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Copper-Mediated Cyanodifluoromethylation of (Hetero)aryl Iodides and Activated (Hetero)aryl Bromides with $TMSCF_2CN$

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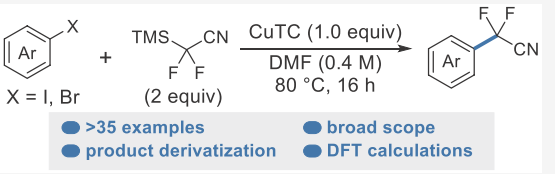
ABSTRACT: Molecules bearing fluorine are increasingly prevalent in pharmaceuticals, agrochemicals, and functional materials. The cyanodifluoromethyl group is unique because its size is closer than that of any other substituted difluoromethyl group to the size of the trifluoromethyl group, but its electronic properties are distinct from those of the trifluoromethyl group. In addition, the presence of the cyano group provides synthetic entry to a wide range of substituted difluoromethyl groups. However, the synthesis of cyanodifluoromethyl compounds requires multiple steps, highly reactive reagents (such as DAST, NSFI, or IF_5), or specialized starting materials (such as α,α-dichloroacetonitriles or α-mercaptoacetonitriles). Herein, we report a copper-mediated cyanodifluoromethylation of aryl and heteroaryl iodides and activated aryl and heteroaryl bromides with $TMSCF_2CN$. This cyanodifluoromethylation tolerates an array of functional groups, is applicable to late-stage functionalization of complex molecules, yields analogues of FDA-approved pharmaceuticals and fine chemicals, and enables the synthesis of a range of complex molecules bearing a difluoromethylene unit by transformations of the electron-poor CN unit. Calculations of selected steps of the reaction mechanism by Density Functional Theory indicate that the barriers for both the oxidative addition of iodobenzene to $[(DMF)CuCF_2CN]$ and the reductive elimination of the fluoroalkyl product from the fluoroalkyl copper intermediate lie in between those of $[(DMF)CuCF_3]$ and $[(DMF)CuCF_2C(O)NMe_2]$.



1. INTRODUCTION

Molecules containing alkyl or aryl fluorides are widespread in materials chemistry and are increasingly prevalent in approved pharmaceuticals[1] and agrochemicals,[2] constituting 20 and 50% of the market, respectively. Fluorine is prevalent because substitution of hydrogen atoms with fluorine can favorably impact the pK_a, lipophilicity, molecular conformation, and metabolic stability of the parent compound.[3] To exert these effects, either an aryl fluoride or an aryltrifluoromethyl group is often installed,[1,4] in large part due to the commercial availability and synthetic accessibility of fluoro- and trifluoromethylarenes.[5−10] Other fluorinated groups, such as mono- and difluoromethyl groups, have beneficial properties,[3] but they are typically used less frequently because they are more difficult to introduce.

One such group is the cyanodifluoromethyl group. A comparison of the modified Swain−Lupton field parameter of a cyano group to that of a fluorine atom (F_{CN} = 0.51, F_F = 0.45)[11] suggests that the cyanodifluoromethyl group is more electron withdrawing than a trifluoromethyl group, and this electron-withdrawing property would deactivate an adjacent aryl group toward oxidative metabolism. The nitrile also provides opportunities for polar and hydrogen-bonding interactions with target substrates and serves as a bioisostere for carbonyl groups, hydroxyl groups, and other hydrogen-bond acceptors.[2,12] Arylacetonitriles are resistant to oxidation when the α-position lacks C−H bonds,[12] and the cyano group in these compounds typically undergoes hydrolysis, rather than releasing cyanide.[13,14] In addition to modulating the electronic properties of the adjacent nitrile and the electrophilicity of the nitrile carbon, the *gem*-difluoromethylene unit itself is commonly invoked as a bioisostere of a carbonyl group, of ether oxygens, or of thioether sulfur atoms.

As a result of these properties, aryl-α,α-difluoroacetonitriles have garnered interest as herbicides,[15,16] pharmaceutical ingredients,[17−20] and liquid crystals (Figure 1a);[21] however, the investigation of aryl-α,α-difluoroacetonitriles has been limited because the cyanodifluoromethyl group is difficult to install. The most common route to cyanodifluoromethylarenes is a multistep sequence beginning with copper-mediated reductive coupling of an aryl iodide with a bromodifluoroester or with deoxofluorination of an aryl 2-oxoacetate to form an aryl-α,α-difluoroester (Figure 1b, i-ii). Subsequent addition of ammonia and dehydration of the resulting amide affords the aryl-α,α-difluoroacetonitrile.[22,23] These syntheses generally

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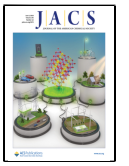

