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Redox-Neutral Decarboxylative and Desulfonylative C(sp^3) Trifluoromethylation: Method Development and Mechanistic Inquiry

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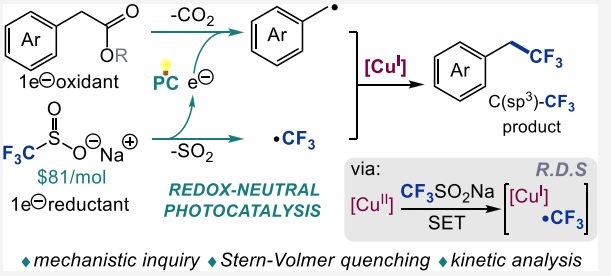
ABSTRACT: Sodium triflinate (CF_3SO_2Na) is an inexpensive bench-stable radical CF_3 source that is often activated by external oxidants such as peroxides. However, despite the commercial accessibility of CF_3SO_2Na, the salt has never been applied to decarboxylative trifluoromethylation due to challenges in controlled cross-radical coupling. We report a redox-neutral approach to decarboxylative C(sp^3) trifluoromethylation of carboxylic acid derivatives. Mechanistic inquiry is performed to address the limitations in scope.



INTRODUCTION

The importance of fluorine in medicinal chemistry cannot be undermined.[1−5] By incorporating fluorine into organic molecules, their physical, chemical, and biological properties can be drastically altered, making it vital for drug discovery.[6] In fact, 57 out of the Top 200 Small Molecule Pharmaceuticals by Retail Sales in 2021 contain fluorine.[7] Trifluoromethylation, especially, is an attractive and powerful method of introducing fluorine into organic motifs, due to the vast number of trifluoromethyl (CF_3) reagents that have emerged over the past few decades (Figure 1a).[6,8−10] However, despite the variety, a majority of CF_3 reagents are very expensive, causing them to be limited in commercial accessibility.[11] Trifluoromethyltrimethylsilane ($TMSCF_3$, also known as Ruppert−Prakash reagent) has been an effective solution to this end, serving as an inexpensive nucleophilic CF_3 source when paired with an anionic initiator such as a fluoride source or a strong base (Figure 1b).[10,12−14] Another attractive solution to this problem is sodium triflinate (CF_3SO_2Na, also known as Langlois reagent), which is an inexpensive, bench-stable, white solid which allows convenient handling and easy storage.[15] Sodium triflinate can serve as a radical CF_3 source via desulfonylation upon a single-electron oxidation, typically achieved in thermal processes through (super)stoichiometric amounts of peroxides.[16−20] Additionally, it was revealed that sodium triflinate could also be activated via photocatalysis in oxidant-free conditions, demonstrated by a radical trifluoromethylation of styrenes.[21−26] On the other hand, independent works from Li and MacMillan demonstrated the use of aliphatic carboxylic acids as alkyl precursors in decarboxylative trifluoromethylation (Figure 1c).[27,28] While organosulfinates have been paired with carboxylic acid derivatives to photocatalytically generate sulfones, the use of sodium triflinates in decarboxylative C(sp^3) trifluoromethylation has not been studied before.[29] This could be in part due to the challenges in controlling the rate of alkyl and CF_3 radical generation in a cross-radical coupling process to avoid decomposition.[30−34] Since a higher fraction of C(sp^3) in potential drug molecules correlates to clinical success, the ability to pair commercially and naturally abundant carboxylic acids with sodium triflinates would be a powerful method of generating these pharmaceutically relevant C(sp^3)−CF_3 bonds.[35−37] This work aims to pair carboxylic acid-derived redox-active esters, which are activated by single-electron reduction, with sodium triflinates, which are activated by single-electron oxidation to achieve redox neutrality in a photocatalytic C(sp^3)−CF_3 bond forming process (Figure 2). By doing so, the reaction avoids potentially hazardous peroxide activators, and at the same time, avoids the use of anionic initiators which can impact the functional group tolerance of the reaction.

