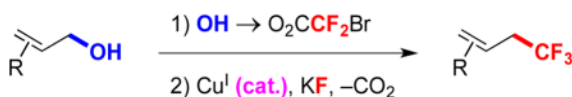# Copper-Catalyzed Decarboxylative Trifluoromethylation of Allylic Bromodifluoroacetates

Brett R. Ambler and **Ryan A. Altman**
Department of Medicinal Chemistry, University of Kansas, 1251 Wescoe Hall Drive, Lawrence, Kansas 66045, United States

Ryan A. Altman: raaltman@ku.edu

Abstract

The development of new synthetic fluorination reactions has important implications in medicinal, agricultural and materials chemistries. Given the prevalence and accessibility of alcohols, methods to convert alcohols to trifluoromethanes are desirable. However, this transformation typically requires four-step processes, specialty chemicals, and/or stoichiometric metals to access the trifluoromethyl-containing product. A two-step copper-catalyzed decarboxylative protocol for converting allylic alcohols to trifluoromethanes is reported. Preliminary mechanistic studies distinguish this reaction from previously reported Cu-mediated reactions.

New synthetic methods for the efficient incorporation of trifluoromethanes into organic molecules are important for the fields of agricultural chemistry,[1] medicinal chemistry,[2] chemical biology,[2a–b] and materials science.[3] As a result, many elegant and important preparations of trifluoromethanes have emerged in recent years.[4] However, many simple, useful, and important transformations have not been achieved.

The ability to convert alcohols into trifluoromethanes using a simple, mild and robust catalytic system represents a desirable transformation. Alcohols are found in materials, bioactive molecules, and many chemical libraries, are readily accessed by many synthetic methods, and provide a wide variety of substrates for synthetic transformations. However, alcohols rarely serve as precursors to trifluoromethanes. Most commonly, the conversion of alcohols into trifluoromethanes requires four-step sequences that: 1) involve undesirable manipulation of oxidation states; 2) require excess time and labor to conduct; 3) generate excess waste; 4) lead to diminished overall yields (eq 1).[5] Alternatively, alcohols can be converted to halides,[6] trifluoroacetates,[6b] halodifluoroacetates,[7] fluorosulfonyldifluoroacetates,[6f,7a] or xanthates,[8] which can be trifluoromethylated in the presence of stoichiometric quantities of transition metals (eq 2). However, for economic and environmental considerations, catalytic methods are desirable. To this end, a Cu-based catalyst recently converted allylic bromides or chlorides (one step from allylic alcohols) to trifluoromethanes using the Ruppert-Prakash reagent (eq 3).[9]

In contrast, we envisioned an attractive approach might involve the conversion of an alcohol to a halodifluoroacetic ester, followed by a catalytic decarboxylative trifluoromethylation (eq 4). Although trifluoromethylation reactions of halodifluoroacetic esters have been conducted using stoichiometric CuI,[6d–e,7,10] catalytic reactions have proven elusive over many years. Herein, we report a Cu-catalyzed conversion of allyl bromodifluoroacetic ester into trifluoromethanes, and preliminary mechanistic findings that distinguish this reaction from analogous Cu-mediated reactions.

Initial screening of catalysts and conditions revealed that the Cu-mediated reaction of cinnamyl bromodifluoroacetate (**1A**) could be adapted to provide a Cu-catalyzed procedure. Several Cu^I salts and ligands provided catalytic activity, and CuI and N,N'-dimethylethylenediamine (DMEDA) were selected as an inexpensive and efficient system that is already available in many synthetic chemistry laboratories and stockrooms worldwide.[11] The optimized catalyst included the use of 10 mol % CuI, 10 mol % DMEDA as a ligand, 25 mol % NaO_2CCF_2Br, KF (2 equiv), in DMF (1.0 M) at 50 °C. Importantly, a beneficial activation procedure was identified that involved the heating of the catalyst and reagents in DMF at 50 °C prior to addition of the substrate (*vide infra*).

