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Trifluoromethylation of Aryl and Heteroaryl Halides with Fluoroform-Derived $CuCF_3$: Scope, Limitations, and Mechanistic Features

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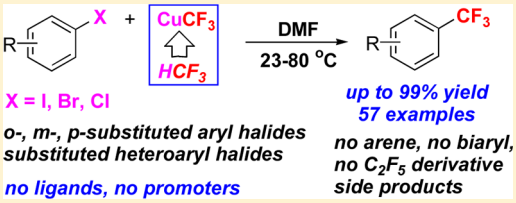
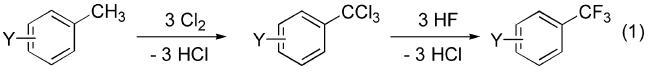
Supporting Information

ABSTRACT: Fluoroform-derived $CuCF_3$ recently discovered in our group exhibits remarkably high reactivity toward aryl and heteroaryl halides, performing best in the absence of extra ligands. A broad variety of iodoarenes undergo smooth trifluoromethylation with the "ligandless" $CuCF_3$ at 23−50 °C to give the corresponding benzotrifluorides in nearly quantitative yield. A number of much less reactive aromatic bromides also have been trifluoromethylated, including pyridine, pyrimidine, pyrazine, and thiazole derivatives as well as aryl bromides bearing electron-withdrawing groups and/or ortho substituents. Only the most electrophilic chloroarenes can be trifluoromethylated, e.g., 2-chloronicotinic acid. Exceptionally high chemoselectivity of the reactions (no side-formation of arenes, biaryls, and C_2F_5 derivatives) has allowed for the isolation of a large number of trifluoromethylated products in high yield on a gram scale (up to 20 mmol). The $CuCF_3$ reagent is destabilized by CuX coproduced in the reaction, the magnitude of the effect paralleling the Lewis acidity of CuX: CuCl > CuBr > CuI. While S_NAr and $S_{RN}1$ mechanisms are not operational, there is a well-pronounced ortho effect, i.e., the enhanced reactivity of ortho-substituted aryl halides 2-RC_6H_4X toward $CuCF_3$. Intriguingly, this ortho-effect is observed for R = NO_2, COOH, CHO, COOEt, $COCH_3$, OCH_3, and even CH_3, but not for R = CN. The fluoroform-derived $CuCF_3$ reagent and its reactions with haloarenes provide an unmatched combination of reactivity, selectivity, and low cost.



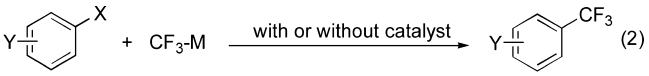
INTRODUCTION

Trifluoromethylated aromatic and heteroaromatic compounds are key building blocks and intermediates in the production of numerous pharmaceuticals, agrochemicals, and specialty materials.[1,2] Aromatic derivatives bearing a CF_3 group are currently manufactured by a two-step process that involves exhaustive radical chlorination of a methyl group on the ring, followed by Swarts-type Cl/F exchange with HF (eq 1).[3] The stoichiometry of this reaction sequence shows that to produce 1 equiv of the desired product, 3 equiv of each Cl_2 and HF are needed and 6 equiv of HCl (chlorine waste) is cogenerated. Being environmentally hazardous, this process also suffers from low functional group tolerance because of the involvement of highly reactive Cl_2, HF, and HCl. Even simple alkyl, alkoxy, acyl, amino, carboalkoxy, etc. groups cannot survive the reaction conditions. The method is also inapplicable to many heteroaromatic substrates.



(1)

An alternative to the two-step process shown in eq 1 would be the selective introduction of the CF_3 group into the desired position on the aromatic or heteroaromatic ring (eq 2). The first example of such a transformation, the reductive coupling of aryl halides with perfluoroalkyl iodides in the presence of Cu metal, was reported by McLoughlin and Thrower[4] in the 1960s. Since then, the area has progressed considerably, largely by the work of the groups of Kumadaki,[5] Yagupolskii,[6] Kondo,[7] Burton,[8] Chen,[9] Fuchikami,[10] and others.[2,11,12] The most notable recent developments include the first aromatic C−CF_3 bond formation at Pd,[13] the synthesis of well-defined Cu(I) trifluoromethylating reagents,[14] the first catalytic trifluoromethylation reactions of haloarenes using Cu[15] and Pd[16] complexes, and oxidative trifluoromethylation of aryl boronic acids and boronates.[17]



