a source of CF_3 is highly challenging due to its high oxidation potential. In this study, we present a novel electrophotochemical approach that enables the use of TFA as the CF_3 source for the selective, catalyst- and oxidant-free trifluoromethylation of (hetero)arenes. Key to our approach is the selective oxidation of TFA over arenes, generating CF_3 radicals through oxidative decarboxylation. This strategy enables the sustainable and environmentally-friendly synthesis of CF_3-, CF_2H- and perfluoroalkyl-containing (hetero)arenes with a broad range of substrates. Importantly, our results demonstrate significantly improved chemoselectivity by light irradiation, opening up new possibilities for the synthetic and medicinal applications of TFA as an ideal yet underutilized CF_3 source.



INTRODUCTION

The trifluoromethyl (CF_3) group is a highly valuable moiety in medicinal chemistry due to its electron-withdrawing nature, high lipophilicity, and unique physicochemical properties that enhance binding selectivity, cell membrane permeability, and *in vivo* metabolic stability of drug molecules.[1] CF_3-substituted aromatic rings are commonly found in various pharmaceutical drugs, such as fluoxetine,[2] cinacalcet,[3] hydroxyflutamide,[4] dutasteride,[5] selinexor,[6] and travoprost.[7] To facilitate the direct trifluoromethylation of (hetero)arenes, many CF_3 reagents, including Langlois' reagent (CF_3SO_2Na),[8] CF_3SO_2Cl,[9] CF_3I,[10] Togni's reagent,[11] $TMSCF_3$,[12] and Umemoto reagent,[13] have been utilized, but they are often expensive, toxic, require lengthy preparation, and generate substantial chemical wastes (Figure 1a). Therefore, it is highly desirable to identify an abundant, cost-effective, and green trifluoromethyl source.

Trifluoroacetic acid (TFA) appears to be an attractive CF_3 source from both economic and sustainability perspectives, as it is inexpensive, readily available, and produces only CO_2 and H_2 as byproducts in the reaction. However, the high oxidation potential of TFA (>+2.24 V vs SCE)[14] has presented significant challenges in its use as a trifluoromethylation reagent. Previous studies required stoichiometric or excess amounts of strong oxidants, such as silver salts, which lead to poor functional group tolerance and overoxidation.[15] Moreover, (hetero)arenes of similar oxidation potentials, such as benzene (E_p = 2.64 V vs SCE),[16] may also undergo competing oxidation, producing undesired byproducts.

In recent years, photocatalysis has emerged as a promising strategy for activating inert compounds in a selective and mild manner. Numerous photocatalytic methods have been developed to generate CF_3 radicals from TFA derivatives, notably trifluoroacetic anhydride (TFAA) for effecting trifluoromethylation of (hetero)arenes, and CF_3-bearing *N*-hydroxybenzimidoyl chloride (NHBC) ester derivatives, which find application in the hydrofluoroalkylation of unactivated olefins.[17] Despite these advances, the direct utilization of TFA as a primary source of CF_3 radicals remains constrained, even within the domain of photocatalysis. Notably, in 2017, Li and co-workers utilized TFA as a CF_3 reagent for the trifluoromethylation of (hetero)arenes, using Rh-modified TiO_2 nanoparticles as the photocatalyst and a substoichiometric amount of $Na_2S_2O_8$ as an external oxidant.[18] Although the use of strong oxidants was avoided in both cases, an external activating reagent was still required to facilitate the reaction due to the limited redox window of photocatalysts.

