JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

Copper-Catalyzed Oxytrifluoromethylation of Unactivated Alkenes

Rong Zhu and Stephen L. Buchwald*

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, United States

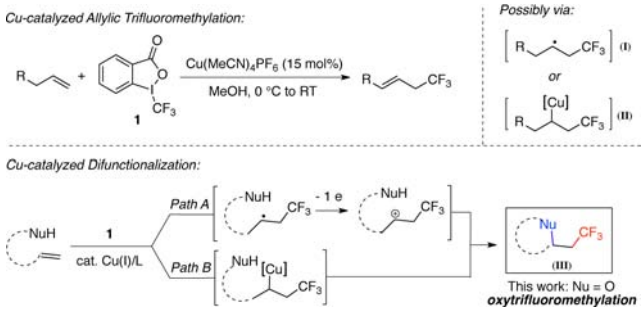
Supporting Information

ABSTRACT: A mild, versatile, and convenient method for the efficient oxytrifluoromethylation of unactivated alkenes based on a copper-catalyzed oxidative difunctionalization strategy has been developed. 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 pharmaceutically and agrochemically 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 those 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 an α-CF_3-alkylcopper species (**II**) that 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 of synthesizing a number of structurally diverse CF_3-containing building blocks in a step-economical fashion.

Scheme 1. Copper-Catalyzed Trifluoromethylation of Unactivated Alkenes



We envisioned that the oxidative difunctionalization of unactived alkenes involving tandem C–CF_3 and C–nucleophile (Nu) bond formation could be achieved through this strategy.[6,7] It was hypothesized that either a single-electron oxidation of the radical intermediate followed by trapping of 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 that is 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.

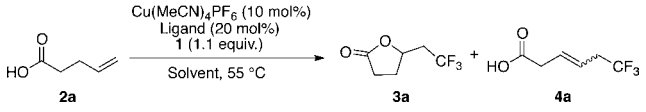
We began our study by examining the reaction of **4**-pentenoic acid (**2a**) in the presence of Togni's reagent (**1**)[9] and a catalytic amount of $Cu(MeCN)_4PF_6$ in methanol. Only the allylic trifluoromethylated product **4a** was observed in this case, suggesting elimination to be the major pathway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

Received: June 15, 2012
Published: July 17, 2012

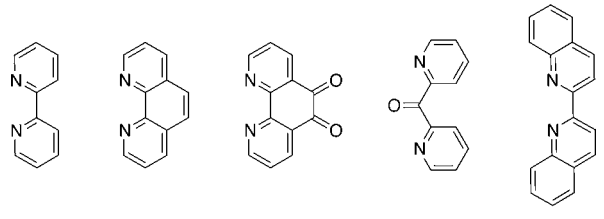
   dx.doi.org/10.1021/ja305840g | J. Am. Chem. Soc. 2012, 134, 12462–12465

Table 1. Ligand Effect[a]



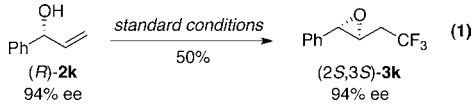
			yield (%)[b]	
entry	solvent	ligand	3a	4a
1	MeOH	–	<5	46
2	MeCN	–	<5	<5
3	MeCN	L1	10	18
4	MeCN	L2	12	11
5	MeCN	L3	11	<5
6	MeCN	L4	86	5
7	MeCN	L5	89	<5
8[c]	MeCN	L5	<5	<5

[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 $Cu(MeCN)_4PF_6$.



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]

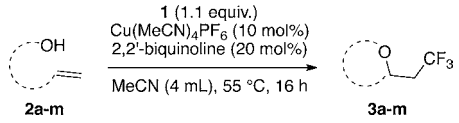
Allylic alcohols (Table 2, entries 11–13) are an especially interesting class of substrates because their oxytrifluoromethylation reactions give rise to 3-trifluoromethyl-1,2-epoxides, which are highly versatile CF_3-containing intermediates. It was found that both aryl- (**2k**, **2m**) and alkyl-substituted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

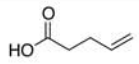
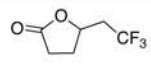
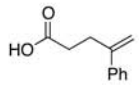
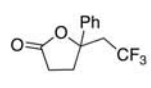
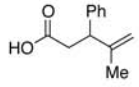
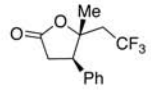
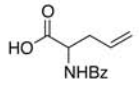
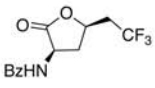
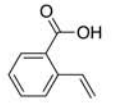
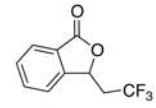
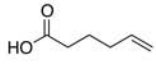
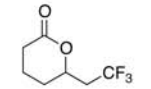
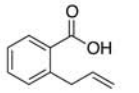
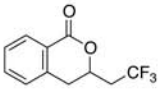
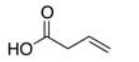
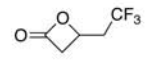
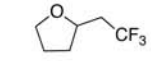
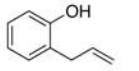
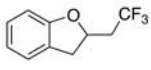
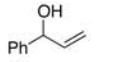
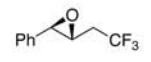
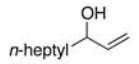
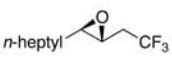
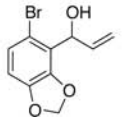
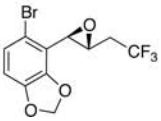


