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General and selective *syn*-carboxylation-trifluoromethylation of terminal alkynes: Application to the late-stage modification of dehydrocholic acid†

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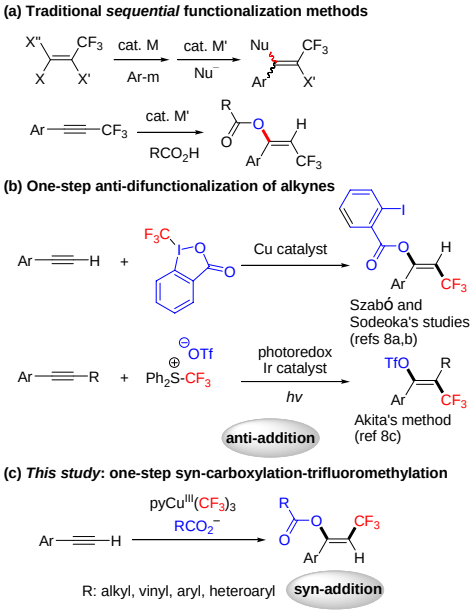
A general and selective method is developed that allows difunctionalization of terminal alkynes by a Cu(III)-CF_3 complex and a carboxylic acid regioselectively and with unusual *syn*-stereochemistry. This method is broadly applicable to various carboxylic acids and terminal alkynes, producing a range of biologically active trifluoromethyl enol carboxylic esters. The synthetic potential of this method is further demonstrated by the late-stage tabbing of a complex pharmaceutical compound dehydrocholic acid.

The relevance of vicinal functionalized trifluoromethylated alkenes has been well recognized in pharmaceuticals, agrochemicals and materials.[1-2] Despite the broad interest, there is currently no general methods for constructing such trifluoromethylated alkene motif with a vicinal Nu group (Nu denotes a nucleophilic group, such as an aryl, halo, oxy or amino group). Traditionally, they are prepared by two major kinds of methods (Scheme 1a): (i) sequential functionalization of polyhalogenated olefins using cross-coupling;[3] and (ii) functionalization of preformed Ar-C≡C-CF_3.[4] However, these methods suffer from a number of drawbacks, including low atom- and step-efficiency, limited substrate scope, and regio- and stereoselectivity issues. Recently, more straightforward methods of trifluoromethylative difunctionalization of alkynes are emerging that enable the synthesis of iodo-trifluoromethylated alkenes,[5] aryl-trifluoromethylated alkenes,[6] and others.[7] Despite the exciting initial success, such difunctionalization reactions are still far from satisfying, and challenges remain significant regarding particularly the generality of the methods, the substrate scope and the mildness of reaction conditions.



Scheme 1 Synthetic methods for vicinal Nu-trifluoromethylated alkenes.

Trifluoromethylated enol carboxylic esters are potentially biologically active compounds that may share some analogous properties to the trifluoromethylated enol phosphate esters. But their synthesis is extremely challenging.[8,9] Sodeoka and Szabó recently independently employed Togni's reagents as both the CF_3 and benzoate source for the difunctionalization of terminal alkynes (Scheme 1b).[8a,b] Despite the novelty and the excellent atom-economy of this reaction, due to the inherent limitation in scope of available and stable Togni's reagents, the reaction scope was rather limited, generating several *ortho-iodobenzoate*-trifluoromethylated styrenes. Later, Akita and co-workers reported a similar strategy of using Yagupol'skii-Umemoto type reagent $[Ph_2SCF_3]^+OTf^-$ as both CF_3 and OTf source to difunctionalize internal alkynes promoted by Ir(III) photoredox catalyst/photo-irradiation (Scheme 1b).[8c] The reaction scope is greatly improved to tolerate a range of internal alkynes, but is still limited to only OTf and OTs.

