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Nicolas Marie, Jun-an Ma, Vincent Tognetti, Dominique Cahard. Photocatalyzed Cascade Hydrogen Atom Transfers for Assembly of Multi-Substituted -SCF<sub>3</sub> and -SCF<sub>2</sub>H Cyclopentanones. *Angewandte Chemie International Edition*, 2024, 63 (34), 10.1002/anie.202407689 . hal-04757388

**HAL Id: hal-04757388**

**<https://hal.science/hal-04757388v1>**

Submitted on 28 Oct 2024

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# Photocatalyzed Cascade Hydrogen Atom Transfers for Assembly of Multi-Substituted $\alpha$ -SCF<sub>3</sub> and $\alpha$ -SCF<sub>2</sub>H Cyclopentanones

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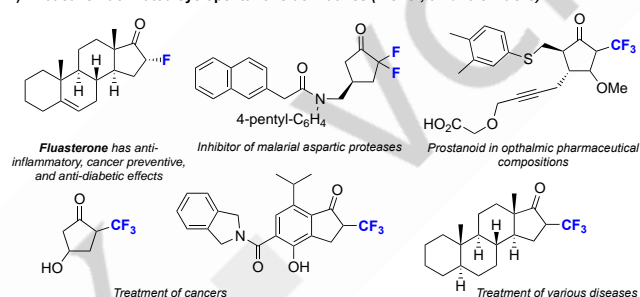
Supporting information for this article is given via a link at the end of the document

**Abstract:** A photocatalyzed formal (3+2) cycloaddition has been developed to construct original polysubstituted  $\alpha$ -SCF<sub>3</sub> cyclopentanones in a regio- and diastereoselective manner. This building block approach leverages trifluoromethylthio alkynes and branched / linear aldehydes, as readily available reaction partners, in consecutive hydrogen atom transfers and C–C bond formations. Difluoromethylthio alkynes are also compatible substrates. Furthermore, the potential for telescoped reaction starting from alcohols instead of aldehydes was demonstrated, as well as process automatization and scale-up under continuous microflow conditions. This prompted density functional theory (DFT) calculations to support a radical-mediated cascade process.

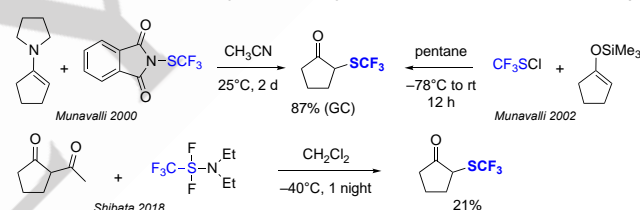
## Introduction

The cyclopentanoid chemotype is omnipresent in natural products and active pharmaceutical ingredients (API's), and the focus of a great deal of research efforts.<sup>[1]</sup> The current challenges in this area are to build highly substituted cyclopentanones by focusing on the molecular diversity that includes fluorinated units.<sup>[2]</sup> Indeed, strategically positioned fluorine atoms contribute to enhance the therapeutic potential of compounds.<sup>[3]</sup> One of the most promising emerging fluorinated motifs is the trifluoromethylthio group SCF<sub>3</sub>, especially in the fields of agrochemistry and medicinal sciences.<sup>[4]</sup> Of major interest, the enhanced lipophilicity of SCF<sub>3</sub>-featuring molecules, expressed by the Hansch's hydrophobic parameter  $\pi(\text{SCF}_3) = 1.44$  versus  $\pi(\text{OCF}_3) = 1.04$  and  $\pi(\text{CF}_3) = 0.88$ , is very appealing to increase the bioavailability of drug candidates. Consequently, the evaluation of SCF<sub>3</sub> derivatives is becoming a frequent feature of any drug development program. Another relevant consideration is a forthcoming change to the European Union regulations on per- and polyfluorinated alkyl substances (PFAS). A proposal has been drafted to restrict the use of fluorinated methyl (CF<sub>3</sub>-) and methylene (-CF<sub>2</sub>-) carbon atom; however, there are a few exceptions notably for compounds with a -CF<sub>2</sub>- or -CF<sub>3</sub> group also bearing a heteroatom, O, N, S.<sup>[5]</sup> In this context, replacing the F, CF<sub>2</sub>, and CF<sub>3</sub> motifs in bioactive molecules, such as those depicted in scheme 1A,<sup>[6]</sup> with the SCF<sub>3</sub> group is a strategy that is being seriously considered as a way of circumventing possible prohibitions. We have therefore initiated research aimed at broadening the molecular diversity towards  $\alpha$ -SCF<sub>3</sub> cyclopentanones. Inspection of the literature revealed that

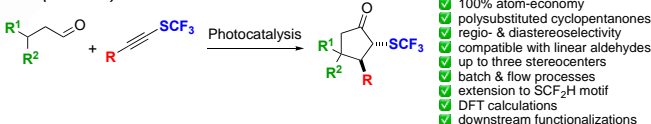
### A) Bioactive fluorinated cyclopentanone derivatives (mono-, di- and trifluoro)



