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Efficient Synthesis of β-CF_3/SCF_3-Substituted Carbonyls via Copper-Catalyzed Electrophilic Ring-Opening Cross-Coupling of Cyclopropanols

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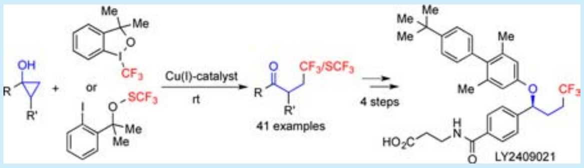
Supporting Information

ABSTRACT: The first copper-catalyzed ring-opening electrophilic trifluoromethylation and trifluoromethylthiolation of cyclopropanols to form C_{sp3}−CF_3 and C_{sp3}−SCF_3 bonds have been realized. These transformations are efficient for the synthesis of β-CF_3- and β-SCF_3-substituted carbonyl compounds that are otherwise challenging to access. The reaction conditions are mild and tolerate a wide range of functional groups. Application to a concise synthesis of LY2409021, a glucagon receptor antagonist that is used in clinical trials for type 2 diabetes mellitus, is reported as well.



Fluorine-containing organic molecules have shown exceptional importance in numerous areas including pharmaceutical industry, agriculture, and material sciences. Among various fluorine-containing groups, trifluoromethyl (CF_3) and trifluoromethylthiol (SCF_3) groups often appear in life-saving drug molecules as well as agrochemicals. Significant advances have been made recently on the installation of CF_3[1] and SCF_3[2] groups on sp^2, sp, and activated sp^3 (cf. allylic, benzylic, α-carbon of carbonyls) carbons. However, synthetic options for the introduction of these valuable groups on nonactivated aliphatic carbons are still very limited.[3]

Due to their intrinsic ring strain and straightforward synthesis, cyclopropanols have been broadly used as starting materials in various transition-metal-mediated or -catalyzed ring-opening cross-coupling reactions.[4] For example, palladium-catalyzed cyclopropanol ring-opening followed by cross-coupling reactions have been developed to form C−C bonds at the β-position.[5] This type of chemistry, however, suffers from competitive β-H elimination to form α,β-unsaturated ketone byproducts or requires special substrates or palladium-ligand combinations to ensure the desired C−C bond formation. Despite the low cost of copper catalyst,[6] copper-catalyzed or -mediated cyclopropanol ring opening cross-coupling reactions have been very rare.[7] We envisioned that cyclopropanols could be converted to various valuable β-substituted carbonyl compounds including β-CF_3/SCF_3-substituted products via copper-catalyzed ring-opening cross-coupling reactions (Figure 1). In the catalytic cycle, the Cu(I) catalyst would be oxidized by generic oxidant **2** to generate Cu(II) or Cu(III) catalyst, which would then promote ring-opening C−C bond cleavage of cyclopropanols and generate Cu(II) or Cu(III) homoenolates **3** depending on the nature of the Cu−Y bond. The latter would then undergo C_{sp3}-Y bond formation to provide product **4** and regenerate the Cu(I) catalyst. This catalytic copper-homoenolate cross-coupling chemistry would render cyclopropanols and the related systems as useful alkyl cross-coupling partners to form important C_{sp3}−C_{sp3} and C_{sp3}−heteroatom bonds.

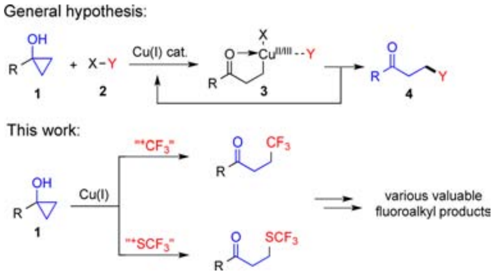


Figure 1. General hypothesis and this work.

