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Copper-Catalyzed Oxytrifluoromethylation of Unactivated Alkenes

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Abstract

A mild, versatile and convenient method for the efficient oxytrifluoromethylation of unactivated alkenes has been developed based on a copper-catalyzed oxidative difunctionalization strategy. This methodology provides access to a variety of classes of synthetically useful CF_3-containing building blocks from simple starting materials.

The incorporation of fluoroalkyl groups and particularly the trifluoromethyl (CF_3) group in pharmaceutical and agrochemical relevant molecules has a significant impact on their physical and biological properties, mainly because of the unique metabolic stability, lipophilicity and electron-withdrawing nature of the trifluoromethyl substituent.[1] The importance of CF_3-containing compounds provides a continuing driving force for the development of more efficient and versatile trifluoromethylation methods.[2] Our research group has focused on the development of new fluorination[3] and trifluoromethylation[4] reactions using transition-metal catalysis. Herein we report a mild and versatile copper-catalyzed oxytrifluoromethylation reaction of unactivated alkenes that allows rapid access to a variety of CF_3-containing building blocks from simple starting materials.

Recently, our group, as well as that of Liu and Wang, independently reported the copper-catalyzed allylic trifluoromethylation of unactivated alkenes (Scheme 1).[4d,5] During the course of our studies, we proposed that this transformation might involve either an α-CF_3-alkyl radical (**I**) or α-CF_3-alkylcopper species (**II**), which subsequently undergoes elimination to afford the allylic trifluoromethyl product. We became interested in the possibility of intercepting this putative intermediate (**I** or **II**), as a means for the synthesis of a number of structurally diverse CF_3-containing building blocks in a step-economical fashion.

We envisioned that the oxidative difunctionalization of unactived alkenes involving tandem C–CF_3 and C–Nu bond formation could be achieved based on this strategy.[6,7] It was hypothesized that either a single electron oxidation of the radical intermediate followed by trapping the resulting carbocation (Path A) or copper-mediated C–Nu bond formation (Path B) would lead to the desired difunctionalization product (**III**).[8] The success of this strategy lies in the identification of a catalytic system efficient for both the C–CF_3 bond formation and the subsequent functionalization steps, as well as the ability to inhibit the competitive elimination pathway. Herein we describe a copper(I)/2,2′-biquinoline catalytic system that incorporates these qualities with oxygen-based nucleophiles.

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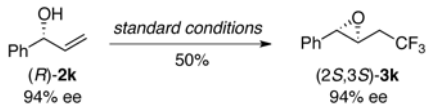
Supporting Information. Experimental procedures, characterization and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

We began our study by examining the reaction of 4-pentenoic acid (**2a**) in the presence of Togni's reagent **1**[9] and a catalytic amount of $Cu(MeCN)_4PF_6$ in methanol. Only allylic trifluoromethylated product **4a** was observed in this case, suggesting elimination as the major pathway (Table 1, entry 1). After examining the effects of solvents and additives, we found that switching to acetonitrile, in the presence of a catalytic amount of 2,2′-bipyridyl (**L1**), the desired oxytrifluoromethylation product **3a** was obtained in 10% yield (entry 3). Encouraged by this result, we evaluated a series of different bidentate pyridine-based ligands, which finally led to the identification of di-2-pyridylketone (**L4**) and 2,2′-biquinoline (**L5**) as being optimal (entry 6 and 7). A nearly 90 % yield of **3a** could be obtained in the presence of either **L4** or **L5**, with only trace of **4a** observed. Both the copper salt and ligand proved to be essential in order for the oxytrifluoromethylation reaction to take place as no **3a** was observed in the absence of either of these components (entry 2 and 8).

With an optimized protocol in hand, we next explored the scope of this oxytrifluoromethylation reaction. Illustrative examples are shown in Table 2. A series of unsaturated aliphatic and aromatic carboxylic acids were found to undergo the desired transformation to give the corresponding trifluoromethylated lactones in good yields (entry 1–8). With regard to the scope of alkene moiety, monosubstituted and geminal disubstituted alkenes were excellent substrates for this reaction.[10] Alkyl and aryl substituents on the carbon–carbon double bond were well tolerated. In terms of the size of the ring formed, δ-, γ-, and even β-lactones proved to be accessible.

Next, we sought to expand the scope of the nucleophile to include other common oxygen-based functional groups. It was found that primary alcohols (Table 2, entry 9) and phenols (entry 10) also served as viable nucleophiles for this reaction.[11]

Allylic alcohols (Table 2, entry 11–13) are an especially interesting class of substrates because their oxytrifluoromethylation reactions give rise to 3-trifluoromethyl-1, 2-epoxides, which are highly versatile CF_3-containing intermediates. It was found that both aryl- (**2k**, **2m**) and alkyl- (**2l**) substituted allylic alcohols furnished the desired products in moderate to good yields. When the enantiomerically enriched **2k** was subjected with the standard protocol, **3k** was produced with no erosion in enantiomeric excess (eq. 1).



