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Photocatalyst-free light-mediated three-component alkoxy-, hydroxy-, and azidotrifluoromethylation of alkenes†

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Photoinduced radical–polar crossover (RPC) reactions generally rely on the use of an external photocatalyst to generate the corresponding radical and ionic species, selected according to the redox potentials of the involved species. Herein, we describe a multicomponent light-induced RPC reaction that does not require an exogenous photocatalyst, enabling the efficient synthesis of diverse 1,2-trifluoromethyl alkyl ethers, alcohols, and azides. This protocol allows for the bifunctionalization of alkenes under mild conditions using purple light and a thianthrenium salt as a trifluoromethylating agent. Mechanistic experiments confirmed the formation of a benzylic sulfonium intermediate that can participate in different nucleophilic substitution reactions, being an alternative photocatalyst-free method to the classical RPC.

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Introduction

Radical/polar crossover (RPC) synthetic methods are gaining considerable interest given their unique mode of reactivity.¹ The main challenge of these protocols is the convenient design of the reaction conditions, where both radical and ionic modes of reactivity are involved.² In recent years, photo-induced net-neutral methods have emerged as a particularly interesting subclass of RPC that utilizes photocatalysts and visible light to trigger the reactivity.³ The chosen photocatalyst plays a pivotal role enabling the single-electron transfer events (oxidation and reduction) across different oxidation states throughout the reaction, which precludes the use of exogenous oxidants or reductants.

A notable application of RPC chemistry is devoted to alkene difunctionalization, which constitutes a powerful strategy to increase molecular complexity in a single step from simple starting materials.⁴ In this framework, the sequential formation of $C(sp^3)$ – CF_3 and $C(sp^3)$ –Nu bonds *via* RPC mech-

nism governed by oxidative quenching has found wide applicability using Togni, Umemoto or Mes-Umemoto reagents, among others.⁵ The appropriate photocatalyst selection induces the desired reactivity in presence of the corresponding nucleophiles.

Typically, the photocatalyst in its excited state reduces the trifluoromethylating reagent yielding a $^{\bullet}CF_3$ radical species that undergoes a Giese-type addition to an alkene. The newly generated carbon-centered radical is ultimately oxidized by the oxidized state photocatalyst $[PC]^{+}$ to the carbocation, which is then trapped *via* polar reaction with the corresponding nucleophile (Fig. 1A). In addition, such organic skeletons can be accessed through transition metal catalysis.⁶ Therefore, new synthetic methods for the construction of sequential $C(sp^3)$ – CF_3 and $C(sp^3)$ –Nu bonds without exogenous catalysts is highly desirable.

In 2021, the Ritter group⁷ presented a bench stable CF_3 -containing sulfonium salt (trifluoromethyl-thianthrenium salt TT- CF_3 OTf), which is synthesized in a single step from Tf_2O and thianthrene. This reagent has proved to be efficient towards formal CF_3^+ , CF_3^- and $^{\bullet}CF_3$ reactivity. Among its use in free-radical based synthesis,⁸ the same research group⁹ presented an intermolecular amidotrifluoromethylation of acrylates *via* α -thianthrenium carbonyl species using the TT- CF_3 OTf reagent (Fig. 1B).

In this study, we present a metal-free method for the intermolecular 1,2-difunctionalization of alkenes for the efficient preparation of CF_3 -containing ethers, alcohols, and azides (Fig. 1C). This protocol does not require exogenous photocata-

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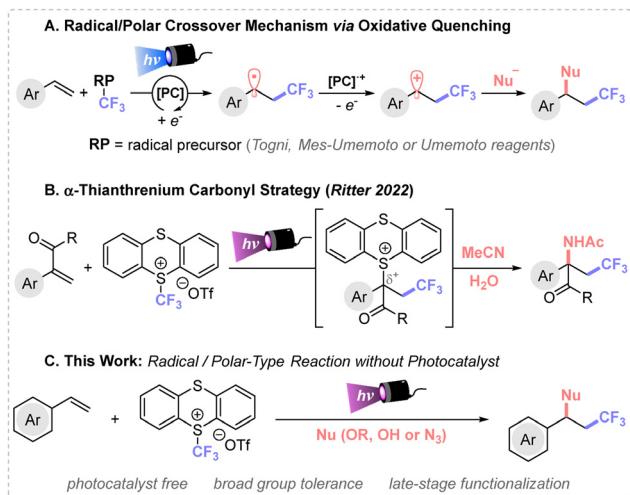


