

Copper-Catalyzed Three-Component Reactions of 2-lodo-2,2-difluoroacetophenones, Alkynes, and Trimethylsilyl Cyanide

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A Cu(l)-catalyzed three-component reaction of 2-iodo-2,2difluoroacetophenones, alkynes, and TMSCN is described. The reaction provided a facile method for the synthesis of difluoroacyl-substituted nitriles, which might be served as potentially useful fluoroorganic intermediates for further transformation in drug discovery. This method has broad substrate scope, good efficiency, and excellent stereoselectivity. Preliminary mechanistic investigation indicated that a radical-mediated process was involved in this cyanodifluoroalkylation reaction.

Difluoromethylene compounds have been widely used in medicinal chemistry and agrochemistry due to that the difluorinated moieties could significantly enhance their lip-ophilicity, metabolic stability, and bioavailability.^[11] Therefore, substantial efforts have been made on the development of difluoroalkylation reactions for the construction of α, α -difluoroketone molecules.^[2] In a general way, the difluoroalkylation methods mainly include metal-mediated cross-coupling reactions of difluoroalkylated reagents with halogenated aromatic hydrocarbons, or olefins,^[3] and radical addition reactions of difluoroalkylated reagents with unsaturated hydrocarbons,^[4] etc.

As we know, alkynes were vital industrial raw materials, and their excellent performance in functionalization was widely concerned.^[5] Among them, the difunctionalization of alkynes for the synthesis of organofluorine compounds via three-component reactions has made significant advancements.^[6] Liang et al. reported a novel method for the synthesis of fluoroalkylated alkenes through palladium-catalyzed three-component reactions with alkynes, ethyl difluoroiodoacetate, and arylboronic acids.^[6a] In 2017, Zhao's group disclosed a palladium-catalyzed reaction of alkynes with diphenylphosphine oxides and ethyl difluoroiodoacetate, providing an attractive approach for the formation of (*E*)- γ , γ -difluoroalkenylphosphines oxides.^[6b] Sub-

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	Supporting information for this article is available on the WWW under https://doi.org/10.1002/ejoc.202001650

sequently, Zhu et al. and Zhang et al. independently reported the palladium-catalyzed difunctionalization of alkynes with ethyl difluoroiodoacetate and $B_2 pin_2$.^[6c,d] A Pd (0)-catalyzed three-component reactions of 2-iodo-2,2-difluoroacetophenones, alkynes, and arylboronic acids was also reported by our group. The application of more difluoroalkylation reagents will facilitate the development of synthetic approaches for varieties of useful fluoroalkylated compounds.^[6e]

In addition, nitriles are versatile organic intermediates,^[7] which can be easily converted into other functional organic compounds with potential applications such as ketones, carboxylic acids, amides and triazoles etc. Despite the importance of nitriles in the field of organic synthesis, the development of concise approaches to fluorine-containing nitriles remains a challenging task. Liang's group reported the synthesis of β -trifluoromethylated acrylonitriles via copper-catalyzed difunctionalization of alkynes with Togni reagent and trimethylsilyl cyanide (TMSCN).^[8] They next disclosed a copper powdermediated reaction with ethyl difluoroiodoacetate, alkynes, and TMSCN for the synthesis of β -difluoroalkylated acrylonitriles.^[9] In 2019, Bao's group has developed a copper-catalyzed cyanoperfluoroalkylation of alkynes with perfluoroalkyl iodides and to produce a variety of perfluoroalkylated TMSCN cyanoalkenes.^[10] In recent years, our group has utilized RCOCF₂I as difluoroalkylating reagents and employed them in different reactions for the construction of diverse difluoroacyl alkenes.^[6e,11] With our continued interest in the introduction of the difluoroacyl group synchronously with other functional groups into alkynes, herein, we reported a copper-catalyzed reaction of 2-iodo-2,2-difluoroacetophenones, alkyne, and trimethylsilyl cyanide (TMSCN) that achieves cyanodifluoroalkylation of simple abundant alkynes with high stereoselectivity via multicomponent radical cascade process (Scheme 1).

In our initial investigation, the reaction of 2-iodo-2,2difluoroacetophenone **1 a**, phenylacetylene **2 a** with TMSCN was chosen as a model reaction to optimize the reaction conditions. The reaction was conducted in anhydrous MeOH at 70 °C with lauryl peroxide (LPO) as the radical initiator, and **L1** as the ligand catalyzed by Cu(CH₃CN)₄BF₄ under the nitrogen (Table 1, entry 1). As expected, results showed that the desired difluoroalkyl-substituted acrylonitrile **3aa** was observed in 73% GC



Scheme 1. Synthesis of difluoroacyl-substituted nitriles catalyzed by copper.





