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Interrupting the Barton–McCombie Reaction: Aqueous Deoxygenative Trifluoromethylation of *O*-Alkyl Thiocarbonates

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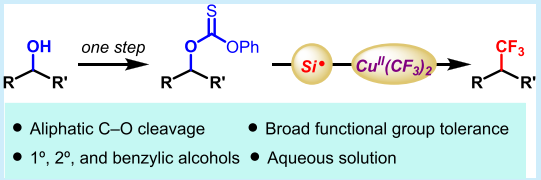
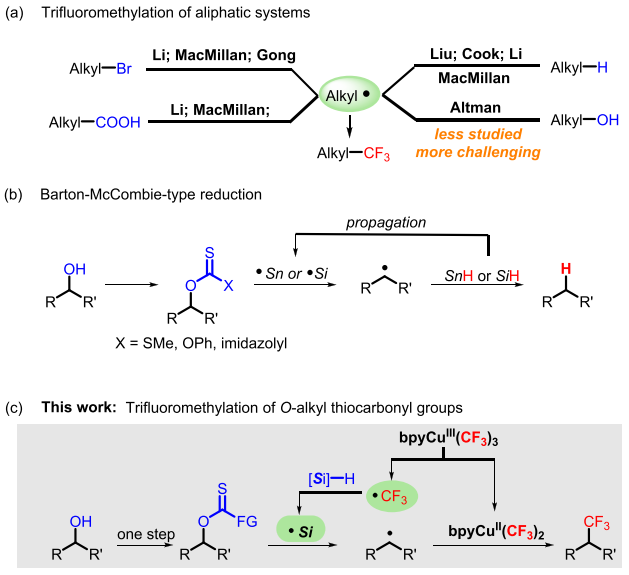
ABSTRACT: The site-selective trifluoromethylation of aliphatic systems remains an important challenge. This work describes a light-driven, copper-mediated trifluoromethylation of *O*-alkyl thiocarbonates. The reaction provides broad functional group tolerance (e.g., alkyne, alkene, phenol, free alcohol, electron-rich and -deficient arenes), thereby offering orthogonality and practicality for trifluoromethylation. A radical organometallic mechanism is proposed.



The installation of trifluoromethyl groups into organic molecules remains an important goal in synthetic organic chemistry. Trifluoromethyl moieties can impart unique properties to pendant molecules—including high electronegativity, lipophilicity, and metabolic stability—which has driven their use in the fields of pharmaceuticals, agrosciences, and materials.[1] For decades, efforts to develop practical trifluoromethylation methods have led to remarkable progress.[2] More recently, several reports describing the formation of the C(sp^3)–CF_3 bond have emerged using nucleophilic trifluoromethylation,[3] electrophilic trifluoromethylation,[4] and trifluoromethyl radical addition to olefins.[2b,5] However, the use of highly specific electrophiles, nucleophiles, and terminal alkenes has partly limited their practical utility. In contrast, the selective trifluoromethylation of unactivated alkyl groups remains highly underdeveloped when compared to that of activated alkyl counterparts.[6] Recent work on the trifluoromethylation of alkyl radical intermediates offers a more direct approach to a wider range of trifluoromethylated compounds.[7] Since alkyl radicals can be generated from readily available aliphatic acids,[7d,e] halides,[7a−c] or in some cases, C(sp^3)–H bonds,[7f−j] this approach offers great diversity in potential starting materials (Scheme 1a).

Alcohols represent one of the most abundant functional groups in both natural and unnatural organic molecules. Scission of alcohol-based C–O bonds offers an intriguing but challenging approach to small molecule diversification.[8] Interestingly, the formation of alkyl radicals from alcohol derivatives provides a promising opportunity for realizing this approach.[9] Work toward this goal has revealed interesting new methods with creative approaches to this problem. For example, Ni- or photoredox-catalyzed radical coupling of oxalates, developed by Gong,[10] Overman,[11] and MacMillan,[12] represent a powerful platform for the transformation of alcohols. Additionally, xanthates, thiocarbonates, and thiocarbamates—bench stable and readily available alcohol derivatives—have a rich history in Barton–McCombie-type reactions to generate carbon-centered radicals (Scheme 1b).[9a,13] Recent work by Altman has demonstrated that xanthates can be applied for Cu^0-mediated C–CF_3 bond formation.[14] Molander[15] and Rousseaux[16] reported the cross coupling of xanthates or thiocarbamates to generate a C(sp^3)–