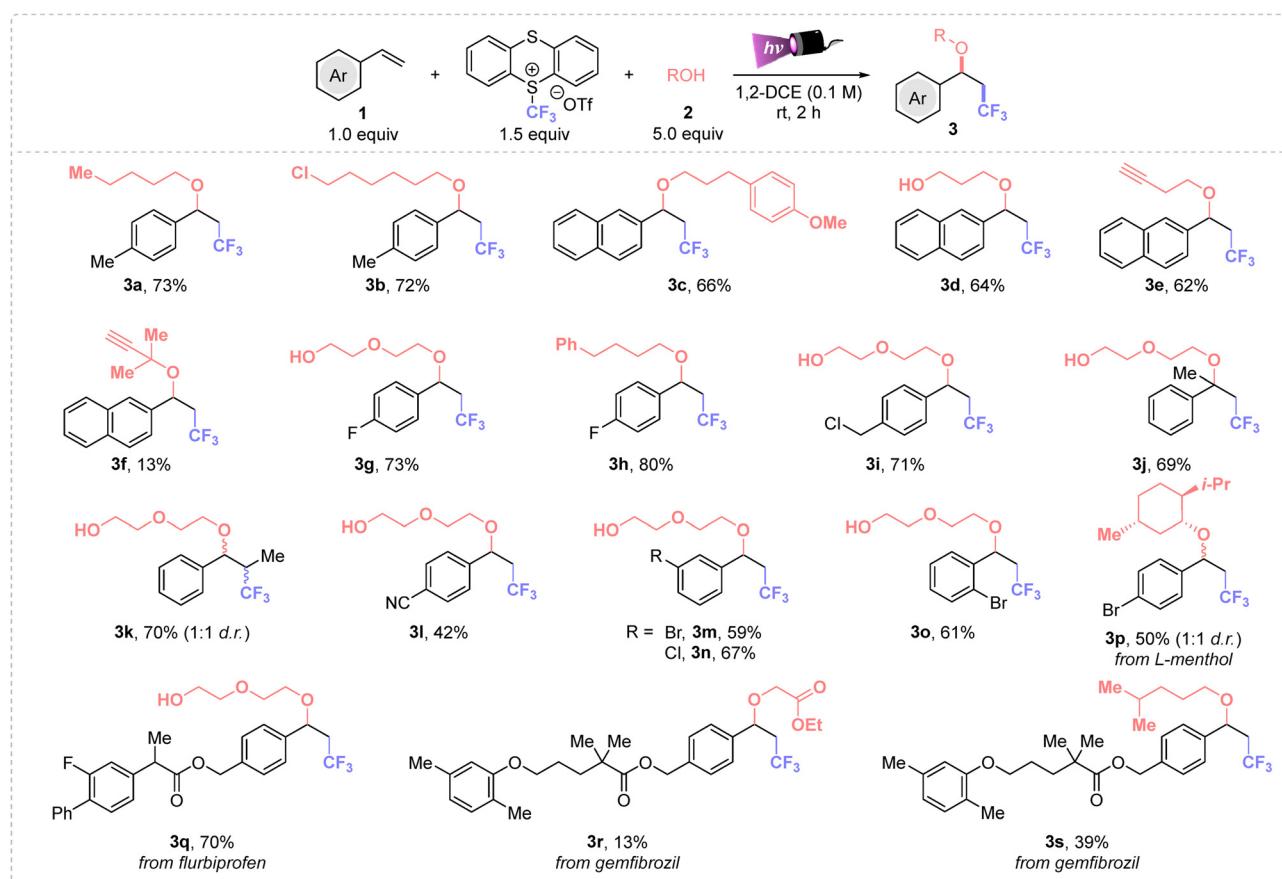
Fig. 1 Different trifluoromethylation reactions, followed by nucleophilic attack by a radical/polar-type strategies.

lysts, allows for the easy recovery of the thianthrene byproduct, and features short reaction times. These advantages make this transformation an attractive alternative to other reported procedures.¹⁰