RESULTS AND DISCUSSION

The work began with optimizing the appropriate conditions that would allow a cross-radical trifluoromethylation (Figure 3). Thus, the decarboxylative trifluoromethylation of **1a** was chosen to be optimized. With 1 equiv of sodium triflinate and 5 mol % of 4CzIPN ($E_{1/2}$ (PC*/PC$^{\bullet-}$) = +1.43 V, $E_{1/2}$ (PC/PC$^{\bullet-}$) = −1.24 V in MeCN), an organic photocatalyst, copper

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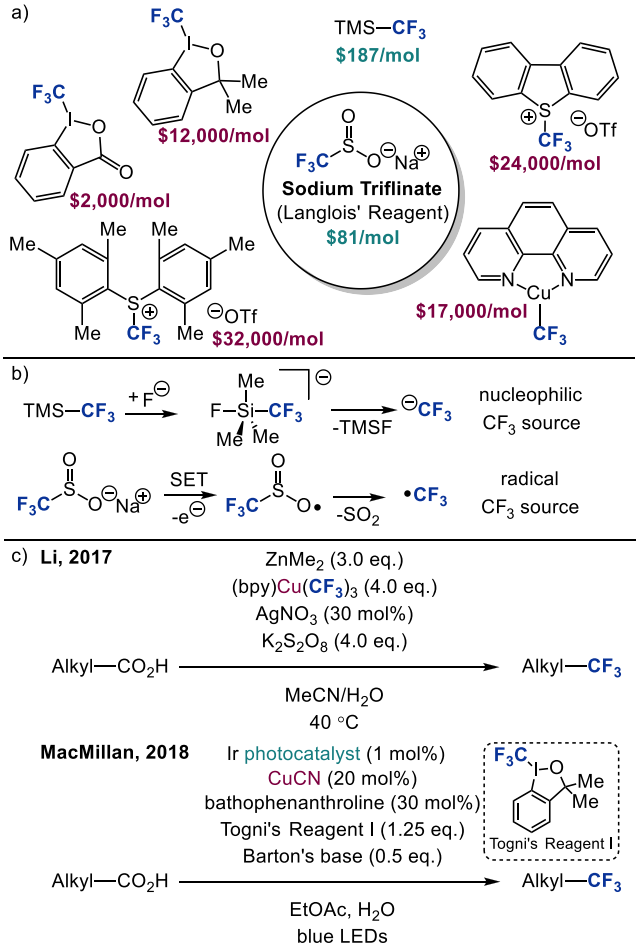


Figure 1. (a) Commercially available CF_3 reagents and their costs in US$/mol. (b) Inexpensive CF_3 reagents and their modes of activation. (c) Literature precedents of decarboxylative C(sp^3) trifluoromethylation.

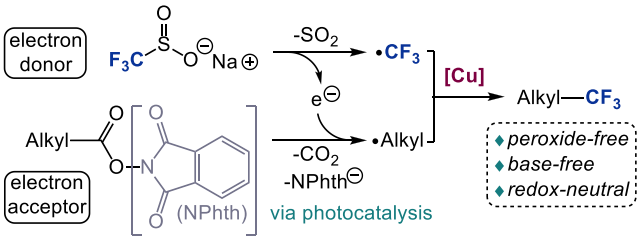
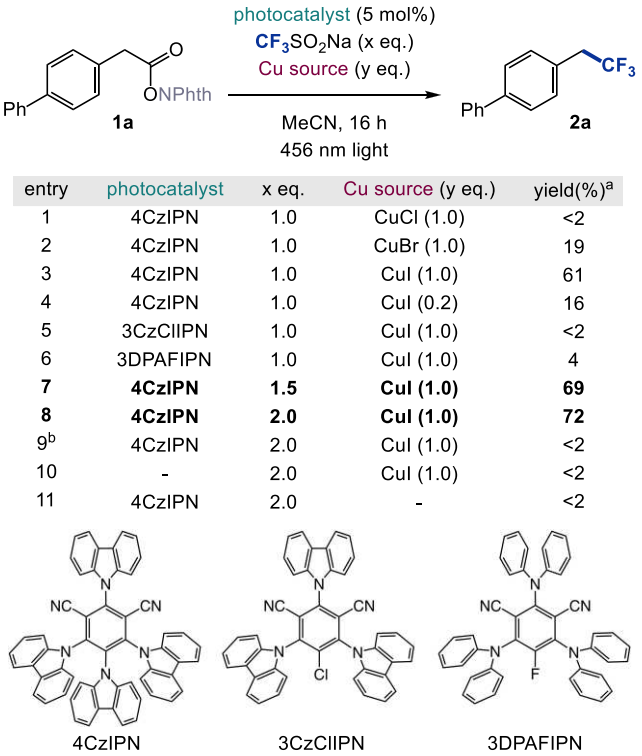


