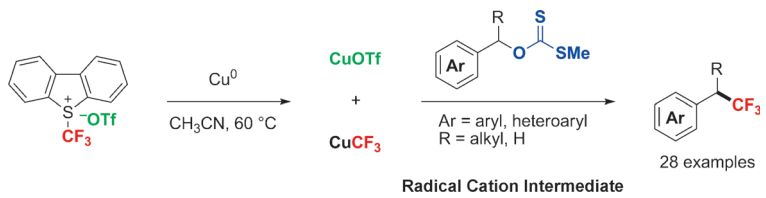

Highly compatible and useful: The copper-mediated trifluoromethylation of benzylic xanthates using Umemoto's reagent as the source of CF_3 to form C–CF_3 bonds is described (see scheme). The method is compatible with an array of benzylic xanthates bearing useful functional groups. A preliminary mechanistic investigation suggests that the C–CF_3 bond forms by reaction of the substrate with in situ generated $CuCF_3$ and CuOTf.

Trifluoromethylation

*L. Zhu, S. Liu, J. T. Douglas, R. A. Altman** ..... ▮▮▮▮–▮▮▮▮

Copper-Mediated Deoxygenative Trifluoromethylation of Benzylic Xanthates: Generation of C–CF_3 Bond from an O-Based Electrophile

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Copper-Mediated Deoxygenative Trifluoromethylation of Benzylic Xanthates: Generation of C–CF_3 Bond from an O-Based Electrophile

Lingui Zhu,[a] Shasha Liu,[a] Justin T. Douglas,[b] and Ryan A. Altman*[a]

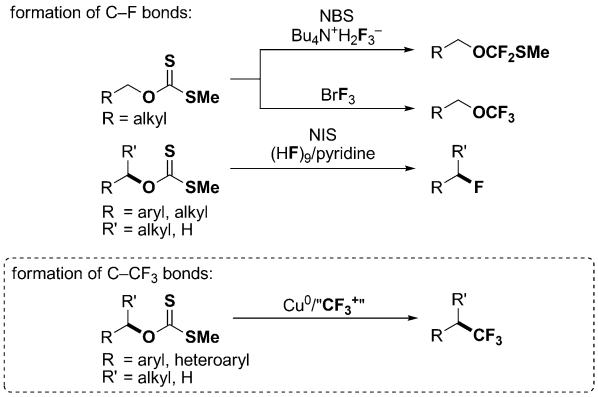
Abstract: The conversion of an alcohol-based functional group, into a trifluoromethyl analogue is a desirable transformation. However, few methods are capable of converting O-based electrophiles into trifluoromethanes. The copper-mediated trifluoromethylation of benzylic xanthates using Umemoto's reagent as the source of CF_3 to form C–CF_3 bonds is described. The method is compatible with an array of benzylic xanthates bearing useful functional groups. A preliminary mechanistic investigation suggests that the C–CF_3 bond forms by reaction of the substrate with in situ generated $CuCF_3$ and CuOTf. Further evidence suggests that the reaction could proceed via a radical cation intermediate.

Keywords: copper · fluorine · radical cation · synthetic methods · trifluoromethylation

Introduction

The incorporation of trifluoromethyl groups (CF_3) into organic molecules imparts profound changes in physical, chemical, and biological properties of molecules.[1] Due to high electronegativity, lipophilicity, and metabolic stability of the trifluoromethyl group, trifluoromethylated compounds have been widely employed in the fields of pharmaceuticals, agrochemicals and materials science.[1,2] Accordingly, various protocols for the introduction of CF_3 into organic molecules have increasingly emerged.[2a,3–5] Specifically, transition-metal-catalyzed or -mediated trifluoromethylation reactions have made remarkable progress.[3–5] For example, Pd-catalyzed trifluoromethylation of C(sp^2)-halides and C(sp^2)–H bonds,[4] and Cu-mediated or Cu-catalyzed trifluoromethylation of halides, boronic acids and terminal alkynes[3g,5] provide access to compounds containing C(sp^2)–CF_3 and C(sp)–CF_3 bonds. However, few examples exist of the generation of C–CF_3 bonds from O-based electrophiles.[6]