Scheme 1. (a) Trifluoromethylation of Aliphatic Systems. (b) Barton–McCombie-Type Reduction. (c) Our Proposed Trifluoromethylation of *O*-Alkyl Thiocarbonyl Groups



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C(sp^2) bond under Ni or Ni/photoredox dual catalysis. However, these reactions only proceed with benzylic-activated xanthates or thiocarbamates.

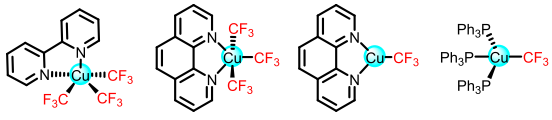
Direct trifluoromethylation of unactivated thiocarbonyl systems remains an important goal.[17] In a search for a general and operationally simple methodology, we envisioned that bpyCu(CF_3)$_3$ (i.e., Grushin's reagent)[18] could be used for the trifluoromethylation of *O*-alkyl xanthates or thiocarbonates. The homolysis of bpyCu(CF_3)$_3$ could generate CF_3-based radical and a highly reactive $Cu^{II}(CF_3)_2$ species.[7a,g,19] The CF_3-based radical could react with a suitable silane to generate an Si-based radical for the subsequent reaction with thiocarbonates. The coupling reaction between the newly formed alkyl radical and $Cu^{II}(CF_3)_2$ species finally gives the trifluoromethylated product.[20] At the outset, it was unclear whether the coupling process would outcompete the direct reduction of the alkyl radical by silane.

With the above design in mind, we began the investigation with the trifluoromethylation of unactivated secondary thiocarbonate **1a**. After extensive examination of the reaction conditions, we identified that visible-light irradiation of bpyCu(CF_3)$_3$/**1a** in the presence of super silane (TTMSS) and $Na_2S_2O_8$ provided the trifluoromethylation product **3a** in 86% yield (Table 1, entry 1). Surprisingly, no desired product was detected when ^{n}Bu$_3$SnH was used, despite its wide application in Barton−McCombie-type reactions (Table 1, entry 2). Triethylsilane and triisopropylsilane were also inferior to super silane (Table 1, entries 3−4). The greater activity of TTMSS may be due more facile reaction with trifluoromethyl radical to produce the active Si-based radical. Switching the copper complex to **2b** decreased the yield, but no product was formed when complex **2c** or **2d** was employed (Table 1, entries 5−7). These results suggest that a Cu(I)CF_3 species was not the active CF_3 source for the reaction even under the reaction conditions. Further investigation revealed that the Si-based radical activated the thiocarbonate preferentially to the CF_3 radical (Table 1, entry 8). Sodium persulfate ($Na_2S_2O_8$) was found to significantly increase the reaction yield (Table 1, entry 9). The persulfate likely serves as a complementary radical initiator for the generation of silyl radical. Interestingly, water proved beneficial in the reaction (Table 1, entry 10). This could be due to the improved solubility of the persulfate in aqueous solvent, and the potential of lowering the reductive elimination energy barrier by aqua complex.[7g] The blue light serves to homolyze **2a** to give CF_3 radical and Cu(II) species (Table 1, entry 11). In addition, the use of 1 equiv thiocarbonate or excess **2a** only gave the desired product in moderate yield respectively (Table 1, entries 13 and 14).