Figure 2. This work.

iodide (CuI) proved to be the most effective among all the copper(I) halides (entries 1–3).[38] Catalytic amounts of CuI drastically decreased the yield, emphasizing the necessity of stoichiometric amounts of copper in the reaction, likely due to the formation of inactive copper phthalimide (entry 4). Other cyanoarene-based photocatalysts, 3CzClIPN ($E_{1/2}$ (PC*/$PC^{\bullet-}$) = +1.56 V, $E_{1/2}$ (PC/$PC^{\bullet-}$) = −1.16 V in MeCN), and 3DPAFIPN ($E_{1/2}$ (PC*/$PC^{\bullet-}$) = +1.09 V, $E_{1/2}$ (PC/$PC^{\bullet-}$) = −1.59 V in MeCN), delivered trace to no product (entries 5 and 6).[38] 3CzClIPN is a strong photooxidant but a mild reductant, while 3DPAFIPN is a strong photoreductant and a mild oxidant. This result highlights the necessity of a well-rounded photocatalyst with both sufficient oxidizing and reducing potentials. Finally, upon increasing the triflinate



entry	photocatalyst	x eq.	Cu source (y eq.)	yield(%)[a]
1	4CzIPN	1.0	CuCl (1.0)	<2
2	4CzIPN	1.0	CuBr (1.0)	19
3	4CzIPN	1.0	CuI (1.0)	61
4	4CzIPN	1.0	CuI (0.2)	16
5	3CzClIPN	1.0	CuI (1.0)	<2
6	3DPAFIPN	1.0	CuI (1.0)	4
7	**4CzIPN**	**1.5**	**CuI (1.0)**	**69**
8	**4CzIPN**	**2.0**	**CuI (1.0)**	**72**
9[b]	4CzIPN	2.0	CuI (1.0)	<2
10	-	2.0	CuI (1.0)	<2
11	4CzIPN	2.0	-	<2

Figure 3. Optimization of reaction conditions. (a) Yield calculated by ^{19}F NMR spectroscopy. (b) No light.

loading to 1.5 equiv, product **2a** was generated at an improved yield of 69% (entry 7). Specifically for this substrate, an increase in loading to 2.0 equiv improved the yield slightly to 72% (entry 8). Finally, control reactions with no light, no photocatalyst, or no copper, all gave no product, highlighting the necessity of all reaction components (entries 9–11).

With the optimized conditions in hand, the substrate scope was investigated (Figure 4). Overall, the reaction was effective with primary benzylic substrates. The reaction of boronic ester and bromide-containing substrates demonstrates orthogonality to Pd-catalyzed cross-coupling (**2b,c**). The reaction is tolerant with oxygen-containing functional groups (**2d–i**). Fluorine-based substrates can also be trifluoromethylated efficiently, hinting at the use of this methodology to make polyfluorinated alkanes (**2j,k**). Simple hydrocarbons can also yield products at good to moderate yields (**2m–o**), as well as the drug-based substrate, isoxepac (**2p**). Most importantly, the reaction is well-suited for substrates with both electron-donating (**2d,f,g,i,o**) and electron-withdrawing functional groups (**2b,e,j–l**).

In addition to the scope, the carboxylic acid isoxepac could also be functionalized to yield the crude redox-active ester **1p** and undergo subsequent photocatalytic trifluoromethylation without purification steps in between to form 44% yield of **2p** at 1.0 mmol scale (Figure 5).

The main side product of the reaction is the homodimer of the benzyl radical (Figure 4, bottom right). Initially, based on literature precedents, the excited photocatalyst was hypothesized to oxidize the triflinate salt to form the CF_3 radical and then return to the ground state by reducing the redox-active ester, generating the alkyl radical (Figure 6a).[31,39] Subsequently, the CF_3 radicals would undergo facile radical capture by [Cu^I] to form [Cu^{II}]-CF_3, and the [Cu^{II}]-CF_3