[a] Reaction conditions: **1a** (0.2 mmol, 1.0 equiv), **2a** (0.3 mmol, 1.5 equiv), TMSCN (0.4 mmol, 2.0 equiv), initiator (0.5 mmol, 2.5 equiv), cat. [Cu] (10 mol%), ligand (20 mol%), solvent (1.0 mL), at 70 °C, 5 h, under N₂. [b] GC yields. [c] LPO (0.4 mmol, 2.0 equiv). [d] LPO (0.6 mmol, 3.0 equiv). [e] Without Cu(CH₃CN)₄PF₆ catalyst. [f] Without L1 ligand. [g] Without LPO initiator.

yield. Unfortunately, the byproduct 4 was also formed from the reaction in a 19% GC yield. Encouraged by this preliminary observation, we attempted to improve the reaction efficiency and to exclude the generation of the byproduct 4 by optimizing the reaction conditions. Among the copper-metal catalysts tested, Cu(CH₃CN)₄PF₆ was found to be the best catalyst (Table 1, entries 2-7), giving the compound 3aa in a raising 83% yield and 4 in only 8% (Table 1, Entry 7). The desired product 3 aa was obtained in lower yields when AIBN or ABVN was used as a radical initiator instead of LPO in the reaction (Table 1, entries 8 and 9). Other solvents such as CH₃CN, DMSO, CH₃COCH₃ and DMF showed inferior results (Table 1, entries 10-13). The yield of 3 aa was decreased when L2-L7 were tested as alternative ligands (Table 1, entries 14-19). Increasing or decreasing the equivalent of LPO did not improve the yield of 3 aa (Table 1, entries 22 and 23). Ultimately, the optimized conditions for the generation of 3aa were determined as 2iodo-2,2-difluoroacetophenone 1 a (1.0 equiv), phenylacetylene **2a** (1.5 equiv) with TMSCN (2.0 equiv) in the presence of $Cu(CH_3CN)_4PF_6$ (10 mol%), L1 (20 mol%), and LPO (2.5 equiv) in MeOH (1.0 mL) at 70 °C for 5 h (Table 1, entry 7). Additional control experiments confirmed that copper-metal catalyst, L1, and LPO were all crucial for this reaction (Table 1, entries 22–24).

With the optimized reaction conditions in hand, we next evaluated the substrate scope of the reaction by employing structurally varied 2-iodo-2,2-difluoroacetophenones. As shown in Table 2, aryl 2-iodo-2,2-difluoroketones bearing electrondonating or -withdrawing groups are all compatible to deliver cyanodifluoroalkylation products (3aa-3ja) in moderate to excellent yields. The substrates containing electron-withdrawing groups give a relatively low yield. Substituent groups were tolerated at the para- and meta- positions of the benzene ring (3ba-3da, 3ha). Unfortunately, the ortho-substituent substrates failed to give the desired products. Furthermore, 2-iodo-2,2-difluoroacetophenones derived from heterocyclic arenes, such as thiophene 1i, reacted smoothly with 2a to afford the compound 3 ia in excellent yield. Pleasingly, we found that the reaction with 1,1-difluoro-1-iodo-4-phenylbutan-2-one 1k and 2a proceeded well to provide 4,4-difluoro-5-oxo-2,7-diphenylhept-2-enenitrile 3ka with a high yield of 81%. When ethyl iododifluoroacetate was used as the substrate, the desired compound 3 la was not achieved, instead, the compound 3 ma was obtained through a transesterification reaction.

Secondly, we examined the reaction scope with respect to the alkyne component by using **1 a** as the fluoroalkyl reagent (Table 3). These alkynes all proceeded efficiently under the optimized reaction conditions to furnish the corresponding products (**3 ab**-**3 ap**) in moderate to good yields with excellent



[a] Reaction conditions: 1 (0.3 mmol, 1.0 equiv), 2a (0.45 mmol, 1.5 equiv), TMSCN (0.6 mmol, 2.0 equiv), LPO (0.75 mmol, 2.5 equiv), $Cu(CH_3CN)_4PF_6$ (10 mol%), L1 (20 mol%), MeOH (1.5 mL), at 70 °C, 5 h, under N₂. [b] Isolated yields.