The conversion of an alcohol-based functional group into a trifluoromethyl analogue is a desirable transformation. Alcohols can be readily converted into xanthates,[7] which are typically employed to generate radical intermediates.[8–11] Besides forming radical intermediates, xanthates can also be converted to useful fluorinated functional groups such as difluoro(thiomethyl)methyl ethers,[12] trifluoromethyl ethers,[12,13] or fluorides,[14] (Scheme 1). However, all these transformations of xanthates only form C–F bonds. In contrast, we describe a copper-mediated deoxygenative trifluoromethylation of benzylic xanthates to form C–CF_3 bond, and an accompanying mechanistic study.



Scheme 1. Transformations of xanthates into fluorinated compounds.

Results and Discussion

To develop a C(sp^3)–CF_3 bond-forming reaction, a range of conditions and trifluoromethylating reagents were scouted for the conversion of benzylic xanthate **1a** into trifluoromethylated product **3a**. The combination of Togni's reagent **2c** (Scheme 2), catalytic Cu^I and 1,10-phenanthroline (1,10-phen) afforded trifluoromethylated product **3a** in 23% yield. However, the use of other Cu^I or Cu^{II} salts, radical initiators, and alternate ligands decreased the yield of **3a**.

Encouraged by recently reported copper-mediated trifluoromethylation reactions of heteroaryl iodides and benzyl bromides,[5c,d] we explored the use of copper powder to promote the reaction (for more details see Supporting Informa-

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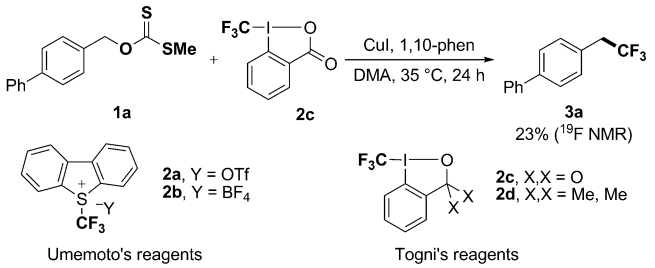
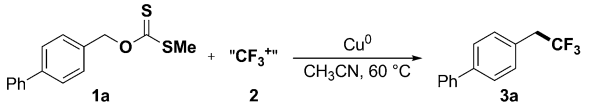


Scheme 2. Initial screening of the trifluoromethylation of xanthates involved reactions of CuI and 1,10-phen.

tion). Treatment of **1a** with Umemoto's reagent **2a** and Cu^0 in DMA provided an increased yield of 42%. Subsequent screening of alternate solvents revealed that polar aprotic solvents, such as DMA, NMP, DMSO, and CH_3CN, facilitated the reaction, while no product was formed in non-polar and ethereal solvents. The use of CH_3CN at 60°C afforded **3a** in the reasonable yield (57%). Further optimization of the reaction involved screening of the fluorinating reagents, and stoichiometry of the reagents (Table 1). For the Cu^0-mediated trifluoromethylation reaction of **1a**, Umemoto's *S*-trifluoromethyl dibenzothiophenium-based reagents **2a** and **b** outperformed Togni's *I*-trifluoromethyl benziodoxole reagents **2c** and **d** (entries 1–4), and triflate **2a** was selected for conducting all subsequent work. Increasing the stoichiometry of Cu^0, while maintaining the stoichiometry of **2a** constant, provided a lower yield of product **3a** (entries 3, 5 and 6). However, simultaneously increasing both the equivalents of **2a** and Cu^0 elevated the yield of **3a** to 78–79% (entries 8–9). Although an improved yield was obtained upon increasing the ratio to 1:4:5 (84%, entry 10), the cost of reagents (relative to this modest improvement in yield) discouraged use of such stoichiometry. In addition, the use of N-, or P-type ligands decreased the yield of product **3a** (for more details of all screening reactions see Supporting Information).

