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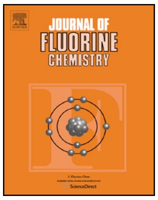

Copper-catalyzed intermolecular cyanotrifluoromethylation of alkenes: Convenient synthesis of CF_3-containing alkyl nitriles

Zhaoli Liang, Fei Wang, Pinhong Chen, Guosheng Liu *

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences,
345 Lingling Road, Shanghai 200032, China

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ABSTRACT

A copper-catalyzed intermolecular cyanotrifluoromethylation of alkenes has been developed, in which the less reactive Togni reagent **2** was used as a CF_3 source and TMSCN was employed as a cyano source. Both activated and unactivated alkenes were suitable for this transformation to give CF_3-containing organonitriles under mild conditions.

1. Introduction

Organonitriles have been widely recognized as important organic compounds and applied in organic synthesis as valuable intermediates and building blocks due to their versatile chemical property and bioactivities [1]. Elegant methodologies have been reported for the conversion of organonitrile to diverse organic compounds, such as organocarboxylic acid, which have extensively been applied in pharmaceuticals and agricultural chemicals [2]. Representative organonitriles and related carboxylic acid exhibited some bioactivity, such as enzyme inhibitor, anti HIV and hNK2 receptor [3] (Fig. 1). Therefore, many efforts have been paid to introduce nitrile group into organic molecules. On the other hand, trifluoromethyl group is prevalent in pharmaceuticals and agrochemicals due to its unique properties [4]. We speculated that, if both CF_3 and nitrile groups can be simultaneously introduced into organic compounds, efficient synthesis of trifluoromethylated organonitriles and related derivatives might be expected, which will shed a light to introduce CF_3 into original leading compounds or drugs to adjust their bioactivity. Herein we report a copper-catalyzed intermolecular cyanotrifluoromethylation of alkenes to construct CF_3-containing organonitriles under very mild conditions [5].

Recently, a notable development of allylic trifluoromethylation of alkenes was reported independently by Buchwald, Liu, Wang and Sodeoka groups [6]. Since then, the trifluoromethylation of alkenes has been disclosed to allowing the effective formation of C_{sp3}–CF_3 bond [7]. Among them, three-component coupling trifluoromethylation reactions have received more and more attention [7c–g,k]. In 2012, our group reported the first difunctionalization of alkenes involving trifluoromethylation using a palladium catalyst [8]. As a continuation of our interest in difunctionalization of alkenes [9], our group recently discovered a copper-catalyzed intermolecular trifluoromethylazidation of alkenes [10], in which a carbon radical or carbon cation intermediate was proposed to be trapped by an azide reagent. Inspired by this result, we envisioned that this carbon radical or carbon cation intermediate might also be trapped by a cyano reagent to introduce both CF_3 and CN groups into the alkenes (Scheme 1). If so, a variety CF_3-containing organonitriles and their derivatives could be expected to achieve through a very efficient approach. Very recently, Szabó and Liang also independently reported copper-mediated or -catalyzed cyanotrifluoromethylation of alkenes with the same strategy using more reactive ester type Togni reagent [5].

2. Results and discussion

In our previous study, trimethylsilyl azide ($TMSN_3$) plays an important role to activate less active Togni reagent (**2**) to generate

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* Corresponding author. Tel.: +86 21 54925346; fax: +86 21 64166128.
E-mail address: gliu@mail.sioc.ac.cn (G. Liu).

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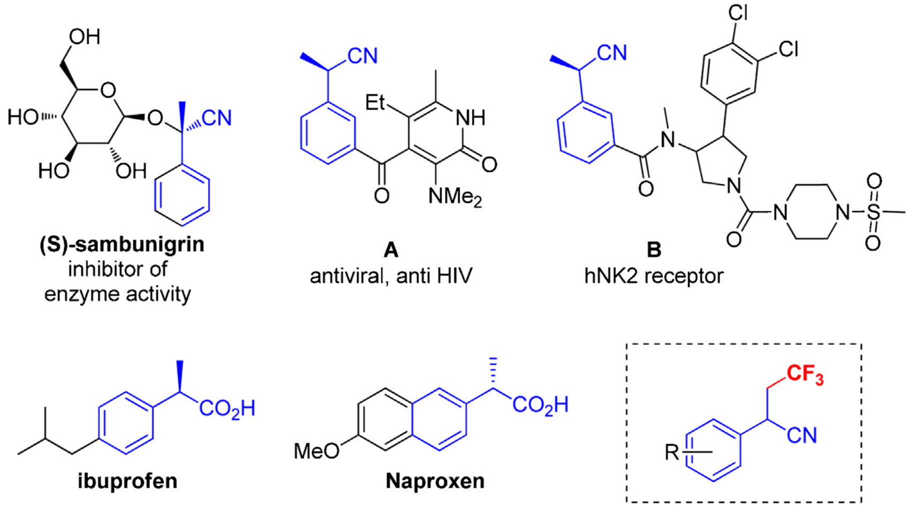
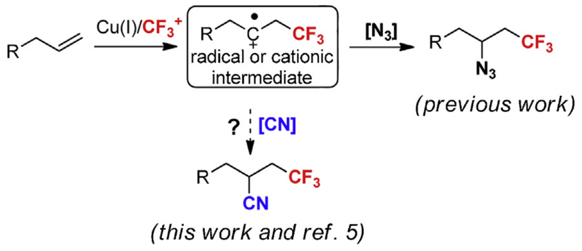


Fig. 1. Representative bioactive trifluoromethylated nitriles and derivative.

