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Photochemical thiocarbonyl difluoride generation enables azetidine synthesis

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The activation of amines into thiocarbamoyl fluorides (TCarbFs) provides access to valuable nitrogen-based functionalities. However, their broader use has been hindered by the reliance on harsh reagents and conditions. Here we report a photochemical method for in situ generation of thiocarbonyl difluoride (TCF) from *N*-trifluoromethylthiophthalimide (Phth–SCF_3) using visible light and organic reductants. This strategy allows the synthesis of structurally complex azetidines from strained azabicyclo[1.1.0]butanes (ABBs). TCF-mediated ring opening followed by semipinacol rearrangement or nucleophilic additions enables direct access to spiro- and fluorinated TCarbF-azetidines in a single step. Mechanistic studies support a single-electron reduction pathway and rationalize the impact of the photocatalyst on the observed selectivity. The discovery offers a general platform for amine activation and addresses a long-standing gap in azetidine functionalization.

The facile activation of amines into synthetically versatile reactive intermediates is a key strategy for accessing or modifying nitrogen-containing functionalities[1]. This approach has fostered the popularity of several commodity reagents (Fig. 1A, left), such as (thio) phosgene, carbonyldiimidazole (CDI), as well as sulfonyl fluorides[2,3], carbonyl difluoride, and thiocarbonyl difluoride (TCF)[4]. TCF activates amines into the corresponding thiocarbamoyl fluorides, powerful synthetic intermediates that can be swiftly transformed into thioureas and thiocarbamates, undergo cross-coupling, and, notably, can be directly converted into the N-CF_3 moieties, valuable yet elusive functionalities in medicinal chemistry[5–10]. Despite its synthetic potential, the chemistry of thiocarbamoyl fluorides (TCarbFs) is limited, as their synthesis historically entails the reaction of thiophosgene as a dimer with antimony trifluoride at temperatures above 400 °C to generate TCF[11,12]. Renewed interest in accessing TCarbFs emerged in 2017, marked by the development of reagents and strategies that offer several advantages over the harsh pioneering synthetic methods[13–21]. The increasing focus on this area has led to the publication of diverse approaches for the synthesis of TCarbFs, with success resorting to the in situ generation of TCF through various means (gray box in Fig. 1A). However, several challenges remain, as the preparation of these TCF sources involves air sensitive reagents and high loadings of fluorinating reagents which unavoidably result in the generation of substantial fluorinated waste[22–24]. For instance, Me_4NSCF_3 is prepared from the highly hygroscopic Me_4NF in combination with CF_3SiMe_3; $Ph_3P^+CF_2CO_2^-$ stems from triphenylphosphine and potassium bromodifluoroacetate; whereas the synthesis of *N*-tosyl, *N*-methyltrifluoromethanesulfenamide (BB23) requires (diethylamino)sulfur trifluoride (DAST) and iodomethane[25].

Regardless of the strategy chosen, it is intriguing that the reactivity of azetidines with TCF remains virtually unexplored (red box in Fig. 1A). Therefore, the direct activation of azetidines into the corresponding TCarbFs would establish an ideal strategy for their functionalization, significantly expanding the chemical space related to this four-membered heterocycle[26,27].

In a separate framework, *N*-trifluoromethylthiophthalimide (Phth-SCF_3)[28], is a well-established reagent commonly employed for the introduction of the SCF_3 group into organic molecules (Fig. 1B, left). Its preparation employs *N*-bromophthalimide and $AgSCF_3$ without the

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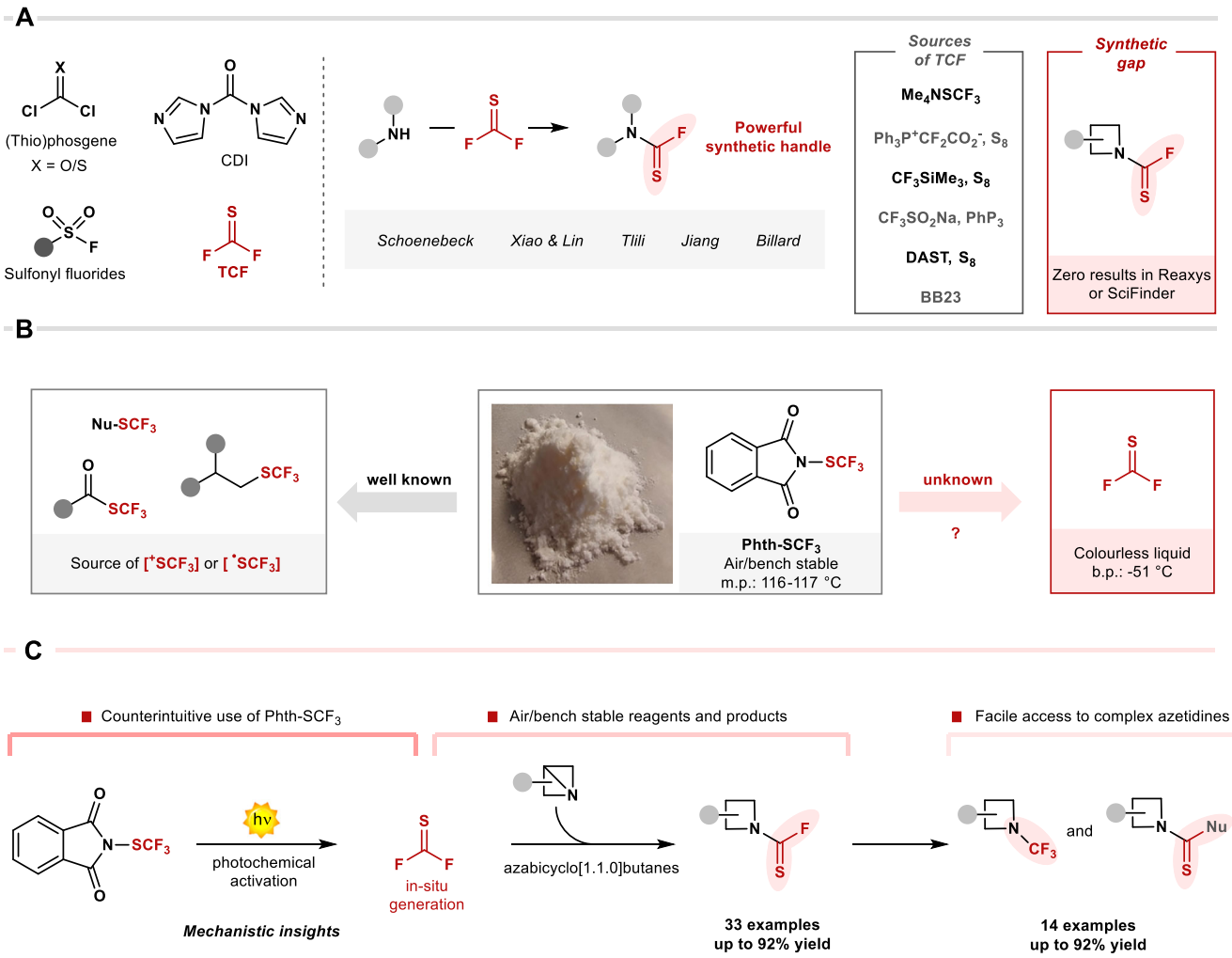


