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Hydroxytrifluoromethylation of Alkenes Using Fluoroform-Derived $CuCF_3$

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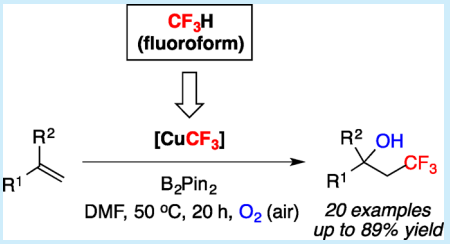
Supporting Information

ABSTRACT: Hydroxytrifluoromethylation of alkenes using the fluoroform (CF_3H)-derived [$CuCF_3$] reagent is described. In the presence of additive B_2Pin_2 and air, this reagent effectively facilitates the addition of hydroxy and trifluoromethyl groups across an alkene double bond, a formal hydroxytrifluoromethylation process. Various β-trifluoromethyl alcohols can be synthesized from simple alkenes where the ultimate CF_3 source is the industrial byproduct fluoroform.

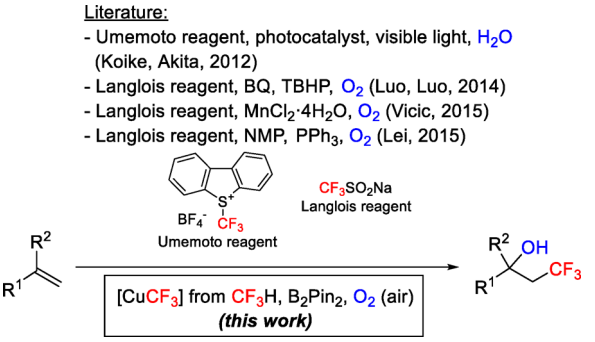


The incorporation of fluorine into drug molecules can significantly improve lipophilicity, permeability, and metabolic stability, as evidenced by the large proportion of marketed fluorine-containing drugs.[1] Synthetic methods for introducing fluorine-containing groups, particularly the trifluoromethyl (CF_3) group, have become increasingly available to industrial chemists in the past few years.[2] Great advances have been made in the trifluoromethylation of arenes and heteroarenes using radical, nucleophilic, and electrophilic CF_3 sources.[2g−i] The constant search for more effective, inexpensive, scalable, and operational simple trifluoromethylation methods has become an important yet challenging priority.

Recent attention has been focused on the addition of the CF_3 group across alkenes and alkynes.[3] These unsaturated starting materials are easily accessible and robust feedstocks. The trifluoromethylation of alkenes with concomitant formation of C−C, C−O, C−N, and C−X bonds is an especially powerful strategy for preparing trifluoromethylated building blocks for bioactive molecules.[3a] In this regard, intra-[4] and intermolecular[5] oxytrifluoromethylation of alkenes has been successfully demonstrated in the synthesis of trifluoromethylated *O*-heterocycles, ketones, and other diverse molecules containing C−O and C−CF_3 bonds. However, there are only a few examples of the concomitant addition of a hydroxy and a trifluoromethyl group across the double bond, a formal *hydroxytrifluoromethylation* process, to provide direct access to useful β-trifluoromethyl alcohols (Scheme 1).[6] These methods suffered from the limitations such as mixture of alcohol and ketone products,[6b,c] use of strong oxidants,[6b] and use of expensive catalysts[6a] and trifluoromethylating reagents.[7]

Grushin's fluoroform-derived [$CuCF_3$] reagent has become an attractive alternative trifluoromethylating reagent in recent years.[8] Fluoroform (CF_3H) is a large-volume byproduct from Teflon manufacturing and is commercially available at low cost. It is also nontoxic and ozone-friendly and, therefore, would be the ultimate source of CF_3 in useful trifluoromethylation reactions.[9] Grushin's group pioneered the applications of

Scheme 1. Hydroxytrifluoromethylation of Alkenes



fluoroform-derived [$CuCF_3$] in various trifluoromethylation method developments.[10] We have also successfully employed this reagent in the trifluoromethylation of terminal alkynes to form C(sp)−CF_3 bonds.[11] However, to the best of our knowledge, there are no examples of the addition of the fluoroform-derived [$CuCF_3$] across alkene moieties to form C(sp^3)−CF_3 bonds.

We set out to investigate the possibility of reacting the fluoroform-derived [$CuCF_3$] with an alkene. The [$CuCF_3$] was prepared from CuCl, *t*-BuOK, and fluoroform according to Grushin's procedure (Scheme 2a).[10a] When the [$CuCF_3$] reagent was added to α-methylstyrene **1a** and the reaction was allowed to run under aerobic conditions, we were delighted to observe 59% NMR yield of the β-trifluoromethyl alcohol product **2a** (Scheme 2b).