If electrophilic trifluoromethylation or trifluoromethylthiolation reagents could be used as oxidants, we expected to install CF_3 or SCF_3 groups at the β-position of saturated carbonyl compounds via copper-catalyzed C_{sp3}−CF_3 or C_{sp3}−SCF_3 bond formation, respectively (Figure 1, Y = CF_3 or SCF_3). This method could provide a complementary and umpolung strategy for synthesizing β-CF_3/SCF_3 substituted ketones,[8] which are otherwise challenging to access via other synthetic methods including the conjugate additions of the corresponding CF_3/SCF_3 nucleophile to α,β-unsaturated carbonyl systems.[9] Due to the rich and diverse chemistry of the carbonyl group, the β-CF_3/SCF_3-substituted products could be readily converted to many useful fluoroalkyl products as well. While mechanistically interesting and synthetically appealing, the proposed catalytic process from **1** to **4** is very challenging because in order to

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selectively form the desired $C_{sp3}-CF_3/SCF_3$ bond, the following competing side reactions must be suppressed: (i) homodimerization of **3** to form 1,6-diketones,[7a] (ii) elimination or oxidation to form α,β-unsaturated enones, and (iii) protonation of **3** to form ethyl ketones. Herein, we report the first copper-catalyzed electrophilic trifluoromethylation and trifluoromethylthiolation of cyclopropanols to synthesize various β-CF_3/SCF-substituted carbonyl compounds with an application to LY2409021 (**17**), a glucagon receptor antagonist that is used in clinical trials for type 2 diabetes mellitus.[10]

We started with cyclopropanol **5a** (Figure 2 and the Supporting Information, Table 1). When it was treated with the first-generation Togni reagent **A** derived from 2-iodobenzoic acid[11] in MeOH with a catalytic amount of $Cu(MeCN)_4BF_4$, desired β-CF_3 ketone **6a** was produced in 40% yield but accompanied by a significant amount of β-iodoketone and α,β-unsaturated ketone byproducts. Further reaction optimization did show that Togni reagent **B** is effective to suppress the formation of these byproducts. Cationic copper catalyst is necessary for high yield in comparison to CuCl, CuBr and CuTc. Increasing the amount of reagent **B** to 1.5 equiv is beneficial, but further increase results in more unidentified byproducts. Overall, we were able to obtain desired β-CF_3 ketone product **6a** in 90% yield with optimized reaction conditions. The reaction does not take place in the absence of copper catalyst.

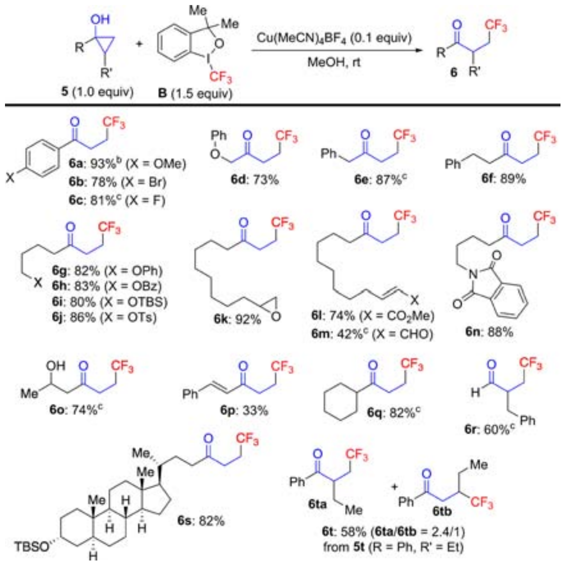

Figure 2. Substrate scope for trifluoromethylation. [a]Isolated yield otherwise noted. [b]0.64 g of **6a** produced. [c]Yield based on ^{19}F NMR.

We then showed that this reaction is very general and tolerates a wide range of functional groups (Figure 2). Both aryl- and alkyl-substituted cyclopropanols worked smoothly to provide the desired β-CF_3 ketones in good to excellent yield. Bromide (**6b**), aryl and alkyl ether (**6a**, **6d**, **6g**), ester (**6h**), primary and secondary TBS-ether (**6i** and **6s**), tosyl (**6j**), epoxide (**6k**), α,β-unsaturated ester/aldehyde (**6l**, **6m**), alcohol (**6o**), and amide (**6n**) functional groups are also compatible with the reaction conditions. Notably, β-CF_3 aldehyde could be synthesized in good yield as well (**6r**). When cyclopropanol **5t** was used, a 2.4/1 mixture of products **6ta** and **6tb** was produced that slightly favored product **6ta**. The reaction is amenable for scale up; **6a** could be produced in a 0.64 g in 93% yield.