With the optimized reaction conditions in hand, the scope of the Cu^0-mediated deoxygenative trifluoromethylation of xanthates was examined (Table 2). For substrates derived from primary benzylic alcohols, xanthates with strong electron-withdrawing substituents (**3i–l**), as well as weak electron-withdrawing and -donating substituents (**3a–f**) provided good yields of products. Even in the presence of reducing Cu^0, an aryl bromide remained intact. For *ortho*-substituted xanthates **1q** and **1r** containing conjugated double bonds, the trifluoromethylation reaction didn't affect the neighboring alkenes. Reactions of xanthates containing heteroaromatic rings such as pyridine and benzothiophene afforded the trifluoromethylated products in good yields (**3s**, **3u**). However, the reaction of a quinoline-based substrate **1t** provided a lower yield of **3t**. Trifluoromethylation of benzyl xanthates bearing methoxy or dimethylamino on the *o*- or *p*-position was generally unsuccessful. For these substrates, the xanthate readily rearranged into the dithiocarbonate, presumably under the Lewis acidic conditions resulting from

Table 1. Effects of trifluoromethylating reagents and stoichiometry of reagents.[a]



Entry	"CF_3^+"	**1**/**2**/Cu^0	Yield [%][b]
1	**2a**	1:2:3	60 (57)[c]
2	**2b**	1:2:3	56
3	**2c**	1:2:3	39
4	**2d**	1:2:3	7
5	**2a**	1:2:2	43
6	**2a**	1:2:4	47
7	**2a**	1:3:3	64
8	**2a**	1:3:4	78
9	**2a**	1:3.5:4.5	79
10	**2a**	1:4:5	84[d]

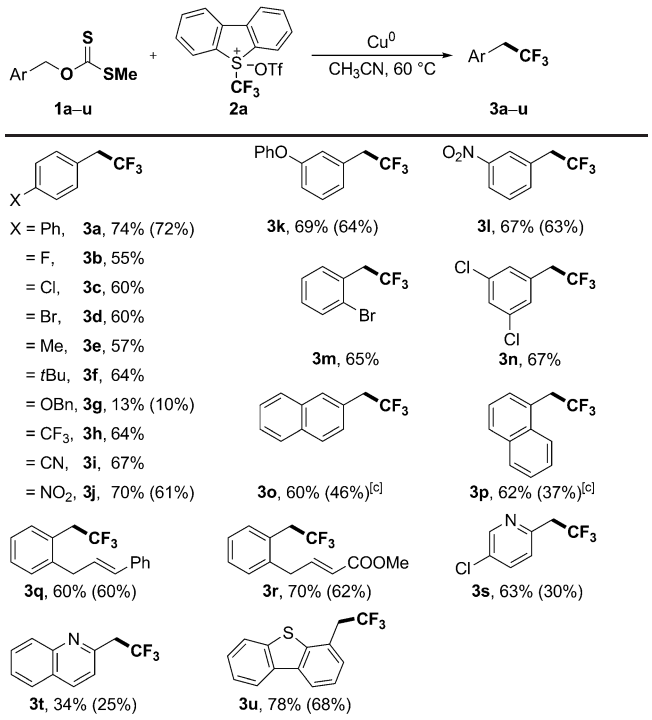
[a] Reaction conditions: **1a** (1.0 equiv), **2**, Cu^0, anhydrous CH_3CN (c = 0.1 M), 60°C, 9 h, under an atmosphere of N_2. [b] Yields were determined by ^{19}F NMR analysis using benzotrifluoride as an internal standard. [c] The reaction time for the yield in parenthesis was 11 h. [d] 20% of **2a** remained by ^{19}F NMR analysis.

the reaction of Cu^0 with **2a**.[15] In many cases, this rearrangement actually prohibited the preparation of xanthates from electron-rich benzylic alcohols.[16] However, trifluoromethylated product **3g** could be obtained in 13% yield.

Xanthates derived from secondary benzylic alcohols also underwent the trifluoromethylation reaction (Table 3), but required slightly more Cu^0 and **2a** than xanthates derived from primary alcohols. Trifluoromethylated products were generated in lower yields than their respective non-branched counterparts (**5a** vs **3a** and **5b** vs **3j**), which may be attributed to the sensitivity of some α-branched benzylic xanthates to Lewis acid (CuOTf).[15] For secondary benzylic xanthates that tolerated the reaction conditions, trifluoromethylation proceeded smoothly in moderate to good yields (**5c**, **5d** and **5g**). As steric hindrance α to the xanthate increased, the yields decreased (**5d–f**). For certain reactions, the separation of the dibenzothiophene byproduct from the trifluoromethylated product was challenging (**3o**, **3p** and **5g**). For these select cases, treatment of the reaction mixture with *m*-CPBA allowed the oxidized dibenzothiophene to be separated by column chromatography in lower yields than suggested by ^{19}F NMR spectroscopy.