Fig. 1 | Rationale and origins of the reactivity. A Selected commodity reagents for amine activation and state-of-the-art in TCF application showcasing azetidine gap. **B** Phth-SCF_3 as versatile reagent. **C** Photochemical activation of Phth-SCF_3 as source of TCF for azetidines synthesis reported in this work.

need of inert atmosphere. Phth-SCF_3 has traditionally served as an electrophile, as a SOMOphile (SOMO = singly occupied molecular orbital), and as a precursor to (trifluoromethyl)thiyl radicals ($^{\bullet}SCF_3$)[29–32]. However, its high synthetic reliability and extensive application for these purposes might result in missed opportunities for the development of new applications. Our research motivation is to offer the scientific community an alternative solution to the safe and efficient generation of TCF for amine activation, by rejuvenating the chemistry of Phth-SCF_3. This study reports an unexpected and previously unrecognized photochemical reactivity of Phth–SCF_3 under the control of light-absorbing organic molecules, enabling the in-situ generation of TCF under mild and operationally friendly conditions (Fig. 1C). Successful implementation of the discovery allows the direct conversion of strained azabicyclo[1.1.0]butanes (ABBs) and other commercially available amines into structurally complex TCarbFs.

Results and discussion

A serendipitous discovery

In conjunction with our research program for developing novel light-mediated transformations on ABBs[33–39], we faced an unforeseen reaction outcome while exploring **1** (Fig. 2A). The reported three-component reaction uses TBCzTrz as photocatalyst (PC) (Fig. S7) and proceeds through triplet sensitization of aldimine **2**, delivering the C3-SCF_3 sulfonylazetidine **3**[40]. Under these conditions, Phth-SCF_3 acts as a SOMOphile for the integration of the SCF_3 group (Figs. S3–S6). In an unexpected turn, performing the same reaction in non-anhydrous ethyl acetate resulted in the formation of compound **4**. A retrosynthetic analysis of **4** (Fig. 2B) allowed us to identify three possible events: (1) formation of the TCarbF unit by opening the ABB **1** in polar fashion leveraged by TCF, (2) generation of a transient electrophilic site at C3 and (3) sulfonamide formation through hydrolysis of **2**. Considering that Phth-SCF_3 is the only fluorine-containing entity in the media, the question thus became: How does one generate TCF from Phth-SCF_3? Exploratory experiments combining **1** with *p*-toluenesulfonamide and Phth-SCF_3 allowed the formation of **4** (Tables S3, S4). Attempted optimization revealed that light and a PC were required, but this transformation had a poor prognosis for improvement; also, similar scaffolds were already investigated in our previous report. The potential to generate a transient electrophilic site at the C3 position was considered a promising strategy for accessing structurally complex azetidines, particularly those in which the nitrogen atom is directly functionalized with a non-protecting group. The knowledge that azabicyclo[1.1.0]butyl carbinols can undergo strain-release reactions upon *N*-activation[41–43], encouraged us to explore TCF as an activator (Fig. 2C). In line with previous reports, we anticipated that the activation of **5** with TCF would be well suited for the generation of an electrophilic C3, facilitating a semipinacol rearrangement, consequently furnishing synthetically flexible products.