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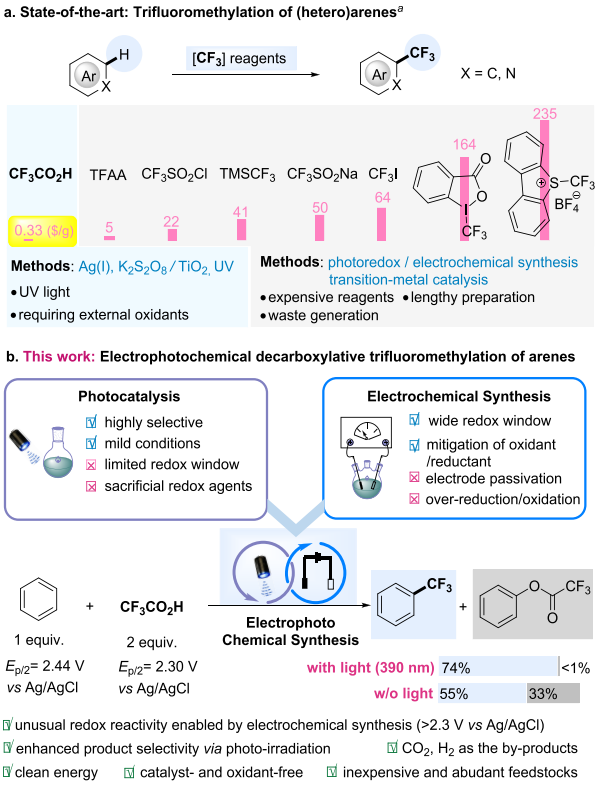


Figure 1. Trifluoromethylation of (hetero)arenes. (a) State-of-the-art: trifluoromethylation of (hetero)arenes. (b) This work: electrophotochemical decarboxylative trifluoromethylation of arenes. The prices are based on Sigma-Aldrich accessed on 27th Oct 2022.

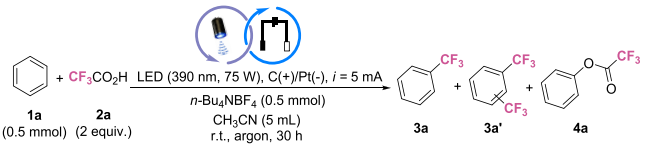
On the other hand, electrochemistry is a potent technique that employs electrons and holes as "traceless" reagents over a broad redox window to reduce reliance on conventional chemical oxidants and reductants. In view of the pressing demand for eco-friendly and sustainable synthesis, electrochemistry has undergone a renaissance in the realm of organic synthesis.[19] Nevertheless, electrochemistry faces certain restrictions due to issues such as inadequate mass transfer, large ohmic drop in organic solvents, electrode passivation, and excessive oxidation/reduction.[20]

Over the past few years, there has been a growing trend of integrating electrochemical and photocatalytic activation techniques via electrophotochemical synthesis. This integration has created a wide range of possibilities for the development of innovative synthetic transformations, both in terms of mechanism and operation.[21] We herein present our successful implementation of electrophotochemical synthesis for the trifluoromethylation of arenes using TFA, highlighting an unprecedented discovery of enhanced product selectivity by photoirradiation (Figure 1b).

RESULTS AND DISCUSSION

Our investigation was initiated with benzene (**1a**) as the model substrate to explore the reaction conditions for trifluoromethylation using TFA (**2a**, 2.0 equiv) (Table 1). Optimal results were obtained in CH_3CN with a constant current of 5 mA in an undivided cell equipped with a graphite plate anode and a platinum plate cathode, under 390 nm LED irradiation at room temperature. The desired CF_3-product **3a** was obtained in 74% yield with 5% of di-CF_3 side products (entry 1). Changing either the anode material to reticulated vitreous carbon (RVC) or the cathode material to graphite decreased the yields of **3a** to 31% and 50%, respectively (entries 2 and 4). When platinum was used as the anode material, no desired product was generated (entry 3). It is noteworthy that in the absence of light, a significant amount (33%) of phenyl trifluoroacetate **4a** was obtained as a byproduct (entry 5). We assessed the effect of light sources with different wavelengths of 370, 427, 440, and 456 nm (entries 6–9) and observed that the formation of byproduct **4a** was generally suppressed in the presence of light irradiation. Importantly, we observed low selectivity of **3a** and **4a** (60% vs 30%) when the reaction was performed at 45 °C in an oil bath (entry 10), indicating that the good selectivity of **3a** under the optimal conditions was attributed to light irradiation rather than the heating effect. When the reaction was conducted under a constant voltage (3.5 V), a lower product selectivity was observed between the formation of **3a** and **4a** (entry 11). Finally, we confirmed that electricity was a prerequisite as no reaction occurred in its absence (entry 12).