Preliminary investigations established that both $CuCF_3$ and in situ generated CuOTf were crucial for activating the xanthate substrate (Scheme 3). No reaction was observed when xanthate **1a** was treated either with Cu^0 in the absence **2a** [Eq. (1)], or with **2a** in the absence of Cu^0 [Eq. (2)]. In both cases, the majority of the starting material was recovered. However, treatment of xanthate **1a** with CuOTf provided dithiocarbonate **6** as the sole major product, potentially by a Lewis acid-mediated cationic rearrangement [Eq. (3)].[15a,b] Treatment of **1a** with 2.0 equiv $CuCF_3$ (formed by reaction of CuI and $TMSCF_3$ in the presence of CsF)[5k] provided product **3a** in 20% ^{19}F NMR yield [Eq. (4)], while the addition of CuOTf (2.0 equiv) to the re-

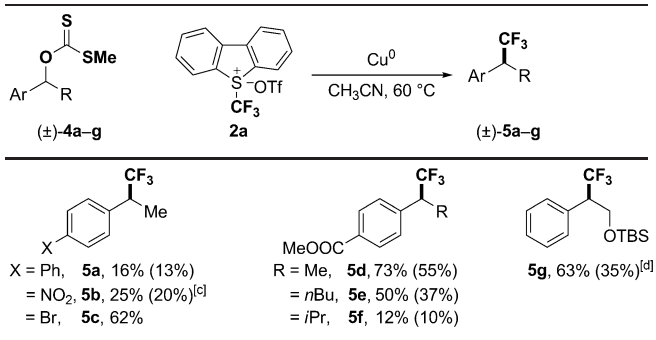
Table 2. Cu^0-mediated trifluoromethylation of benzylic xanthates **1**.[a,b]



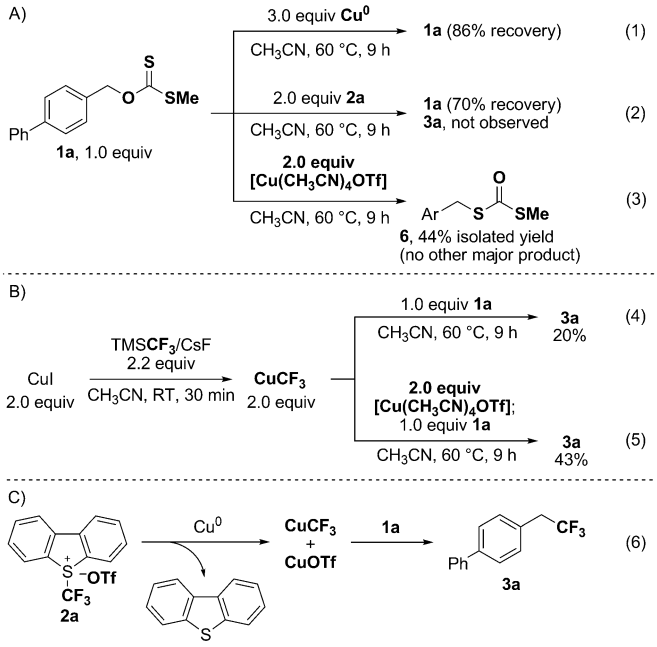
[a] Reaction conditions: **1a–u** (1.0 equiv), **2a** (3.0 equiv), Cu^0 (4.0 equiv), anhydrous CH_3CN ($c = 0.1$ M), 60 °C, 9 h, under an atmosphere of N_2. [b] Yields were determined by ^{19}F NMR analysis using benzotrifluoride as an internal standard (average of two runs) and the figures in parenthesis refer to the isolated yields after purification (average of two runs). [c] Isolated yield after using *m*-CPBA to facilitate separation of dibenzothiophene.

action mixture increased the yield of product **3a** to 43% [Eq. (5)]. Based on these results a plausible mechanism involves reaction of Cu^0 with **2a** to generate CuOTf and $CuCF_3$,[5c] followed by reaction of this combination of reagents with **1a** [Eq. (6)]. In this sequence, CuOTf, presumably activates the xanthate towards trifluoromethylation.