### B) Prior art: direct trifluoromethylthiolation of cyclopentanones (absence of substrate scope)



### C) Novelty: building block approach by (3+2) cycloaddition (this work)



**Scheme 1.** A) Examples of bioactive molecules featuring a fluorinated cyclopentanone motif. B) Previous synthetic methods towards  $\alpha$ -SCF<sub>3</sub> cyclopentanones. C) This work: photocatalyzed (3+2) cycloaddition of SCF<sub>3</sub> alkynes and aldehydes.

the late-stage introduction of an electrophilic SCF<sub>3</sub> group onto the five-membered ring was achieved only on the bare cyclopentanone through enamine or silyl enol ether derivatives as reported by Munavalli and co-workers,<sup>[7]</sup> or by deacylative trifluoromethylthiolation according to Shibata's conditions (Scheme 1B).<sup>[8]</sup> The co-formation of bis-SCF<sub>3</sub> adducts or the use of one-of-a-kind trifluoromethyl analogue of diethylaminosulfur trifluoride (CF<sub>3</sub>-DAST) together with the absence of substrate scope prompted us to investigate a general building block approach exploiting SCF<sub>3</sub> alkynes as key components (Scheme 1C).

Photocatalyzed chemical reactions continue to gain momentum as a very useful approach for the generation of radical species

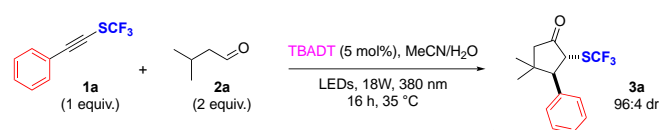
## RESEARCH ARTICLE

and are at the cutting edge of innovation for the assembly of various chemical scaffolds.<sup>[9]</sup> In this context, motivated by the green and sustainable aspects of photoredox catalytic processes, we hypothesized that acyl radicals emanated from aldehydes could react with SOMOphilic SCF<sub>3</sub> alkynes for the construction of  $\alpha$ -SCF<sub>3</sub> cyclopentanones in a cascade of hydrogen atom transfers and C–C bond formations (Scheme 1C). While the generation of the acyl radical is reasonable, its reactivity towards alkynes featuring the purely inductive SCF<sub>3</sub> motif (–I effect) and the cascade process remain to be demonstrated. Addressing this fundamental issue, the objective of this research work is the supply of *de novo* trifluoromethylthiolated carbocycles of great value as new chemical platforms for further structural transformations and biological evaluations. Herein, we report the effectiveness of the (3+2) cycloaddition process that gives an unprecedented regio- and diastereoselective convergent access to polysubstituted  $\alpha$ -SCF<sub>3</sub> cyclopentanones. In order to validate the reaction mechanism, control experiments and DFT calculations were performed to support each individual step of the overall sequence of cycloaddition.

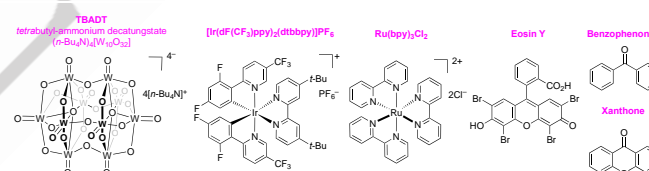
## Results and Discussion

The model reaction chosen for optimization of the reaction conditions involved readily available SCF<sub>3</sub> phenylacetylene **1a**<sup>[10]</sup> and 3-methylbutanal **2a** under photocatalysis (Table 1). Motivated by the wealth of information in the literature, we looked for suitable photocatalytic conditions by screening both metal- and organophotocatalysts at the appropriate wavelength. Of the photoredox systems tested, we were pleased to isolate the desired  $\alpha$ -SCF<sub>3</sub> cyclopentanone **3a** in 84% yield by using the polyoxometalate *tetrabutylammonium decatungstate* (*n*-Bu<sub>4</sub>N)<sub>4</sub>[W<sub>10</sub>O<sub>32</sub>] (TBADT)<sup>[11]</sup> as the photocatalyst of choice (Table 1, entry 1 versus entries 2–6). The reaction was performed in a mixture acetonitrile / water 10:1 at ambient temperature, corrected to 35°C due to the heat of the 18W, 380 nm LEDs. TBADT is renowned for its ability to homolytically cleave the acyl C–H bond in aldehydes to generate an acyl radical, nucleophilic in nature, for reaction with various electrophiles;<sup>[12]</sup> here, the novelty lies in the use of electrophilic SCF<sub>3</sub> alkynes. Control experiments in the absence of photocatalyst or light have demonstrated the absolute necessity of these two elements for the reaction to take place (entries 7 and 8). Reducing the reaction time from 16 h to 10 h did not allow full conversion (entry 9). Likewise, the yield in **3a** dropped to 62% when using 1.5 equivalent of 3-methylbutanal instead of 2 equivalents (entry 10). Deviation from the 380 nm wavelength of the light-emitting diode (LED) was detrimental to the conversion (entry 11). Carrying out the cycloaddition in other solvents, including *N,N*-dimethylformamide (DMF), acetone, and acetonitrile alone, resulted in inferior results (entries 12–14). The presence of water as cosolvent ensures faster successful completion by homogenization of the reaction medium. Product **3a** features two contiguous stereogenic centers for which the *trans*-relationship was clearly established by crystallization and single-crystal X-ray diffraction (SC-XRD) analysis (see ESI and Scheme 2).