Three parameters, including reaction concentration, ligand, and activation of the catalyst, proved most critical for obtaining a high yield of product (Table 1). Compared with the optimized reaction conditions (entry 1), reactions run at lower concentration (entry 2), or without employing the activation procedure (entry 3) provided less efficient catalyst systems as defined by the ratio of yield/conversion. Employing the activation procedure, the use of CuI/DMEDA seemed to provide a less-active catalyst than that derived from CuI alone at the 1.5 h time point (entries 1, 4); however, when the reactions were allowed to proceed to full conversion, a higher yield of product was reproducibly obtained using CuI/DMEDA (entries 5–6). Thus, DMEDA could serve to stabilize the active catalyst against decomposition near the end of the reaction.

A variety of 2-, 3- and 4-substituted cinnamyl bromodifluoroacetates (**2A**) were compatible with the present reaction (Table 4). Electron-deficient (entries 1–5) and electron-neutral cinnamyl systems (entries 7–8) reacted in good yields, although an electron rich substrate provided the product in slightly lower yield (entry 9). In general, substrates capable of affording resonance stabilized allyl cations (e.g., 4-NMe$_2$) were unstable to both acidic and basic conditions, which limited purification and storage of this class of substrates. Aryl (pseudo)halides were well tolerated, and did not undergo aromatic trifluoromethylation (entries 1–3, 6). In addition, compounds bearing heterocycles were tolerated (entries 9–10). Finally, on an 8 mmol scale, over 1.9 g of material was obtained in high yield (entry 2), which suggests that the present reaction could be amenable to larger scale processes.

Disubstituted and non-conjugated allylic esters (**3A**) containing a diverse array of functional groups provided moderate to good yields of *E* alkene products (**3B**, Table 3). Substituents at the α and β positions of the styrene were tolerated (entries 1–3), and non-conjugated allylic systems displayed good reactivity (entries 4–7). Several aliphatic functional groups were compatible with the reaction, including esters, imides, and benzyl ethers (entries 5–7). In entries 5–6, diastereomeric mixtures of substrates (**3A**, $E/Z = 4:1$) provided thermodynamically-stable *E*-allyl trifluoromethane products **3B** in excellent selectivities ($E/Z > 19:1$). Further, the reaction of a pure *Z*-alkene substrate afforded the *E* product in excellent diastereoselectivity (entry 7). When monitoring the reaction by both GC/FID and ^{19}F NMR, slow isomerization of the substrate was observed, while the *E*-product was formed in greater than 15:1 dr throughout the course of the reaction. In control reactions, the *Z*-substrate was stable when treated with KF in DMF at 50 °C. These data could implicate the existence of a π-allyl intermediate that reacts to generate the more stable *E*-product.[6b,9]

However at present, other explanations for this isomerization phenomenon cannot be excluded.

Using the Cu/DMEDA-based catalyst system, bromodifluoroacetic esters provided unique reactivity (Table 4). A trend of increasing reactivity was observed for cinnamyl trifluoroacetate < chlorodifluoroacetate < bromodifluoroacetate (entries 1–3);[12] however, the reaction of cinnamyl difluoroiodoacetate provided a low yield of product (entry 4). It was hypothesized that I⁻, generated as a byproduct of the reaction, inhibited catalysis. In support of this theory, the addition of exogenous KI to the reaction of cinnamyl bromodifluoroacetate decreased the yield of product (entry 5). Combined, these two findings suggest that I⁻ does not participate in the catalytic reaction. In fact, the Cu-catalyzed reaction could be conducted in the complete absence of I⁻ (entry 6), a key feature that distinguishes the present Cu-catalyzed reaction from previously reported Cu-mediated reactions.[7]

Although thorough mechanistic studies have not been conducted, the present Cu-catalyzed reaction likely involves a mechanism distinct from CuI-mediated reactions of allyl halodifluoroacetates. For the Cu-catalyzed reaction, the activation procedure presumably serves to convert the precatalytic combination of $CuI/DMEDA/NaO_2CCF_2Br/KF$ into the active catalyst, $L_nCu–CF_3$ (Scheme 2A). $L_nCu–CF_3$ can then promote direct trifluoromethylation of the substrate without participation of I⁻. The substitution reaction potentially involves a π-allyl intermediate, which has been proposed in other allylic substitution reactions using $L_nCu–CF_3$ in both stoichiometric[6b] and catalytic[9] systems. In contrast, the Cu-mediated reaction invokes I⁻ as a key feature of the mechanism (Scheme 2B).[7a] In this case, I⁻ participated by converting the bromodifluoroacetic ester to an allyl iodide, which then reacted with Cu–CF₃. Studies to thoroughly explore the mechanism of the present transformation, including the activation procedure, are ongoing, and results will be presented in due time. Further, ongoing work aims to expand the scope of this process to alternate classes of substrates are currently underway.