We then wondered whether this new catalytic cycle could be transferred to make β-SCF_3-substituted ketones. While simply replacing Togni reagent **B** with other electrophilic SCF_3 reagents did not give a satisfactory outcome, we were able to quickly optimize the reaction (see the Supporting Information, Table 2) and found that β-SCF_3-substituted ketones could be prepared in good to excellent yield with $CuSCF_3$ (0.1 equiv), bipyridine (0.2 equiv), and 2.0 equiv of reagent **C**[12] in DMSO at room temperature. $CuSCF_3$ is superior to other copper catalysts because it avoided the introduction of noninnocent anionic counterions to complicate the cross-coupling process. Again, the substrate scope of this reaction is broad, and many functional groups are compatible with the mild reaction conditions (Figure 3). Notably, terminal olefins that are incompatible in the β-trifluoromethylation conditions (Figure 5, **5v** → **22**) are well tolerated in the trifluoromethylthiolation conditions (cf. **7v**).

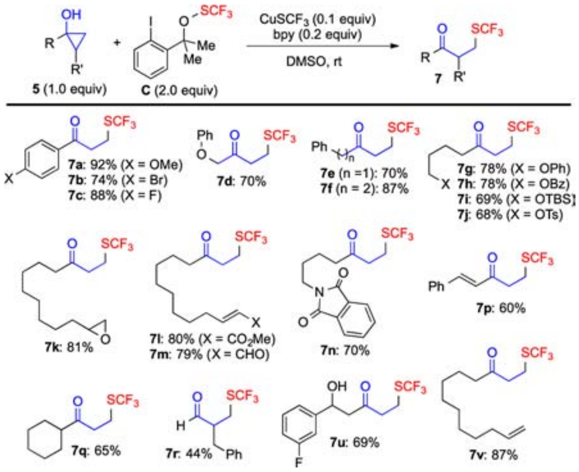

Figure 3. Substrate scope for trifluoromethylthiolation.

The β-CF_3/SCF_3-substituted ketone products could be readily converted to other valuable CF_3/SCF_3-containing compounds (Figure 4A and the Supporting Information, Figures 1 and 2). For example, **6a** could be transformed to indole **8** via Fisher indole synthesis, alkyne **9** via a one-carbon homologation, or amine **10** via reductive amination reaction. It could be reduced to **11** as well,

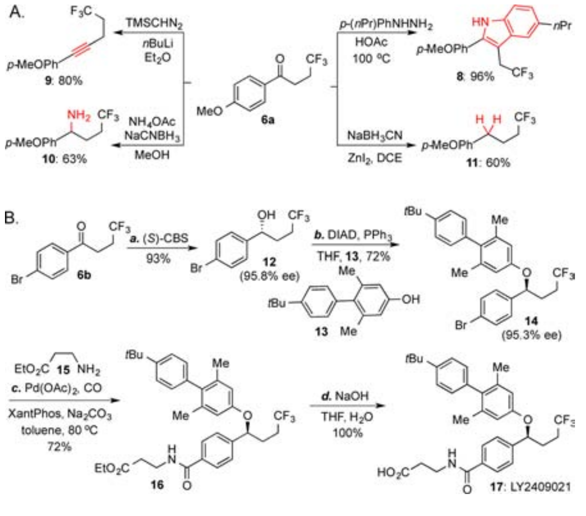

Figure 4. Representative transformation of β-CF_3-substituted ketones and an efficient synthesis of LY2409021.

which renders the carbonyl group derived from cyclopropanol a traceless group. Similar synthetic transformations could be conducted on the corresponding β-SCF_3-substituted carbonyl products as well (see the Supporting Information, Figure 2). We then applied the trifluoromethylation reaction to synthesize a therapeutic candidate LY2409021 (Figure 4B). LY2409021 is a glucagon receptor antagonist that is currently used in clinical trials for type 2 diabetes mellitus. Its CF_3-containing alkyl chain has been shown to be critical for its activity. Our synthesis started with β-CF_3 ketone **6b**. After CBS reduction and Mitsunobu reaction with **13**, **6b** was converted to **14** in excellent yield and enantioselectivity. The bromide group of **14** then served as a convenient handle to synthesize **16** via a palladium-catalyzed carbonylative amination reaction.[13] The latter was then converted to LY2409021 (**17**) upon hydrolysis.

