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Copper-Catalyzed Decarboxylative Atom Transfer Radical Addition of Iododifluoroacetate to Alkynyl Carboxylic Acids

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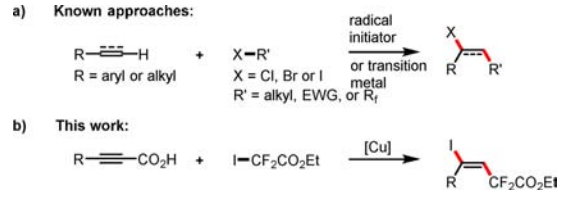
Supporting Information

ABSTRACT: The first example of copper-catalyzed decarboxylative atom transfer radical addition of alkynyl carboxylic acids has been developed with a readily available fluoroalkyl halide. This novel protocol has demonstrated a unique difunctionalization of nonterminal alkynes with a broad substrate scope and excellent functional-group tolerance. Mechanistic investigations revealed that the catalytic cycle was initiated by the attack of a difluoroalkyl radical to an in situ generated alkynylcopper species.

Fluorine-containing structural motifs play important roles in biologically active compounds, especially pharmaceuticals and agrochemicals, due to the drastic enhancement of lipophilicity, metabolic stability, and bioavailability relative to the parent molecules via the incorporation of fluorine atoms or fluorine-containing groups.[1] As a result, the selective introduction of fluorine or fluorinated groups onto the particular position in small organic molecules has been developed as a powerful strategy in drug design.[2] Accordingly, the development of efficient fluoroalkylation methods, especially mediated or catalyzed by transition-metal catalysts, has attracted extensive research attention in recent decades.[3]

Starting from the pioneering work by Kharasch and coworkers,[4] atom transfer radical addition (ATRA) has been developed as a reliable method to introduce two functional groups onto unsaturated C−C bonds in one step.[5] Typically initiated by radical initiators[6] or by transition-metal catalysis,[7] ATRA represents a practical synthetic path to difunctionalization of alkenes or alkynes with activated halides in a highly atom-economic way and provides the corresponding alkyl or vinyl halides as important intermediates for further transformation (Scheme 1a). However, the unsaturated acceptors have been strictly limited to terminal alkenes and alkynes and, thus, are still hampered by the instability and low availability of the corresponding unsaturated substrates. In our continuous efforts to develop transition-metal-catalyzed fluoroalkylation methods,[8] we envisioned that alkynyl carboxylic acids, readily available coupling partners in metal-catalyzed decarboxylative coupling reactions,[9] could be feasible precursors to terminal unsaturated compounds (Scheme 1b). Herein, we report the first example of copper-catalyzed decarboxylative atom transfer radical addition of alkynyl carboxylic acids, initiated by fluoroalkyl radicals generated by copper catalysts, affording fluoroalkylated alkenyl iodides in a highly efficient way.[10]

Scheme 1. Atom Transfer Radical Addition with Fluoroalkyl Halides



Our study commenced with 3-phenylpropiolic acid (**1a**) used as the model substrate and ethyl iododifluoroacetate (**2**) as the fluoroalkyl coupling partner in the presence of a catalytic amount of CuCl (10 mol %) in 1,4-dioxane at 100 °C. The desired product **3a** was obtained successfully in a good yield (84%) using 1,10-phenanthroline (20 mol %) as the ligand (entry 1, Table 1). Reducing the amount of 1,10-phenanthroline to 10 mol % gave a slightly lower yield (entry 2). Next, a variety of copper species, including cuprous salts (CuBr, CuI, Cu_2O) and cupric salts [$Cu(acac)_2$, $Cu(OAc)_2$, $Cu(OTf)_2$] were examined carefully, which indicated both Cu(I) and Cu(II) worked well in this catalytic system (entries 1−9), and Cu_2O gave the best yield (90%) (entry 5). Accordingly, increasing the amount of Cu_2O to 10 mol % resulted in a slightly higher yield (entry 11). Furthermore, a general survey of ligands was also performed, which showed bidentate nitrogen ligands were the optimal choice, and 1,10-phenanthroline was still the best ligand (entries 13−17). To improve the yield further, we assessed the effect of reaction temperature and solvents on the conversion and found that no higher yield could be obtained by decreasing or increasing the temperature or changing the solvent (entries 18−23). Finally, several control experiments were performed, which showed only a 25% yield of the desired product **3a** was afforded when ligands were excluded (entry 24), and no **3a** was obtained without a copper catalyst (entry 26).