In conclusion, a catalytic method for the conversion of allylic alcohols to trifluoromethanes via bromodifluoroacetic esters has been developed. Conjugated and non-conjugated substrates bearing a variety of functional groups afford α-substituted trifluoromethylated products in moderate to good yield and excellent diastereoselectivity for the *E*-stereoisomer. Beneficial aspects of this transformation include: 1) employment of a mild, inexpensive and atom-economical source of CF_3 in near-stoichiometric quantity; 2) development of a shortened strategy for converting readily available allylic alcohols into trifluoromethyl analogs; 3) the ability to conduct trifluoromethylation reactions using only a catalytic quantity of metal. Finally, functionalization of the allyl trifluoromethane-based product should be useful for accessing more complex fluorinated compounds.[7b,13]

Supplementary Material

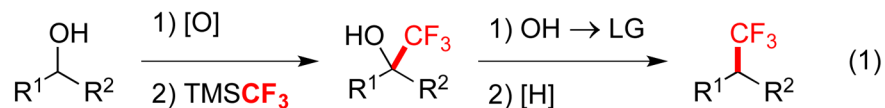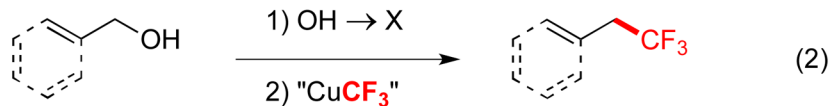Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

References

1. Theodoridis, G. Fluorine-Containing Agrochemicals: An Overview of Recent Developments. In: Tressaud, A., editor. Fluorine and the Environment: Agrochemicals, Archaeology, Green Chemistry & Water. Elsevier B. V; Amsterdam: 2006.

2. (a) Bégué, J-P.; Bonnet-Delpon, D. Bioorganic and Medicinal Chemistry of Fluorine. John Wiley & Sons; Hoboken: 2008. (b) Ojima, I., editor. Fluorine in Medicinal Chemistry and Chemical Biology. Blackwell Publishing Ltd; West Sussex: 2009.

3. (a) Patil Y, Ameduri B. Prog Polym Sci. 2013; 38:703.(b) Dhara MG, Banerjee S. Prog Polym Sci. 2010; 35:1022.

4. For some recent reviews, see: Liang T, Neumann CN, Ritter T. Angew Chem, Int Ed. 2013; 52:8214.Liu G. Org Biomol Chem. 2012; 10:6243. [PubMed: 22733139] Hollingworth C, Gouverneur V. Chem Commun. 2012; 48:2929.Tomashenko OA, Grushin VV. 2011; 111:4475.

5. (a) Fustero S, Román R, Sanz-Cervera JF, Simón-Fuentes A, Bueno J, Villanova S. J Org Chem. 2008; 73:8545. [PubMed: 18855479] (b) Del Valle JR, Goodman M. Angew Chem, Int Ed. 2002; 41:1600.(c) Jeannot F, Gosselin G, Mathe C. Org Biomol Chem. 2003; 1:2096. [PubMed: 12945900] (d) Qiu XL, Qing FL. J Org Chem. 2002; 67:7162. [PubMed: 12354018] (e) Serafinowski PJ, Brown CA. Tetrahedron. 2000; 56:333.(f) Chang, J.; Liu, K.; McEachem, EJ.; Mu, C.; Selenick, HG.; Shi, F.; Vocaldo, DJ.; Wang, Y.; Wei, Z.; Zhou, Y.; Zhu, Y. WO 2012062157 A1. May 18. 2012 (g) Tam, TF.; Leung-Toung, R.; Wang, Y.; Zhao, Y. WO 2008116301 A1. Oct 2. 2008

6. (a) Kobayashi Y, Yamamoto K, Kumadaki I. Tetrahedron Lett. 1979; 20:4071.(b) Larsson JM, Pathipati SR, Szabó KJ. J Org Chem. 2013; 78:7330. [PubMed: 23786623] (c) Bouillon J-P, Maliverney C, Merenyi R, Viehe HG. J Chem Soc, Perkin Trans. 1991; 1:2147.(d) Su DB, Duan JX, Chen QY. Tetrahedron Lett. 1991; 32:7689.(e) Duan JX, Su DB, Chen QY. J Fluorine Chem. 1993; 61:279.(f) Chen QY. J Fluorine Chem. 1995; 72:241.