**Table 1.** Selected results for optimization of the reaction conditions.<sup>[a]</sup>

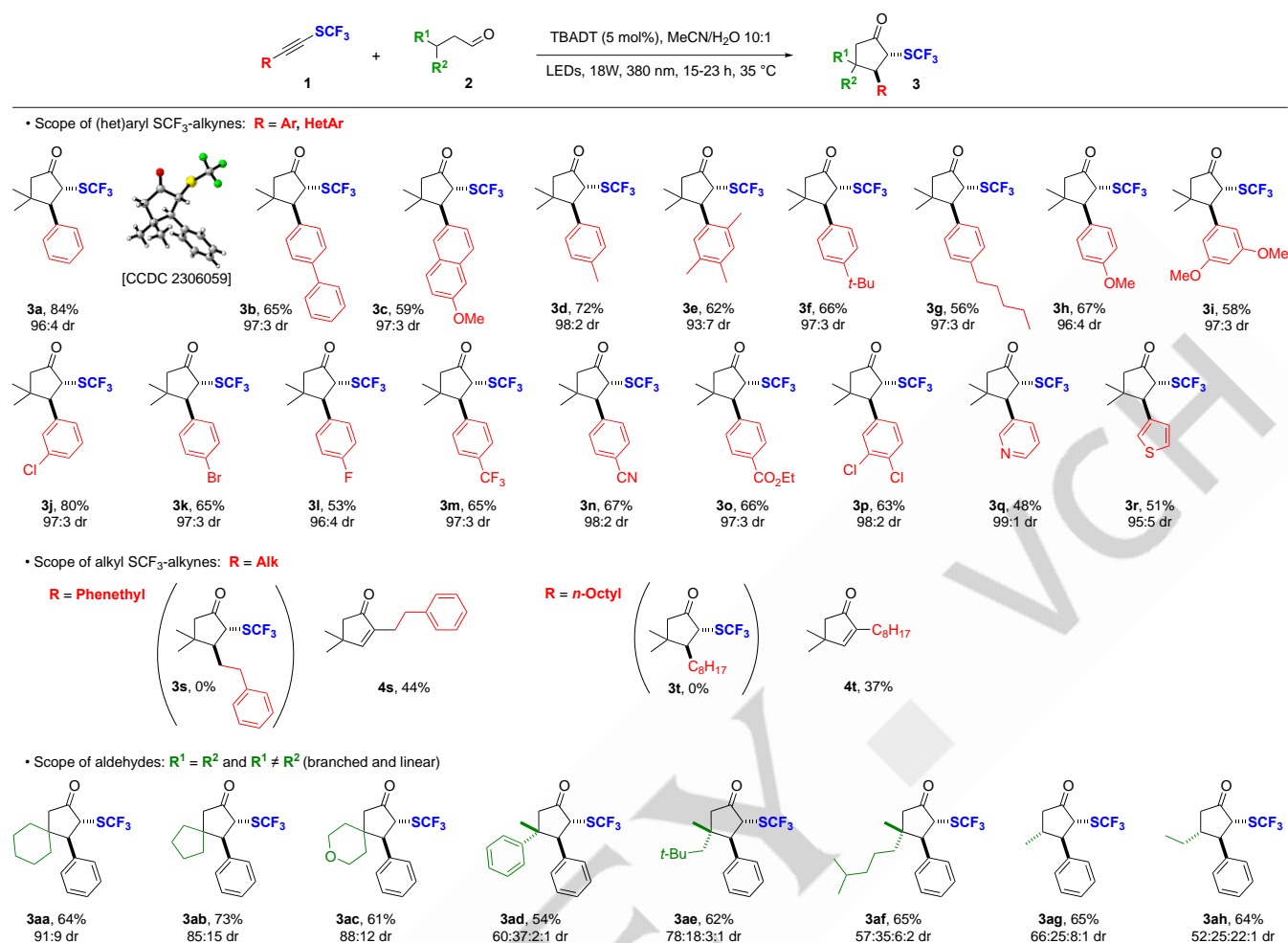


Entry	Deviations from above	Yield <sup>[b]</sup>
1	None	84
2	Ir[dF(CF <sub>3</sub> )ppy] <sub>2</sub> (dtbpy)PF <sub>6</sub> / LEDs 450 nm instead of TBADT / LEDs 380 nm	0
3	Ru(bpy) <sub>3</sub> Cl <sub>2</sub> / LEDs 450 nm instead of TBADT / LEDs 380 nm	<5
4	Eosin Y / LEDs 525 nm instead of TBADT / LEDs 380 nm	0
5	Benzophenone instead of TBADT	21
6	Xanthone instead of TBADT	29
7	No photocatalyst	0
8	No LED irradiation	0
9	10 h instead of 16 h	49
10	1.5 equiv. of <b>2a</b> instead of 2 equiv.	62
11	LEDs 425 nm instead of LEDs 380 nm	<5
12	DMF instead of MeCN/H <sub>2</sub> O	31
13	Acetone instead of MeCN/H <sub>2</sub> O	43
14	MeCN instead of MeCN/H <sub>2</sub> O	71



[a] **1a** (0.25 mmol), **2a** (0.50 mmol), TBADT (5 mol %) in MeCN/H<sub>2</sub>O 10:1 (2.5 mL). [b] Isolated yield of **3a**.