Table 1. Optimization of Trifluoromethylation of Benzene Using TFA



entry[a]	deviation from optimal conditions	yield (%)3a/3a′/4a[b]
1	none	74/5/trace
2	RVC(+) instead of C(+)	31/5/6
3	Pt(+) instead of C(+)	0/0/0
4	graphite(−) instead of Pt(−)	50/trace/15
5	no light	55/6/33
6	370 nm instead of 390 nm LED light	75/16/trace
7	427 nm instead of 390 nm LED light	60/18/trace
8	440 nm instead of 390 nm LED light	64/20/4
9	456 nm instead of 390 nm LED light	66/15/8
10	heating at 45 °C	60/5/30
11	constant voltage = 3.5 V	50/4/20
12	no electricity	0

[a]Optimal conditions: benzene (0.5 mmol), TFA (2.0 equiv), *n*-Bu_4NBF_4 (0.5 mmol), CH_3CN (5 mL). Graphite plate anode and Pt plate cathode, electrolysis at room temperature under a constant current of 5 mA (current density = 3.3 mA/cm^2), LED (390 nm, 75 W). [b]Yields were determined by analysis of the crude ^{19}F NMR spectra using fluorobenzene as an external standard.

Utilizing optimized reaction conditions, we conducted a scope investigation of the trifluoromethylation reaction utilizing TFA as the CF_3 source across a range of (hetero) arenes (Table 2). Our results demonstrate that monosubstituted arenes with a diverse array of functional groups, including halogens (F, Cl, Br, I) (**3b**-**3e**), ketones (**3f**, **3g**), esters (**3h**, **3i**), difluoromethyl (**3j**), trifluoromethyl (**3k**), nitrile (**3l**), pinacol boronic ester (**3m**), sulfonyl (**3n**), and phosphate (**3o**), were well-tolerated with synthetically useful yields. Disubstituted benzenes featuring electron-withdrawing groups, including 1,2- (**3q**-**3s**) and 1,4-disubstitution (**3t**-**3ah**), as well as substrates containing two aromatic rings (**3ai**), were also trifluoromethylated with moderate yields. The regioselectivity of the reaction varied depending on the substrate. Specifically, when Disubstituted arenes contained an additional CF_3 group, trifluoromethylation preferentially occurred *meta*- to the CF_3 group (**3ad**-**3ah**). Moreover, it is worth noting that

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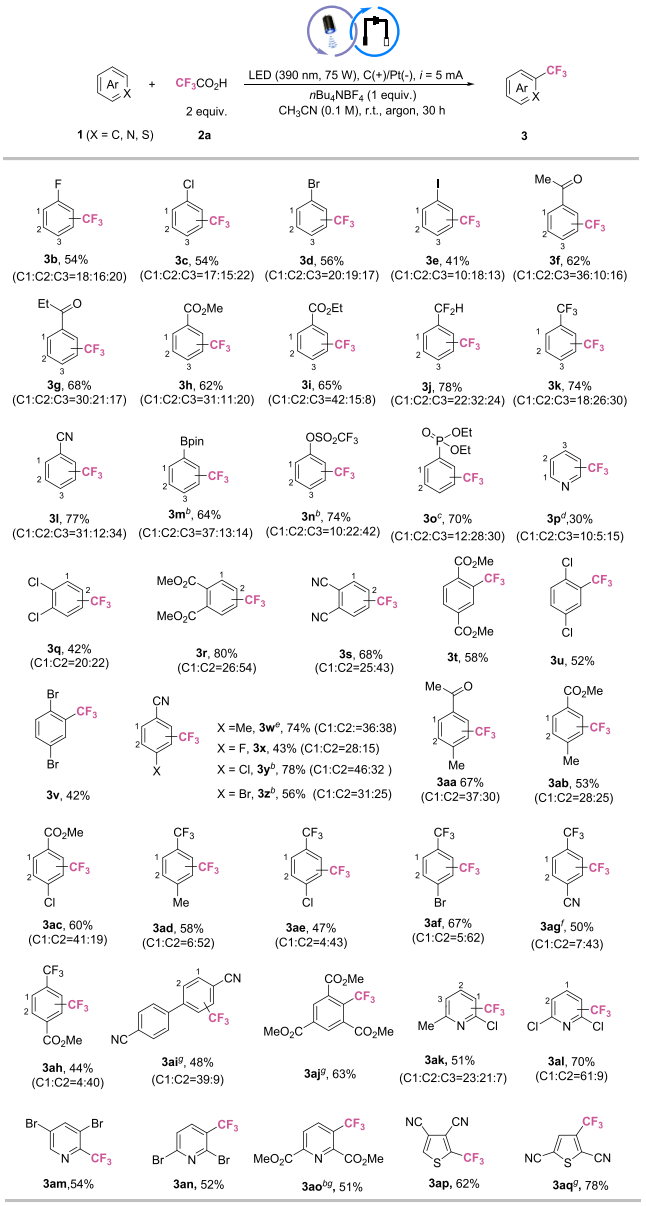
Table 2. Scope of Trifluoromethylation of (Hetero)arenes with TFA[a]