7. (a) Duan J-X, Chen Q-Y. J Chem Soc, Perkin Trans. 1994; 1:725.(b) Tan L, Chen C-y, Larsen RD, Verhoeven TR, Reider PJ. Tetrahedron Lett. 1998; 39:3961.

8. Zhu L, Liu S, Douglas JT, Altman RA. Chem Eur J. 2013; 19:12800. [PubMed: 23922222]

9. Miyake Y, Ota S-i, Nishibayashi Y. Chem—Eur J. 2012; 18:13255. [PubMed: 22965685]

10. (a) MacNeil JG Jr, Burton DJ. J Fluorine Chem. 1991; 55:225.(b) Duan JX, Su DB, Wu JP, Chen QY. J Fluorine Chem. 1994; 66:167.(c) Langlois BR, Roques N. J Fluorine Chem. 2007; 128:1318.(d) McReynolds KA, Lewis RS, Ackerman LKG, Dubinina GG, Brennessel WW, Vicic DA. J Fluorine Chem. 2010; 131:1108.(e) Li Y, Chen T, Wang H, Zhang R, Jin K, Wang X, Duan C. Synlett. 2011; 12:1713.(f) Schareina T, Wu XF, Zapf A, Cotté A, Gotta M, Beller M. Top Catal. 2012; 55:426.

11. Surry DS, Buchwald SL. Chem Sci. 2010; 1:13–31. [PubMed: 22384310]

12. At higher temperatures, the chlorodifluoroacetic ester provided mild activity, while the trifluoroacetic ester provided no reactivity.

13. (a) Shimizu R, Egami H, Hamashima Y, Sodeoka M. Angew Chem, Int Ed. 2012; 51:4577.(b) Wang CJ, Sun X, Zhang X. Angew Chem, Int Ed. 2005; 44:4933.
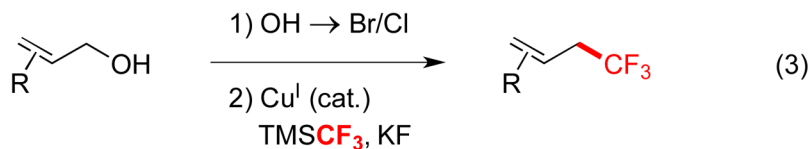
• *Multi-step Sequences (ref 5)*

$$\text{R}^1\text{CH(OH)R}^2 \xrightarrow[\text{2) TMSCF}_3]{\text{1) [O]}} \text{R}^1\text{C(OH)(CF}_3\text{)R}^2 \xrightarrow[\text{2) [H]}]{\text{1) OH} \rightarrow \text{LG}} \text{R}^1\text{CH(CF}_3\text{)R}^2 \quad (1)$$

• *Stoichiometric Metals (ref 6–8)*

$$\text{ArCH}_2\text{OH} \xrightarrow[\text{2) "CuCF}_3\text{"}]{\text{1) OH} \rightarrow \text{X}} \text{ArCH}_2\text{CF}_3 \quad (2)$$

$$X = \text{Cl, Br, I, O}_2\text{CF}_3\text{, O}_2\text{CCF}_2\text{Br, OC(S)SMe}$$