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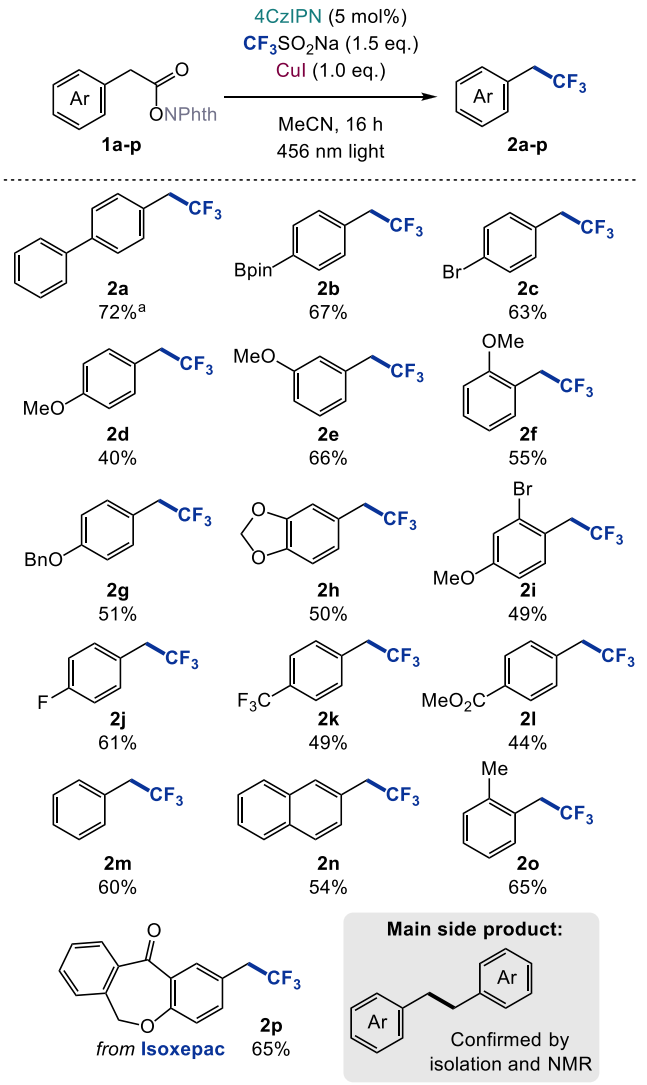

Figure 4. Primary benzylic substrate scope. Yields reported are determined by ^{19}F NMR spectroscopy due to the volatility of several products. For isolated yields and additional details, refer to the Supporting Information (SI). (a) 2.0 equiv of CF_3SO_2Na instead of 1.0 equiv.

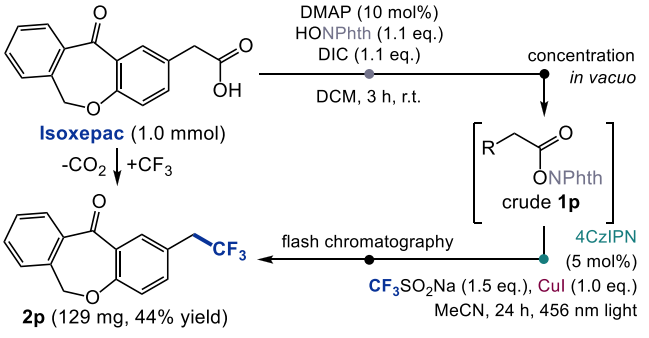

Figure 5. The 1.0 mmol scale functionalization−photocatalysis sequence. Isolated yield is reported. Refer to SI for more details.

would capture the alkyl radical to form the alkyl-CF_3 product. However, since [Cu^{II}] species are known to react with alkyl radicals at rates nearing diffusion, the presence of this homodimer was surprising.[31,40,41] Furthermore, upon applying

