Communication

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Silver-Catalyzed Decarboxylative Trifluoromethylation of Aliphatic Carboxylic Acids

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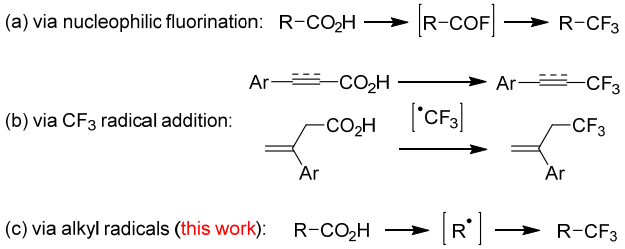
Supporting Information Placeholder

ABSTRACT: The silver-catalyzed decarboxylative trifluoromethylation of aliphatic carboxylic acids is described. With $AgNO_3$ as the catalyst and $K_2S_2O_8$ as the oxidant, the reactions of aliphatic carboxylic acids with (bpy)Cu(CF_3)$_3$ (bpy = 2,2'-bipyridine) and $ZnMe_2$ in aqueous acetonitrile at 40 °C afford the corresponding decarboxylative trifluoromethylation products in good yield. The protocol is applicable to various primary and secondary alkyl carboxylic acids and exhibits wide functional group compatibility. Mechanistic studies reveal the intermediacy of $^-$Cu(CF_3)$_3$Me, which undergoes reductive elimination and subsequent oxidation to give Cu(CF_3)$_2$ as the active species responsible for the trifluoromethylation of alkyl radicals.

Trifluoromethyl group is a privileged structural motif in pharmaceuticals and agrochemicals owing to its profound effect on properties such as lipophilicity, permeability and metabolic stability. Thus, the introduction of trifluoromethyl groups into organic molecules, in particular C-trifluoromethylation, is an important strategy in preparative organic chemistry.[1–3] A number of methods have been developed for C(sp^3)–CF_3 bond formation, including the trifluoromethylation of carbon-centered nucleophiles,[2] electrophiles[4] and radicals,[5] and the addition of CF_3 radicals to unsaturated moieties.[3] Furthermore, Toste and coworkers introduced the formal C(sp^3)–CF_3 reductive elimination from Au(III) complexes via "fluoride-rebound" mechanism, allowing the synthesis of ^{18}F-radiolabeled aliphatic CF_3-containing compounds.[6] Despite the significant progress in the field, site-specific C(sp^3)-trifluoromethylation of complex molecules, especially in late stages, is still challenging.

Carboxylic acids are ideal raw materials for chemical synthesis due to their ready availability, high stability and low cost. The conversion of CO_2H to CF_3 is therefore a subject of great interest (Scheme 1). Nucleophilic fluorination of carboxylic acids[7] with fluorinating agents such as SF_4,[7a] $PhSF_3$,[7f] Deoxofluor,[7b–7d] or BrF_3[7e] provides the corresponding trifluoromethylated products via the intermediacy of acyl fluorides (Scheme 1a). However, these methods suffer from harsh reaction conditions and limited substrate scope. The decarboxylative trifluoromethylation of propiolic acids and α,β- or β,γ-unsaturated acids was also reported (Scheme 1b).[8] This transformation likely involves the addition of trifluoromethyl radicals to C=C or C≡C bonds followed by decarboxylation. However, the decarboxylative trifluoromethylation of aliphatic carboxylic acids remains a challenging task (Scheme 1c). This unique decarboxylative alkyl–CF_3 cross coupling[9–11] should be of much broader application in the synthesis of trifluoromethylated compounds. Herein we report the silver-catalyzed decarboxylative trifluoromethylation of aliphatic carboxylic acids.