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†Electronic Supplementary Information (ESI) available: Experimental details, additional results, characterization data and NMR spectra for all the products. See DOI: 10.1039/x0xx00000x

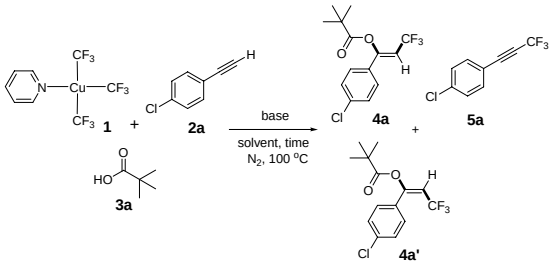
Remarkably, in these reports *anti*-addition of CF_3 and carboxylate/sulfonate across the triple bond of alkynes were achieved. To our knowledge, selective one-step *syn*-difunctionalization across the triple bond of alkynes by a CF_3 and a carboxylate has thus far been unknown.

In continuation of our recent interest in developing Cu(III)-CF_3 chemistry,[10-12] we envisioned the possibility of achieving carboxylation-trifluoromethylation of alkynes using Cu(III)-CF_3 complexes as novel CF_3 precursors and abundant carboxylic acids as the ideal carboxylate source. The introduction of the CF_3 and carboxylate functionality from two independent reagents allows free manipulation of both carboxylate and CF_3 precursors. The ready availability and wide scope of carboxylic acids could greatly enhance the generality and scope of the reaction. To prove this hypothesis, we describe in this paper the development of a general, efficient and selective carboxylation-trifluoromethylation of alkynes that is efficient for a broad range of terminal alkynes and an almost full spectrum of types of carboxylic acids (Scheme 1c). More, unusual *syn*-installation of a carboxylate and a CF_3 across the triple bond of alkynes is achieved that is complementary to previous anti-stereochemistry (Scheme 1c).

Our study began by reaction of (py)$Cu^{III}(CF_3)_3$ (**1**) (py denotes pyridine),[10c] *para*-chlorophenylacetylene (**2a**) and pivalic acid (**3a**) at 100°C under N_2 (Table 1). When a strong base NaO*t*Bu was used in DMF, the reaction occurred to produce a mixture of **4a**, **4a′** and **5a** in 4 hours as determined by ^{19}F NMR spectroscopy (entry 1).[13] When the reaction time was extended to 8 hours, the byproducts **4a′** and **5a** were significantly reduced while the desired **4a** increased to 67% (entry 2). Further extending the time to 12 hours increased the yield to 72% while almost completely diminished **4a′** and **5a** (entry 3). The combinational use of NaO*t*Bu and DMF is found to be crucial to this reaction, which might be attributed to the better solubility of the base in the reaction solution. Performing the reaction in toluene or NMP led to either no product or much lower yield of **4a** (entries 4,5). Using KO*t*Bu or KF led to neglectable formation of **4a** (entries 6,7). Noteworthy, the Cu(III)-CF_3 complex **1** is optimal for this reaction; using (phen)$Cu^{III}(CF_3)_3$ (phen denotes phenanthroline)[10b] led to the decomposition of **4a** and the formation of acyl fluorides as shown by ^{19}F NMR spectroscopy.[14] The stoichiometry of 4 equivalents of carboxylic acids is also crucial to the efficient generation of **4a** because reducing **3a** to 2 equivalents led to trace amount of **4a** due to the decomposition to acyl fluorides although the reasons are currently not well understood.

A range of terminal arylalkynes[15] were found to react efficiently under the optimal conditions (Table 1, entry 3), tolerating various functional groups on the aryl ring, including fluoro, chloro, bromo, trifluoromethyl, alkyl, cyano, keto, nitro and even aldehyde (Table 2). Heteroaryl, e.g., 3-pyridylacetylene (**2j**) also reacted smoothly with pivalic acid and complex **1** to give the *syn*-addition product **4j** in a good yield of 72%. In the case of *para*-methyl and -methoxy phenylacetylenes **2m** and **2n**, in addition to the major formation of **4m** and **4n** in 72% and 66% yields, the