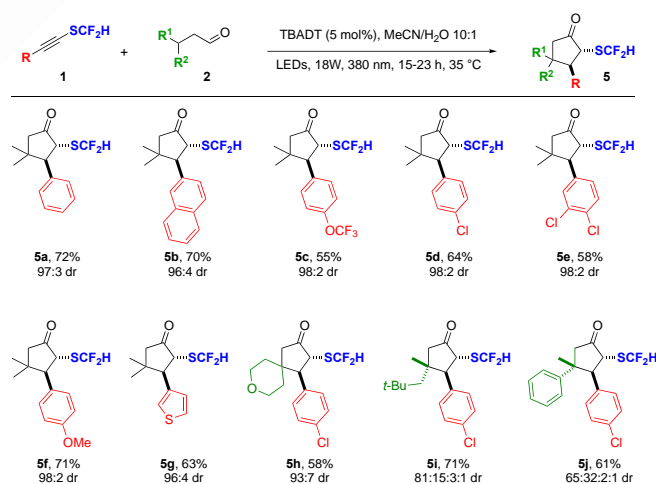
With the optimized conditions in hand, the substrate scope of this (3+2) cycloaddition was evaluated, starting with aryl SCF<sub>3</sub>-alkynes (Scheme 2, R = Ar). Aryls featuring electron-donating groups (alkyls at *ortho*, *meta*, *para* positions, phenyl and methoxy), halogens (fluorine, chlorine and bromine), or electron-withdrawing groups (trifluoromethyl, cyano, ester) led to the desired cyclized products in moderate to good yields (16 examples, **3a–3p**, 53–84%). The presence of a heteroaromatic alkyne substituent (pyridine, thiophene), instead of an aryl, slightly altered the effectiveness of the reaction (**3q** and **3r**, 48% and 51% yield, respectively). Interestingly, the diastereoselectivity is high, >93:7 and up to 99:1, in favor of the *trans* isomer as determined by the coupling constant <sup>3</sup>J<sub>H-H</sub> = 13.4 Hz and SC-XRD for **3a**. In addition, we investigated the cycloaddition of alkyl SCF<sub>3</sub>-alkynes (Scheme 2, R = phenethyl and *n*-octyl). These substrates were not suitable for the desired cascade transformation; instead, non-fluorinated  $\alpha$ -alkyl cyclopentenones **4s** and **4t** were isolated. Two important comments can be made at this point: first, the regioselectivity of the (3+2) cycloaddition was reversed compared to aryl SCF<sub>3</sub>-



Scheme 2. Scope of the (3+2) cycloaddition.

alkynes; second, the SCF<sub>3</sub> group was eliminated to end up with an unsaturation. Here, SCF<sub>3</sub> can be seen as a directing traceless group<sup>[13]</sup> to afford  $\alpha$ -alkyl cyclopentenones that are otherwise difficult to synthesize but outside the scope of our study. A control experiment was carried out with 4-phenyl-1-butyne not bearing the SCF<sub>3</sub> group; its reaction with 3-methylbutanal gave no **4s** product, clearly indicating the crucial role of SCF<sub>3</sub>.

The substrate scope was further extended to various aldehyde partners. At first, achiral aldehydes (**R<sup>1</sup> = R<sup>2</sup>**) were used leading to products **3aa-3ac** in 61-73% yields as mixtures of two diastereomers in dr >85:15 (Scheme 2). Further chiral aldehydes (**R<sup>1</sup> ≠ R<sup>2</sup>**) were engaged in the (3+2) cycloaddition to end up with products **3ad-3af** in 54-65% yields as mixtures of four diastereomers due to the additional stereogenic center. Subsequently, phenyl SCF<sub>3</sub>-alkyne **1a** reacted efficiently with linear aldehydes possessing secondary C–H bonds at the  $\beta$  position (*n*-butanal and *n*-pentanal) to provide the corresponding  $\alpha$ -SCF<sub>3</sub> cyclopentanones **3ag** and **3ah** in 65 and 64% yields, respectively, albeit with moderate dr values (Scheme 2). In an extension of the method to SCF<sub>2</sub>H phenylacetylene, we were pleased to obtain the  $\alpha$ -SCF<sub>2</sub>H cyclopentanone **5a** in 72% yield and 97:3 dr (Scheme 3). To validate the fact that SCF<sub>2</sub>H alkynes

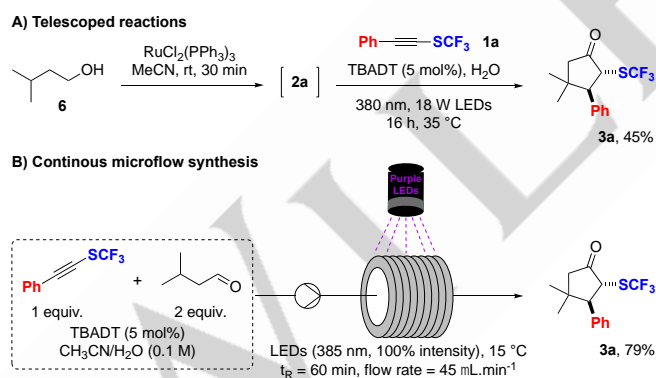
Scheme 3. Extension to the synthesis of  $\alpha$ -SCF<sub>2</sub>H cyclopentanones.