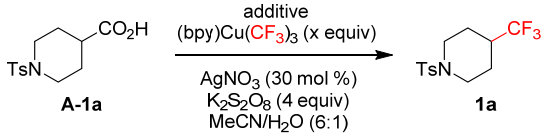
Scheme 1. Conversion of Alkyl–CO_2H to Alkyl–CF_3



The generation of alkyl radicals via silver-catalyzed decarboxylation of carboxylic acids is well documented.[12, 13] We recently reported the trifluoromethylation of alkyl halides with (bpy)Cu(CF_3)$_3$ (bpy = 2,2'-bipyridine) and excess Et_3SiH via the proposed CF_3 group transfer from Cu(II)–CF_3 complexes to alkyl radicals.[5] However, this reductive trifluoromethylation method is not compatible with the oxidative decarboxylation of aliphatic carboxylic acids due to the mismatch of reaction conditions. The combination of a copper source (*e.g.*, Cu(OTf)$_2$) and a CF_3 reagent was also screened for $AgNO_3$/$K_2S_2O_8$-mediated decarboxylative trifluoromethylation of model substrate *N*-tosylpiperidine-1-carboxylic acid (**A-1a**). Unfortunately, no expected trifluoromethylation product **1a** could be detected (see Table S1 in the Supporting Information). We envisioned that (bpy)Cu(CF_3)$_3$[14] should be activated before subjected to oxidative decarboxylation conditions (Table 1). Thus, (bpy)Cu(CF_3)$_3$ was treated with an activating agent in acetonitrile at room temperature for 30 minutes, followed by the addition of **A-1a**, $AgNO_3$, $K_2S_2O_8$ and water. A number of additives were screened as the activating agent. The product **1a** was not formed when $NaBH_4$, $PhSiH_3$ or Et_3SiH was used as the additive (entries 2–4, Table 1). Pleasingly, **1a** was obtained in 54% yield when $ZnMe_2$ was used as the additive (entry 5, Table 1). $ZnEt_2$ showed an effect similar to $ZnMe_2$ (entry 6, Table 1). In contrast, **1a** was observed in a

very low yield when MeMgCl was used in place of $ZnMe_2$ (entry 7, Table 1). After further adjustment of the reagent ratios and reaction temperature (entries 8–11, Table 1), the use of $(bpy)Cu(CF_3)_3$ (4 equiv)/$ZnMe_2$ (3 equiv) as the CF_3 source and $AgNO_3$ (30 mol %)/$K_2S_2O_8$ (4 equiv) as the decarboxylation system at 40 °C gave **1a** in 93% yield (entry 11, Table 1). Finally, control experiments indicated that both $AgNO_3$ and $K_2S_2O_8$ were required for the trifluoromethylation (entries 12 and 13, Table 1).