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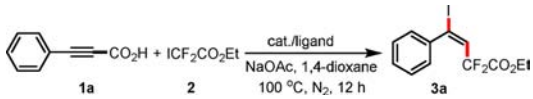
Table 1. Optimization of Conditions[a,b]

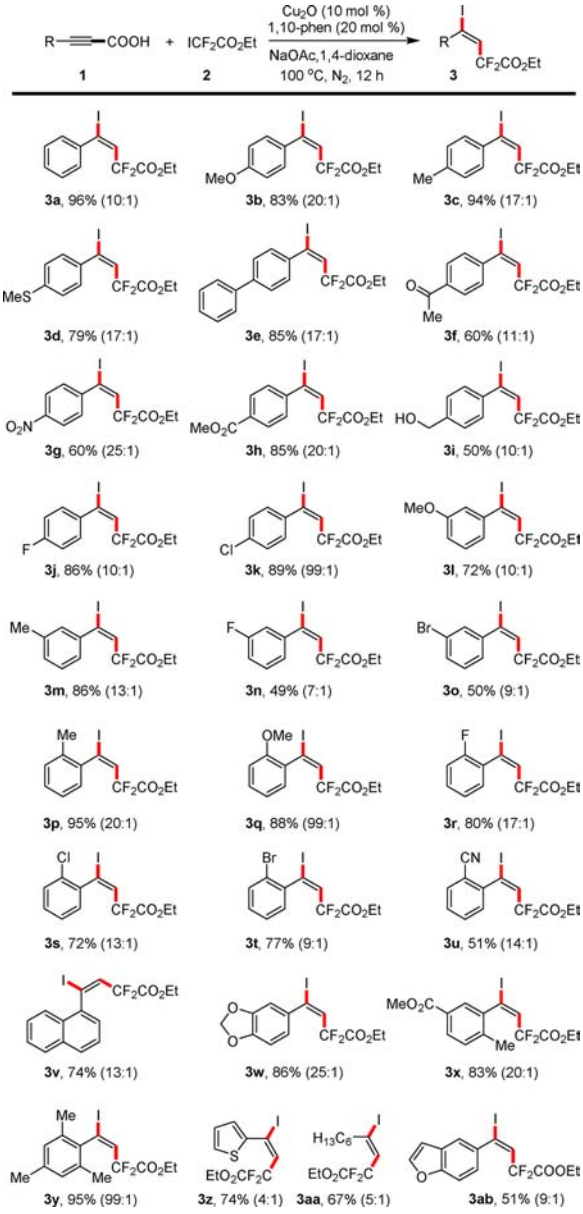


entry	cat. (mol %)	ligand (mol %)	yield (%)
1	CuCl (10)	1,10-phen (20)	84
2	CuCl (10	1,10-phen (10)	75
3	CuBr (10)	1,10-phen (20)	53
4	CuI (10)	1,10-phen (20)	41
5	Cu_2O (5)	1,10-phen (20)	90
6	$Cu(acac)_2$ (10)	1,10-phen (20)	80
7	$Cu(acac)_2$ (10)	1,10-phen (10)	76
8	$Cu(OAc)_2$ (10)	1,10-phen (20)	64
9	$Cu(OTf)_2$ (10)	1,10-phen (20)	62
10	Cu_2O (5)	1,10-phen (10)	84
11	Cu_2O (10)	1,10-phen (20)	96
12	Cu_2O (10)	PPh_3 (20)	46
13	Cu_2O (10)	dppp (20)	57
14	Cu_2O (10)	Pyr (20)	43
15	Cu_2O (10)	tby (20)	84
16	Cu_2O (10)	TMEDA (20)	90
17	Cu_2O (10)	DMEDA (20)	86
18[c]	Cu_2O (10)	1,10-phen (20)	90
19[d]	Cu_2O (10)	1,10-phen (20)	92
20[e]	Cu_2O (10)	1,10-phen (20)	88
21[f]	Cu_2O (10)	1,10-phen (20)	77
22[g]	Cu_2O (10)	1,10-phen (20)	82
23[h]	Cu_2O (10)	1,10-phen (20)	79
24	Cu_2O (10)	–	25
25[i]	Cu_2O (10)	1,10-phen (20)	84
26	–	1,10-phen (20)	0

[a]Unless otherwise noted, the reaction conditions were as follows: **1a** (0.2 mmol, 1.0 equiv), **2** (0.3 mmol, 1.5 equiv), 1,4-dioxane (1.0 mL), N_2. [b]Isolated yield. [c]90 °C. [d]110 °C. [e]Et_2O was used as solvent. [f]THF was used as solvent. [g]MeCN was used as solvent. [h]CH_2Cl_2 was used as solvent. [i]No NaOAc was added