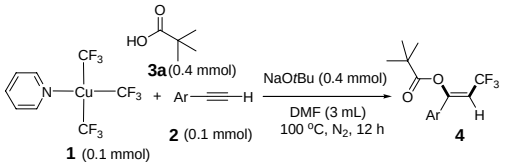
Table 1 Optimization of the reaction conditions [a]

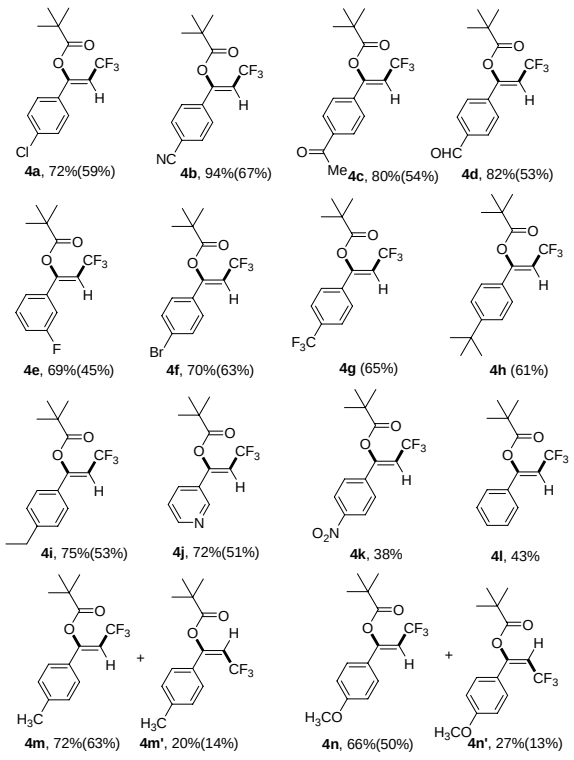


entry	base	solvent	time	yield (%)[b] 4a	4a'	5a
1	NaO*t*Bu	DMF	4	54	11	28
2	NaO*t*Bu	DMF	8	67	6	16
3	NaO*t*Bu	DMF	12	72	0	12
4	NaO*t*Bu	toluene	8	0	0	0
5	NaO*t*Bu	NMP	8	54	5	0
6	KO*t*Bu	DMF	8	trace	-	-
7	KF	DMF	8	trace	-	-

[a] Reaction conditions: **1** (0.1 mmol), **2a** (0.1 mmol), **3a** (0.4 mmol), base (0.4 mmol), 4,4′-difluorobiphenyl (0.1 mmol, internal standard) and solvent (3 mL) stirred at 100 °C under N_2. [b] ^{19}F NMR yield based on **2a**.