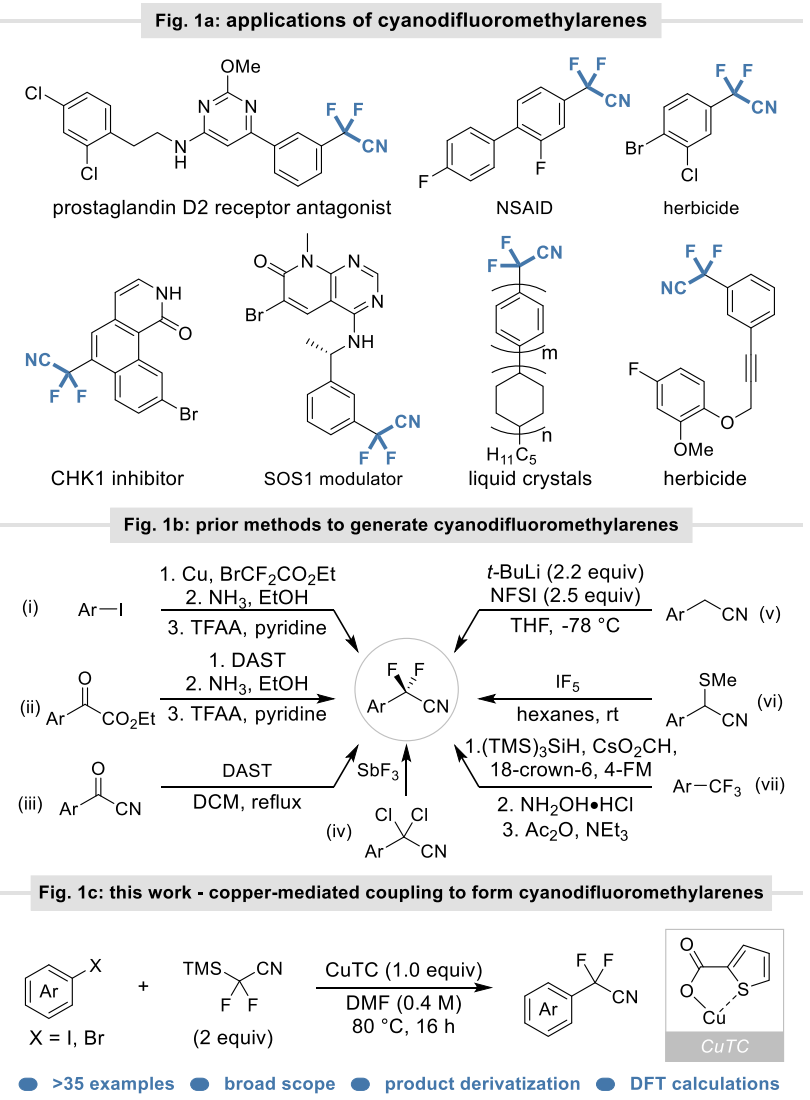

Figure 1. (a) Applications of cyanodifluoromethylarenes, (b) prior methods to generate cyanodifluoromethylarenes, and (c) this work: copper-mediated coupling to form cyanodifluoromethylarenes. TFAA = trifluoroacetic acid; 4-FM = 4-formylmorpholine.

occur in low overall yields and require de novo construction of each cyanodifluoromethylarene. Introduction of the [$-CF_2CN$] group by alternative routes involving the formation of a C−F bond requires harsh conditions and highly reactive or toxic reagents, such as *N*,*N*-diethyl-1,1,1-trifluoro-λ^4-sulfanamine (DAST),[21] SbF_3,[24] *N*-fluorobenzenesulfonamide,[25] or IF_5 (Figure 1b, iii-vi).[26] The functional group tolerance of such C−F bond-forming reactions, therefore, is limited, and these methods are not typically amenable to rapid diversification of the aryl substituent. Recently, Wright and Bandar reported a base-promoted reductive coupling platform for the defluorofunctionalization of trifluoromethylarenes (Figure 1b, vii),[27] but this methodology, again, requires multiple steps to access the corresponding aryldifluoroacetonitrile.

Copper-mediated and copper-catalyzed fluoroalkylation reactions have been developed for the synthesis of trifluoromethylarenes,[28−33] aryldifluoromethylesters,[34,35] and aryldifluoromethylamides.[36] We sought to develop a coupling of aryl halides with a nucleophilic form of the cyanodifluoromethyl group to address the lack of suitable methods to synthesize aryl-α,α-difluoroacetonitriles rapidly, with broad scope, and in a fashion applicable to compounds of potential biological interest.

We report the copper-mediated coupling of aryl and heteroaryl iodides and electron-poor bromides with 2,2-difluoro-2-(trimethylsilyl)acetonitrile ($TMSCF_2CN$, **1**). This method (Figure 1c) delivers a diverse range of cyanodifluoromethylarenes in high yields with a simple, commercially available, inexpensive copper compound. The reaction tolerates a wide range of functional groups, making it suitable for the synthesis of complex, drug-like molecules, and density functional theory (DFT) calculations show that the barriers to oxidative addition and reductive elimination involving cyanodifluoromethyl copper complexes are lower in energy than those to oxidative addition and reductive elimination involving analogous trifluoromethylcopper complexes.