With the optimized reaction conditions in hand, we next focused on broadening the scope of alkynyl carboxylic acids **1** with this atom transfer radical addition protocol, as shown in Scheme 2. A large number of para-substituted arylpropiolic acids installed with either electron-donating substituents, such as OMe, Me, SMe, and Ph (**1b**−**1e**), or electron-withdrawing substituents, such as C(O)Me, NO_2, CO_2Me, CH_2OH, F, and Cl (**1f**−**1k**), gave good to excellent yields of the corresponding difunctionalization products in our new catalytic system. It is worth noting that normally unstable functional groups such as CH_2OH could be well tolerated in this transformation. Meanwhile, meta-substituted arylpropiolic acids have also been successfully decarboxylated, and an atom transfer radical was added to afford the desired product (**3l**−**3o**). Notably, steric hindrance in the ortho-substituted substrates has also no effect in this catalytic system, and satisfactory yields were afforded in all cases (**3p**−**3v**). Moreover, di- and trisubstituted arylpropiolic acids could also afford the desired products (**3w**−**3y**). Intriguingly, good to excellent *E*/*Z* selectivities were observed for all cases in which phenylpropiolic acid or its derivatives were examined, which demonstrated the excellent stereoselectivity of this new catalytic transformation. Remarkably, decarboxylative atom transfer radical addition of heteroarene-based propiolic acids also proceeded smoothly to afford the corresponding functional styrenes with acceptable yields, albeit with relatively

Scheme 2. Substrate Scope of Alkynyl Acids[a,b]



[a]Unless otherwise noted, the reaction conditions were as follows: **1** (0.2 mmol, 1.0 equiv), **2** (0.3 mmol, 1.5 equiv), Cu_2O (10 mol %), 1,10-phen (20 mol %), NaOAc (0.3 mmol, 1.5 equiv), 1,4-dioxane (1.0 mL), 100 °C, 12 h, N_2. [b]Isolated yield. The ratios in parentheses are *E*/*Z* ratios, determined by ^{19}F NMR spectroscopy of crude products.

lower *E*/*Z* selectivity (**3z**). Finally, alkylated propiolic acid **1aa** was compatible with this catalytic system, giving difunctional alkyl olefin **3aa** with a moderate yield and stereoselectivity.

To gain insights into the mechanism of this iodofluoroalkylation, a series of control experiments were then carried out. First, when 1.0 equiv of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), a radical scavenger, was added into the standard reaction conditions, none of the desired product **3a** was obtained, while TEMPO-captured product **4** could be detected by ^{19}F NMR and GC-MS (Scheme 3, eq 1). This revealed a possible radical pathway was involved in the catalytic cycle. The fluoroalkyl radical path was also implicated by successful trapping of the $EtO_2CF_2C\cdot$ radical using *β*-pinene under the standard conditions, which afforded the ring-opened diene **5** as an

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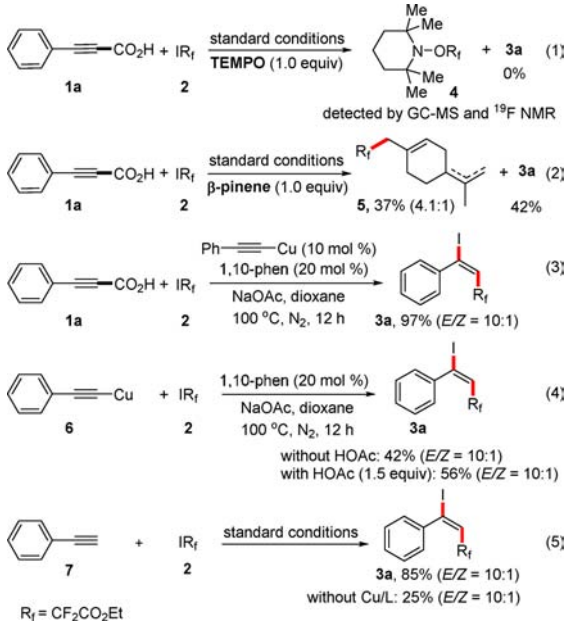
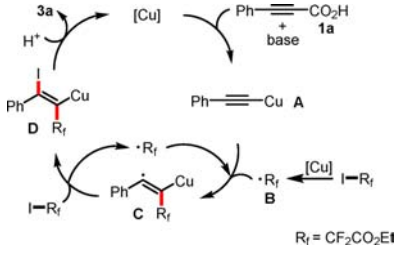
Scheme 3. Preliminary Mechanistic Studies