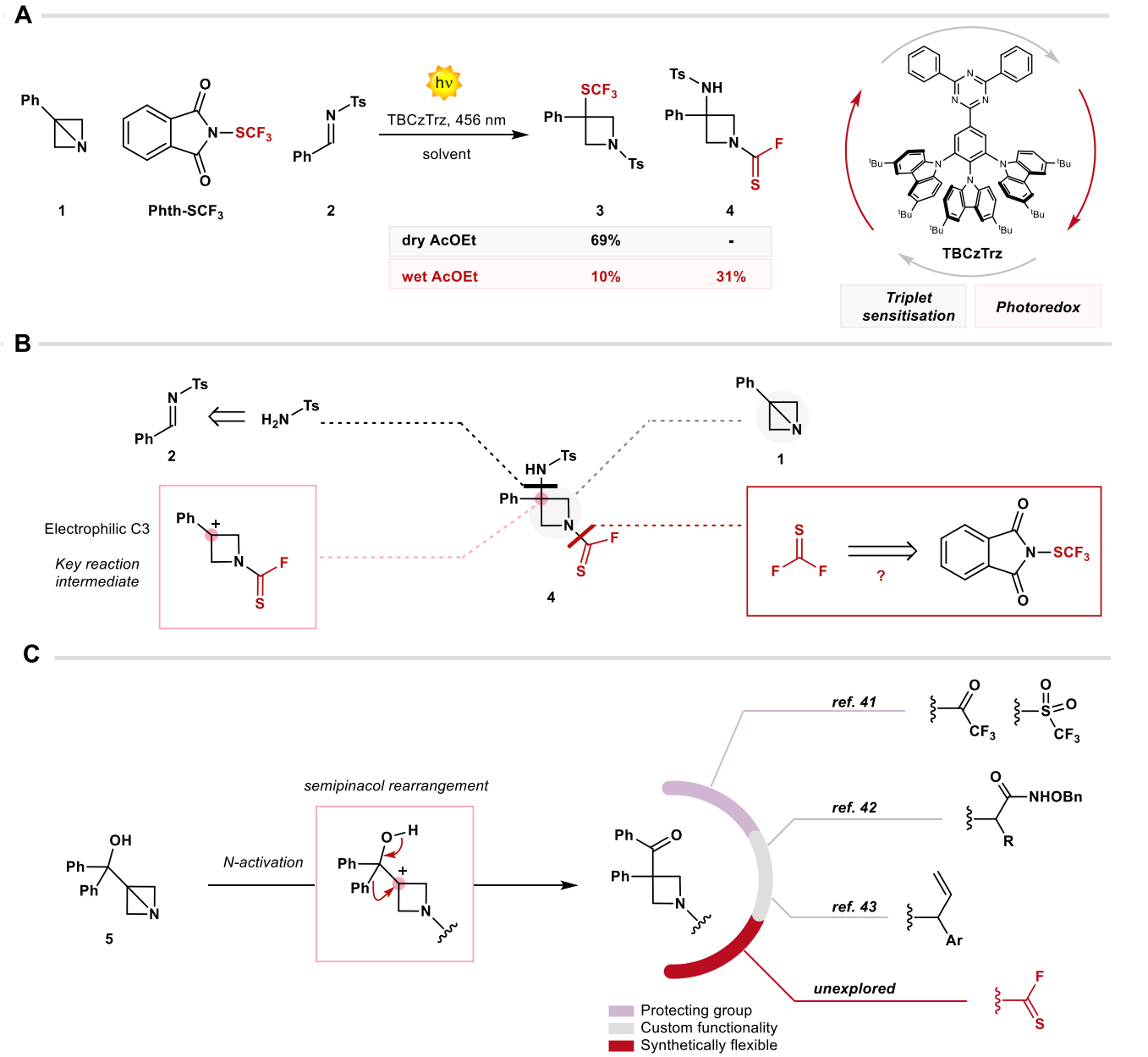


Fig. 2 | Progress toward a profitable *N*-functionalization. A Unexpected reactivity through dual performance of TBCzTrz. **B** Retrosynthetic analysis to explain the origins of **4**. **C** Hypothesized semipinacol rearrangement for functionalization of **5** and related state-of-the-art.

Development of a light-mediated semipinacol rearrangement

Initial experimentation focused on clarifying if the targeted reactivity could be achieved by exclusively polar means. The reaction of **5** with tetramethylammonium trifluoromethanethiolate (Me_4NSCF_3) as a documented source of TCF[44], did not afford the expected product **6**; the use of additives or alternative solvents proved unsuccessful (Table S5). We thus proceeded to evaluate the photochemical domain, screening different parameters for the reaction between **5** and Phth-SCF_3 (Table S6). Mixing **5** (1 equiv) with Phth-SCF_3 (2.5 equiv) and TBCzTrz (2.5 mol %) under 427 nm irradiation, gave 21%, with no recovery of starting material and low selectivity with respect to the undesired spiroepoxy azetidine **7** (6% yield). Further tests of additives led to a refined protocol involving commercially available Hantzsch ester (HE, 2.5 equiv) and toluene as solvent (Fig. 3A and Table S6). These conditions afforded **6** in 69% yield, with improved selectivity (**7** = 9% yield, ^{19}F NMR yields). During this optimization phase (see Tables S3–S7), we realized that removing the PC while exploiting the photoactivity of HE, it is possible to access **6** although with a diminished selectivity (Fig. 3A). Interestingly, replacing Phth-SCF_3 with the N-SCF_3 derivatives of succinimide (Succ-SCF_3) and saccharin (Sacc-SCF_3), led to **6** in 52% (**7** = 19%) and 0% yield (**7** = 0%), respectively (Fig. 3A).

Mechanistic investigations

Mechanistic studies gave insight into the evolution of Phth-SCF_3 and how it serves as an activator of the ABBs to access TCarbF azetidines (Fig. 3B). Time-resolved luminescence experiments on TBCzTrz were performed to provide evidence on the primary photochemical process. While negligible quenching of the prompt fluorescence (PF) of TBCzTrz is observed in the presence of all reactants ($\tau \sim 19$ ns as

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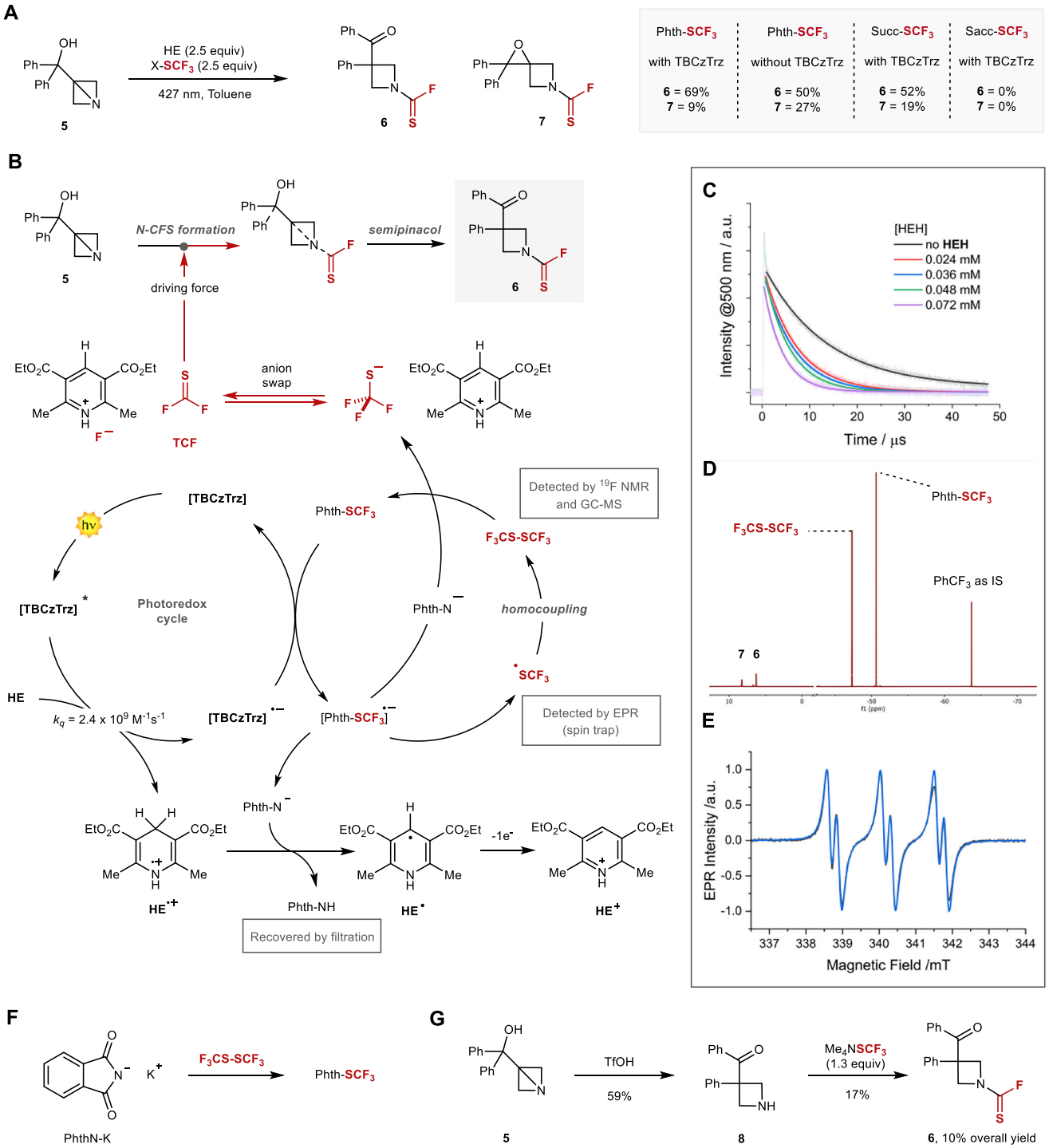