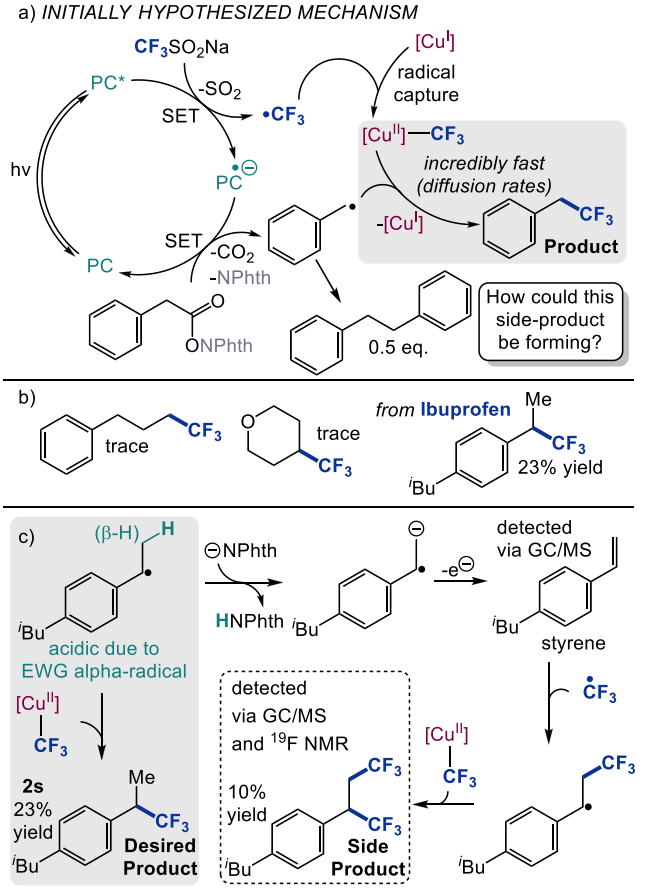

Figure 6. (a) Initially hypothesized mechanism and its discrepancy with the observed side-product. (b) Substrate limitations of the current method. For reaction conditions, refer to Figure 4. (c) Additional side-reactivity of ibuprofen.

the optimized conditions to substrates other than those that generate primary benzylic radicals, the reaction formed trace product (instead forming the H-quench product) or the yields were significantly reduced (Figure 6b). Upon a closer analysis of the reaction of ibuprofen-based substrate, a styrene-based product and a ditrifluoromethylated product were also observed along with the desired product (Figure 6c). The acidic β-proton is an ample site for deprotonation to form styrene (supported by a deleterious radical polar crossover), and a CF_3 radical can add to the competitively reactive terminal position of the styrene to yield a net-ditrifluoromethylated product. Furthermore, the increased stability of the secondary radical encourages a faster radical generation, which creates room for more undesired side-reactivity.[42] If the reaction was following the initially proposed mechanism, the alkyl radical would be captured in diffusion-nearing rates, and these side-reactions would not be observed.

Hence, we proceeded to address the substrate limitations of this method through mechanistic inquiry. As a first step, a Stern−Volmer quenching plot was obtained (Figure 7).[43,44] A higher slope in a plot of I_0/I against the concentration of a reagent indicates a higher likelihood of it quenching the excited state photocatalyst in a reaction. The plot revealed the highest slope for CuI, followed by CF_3SO_2Na and redox-active ester (**1m**), respectively. This study demonstrated that CuI was the most likely to quench the excited state 4CzIPN.

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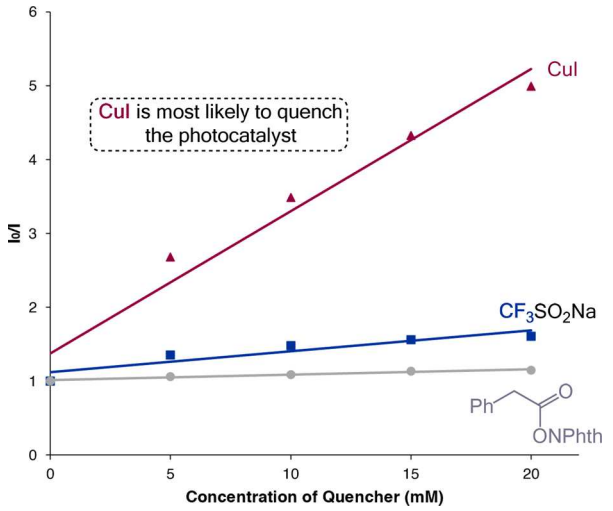

Figure 7. Stern–Volmer quenching plot of the reagents.

Therefore, two different mechanisms were possible: reductive quenching of the photocatalyst to form [Cu^{II}], or oxidative quenching to form [Cu^0], although the latter is unlikely due to challenging reduction potentials (Figure 8a).