isomeric mixture (Scheme 3, eq 2). Next, when 10 mol % of preprepared (phenylethynyl)copper **6** was added into the reaction system instead of Cu_2O, the desired **3a** was obtained smoothly in 97% yield, which indicated **6** may serve as a key intermediate in the cycle (Scheme 3, eq 3). While the subjection of ethynylbenzene **7** into the standard conditions could also afford **3a** in good yield, we then tried to reveal the real radical acceptor. Accordingly, stoichiometric, preprepared (phenylethynyl)copper **6** gave almost the same moderate yields with or without addition of HOAc, which supposedly was produced via abstraction of a proton from propiolic acid with NaOAc and could quench the copper species **6** to ethynylbenzene **7** (Scheme 3, eqs 3 and 5). These results showed the quenching step of (phenylethynyl)copper **6** to ethynylbenzene **7** may not be involved in the catalytic cycle.

On the basis of the above results and previous reports,[11] a plausible mechanism involving a copper-initiated decarboxylative fluoroalkyl radical addition catalytic cycle was proposed (Scheme 4). The catalytic cycle was initiated by copper-catalyzed

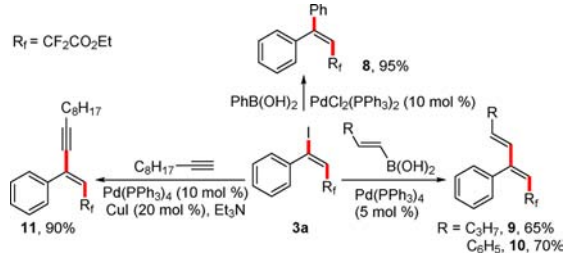
Scheme 4. Plausible Mechanism



decarboxylation of phenylpropiolic acid **1a**, which afforded the (phenylethynyl)copper species **A**. Meanwhile, reduction of fluoroalkyl iodide **2** is catalyzed by copper via a single-electron transfer to afford the fluoroalkyl radical **B**, which attacked the (phenylethynyl)copper species **A** to give the vinyl radical **C**. The carbon radical **C** could abstract an iodine atom from R_fI to result in formation of intermediate **D**, and regenerating of the $R_f\cdot$ radical through a chain transfer mechanism. Finally, intermediate **D** was quenched by proton to afford the desired iodofluoroalkylated product **3a** and regenerate the copper catalyst.

To demonstrate the synthetic potential of this newly developed method, fluorinated alkyl iodide **3a** was next studied to evaluate its reactivity toward the known palladium-catalyzed cross-coupling reactions that would form a variety of fluoroalkylated alkenes (Scheme 5). Upon treatment of **3a**

Scheme 5. Synthetic Transformations of 3a



with phenylboronic acid, alkenylboronic acids, and 1-decyne in the presence of a catalytic amount of palladium species, the fluorinated alkenyl iodide **3a** was coupled with aryl, alkenyl, and alkynyl structural motifs smoothly, which clearly show the value of the method to the synthesis of fluorine-containing compounds or intermediates.

The synthetic potential of this protocol was further elaborated by successful application to the late-stage iododifluoromethylation of biologically active compounds. As shown in Scheme 6, the subjection of estrone-derived propiolic acid **12**

Scheme 6. Decarboxylative Iododifluoromethylation of Estrone-Based Propiolic Acid 12

into the standard conditions afforded the fluorine-containing vinyl iodide **13** in good yield. While fluoroalkylated **13** with an embedded iodine atom could be further converted to different fluorine-containing estrone derivatives, this outcome indeed showed the great potential of this iodofluoroalkylation method in drug discovery and screening.

In conclusion, we have developed a novel copper-catalyzed decarboxylative atom transfer radical addition of alkynyl carboxylic acids. Compared with the known ATRA reactions, this transformation demonstrated the first example of iodofluoroalkylation of nonterminal alkynes with a broad substrate scope and excellent functional-group tolerance. Mechanistic investigations revealed that the catalytic cycle was initiated by the attack of a difluoroalkyl radical to the in situ generated alkynylcopper species. Further investigations into the detailed mechanism and application of this protocol to modify biologically active compounds are still ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

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Experimental procedure and characterization of all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(10) $BrCF_2CO_2Et$ and $ClCF_2CO_2Et$ were used to replace ICF_2CO_2Et in our catalytic system, but none of the desired ATRA product was obtained for both reagents. 3-(Pyridine-2-yl)propiolic acid afforded the ATRA product as an unseparated mixture.

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