Fig. 3 | Experimental mechanistic analysis. A Representative variations from the optimized conditions. **B** Proposed reactivity for the photocatalyzed scenario. **C** Time-resolved Stern-Volmer of TBCzTrz showing HE as quencher at different concentrations. **D** ^{19}F NMR of a reaction aliquot (4 h) without evaporation showing the fluorine-containing specimens in reaction. **E** EPR of trapped $^{\bullet}SCF_3$ radical by PBN. **F** F_3CSSCF_3 as electrophile for preparing Phth-SCF_3. **G** Two-steps strategy to access **6**.

measured by time-correlated single photon counting, see Fig. S13), laser flash photolysis (LFP) experiments demonstrate that the delayed fluorescence (DF) component is efficiently quenched by the HE (bimolecular rate constant of $k = 2.4 \times 10^9 M^{-1}s^{-1}$, Fig. 3C), whereas quenching by **5** or by the Phth-SCF_3 is substantially less effective (bimolecular rate constants of $k = 3.7 \times 10^6$ and $5.0 \times 10^5 M^{-1}s^{-1}$, respectively, Figs. S14–S19). Additionally, steady-state absorption studies of the reaction components showed no evidence of ground-state associations (Fig. S20). Altogether, these experiments indicate that the main photochemical event involves the interaction between the triplet excited state of TBCzTrz and HE. The progress of the reaction was monitored using ^{19}F NMR, which showed a signal at −46.9 parts per million (ppm) (Fig. 3D). This signal was assigned to bis(trifluoromethyl)disulfide (F_3CSSCF_3). Additionally, analysis of both the headspace and the reaction bulk by gas chromatography-mass spectrometry (GC-MS) corroborated the presence of F_3CSSCF_3

(Figs. S53, S54). The formation of F_3CSSCF_3 under the given reaction conditions can be exclusively attributed to the homocoupling of the $^{\bullet}SCF_3$ radical, providing key mechanistic insight into the reaction pathway. In agreement with the literature[32], electrochemical studies revealed that the one electron reduction of Phth-SCF_3 triggers its heterolytic scission, resulting in the formation of the phthalimide anion (Phth-N^-) and $^{\bullet}SCF_3$. This knowledge allowed us to assume that reductive quenching of TBCzTrz by the HE (TBCzTrz* + HE → TBCzTrz$^{\bullet-}$ + HE$^{\bullet+}$), followed by single electron transfer (SET) with Phth-SCF_3 (E_{ox} TBCzTrz $^{\bullet-}$/TBCzTrz = −1.58 V vs SCE (DCM), E_{red} Phth-SCF_3/Phth-$SCF_3^{\bullet-}$ = −1.44 V vs SCE (DCM)) generates (Phth-N^-) together with $^{\bullet}SCF_3$, restoring the ground state of the PC. To further corroborate the generation of $^{\bullet}SCF_3$, while gathering more information about the overall mechanistic machinery, electronic paramagnetic resonance (EPR) studies were conducted. A reaction mixture of TBCzTrz and Phth-SCF_3, with or without **5**, was incubated in the presence of PBN (*N*-tert-Butyl-α-phenylnitrone) as a spin trap. The samples were kept either in the dark or subjected to irradiation under conditions optimized for the reaction. While the solutions were EPR silent in the absence of irradiation, the spectra obtained after irradiation revealed the presence of a single, identical radical species in both solutions (Fig. 3E, Figs. S40, S41). This observation ruled out the possibility that the trapped radical originated from the heterocycle. The fact that azetidines **6** and **7** were formed in comparable overall yields regardless of the presence or absence of the photocatalyst, albeit with differences in selectivity (Figs. S50, S51), prompted us to perceive these synthetic transformations as two distinct mechanistic scenarios.

We propose that in the photocatalyzed scenario (Fig. 3B), both the (Phth-N^-) and ($^{\bullet}SCF_3$) generated upon one electron reduction of Phth-SCF_3, enter a loop in which the $^{\bullet}SCF_3$ radical undergoes homocoupling, as its polarity mismatch renders it unreactive toward the substrates in solution. Subsequently, the nucleophilic addition of (Phth-N^-) on the newly formed dimer regenerates Phth-SCF_3 and yields the trifluoromethanethiolate anion ($^-SCF_3$). The feasibility of this step was independently corroborated by treating potassium phthalimide (PhthN-K) with freshly prepared F_3CSSCF_3 (Fig. 3F, S44–46). Once generated, the ($^-SCF_3$) anion undergoes fluoride extrusion, forming TCF. We believe this step is aided by the nature of the involved counterions and driven by the irreversible reaction between TCF and the ABB. Next, the so activated ABB **5** undergoes semipinacol rearrangement leading to **6**. It is worth noting that under the proposed reaction platform, two photons are responsible for the generation of one molecule of TCF. In fact, as the loop is fueled with two molar equivalents of Phth-SCF_3 and HE to produce one molar equivalent of **6**, we surmise it is profitable until depletion of **5**.

