

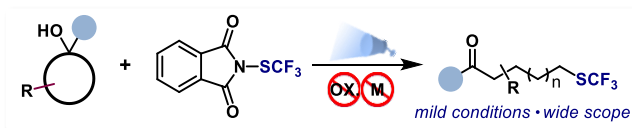
# Metal- and Oxidant –Free, Remote Trifluoromethylthiolation enabled by Organophotocatalytic C-C Bond Cleavage

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Supporting Information



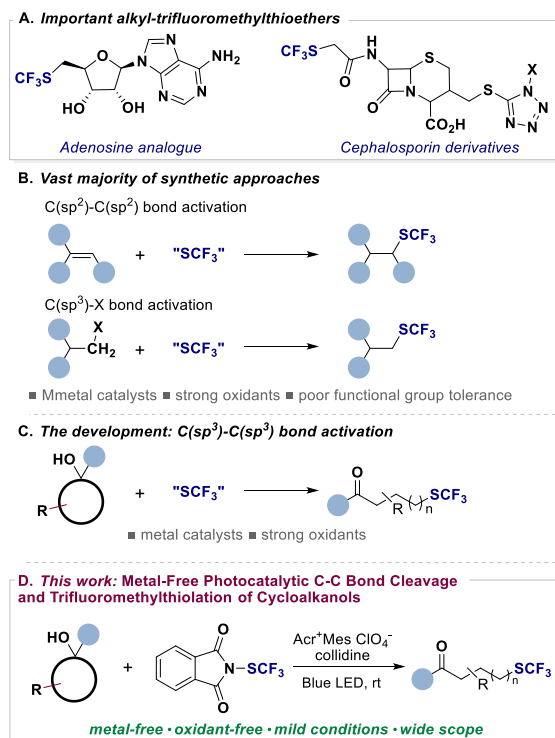
**ABSTRACT:** The first metal-free ring opening / trifluoromethylthiolation of cycloalkanols for the formation of remote C(sp<sup>3</sup>)-SCF<sub>3</sub> bonds has been developed. A variety of trifluoromethylthiolated carbonyl compounds, that are otherwise difficult to achieve, were prepared in good yields under mild reaction conditions. The reaction is assumed to proceed via C-C bond cleavage of the alkoxy radical species generated via a photoredox enabled intramolecular proton-coupled electron transfer (PCET) process, followed by trifluoromethylthiolation of the resulting C-centered radical with the electrophilic *N*-(trifluoromethylthio)phthalimide reagent.

The incorporation of trifluoromethylthio group (SCF<sub>3</sub>) into drug molecules can modulate their physicochemical and biological properties and consequently enhance the drugs pharmacological efficiency and properties.<sup>1,2</sup> As a result, tremendous efforts have been devoted to the synthesis of these fluorine-containing molecules. In this regard, alkyl-SCF<sub>3</sub> compounds are commonly found in various drugs, pesticides and bioactive compounds (Scheme 1A)<sup>2b,c</sup> and have thus attracted the attention. Although methods, including trifluoromethylthiolation of olefins,<sup>3a</sup> alkyl halides,<sup>3b</sup> alkylboronic acids,<sup>3c,g</sup> carboxylic acids,<sup>3d</sup> alcohols<sup>3e</sup> and C(sp<sup>3</sup>)-H bonds exists,<sup>3f,i</sup> these approaches suffer from problems regarding the use of transition-metal catalysis, super-stoichiometric amounts of strong oxidants or high reaction temperatures (Scheme 1B),<sup>3a,b</sup> which can limit the functional group tolerance and further medical applications.

To address the challenge of efficient synthesis of alkyl-SCF<sub>3</sub> compounds, we sought to design an applicable methodological approach that provides access to this class of compounds under mild conditions.

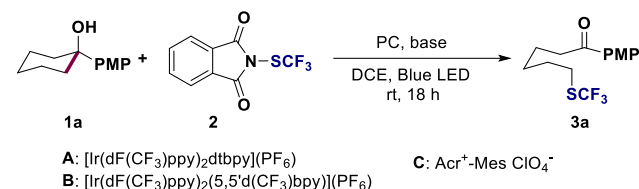
One of the high atom and step economic approaches to rapidly construct complex organic frameworks makes use of C-C bond activation.<sup>4</sup> In recent years, several seminal contributions have been made in photoredox catalysis mediated C-C bond β-scission reactions of tertiary alcohols by the groups of Chen<sup>5</sup> and Knowles<sup>6</sup>. Since then, a series of fragmentations and