To demonstrate further the synthetic utility of the products derived from this method, oxytrifluoromethylation product **3m** was shown to undergo epoxide opening in good yields in the presence of a number of different nucleophiles, including an azide, a Grignard reagent, a thiol, and a fluoride (Scheme 2). A series of highly functionalized CF_3-containing building blocks (**5**–**8**) that are otherwise difficult to access were easily 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)/pyridine-based bidentate ligand system is suggestive of an atom transfer-type radical addition pathway.[8b,12] Furthermore, the oxytrifluoromethylation reaction was found to be completely inhibited by the addition of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), a known radical scavenger.[13]

Table 2. Copper-Catalyzed Oxytrifluoromethylation[a]

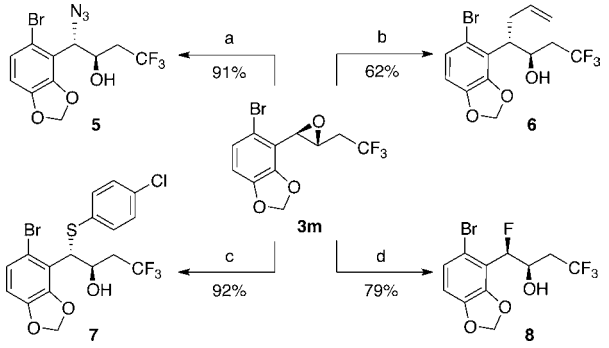


Entry	Substrate		Product		Yield (%)[b]
1		2a		3a	76
2		2b		3b	81
3		2c		3c	94 (dr 2.2:1)
4		2d		3d	74 (dr 2.8:1)
5[c]		2e		3e	64
6		2f		3f	71
7		2g		3g	77
8[c]		2h		3h	42[e]
9		2i		3i	73[e]
10[d]		2j		3j	35
11[c,f]		2k		3k	50 (dr 10:1)
12		2l		3l	70 (dr 4:1)
13[c]		2m		3m	64 (dr >20:1)

[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, averages of two runs. Diastereomeric ratios were 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.

dx.doi.org/10.1021/ja305840g | J. Am. Chem. Soc. 2012, 134, 12462–12465

Scheme 2. Versatile Transformations of 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) $BF_3{\cdot}Et_2O$ (0.33 equiv), DCM, −15 °C, 5 min.

In conclusion, a mild, versatile, and convenient method for the efficient oxytrifluoromethylation of unactivated alkenes based on a copper(I)/2,2′-biquinoline catalytic system has been developed. 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 of the reactions were carried out using a simple, user-friendly benchtop setup. 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.

■ ASSOCIATED CONTENT

Supporting Information

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

■ AUTHOR INFORMATION

Corresponding Author

sbuchwal@mit.edu

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Institutes of Health for financial support of this work (Grant GM46059). This activity was supported in part by an educational donation provided by Amgen, for which we are grateful. We thank Dr. Thomas J. Maimone for helpful discussions. The Varian 300 MHz and Bruker 400 MHz NMR spectrometers used in this work were purchased with funds from the National Science Foundation (Grants CHE 9808061 and DBI 9729592) and the National Institutes of Health (1S10RR13886-01), respectively.

■ REFERENCES

(1) (a) Yamazaki, T.; Taguchi, T.; Ojima, I. In *Fluorine in Medicinal Chemistry and Chemical Biology*; Ojima, I., Ed.; Wiley-Blackwell: Chichester, U.K., 2009; p 3. (b) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (c) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320.

(2) For selected reviews, see: (a) Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature* **2011**, *473*, 470. (b) Shimizu, M.; Hiyama, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 214. (c) Schlosser, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 5432. (d) Tomashenko, O. A.; Grushin, V. V. *Chem. Rev.* **2011**, *111*, 4475. (e) Umemoto, T. *Chem. Rev.* **1996**, *96*, 1757. (f) Ma, J.-A.; Cahard, D. *Chem. Rev.* **2008**, *108*, PR1. (g) Prakash, G. K. S.; Yudin, A. K. *Chem. Rev.* **1997**, *97*, 757. (h) Besset, T.; Schneider, C.; Cahard, D. *Angew. Chem., Int. Ed.* **2012**, *51*, 5048 and references therein.