2. RESULTS AND DISCUSSION

2.1. Development of Reaction Conditions for the Coupling of Aryl Iodides with $TMSCF_2CN$. Copper-mediated and copper-catalyzed fluoroalkylation reactions often require transmetalation of the fluoroalkyl group from a main group element to copper, and the rate of such

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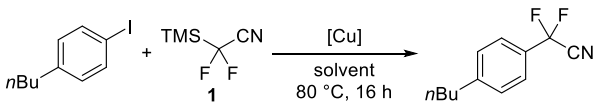
transmetalation depends on the LX-type ligand on copper. We envisioned that a silicon-based reagent[37] containing the desired fluoroalkyl group,[38] TMS-CF_2CN (**1**), could transfer the cyanodifluoromethyl group to a copper compound containing the proper X-type ligand that would be replaced by the CF_2CN unit. The resulting fluoroalkyl copper species could then undergo oxidative addition of an aryl halide, followed by reductive elimination to deliver the desired product, but the effect of the nitrile in a fluoroalkyl group on these two steps is unknown. To investigate the potential of this scenario, we conducted a set of experiments with 1-*n*-butyl-4-iodobenzene, a series of Cu(I) complexes, and $TMSCF_2CN$ (Table 1).

Table 1. Evaluation of Conditions for the Copper-Mediated Coupling of Aryl Iodides and $TMSCF_2CN$ (1)



entry	[Cu] (equiv)	equiv **1**	solvent (M)	yield (%)[a]
1	CuI (2.0)	5.0	DMSO (0.2)	16
2	CuDPP (2.0)	5.0	DMSO (0.2)	84
3	CuDPP (2.0)	5.0	DME (0.2)	91
4	CuDPP (1.0)	5.0	DME (0.2)	73
5	CuDPP (1.0)	2.0	DME (0.2)	76
6	CuDPP (1.0)	2.0	NMP (0.2)	96
7	CuDPP (1.0)	2.0	DMF (0.2)	96
8	CuDPP (1.0)	2.0	DMF (0.4)	99
9	CuDPP (0.5)	2.0	DMF (0.4)	48
10[b]	CuDPP (1.0)	2.0	DMF (0.4)	99
11	CuTC (1.0)	2.0	DMF (0.4)	99

[a]Determined by ^{19}F NMR spectroscopy with α,α,α-trifluorotoluene as an internal standard. [b]Reaction time = 1 h. See Supporting Information for additional details.

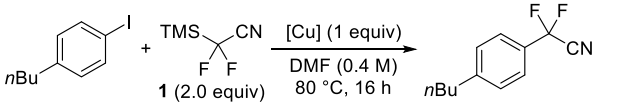
After evaluating a variety of Cu(I) reagents, we found that Cu(I) diphenylphosphinate (CuDPP) mediated the cyanodifluoromethylation with excess **1** in DMSO and DME (entries 2−3). The reactions in DMF as solvent occurred with one, rather than two, equiv of copper and with just 2 equiv of **1** (entry 8). Reactions with 0.5 equiv of Cu occurred in only 48% yield (entry 9). Ultimately, we found that the inexpensive Cu(I) thiophenecarboxylate (CuTC) complex mediated the reaction in DMF in high yield (entry 11). Reactions conducted with added ligands, such as 1,10-phenanthroline or bipyridine, that are common in copper-mediated transformations and reactions conducted with oxalamide- or oxalylhydrazide-bound copper species resulted in lower yields than those without added ligands in all cases (see Table S2 in the Supporting Information).

We hypothesize that $TMSCF_2CN$ undergoes transmetalation to copper by a cyclic transition state involving the carboxylate group of the thiophenecarboxylate ligand. No decomposition of **1** in the presence of the reaction partners and solvent in the absence of CuTC is observed. In principle, the reaction could be rendered catalytic by addition of NaTC or NaDPP to regenerate CuTC or CuDPP from the presumed CuI or CuBr product. However, NaDPP, NaTC, and other exogeneous activators of organosilanes, such as KF or CsF, lead to decomposition of silane **1** over the course of the reaction at 80 °C (see Tables S3 and S4 in the Supporting Information for these data).

CuTC is less expensive than CuDPP, and reactions conducted with CuTC generally delivered the products in similar yields to those of reactions conducted with CuDPP (see Figure S3 in the Supporting Information). When compared to the cost of common catalysts used in fluoroalkylation reactions such as (BrettPhos)Pd-G3,[39] at the appropriate stoichiometry, the cost of CuTC is among the lowest available ($0.25/mmol; see Table S5).