Table 1. Optimization of Reaction Conditions

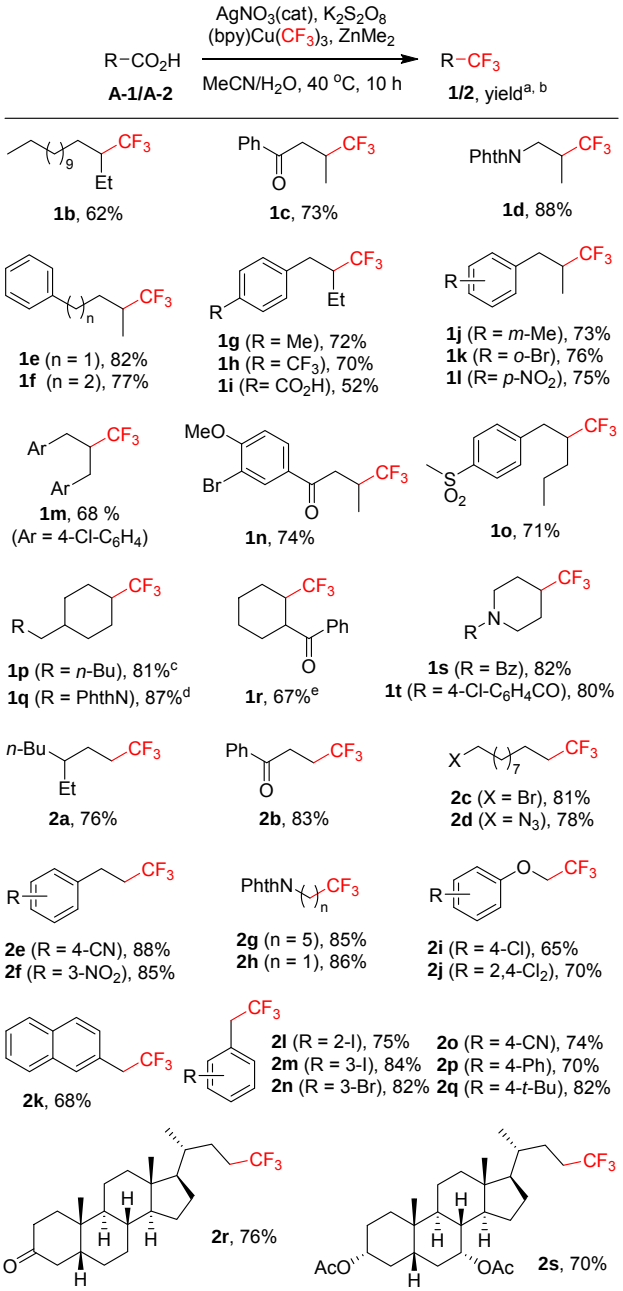


entry[a]	x	additive (equiv)	temp/time	yield (%)[b]
1	2	none	rt, 24 h	0
2	2	Et_3SiH (2)	rt, 24 h	0
3	2	Ph_3SiH (2)	rt, 24 h	0
4	2	$NaBH_4$ (2)	rt, 24 h	0
5	2	$ZnMe_2$ (2)	rt, 24 h	54
6	2	$ZnEt_2$ (2)	rt, 24 h	49
7	2	MeMgCl (2)	rt, 24 h	7
8	3	$ZnMe_2$ (2)	rt, 24 h	72
9	3	$ZnMe_2$ (3)	rt, 24 h	71
10	4	$ZnMe_2$ (3)	rt, 24 h	86
11	**4**	**$ZnMe_2$ (3)**	**40 °C, 10 h**	**93 (88)**
12[c]	4	$ZnMe_2$ (3)	40 °C, 10 h	0
13[d]	4	$ZnMe_2$ (3)	40 °C, 10 h	0

[a] Reaction conditions: $(bpy)Cu(CF_3)_3$, additive, MeCN (12 mL), rt, 30 min; then **A-1a** (0.2 mmol), $AgNO_3$ (0.06 mmol), $K_2S_2O_8$ (0.8 mmol), H_2O (2 mL), rt (or 40 °C), 24 h (or 10 h). [b] ^{19}F NMR yield (with 4-bromo-1-fluorobenzene as the internal standard) based on **A-1a**, isolated yield in parentheses. [c] Without $AgNO_3$. [d] Without $K_2S_2O_8$.

With the optimized conditions in hand (entry 11, Table 1), we aimed to define the scope of the method. As shown in Scheme 2, a wide range of differentially substituted secondary alkyl carboxylic acids **A-1** were readily converted to the corresponding trifluoromethylated products **1b–1t** in good to excellent yield. Notably, both *cis*- and *trans*-2-benzoylcyclohexane-1-carboxylic acid gave rise to the same product **1r**. Primary alkyl carboxylic acids (**A-2**) are also good coupling partners in the decarboxylative trifluoromethylation and the expected products **2a–2g** were obtained in satisfactory yield. The protocol is also applicable to α-amino acids, α-oxy acids and benzylic acids, as exemplified by the efficient synthesis of **2h–2q**. Of particular note, sensitive functional groups such as alkyl bromide (**2c**), alkyl azide (**2d**) and aryl iodides (**2l** and **2m**) were well tolerated. Furthermore, the synthesis of trifluoromethylated steroids **2r** and **2s** demonstrates the suitability of this method for the late-stage modification of complex molecules. Aromatic acids were inert under the above reaction conditions, thus allowing the design of chemoselective decarboxylation. For example, trifluoromethylated benzoic acid **1i** was prepared from the corresponding diacid **A-1i**. In contrast, tertiary alkyl carboxylic acids underwent decomposition and did not give the products of trifluoromethylation presumably because of steric effects.[5]