behave in the same way as SCF<sub>3</sub> alkynes, we prepared a series of  $\alpha$ -SCF<sub>2</sub>H cyclopentanones **5a-j** covering all kind of substituents (Scheme 3). Interestingly, dr values of all  $\alpha$ -SCF<sub>2</sub>H cyclopentanones **5** were slightly superior to those of analogous  $\alpha$ -SCF<sub>3</sub> cyclopentanones **3**. Compounds **5**, bearing a SCF<sub>2</sub>H group, are very valuable for designing bioactive molecules with a finely-

## RESEARCH ARTICLE

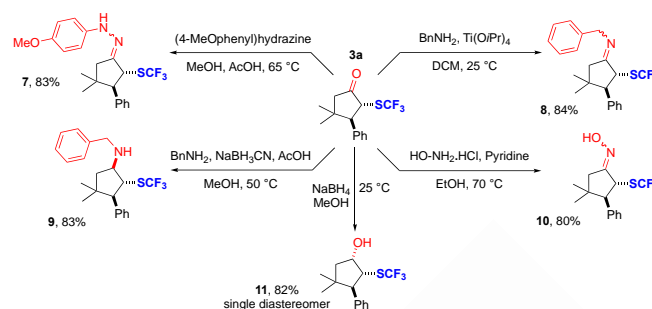
tuned lipophilicity compared with  $\text{SCF}_3$  analogues **3**, as well as an H-bonding capacity that does not exist in **3**.<sup>[14]</sup> Our recent interest for the chemistry of  $\text{SF}_5$  molecules incited us to test  $\text{SF}_5$  phenylacetylene but the bulkiness of this motif was too great a hurdle.<sup>[15]</sup> Switching from sulfur  $\text{SCF}_3$  to selenium  $\text{SeCF}_3$  alkynes did not give the desired corresponding cyclopentanones because of photocatalyzed diselenide formation concomitantly with  $\text{CF}_3$  extrusion. Finally, to illustrate the “fluorine effect”,<sup>[16]</sup> we prepared two non-fluorinated SMe alkynes that were engaged under the optimized conditions of the (3+2) cycloaddition and we found that no reaction had taken place, the starting alkynes having been recovered unchanged (see ESI for the complete substrate scope).

Admittedly, aldehydes are versatile building blocks but they are less stable than alcohols; moreover, alcohols are precursors of most aldehydes used in our study. Therefore, we surmised that starting from alcohol **6** in a telescoped one-pot process that include an oxidation by means of a ruthenium catalyst followed by the (3+2) cycloaddition would lead to the desired cyclopentanone. Gratifyingly, **3a** was obtained in 45% yield (Scheme 4A). As part of our overall study, we examined the access to  $\alpha$ - $\text{SCF}_3$  cyclopentanones from a technological point of view via continuous microflow synthesis. Indeed, flow chemistry is increasingly developed in industry and academia,<sup>[17]</sup> covering photochemical reactions.<sup>[18]</sup> We set up the experimental microflow conditions on a Corning® Advanced-Flow™ reactor with a residence time of 60 min (Scheme 4B). The reaction was much faster than in batch as a result of a much larger surface/volume ratio in the tubular photoreactor combined with a uniform irradiation by a high-power LED source; cyclopentanone **3a** was obtained in 79% yield within 1 h instead of 16 h in batch.



**Scheme 4.** A) Telescoped reactions starting from alcohol **6**. B) Continuous microflow photocatalyzed (3+2) cycloaddition.

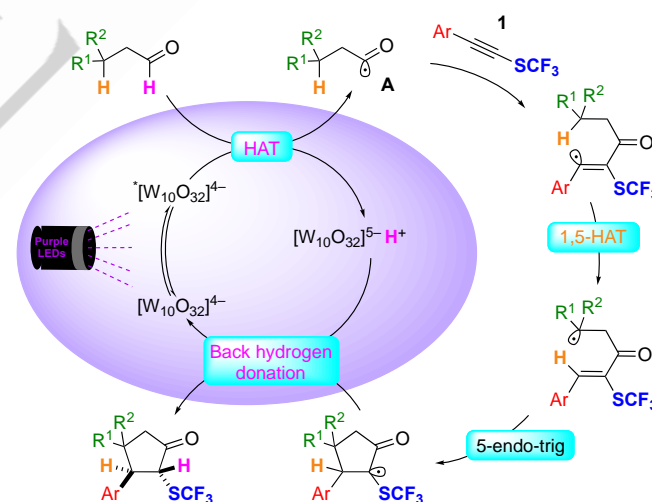
Finally, we carried out downstream functionalizations (Scheme 5). First, nitrogen-containing derivatives were prepared from  $\alpha$ - $\text{SCF}_3$  cyclopentanone **3a**, which can be readily transformed into  $\alpha$ - $\text{SCF}_3$  hydrazine **7** in 83% yield. Also, treatment of **3a** with benzylamine and titanium *iso*-propoxide efficiently gave  $\alpha$ - $\text{SCF}_3$  imine **8** in 84% yield while reductive amination of **3a** afforded amine **9** having three contiguous carbon stereocenters in 83% yield. Ketoxime **10** was obtained by condensation of hydroxylamine hydrochloride with **3a** in 80% yield. Interestingly, the stereoselective sodium



**Scheme 5.** Downstream functionalizations of  $\alpha$ - $\text{SCF}_3$  cyclopentanone **3a**.

borohydride reduction of  $\alpha$ - $\text{SCF}_3$  cyclopentanone **3a** afforded cyclopentanol **11** in 82% yield as a single diastereomer.