Building on the fact that the formation of TCF from ($^-SCF_3$) is not a spontaneous event[13–15], together with the described lack of reactivity of tertiary amines towards TCF and the recovery of unreacted substrates in the polar tests (Table S5), we cannot exclude the possibility of an alternative activation system for compound **5**. Reductive quenching of the PC by HE generates [HE$^{\bullet+}$], which is sufficiently acidic $pK_a \approx 2$[45–47] to protonate and generate the corresponding ammonium species of compound **5**[48,49], stabilized by the ($^-SCF_3$) anion. This interaction could facilitate the formation of TCF and concurrently promote the semipinacol rearrangement (Fig. S49). The feasibility of this hypothesis was assessed by dissecting the overall transformation into two individual steps: i) the acid-mediated opening of compound **5**, followed by ii) the treatment with Me_4NSCF_3 to afford compound **6** (Fig. 3G, Figs. S47, S48). Although this pathway appears reasonable, the free NH azetidine **8** resulting from the semipinacol rearrangement was never detected in the photochemical reactions, thereby hindering us from presenting this mechanistic premise.

Alternatively, in the absence of PC, light irradiation promotes HE to its singlet excited state [HE]*.

This species is anticipated to be responsible for the one electron reduction of Phth-SCF_3 entering the loop as described above (Fig. S56). Indeed, luminescence studies show that the fluorescence of HE is efficiently quenched upon the addition of increasing amounts of Phth-SCF_3 (Fig. S21) and Stern–Volmer analysis yields a bimolecular rate constant of $k = 1.8 \times 10^{10}\ M^{-1}s^{-1}$. This process is thermodynamically allowed by ca 0.6 eV according to the estimated redox potentials (E_{ox} HE*/HE$^{\bullet+}$ = −1.93 V vs SCE, E_{red} Phth-SCF_3/Phth-$SCF_3^{\bullet-}$ = −1.29 V vs SCE in MeCN). Based on the experimental observations and gathered spectroscopical evidence, we posit that the relative rate of formation of the ($^{\bullet}SCF_3$) anion highly impacts on the final selectivity between **6** and **7**. When TBCzTrz is included, the concentration of the reactive specimens is very low, because the loop is fed in catalytic fashion; contrary to the stoichiometric amounts of [HE]*. Spectroelectrochemistry (SEC) studies allowed us to follow the evolution of HE towards the pyridine analogue and confirm the formation of the (Phth-N^-) anion (see Figs. S31–S38). These observations aided us in discarding the participation of the (Phth-N^-) anion in any light-induced event[50]. Further EPR experiments involved mixtures of Phth-SCF_3 with and without HE incubated with a different spin trap (MNP, 2-methyl-2-nitrosopropane). These solutions were either kept in the dark or subjected to irradiation. Notably, significant radical formation was observed only in the irradiated mixture containing Phth-SCF_3, HE, and MNP (Figs. S42, S43). The EPR spectrum confirmed the generation of an SCF_3 radical, accompanied by a modest signal (~10%) corresponding to a C–H-centered radical, attributed to the Hantzsch ester radical [HE$^{\bullet}$]. Importantly, regardless of the presence or absence of the photocatalyst, both HE and Phth-SCF_3 were fully converted into the corresponding pyridine derivative and phthalimide (Phth-NH), indicating that the same radical species are formed under all reaction conditions.

Generality of the method

This optimized protocol afforded various TCarbF (spiro)azetidines **9-25** containing a quaternary centre with yields up to 95% (Fig. 4, conditions A). The generality of the process includes multiple (hetero) aromatic rings as the migrating group, a variety of azaspiro[3.n]alkane ring systems ($n = 5$, 6, 7), and azetidine-containing analogues of oxcarbazepine, naproxen and ibuprofen. Additionally, olefins proved successful as migrating group (**26, 26', 27, 27'**), displaying an effect of the mechanistic platform on the final stereochemistry (*E/Z*) and pleasingly unreactive towards the possible $^{\bullet}SCF_3$ addition. We also showcased the possibility of conducting the reaction on a bigger scale as compounds **17, 18**, and **21** were furnished in synthetically useful yields (69%, 83%, 81%, respectively performing in 1 mmol scale. **21** was obtained in 66% yield operating in 17 mmol scale).

Drawing from the success of the semipinacol rearrangement, we proceeded to investigate an alternative family of ABBs for TCF activation. Initial experiments with **1** revealed the mono-fluorination at the C3 position in the final azetidines (Table S4). This finding not only offered further evidence that the activation of ABBs via the developed method proceeds through polar ring opening but also facilitates access to complex molecular structures that are typically difficult to obtain[51]. During the exploratory stage of this synthetic variation, we observed an intriguing, yet useful effect on the reaction outcome when conducting the reaction with and without the photocatalyst. The use of 5TBCzBn (Fig. 5, conditions B), diminished the yield of the mono-fluorinated azetidine, delivering as the major product the analogue with the SCF_3 functionality incorporated at C3 (compare **28** and **34**, 77%/22% yield). Conversely, the removal of the PC (Fig. 5, condition C) reversed the outcome (compare **28** and **34**, 27%/72% yield), preserving the reaction efficiency (Fig. S57). Diverse representative functionalities were evaluated, displaying good yields and a high impact on the anion trapping selectivity. The lack of an absolute chemodivergency on the method might be attributed to a