Table 1. Optimization of Reaction Conditions[a]

1a 3a

entry	deviation	yield[b] (%)
1	none	86
2	^{n}Bu$_3$SnH instead of TTMSS	4
3	Et$_3$SiH instead of TTMSS	20
4	^{i}Pr$_3$SiH instead of TTMSS	40
5	**2b** instead of **2a**	74
6	**2c** instead of **2a**	nd
7	**2d** instead of **2a**	nd
8	no TTMSS	nd
9	no $Na_2S_2O_8$	15
10	no H_2O	18
11	no $h\nu$	nd
12	under air	10
13	1 equiv of **1a**	57
14	1 equiv of **1a**, 2 equiv of **2a**	40[c]



2a 2b 2c 2d

[a]Performed with **1a** (0.1 mmol, 2 equiv or 0.05 mmol, 1 equiv), **2a** (0.05 mmol, 1 equiv or 0.1 mmol, 2 equiv) in solvent (0.056 M) for 3 h at room temperature. nd = not detected. [b]Yields were based on the Cu reagent and reported on the basis of ^{19}F NMR analysis using $PhCF_3$ as an internal standard. [c]Yield was based on **1a**.

With the above optimized conditions in hand, we next evaluated a range of unactivated thiocarbonates (Scheme 2a). The electron-rich arenes were well tolerated in this protocol, thus giving the trifluoromethylation products **3a**, **3b**, and **3f** in moderate-to-high yields. For the substrates with different amides and phthalimide, the trifluoromethylation also delivered products **3c**−**3e** in good yields. The reaction was also compatible with molecules bearing alkyne (**1g**) or conjugated and terminal alkenes (**1h**, **1i**), thereby highlighting the selectivity of the underlying radical reactions. In spite of numerous reports detailing the reaction of unsaturated C−C bonds and arenes with CF_3 radical,[2,5] such functional groups were well tolerated in the reaction. Under these reaction conditions, the CF_3 radical generated from Grushin's reagent is quenched rapidly by TTMSS to release Si radical, which avoids reaction of the CF_3 radical with arenes or other units of unsaturation. In competition experiments with primary and secondary thiocarbonates (e.g., **1j**), the secondary thiocarbonate was selectively trifluoromethylated with only a trace amount of the primary trifluoromethylated product. The reaction tolerated tosylated (**1k**) and silylated (**1l**) substrates, with selective trifluoromethylation in high yields. Heteroarenes were well tolerated in the reaction, giving the product **3m** in 70% yield. Cyclic seven- and six-membered rings were suitable, which delivered the trifluoromethylation products **3n**−**3q** in moderate yields. In addition, trifluoromethylation of thymidine derivative provided CF_3 analogue **3r** in 39% yield and excellent diastereoselectivity, which clearly shows the potential of facile trifluoromethylation of complex molecules. Primary thiocarbonates **1s** and **1t** were subjected to the trifluoromethylation, producing the products in 33 and 28% yields, respectively. We attribute the low yields of primary substrates to likely slower initiation and higher energy carbon-based radicals relative to secondary substrates.

Next, benzylic thiocarbonates were surveyed in the reaction (Scheme 2b). For substrates derived from primary benzylic alcohols, thiocarbonates with a range of functional groups provided moderate to good yields of the products. The tolerance of Bpin (**1u**), OMs (**1v**), alcohols (**1w**, **1x**), electron-deficient (**1y**, **1z**) and -rich arenes (**1aa**) implies great potential for this methodology in diverse contexts. In particular, the tolerance of secondary and tertiary alcohols makes it more competitive than the trifluoromethylation of alkyl halides, since