In light of the literature data on TBADT-mediated reactions and (3+2) cycloadditions, we propose the mechanism illustrated in Scheme 6. TBADT undergoes purple light absorption to reach an excited state responsible of a free radical-mediated homolytic bimolecular substitution by hydrogen atom transfer (HAT) with the aldehyde.<sup>[11d]</sup> It generates the corresponding C-centered acyl radical **A** and  $[\text{W}_{10}\text{O}_{32}]^{5-}\text{H}^+$ , which in turn will be involved in a back hydrogen donation for delivery of the final cyclopentanone. The acyl radical **A** reacts regioselectively onto the aryl alkyne **1** at the C- $\text{SCF}_3$  carbon followed by translocation of the radical by 1,5-HAT. Subsequently, the  $\text{C}_{\text{sp}^3}$  radical engages in a 5-endo-trig anti-Baldwin cyclization and further back hydrogen donation from  $[\text{W}_{10}\text{O}_{32}]^{5-}\text{H}^+$  ends up with the desired  $\alpha$ - $\text{SCF}_3$  cyclopentanone.



**Scheme 6.** Proposed mechanism for the photocatalyzed cascade transformation of aryl  $\text{SCF}_3$ -alkynes and aldehydes.

To underpin this mechanism and interpret the difference in reactivity between aryl- and alkyl  $\text{SCF}_3$ -alkynes, we carried out investigations through experiments and by DFT calculations. In the presence of a radical scavenger 2,2,6,6-tetramethylpiperidin-1-yloxy (TEMPO), the reaction was completely shut down and TEMPO-adduct of 3-methylbutanal was detected by HRMS (see ESI), suggesting the presence of acyl radicals in this

transformation. This radical pathway was subsequently scrutinized by DFT calculations (see ESI for computational details). We first considered SCF<sub>3</sub> alkynes **1**, with Et and Ph substituents, and aldehyde **2a** after the generation of reactive radical **A**; the DFT investigation of photophysical catalysis (purple circle in scheme 6) being outside our scope. The first studied step corresponds to the addition of **A** to **1**. For each possible radical addition at either C<sub>R</sub> or C<sub>S</sub> of the C–C≡C–S sequence, several conformations are possible for the transition state (TS), differing mainly in the C<sub>S</sub>C<sub>R</sub>C<sub>α</sub>O and C<sub>R</sub>C<sub>S</sub>SC<sub>F</sub> dihedral angles (Figure S6). An extensive sampling of the potential energy surface (PES) enabled us to locate 19 TSs for this first step, leading irreversibly to the **B<sub>addS</sub>** or **B<sub>addR</sub>** products (Figure S7 and Scheme 7).

In the Ph case, the standard Gibbs activation barriers associated with **TS<sub>addS</sub>** (resp. **TS<sub>addR</sub>**) are in the range [14.2; 16.7] (resp. [15.8; 17.2]) kcal mol<sup>-1</sup>; all of these values can be achieved at room temperature, with the two ranges partially overlapping. The same conclusion also holds in the Et case. This interlacing of the two pathways underlines the importance of adequate PES sampling to correctly account for regioselectivity. We next assumed that the regioselectivity is kinetically driven; thus, one has to compare the lowest TSs for both paths. We computed the  $\Delta G_{pref}^0 = \Delta G^0(\text{TS}_{addS}^1) - \Delta G^0(\text{TS}_{addR}^2)$  preferential Gibbs energy: -1.61 kcal mol<sup>-1</sup> for R=Ph and 2.59 kcal mol<sup>-1</sup> for R=Et, suggesting that regioselectivity is opposite (see ESI for the influence of the exchange-correlation functional on this statement).

This raises the question of whether these preferences can be rationalized in terms of reactivity descriptors. As discussed in ESI, regioselectivity stems from an intricate balance between charge and orbital controls, but these descriptors can however give insight into the fluorine effect and the absence of observed reactivity with the SMe alkyne. Indeed, while atomic charges for the C<sub>S</sub> atom with R=Ph are similar in the SMe and SCF<sub>3</sub> compounds, a dramatic decrease of this intrinsic site reactivity (amounting to -28%) was satisfyingly computed from an orbital control point of view (see ESI for the details).

We then validated that this computational protocol was able of matching other experimental results. We considered a substituent in *para* position of the Ph group with either an inductive (F atom) or a negative mesomeric (CN group) effect. In both cases,  $\Delta G_{pref}^0$  values, calculated after full re-optimizations of **TS<sub>addS</sub><sup>1</sup>** and **TS<sub>addR</sub><sup>2</sup>**, were still negative (-1.5 kcal mol<sup>-1</sup> for both) with activation barriers (14.2 and 13.3 kcal mol<sup>-1</sup>, respectively) consistent with the high yields experimentally obtained. Complementarily, a second aliphatic compound (R=PhCH<sub>2</sub>CH<sub>2</sub>), experimentally tested, was theoretically investigated. The positive  $\Delta G_{pref}^0$  value (3.4 kcal