(1)

To further demonstrate the synthetic utility of the products derived from this method, oxytrifluoromethylation product **3m** was shown to undergo epoxide opening in good yields in the presence of a number of different nucleophiles including an azide, a Grignard reagent, a thiol and fluoride (Scheme 2). A series of highly functionalized CF_3-containing building blocks (**5**–**8**), which are otherwise difficult to access, could easily be prepared from the simple allylic alcohol **2m** in two steps.

While the mechanistic details of this copper-catalyzed oxytrifluoromethylation reaction remain unclear at present, the use of a copper(I)/bidentate pyridine-based ligand system is suggestive of an atom transfer-type radical addition pathway.[8b,12] Further, the oxytrifluoromethylation reaction was found to be completely inhibited by addition of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), a known radical scavenger.[13]

In conclusion, a mild, versatile and convenient method for the efficient oxytrifluoromethylation of unactivated alkenes has been developed based on a copper(I)/ 2,2′-biquinoline catalytic system. Carboxylic acids, alcohols and phenols all serve as suitable nucleophiles under the conditions developed. The reaction conditions are compatible with a range of functional groups including amides, β-lactones, epoxides and aryl bromides. All the reactions were carried out using simple, user-friendly bench-top set-up. This methodology allows rapid access to a variety of synthetically useful building blocks such as CF_3-containing lactones, cyclic ethers, and epoxides from simple starting materials. We are continuing work to gain insight into the reaction mechanism and expand the scope of this copper-catalyzed alkene difunctionalization strategy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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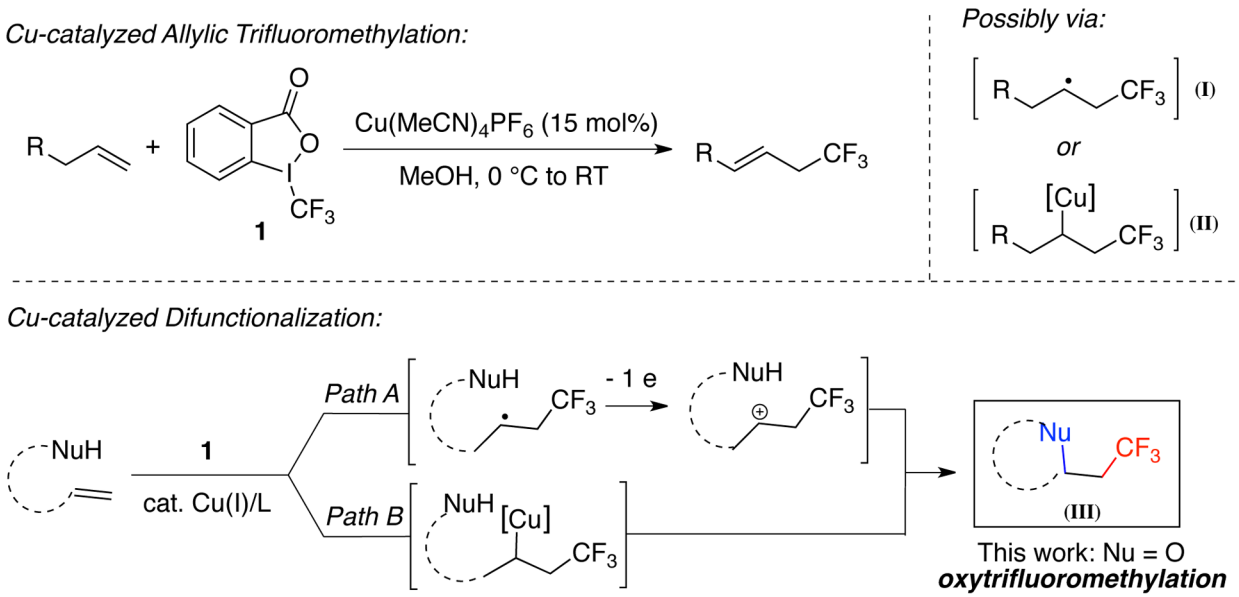
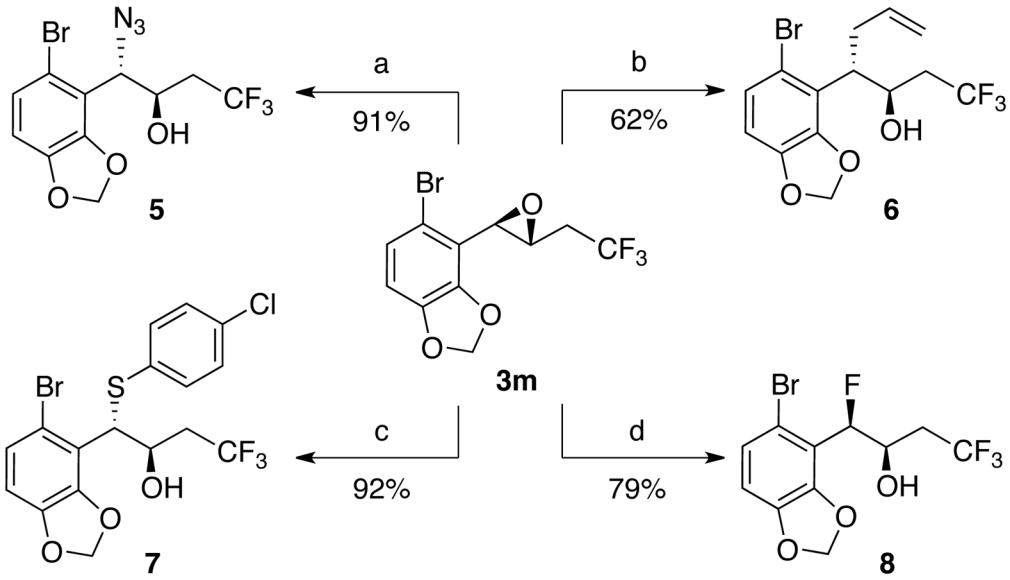
10. Low yields were obtained with 1,2-disubstituted alkene substrates. For instance, under the standard conditions, (*E*)-5-phenyl-4-pentenoic acid furnished the expected oxytrifluoromethylation product in only 11% yield as determined by ^{19}F NMR spectroscopy.
11. In preliminary experiments, the reactions of substrates containing secondary amides or sulfonamides in place of carboxylic acids gave little or no yield of the desired product.
12. C–O bond formation was observed as a side reaction in a photoredox-catalyzed atom transfer radical addition reaction: Nguyen JD, Tucker JW, Konieczynska MD, Stephenson CRJ. J Am Chem Soc. 2011; 133:4160. [PubMed: 21381734]
13. However, neither of the TEMPO adducts derived from CF_3• or the proposed α-CF_3-alkyl radical (**I**) was observed in the inhibition experiment, preventing us from making further conclusions. See supporting information for detail. For recent examples of arene trifluoromethylation involving a trifluoromethyl radical: Nagib DA, MacMillan DWC. Nature. 2011; 480:224. [PubMed: 22158245] Ji Y, Brueckl T, Baxter RD, Fujiwara Y, Seiple IB, Su S, Blackmond DG, Baran PS. Proc Natl Acad Sci. 2011; 108:14411. [PubMed: 21844378] Ye Y, Sanford MS. J Am Chem Soc. 2012; 134:9034. [PubMed: 22624669]