Although our studies were conducted in a nitrogen-filled glovebox, the reaction also proceeded smoothly when using Schlenk techniques or when assembling under air and flushing the reaction vessel with nitrogen before heating (Table 2, entries 3 and 4). The reaction proceeded at room temperature, albeit at a slower rate (entries 5−6), so further reactions were conducted at 80 °C to increase the rate of the cyanodifluoromethylation reaction.

Table 2. Yield of the Cyanodifluoromethylation Reaction under Various Conditions[a]



entry	conditions	yield w/CuTC (%)	yield w/CuDPP (%)
1	standard conditions	99	99
2	under air	25	45
3	Schlenk technique	99	93
4	under air + N_2 purge	91	36
5	rt, 48 h	99	99
6	rt, 1 equiv **1**, 48 h	96	99

[a]Determined using ^{19}F NMR spectroscopy with α,α,α-trifluorotoluene as an internal standard.

The $TMSCF_2CN$ nucleophile **1** was synthesized on decagram-scale batches at Berkeley and was stable on the benchtop for over six months. This reagent is currently available in small-scale batches from Enamine while a process-scale synthesis is being developed.

2.2. Scope of the Cyanodifluoromethylation Reaction. Having established conditions that deliver coupled product in high yield, we explored the scope of the copper-mediated cyanodifluoromethylation with an array of aryl and heteroaryl iodides and bromides (Chart 1). Products of the cyanodifluoromethylation reaction with low molecular weights were often too volatile to isolate in yields approaching those of the crude material. These products were converted in a one-pot procedure, as shown at the top of Chart 1, to more tractable derivatives for purification. Some products underwent decomposition to some degree upon purification by flash column chromatography, although this decomposition did not prevent isolation of pure material. A wide range of aryl iodides, including electron-poor (**3a**−**e**), electron-neutral (**3f**−**g**), and electron-rich arenes (**3h**−**i**) reacted under the developed conditions. Those containing common functional groups, including bromides and chlorides (**3a**−**b**, **3j**), esters (**3c**), nitro groups (**3d**), and carbamates (**3i**) reacted in high yield. An aryl iodides bearing an ortho-isopropyl (**3k**) substituent reacted, as did those with 2,6-dichloro (**3l**) and 2-methyl-6-ethyl (**3m**) groups. Meta-substituted iodoarenes (**3n**−**p**) also reacted, as did heterocycles, such as dibenzofuran (**3s**), pyridine (**3t**), and bipyrazole (**3u**). The yield of product **3r** on a 1 g scale was similar to the yield of **3r** on a 0.1 mmol scale,

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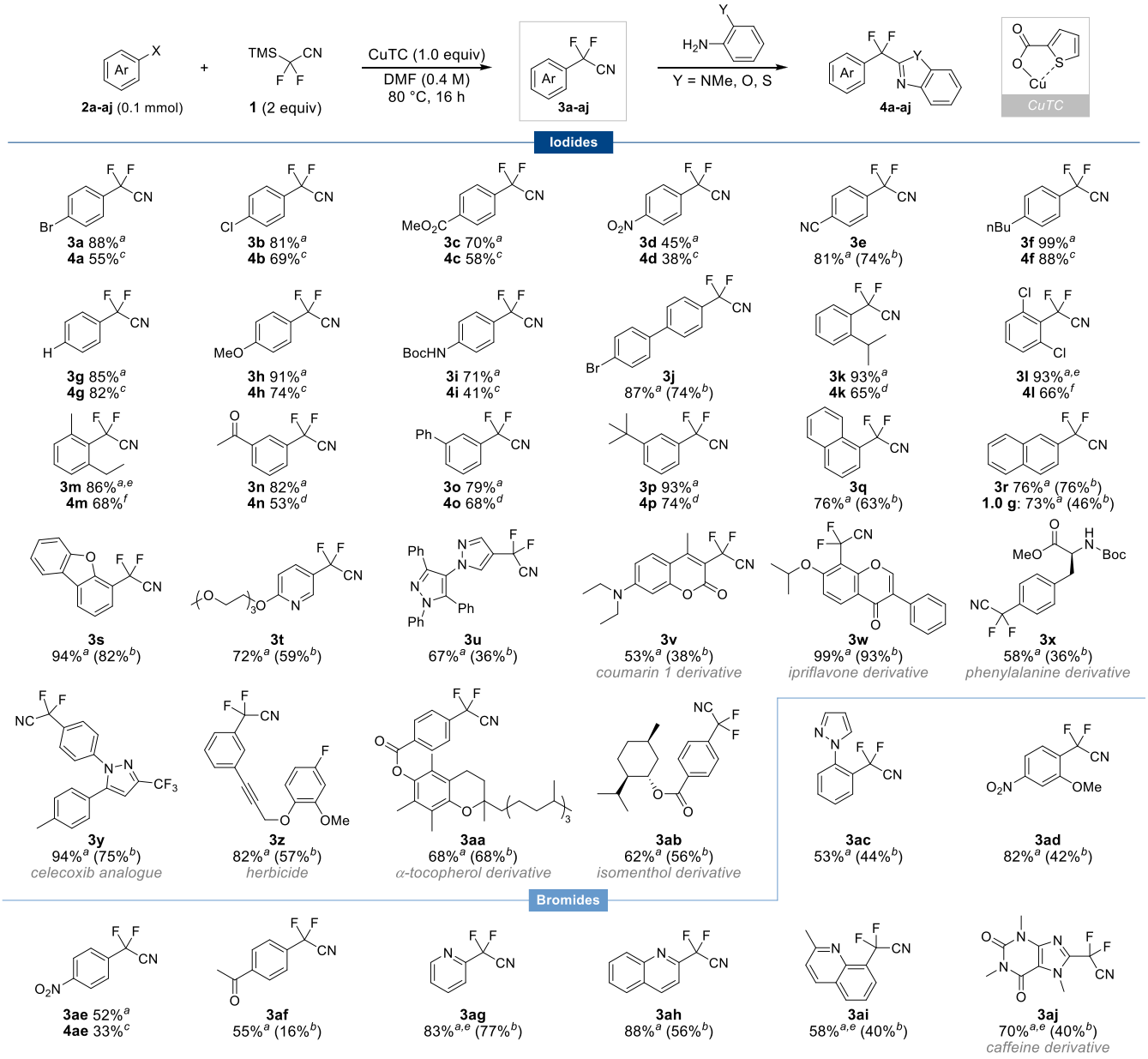
Chart 1. Scope of (Hetero)aryl Iodides and Activated (Hetero)aryl Bromides That Undergo the Cyanodifluoromethylation Reaction with $TMSCF_2CN$ (1).[a]