Table 3. Cu^0-mediated trifluoromethylation of racemic α-branched benzylic xanthates **4**.[a,b]



[a] Reaction conditions: (±)-**4a–g** (1.0 equiv), **2a** (4.0 equiv), Cu^0 (5.4 equiv), anhydrous CH_3CN ($c = 0.1$ M), 60 °C, 9 h, under an atmosphere of N_2. [b] Yields were determined by ^{19}F NMR analysis using benzotrifluoride as an internal standard (average of two runs) and the figures in parentheses refer to the isolated yields after purification (average of two runs). [c] The reaction was run at 40 °C. [d] Isolated yield after using *m*-CPBA to facilitate separation of dibenzothiophene.

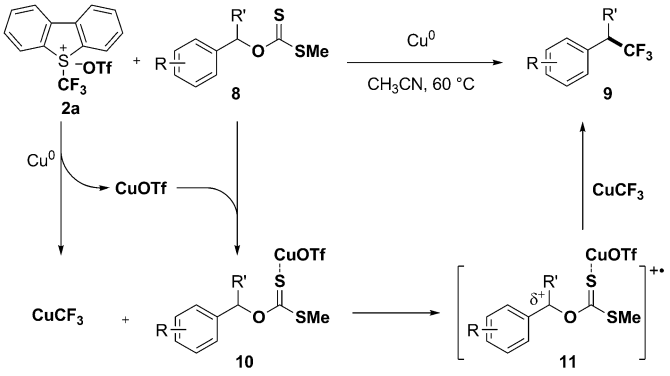


Scheme 3. A) Substrate **1a** was stable in the presence of Cu^0 or **2a**, but was activated by CuOTf. B) Treatment of **1a** with $CuCF_3$ provided **3a**, but the yield of **3a** increased in the presence of added CuOTf. C) A plausible mechanism involves reduction of **2a** to form $CuCF_3$ and CuOTf.[5c] Both Cu-based species are involved in trifluoromethylation.