Scheme 1.
Copper-catalyzed trifluoromethylation of unactivated alkenes.



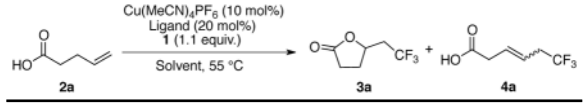
Scheme 2.

Versatile transformations of the oxytrifluoromethylation product 3m.[a]

[a]Reaction conditions: (a) NaN_3 (3 equiv.), NH_4Cl (2 equiv.), H_2O/MeOH, 80 °C, 3 h; (b) Allylmagnesium bromide (3 equiv.), Et_2O, RT, 2 h; (c) *p*-ClC_6H_4SH (2 equiv.), NaOH (2 equiv.), dioxane/H_2O, 65 °C, 2 h; (d) BF_3•Et_2O (0.33 equiv.), DCM, −15 °C, 5 min.

Table 1

Ligand effect.[a]



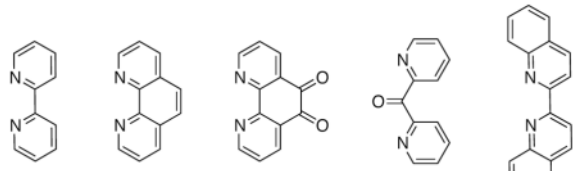
2a 3a 4a

Entry	Solvent	Ligand	Yield (%)[b]	
			3a	4a
1	MeOH	-	< 5	46
2	MeCN	-	< 5	< 5
3	MeCN	**L1**	10	18
4	MeCN	**L2**	12	11
5	MeCN	**L3**	11	< 5
6	MeCN	**L4**	86	5
7	MeCN	**L5**	89	< 5
8[c]	MeCN	**L5**	< 5	< 5

[a]Reaction conditions: $Cu(MeCN)_4PF_6$ (10 mol%), ligand (20 mol%), **2a** (0.10 mmol, 1.0 equiv.), **1** (1.1 equiv.), solvent (1.0 mL), 55 °C, 16 h.