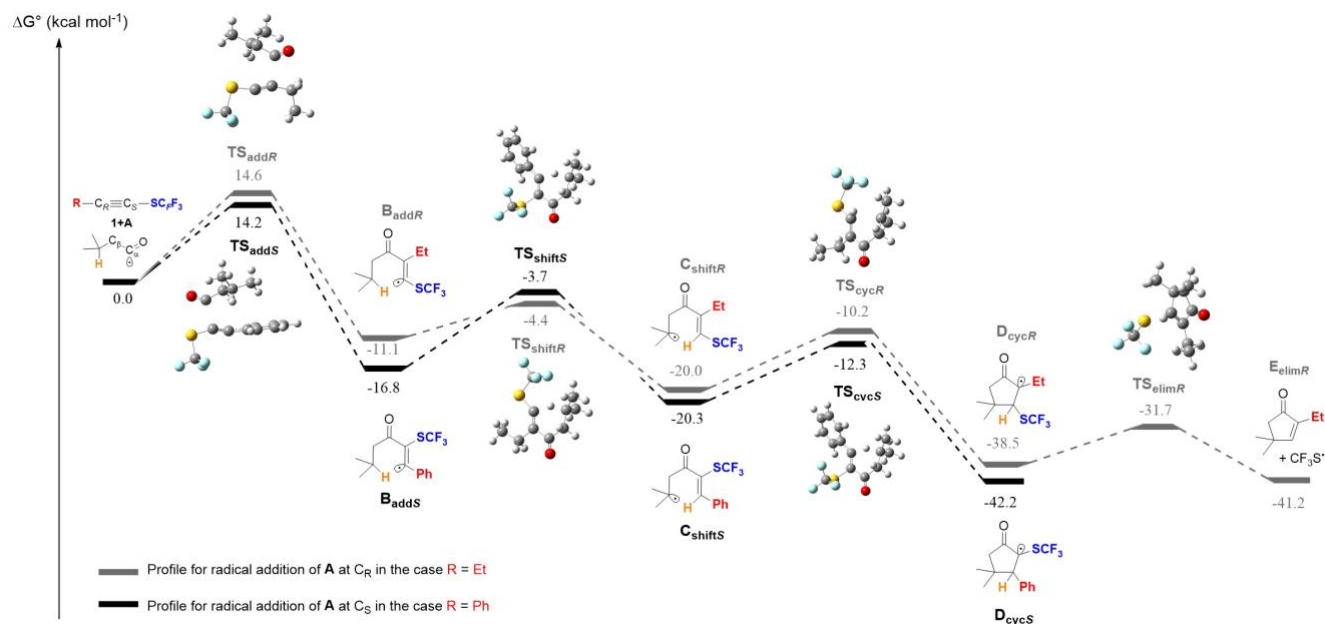
mol<sup>-1</sup>) is again in line with the opposite regiochemistry (with a moderate (15.2 kcal mol<sup>-1</sup>) activation Gibbs energy).

From the kinetically favored intermediates (**B<sub>addS</sub><sup>Ph1</sup>** and **B<sub>addR</sub><sup>Et2</sup>**), the next step involves a 1,5-hydrogen atom transfer (HAT) (Scheme 6). The corresponding TSs (**TS<sub>shiftS</sub><sup>Ph</sup>** and **TS<sub>shiftR</sub><sup>Et</sup>**, Figure S8) feature an almost planar structure around the transferred H atom that lies approximately in the middle of the two carbons. In the Ph case, the activation Gibbs energy is equal to 13.1 kcal mol<sup>-1</sup>, leading to radical **C<sub>shiftS</sub><sup>Ph</sup>**, more stable than **B<sub>addS</sub><sup>Ph1</sup>**. In the Et case, the H shift is even more favored since the Gibbs activation barrier was found equal to 6.7 kcal mol<sup>-1</sup>.

This 1,5-HAT step is then followed by the 5-endo-trig cyclization (Scheme 6 and Figure S8), leading to radical cyclopentanone structures, either **D<sub>cycS</sub><sup>Ph</sup>** or **D<sub>cycR</sub><sup>Et</sup>**, through **TS<sub>cycS</sub><sup>Ph</sup>** or **TS<sub>cycR</sub><sup>Et</sup>**. In both cases, the Gibbs activation energies are quite low (8.0 and 9.8 kcal mol<sup>-1</sup>, respectively), and correspond to an irreversible process. In the Ph case, the final product (**3a**, scheme 2), is simply obtained by a hydrogen exchange (not studied by DFT) with the photocatalyst. Indeed, the initial TBADT species had abstracted a H atom from the aldehyde to generate **A** and [W<sub>10</sub>O<sub>32</sub>]<sup>5-</sup>H<sup>+</sup>, which can now be transferred back to **D<sub>cycS</sub><sup>Ph</sup>**, regenerating the organometallic complex in its active form.

This step proceeds in such a way that, in the final product, the SCF<sub>3</sub> and the Ph groups are in *trans* or in *cis* relationship. On the one hand, the radical in **D<sub>cycS</sub><sup>Ph</sup>** is locally almost planar and the dihedral angular deformation required for either the *trans* or *cis* geometries is almost energetically costless (see the corresponding potential energy surface in ESI), so that the formation of both products is kinetically possible. On the other hand, DFT calculations revealed that the *anti*-stereoisomer of **3a** is considerably more stable from a thermodynamical point of view (about 4.8 kcal mol<sup>-1</sup> in terms of Gibbs energy) than the *cis*-stereoisomer, in agreement with experimental selectivity.