•*Catalyzed Trifluoromethylation of Halides (ref 9)*

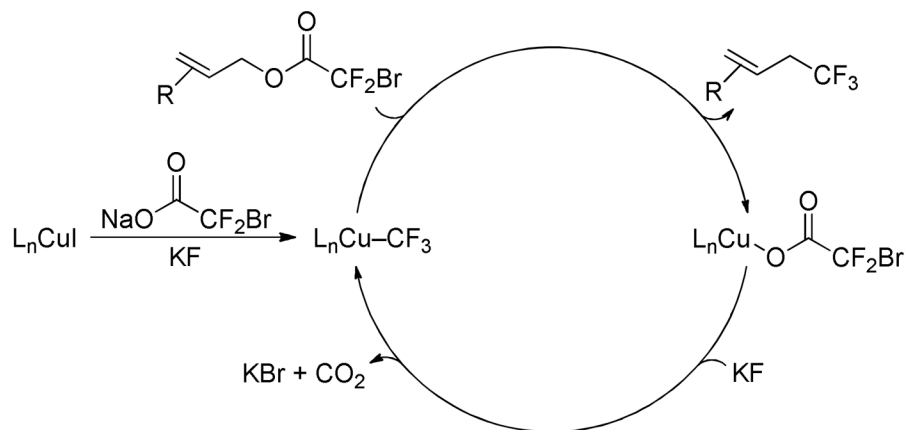$$\xrightarrow[\substack{\text{2) Cu}^{\text{I}}\text{ (cat.)}\\ \text{TMSCF}_3\text{, KF}}]{\text{1) OH} \rightarrow \text{Br/Cl}} \quad (3)$$

• *This Work: Catalyzed Reaction of Halodifluoroacetates*

$$\xrightarrow[\text{2) Cu}^{\text{I}}\text{ (cat.), K}\textbf{F}\text{, } -\text{CO}_2]{\text{1) OH} \rightarrow \text{O}_2\text{CCF}_2\text{Br}} \quad (4)$$
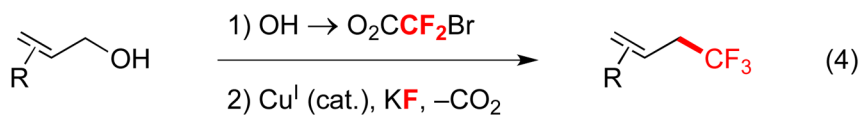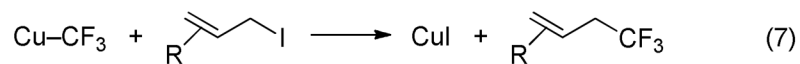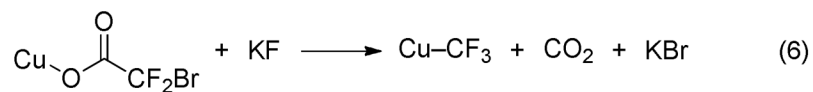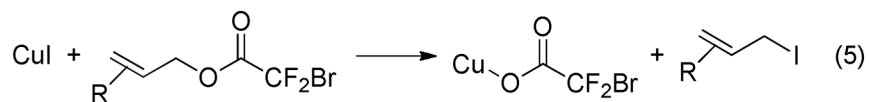
Scheme 1.
An Economical Approach for the Conversion of Allylic Alcohols to Trifluoromethanes
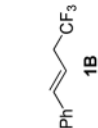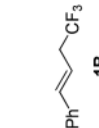
A) Proposed Iodide-free Cu-Catalyzed Reaction

B) Previous Cu-Mediated Reaction Requires Iodide

$$Cu I + \text{(allyl CF}_2\text{Br ester)} \longrightarrow Cu\text{-O-C(O)CF}_2Br + R\text{-allyl-I} \qquad (5)$$

$$Cu\text{-O-C(O)CF}_2Br + KF \longrightarrow Cu\text{-}CF_3 + CO_2 + KBr \qquad (6)$$

$$Cu\text{-}CF_3 + R\text{-allyl-I} \longrightarrow Cu I + R\text{-}CF_3 \qquad (7)$$

Scheme 2.
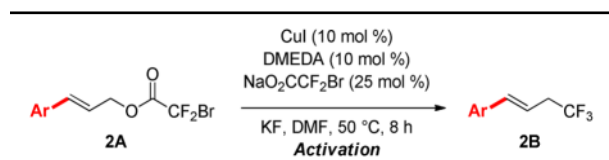Proposed Catalytic Cycle Involving a Reactive Cu–CF$_3$ Species.