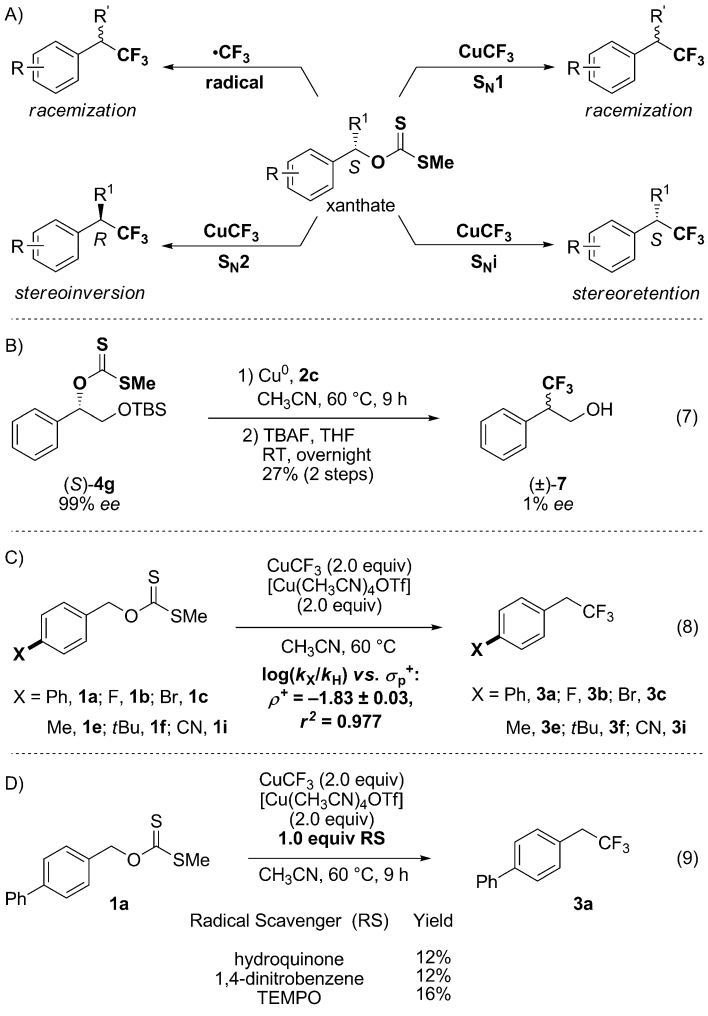
Further experiments detected both radical and cationic character for the interaction between **1a** and $CuCF_3$/CuOTf (Scheme 4). Xanthates undergo reactions that proceed by radical, S_N2, S_Ni and S_N1 pathways (**A**).[8–10,14–16] In order to distinguish between these mechanisms, enantiomerically pure xanthate (*S*)-**4g** was prepared from commercially available (*S*)-1-phenylethane-1,2-diol (99% *ee*). Trifluoromethylation of (*S*)-**4g**, and subsequent desilylation provided known alcohol (±)-**7** [Eq. (7)].[17] Thus, pathways proceeding by net S_N2 (anticipated stereoinversion) or S_Ni (anticipated stereoretention) reactivity were discounted, and further evidence was sought to distinguish between radical and S_N1 mechanisms. Using a series of *p*-substituted benzylic xanthates, a Hammett plot was constructed in order to establish the relationship between electronic structure of the substrate and the rate of trifluoromethylation using the $CuCF_3$/CuOTf system (see Figure 1 in Supporting Information). A linear free energy correlation of $\log(k_X/k_H)$ versus σ_p^+ ($\rho^+ = -1.82 \pm 0.03$, $r^2 = 0.977$) indicated that the trifluoromethylation between $CuCF_3$/CuOTf system and xanthates develops positive charge at the benzylic position near the transition state.[18a,19] Moreover, a weaker correlation between $\log(k_X/k_H)$ and σ_p ($\rho = -2.06 \pm 0.03$, $r^2 = 0.964$) and a scattered plot of $\log(k_X/k_H)$ versus $\sigma_p^{\bullet}$ excluded a pathway involving homolytic cleavage of the C–O bond to generate neutral radicals.[18–20] Although the value of ρ^+ is negative, the magnitude is less than many S_N1-type reactions of benzylic elec-

trophiles.[21] This could be attributed to the weak Lewis acidic nature of CuOTf, which generates weak positive charge at benzylic position in the transition state.[15a,b,22] Alternatively, the small negative value for ρ^+ could be attributed to a pathway involving a benzylic radical cation intermediate.[23] The reaction of **1a** with a pregenerated combination of $CuCF_3$/CuOTf was inhibited in the presence of several radical scavengers, including 1,4-dinitrobenzene, hydroquinone, and 2,2,6,6-tetramethyl-1-piperidinyloxy [TEMPO, Eq. (9)]. Combined, these results establish both radical and cationic character in the trifluoromethylation process.

Based on the above results and previous reports,[5c,14–16,19–23] we propose a plausible mechanism for Cu^0-mediated deoxygenative trifluoromethylation of benzylic xanthates using Umemoto's reagent **2a** (Scheme 5). Reduction of **2a** by Cu^0 in situ provides $CuCF_3$ in addition to CuOTf.[5c] This combination of reagents reacts with xanthate (**8**) to afford the trifluoromethylated product (**9**) via a proposed cationic radical intermediate (**11**). In this sequence, CuOTf serves as an activating agent for the xanthate (**10**).



Scheme 5. Possible pathways for the interaction of $CuCF_3$ with xanthates.



Scheme 4. A) Possible pathways for the interaction of $CuCF_3$ with xanthates. B) Racemization of (*S*)-**4g** discounts S_N2 and S_Ni reaction pathways. C) A linear free energy correlation of $\log(k_X/k_H)$ versus σ_p^+ establishes the build-up of cationic charge at the benzylic position at the transition state. See Supporting Information for more details. D) Reaction of **1a** was inhibited by multiple radical scavengers.