(2)

In spite of the substantial progress in the area, there have been no reports on a potentially industrially viable method that could replace the currently used technology (eq 1). A key reason for this is the high cost of the CF_3 reagents (primarily CF_3SiMe_3 and CF_3SiEt_3) and ligands employed in the Ar−CF_3 coupling reactions.[2] Much less expensive, easily accessible sources of the CF_3 group are needed for aromatic and other trifluoromethylation reactions. Furthermore, these reactions should occur efficiently and selectively in the absence of cost-prohibitive ligands. It is also noteworthy that, in general, aryl halides are preferred over the corresponding boronic acids as the latter is usually prepared from the former.

Fluoroform (trifluoromethane, CHF_3, HFC-23) has long been recognized as the most readily available, cheap, and atom-economical CF_3 source.[2,18−22] A side product of Teflon manufacturing, fluoroform is generated in an amount of over

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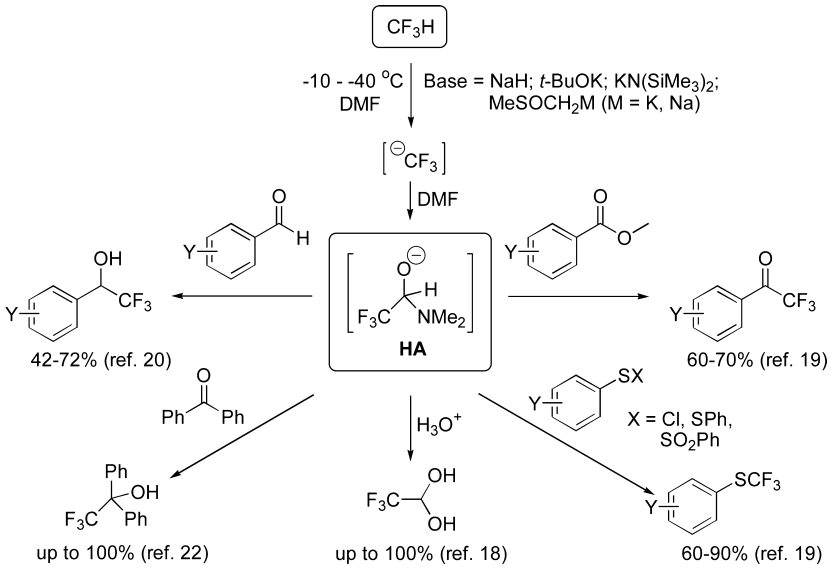
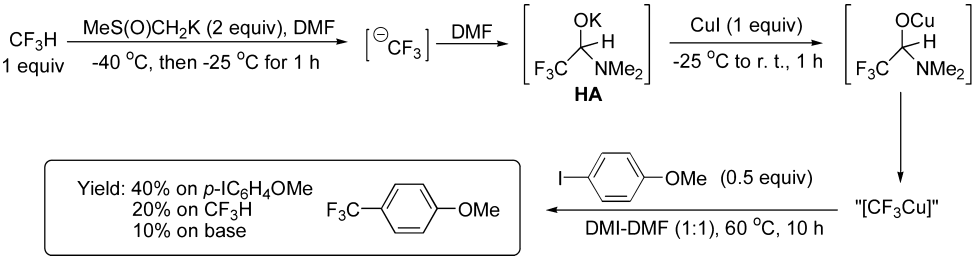
Scheme 1



Scheme 2



20000 t per annum. While being nontoxic and ozone-friendly, CHF_3 is a potent greenhouse gas[23,24] (bp = −82 °C) with a 264-year atmospheric lifetime and a global warming potential over 10^4 that of CO_2. Therefore, the CHF_3 side-product should be either destroyed in what is a costly incineration process, or, much more preferably, used as a feedstock for manufacturing fluorochemicals.[23] Chemoselective activation of fluoroform, however, is a nontrivial challenge.