Encouraged by this newfound reactivity of [$CuCF_3$], we subsequently began the optimization studies with **1a** (Table 1).[12] Screening of solvents did not significantly improve the yield from the benchmark result. However, a dramatic increase in reactivity was obtained when bis(pinacolato)diboron

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Scheme 2. (a) Preparation of Fluoroform-Derived [$CuCF_3$] by Grushin's Method. (b) Initial Result of the Hydroxytrifluoromethylation of α-Methylstyrene 1a

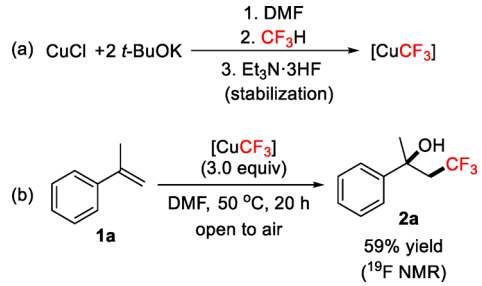
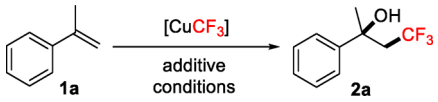


Table 1. Optimization Studies[a]



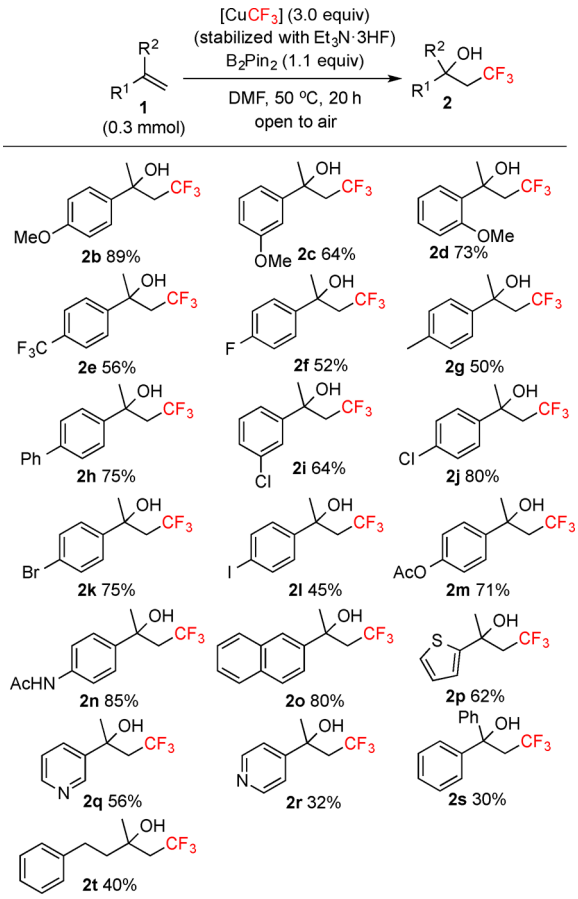
entry	CuCl/Et_3N·3HF[b]	[$CuCF_3$] (equiv)	B_2Pin_2 (equiv)	yield[c] (%)
1	1:0.76	3.0	0	59
2	1:0.76	3.0	0.25	70
3	1:0.76	3.0	0.5	76
4	**1:0.76**	**3.0**	**1.1**	**92, 88**[d]
5	1:0.76	2.5	1.1	85
6	1:0.76	2.0	1.1	79
7[e]	1:0.76	2.0	1.1	75
8[f]	1:0.76	2.0	1.1	62
9[e]	1:0.80	2.0	1.1	71
10[e]	1:0.60	2.0	1.1	59
11[e]	1:0.53	2.0	1.1	56
12[g]	1:0.76	3.0	1.1	0
13[h]	1:0.76	3.0	1.1	86

[a]General conditions: [$CuCF_3$] in DMF solution (prepared from CuCl/*t*-BuOK/fluoroform by the procedure in ref 10a and stabilized by Et_3N·3HF) and **1a** (0.1 mmol in DMF, 0.05 M); reaction was run open to air, 50 °C, 20 h. [b]Molar ratio of CuCl to Et_3N·3HF for the preparation of [$CuCF_3$]. [c]Yield was determined by ^{19}F NMR analysis using benzotrifluoride as the internal standard. [d]Isolated yield. [e]0.1 M concentration. [f]0.2 M concentration. [g]Reaction was run under argon. [h]Reaction was run under oxygen (balloon).