TMSCN (0.6 mmol, 2.0 equiv), LPO (0.75 mmol, 2.5 equiv), Cu(CH₃CN)₄PF₆ (10 mol%), L1 (20 mol%), MeOH (1.5 mL), at 70 °C, 5 h, under N₂. [b] Isolated yields.

stereoselectivity. The aryl acetylenes bearing electron-withdrawing substituents gave lower yield than those with electrondonating groups, including Me (**3ab**, **3af**), $n-C_2H_5$ (**3ac**), t–Bu (**3ad**), $n-C_5H_{11}$ (**3ae**), OMe (**3ah**), Ph (**3am**) at the para- or meta- position on the phenyl ring. Furthermore, halogencontaining substrates turned out to be operational reactants, yielding the acrylonitrile products (**3ag**, **3aj–3al**) with good efficiency. Interestingly, 2- or 3-ethynylthiophene derivatives (**2n**, **2o**) reacted extremely well to provide corresponding products **3an** and **3ao**, and even, 2-ethynylthiophene afforded 4,4-difluoro-5-oxo-5-phenyl-2-(thiophen-2-yl) pent-2-enenitrile (**3an**) in 79% yield. Notably, the satisfactory yield of the difluoroalkyl-substituted acrylonitrile **3ap** was observed in this case when ethynylcyclohexene was subjected to the threecomponent reaction.

The NOESY experiment was offered to provide the data for the determination of the stereochemistry of compound **3 aa** (See Supporting Information). The spectrum shows that there is no correlation between hydrogen in C=C bond and hydrogen in benzene ring, which means that compound **3 aa** is mainly in *E*-configuration. Furthermore, a second signal appears next to the main product in almost all the ¹⁹F NMR-spectra, which might show that the *Z*-isomer of the desired compound is also obtained. The ratio of the two isomers of the cyanodifluoroalkylated products **3** is showed in table 2 and table 3 according to the ¹⁹F NMR-spectra. A reduction reaction was performed to demonstrate the synthetic utility of the cyanofluoroalkylation products. The reaction between compound **3aa** and DIBAL proceeded smoothly to afford the reduced product **5a** in 52% yield (Scheme 2).

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Several control experiments were designed to interrogate the reaction mechanism. The reaction was completely suppressed when the radical scavenger 2,2,6,6-tetramethyl-1-oxylpiperidine (TEMPO) was added under the standard conditions, which indicates that a radical path might be involved in the process (Scheme 3a). No desired product **3 aa** was detected in the absence of LPO (Scheme 3b). Furthermore, the adduct product **4** was used to react with TMSCN under the standard reaction conditions. However, the cyanodifluoroalkylation product **3 aa** was not obtained, and an almost quantitative yield of **4** was recovered. These results suggested that the possibility of **4** as the reaction intermediate was precluded (Scheme 3c).

On the basis of the control experiments above and previous literature reports,^[12] a plausible reaction mechanism is proposed similar to Bao's report (Scheme 4).^[10] First, LPO reacted with L1Cu(I) catalyst (A) to form an undecyl radical and an L1Cu(II) complex (B), which undergoes a ligand exchange with TMSCN to produce an L1Cu(II)CN species (C). Subsequently, the undecyl radical reacts with 2-iodo-2,2-difluoroacetophenones through a radical relay process to afford a benzoyldifluoroalkyl radical (RCOCF₂·), which immediately attacks an alkyne to generate a vinyl radical intermediate. Finally, the active copper (II) species (C) reacts with the vinyl radical to produce the desired three-component products and the regenerated L1Cu(I) species (A).

In summary, we have reported a Cu(I)-catalyzed threecomponent reaction of 2-iodo-2,2-difluoroacetophenones, al-



Scheme 2. The reaction between compound 3 aa and DIBAL.





Scheme 3. Mechanistic studies.



Scheme 4. Proposed mechanism.

kynes, and TMSCN for the synthesis of difluoroacyl-substituted nitriles, which could be served as important synthons in organic synthesis. The present method offers several advantages including broad fluorinated substrate scope, good yields of products, and excellent stereoselectivity. Preliminary mechanistic investigation indicated that a radical-mediated process was involved in this cyanodifluoroalkylation reaction.

Acknowledgements

We are grateful for financial supports from the National Natural Science Foundation of China (Nos. 21672151 and 21602136).

Conflict of Interest

The authors declare no conflict of interest.

Keywords: Copper • Homogeneous catalysis • Cyanodifluoroalkylation • Difluoroalkylation • Nitriles • Synthetic methods

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Manuscript received: December 22, 2020 Revised manuscript received: January 15, 2021 Accepted manuscript online: January 18, 2021