Results and discussion

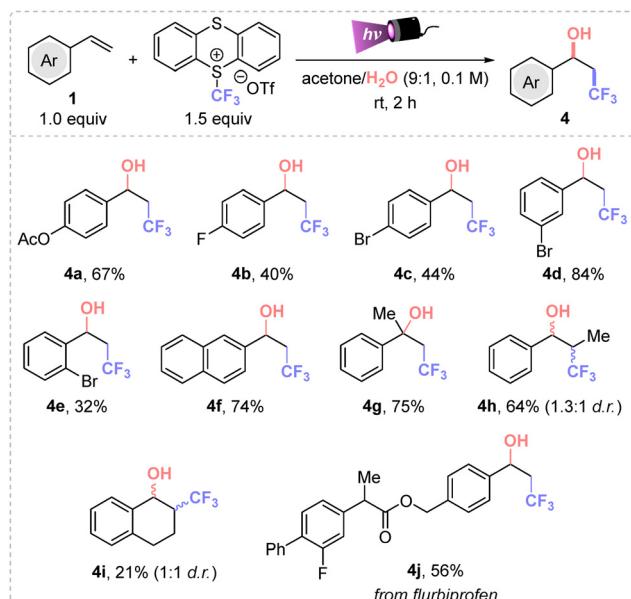
First, we explored the alkoxytrifluoromethylation process using the trifluoromethyl-thianthrenium salt as the CF_3 source, *n*-pentanol as nucleophile and 4-vinyltoluene as the model alkene. The screening revealed that the use of 1.5 equiv. of TT- CF_3OTf and 5.0 equiv. of the alcohol in 1,2-dichloroethane as solvent (0.1 M) yielded product **3a** in 73% yield (see Tables S1 and S2 in the ESI†).

The optimal conditions were applied to a wide range of styrenes (Scheme 1), where first different primary alcohols were tested obtaining the desired compounds from moderate to high yields. Both electron-poor and weak electron-donating substituents were suitable to this alkoxytrifluoromethylation process (**3a–r**). Notably, ether **3i** derived from *p*-vinylbenzyl chloride was obtained in high yield, and no nucleophilic substitution to the chlorinated benzylic position was detected, showcasing the high selectivity of this process. Moreover, products **3p–s** evidenced the potential of this methodology for late-stage functionalization of complex molecules. Disubstituted styrenes (α -methyl and *trans*- β -methyl styrenes) afforded **3j–k** in good yields, displaying that steric effects do not affect to the Giese addition step, neither the nucleophilic attack. Furthermore, the substitution position on the aromatic



Scheme 1 Scope of ethers. Standard conditions: **1** (0.25 mmol), **2** (5.0 equiv.) and TT- CF_3OTf (1.5 equiv.), in dry degassed 1,2-DCE (2.5 mL, 0.1 M) under purple Kessil irradiation ($\lambda_{\text{max}} = 390$ nm) for 2 h at rt under inert atmosphere. DCE = dichloroethane.