[a]Arenes (0.5 mmol), TFA (2 equiv), *n*-Bu_4NBF_4 (0.5 mmol), CH_3CN (5 mL). Yields and regioselectivity were determined by analysis of the crude ^{19}F NMR spectra using fluorobenzene as an external standard. [b]TFA (5 equiv), 40 h. [c]Graphite as anode, graphite as cathode, TFA (5 equiv), 40 h. [d]RVC as anode, Pt as cathode, TFA (3 equiv), 20 h. [e]TFA (10 equiv), 40 h. [f]TFA (10 equiv), 50 h. [g]Isolated yields.

even sterically hindered trisubstituted benzene (**3aj**) exhibited good reactivity, yielding a product with a 63% yield. Furthermore, the trifluoromethylation of heteroaromatic compounds, which are often challenging substrates when subjected to electrochemical conditions due to their susceptibility to oxidation, has been achieved successfully. Pyridines carrying chloro, bromo, and ester substituents have been effectively employed, yielding products **3ak**-**3ao** in moderate to good yields. Additionally, thiophenes have demonstrated compatibility, providing the corresponding trifluoromethylated products (**3ap**-**3aq**).

To demonstrate the practical utility and versatility of our electrophotochemical protocol, we explored its potential in the late-stage functionalization (LSF) of complex pharmaceuticals, natural products, and their derivatives (Figure 2a). Notably,

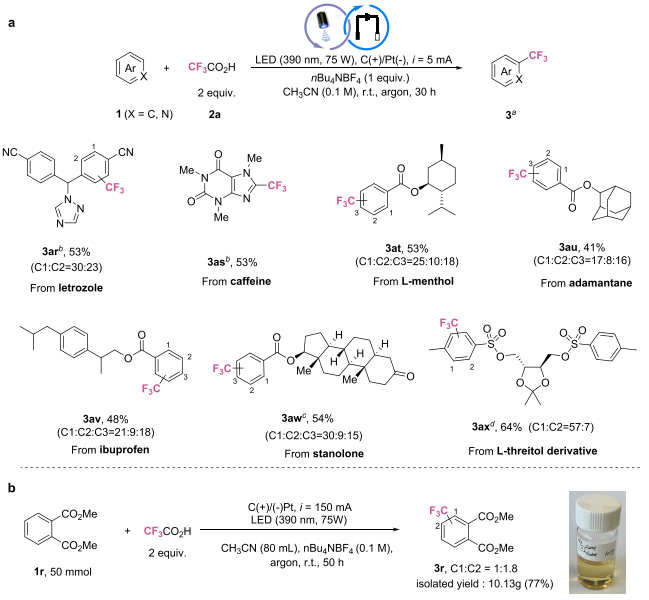


Figure 2. Synthetic applications. (a) Late-stage functionalization of pharmaceuticals, natural products and derivatives; (b) decagram scale synthesis. [a]arenes (0.5 mmol), TFA (2 equiv), *n*-Bu_4NBF_4 (0.5 mmol), CH_3CN (5 mL). Yields and regioselectivity were determined by analysis of the crude ^{19}F NMR spectra using fluorobenzene as an internal standard. [b]Aromatic substrate (0.3 mmol), TFA (5 equiv), RVC as anode, Pt as cathode, isolated yields. [c]Aromatic substrate (0.2 mmol), TFA (2 equiv). [d] TFA (4 equiv), 40 h.