Scheme 2. Decarboxylative Trifluoromethylation of Carboxylic Acids

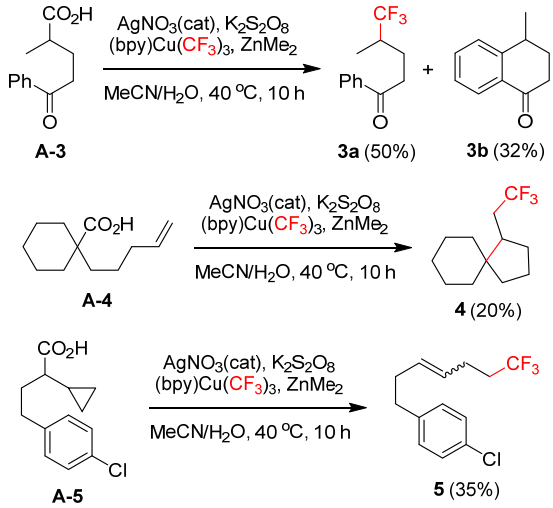


[a] Reaction conditions: **A-1** or **A-2** (0.2 mmol), $(bpy)Cu(CF_3)_3$ (0.8 mmol), $ZnMe_2$ (0.6 mmol), $AgNO_3$ (0.06 mmol), $K_2S_2O_8$ (0.8 mmol), MeCN (12 mL), H_2O (2 mL), 40 °C, 10 h. [b] Isolated yield based on **A-1** or **A-2**. [c] *Cis* : *trans* = 36:64. [d] *Cis* : *trans* = 45:55. [e] *Cis* : *trans* = 10:90.

To gain further insight into the decarboxylative trifluoromethylation, radical clock experiments[15] were carried out (Scheme 3). The reaction of **A-3** under the optimized conditions afforded the trifluoromethylation product **3a** (50%) and the cyclization product **3b** (32%). Hepta-6-enoic acid **A-4** underwent a decarboxylation–cyclization–trifluoromethylation sequence, yielding product **4**. When cyclopropylacetic acid **A-5** was subject-

ed to the optimized conditions for the decarboxylative trifluoromethylation of carboxylic acids, the ring-opening product **5** was isolated in 35% yield. These results suggest the intermediacy of alkyl radicals.

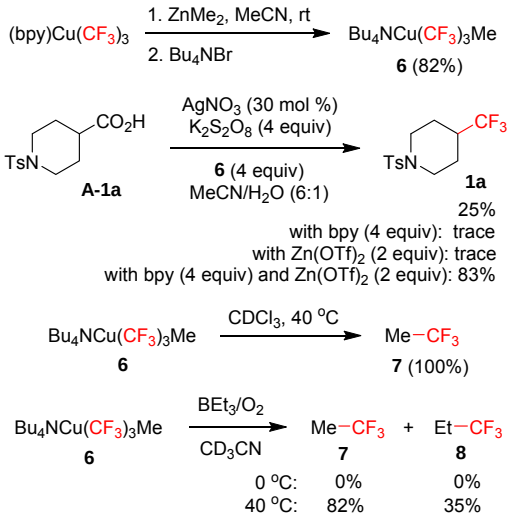
Scheme 3. Radical Clock Experiments



To gain further insight into the role of $ZnMe_2$ in the decarboxylative trifluoromethylation, the following mechanistic experiments were carried out (Scheme 4). Upon addition of $ZnMe_2$ (0.5 equiv) into the MeCN solution of $(bpy)Cu(CF_3)_3$ at room temperature, the yellow solution turned to colorless. ^{19}F NMR indicated that two new peaks arose at δ -30.1 and -32.0 ppm in a 2:1 integral ratio. To identify the new intermediate, an equimolar amount of Bu_4NBr was added into the solution. A white precipitate ($ZnBr_2$) was immediately formed. After the usual workup, complex $Bu_4NCu(CF_3)_3Me$ (**6**) was obtained in 82% yield, whose structure was unambiguously established by X-ray diffraction experiments (Figure 1). When **6** was used in place of $(bpy)Cu(CF_3)_3/ZnMe_2$ in the $AgNO_3$-catalyzed decarboxylative trifluoromethylation of acid **A-1a**, the product **1a** was obtained in 25% yield. In contrast, only a trace amount of **1a** could be detected when the reaction was carried out in the presence of bpy (4 equiv) or $Zn(OTf)_2$ (2 equiv). However, **1a** was achieved in 83% yield when both bpy and $Zn(OTf)_2$ were present. The roles of bpy and $Zn(OTf)_2$ in the trifluoromethylation remain unclear. Complex **6** is air and water tolerant, and stable for weeks in refrigerator. However, it gradually decomposes at room temperature. When the $CDCl_3$ solution of **6** was heated up at 40 °C for 10 h, 1,1,1-trifluoroethane (**7**) was formed quantitatively (by ^{19}F NMR).[16] Complex **6** was then directly treated with ethyl radicals formed from Et_3B under an O_2 atmosphere. Neither **7** nor 1,1,1-trifluoropropane (**8**) could be detected when the reaction was conducted at 0 °C. In contrast, both **7** (82%) and **8** (35%) were observed when the reaction was performed at 40 °C. These experiments suggest that the active species responsible for the trifluoromethylation is probably generated after the reductive elimination of **6**.