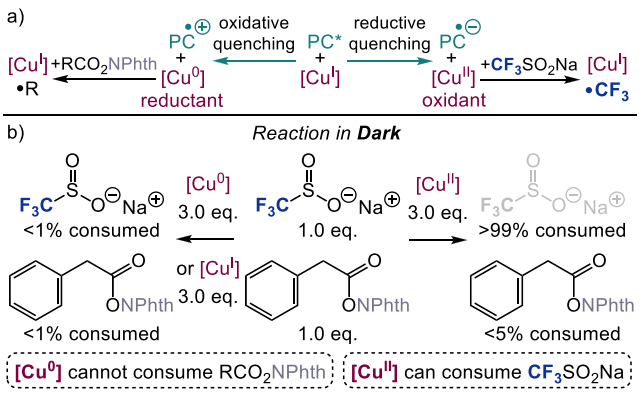

Figure 8. (a) Two possible quenching mechanisms. (b) Mechanistic probe of the viability of copper salts as reductants and oxidants. [Cu^0] = Cu powder, [Cu^I] = CuI, [Cu^{II}] = $CuBr_2$. Reaction run in CD_3CN and analyzed by ^1H and ^{19}F NMR spectroscopy.

After these copper species are formed, they would then oxidize the sodium triflinate for the case of [Cu^{II}] or reduce the redox-active ester for the case of [Cu^0]. Thus, the confirmation of the viability of these copper-mediated reductive and oxidative processes would unveil the possible oxidation state of the copper after the photocatalyst is quenched. Therefore, a mixture of 1.0 equiv of triflinate and 1.0 equiv of redox-active ester **1m** was subjected to 3.0 equiv of copper salts of three different oxidation states ([Cu^0], [Cu^{II}], and [Cu^I] as control, Figure 8b). [Cu^0] powder and [Cu^I] iodide did not react with either the triflinate or the redox-active ester. However, [Cu^{II}] bromide completely consumed the triflinate after 16 h of stirring in the dark, with a peak detected by ^{19}F NMR that tentatively indicated a copper-CF_3 adduct at −19 ppm (NOTE: $CuBr_2$ was used in place of CuI_2 because the latter is unstable and therefore inaccessible. Refer to SI for more details).[45,46] This hints at a reductive quenching mechanism, which would form [Cu^{II}] as an oxidant that would then desulfonylate the sodium triflinate. This is significant, as [Cu^{II}] is not commonly invoked in the activation of sodium triflinates in the absence of peroxides or photocatalytic oxidants.

Finally, we wanted to study the relationship between the rate-determining step and the redox-active ester. The presence of the alkyl homodimer side-product indicated that a rapid alkyl radical generation was in place in comparison to the rate-determining step. Thus, we hypothesized that the redox-active ester would be unrelated to the rate-determining step. The initial rates of five different substrates **2a**,**d**,**j**,**k**,**m** containing the functional groups *p*-Ph, *p*-MeO, *p*-F, *p*-CF_3, and *p*-H, respectively, were obtained to investigate whether there was a linear free energy relationship in place (Figure 9). When

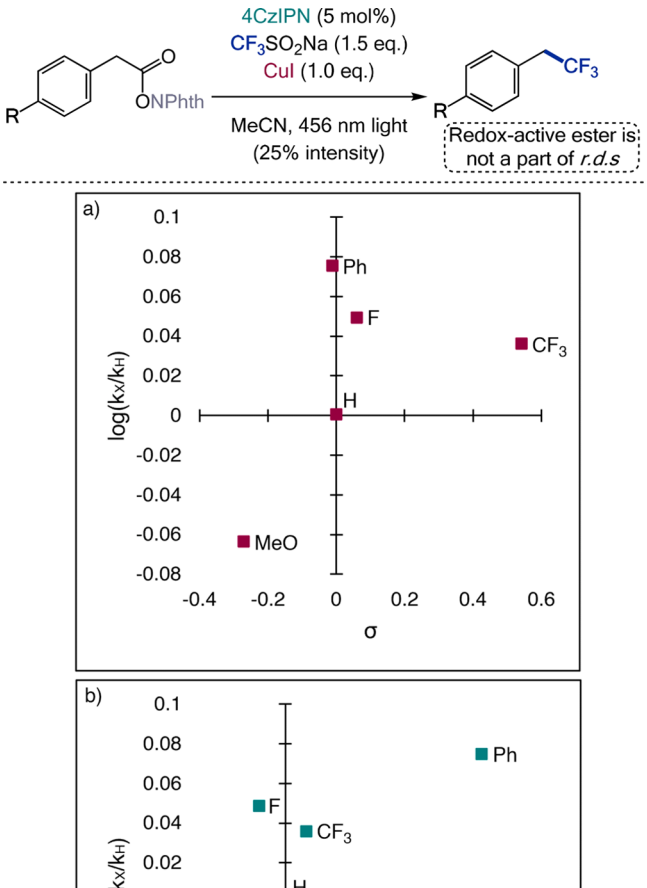

Figure 9. Plots of log (k_X/k_H) with respect to (a) Hammett parameters and (b) Creary parameters. r.d.s = rate-determining step.