our protocol demonstrated effectiveness when applied to readily available drug molecules, including the anticancer drug letrozole and the stimulant caffeine, yielding trifluoromethylated products (**3ar**-**3as**) in synthetically useful yields. Furthermore, substrates derived from menthol, adamantane, stanolone, and L-threitol exhibited favorable reactivity within this framework. Additionally, we successfully scaled up this electrophotochemical trifluoromethylation reaction to a 50.0 mmol scale, resulting in the isolation of over 10 g of product **3r** in 77% yield (Figure 2b). The attainment of LSF and the remarkable scalability, often a challenging feat in electrochemical reactions, underscore the practical applicability of our method, particularly in the domain of medicinal chemistry.

The incorporation of perfluoroalkyl groups (Rf = C_2H_5, C_3F_7, C_4F_9, C_5F_{11}, C_6F_{13}, *etc.*) into drug molecules is also a matter of great importance, as the fluorous chain can significantly improve the metabolic stability of the parent molecules.[4,22] Our electrophotochemical protocol can be extended to the perfluoroalkylation of arenes using various readily available polyfluoric acids as perfluoroalkylating reagents, as illustrated in Table 3. polyfluoric acids **2b**-**2f**, possessing oxidation potentials (2.10−2.35 V vs Ag/AgCl), exhibited comparable reactivity to that of TFA and were successfully incorporated onto arene **1aj** with moderate yields. Additionally, we endeavored to extend our protocol to the difluoromethylation of (hetero)arenes utilizing difluoroacetic acid (**2g**). With an oxidation potential of 2.09 V vs Ag/AgCl, difluoroacetic acid exhibited the capability to facilitate

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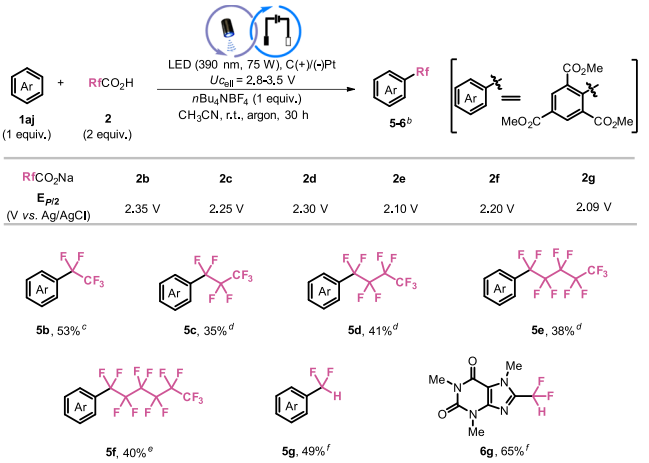
Table 3. Scope of Other Fluoroalkyl Carboxylic Acids for the Per- and Difluoroalkylation[a]



[a]**1ak** (0.5 mmol), RfCO$_2$H (2 equiv), n-Bu$_4$NBF$_4$ (0.5 mmol), CH$_3$CN (5 mL). [b]Isolated yields. [c]U_{cell} = 2.8 V. [d]U_{cell} = 3.0 V. [e]U_{cell} = 3.5 V. [f]I = 5 mA, RVC as anode, Pt as cathode, 12 h, isolated yields.

difluoromethylation reactions with both arenes and heteroarenes under our established conditions, affording products **5g** and **6g** in moderate yields. The successful implementation of this methodology in both perfluoroalkylation and difluoroalkylation employing the readily available corresponding carboxylic acids not only broadens the synthetic scope of this protocol but also advances the prospects for the future development of per- and difluoroalkyl compounds for drug discovery.

Various experiments were conducted to gain insight of the reaction mechanisms. When 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was used as a radical trapping reagent under the standard reaction conditions, the reaction was suppressed, and TEMPO−CF$_3$ adduct was detected by ^{19}F NMR spectroscopy (Figure 3a). Additionally, formations of both H$_2$ and CO$_2$ were detected under the standard reaction conditions (Figure 3b). All these control experiments supported the generation of CF$_3$ radical from TFA via oxidative decarboxylation.