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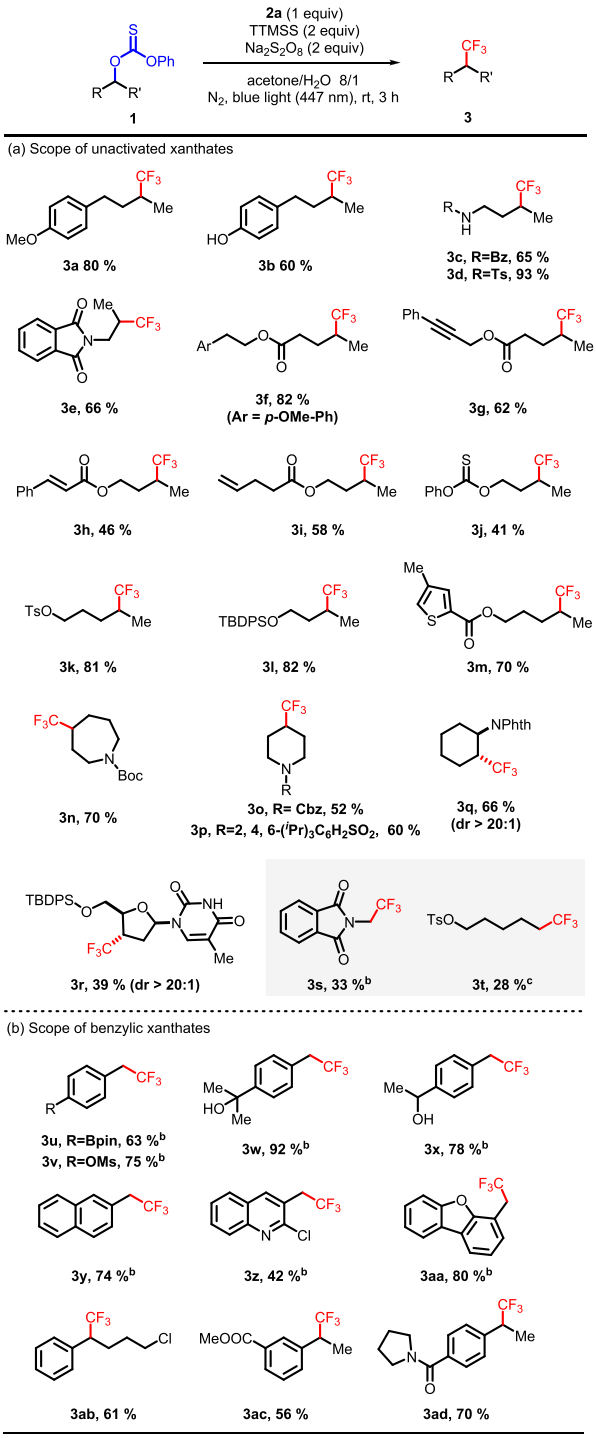
Scheme 2. Scope of Thiocarbonates[a]

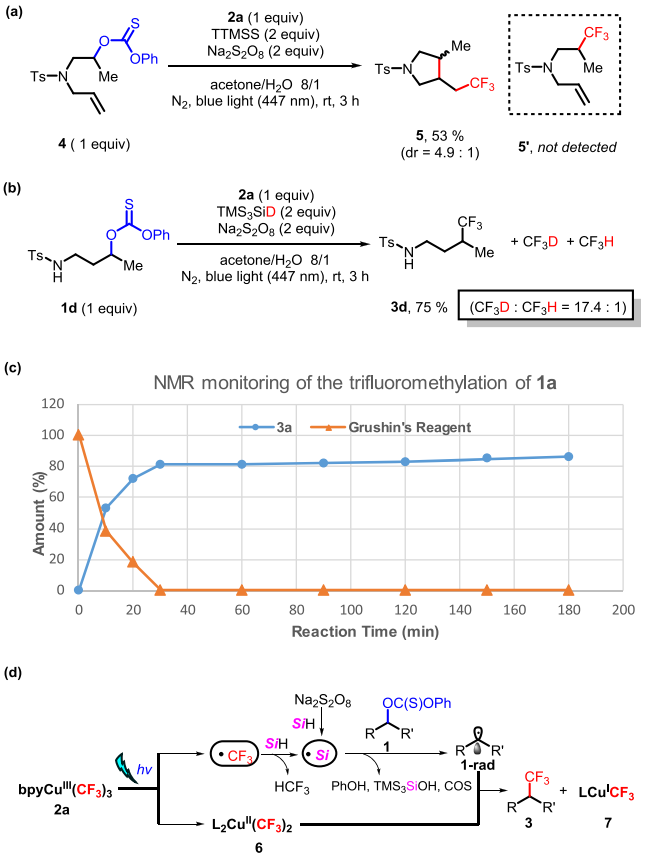


[a]Unless otherwise specified, all reactions were performed with thiocarbonate **1** (0.4 mmol, 2 equiv), **2a** (0.2 mmol, 1 equiv), $Na_2S_2O_8$ (0.4 mmol, 2 equiv), and TTMSS (0.4 mmol, 2 equiv) in acetone/H_2O 8/1 (0.056 M) for 3 h at room temperature. Isolated yields. [b]Thiocarbonate **1** (0.2 mmol, 1 equiv), $Na_2S_2O_8$ (0.2 mmol, 1 equiv), and TTMSS (0.2 mmol, 1 equiv) were used. [c]Thiocarbonate **1** (0.2 mmol, 1 equiv) was used; 2-butanone was used instead of acetone; 70 °C; reaction time was 6 h.