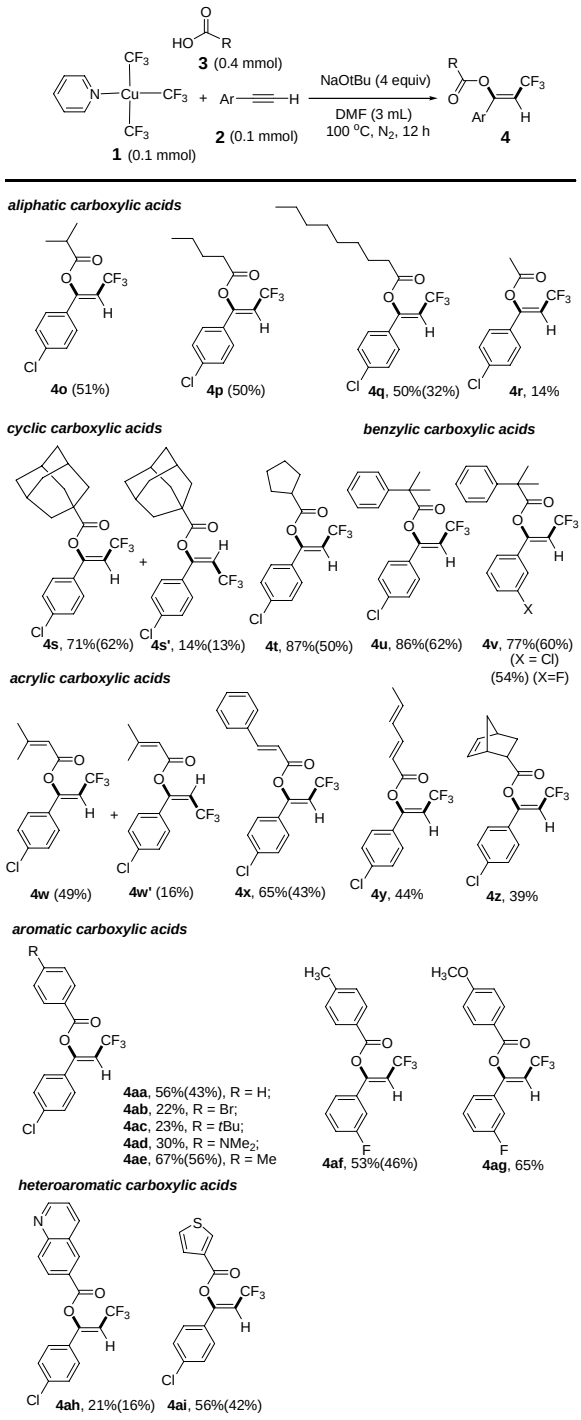
Table 2 Substrate scope of terminal alkynes [a]





[a] Both ^{19}F NMR and isolated yields (in parentheses) are provided if available.

Table 3 Substrate scope of carboxylic acids [a,b]

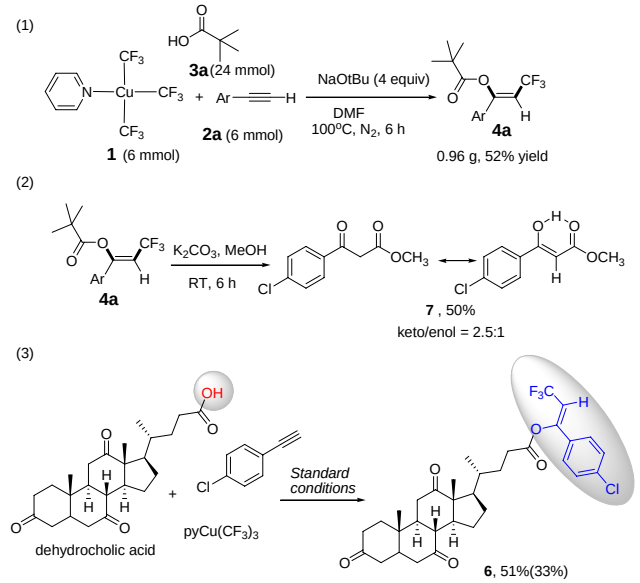


[a] Reaction conditions: **1** (0.1 mmol), **2** (0.1 mmol), **3** (0.4 mmol), NaO*t*Bu (0.4 mmol), 4,4′-difluorobiphenyl (0.1 mmol, internal standard) and solvent (3 mL) stirred at 100 °C under N_2. [b] Both ^{19}F NMR and isolated yields (in parentheses) are provided if available.

stereoisomeric (*E*)-products **4m′** and **4n′** arising from *anti*-addition of pivalate and CF_3 were also isolated in minor 20% and 27% yields.

Additionally, a broad range of carboxylic acids can participate in the *syn*-carboxylation-trifluoromethylation of alkynes (Table 3), including cyclic and acyclic aliphatic carboxylic acids, benzyl carboxylic acids, acrylic acids, benzoic acids and heteroaryl carboxylic acids. Generally, the *syn*-addition products were selectively obtained without significant formation of regio- or stereoisomers except the case of adamantyl and isopentenyl carboxylic acids wherein *anti*-addition products **4s′** and **4w′** could also be generated in minor amounts.