## Scheme 1. Motivation and synthetic strategy



functionalizations of C-C bonds of tertiary cycloalkanols through a radical  $\beta$ -scission process has been developed.<sup>7</sup> Recently, Zhang<sup>8</sup> and Shen<sup>9</sup> described the silver-mediated oxidative trifluoromethylthiolation of cycloalkanols for the synthesis of trifluoromethylthiolated ketones (Scheme 1C). Despite these achievements, the metal catalyst free, oxidant free construction of C(sp<sup>3</sup>)-SCF<sub>3</sub> bonds has not been addressed yet and it is highly desirable. During our continuous efforts devoted to the field of photoredox catalysis,<sup>10</sup> we aimed at exploring the photoredox-catalyzed C-C bond cleavage and trifluoromethylthiolation reaction of cycloalkanols under mild conditions (Scheme 1D).<sup>11</sup>

**Table 1. Optimization of the Reaction Conditions<sup>a</sup>**



Entry	PC	Base	Yield (%) <sup>b</sup>
1 <sup>c</sup>	A	collidine	10
2 <sup>c</sup>	B	collidine	35
3 <sup>c</sup>	C	collidine	45
4	C	collidine	61
5	C	2,3-lutidine	27
6	C	2,4-lutidine	33
7	C	2,6-lutidine	43
8	C	pyridine	trace
9	C	NEt <sub>3</sub>	-
10	C	collidine	33
11	--	collidine	-
12	C	--	-
13 <sup>d</sup>	C	collidine	-

<sup>a</sup>Reagents and conditions: **1a** (0.1 mmol), **2** (0.05 mmol), **C** (7 mol %), DCE (1 mL), room temperature, blue light, 18 h. <sup>b</sup>Yield after isolation. <sup>c</sup>PC 3 mol %. <sup>d</sup>No light. PMP = *p*-methoxyphenyl.

To validate the feasibility of our strategy, the reaction of cyclohexanol **1a** with *N*-trifluoromethylthio-phthalimide **2**, introduced by Munavalli group<sup>12</sup> and exploited also by us,<sup>3e-h</sup> was investigated under photocatalytic conditions. In the presence of photocatalyst **A** and collidine as base, the desired C-C bond-cleavage/trifluoromethylthiolation product **3a** was obtained in 10% yield (Table 1, entry 1). Encouraged by this promising result, further photocatalysts were evaluated. The yield improved when Acr<sup>+</sup>-Mes ClO<sub>4</sub><sup>-</sup> was employed as photocatalyst (entries 1-3). Next, we explored the influence of bases and concluded that collidine is the best choice as the reaction outcome was 61% yield (entries 4-9). Control experiments revealed the importance of the Acr<sup>+</sup>-Mes ClO<sub>4</sub><sup>-</sup> catalyst, collidine and light, as no desired product was observed in the absence of either catalyst, base or light (entries 11-13).

**Table 2. Reaction Scope<sup>a</sup>**

Starting Material	Product	Yield
<b>1a</b>	<b>3a</b>	61%
<b>1b</b>	<b>3b</b>	61%
<b>1c</b>	<b>3c</b>	77%
<b>1d</b>	<b>3d</b>	70%
<b>1e</b>	<b>3e</b>	49%
<b>1f</b>	<b>3f</b>	72%
<b>1g</b>	<b>3g</b>	70%
<b>1h</b>	<b>3h</b>	63%
<b>1i</b>	<b>3i</b>	52%
<b>1j</b>	<b>3j</b>	56%
<b>1k</b>	<b>3k</b>	70%
<b>1l</b>	<b>3l</b>	61%
<b>1m</b>	<b>3m</b>	34%

<sup>a</sup>Reagents and conditions: **1** (0.4 mmol, 2 equiv), **2** (0.2 mmol, 1 equiv), Acr<sup>+</sup>-Mes ClO<sub>4</sub><sup>-</sup> (7 mol %), DCE 4 mL, collidine (0.4 mmol, 2 equiv), room temperature, blue light, 18 h, yield after isolation. PMP = *p*-methoxyphenyl.

With the optimized conditions in hand, the scope of the C-C bond cleavage/trifluoromethylthiolation reaction was studied (Table 2). In general, cycloalkanols **1a-1h** with various ring sizes reacted smoothly and gave the corresponding remotely trifluoromethylthiolated ketones **3a-3h** in moderate to good yields (49-77%). Furthermore, to our delight, tetrahydropyranol **1i** also worked well to afford the corresponding trifluoromethylthiolation product **3i** in 55% yield. In the cases of unsymmetrical cycloalkanols **1j-1l**, high selectivities were observed for the bond scission, with the formation of the more stable radical intermediate upon carbon-carbon bond cleavage (**3j-3l**). Additionally, the tetralone derived benzocycloalkanol **1m** was also tolerated and gave the desired product **3m** in 34% yield. In addition, a large-scale reaction was performed with substrate **1a**, and the corresponding product was obtained with a slightly lower yield (48% vs 61%).

