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Synthesis of β-Difluoroalkylated Acrylonitriles in the Presence of Copper Powder

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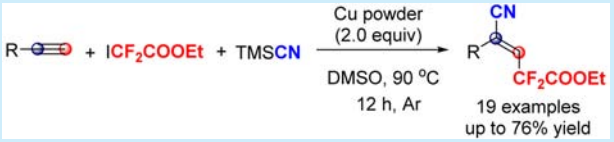
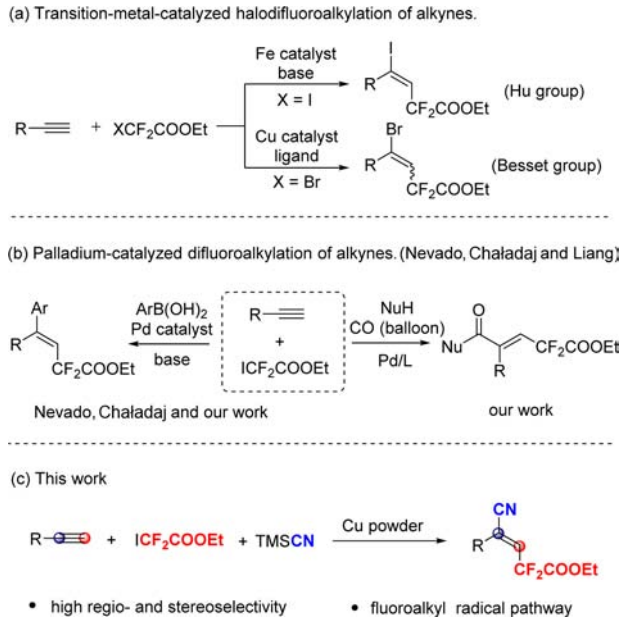
Supporting Information

ABSTRACT: A highly regio- and stereoselective copper-mediated cyanodifluoroalkylation of alkynes with ethyl difluoroiodoacetate and trimethylsilyl cyanide (TMSCN) is described. The three-component coupling reaction provides straightforward access to a variety of useful difluoroalkyl-substituted acrylonitriles. The introduction of the nitrile unit is of great importance in drug discovery for the modification of this fragment. Preliminary mechanistic investigations indicate that a vinyl iodide intermediate and a difluoroalkyl radical might be involved in this transformation.



Organofluorine compounds usually exhibit specific properties as compared with their parent molecules in organic synthesis.[1] Consequently, considerable efforts have been devoted for the introduction of fluorinated moieties into target molecules.[2,3] In contrast to the progress achieved in the trifluoromethylation field, strategies to access CF_2R-containing compounds are less abundant for the lack of good difluoromethylation reagents,[4] even if they exhibit the ability to be modificated into other fluorinated moieties.[5] The traditional methods to synthesize CF_2-containing molecules are mainly from the following three aspects: (1) Transition-metal-mediated cross-coupling reactions of difluoroalkyl species with halogenated arenes,[6] alkenes,[7] or arylboronic acids;[8] (2) Difluoroalkylation of the C−H bonds of unsaturated compounds;[9,10] (3) Difluoroalkylation of alkenes or alkynes based on an intermolecular difunctionalization strategy.[11] Recently, Zhang,[12] Pannecoucke,[13] and related groups[14,15] have made significant advancements in this area. Nevertheless, using these methods, there are merely three types of transition-metal-catalyzed difluoroalkylation reactions for compounds comprising a less reactive C≡C bond. One straightforward approach is the halodifluoroalkylation of alkynes reported by the Hu[16] and Besset[17] group in 2014, respectively (Scheme 1a). For the three-component aryldifluoroalkylation reactions, Nevado,[18] Chaładaj,[19] and our group[20] independently reported the palladium-catalyzed difunctionalization of alkynes with ethyl difluoroiodoacetate and arylboronic acids (Scheme 1b). In 2016, a palladium catalyzed stereoselective difluoroalkylation and carbonylation of alkynes was also reported by our group (Scheme 1b).[21] Due to few reports and great potential in this area, the development of concise approaches to introduce the difluoroalkyl group synchronously with other functional groups into alkynes remains a challenging task.