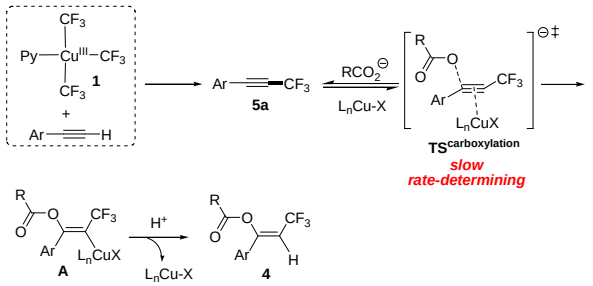
The reactions can be easily scaled up. For example for the preparation of **4a**, when the reaction was scaled up to 60 mmol level, **4a** was isolated in 0.96 g (52% yield), only slightly lower than the isolated yield of 59% at a 0.1 mmol scale (Scheme 2, eq 1). To show the potential usefulness of the products **4**, alcolysis of the **4a** by excess methanol as the solvent in the presence of K_2CO_3 led to the formation of benzoyl acetate **7** in a 50% isolated yield (eq 2). Possibly, the methanol abstracts the acyl group to give α-CF_3 enolate that undergoes further alcolysis of the CF_3 group.



Scheme 2 Scale-up study and synthetic applications.

As a further demonstration of the synthetic potential, it was applied to the functionalization of dehydrocholic acid, a pharmaceutical that can treat cholic diseases. Thus, the terminal carboxylic group is converted to the fluorinated enol ester in an acceptable yield (Scheme 2, eq 3). This tabbing may have a significant influence on the basic properties (in particular, metabolic stability and cell permeability) of the resulting compound, which is potentially valuable to the in vivo delivery and metabolic stability of pharmaceuticals.

Based on some mechanistic studies and the experimental observations,[16] a plausible mechanism profile is proposed to involve the initial generation of intermediate of type **5a** (Scheme 3), which then undergoes rate-limiting carboxylation with the assistance of bulky Cu complexes to give the desired products. The coordination of bulky Cu complex is believed to be important to achieve high syn-stereoselectivity. Further efforts are required to fully clarify the details of each reaction step.



Scheme 3 A plausible mechanism.

In conclusion, a *syn*-carboxylation-trifluoromethylation reaction across the triple bond of terminal alkynes is developed to produce regio- and stereoselectively trifluoromethylated enol esters. This reaction uses a key Cu(III)-CF_3 complex as the CF_3 source and carboxylic acids as the carboxylate source to difunctionalize terminal alkynes with high regio- and stereoselectivity. It is applicable to a broad range of carboxylic acids and alkynes, can be easily scaled up to gram scale, and has be applied to the late-stage functionalization of dehydrocholic acid.

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Conflicts of interest

There are no conflicts of interest to declare.

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13 **4a**, **4a'** and **5a** feature ^{19}F signals at *ca.* -58.5, -55.5 and -50.0 ppm. Some byproducts **4'** were isolated and fully characterized as shown in Tables 2 and 3. The major NMR differences are summarized for **4** and **4'** in Figure S1 in ESI†.

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16 For some mechanistic studies, see ESI† for more details.

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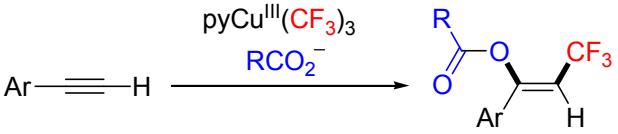

single isomer

(R: alkyl, benzyl, vinyl, aryl, heteroaryl)

36 examples

A general and selective *syn*-carboxylation-trifluoromethylation across the triple bond of terminal alkynes is developed by virtue of a reactive Cu(III)-CF_3 complex, which produces a broad range of biologically active trifluoromethylated enol esters with excellent regio- and stereoselectivity.