Copper-Promoted Reductive Cross-Coupling for Cyanodifluoromethylation of (Hetero)aryl Iodides with BrCF$_2$CN

Xin-Jun Yang,[§] Zheng Wang,[§] Qin-Yuan Ni, Jin-Hong Lin,* and Ji-Chang Xiao*

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ABSTRACT: The cyanodifluoromethyl group (−CF$_2$CN) has emerged as a valuable fluorinated motif, with growing recognition for its potential applications in medicinal chemistry and materials science. However, its efficient incorporation into organic compounds remains a synthetic challenge. Herein, we report a copper-promoted reductive cross-coupling protocol for the cyanodifluoromethylation of (hetero)aryl iodides using bromodifluoroacetonitrile (BrCF$_2$CN) as a cost-effective and readily available reagent. This method demonstrates broad substrate compatibility, delivering target products in moderate to good yields under mild and operationally simple conditions. Successful gram-scale synthesis and late-stage functionalization of complex molecules further highlight the utility of the protocol.

Copper-promoted reductive cross-coupling for cyanodifluoromethylation

BrCF$_2$CN + Ar—I → (Cu) → Ar—CF$_2$CN

■ Direct Cyanodifluoromethylation   ■ Broad Scope
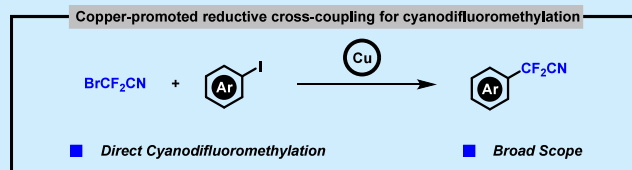
Due to the properties of the fluorine atom, such as high electronegativity and small atomic radius, strategic replacement of a hydrogen atom with fluorine in organic compounds enables effective modulation of molecular properties including molecular conformation, acidity/basicity, and lipophilicity, which has propelled the widespread application of fluorinated organic compounds in pharmaceuticals, agrochemicals, and functional materials.[1−4] Over the past decades, significant progress has been made in incorporating diverse fluorinated groups (e.g., F, CF$_2$H, CF$_3$, OCF$_3$, SCF$_3$, SF$_5$) into molecular frameworks.[5] Despite these advancements, the existing library of fluorinated motifs remains relatively limited to meet the growing demands for structural and functional diversity in life and materials science.[6] The cyanodifluoromethyl group (−CF$_2$CN), an emerging fluorinated group combining a difluoromethylene unit (−CF$_2$−) with a cyano group (−CN), has received increasing research interest.[7−9] The cyanodifluoromethyl group (−CF$_2$CN) shares conceptual similarities with halodifluoromethyl groups (XCF$_2$−, X = Cl, Br, or I) through the pseudohalogen analogy of the cyano moiety. This structural relationship suggests potential parallels in chemical behavior; yet, the unique profile of the CF$_2$CN group may enable distinct functional characteristics. For example, the Hammett constants of the CF$_2$CN group (σ_p = 0.40, σ_m = 0.43), displaying values higher than those of the OCF$_3$ group (σ_p = 0.35, σ_m = 0.38) while remaining slightly lower than the CF$_3$ group (σ_p = 0.54, σ_m = 0.43), exhibit its intermediate electron-withdrawing property.[9,10] After being introduced into molecules as a building block, this modulation could reduce electron density of the adjacent group, thereby enhancing its oxidation resistance and improving metabolic stability. Notably, the −CF$_2$− unit serves as a bioisostere of an oxygen atom[11] or a −C(CH$_3$)$_2$− group,[12] and the CN group mimics hydroxyl, halogen, and carbonyl groups.[13] In addition,

the CN group exhibits remarkable versatility in undergoing diverse chemical transformations. These unique properties enable cyanodifluoromethyl-substituted compounds (R-CF$_2$CN) to not only function as intact molecular architectures but also serve as versatile synthons, offering broad synthetic possibilities for constructing complex molecules.[14,15] Additionally, R-CF$_2$CN compounds have demonstrated significant application potential in various fields such as drug molecule design and liquid crystal material development.[16−18]