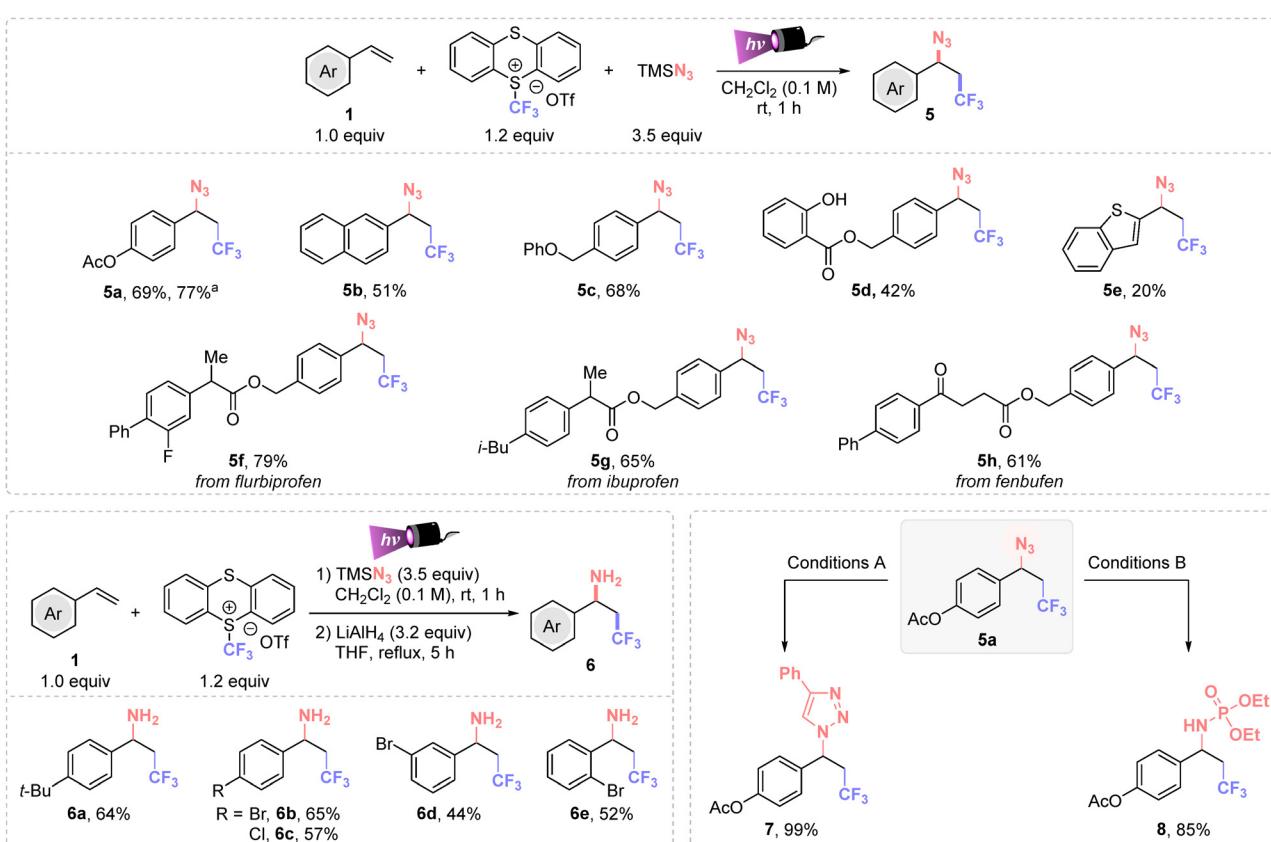


Scheme 2 Scope of alcohols. Standard conditions: **1** (0.25 mmol) and TT-CF₃OTf (1.5 equiv.), in dry degassed mixture of acetone/H₂O (2.5 mL, 0.1 M) under purple Kessil irradiation ($\lambda_{\text{max}} = 390$ nm) for 2 h at rt under inert atmosphere.

ring do not have direct impact on the reactivity, thus we could isolate **3m–p** in similar yields.

Then, the scope of the reaction was expanded to various alkyl alcohols, observing that primary, secondary (**3p**) and tertiary alcohols (**3f**) can be tethered in the final molecule. In addition, a 13% of **3f** was achieved from tertiary 2-methylbut-3-yn-2-ol. Different functional groups derived from the alcohol were also well tolerated such as a chloro handle (**3b**), which can be used for further diversification, terminal alkynes (**3e–f**), susceptible to undergo radical insertion, and ester (**3r**), among others. Notably, ethylene glycol and 1,3-propanediol were successfully used as diol nucleophiles. Importantly, products derived from a double nucleophilic attack were not detected, affording exclusively ethers **3d**, **3g**, **3i–o** and **3q**. Furthermore, L-menthol was also a suitable oxygenated nucleophile for this transformation, affording **3p** in 50% yield and 1:1 diastereomeric ratio. Unfortunately, nonactivated alkenes or phenylacetylene did not proceed well (see Section 2.2.3 in the ESI†).

Additionally, we focused on studying the hydroxytrifluoromethylation protocol using water as nucleophile for the synthesis of **4** (Scheme 2). The difunctionalization of various styrenes was successfully accomplished employing a mixture of acetone/water in a 9:1 ratio (Scheme 2). Optimization studies are detailed in the ESI†. Different trifluoromethyl alcohols



Scheme 3 Scope of azides and derivatives. Standard conditions: **1** (0.5 mmol), TT-CF₃OTf (1.2 equiv.) and TMSN₃ (3.5 equiv.), in dry degassed CH₂Cl₂ (5 mL, 0.1 M) under purple Kessil irradiation ($\lambda_{\text{max}} = 390$ nm) for 1 h at rt under inert atmosphere. ^a Large scale synthesis. Conditions A: phenyl acetylene (3.0 equiv.) and CuI (30 mol%), in THF for 16 hours at 60 °C. Conditions B: triethylphosphite (2.0 equiv.) in CH₂Cl₂ for 16 hours at rt.



were obtained in moderate to good yields (**4a–j**). The formation of **4g** and **4h** in high yields from the corresponding *α*-methyl and *trans*-*β*-methyl styrenes was also remarkable. Then, *meta*-bromostyrene afforded the final product **4d** in higher yield than the corresponding *para*- and *ortho*-bromo styrenes. Also, the flurbiprofen derivative **4j** was afforded in 56% isolated yield.