Table 1

Sensitivity of Cu-Catalyzed Trifluoromethylation to Concentration, Ligand, and Activation of Catalyst.[a]

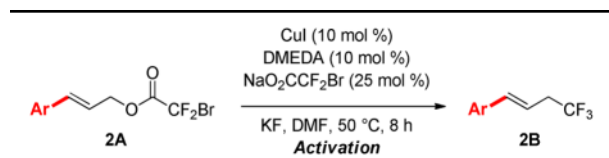| entry	activation	[1A] (M)	DMEDA (mol %)	yield[b] (%)	conv[b] (%)	yield/conv
1		1.0	10	52	64	0.82
2		0.33	10	63	85	0.74
3	–	1.0	10	26	54	0.49
4		1.0	0	66	79	0.83
5[c]		1.0	10	83	100	0.83
6[c]		1.0	0	72	100	0.72
7	–	1.0	0	50	66	0.76
8	–	0.33	0	52	78	0.67

[a]Reactions were performed with 0.20 mmol substrate, 0.050 mmol NaO2CCF2Br, 0.40 mmol KF in 0.20 mL DMF at 50 °C for 1.5 h.

[b]Conversion and yield data were determined by GC/FID analysis using dodecane as an internal standard. Each data point represents an average of 2–4 experiments.

[c]The reactions were run for 8 h instead of 1.5 h.

Table 2

Substituted Cinnamyl Bromodifluoroacetates Undergo Decarboxylative Trifluoromethylation.[a]

entry	Ar	Yield (%)[b]
1	Br-substituted aryl	81 (82)
2[c]		89 (87)
3	Cl-substituted aryl	72 (76)
4	F3C-substituted aryl	71 (75)
5	O2N-substituted aryl	83 (80)
6	OTf-substituted aryl	75 (75)
7	F-substituted aryl	65 (79)
8	Me-substituted aryl	71 (79)
9	MeO-substituted aryl	57 (60)
10	thiophene-substituted aryl	80 (78)

entry	Ar	Yield (%)[b]
11		58 (57)

[a] Reactions were performed with 0.20 mmol substrate, 0.020 mmol CuI, 0.020 mmol DMEDA, 0.050 mmol NaO_2CCF_2Br, 0.40 mmol KF in 0.20 mL DMF at 50 °C for 8 h following 10 min activation.

[b] Isolated yield, number in parentheses indicates ^{19}F NMR yield using α,α,α-trifluorotoluene as an internal standard.

[c] Reaction conducted on an 8 mmol scale.

Table 3

Disubstituted and Non-Conjugated Allylic Bromodifluoroacetates Undergo Decarboxylative Trifluoromethylation.[a]

entry	E/Z of 3A[b]	product	E/Z of 3B[c]	yield (%)[d]
1	>98:2		>98:2	55 (60)
2	>98:2		>98:2	74 (80)
3	–		–	56 (51)
4	>98:2		>98:2	78 (75)
5[e]	78:22		97:3	76 (75)
6[e]	79:21		98:2	85 (82)
7	<2:98		96:4	81 (79)

[a]Reactions were performed with 0.20 mmol substrate, 0.020 mmol CuI, 0.020 mmol DMEDA, 0.050 mmol NaO_2CCF_2Br, 0.40 mmol KF in 0.20 mL DMF at 50 °C for 8 h following 10 min activation.

[b]Determined by ^{1}H NMR.

[c]Determined by ^{19}F NMR.

[d]Isolated yield, number in parentheses indicates ^{19}F NMR yield using α,α,α-trifluorotoluene as an internal standard.

[e]18 h.

Table 4

Unique Reactivity of Allyl Bromodifluoroacetes.[a]

entry	X	Y	other	conv (%)[b]	yield (%)[b]	yield/conv
1	F	I	-	26	0	0
2	Cl	I	-	31	1	0.03
3	Br	I	-	52	46	0.88
4	I	I	-	53	25	0.47
5	Br	I	+100% KI	68	38	0.56
6	Br	(MeCN)₄PF₆	8 h	>99	79	0.79

[a]Reactions were performed with 0.20 mmol substrate, 0.050 mmol NaO2CCF2Br, 0.40 mmol KF in 0.20 mL DMF at 50 °C for 1.5 h.

[b]Conversion and yield data were determined by GC/FID analysis using dodecane as an internal standard.