Scheme 1. Transition-Metal-Catalyzed or -Mediated Difluoroalkylation of Alkynes



It is well-known that nitriles are an important class of organic compounds.[22] The preparations of such compounds have received significant attention. In 2014, our group reported a copper-catalyzed, intermolecular cyanotrifluoromethylation of alkenes.[23] On this basis, the formation of two C−C bonds across the alkynes can be achieved concurrently in a single pot

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operation. In contrast to alkyl nitriles, α,β-unsaturated nitriles are widely applied as feedstocks in the Diels–Alder reaction, which is a powerful synthetic tool in the design of bioactive molecules and natural products.[24] Consistent with the previous work of our group, we herein report the highly regio- and stereoselective copper-mediated cyanodifluoroalkylation of alkynes with ethyl difluoroiodoacetate and trimethylsilyl cyanide (TMSCN) (Scheme 1c). This work provides rapid assemblies of valuable difluoroalkyl-substituted acrylonitriles.

We began the optimization of reaction conditions by utilizing phenylacetylene **1a**, ethyl difluoroiodoacetate, and TMSCN as model substrates. The iododifluoroalkylation product **4a** was isolated in 70% yield with the CuBr catalyst at 80 °C under argon in 1,4-dioxane (Table 1, entry 1), which is the same as

Table 1. Optimization of the Reaction Conditions for Cyanodifluoroalkylation of Alkynes[a]

1a 2a 3a 4a

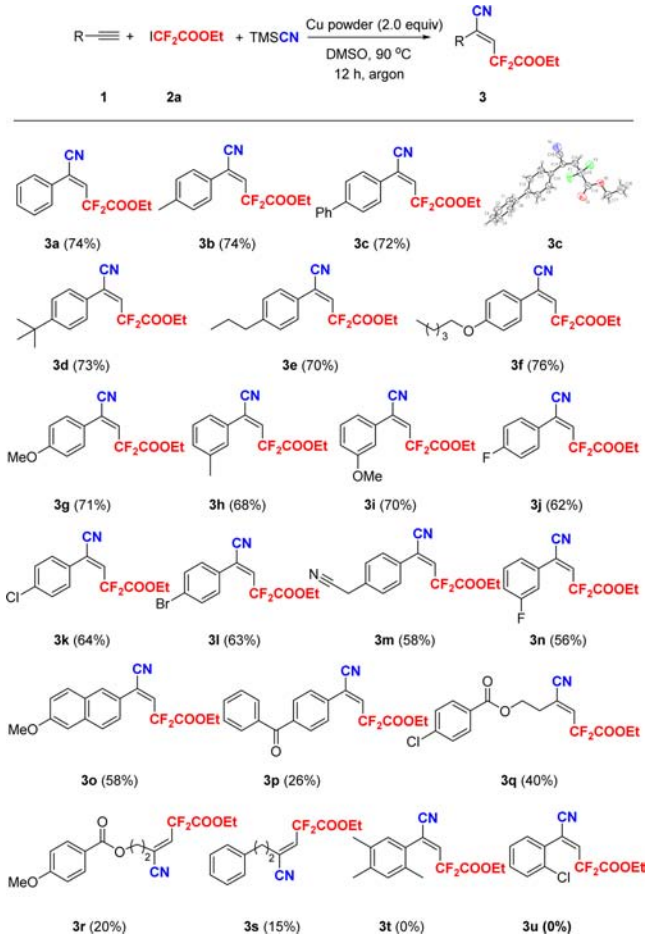
entry	additive	base (equiv)	solvent	yield[b] (%)
1	CuBr (10%)	Cs_2CO_3 (1.0)	1,4-dioxane	**3a**/**4a** (0/70)
2	Cu (10%)	Cs_2CO_3 (1.0)	1,4-dioxane	**3a**/**4a** (0/71)
3	Cu (10%)	—	1,4-dioxane	**3a**/**4a** (0/65)
4	Cu (2.0 equiv)	—	1,4-dioxane	**3a**/**4a** (0/81)
5	Cu (2.0 equiv)	—	DMF	**3a**/**4a** (31/30)
6	Cu (2.0 equiv)	—	toluene	**3a**/**4a** (0/78)
7	Cu (2.0 equiv)	—	NMP	**3a**/**4a** (29/30)
8	Cu (2.0 equiv)	—	DMAc	**3a**/**4a** (25/32)
9	Cu (2.0 equiv)	—	DMSO	**3a**/**4a** (69/9)
10[c]	Cu (2.0 equiv)	—	DMSO	**3a**/**4a** (74/6)
11	Cu (2.0 equiv)	Cs_2CO_3 (1.0)	DMSO	0
12	Cu (1.0 equiv)	—	DMSO	**3a**/**4a** (67/7)
13[d]	—	—	DMSO	0