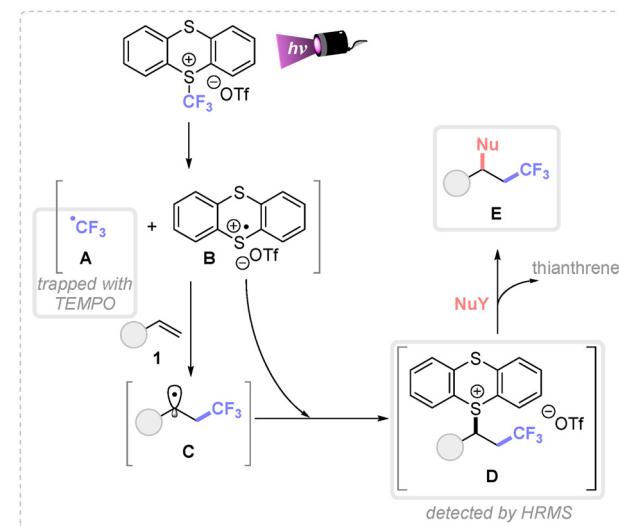
Then, we compared the efficiency of the method with other nucleophilic partners than oxygenated ones. Azides are versatile functional groups that can be engaged in several transformations to easily increase molecular complexity. Thus, azidotrifluoromethylation of different (hetero)arylethylenes was achieved within minutes, using 3.5 equiv. of TMNS_3 and dichloromethane as solvent (Scheme 3). A detailed optimization study is provided in the ESI (Table S5†). This protocol allowed the synthesis of different trifluoromethyl azides (**5a–e**) in moderate to good yields. Additionally, important pharmaceutical derivatives (flurbiprofen, ibuprofen and fenbufen) were successfully difunctionalized in high yields (**5f–h**). These examples highlight that this synthetic method enables the simultaneous late-stage installation of CF_3^- and N_3^- groups in complex molecules.

Importantly, 1,2-aminotrifluoromethylated compounds are easily accessible using a straightforward two-step synthesis (Scheme 3, bottom left). This involved the sequential $\text{C}(\text{sp}^3)\text{-CF}_3$ and $\text{C}(\text{sp}^3)\text{-N}_3$ bonds formation followed by a LiAlH_4 reduction. This protocol is particularly advantageous for 1,2-trifluoromethylated azides that may present issues during the isolation process from the thianthrene side product. The use of *ortho*-, *meta*- and *para*-bromo-, *para*-chloro- and 4-*tert*-butylstyrenes successfully afforded the corresponding trifluoromethylated benzylic amines **6a–e** in good yields.

The synthetic value of this multicomponent reaction was proved by the scalability of the reaction (Scheme 3, **5a** isolated in 77% yield), and by downstream transformations of **5a**. The formation of triazol **7** and iminophosphorane **8** were successfully achieved in 99 and 85%, respectively (Scheme 3, bottom right).

Finally, to elucidate the plausible mechanism involved in these transformations, control experiments were performed. The necessity of 390 nm Kessil lamp evidenced the photochemical nature of this transformation and the use of TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl) inhibited the reaction detecting the TEMPO- CF_3 adduct by GCMS (Scheme 4).

Based on these experimental observations and related literature,^{4h,8} a plausible mechanism is depicted in Scheme 4. First, the direct irradiation of the TT- CF_3OTf salt generates the corresponding trifluoromethyl radical **A** and the thianthrene radical cation **B**, by σ -homolytic cleavage of the S–C bond. Given the different reactivity of both species, **A** undergoes a fast and irreversible Giese addition with the activated alkene, forming the carbon-centered radical intermediate **C**. Then, this species yields the cationic species **D** by a radical–radical coupling with the persistent radical **B**. Remarkably, intermediate **D** was detected by HRMS analysis. Finally, the corresponding nucleophile attacks the most electrophilic position of



Scheme 4 Proposed mechanism.

intermediate **D**, displacing the thianthrene leaving group and forming the desired product **E**.

Conclusions

In conclusion, an operationally simple protocol for the alkoxy-, hydroxy-, and azidotrifluoromethylation of styrene derivatives is reported. These methods allowed the subsequent formation of a $\text{C}(\text{sp}^3)\text{-C}(\text{sp}^3)$ and $\text{C}(\text{sp}^3)\text{-heteroatom}$ bonds from commercially or readily available compounds in one step. This difunctionalization method do not require the use of metals or exogenous photocatalysts. The efficiency of this reaction relies on the generation of $\cdot\text{CF}_3$ and thianthrene radical cation after homolytic fragmentation of the fluorinated reagent by simple 390 nm irradiation. The key intermediate is the sulfonium intermediate **D** that have shown to be versatile towards different substitution reactions. Moreover, the large-scale preparation and late-stage functionalization of pharmaceuticals illustrates the utility of this reported difunctionalization method.

Author contributions

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

Data availability

The data supporting this article have been included as part of the ESI.† Experimental procedures and analytical data (NMR, MS, IR, and melting points) can be found in the ESI.† Copies of NMR spectra are also provided.



Conflicts of interest

There are no conflicts to declare.

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