To gain information about the reaction mechanism, we investigated the effect of TEMPO on both the trifluoromethylation and trifluoromethylthiolation reactions (Figure 5). Very different results were obtained when a 1/1 ratio of TEMPO to **B**/**C** was added. For the trifluoromethylation reaction, TEMPO−CF_3 (**20**) was obtained in 95% yield with 98% yield of **19**, 37% yield of **18**, as well as 63% recovery of recycled **5a**. The formation of **20** indicates the involvement of CF_3 radical, which was supported by the conversion of cyclopropanol **5v** with a terminal olefin to double trifluoromethylated product **22**.[14] In the case of trifluoromethylthiolation, no TEMPO−SCF_3 (**21**) was obtained. When substrate **5w** was used in the trifluoromethylthiolation reaction, **7w** was produced in 54% yield, and the terminal olefin is tolerated under the reaction conditions. In this case, no cyclized product **23** was observed, indicating that a copper-promoted radical cyclopropanol ring-opening process to produce an β-alkyl radical was unlikely[15] and copper-promoted β-carbon elimination might be involved to generate a copper homoenolate. When enone **18** was subjected to the trifluoromethylation or trifluoromethylthiolation reaction, no **6a** or **7a**, respectively, was obtained, which suggest that α,β-unsaturated ketone intermediate is not involved in the production of the desired product.

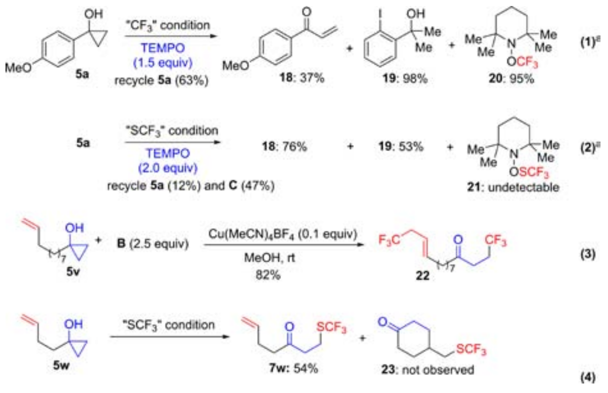

Figure 5. Preliminary probe of reaction mechanisms. [a]Yield based NMR analysis with internal standard.

With these preliminary observations, a mechanistic model involving several plausible pathways was proposed (Figure 6). One possibility is that the reactions may proceed with oxidation of Cu(I) catalyst by reagent **B**/**C** to form a Cu(II) intermediate **D** as well as the CF_3/SCF_3 radical.[14] Intermediate **D** would then undergo ligand exchange with cyclopropanol **5** to form **E**, which would proceed with cyclopropane ring C−C bond cleavage to provide homoenolate **F**.[7a,b] C_{sp3}−Y bond formation from **F** would produce product **6**/**7** and regenerate Cu(I) catalyst. At this stage, the possibility of involving Cu(III) intermediates (cf. **B**/**C** → **D′** → **E′** → **F′** → **6**/**7**) cannot be ruled out. Since distinct patterns of reactivity have been observed, the trifluoromethylation and trifluoromethylthiolation reactions may proceed in different pathways as well, and further studies are necessary to understand these processes

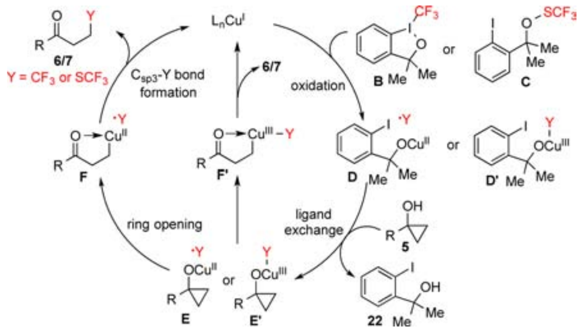

Figure 6. Proposed catalytic cycle.

In summary, the first Cu-catalyzed trifluoromethylation and trifluoromethylthiolation of cyclopropanols have been developed to synthesize β-CF_3/SCF_3-substituted carbonyl compounds. The reaction conditions are mild and compatible with a wide range of functional groups. The products can be readily transformed to many other useful CF_3/SCF_3-containing compounds which are otherwise difficult to access. Their potential application has been demonstrated by preparing LY2409021, a clinical drug for type 2 diabetes mellitus. While the detailed reaction mechanisms have not yet been understood, these two novel catalytic reaction modes of copper-homoenolate chemistry render cyclopropanol and related systems valuable alkyl cross-coupling partners and open new gates for discovering new reactivity and reaction modes for C_{sp3}−C_{sp3} or C_{sp3}−heteroatom bond formation.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and characterization for new compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

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Notes

The authors declare no competing financial interest.

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