Despite its attractive properties, the introduction of a CF$_2$CN group poses significant synthetic challenges. Conventional methods typically involve multistep sequences. For example, the CF$_2$CO$_2$Et group is first introduced into molecules to generate R-CF$_2$CO$_2$Et, which is subsequently converted to R-CF$_2$CN through amination followed by dehydration (Scheme 1A, eq a).[19] And defluorinative cyanation of R-CF$_3$ through selective C−F bond cleavage offers another pathway (Scheme 1A, eq b).[20] However, these methods often suffer from a limited scope of substrates. In addition to the routes of introducing a cyano group into RCF$_2$-containing substrates, alternative routes involve fluorination of CN-containing substrates, including deoxygenative fluorination of R-COCN with DAST (Scheme 1A, eq c),[18] desulfurizing fluorination of benzyl sulfides with IF$_5$ (Scheme 1A, eq d),[21] dehydrogenative fluorination of R-CH$_2$CN with NFSI (Scheme 1A, eq e),[22] or fluorine-chlorine exchange in R-
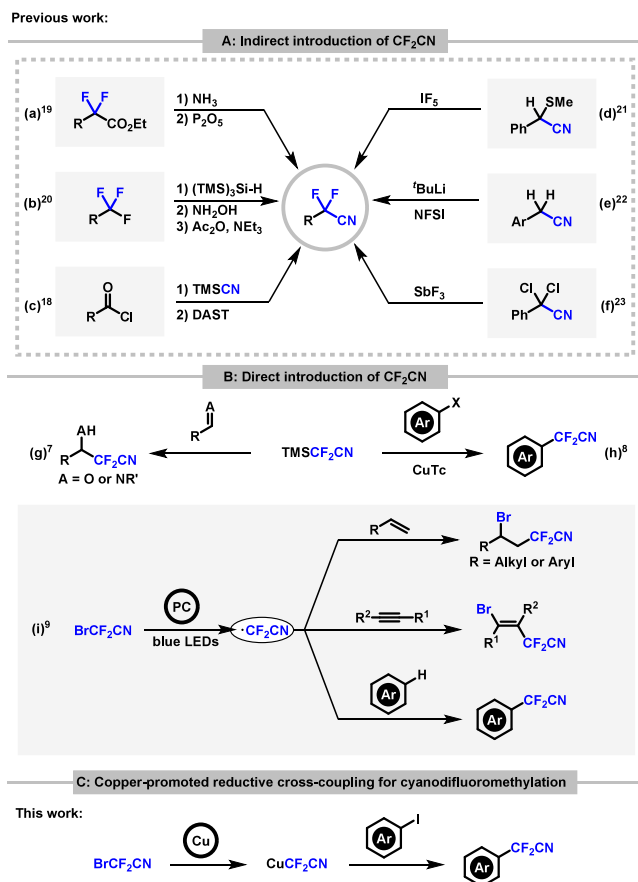
Scheme 1. Introduction of the −CF₂CN Group[a]

[a]A: Indirect introduction of the −CF₂CN group. B: Direct introduction of the −CF₂CN group. C: Our work on copper-promoted reductive cross-coupling for cyanodifluoromethylation.
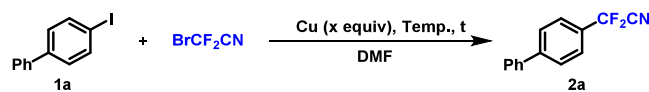
CCl₂CN substrates (Scheme 1A, eq f).[23] Reliance on hazardous fluorinating reagents or difficultly prepared substrates severely limits their practical utility. In contrast to these indirect strategies, direct cyanodifluoromethylation represents a conceptually streamlined alternative. Nevertheless, few reports have successfully investigated this process. In 2012, A. D. Dilman's group developed a cyanodifluoromethylation reagent (TMSCF₂CN), prepared by insertion of difluorocarbene into TMSCN, and reported the groundbreaking nucleophilic cyanodifluoromethylation of aldehydes and imines (Scheme 1B, eq g).[7] In 2017, J. F. Hartwig's group observed that the rate of reductive elimination of cyanodifluoromethyl aryl palladium species was very slow, with a half-life of 845 min, suggesting significant challenges in palladium-catalyzed cyanodifluoromethylation.[24] In 2024, the same group achieved a breakthrough, reporting a pioneering copper-mediated cyanodifluoromethylation of aryl and heteroaryl iodides as well as electron-poor aryl and heteroaryl bromides using TMSCF₂CN (Scheme 1B, eq h).[8]