[a]Reaction conducted with 0.1 mmol (hetero)aryl halide; [a]yield of the cyanodifluoromethylarene determined by ^{19}F NMR spectroscopy with α,α,α-trifluorotoluene as an internal standard; [b]isolated yields of the cyanodifluoromethylarene; [c]isolated yield of the benzimidazole (Y = NMe); [d]isolated yield of the benzoxazole (Y = O); [e]one equiv of CuDPP used instead of CuTC; [f]isolated yield of the benzothiazole (Y = S).

although the product did decay by hydrolysis of the nitrile to a greater extent during chromatographic purification on a large scale than on a small scale.

The applicability of this method to the late-stage diversification of more structurally complex molecules was assessed. Derivatives of the laser dye coumarin 1 (**3v**), ipriflavone (**3w**), phenylalanine (**3x**), and an analogue of the NSAID celecoxib (**3y**) all formed in good to high yield from the corresponding iodide. An herbicide bearing an alkyne (**3z**) and derivatives of vitamin E (**3aa**) and isomenthol (**3ab**) were also produced using this reaction.

Bromides of electron-poor arenes and of heteroarenes also underwent cyanodifluoromethylation. An aryl bromide with an *ortho*-pyrazole group (**3ac**) and aryl bromides bearing electron-withdrawing groups (**3ad-af**) reacted in good yields. 2-Bromopyridines (**3ag**) and quinolines bearing a bromide proximal to nitrogen (**3ah-ai**) reacted. Biologically active heteroaryl bromides were also suitable for this transformation; an analogue of caffeine (**3ao**) was synthesized using this method. The yields of products from additional (hetero)aryl halides that were not isolated and those that did not react, as determined by ^{19}F NMR spectroscopy, are provided in the Supporting Information.

2.3. Functionalization of the Coupled Products. Because examples of aryl-α,α-difluoroacetonitriles are rare, we sought to explore the reactivity of the cyanodifluoromethyl group. The aryl-α,α-difluoroacetonitrile products undergo a wide range of reactions and enable the synthesis of molecules

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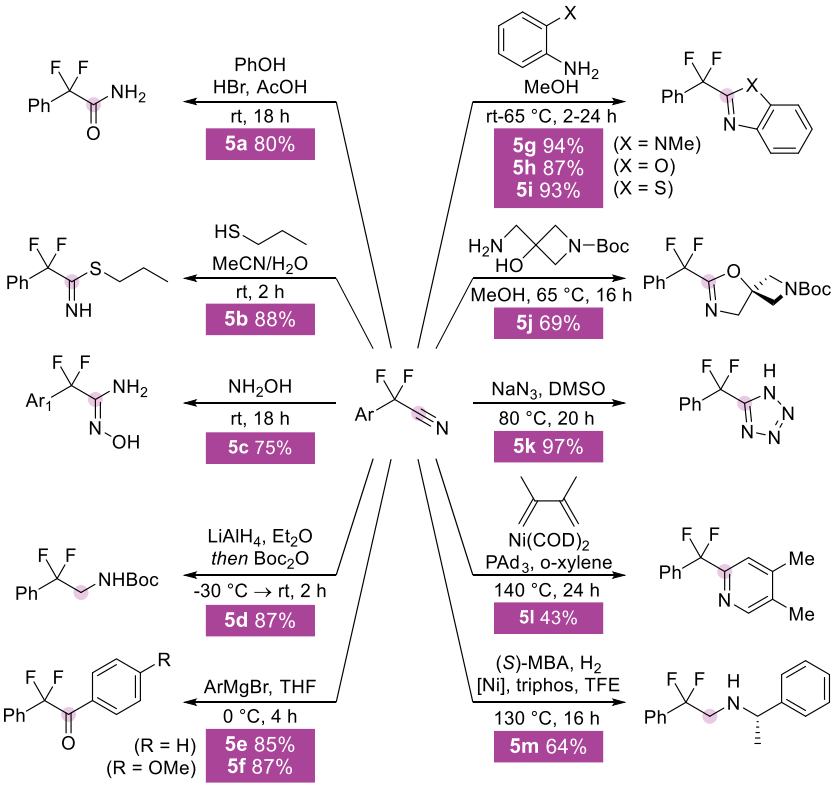
Chart 2. Functionalization Reactions of Aryl-α,α-difluoroacetonitriles.[a]