We were intrigued by the observed enhancement of chemoselectivity toward the desired trifluoromethylation reaction over the trifluoroacetoxylation side reaction under light irradiation and sought to investigate this effect further. To the best of our knowledge, no previous studies have reported this light-enhanced chemoselectivity under electrochemical conditions. In order to probe the effect of light, we conducted cyclic voltammetry (CV) measurements of benzene and CF$_3$CO$_2$Na in acetonitrile with and without light irradiation. The small difference in oxidative potential between CF$_3$CO$_2$Na and benzene (0.14 V, Figure 3c) indicated the challenge in achieving selective oxidation of TFA in the presence of benzene. Furthermore, the impact of light on the oxidation potential of both substrates was minimal, ruling out photo differentiation of the substrates' oxidative potentials as the origin of the observed improved selectivity.

To explore this effect further, we conducted photocurrent response measurements by switching on and off an LED light

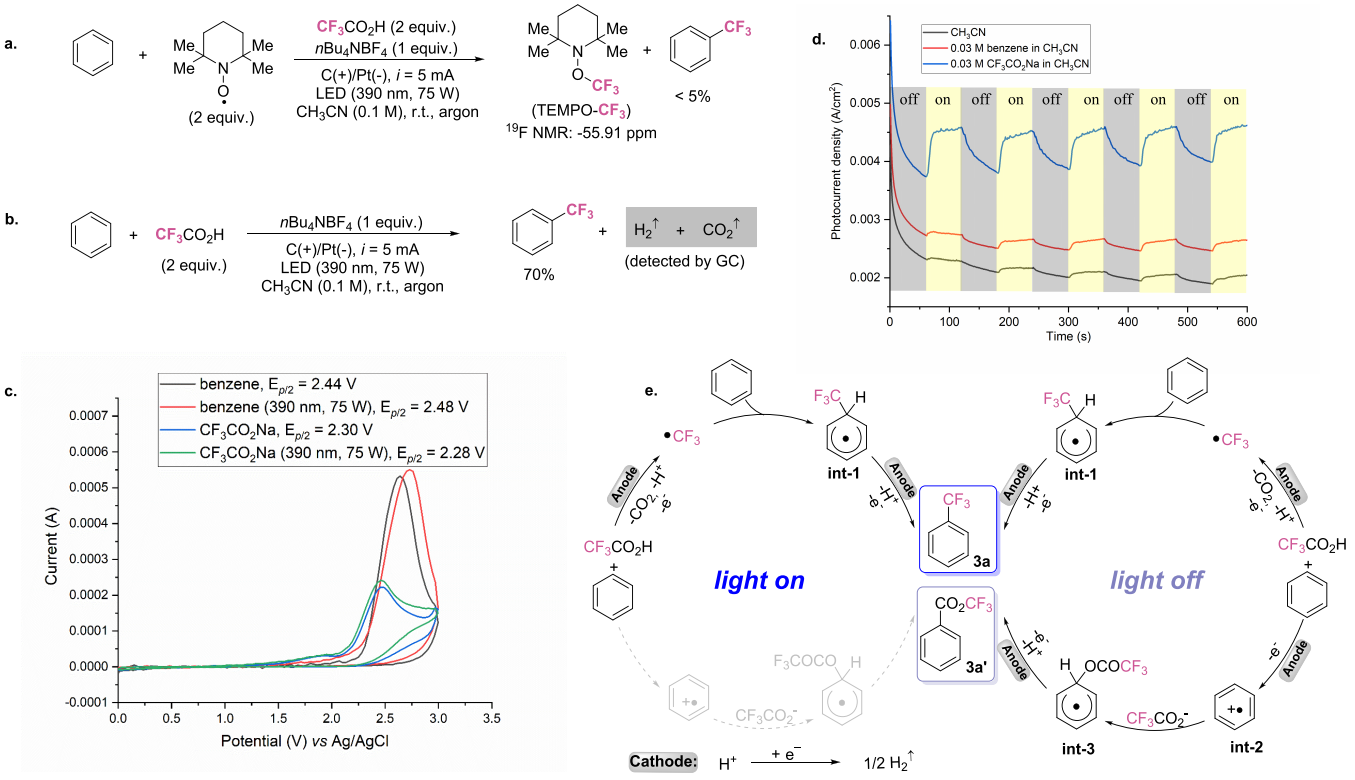


Figure 3. Supporting mechanistic studies and plausible mechanisms. (a) Capture of the trifluoromethyl radical by TEMPO. (b) Detection of H$_2$ and CO$_2$ as byproducts. (c) CV measurements of benzene and CF$_3$CO$_2$Na with or w/o light. (d) Photocurrent response by switching on and off with LED light (390 nm, 75 W) under V = 2.5 V (vs Ag/AgCl) for background MeCN solvent (black line), benzene (red line), and CF$_3$CO$_2$Na (blue line), respectively. (e) Proposed reaction mechanisms.

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(390 nm, 75 W) with a voltage of 2.5 V (*vs* Ag/AgCl) for the background acetonitrile solvent, benzene, and CF_3CO_2Na using a graphite plate anode. Our results showed that under light irradiation, a photocurrent was generated with both CF_3CO_2Na and benzene, with CF_3CO_2Na exhibiting a significantly higher current intensity than benzene (Figure 3d). However, in the absence of light, the current intensity of both CF_3CO_2Na and benzene diminished. This observation suggested that $CF_3CO_2^-$ is oxidized more readily than benzene under light irradiation, and are align with the observed improvement in selectivity for product **3a** under electrophotochemical conditions. One possible explanation is that the graphite plate anode, although conductive, may undergo oxidation at the anodic potential applied. This oxidation process introduces a band gap in the graphite, making it responsive to light irradiation and allowing the formation of electron−hole pairs.