[b]Determined by ^{19}F NMR spectroscopy using $PhCF_3$ as an internal standard.

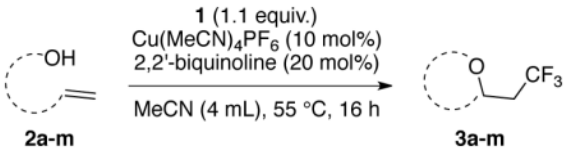
[c]Without $Cu(MeCN)_4PF_6$.

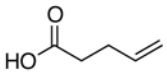
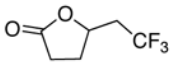
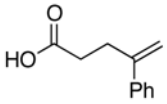
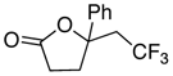
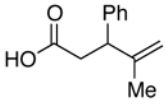
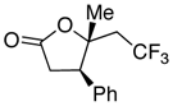
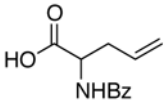
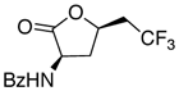
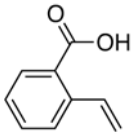
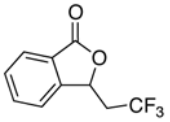
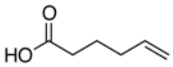
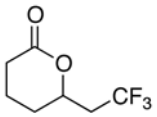
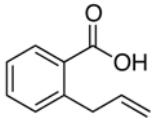
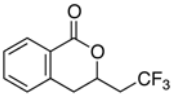
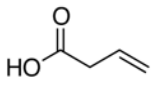
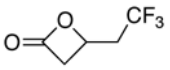
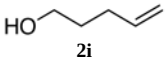
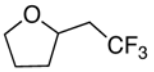


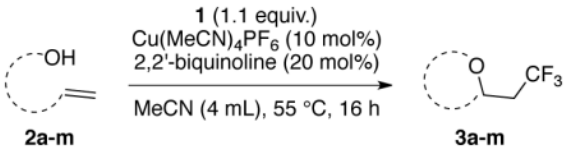
L1 L2 L3 L4 L5

Table 2

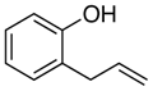
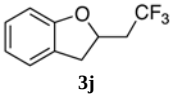
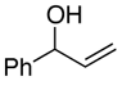
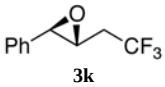
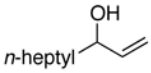
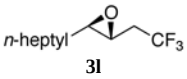
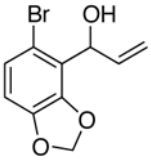
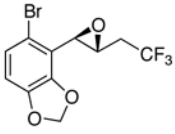
Copper-catalyzed oxytrifluoromethylation.[a]



Entry	Substrate	Product	Yield (%)[b]
1	 2a	 3a	76
2	 2b	 3b	81
3	 2c	 3c	94 (dr 2.2:1)
4	 2d	 3d	74 (dr 2.8:1)
5[c]	 2e	 3e	64
6	 2f	 3f	71
7	 2g	 3g	77
8[c]	 2h	 3h	42[e]
9	 2i	 3i	73[e]



2a-m 3a-m

Entry	Substrate	Product	Yield (%)[b]
10[d]	 2j	 3j	35
11[c,f]	 2k	 3k	50 (dr 10:1)
12	 2l	 3l	70 (dr 4:1)
13[c]	 2m	 3m	64 (dr >20:1)

[a] Reaction conditions: $Cu(MeCN)_4PF_6$ (10 mol%), 2,2′-biquinoline (20 mol%), **2** (0.50 mmol, 1.0 equiv.), **1** (1.1 equiv.), MeCN (4 mL), 55 °C, 16 h.

[b] Isolated yields, average of two runs. Diastereo ratio determined by ^{19}F NMR and ^{1}H NMR spectroscopic analysis. Structures of the major diastereomers are shown.

[c] $Cu(MeCN)_4PF_6$ (20 mol%) and 2,2′-biquinoline (30 mol%) were used.

[d] $Cu(MeCN)_4PF_6$ (20 mol%) and di-2-pyridyl ketone (30 mol%) were used.

[e] Determined by ^{19}F NMR spectroscopy using $PhCF_3$ as an internal standard.

[f] The reaction did not go to full conversion.