[a]See Supporting Information for detailed reaction conditions. Ar_1 = 4-*n*BuC_6H_4.

containing a benzylic difluoromethylene unit (Chart 2). Several of these reactions highlight the enhanced electrophilicity of the nitrile imparted by the vicinal fluorine atoms.

The nitrile carbon reacts with a range of nucleophiles. Acid-catalyzed addition of water gave α,α-difluoroamide **5a** in 80% yield. The addition of propylthiol and hydroxylamine formed imidothioate **5b** and hydroxyformamide **5c**. Hydroxyformamides, such as **5c**, can be used to synthesize α,α-difluoro oxadiazoles[40] and other heterocycles. Reduction and protection of the cyanodifluoromethylarene afforded β,β-difluoroamide **5d** in 60% yield. Like the addition of hydrides, the addition of organomagnesium reagents formed aryl-α,α-difluoromethyl ketones **5e–f** in high yields. While one might be concerned about the abstraction of fluoride by electrophilic metals, this was not observed.

Condensations of ortho-substituted anilines also occurred to form benzimidazole **5g**, benzoxazole **5h**, and benzothiazole **5i**. Molecules containing the benzylic benzimidazole motif have been investigated as LRRK2 inhibitors[41] and as potent analgesics,[42] and this route provides access to difluorinated analogues of these compounds. Current methods to form such aryl-α,α-difluoroheterocycles require the use of a preformed heteroaryl-CF_2Br coupling partner, limiting opportunities for rapid diversification.[43] The novel α,α-difluorinated [3.4]-spirocycle **5j** also formed by the addition of a β-amino alcohol. We have demonstrated that these cycloaddition reactions can be conducted without isolation of the intermediate aryldifluoroacetonitrile (see Supporting Information).

The aryl cyanodifluoromethyl compounds also underwent cycloaddition and hydrogenative coupling reactions. Sodium azide reacted cleanly with the cyano group to give α,α-difluorinated tetrazole **5k**, which belongs to a class of compounds that has been investigated as URAT1 inhibitors.[44] A nickel-catalyzed dehydrogenative [4 + 2] reaction generated aryl-α,α-difluoropyridine **5l** in moderate yield when using PAd_3 as ligand.[45] Finally, a nickel-catalyzed hydrogenative C–N coupling with (*S*)-methylbenzylamine provided β,β-difluorinated secondary amine **5m**.[46] Thus, the elaboration of cyanodifluoromethylarenes prepared by our coupling reaction enables the construction of a wide range of structurally diverse α,α-difluoromethylarenes from aryl or heteroaryl halides, $TMSCF_2CN$, and additional components that are commonly available.

To assess the differences in reactivity imparted by the fluorine atoms, we conducted a selection of control reactions with benzyl nitrile under analogous conditions (see Supporting Information for details). After 30 min, the fluorinated amide **5a** formed in 70% yield, while the hydrolysis of benzyl nitrile converted only 34% of the nitrile to the amide. The addition of thiols or hydroxylamines to arylacetonitriles typically requires forcing conditions[47] or an acid catalyst,[48] and no product was observed from reactions of benzyl nitrile with these two reagents under conditions for reactions of **5b** and **5c**. The reduction of arylacetonitriles lacking fluorine substitution at the benzylic position also often requires high temperatures or catalysts to proceed; the addition of LAH to benzyl nitrile under analogous conditions for **5d** formed no reduced product.[49,50] Cyclization reactions to form products analogous to benzothiazole **5i** without fluorine atoms did not proceed under analogous conditions, even with the addition of $AlCl_3$ as Lewis acid.[51−53] We ascribe the demonstrated difference in reactivity between aryldifluoroacetonitriles and arylacetonitriles to the inductive effect of the fluorine atoms adjacent to the nitrile carbon.