**Table 3. Reaction Scope**<sup>a</sup>

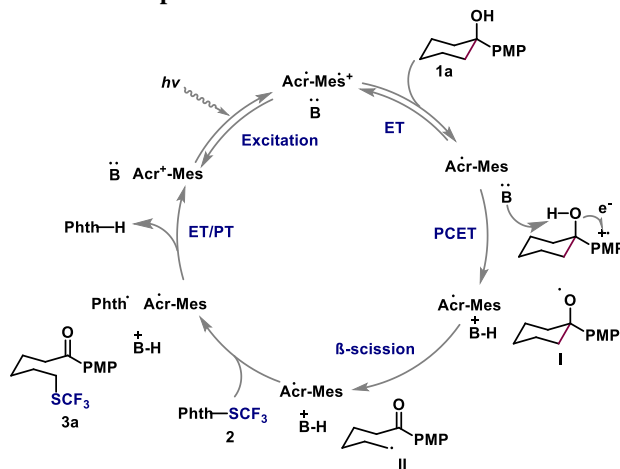
Product	Yield
	35%
	53%
	50%
	47%
	55%
	51%
	57%

<sup>a</sup>Reagents and conditions: **1** (0.4 mmol, 2 equiv), **2** (0.2 mmol, 1 equiv), Acr<sup>+</sup>-Mes ClO<sub>4</sub><sup>-</sup> (7 mol %), DCE 4 mL, collidine (0.4 mmol, 2 equiv), room temperature, 18 h, blue light, yield after isolation.

Next, we turned our attention to the variation of the aromatic system of the cycloalkanols. In addition to anisole, the success of this C-C bond cleavage/trifluoromethylthiolation strategy could be further extended to various electron rich arenes albeit with slightly decreased yields (Table 3). Disubstituted anisole

derivatives were also suitable substrates for this transformation (**3n** and **3o**). Monosubstituted aromatics such as phenyl ethers (**1p** and **1q**) as well as biphenyl (**1r**) derivatives underwent the ring opening /trifluoromethylthiolation smoothly. Notably, the photochemical oxidation of benzofuran and naphthalene derivatives proved successful, giving the corresponding products **3s** and **3t** in moderate yields.

### Scheme 2. Proposed Mechanism



Based on these experimental results a plausible mechanism for this photocatalytic C-C bond scission and trifluoromethylthiolation is outlined in Scheme 2. Under visible light irradiation, Acr<sup>+</sup>-Mes ClO<sub>4</sub><sup>-</sup> absorbs a photon leading to the photocatalyst excited state ( $E_{1/2}[^*P/P^*] = 2.06$  V).<sup>13</sup> The electron-rich arene substituent of cycloalkanol **1a** ( $E_{p/2} = 1.6$  V vs SCE) is oxidized by the excited state of the photocatalyst and furnishes a transient radical cation. After deprotonation of the hydroxyl group by the Brønsted base, an intramolecular proton-coupled electron transfer<sup>14</sup> occurs in concert with single electron reduction of the radical cation to achieve the key alkoxy radical intermediate **I**. The alkoxy radical can weaken the adjacent C-C bonds and easily generate an aryl ketone (**II**) with a distal alkyl radical via  $\beta$ -scission. PhthSCF<sub>3</sub> **2** can then trap the radical intermediate **II**, affording the desired product **3a**. The resulting Phth<sup>\*</sup> radical is then reduced by Acr<sup>+</sup>-Mes to Phth<sup>-</sup> and protonated by the conjugated acid of the Brønsted base B<sup>+</sup>-H, meanwhile regenerating the acridinium photocatalyst and completing the photocatalytic cycle.

In summary, we have developed a metal and oxidant free method for the C-C bond cleavage of cycloalkanols with subsequent trifluoromethylthiolation. This reaction performed efficiently under mild reaction conditions with blue LED irradiation and delivered the desired products in moderate to good yields. We are confident that this ring opening trifluoromethylthiolation strategy is a valuable alternative to existing protocols for the synthesis of bioactive and pharmaceutical ketone products and their derivatives.

### ASSOCIATED CONTENT

#### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: XXXX/XXXXX.

Detailed experimental procedures, spectral data for all compounds, and copies of <sup>1</sup>H, <sup>13</sup>C, and <sup>19</sup>F NMR spectra (PDF).

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### Notes

The authors declare no competing financial interest.

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