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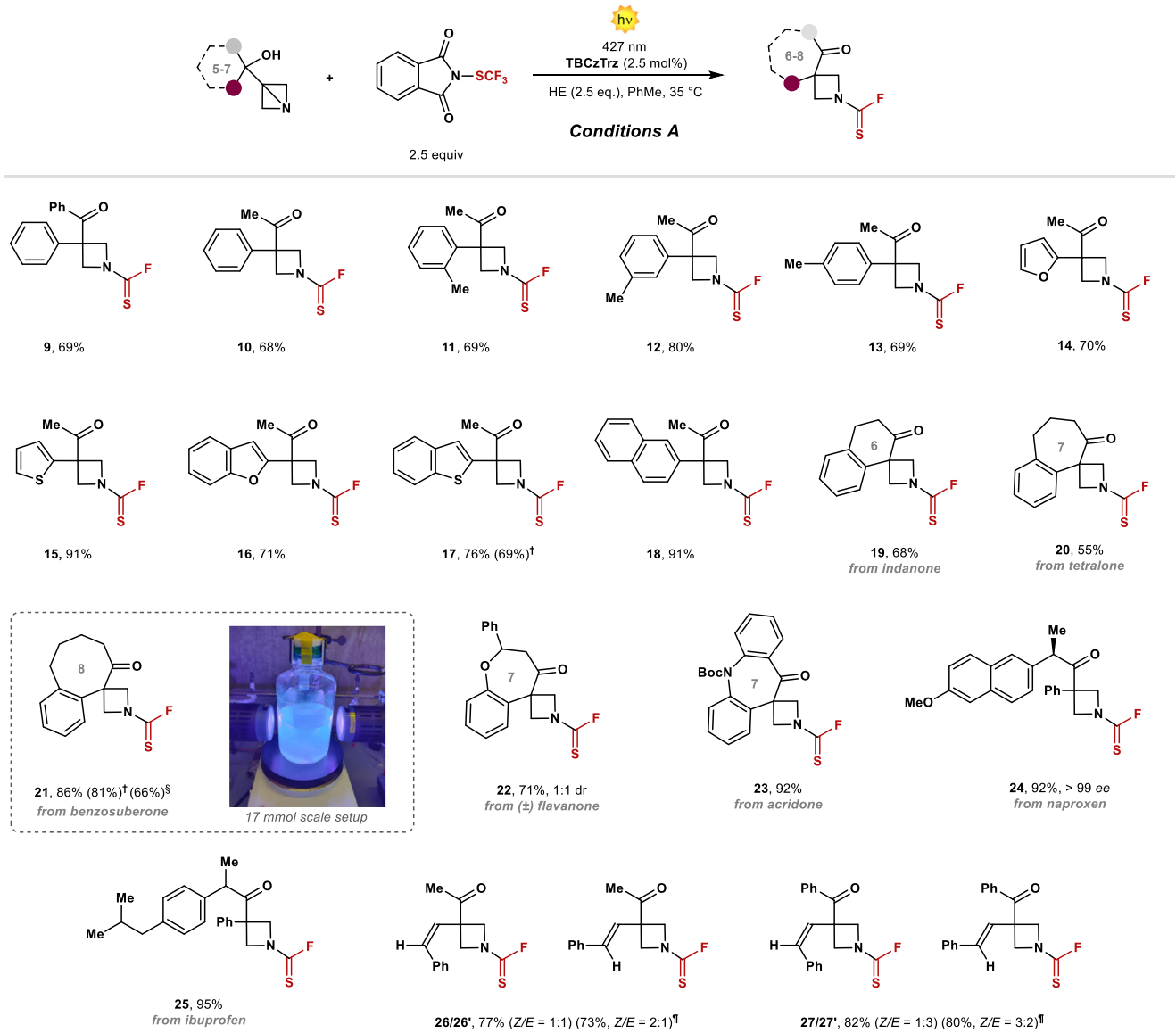


Fig. 4 | Scope of light-promoted semipinacol rearrangement as strategy. ABB (0.05 mmol, 1 equiv), Phth-SCF_3 (31 mg, 0.125 mmol, 2.5 equiv), Hantzsch ester (32 mg, 0.125 mmol, 2.5 equiv) and TBCzTrz (1.4 mg, 2.5 mol%) were dissolved in toluene (0.7 mL). The reactions were irradiated using a Kessil lamp 427 nm) for 21 h at 35 °C. ^{19}F NMR yields using α,α,α-trifluorotoluene as internal standard are shown. Reactions were conducted on a 0.05 mmol scale (unless otherwise noted) and the reported yield is the average of triplicate analysis. †Reaction performed in 1.0 mmol scale (single analysis). §Reaction performed in 17 mmol scale without TBCzTrz (single analysis). ¶Reaction performed without TBCzTrz.

variety of physicochemical factors, such as anion stability by solvation, as well as stereo- and electronic parameters. Beyond doubt, the incorporation of single fluorine atoms and the SCF_3 group is of significant interest for tuning active pharmaceutical ingredients[52,53]. However, and more important, these examples further substantiate the hypothesis that fluoride (^-F) and ($^-SCF_3$) anions are generated during the reaction.

The N-CF_3 fragment and other synthetic manipulations

Among the synthetic strategies that allow the preparation of N-CF_3 derivatives, the direct fluorination of thiocarbamoyl fluorides is one of the most straightforward approaches. As a proof of concept, we subjected some of the TCarbFs obtained in our study to standard fluorination conditions (Fig. 6A, left), displaying the corresponding N-CF_3 azetidine derivatives **40**-**46** in good yields (62%-91%). The lack of general methodologies for synthesizing these biorelevant functionalities represents an open challenge in organic synthesis. In this regard, it is noteworthy that the only available method to access N-CF_3 azetidine relies on the pyrolysis of perfluorooxazinane **55**[54], obtaining the corresponding perfluorinated azetidine **56** (Fig. 6B). We then set out to transform selected primary and secondary amines into the corresponding thioureas (Fig. 6A, right). (*S*)−2-Phenylglycinol showcased its selective N-functionalization leading to **47**. Anisylamine produced 48 in 91% yield and served as a valuable precursor for the synthesis of aminotetrazole **49**, the core structure of a LPA1 antagonist[55].

Additionally, the acetal of 1-aminoglycerol, along with tryptamine and amoxapine, was employed to successfully functionalize various mono-fluoro- and thiotrifluoromethyl-containing azetidines **50**-**54**. Subsequently, the generality of the developed photochemical method for the TFC-based activation of feedstock amines was investigated (Fig. 6C). A set of structurally diverse candidates was efficiently