We have long been interested in the development of efficient fluorinated reagents for incorporating fluorine-containing groups.[25] In 2019, we reported a photocatalyzed cyano-difluoromethylation of alkenes using a Ph₃P⁺CF₂CO₂⁻/NaNH₂(or NH₃) reagent system which enabled the incorporation of HCF₂ and CN groups into molecules. In that work, the HCF₂ and CN groups were introduced separately.[26] We then began to consider how to introduce the CF₂CN group as

a whole. BrCF₂CN can be easily accessible and scaled up to hundreds of grams, making it a promising cyanodifluoromethylation source.[27] Our recent discovery highlights BrCF₂CN as an effective reagent for cyanodifluoromethylation of alkyl alkenes, aryl alkenes, alkynes, and (hetero)arenes under photocatalytic conditions (Scheme 1B, eq i).[9] We found that the C−H cyanodifluoromethylation of electron-poor or electron-neutral arenes had significantly lower yields, likely due to the electrophilic nature of the cyanodifluoromethyl radical. And we found that the activation of BrCF₂CN via copper powder appeared to be feasible to introduce the CF₂CN group into arenes when determining the Hammett constants of the CF₂CN group. Therefore, we hypothesized that the reaction of BrCF₂CN with copper powder might generate a transient cyanodifluoromethyl copper species (CuCF₂CN) to transfer the CF₂CN group. Expanding on this research, we successfully introduce a copper-promoted reductive cross-coupling method in this study, enabling the cyanodifluoromethylation of (hetero)aryl iodides with BrCF₂CN (Scheme 1C). This mild strategy features high efficiency and good functional group tolerance, making it attractive for the late-stage functionalization of structurally complex molecules.

We started our investigation by treating 4-iodobiphenyl (1a) with BrCF₂CN in DMF at room temperature. To our delight, desired product 2a was observed in 25% yield (Table 1, entry

Table 1. Optimization of Reaction Conditions[a]

Entry	x (equiv)	Temp. (°C)	t (h)	Yield (%)[b]
1	1.0	rt	15	25
2	2.5	rt	15	43
3	1.0	40	15	34
4	1.5	40	15	53
5	2.0	40	15	65
6	2.5	40	15	82
7	3.0	40	15	86
8	3.5	40	15	80
9	4.0	40	15	78
10	5.0	40	15	69
11	3.0	40	18	86
12	3.0	40	12	86 (79[c])

[a]Reaction conditions: A mixture of 1a (0.50 mmol, 1.0 equiv), BrCF₂CN (1.25 mmol, 2.5 equiv), Cu (x equiv) and DMF (2.5 mL) was stirred at Temp. (oil bath) for t under a N₂ atmosphere. [b]Yields were determined by ¹⁹F NMR spectroscopy with trifluoromethylbenzene as an internal standard. [c]Isolated yield.

1). Inspired by this result, we next optimized the reaction conditions by screening Cu powder equivalents, reaction temperature, and reaction time. Increasing the loading of Cu powder from 1.0 to 2.5 equiv enhanced the yield of 2a to 43%, albeit with incomplete substrate conversion (entry 2). To accelerate the reaction rate, the reaction temperature was elevated to 40 °C, which significantly promoted the formation of target products (entry 6). Further analysis demonstrated that decreasing the copper equivalents led to a gradual decline in the yield (entries 3−5). Excessive copper loading proved counterproductive, likely due to unproductive side reactions (entries 8−10). Notably, the optimal performance was

achieved with 3.0 equiv of Cu powder, delivering **2a** in 86% ^{19}F NMR yield (entry 7). Prolonging the reaction time has no improvement on the reaction yield (entry 11). Finally, we established the optimized conditions as follows: the reaction mixture with a molar ratio of aryl iodide/BrCF$_2$CN/Cu powder = 1.0:2.5:3.0 was stirred in DMF at 40 °C under a nitrogen atmosphere for 12 h (entry 12).

With the optimized reaction conditions in hand, the substrate scope of the cyanodifluoromethylation reaction was investigated. As shown in Scheme 2, a wide range of