log(k_X/k_H) was plotted against Hammett parameters, the plot showed no trend, showing an absence of sensitivity to polar functional groups on the redox-active ester.[47] The rates were also plotted against Creary parameters, as they are often invoked for rate-determining transition states that have radical character.[48−50] Similar to the Hammett parameters, Creary parameters also showed no trend, showing an absence of

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sensitivity to radical stabilizing groups. Overall, this result points to the lack of involvement of the redox-active ester in the rate-determining step of the reaction either in a polar or a radical manner as predicted.

Based on the observed side-products and experimental evidence, a newly revised mechanism is proposed (Figure 10).

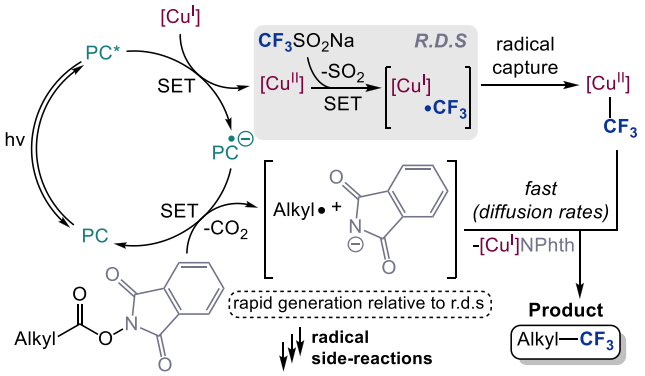

Figure 10. Revised proposed mechanism based on experimental data. r.d.s. = rate-determining step.

First, the photocatalyst is excited by light and then oxidizes the CuI (supported by Figure 7). The photocatalyst in a reduced state then returns to the ground state through a single-electron reduction of the redox-active ester, which promptly undergoes decarboxylation to generate an alkyl radical. This reduction step is not rate-determining (supported by Figure 9). Meanwhile, the [Cu^{II}] species that is formed from the photocatalytic quench oxidizes the sodium triflinate in a single-electron transfer process to yield [Cu^{I}] and CF_3 radical (supported by Figure 8). The [Cu^{I}] species then promptly captures the CF_3 radical within the solvent cage to form a [Cu^{II}]-CF_3 adduct. As soon as the adduct is formed, the aforementioned alkyl radical reacts with the adduct to form the alkyl-CF_3 product. The exact detail of this bond-forming step is unknown, as both an S_H2-type pathway and a one-electron oxidative addition and then subsequent reductive elimination pathway have been proposed in the literature.[9,27,31,33,39,46,51] In the total mechanism, the [Cu^{II}]-mediated oxidation of sodium triflinate is proposed to be rate-determining, in which case the alkyl radicals that are rapidly generated either persists until there is a significant buildup of [Cu^{II}]-CF_3 or decomposes to form side-products (supported by Figures 4, 6b, and 9).

CONCLUSION

Overall, we have developed a novel cross-radical strategy in constructing pharmaceutically relevant C(sp^3)−CF_3 bonds with an inexpensive bench-stable CF_3 source and an abundant alkyl precursor. However, the current method is heavily limited to primary benzylic substrates. These limitations are explained by a deeper understanding of the mechanism driven by kinetic analysis and experimental evidence. Based on these new mechanistic insights, further work is currently underway in our lab to improve the scope of this reaction to achieve a general method for decarboxylative and desulfonylative C(sp^3) trifluoromethylation.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study is available in the published article and Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.3c00872.

Experimental details, procedures, mechanistic data, ^{1}H, ^{13}C, and ^{19}F NMR spectra, and characterization for all new compounds (PDF)

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Author Contributions

All authors have given approval to the final version of the manuscript.

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Notes

The authors declare no competing financial interest.

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