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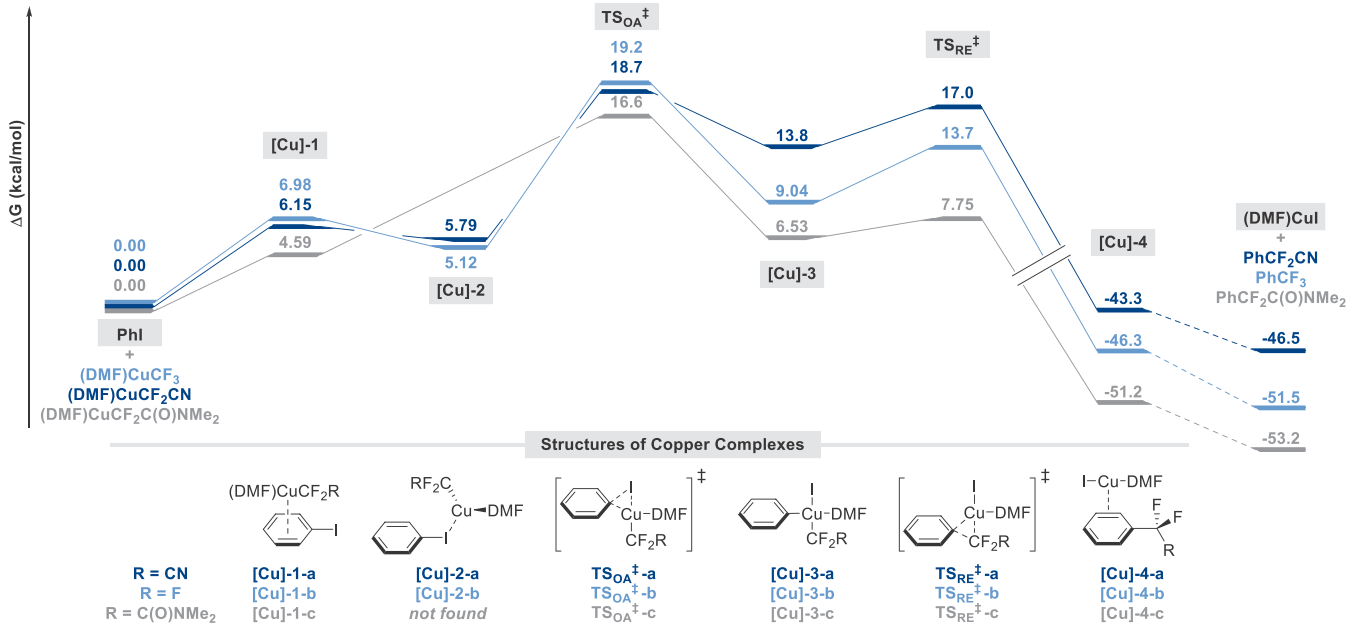

Figure 2. Computed free energy diagram for the reaction of PhI with [(DMF)CuCF$_2$R], in which R = CN, F, and C(O)NMe$_2$. Gibbs free energies calculated at the def2-TZVP level of theory for Cu and I with accompanying ECP; all other atoms were treated at the def2-SVPD level. Solvent = DMF, temperature = rt. Empirical dispersion is considered. See Supporting Information for additional details.

2.4. Analysis of the Cyanodifluoromethylation Reaction by DFT Calculations. Having developed a method for the widely applicable conversion of aryl and heteroaryl iodides and bromides to cyanodifluoromethylarenes, we conducted calculations with DFT to gain information on the barriers for reaction of aryl halides with the difluorocyanomethyl copper complex, relative to those for related fluoroalkyl copper complexes. To do so, we computed the barriers to oxidative addition of PhI to the [(DMF)CuCF$_2$R] intermediate and reductive elimination from the resulting [(DMF)Cu(Ph)(I)-CF$_2$R] complex.[54,55] Unless otherwise noted, the energies we report are Gibbs free energies in kcal/mol for reactions computed with a DMF solvent continuum (see Supporting Information for complete computational details).

The combined energy of [(DMF)CuCF$_2$R] and PhI was set to zero, and the copper complexes containing two DMF ligands, [(DMF)$_2$CuCF$_2$R], were computed to be higher in energy than the complexes [(DMF)CuCF$_2$R] by 7.34, 7.00, and 11.8 kcal/mol for R = CN, F, and C(O)NMe$_2$, respectively. Computational[47] and experimental[55,56] studies of copper-mediated trifluoromethylation reactions imply that [(S)Cu(nucleophile)] (S = DMSO, DMF) complexes oxidatively add iodoarenes more rapidly than do [(L)Cu-(nucleophile)]$^{n-}$ (L = phen, n = 0; L = halide, nucleophile, n = 1) complexes. We calculated the pathways in which one DMF remains bound to the copper because the computed free energies for oxidative additions occurring to [(DMF)CuCF$_3$] reported by Grushin and co-workers were lower than those for the combination of dissociation of DMF from [(DMF)$_2$CuCF$_3$] and oxidative addition.[54] The mechanism in which one DMF remains bound to Cu has been shown to reproduce the results of Hammett studies accurately and to capture the effects of ortho-substitution on reaction rate.