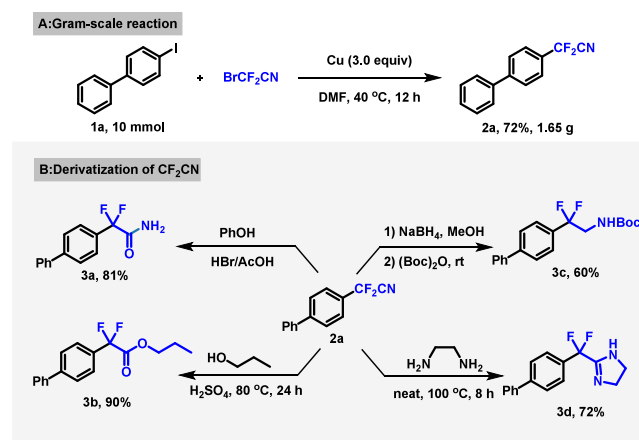## Scheme 2. Scope of Cyanodifluoromethylation of (Hetero)aryl Iodides[a]
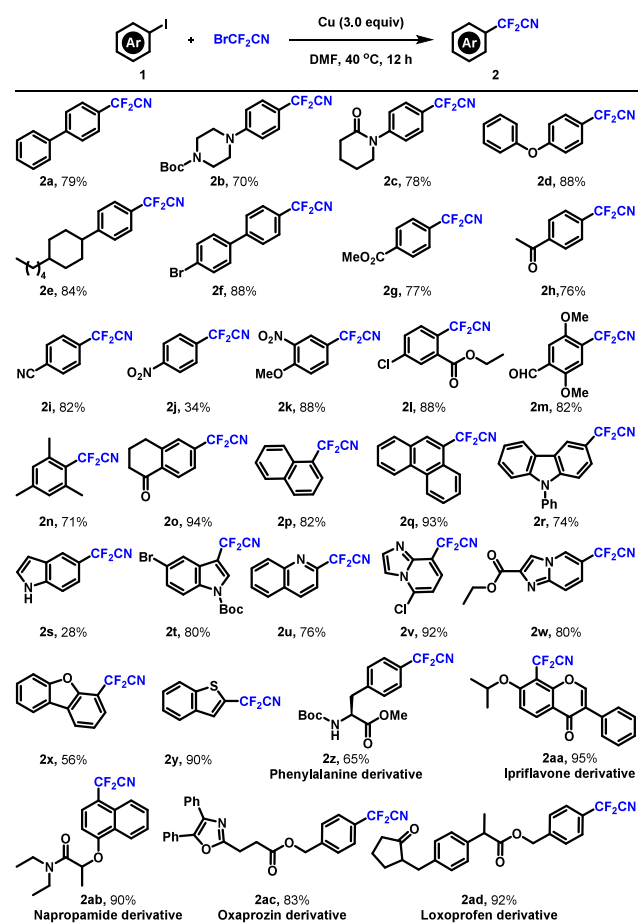
[a]Isolated yields are shown. Reaction conditions: **1** (0.50 mmol, 1.0 equiv), BrCF$_2$CN (1.25 mmol, 2.5 equiv), Cu (1.50 mmol, 3.0 equiv) and DMF (2.5 mL) at 40 °C, 12 h, N$_2$.

(hetero)aryl iodides afforded the desired products in moderate to good yields. (Hetero)aryl iodides bearing significant structural variations in substituents reacted very well, indicating that the electronic effects of substituents on the aromatic ring do not significantly impact the transformation of the target products, which successfully compensated for the substrate range of photocatalytic C−H cyanodifluoromethylation of (hetero)arenes. Simple monosubstituted aryl iodides bearing a broad array of functional groups, including phenyl (**2a**), 4-Boc-piperazinyl (**2b**), 2-oxopiperidinyl (**2c**), phenoxy (**2d**), 4-pentylcyclohexyl (**2e**), 4-bromophenyl (**2f**), ester (**2g**), acetyl (**2h**), and cyano (**2i**), were well compatible under standard conditions. The nitro-substituted substrate (**2j**)

exhibited a low isolated yield in the cyanodifluoromethylation reaction, likely due to the volatility of the product. In addition to monosubstituted substrates, disubstituted (**2k**−**2l**) and trisubstituted (**2m**−**2n**) aryl iodides were also smoothly converted. Notably, 2,4,6-trimethyliodobenzene (**2n**) delivered the target product in 71% yield, indicating that the reaction is minimally influenced by steric effects. Bicyclic aryl iodides bearing a carbonyl group (**2o**) and π-extended naphthyl (**2p**) or phenanthryl iodides (**2q**) also showed good reactivity for this transformation. Importantly, a wide range of heteroaromatic iodides, such as carbazole (**2r**), indole (**2s**−**2t**), quinoline (**2u**), imidazopyridine (**2v**-**2w**), dibenzofuran (**2x**), and benzothiophene (**2y**) motifs, were all suitable substrates, providing the corresponding products in moderate to good yields. Additionally, the synthetic value of the protocol was further underscored by the successful modification of derivatives of various complex molecular structures, including phenylalanine (**2z**), ipriflavone (**2aa**), napropamide (**2ab**), oxaprozin (**2ac**), and loxoprofen (**2ad**).