(3) (a) Watson, D. A.; Su, M.; Teverovskiy, G.; Zhang, Y.; García-Fortanet, J.; Kinzel, T.; Buchwald, S. L. *Science* **2009**, *325*, 1661. (b) Maimone, T. J.; Milner, P. J.; Kinzel, T.; Zhang, Y.; Takase, M. K.; Buchwald, S. L. *J. Am. Chem. Soc.* **2011**, *133*, 18106.

(4) (a) Cho, E. J.; Senecal, T. D.; Kinzel, T.; Zhang, Y.; Watson, D. A.; Buchwald, S. L. *Science* **2010**, *328*, 1679. (b) Senecal, T. D.; Parsons, A. T.; Buchwald, S. L. *J. Org. Chem.* **2011**, *76*, 1174. (c) Cho, E. J.; Buchwald, S. L. *Org. Lett.* **2011**, *13*, 6552. (d) Parsons, A. T.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 9120. (e) Parsons, A. T.; Senecal, T. D.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2012**, *51*, 2947.

(5) (a) Xu, J.; Fu, Y.; Luo, D.-F.; Jiang, Y.-Y.; Xiao, B.; Liu, Z.-J.; Gong, T.-J.; Liu, L. *J. Am. Chem. Soc.* **2011**, *133*, 15300. (b) Wang, X.; Ye, Y.; Zhang, S.; Feng, J.; Xu, Y.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2011**, *133*, 16410. For related transformations, see: (c) Shimizu, R.; Egami, H.; Hamashima, Y.; Sodeoka, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 4577. (d) Chu, L.; Qing, F.-L. *Org. Lett.* **2012**, *14*, 2106. (e) Janson, P. G.; Ghoneim, I.; Ilchenko, N. O.; Szabó, K. J. *Org. Lett.* **2012**, *14*, 2882.

(6) For recent examples of transition-metal-catalyzed oxidative difunctionalization of unactivated alkenes involving tandem C−O/C−C bond formation, see: (a) Nicolai, S.; Erard, S.; González, D. F.; Waser, J. *Org. Lett.* **2010**, *12*, 384. (b) Pathak, T. P.; Gligorich, K. M.; Welm, B. E.; Sigman, M. S. *J. Am. Chem. Soc.* **2010**, *132*, 7870. (c) Matsuura, B. S.; Condie, A. G.; Buff, R. C.; Karahalis, G. J.; Stephenson, C. R. J. *Org. Lett.* **2011**, *13*, 6320. (d) Zhu, R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2012**, *51*, 1926. (e) Miller, Y.; Miao, L.; Hosseini, A. S.; Chemler, S. R. *J. Am. Chem. Soc.* **2012**, *134*, 12149.

(7) For halotrifluoromethylation and -perfluoroalkylation of olefins via atom transfer radical addition, see: (a) Kamigata, N.; Fukushima, T.; Yoshida, M. *J. Chem. Soc., Chem. Commun.* **1989**, 1559. (b) Kamigata, N.; Fukushima, T.; Terakawa, Y.; Yoshida, M.; Sawada, H. *J. Chem. Soc., Perkin Trans. 1* **1991**, 627. (c) Zou, X.; Wu, F.; Shen, Y.; Xu, S.; Huang, W. *Tetrahedron* **2003**, *59*, 2555. For trifluoromethylation of alkenes catalyzed by palladium, see: (d) Mu, X.; Wu, T.; Wang, H.; Guo, L.; Liu, G. *J. Am. Chem. Soc.* **2012**, *134*, 878. (e) Fuchikami, T.; Shibata, Y.; Urata, H. *Chem. Lett.* **1987**, 521.

(8) (a) Minisci, F. *Acc. Chem. Res.* **1975**, *8*, 165. (b) Clark, A. J. *Chem. Soc. Rev.* **2002**, *31*, 1. (c) Wendlandt, A. E.; Suess, A. M.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 11062.

(9) Eisenberger, P.; Gischig, S.; Togni, A. *Chem.—Eur. J.* **2006**, *12*, 2579.

(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. See: Nguyen, J. D.; Tucker, J. W.; Konieczynska, M. D.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2011**, *133*, 4160.

(13) However, neither of the TEMPO adducts derived from $CF_3{\cdot}$ or the proposed *α*-CF_3-alkyl radical (**I**) was observed in the inhibition experiment, preventing us from drawing further conclusions. See the Supporting Information for details. For recent examples of arene trifluoromethylation involving a trifluoromethyl radical, see: (a) Nagib,

D. A.; MacMillan, D. W. C. *Nature* **2011**, *480*, 224. (b) Ji, Y.; Brueckl, T.; Baxter, R. D.; Fujiwara, Y.; Seiple, I. B.; Su, S.; Blackmond, D. G.; Baran, P. S. *Proc. Natl. Acad. Sci. U.S.A.* **2011**, *108*, 14411. (c) Ye, Y.; Sanford, M. S. *J. Am. Chem. Soc.* **2012**, *134*, 9034.