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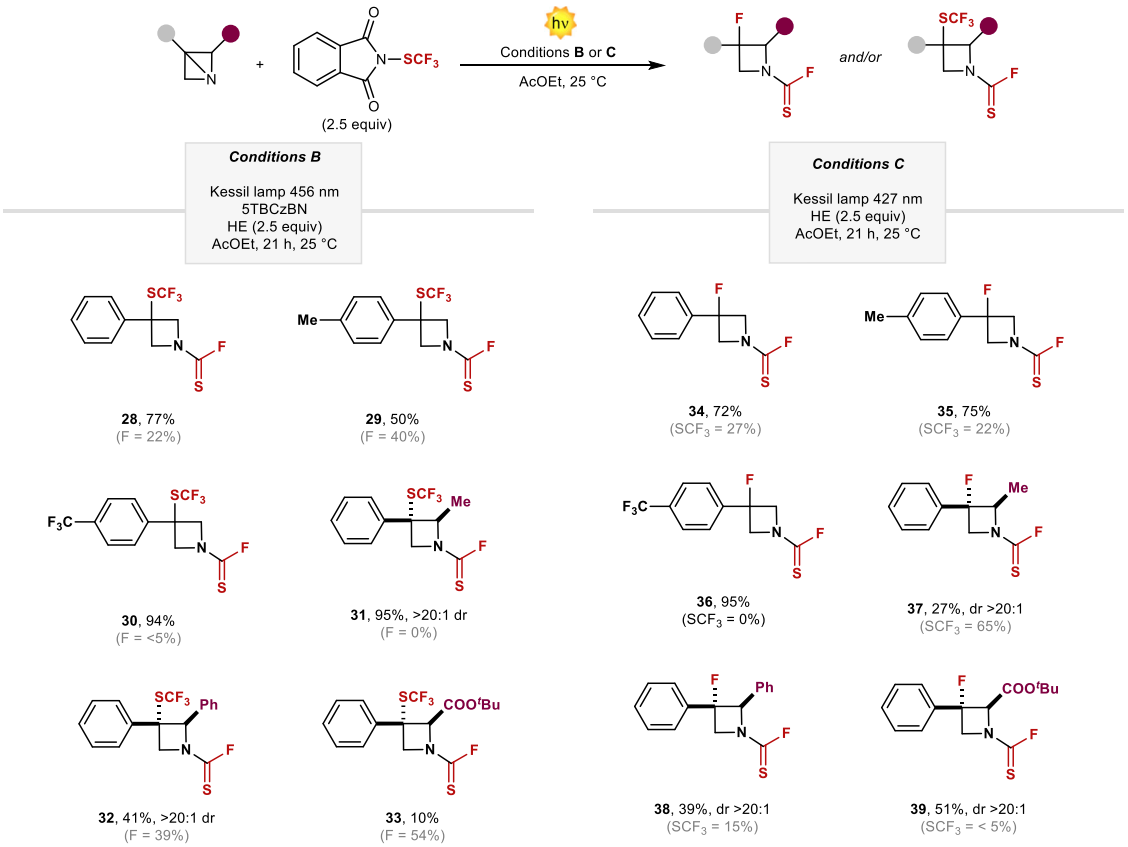


Fig. 5 | Scope of the anion trapping strategy. ABB (0.05 mmol, 1 equiv), Phth-SCF_3 (31 mg, 0.125 mmol, 2.5 equiv), Hantzsch ester (32 mg, 0.125 mmol, 2.5 equiv) and 5TBCzBN (1.4 mg, 2.5 mol%) was added (only if indicated) were dissolved in ethyl acetate (0.7 mL). Reactions were irradiated using a Kessil lamp (456 or 427 nm) for 21 hours. ^{19}F NMR yields using α,α,α-trifluorotoluene as internal standard are shown. The reported yield is the average of triplicate analysis. The yields reported in gray refer to the yields of the opposite F/SCF_3 azetidine derivatives.

transformed into the corresponding TCarbFs **57**-**61** in good yields (46%-97%). The designed protocol profits from the photoactivity of HE as a reductant, circumventing the risk of unintended oxidation of the employed amines that photoredox catalysis represents. Having established the developed photochemical protocol as a general strategy for activating not only strained ABBs but also a broader range of amines, we turned our attention to the lack of a general process to access TCarbF azetidines. Since the direct treatment of **5** with Me_4NSCF_3 failed to yield **6**, and considering the obtained results through the two-steps strategy, (Fig. 3G) we performed a comparative study using commercially available azetidine **62** as model substrate (Fig. 6D).

Under photochemical conditions, compound **63** was obtained in 25% yield, whereas thermal treatment with Me_4NSCF_3 yielded **63** in 14% yield, alongside 13% of the thiourea **64**.

We speculatively attribute the diverse selectivity to differences in the kinetics of in-situ TCF generation, reinforcing the premise that this discovery represents a reliable synthetic solution.

Inspired by an initial serendipitous observation, we have revealed an unpredictable reactivity of Phth-SCF_3 under light-driven one-electron chemistry, expanding its use in organic synthesis. This discovery accesses azetidine frameworks that have remained challenging to synthesize using pre-existing strategies. The method differs critically from other in-situ TCF generation protocols in the markedly facile preparation and handling of the reagent. Mechanistic investigations revealed that Phth-SCF_3 undergoes a photoinduced single-electron reduction, ultimately generating TCF, and we hope this concept will find applications in other research fields. More broadly, we are confident that this work marks a significant advance in photochemical transformations, particularly those involving reagents whose reactivity diverges from traditional expectations, paving the way for new reaction design and mechanistic understanding.