Subsequently, the scalability of this protocol was successfully demonstrated through a gram-scale experiment. As illustrated in Scheme 3, **1a** and BrCF$_2$CN afforded 1.65 g of the target

Scheme 3. Synthetic Application[a]

[a]A: Gram-scale reaction. B: Derivatization of a cyanodifluoromethylation product.

product in 72% isolated yield. The reaction efficiency remained comparable to that of the small-scale reaction (0.5 mmol, 79%), indicating the robustness and practicality of the current strategy. Finally, the synthetic utility of this method was further validated by diverse transformations of the [CF$_2$CN]-containing product. The acid-catalyzed hydrolysis of the CF$_2$CN group efficiently yielded difluoroacetamide **3a**. Upon treatment with H$_2$SO$_4$, compound **2a** reacted with propanol to afford the difluoroacetate ester **3b** in 90% yield. Notably, the strong electron-withdrawing inductive effect of fluorine atoms enhanced the reactivity of the cyano group, enabling its reduction to difluoroethylamine with NaBH$_4$ under mild conditions. Furthermore, traditionally challenging difluoromethyl-containing imidazoline **3d** was conveniently synthesized in one step. These results clearly show that the CF$_2$CN group could serve as a versatile linchpin for the construction of valuable fluorinated building blocks.

Control experiments showed that the reaction rate of BrCF$_2$CN with copper powder was much faster than that of 4-

iodobiphenyl under the same conditions (see Supporting Information). Based on the above results and previous literature,[8,28−31] a plausible reaction mechanism was proposed as shown in Scheme 4. $BrCF_2CN$ could react with copper

Scheme 4. A Plausible Reaction Mechanism
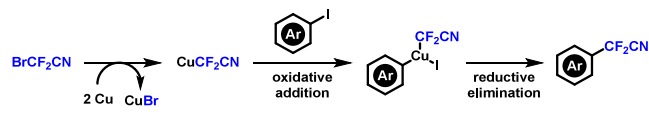
powder to form the $CuCF_2CN$ intermediate. Subsequent oxidative addition of iodoarene (ArI) to the copper(I) species affords the $[Cu(Ar)(CF_2CN)(I)]$ complex, which features aryl, cyanodifluoromethyl, and iodo ligands. This transient organocopper(III) species ultimately undergoes reductive elimination to produce the corresponding cyanodifluoromethylated aromatic compound.

In summary, we have successfully developed a copper-promoted reductive cross-coupling strategy for the cyanodifluoromethylation of (hetero)aryl iodides using $BrCF_2CN$ as an efficient cyanodifluoromethylating reagent. This method exhibits excellent functional group tolerance and accommodates a broad range of substrates in moderate to good yields. Successful application in the late-stage functionalization of structurally complex molecules and gram-scale reaction highlights its potential for practical implementation. The diversified transformations of the resulting cyanodifluoromethylated compounds show that the CF_2CN group could serve as a key synthon to afford various difluoromethylene-containing compounds. Though detailed mechanistic studies are currently underway to elucidate the reaction pathway, we anticipate that this study may stimulate interest in the CF_2CN group.

Methods. A 10 mL Schlenk tube equipped with a magnetic stirring bar was charged with (hetero)aryl iodide (0.5 mmol, 1.0 equiv, if it is a solid) and Cu powder (95.3 mg, 1.5 mmol, 3.0 equiv) under an air atmosphere. The tube was evacuated and refilled with N_2 (three times). The solution of $BrCF_2CN$ in DMF (0.5 mmol/mL, 2.5 mL) and a (hetero)aryl iodide (0.5 mmol, 1.0 equiv, if it is a liquid) were added. (Note: If the (hetero)aryl iodide is a solid, it was first added to the Schlenk tube along with the Cu powder, followed by nitrogen purging, and then, $BrCF_2CN$ was added. And if the (hetero)aryl iodide is a liquid, Cu powder was first added to the Schlenk tube, followed by nitrogen purging, and then $BrCF_2CN$ and the (hetero)aryl iodide were added.) The mixture was stirred at 40 °C for 12 h under a nitrogen atmosphere. The final mixture was diluted with EtOAc or DCM. Then, the mixture was filtered through a Celite pad. The filtrate was washed with brine and then concentrated. The residue was subjected to flash column chromatography using petroleum ether/ethyl acetate as the eluent to afford the desired product.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

ⓢ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.5c02046.

Experimental procedures, characterization data, and NMR spectra. (PDF)

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Author Contributions

§X.-J.Y., J.-H.L. and J.-C.X. designed the experiments. X.-J.Y., Z.W., and Q.-Y.N. performed the experiments. X.-J.Y., Z.W., J.-H.L. and J.-C.X. analyzed the data and wrote the manuscript. X.-J.Y. and Z.W. contributed equally. J.-C.X. directed the project. All authors reviewed and edited the manuscript.

Notes

The authors declare no competing financial interest.

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