Conclusion

In summary, a Cu^0-mediated deoxygenative trifluoromethylation of benzylic xanthates using Umemoto's reagent as the source of CF_3 has been developed. The protocol provides access to a wide variety of trifluoroethylarenes bearing sensitive functional groups in moderate to good yields in two steps from widely available benzylic and heterobenzylic alcohols. The xanthates bearing π-donating substituents at the 2- or 4-position were not generally compatible with the trifluoromethylation process, likely because of the sensitivity of these compounds to heat and Lewis acidic conditions. A preliminary mechanistic investigation suggests that the trifluoromethylation process involves a radical cation intermediate. Further, this mechanism might be relevant to other trifluoromethylation reactions of electrophiles that employ stoichiometric $CuCF_3$.[5d,24] We anticipate that the insight gained will accelerate the development of more atom-economical trifluoromethylation reactions, as well as alternate reactions of xanthate electrophiles.

Experimental Section

General procedure for the preparation of benzylic xanthates 1a–u (except for 1r) and 4a–g:[6] Under an atmosphere of nitrogen, a solution of alcohol (1.0 equiv) in anhydrous THF (2–4 mL) was added at 0 °C to a suspension of NaH (60% dispersion in mineral oil, 2.5 equiv) and imidazole (5–8% equiv) in anhydrous THF (generally $c = 0.5$ M). The mixture was stirred at room temperature for 30 min and H_2 gas was released. CS_2 (2.5 equiv) was added, and the resulting mixture was stirred at room temperature for 0.5–1 h. MeI (2.5 equiv) was added, and the mixture was stirred at room temperature until the reaction was completed as monitored by TLC (usually about 1 h). The reaction was cooled to 0 °C, and quenched with a saturated aqueous solution of ammonium chloride. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate thrice. The combined organic layers were washed with brine, and dried over Na_2SO_4. After concentration under vacuum, the residue was purified by flash column chromatography using 0–5% ethyl

acetate/hexane or dichloromethane/hexane as the eluent to afford xanthates **1a–u** (except for **1r**) and **4a–g**.

General procedure for the trifluoromethylation of benzylic xanthates 1a–u: Under an atmosphere of nitrogen, anhydrous CH_3CN ($c = 0.1$ M) was added to a sealed vial equipped with xanthate **1a–u** (1.0 equiv), Umemoto's reagent (3.0 equiv), copper powder (4.0 equiv) and a stir bar at room temperature (when xanthate was oil, it was added as a solution in CH_3CN). Subsequently, the mixture was stirred at 60 °C for 9 h, and then cooled to room temperature. Benzotrifluoride (1.0 equiv) was added as an internal standard, and the resulting mixture was stirred at room temperature for 5 min. After standing for 5 min, an aliquot of the upper clear solution was removed, and subjected to ^{19}F NMR analysis to determine the yield of product **3a–u**. The NMR aliquot was returned to the crude reaction mixture, and the solvent was removed in vacuo and the residue was purified using RediSep R_f Silica cartridge on a Teledyne ISCO CombiFlash Purification System (0–5% EtOAc/hexane as eluent) to provide the corresponding product.

General procedure for the trifluoromethylation of racemic α-branched xanthates 4a–g: Under an atmosphere of nitrogen, anhydrous CH_3CN ($c = 0.1$ M) was added to a sealed vial equipped with xanthate **4a–g** (1.0 equiv), Umemoto's reagent (4.0 equiv), copper powder (5.4 equiv) and a stir bar at room temperature (when xanthate was oil, it was added as a solution in CH_3CN). Subsequently, the mixture was stirred at 60 °C for 9 h and then cooled to room temperature. Benzotrifluoride (1.0 equiv) was added as an internal standard and the resulting mixture was stirred at room temperature for 5 min. After standing for 5 min, an aliquot of the upper clear solution was remove and subjected to ^{19}F NMR analysis to determine the yield of product **5a–g**. For product **5a**, **5b**, and **5d–g**, the NMR aliquot was returned to the crude reaction mixture, and the solvent was removed in vacuo and the residue was purified by flash chromatography (0–5% EtOAc/hexane as eluent) to provide the corresponding product.

Acknowledgements

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