(B_2Pin_2) was used as an additive (entries 1–4). Similar rate acceleration effects by B_2Pin_2 in copper-catalyzed trifluoromethylation of alkenes have been reported by the Szabó group.[13] A good yield (88%, 75% at 1.0 mmol scale) of product **2a** was isolated with 1.1 equiv of B_2Pin_2 (entry 4). Other additives including pinacolborane (HBPin) and tetramethylethylenediamine (TMEDA) were not effective. Lowering the equivalents of [$CuCF_3$] led to a decrease in yield (entries 4–6). The reaction was most suitably run in 0.05 M concentration; higher concentrations diminished the yields (entries 6–8). Grushin reported that the fluoroform-derived [$CuCF_3$] reagent needs to be stabilized by addition of triethylamine trihydrofluoride (Et_3N·3HF).[10a] We found that subtle differences in the amounts of Et_3N·3HF during the preparation of [$CuCF_3$], as represented by the molar ratio of CuCl/Et_3N·3HF, had effects on the yield (entries 7, 9–11). The optimal molar ratio of 1:0.76 was found (entry 7), which required more Et_3N·3HF than in Grushin's original procedure (1:0.33). The aerobic conditions were crucial for product formation. When the reaction was run under argon, no product was observed (entry 12), yet replenishing oxygen to the reaction restored reactivity (entry 13). Reaction at room temperature and 80 °C gave much lower yield. Other oxidants were screened and found to be ineffective for product formation.[12]

Next, the scope of the reaction was investigated using the fluoroform-derived [$CuCF_3$] under optimized conditions (Scheme 3). A variety of β-trifluoromethyl alcohols **2b–t**

Scheme 3. Scope of Alkenes in Hydroxytrifluoromethylation Reactions



were synthesized by this method. Reaction yields were generally higher for electron-rich substrates (e.g., **2b**,**n** vs **2c**,**e**,**m**). For substrates with lower yields, we observed incomplete conversions even after prolonged reaction times. Substituents were tolerated at the *para*, *meta*, and *ortho* positions of the benzene ring (e.g., **2b–d**). Substrate containing aryl iodide gave a lower yield (**2l**) possibly due to the high reactivity of the Ar–I bond; however, aryl chloride (**2j**) and bromide (**2k**) afforded reasonable yields despite the fact that they were known to react with fluoroform-derived [$CuCF_3$] in aromatic trifluoromethylation reactions.[10e]

The lower yield of aryl fluoride (**2f**) was partially due to the volatile substrate **1f**. Substrates containing benzylic C–H only gave moderate yield (**2g**). Naphthyl (**2o**), biphenyl (**2h**), and heteroaromatic (**2p–r**) motifs were also demonstrated. The purifications of polar products **2q** and **2r** were found to be difficult, causing yield losses (^{19}F NMR yields were 77% and 56%, respectively). When the methyl group of α-methylstyrene was replaced with a larger group, for example, ethyl (12%), *n*-propyl (14%), or benzyl (18%), reaction yields dropped dramatically, indicating sensitivity toward the steric environment around the alkene. However, 1,1-diphenylethylene (**1s**)

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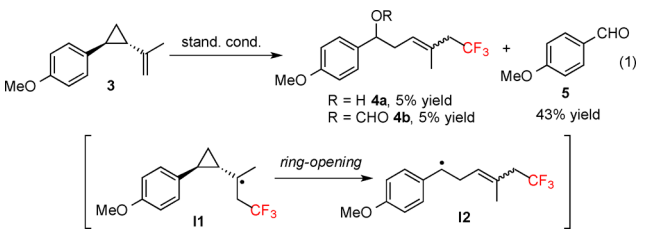
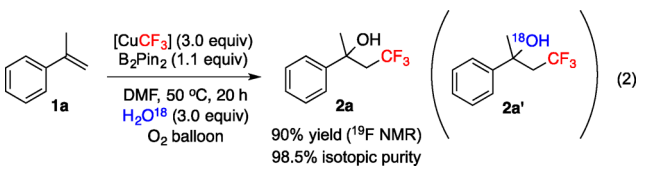
did afford the product in 30% yield, and the 1,1-dialkyl substrate (**1t**) was also reactive. The reaction was limited to 1,1-disubstituted alkenes, and only 10% product was detected by NMR when styrene was used as the substrate. 1,2-Disubstituted alkene (*trans*-stilbene) and enone (acrylophenone) were unreactive.[12]