The traditional strategy to use CHF_3, a weak acid (pK_a = 27 in water),[25] in synthesis is based on deprotonation with strong alkali metal[18−22] or electrogenerated[26] organic bases. These reactions are conventionally conducted at low temperatures in DMF in order to minimize the facile decomposition of the CF_3^- carbanionic species to difluorocarbene. Under such conditions, the CF_3^- adds across the C═O bond of DMF to give the corresponding hemiaminolate (**HA**) that serves as a "reservoir" of the CF_3 nucleophile. Although unstable at room temperature, this hemiaminolate decomposes only slowly if kept cold (hours at −20 °C).[20b] A summary of selected well-known trifluoromethylation reactions using this methodology is presented in Scheme 1. Most recently, it was demonstrated by two groups[27,28] that similar transformations can be performed in solvents other than DMF, such as THF, ether, and toluene. Using the Roques−Russell[18,19] $CHF_3/KN(SiMe_3)_2$ system, Prakash et al.[27] prepared R_3SiCF_3 (42−80% yield) and CF_3SO_3H (18% yield) from R_3SiCl and S_8, respectively. To eliminate the need for DMF, however, these reactions must be conducted at a much lower temperature (−78 °C), making the deprotonation methodology even less suitable for larger scale operations aimed at utilization of the side-produced fluoroform (see above). Shibata and co-workers[28] reported CHF_3 deprotonation with Schwesinger's phosphazene base *t*-Bu-P4[29] in THF. While being methodologically interesting, this reaction[28] employs stoichiometric quantities of costly *t*-Bu-P4 and still requires a low temperature (−30 °C) to proceed smoothly. An example of aromatic trifluoromethylation via a multistep procedure using the deprotonation methodology has been reported (Scheme 2).[20b] The reaction of CHF_3 with dimsyl potassium in DMF at −25 to −40 °C gave **HA** that was converted to its Cu analogue and eventually to $CuCF_3$ that effected the trifluoromethylation of *p*-iodoanisole in 10−40% yield.

A methodologically different approach to activation of fluoroform was proposed by Folleas et al. in 2000.[20b] In their report, they wrote: *"Our first attempts to generate trifluoromethyl metal with M = Cu and Zn from fluoroform were based on the metallation concept with basic organocopper and organozinc derivatives in order to directly obtain the trifluoromethyl copper or zinc derivatives. However, whatever the organometallic used ($(nBu)_2CuLi$, $(nBu)_2CuCNLi_2$, $(nBu)_3CuCNLi_3$, $tert\text{-}Bu_2CuCNLi_2$, Et_2Zn, $(nBu)_3ZnLi$, AllylZnBr,...) in different conditions (heating, sonication, in pressurised flask) or different solvents (Et_2O, THF, HMPA) no trace of the corresponding trifluoromethyl organometallic was detected".*[20b] This quote provides an indication of the scale of the challenge that was overcome only over a decade later when two groups discovered the first reactions of direct zincation and cupration of fluoroform.

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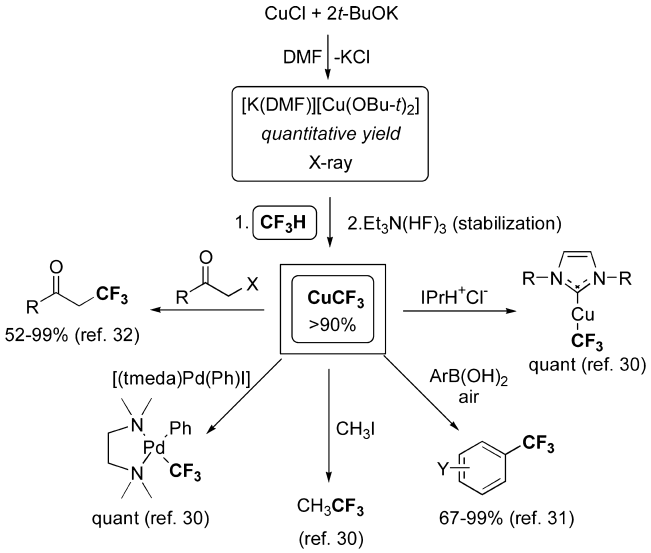
In 2011, Popov, Lindeman, and Daugulis[12b] reported the zincation of R_fH (R_f = perfluoroalkyl), while our group[2,30] disclosed the first reaction of direct cupration of fluoroform. The Daugulis method[12b] employing zinc bis-2,2,6,6-tetramethylpiperidide is useful for higher R_fH. For trifluoromethylation reactions, however (R_f = CF_3), the method is less efficient because of α-fluoride elimination leading to C_2F_5 derivatives at the elevated temperatures required for CF_3 transfer to Cu in order to utilize the originally produced $Zn(CF_3)_2$.