Figure 2 shows the computed reaction coordinates for the reaction of PhI with [(DMF)CuCF$_2$R], in which R = CN, F, and C(O)NMe$_2$. Complexes [**Cu**]-**1a**–**c** containing the cyanodifluoromethyl, trifluoromethyl, and difluoro amide enolate groups are formed by coordination of the arene π system to the copper species prior to oxidative addition. The cyanodifluoromethyl- and trifluoromethylcopper species were computed to form a Lewis acid–base pair with the iodine atom of PhI ([**Cu**]-**2a** and [**Cu**]-**2b**), while no complex between PhI and the copper difluoroamide enolate was located along the pathway to oxidative addition. The barriers for the step that cleaves the C–I bond in iodobenzene were computed to be 12.9, 14.1, and 12.0 kcal/mol for R = CN, F, and C(O)NMe$_2$, respectively, while the overall barriers for reaction of PhI with the [(DMF)CuCF$_2$R] complexes were computed to be 18.7, 19.2, and 16.6 kcal/mol, respectively.

Due to the lower endothermicity of the oxidative addition of PhI to the cyanodifluoromethyl copper complex than to the trifluoromethyl copper complex, the transition state for the cyanodifluoromethylation should be earlier than that for the analogous trifluoromethylation reaction. This hypothesis is supported by our calculations: the Cu–C$_{ipso}$ distance in **TS$_{OA}$‡-a** for oxidative addition of PhI to the difluorocyanomethyl copper complex is longer (2.08 vs 2.05 Å), and the Ph–I bond is shorter (2.31 vs 2.34 Å) than those in transition state **TS$_{OA}$‡-b** for oxidative addition of PhI to the trifluoromethyl copper complex.

The arylcopper complexes [**Cu**]-**3-a**–**c** formed by oxidative addition all adopt a distorted square-planar geometry. Complex [**Cu**]-**3-a** is more destabilized, relative to the starting materials, than are complexes [**Cu**]-**3-b** and [**Cu**]-**3-c**. The difference in energy between transition state **TS$_{RE}$‡-a** and complex [**Cu**]-**3-a** is smaller than the difference in energy between transition state **TS$_{RE}$‡-b** and complex [**Cu**]-**3-b**. The calculated energy differences indicate that reductive elimination to form the cyanodifluoromethylarene product occurs with a lower barrier than the formation of the analogous trifluoromethylarene product.

The reductive eliminations from copper complexes [**Cu**]-**3-a**–**c** proceed through transition states **TS$_{RE}$‡-a**–**c** to form the fluoroalkylarene complexes [**Cu**]-**4-a**–**c** with barriers of just

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3.2, 4.7, and 1.2 kcal/mol, respectively. Oxidative addition is computed to be rate-determining because the differences in energies between $\mathbf{TS_{RE}}^{‡}$-**a**−**c** and [**Cu**]-**3**-**a**−**c**, respectively, are smaller than the differences between $\mathbf{TS_{OA}}^{‡}$-**a**−**c** and [**Cu**]-**3**-**a**−**c** for each of the fluoroalkyl groups investigated. Our group has previously identified by computation[57] a stabilizing interaction between the palladium center and the nitrile CN bond during reductive elimination from a phosphine-ligated fluoroalkyl−arylpalladium complex; however, we did not identify an analogous stabilizing interaction between the copper center and the nitrile CN bond in [**Cu**]-**3**-**a**−**c** using an independent gradient model based on Hirschfield partitions (IGMH analysis).[58]

3. SUMMARY

We have developed a copper-mediated cyanodifluoromethylation of aryl and heteroaryl iodides and electron-poor aryl and heteroaryl bromides with $TMSCF_2CN$ that occurs with inexpensive, commercially available CuTC, with broad functional group compatibility, and without the need for exogenous ligand. We demonstrate that this method can be applied to the late-stage functionalization of complex molecules, and we show that the cyanodifluoromethyl group is a versatile synthon to generate a diverse range of products containing an aryl-α,α-difluoromethylene unit. DFT calculations suggest that the barriers to both oxidative addition and reductive elimination are lower for the copper-mediated cyanodifluoromethylation than for the copper-mediated trifluoromethylation with the same DMF-ligated copper center, and that oxidative addition is rate-limiting.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.4c03618.

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

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Notes

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■ ABBREVIATIONS

CuTC, copper(I) thiophenecarboxylate; CuDPP, copper(I) diphenylphosphinate; TFAA, trifluoroacetic acid; 4-FM, 4-formylmorpholine; DFT, density functional theory

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