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), TMSCN (0.4 mmol), catalyst, 12 h, 80 °C, under argon. [b]Isolated yield. [c]The reaction was conducted at 90 °C. [d]Without copper catalyst.

Hu's results (Scheme 1a). A similar yield of **4a** was also obtained when copper powder was used instead of CuBr (Table 1, entry 2). Stoichiometric amounts of copper powder were used in the following investigation. A short survey on solvents indicated that the property of the solvent was crucial for this transformation; the desired product difluoroalkyl-substituted acrylonitrile **3a** was successfully obtained in a polar solvent. A 69% yield of product **3a** was isolated in dimethyl sulfoxide (DMSO) (Table 1, entry 9). A higher temperature of 90 °C could increase the yield to 74% (Table 1, entry 10). No significant progress in the yield was obtained in subsequent attempts. Control reactions demonstrated that no reaction occurred in the absence of copper powder. As a consequence, the optimized reaction conditions were confirmed by using copper powder (2.0 equiv), TMSCN (2.0 equiv), and ethyl difluoroiodoacetate (1.5 equiv) in DMSO at 90 °C under argon.

Subsequently, the scope of a series of alkynes **1** with ethyl difluoroiodoacetate and TMSCN was investigated under the optimized conditions. As described in Scheme 2, the reaction proceeded smoothly in most cases to give the corresponding products in moderate to good yields with excellent stereoselectivity. The NMR-based structure of difluoroalkyl-substituted acrylonitrile **3c** was confirmed by X-ray diffraction. Phenylacetylene bearing electron-donating substituents gave higher yields than those bearing electron-withdrawing ones on the aryl ring. The methoxy naphthyl substrate **1o** participated in this cyanodifluoroalkylation reaction and provided the corresponding product in a satisfactory yield. A significant drop in the reactivity was found when phenylacetylene with a keto-moiety on the *para*-position of phenyl ring **1p** was explored under the optimal conditions. It should be mentioned that the linear alkyne **1q** showed a competent reaction partner for this transformation, leading to the desired product in 40% yield. Sterically hindered substrates such as 2,4,5-trimethyl- and 2-chlorophenylacetylene failed to undergo this cyanodifluoroalkylation reaction as expected.

Scheme 2. Substrate Scope for the Cyanodifluoroalkylation of Alkynes[a,b]



[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.3 mmol), TMSCN (0.4 mmol), Cu powder (2.0 equiv), DMSO (1.0 mL), 12 h, 90 °C, under argon. [b]Isolated yields.

To gain more insights into the cyanodifluoroalkylation process, some necessary trapping experiments were performed. First, two reactions were conducted to investigate whether the iododifluoroalkylation product was the reaction intermediate. As a result, only 16% of **4a** was isolated in the absence of TMSCN (Scheme 3a). The iododifluoroalkylation compound **4a** used as starting material under the optimized conditions resulted in an even lower conversion; a 9% yield of the corresponding cyanodifluoroalkylation product **3a** was thus obtained (Scheme 3b). These experiments suggest that part of