[23,24] This suspicion was experimentally supported by the increased current under light irradiation of the background MeCN solvent (as depicted in Figure 3d, black line). The increased generation of charge carriers in the graphite plate anode may have contributed to the higher photocurrent observed for CF_3CO_2Na compared to benzene under light irradiation. As $CF_3CO_2^-$ is attracted more strongly to the positively charged anode, improved mass transfer via electromigration likely occurs. In contrast, there was no such ion interaction between neutral benzene and the anode. However, we cannot exclude the possibility of the generation of hot electrons in graphite under light irradiation that triggers the ion interactions, even though the hot electrons and holes dissipate in ultrafast time scales.[25]

Based on all the experimental studies, a reaction mechanism was proposed as shown in Figure 3e. Under light-irradiation, the enhanced mass transfer due to ion interactions under electrophotochemical conditions facilitates anodic oxidation of TFA, leading to the formation of CF_3 radical via decarboxylation. This radical subsequently adds to benzene to generate intermediate **int-1**, which is converted to the desired product **3a** through another single electron oxidation and deprotonation. In contrast, in the absence of light, the oxidation of benzene becomes a prominent side reaction. Nucleophilic attack of $CF_3CO_2^-$ to the phenyl radical cation (**int-2**) forms **int-3**, which furnishes fluoroacetoxylation product **4a** through oxidative rearomatization on the anode. Meanwhile, the released protons undergo single-electron reduction to produce H_2 on the cathode.

CONCLUSIONS

In summary, we have developed a electrophotochemical approach for the direct trifluoromethylation of (hetero)arenes using TFA as a sustainable CF_3 source, in the absence of any catalyst or oxidant. Our reaction conditions permit various electron-neutral and electron-poor (hetero)arenes to serve as the substrates. This straightforward protocol can readily be extended to encompass perfluoroalkylation and difluoroalkylation by leveraging commercially available polyfluoric acids and difluoroacetic acid, respectively. The unprecedented photoinduced chemoselective enhancement can be attributed to the acceleration of the oxidation of $CF_3CO_2^-$ under anodic light irradiation. Our investigation not only offers new prospects for the synthetic application of TFA as a CF_3 source, but also introduces a novel approach to integrate light and electrochemical reactions for achieving otherwise challenging organic transformations.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.3c10148.

General procedures, tables of reaction optimizations, analytical data, and characterization data for all the products (PDF)

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Notes

The authors declare no competing financial interest.

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