However, such hydrogen transfer to the cyclic radical was not observed in the aliphatic cases where the C–S bond in **D<sub>cycR</sub><sup>Et</sup>** was broken. We thus performed a relaxed energy scan on this coordinate both starting from **D<sub>cycS</sub><sup>Ph</sup>** or **D<sub>cycR</sub><sup>Et</sup>**. As shown in Figure S9, while energy increases linearly with increasing C–S distance (hence not allowing for bond breaking) for the Ph case, there is, conversely, an energy maximum around 2.6 Å starting from **D<sub>cycR</sub><sup>Et</sup>**. Subsequent optimization of this point provided **TS<sub>elimR</sub><sup>Et</sup>** for the SCF<sub>3</sub> elimination (see Figure S8). Whether or not SCF<sub>3</sub> elimination occurred could therefore be attributed to the considerable difference between the two C–S bond strengths involved, which are reflected by the electron density values at the corresponding bond critical point (see ESI for details).



**Scheme 7.** Gibbs energy profiles (with simplified notations) for the two privileged reaction pathways at the M06-2X/6-311++G(2d,2p) acetonitrile IEF-PCM level of theory, and views of the transition state structures. Atomic color code: H in white, C in grey, O in red, S in yellow and F in bright blue.

This DFT study has enabled us to validate a mechanism that is consistent with the main experimental results, the privileged paths being presented in Scheme 7. It has also highlighted that the regioselectivity can only be tackled by in-depth sampling of the potential energy surface and that the  $\text{SCF}_3$  elimination can be ascribed to the large energy difference of the C–S bond in the cyclopentanone radical.

## Conclusion

We designed a new disconnection strategy for the straightforward synthesis of  $\alpha$ - $\text{SCF}_3$ -multisubstituted cyclopentanones that does not rely on unselective late trifluoromethylthiolation. This efficient protocol leverages monochromatic radiation and redox-neutral conditions of the decatungstate anion of TBADT as hydrogen atom transfer photocatalyst. In the case of alkyl  $\text{SCF}_3$ -alkynes, we unveiled a regiodivergent reaction resulting in the formation of  $\alpha$ -alkyl cyclopentanones. Furthermore, the scope of alkynes could be extended to  $\text{SCF}_2\text{H}$  alkynes, and  $\alpha$ - $\text{SCF}_2\text{H}$  cyclopentanones were also prepared. The potential for telescoped reaction starting from alcohols instead of aldehydes was demonstrated, as well as process automatization and scale-up under continuous microflow conditions. Experiments and DFT calculations substantiated the mechanism of this photocatalyzed (3+2) cycloaddition that proceed via a radical-mediated cascade process. Building on our new expertise, applications of this method to the synthesis of potentially bioactive drugs are currently the subject of research in our laboratory.

## Supporting Information

The authors have cited additional references within the Supporting Information.<sup>[19], [20], [21], [22], [23], [24], [25], [26], [27], [28], [29], [30], [31],</sup>

[32], [33], [34], [35], [36], [37], [38], [39], [40], [41], [42], [43]. For supplementary crystallographic data see reference [44].

## Acknowledgements

Our research was supported by the Centre National de la Recherche Scientifique CNRS, University of Rouen Normandy, INSA Rouen Normandy, European Regional Development Fund (ERDF), Labex SynOrg (ANR-11-LABX-0029), Carnot Institute I2C, the graduate school for research XL-Chem (ANR-18-EURE-0020XL CHEM) and the National Natural Science Foundation of China (92156025). N.M. is grateful to the French “Ministère de la Recherche et de l'Enseignement Supérieur” for a doctoral fellowship. Experiments in flow were made possible by EU programs FEDER/FSE 20E04976 and FNADT-DRACCARE (N)15179. The “Centre Régional Informatique et d'Applications Numériques de Normandie” (CRIANN) is acknowledged for providing access to computational resources.

**Keywords:** cyclopentanone • trifluoromethylthio group • photocatalysis • polyoxometalate • DFT

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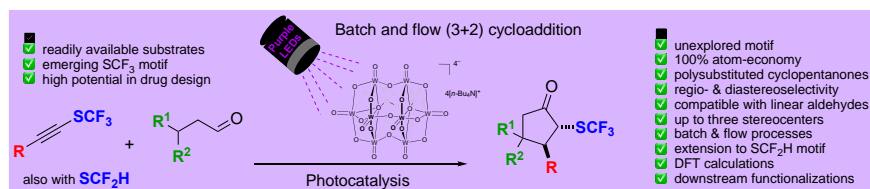
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## Entry for the Table of Contents)



A photocatalyzed (3+2) cycloaddition has been developed for the synthesis of multi-substituted  $\alpha$ -SCF<sub>3</sub> and  $\alpha$ -SCF<sub>2</sub>H cyclopentanones. The strengths are multiple including green aspects (atom-economy, photocatalysis, continuous microflow synthesis). Each step of the reaction mechanism was deciphered by DFT calculations. This work expands the scope of possibilities, which means gaining access to novel fluorinated scaffolds for biological evaluation.

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