CF_3 radical in the presence of copper catalyst. Thus, the initial study was focused on the reaction of styrene (**1a**) with Togni reagent (**2**) in the presence of copper catalysts, and trimethylsilyl cyanide (TMSCN) was employed as a cyano source. As shown in Table 1, the reaction of **1a** did afford the desired cyanotrifluoromethylation product **3a** in the presence of 5 mol% $Cu(CH_3CN)_4PF_6$ in DMSO at room temperature (Table 1, entry 1). Solvent screening implied that DMSO was the best solvent for this reaction. Then different copper salts were applied into the reaction which showed that all listed copper salts could catalyze this reaction (entries 2–8). Firstly, copper catalysts, such as CuTc and $(CuOTf)_2{\cdot}C_6H_6$, were tested to give only moderate yield (entries 2 and 3). Secondly, when copper(II) catalyst was used, the yield was not improved (entry 4). And the copper powder was also used to catalyze this reaction, albeit in low yield (entry 5). Finally, copper complexes with bidentate nitrogen ligand **L1**–**L3** were used, and the yield was improved significantly to 93% in the presence of 10 mol% (**L3**)CuBr (entries 6–8). The yield was decreased to 85% with lowered catalyst loading (5%) (entry 9). The combination of CuBr and ligand **L3** to generate the copper complex *in situ* was not as effective as the prepared complex (entry 10). Control experiment showed that no reaction took place in the absence of a copper catalyst (entry 11).

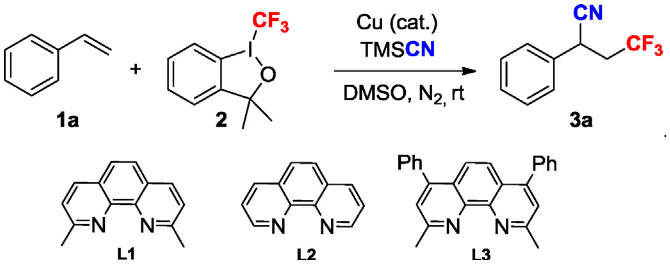
With the optimized reaction conditions in hand, the substrate scope was investigated and the results are summarized in Table 2. Styrenes **1a**–**1j** bearing various substituents on the aromatic ring, including electron-donating and electron-withdrawing groups, were compatible with this reaction condition to give **3a**–**j** in good to excellent yields. Among them, substrates **1c**–**1d**, **1g**–**1h** bearing halides gave the corresponding products **3c**–**d**, **3g**–**h** in 84–98% yield without loss of halides. In additional, the reaction of cyclic styrene **1k** afforded a desired product **3k** in 73% yield with excellent diastereoselectivity (>20:1).

Intrigued by the results of styrenes, we extended the substrate scope to aliphatic substituted alkenes. To our delight, the reaction of alkyl substituted alkenes proceeded smoothly to give desired products. For instance, simple alkene **1l** could be transformed to **3l** in 74% yield. Importantly, the reaction of enamine substrate **1m** proceeded well to give **3m** in good yield, which could be transformed to 2-amino-4,4,4-trifluorobutanenitrile as an important building block after deprotection. The reaction of **1n**–**p** with an imide group afforded **3n**–**p** in good yields. A free proton of *N*-allylaniline **1q** did



Scheme 1. Copper-catalyzed intermolecular difunctionalization of alkenes.

Table 1
Optimization of reaction condition.[a]



Entry	Catalyst (mol%)	Yield (%)[b]
1	$Cu(CH_3CN)_4PF_6$ (5)	76
2	CuTc (5)	50
3	$(CuOTf)_2{\cdot}C_6H_6$ (5)	61
4	$CuBr_2$ (10)	56
5	Cu powder (5)	27
6	(**L1**)CuBr (10)	76
7	(**L2**)CuBr (10)	80
8	(**L3**)CuBr (10)	93
9	(**L3**)CuBr (5)	85
10[c]	(**L3**)CuBr (10)	87
11[d]	-	0

[a] Reaction conditions: **1a** (0.1 mmol), Cu catalyst (10 mol%), TMSCN (0.2 mmol), Togni reagent **2** (0.15 mmol) in DMSO (0.5 mL) at room temperature in 0.5 h.

[b] NMR yield, determined by ^{19}F NMR spectroscopy using *N*,*N*-dimethyltrifluoroacetamide (DMA-CF_3) as an internal standard.

[c] CuBr and **L3** were added separately.

[d] Without copper catalyst.

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