the halides are usually derived from alcohols and additional steps would be required to protect the free alcohols. For thiocarbonates derived from secondary benzylic alcohols, substrates bearing chloride, ester, and amide afforded the secondary trifluoromethylated products (**3ab**–**3ad**) in moderate yields.

To explore the mechanism, we performed a series of straightforward experiments (Scheme 3). First, when we

Scheme 3. Mechanistic Studies



subjected thiocarbonate **4** to the trifluoromethylation reaction, cyclization product **5** was obtained in 53% yield, wherein the linear trifluoromethylation product **5′** was not detected in the reaction (Scheme 3a), thereby supporting a secondary carbon-based radical intermediate. Additionally, significant quantities of fluoroform is produced in the reaction. Treatment of thiocarbonate **1d** with deuterium-labeled silane (TMS_3SiD) under the standard conditions gave primarily DCF_3 (Scheme 3b), suggesting that the majority of CF_3 radical is quenched by silane (see the SI). Furthermore, NMR monitoring of the trifluoromethylation of model substrate **1a** shows that the production of **3a** is directly related to the amount/concentration of Grushin's reagent **2a** (Scheme 3c). During the first 30 min of irradiation, the yield of **3a** reached 81% with complete consumption of the Grushin's reagent. After 30 min, the rate of product formation decreases significantly, with only 5% additional yield achieved after 2.5 h (see the Supporting Information for details).

Taken together, these studies support the basic mechanistic outline in Scheme 3d. Blue-light irradiation serves to facilitate the homolysis of **2a** and enables the rapid generation of CF_3 radical and Cu(II) species **6**.[7g,19] Then, the reaction between CF_3 radical and silane produces the Si-based radical[7a,g] that goes on to react with the thiocarbonate. Another possible pathway to generate the Si-based radical is the reaction of

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silane with persulfate, which is likely a slower process. Meanwhile, the persulfate may also facilitate the coupling process through the transition-metal counterion effect of sulfate as suggested previously.[19] The Si-based radical subsequently reacts with the thiocarbonate to release alkyl radical **1-rad**, which is the same process as Barton–McCombie-type reactions.[13] The representative byproducts (e.g., phenol, TMS_3SiOH) were also observed in the reaction.[21] Finally, the alkyl radical **1-rad** undergoes a coupling reaction with Cu(II) species **6** to provide the trifluoromethylation product along with the Cu(I) species **7**.[7a,d,g,19,20]

In the reaction, the CF_3 radical is quenched with silane (TTMSS/BDE ~84 kcal/mol) to form fluoroform (BDE ~106 kcal/mol),[22] which inhibits radical attack of arenes or unsaturated C–C bonds, thereby leading to the broad functional group tolerance observed in this chemistry. Experimentally, small quantities of Barton–McCombie reduction product were observed (<10%) along with the remaining silane. This is likely due to the rapid H atom abstraction from silane by the CF_3 radical to suppress Barton–McCombie product formation. Moreover, the coupling between **1-rad** and **6** appears faster than the reductive hydrogenation process, thus preferentially producing the desired products.

In summary, we have disclosed a mild, Cu-mediated deoxygenative trifluoromethylation of unactivated and benzylic thiocarbonates. It represents a practical method for the radical trifluoromethylation of unactivated alcohol-derived substrates. The protocol tolerates a wide range of functional groups and electron-rich and -deficient arenes and can be used in the trifluoromethylation of complex molecules. As such, this methodology should find general use in a range of chemical applications.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c04039.

Experimental details, compound characterization, and NMR data (PDF)

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Notes

The authors declare no competing financial interest.

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