Literature reports on hydroxytrifluoromethylation of alkenes invoked the participation of a CF_3 radical species, derived from Umemoto reagent[6a] or Langlois reagent (CF_3SO_2Na),[6b−d] therefore suggesting that a radical pathway could be at play in our reaction using fluoroform-derived [$CuCF_3$]. When a radical scavenger TEMPO was added to the standard reaction conditions, we observed significant yield decreases (1.0 equiv of TEMPO, 49% yield; 2.0 equiv of TEMPO, 9% yield; cf. Table 1, entry 4). Using a radical clock substrate **3** under the standard conditions yielded the ring-opening products **4** and aldehyde **5** (eq 1), which provided strong evidence for a radical mechanism through proposed intermediates **I1** and **I2**.[14]



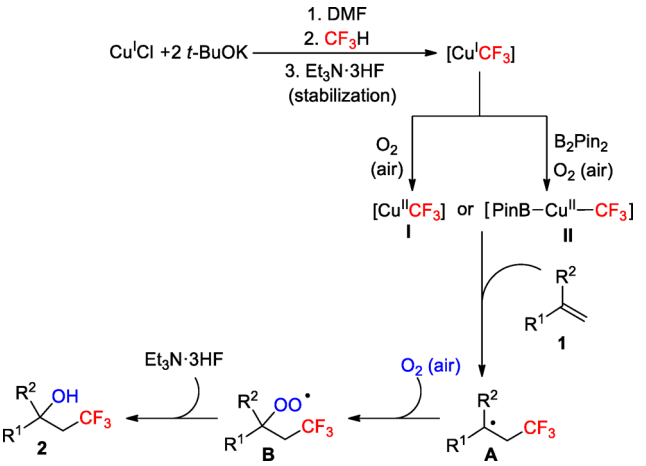
To investigate if a residual amount of water in the reaction mixture could be the source of OH in product **2**, we added ^{18}O-labeled water to the standard conditions and carried out the reaction under an oxygen atmosphere (eq 2). Even in the



presence of a large excess of $H_2{}^{18}O$, the corresponding ^{18}O-labeled product **2a′** was essentially undetected by mass spectrometry. Instead, unlabeled product **2a** was obtained in similar yields as before (cf. Table 1, entries 4 and 13) with 98.5% isotopic purity, therefore ruling out the possibility of water participating in the reaction pathway.

Based on the above studies and known literature evidence, we propose the following mechanism for the hydroxytrifluoromethylation reaction (Scheme 4). The initially formed [Cu(I)CF_3] reagent is easily oxidized to [Cu(II)CF_3] complex **I** in air.[10b] In the presence of B_2Pin_2 and air, transmetalation and oxidation take place to give [PinB−Cu(II)−CF_3] complex **II**.[13c,15] Similar processes have been described in Cu-catalyzed borylation reactions,[16] although we did not observe any borylated intermediates in this reaction. Either complex **I** or **II** is able to undergo homolytic cleavage of the Cu−CF_3 bond to transfer a CF_3 radical to alkene **1** resulting in the tertiary radical species **A** (cf. eq 1). The less stable secondary radical arising from styrene may account for its poor yield. The [PinB−Cu(II)−CF_3] complex **II** is more effective at transferring the CF_3 group, owing to the strong σ-donating ability of the BPin ligand to copper,[13c,16a−c] leading to higher yields (cf. Table 1, entries 1−4). Although Cu(II) complexes are invoked here, the involvement of Cu(III) and polynuclear species

Scheme 4. Proposed Mechanism



should not be completely ruled out.[17] The radical intermediate **A** is further captured by O_2 from air to form the peroxide radical **B** (cf. eq 2).[6d,18] Finally, the β-trifluoromethyl alcohol product **2** is obtained upon hydrogen abstraction and reduction by $Et_3N{\cdot}3HF$.[6d]

In conclusion, we have discovered the hydroxytrifluoromethylation reaction of alkenes using Grushin's fluoroform-derived [$CuCF_3$] reagent. The reaction conditions are mild using air as the oxidant. The importance of B_2Pin_2 as an additive has been demonstrated and a radical reaction mechanism is proposed. Synthetically useful β-trifluoromethyl alcohols can be prepared with good functional group tolerance. Continuing exploration of novel C−CF_3 bond formations using the fluoroform-derived [$CuCF_3$] reagent is ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01085.

Experimental procedures and characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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