Methods

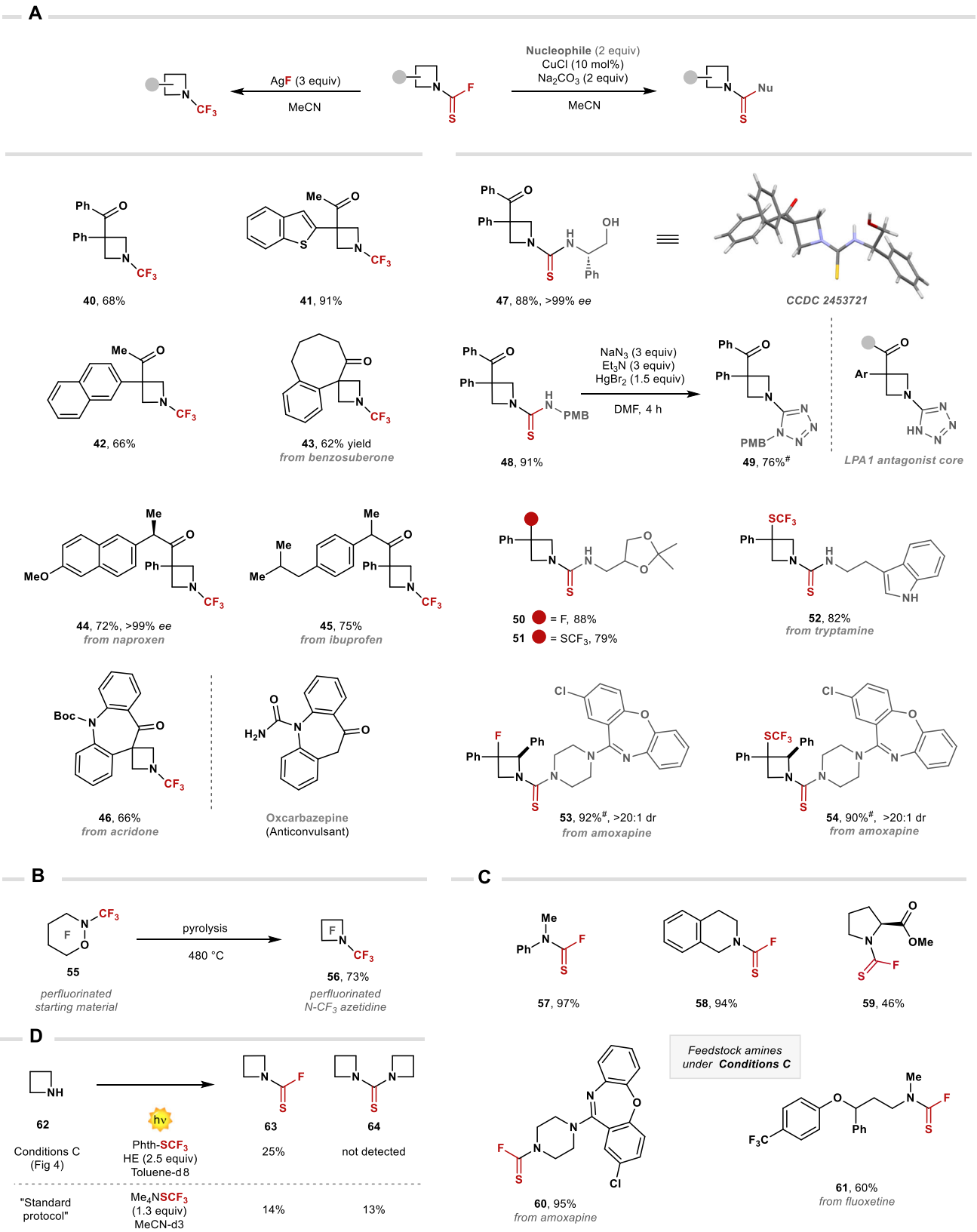
Photocatalyzed semipinacol rearrangement

A 4 mL glass vial containing an oven dried Teflon coated stirring bar, was charged with the corresponding ABB (0.05 mmol, 1 equiv), Phth-SCF_3 (31 mg, 0.125 mmol, 2.5 equiv), Hantzsch ester (32 mg, 0.125 mmol, 2.5 equiv) and TBCzTrz (1.4 mg, 2.5 mol%). The vial was closed using a screw cap with hole (PTFE/silicone septum) and purged with argon for 1 min. Under argon flux, previously deoxygenated toluene (0.7 mL) was added using a syringe. The reaction was irradiated under stirring for 21 h using the photochemical setup presented in the supplementary information. After completion, the reaction mixture was filtered to remove the resulting insoluble phthalimide, the filtrate was evaporated under reduced pressure and purified by flash column chromatography.

Photocatalyzed anion trapping strategy

A 4 mL glass vial containing an oven dried Teflon coated stirring bar, was charged with the corresponding ABB (0.05 mmol, 1 equiv), Phth-

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SCF_3 (31 mg, 0.125 mmol, 2.5 equiv) and Hantzsch ester (32 mg, 0.125 mmol, 2.5 equiv). 5TBCzBN (1.4 mg, 2.5 mol%) was added only if indicated. The vial was closed using a screw cap with hole (PTFE/silicone septum) and purged with argon for 1 min. Under argon flux, previously deoxygenated ethyl (0.7 mL) was added using a syringe. The reaction was irradiated under stirring for 21 h using the photochemical setup presented in the supplementary information. After completion, the reaction mixture was filtered to remove the resulting

Fig. 6 | Applications. A Thiocarbamoyl fluoride interconversion. Thiocarbamoyl fluoride (1.0 equiv) and AgF (3.0 equiv) were dissolved in acetonitrile (0.06 M) and stirred at 50 °C for 4 hours. **B** Only reported synthesis of N-CF_3 azetidines. **C** Implementation of discovery to feedstock amines. Amine (0.05 mmol, 1 equiv), Phth-SCF_3 (31 mg, 0.125 mmol, 2.5 equiv) and Hantzsch ester (32 mg, 0.125 mmol, 2.5 equiv) were dissolved in ethyl acetate (0.7 mL). Reactions were irradiated using a Kessil lamp (427 nm) for 21 hours. **D** Comparative evaluation of azetidine functionalization. The photochemical variation requires azetidine **62** (0.05 mmol, 1 equiv), Phth-SCF_3 (31 mg, 0.125 mmol, 2.5 equiv) and Hantzsch ester (32 mg, 0.125 mmol, 2.5 equiv) dissolved in toluene-d_8 (0.7 mL). Reaction mixture was irradiated unsing a Kessil lamp (427 nm) for 21 hours. The "standard protocol" requires **62** (0.05 mmol, 1 equiv), Me_4NSCF_3 (0.065 mmol, 1.3 equiv) dissolved in MeCN-d_3 (0.7 mL). The reaction mixture was stirred for 1 h. ^{19}F NMR yields using α,α,α-trifluorotoluene as internal standard are shown (unless otherwise noted). #Yield after isolation is shown.

insoluble phthalimide, the filtrate was evaporated under reduced pressure and purified by flash column chromatography.

Data availability

All data are available in the main text or supplementary information. Crystallographic data is available from the Cambridge Crystallographic Data Centre with the following codes: **4** (CCDC 2453720) and **47** (CCDC 2453721). Copies of the data can be obtained free of charge via https://www.ccdc.cam.ac.uk/structures. Additional data is available from the corresponding author upon request. Correspondence and requests for materials should be addressed to Luca Dell'Amico, luca.dellamico@unipd.it.

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Author contributions

R.I.R. conceived the project and devised the experiments with L.D. R.I.R., J.P., G.A., and G.C. carried out the reactions and isolated and characterized the products. L.D., R.I.R., and J.P. rationalized the experimental results. F.D., M.N., and M.B. performed the spectroscopic investigations using TAS and EPR. S.V. performed the electrochemical studies. G.P. performed the X-ray analysis. L.D. and R.I.R. wrote the manuscript with contributions from all the authors. L.D. and R.I.R. directed the work.

Competing interests

The authors declare no competing interests.

Additional information

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