A tentative mechanism for the decarboxylative trifluoromethylation is shown in Figure 2. Interaction of $(bpy)Cu(CF_3)_3$ with $ZnMe_2$ generates the $^-Cu(CF_3)_3Me$ anion that undergoes reductive elimination to produce $MeCF_3$ and the $^-Cu(CF_3)_2$ anion. The latter is then oxidized to $Cu(CF_3)_2$. The Ag(II)-mediated oxidative decarboxylation of aliphatic carboxylic acids gives the corresponding alkyl radicals. Subsequent CF_3 group transfer from $Cu(CF_3)_2$ to alkyl radicals provides the final product.

Scheme 4. Mechanistic Experiments



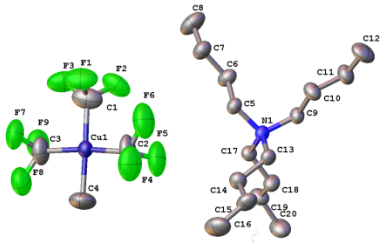


Figure 1. ORTEP drawing of $Bu_4NCu(CF_3)_3Me$ (**6**) with all H atoms omitted for clarity and ellipsoids set at 30% probability. Selected bond distances (Å): Cu–C1 1.936(10), Cu–C2 1.830(10), Cu–C3 1.873(9), Cu–C4 1.964(11).

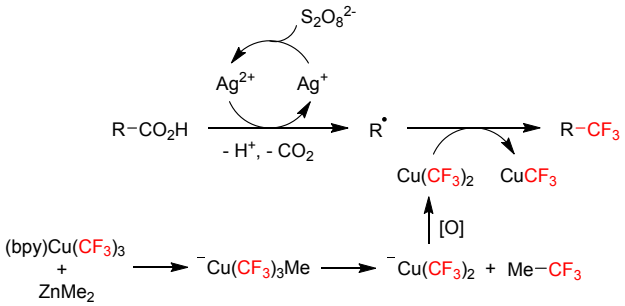


Figure 2. Proposed mechanism.

Organocopper(III) complexes are recognized as important intermediates in Cu(I)-mediated reactions.[17] Of the few organocopper(III) complexes characterized by X-ray diffraction experiments,[14, 17, 18] complex **6** is the only one having a Me–Cu(III) bond. In the solid state, the $^-Cu(CF_3)_3Me$ anion displays a square planar geometry. The Me–Cu bond is slightly longer than any of the CF_3–Cu bonds in **6** (see Figure 1 caption). The CF_3–Cu bond lengths are shorter in **6** than in the $^-Cu(CF_3)_4$ anion (1.944(3)–

1.964(2) Å).[14] Further investigations on the reactivity of complex **6** are currently underway.

In conclusion, we have developed a practical protocol for the decarboxylative trifluoromethylation of aliphatic carboxylic acids in aqueous solution. This method is easily operational, mild and efficient. In view of its generality and excellent functional group compatibility, this transformation should find application in organic synthesis.

ASSOCIATED CONTENT

Supporting Information

Full experimental details, characterizations of new compounds, copies of ^{1}H, ^{13}C and ^{19}F NMR spectra (PDF), and X-ray crystal structure of **6** (CIF). The material is available free of charge on the ACS Publications website.

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Notes

The authors declare no competing financial interests.

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SYNOPSIS TOC.