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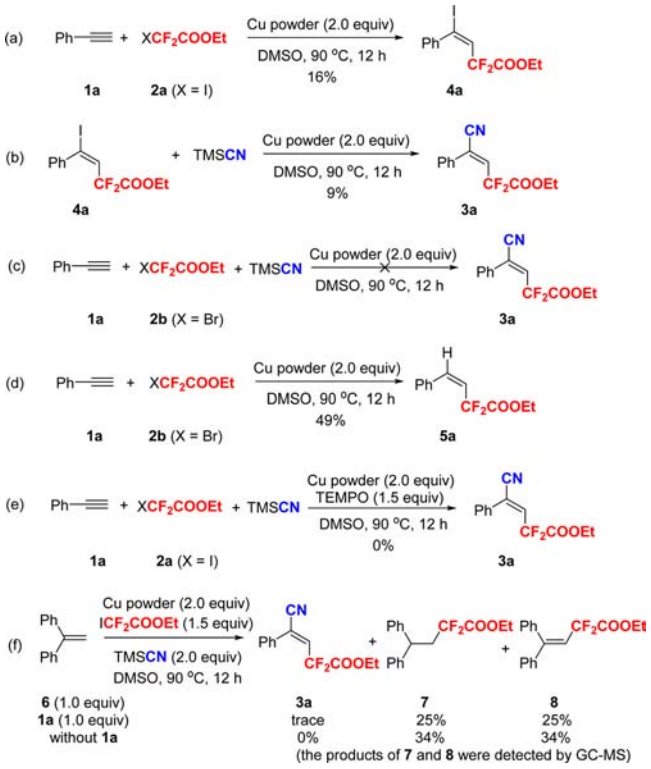
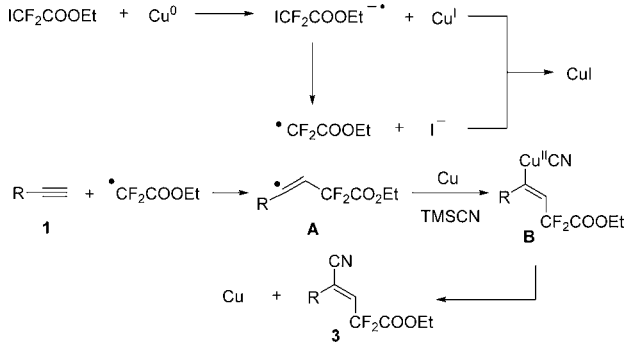
Scheme 3. Trapping Experiments



this transformation proceeded via a vinyl iodide intermediate. No β-difluoroalkylated acrylonitrile was obtained when ethyl bromodifluoroacetate was used instead of ethyl difluoroiodoacetate as the source of CF_2 (Scheme 3c), and a hydrodifluoroalkylation product **5a** (49%) could be obtained without TMSCN (Scheme 3d). Second, when the reaction was carried out in the presence of TEMPO, a radical scavenger, the desired transformation was shut down and a trace amount of the TEMPO−CF_2COOEt adduct was detected by GC−MS (Scheme 3e). Additionally, when a stoichiometric amount of 1,1-diphenylethylene **6**, in the presence or absence of phenylacetylene **1a**, was added as a radical trapper to this control experiment (Scheme 3f), no desired coupling product **3a** could be isolated. However, the CF_2COOEt-containing compounds **7** and **8** with a 1:1 ratio were mainly obtained in both cases, in which the total yield of **7** and **8** could be increased to 34% without alkyne **1a**. On the basis of these preliminary results, a mechanism involving a difluoroalkyl radical pathway might be involved in the present reactions. As described in Scheme 4, the difluoroalkyl radical might come from the redox reaction of ethyl difluoroiodoacetate with copper powder. The difluoromethyl radical species was added to the C−C triple bond of alkyne, and the radical intermediate **A** was formed. The radical intermediate **A** reacted with copper powder and TMSCN to generate the copper(II) cyanide complex **B** in *trans*-stereochemistry. Subsequent reductive elimination of the copper(II) cyanide complex **B** produced the desired cyanodifluoroalkylation product **3** with the simultaneous release of Cu(0).

In summary, we have developed an unprecedented copper-mediated cyanodifluoroalkylation of alkynes with trimethylsilyl cyanide and ethyl difluoroiodoacetate. This three-component coupling reaction provides a general method for the expeditious synthesis of various β-difluoroalkylated acrylonitriles in a

Scheme 4. A Possible Radical Pathway



stereodefined manner, and the introduction of a nitrile unit is of great importance in drug discovery for the modification of these fragments. We expect that this transformation may provide new insight into the difluoroalkylation reaction of alkynes and find applications to synthesize complex heterocycles. Further explorations to uncover the reaction mechanism are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02627.

Detailed experimental procedures, spectral data for all new compounds, crystallographic data (PDF)

Crystallographic data for **3c** (CIF)

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Notes

The authors declare no competing financial interest.

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