Our method[30] is based on a novel ate complex reagent, $[K(DMF)][(t\text{-BuO})_2Cu]$, that is formed quantitatively upon treatment of CuCl with 2 equiv of *t*-BuOK. This dialkoxycuprate, generated in situ or preisolated, reacts with CHF_3 at room temperature and atmospheric pressure within minutes to give rise to $CuCF_3$ in >90% yield. Stabilization of the thus produced trifluoromethyl copper(I) with a source of HF such as $Et_3N{\cdot}3HF$ (TREAT HF) furnishes the reagent that is stable at room temperature for days.[30]

We have recently demonstrated that our $CuCF_3$ reagent can be used for high-yielding trifluoromethylation reactions of various substrates, including transition metal complexes,[30] arylboronic acids,[31] and α-haloketones[32] (Scheme 3).[33] We have also preliminarily communicated[30] trifluoromethylation of a handful of iodoarenes under nonoptimized conditions to demonstrate a proof of concept. Herein, we report the first systematic, detailed study of trifluoromethylation of aryl and heteroaryl iodides, bromides, and chlorides with the new easily accessible, low-cost fluoroform-derived $CuCF_3$ reagent.

Scheme 3



RESULTS

Of all haloarenes, aryl iodides are most reactive in a broad variety of Cu-promoted/catalyzed coupling reactions, trifluoromethylation being no exception.[2,4−12,14,15] Both structurally undefined $CuCF_3$[2] and its adequately characterized derivatives $[(NHC)CuCF_3]$,[14] $[(phen)CuCF_3]$,[12c] $[(Ph_3P)_3CuCF_3]$,[12d] $[(Ph_3P)(phen)CuCF_3]$,[12d] and $[(bathophen)CuCF_3]$[12e] have been shown to trifluoromethylate various iodoarenes quite efficiently. In contrast, only a very limited number of Cu-promoted trifluoromethylation reactions of more cost-attractive yet much less reactive bromoarenes have been reported.[2,12c] The lower reactivity of the Ar−Br bond toward Cu(I) is often insufficient to achieve satisfactory conversions and yields in Cu-promoted trifluoromethylation reactions. Examples of trifluoromethylation of the least reactive aryl chlorides are extremely rare.[2]

Trifluoromethylation of Aryl Iodides. The vast majority of previously reported Cu-mediated/catalyzed trifluoromethylation reactions of aromatic electrophiles occur efficiently only in the presence of a specifically added ligand,[2] most commonly phenanthroline. In contrast, our fluoroform-derived $CuCF_3$ is reactive toward iodoarenes in the absence of any added ligands.[30] Moreover, it was found in the current work that adding various ligands, including phenanthroline, tertiary phosphines, and pyridine to our $CuCF_3$ reagent not only did not have a beneficial effect on the trifluoromethylation reaction, but often resulted in diminished reactivity and lower selectivity and yield.

Prior to the stabilization[30] with TREAT HF[34] (see above), fluoroform-derived $CuCF_3$ reacted with iodobenzene and other simple iodoarenes at as low as room temperature to give the corresponding benzotrifluorides. This Ar−CF_3 coupling was complicated, however, by the competing alkoxylation reaction leading to *tert*-butyl ethers, *t*-BuOAr (Scheme 4). The stabilization with TREAT HF not only gave a much more robust $CuCF_3$ reagent but also suppressed altogether the undesired alkoxylation, apparently due to neutralization of the *tert*-butoxide formally present in the originally produced $CuCF_3$ solution. Furthermore, it was found that performing the reaction in the presence of 0.2 equiv of extra TREAT HF had a beneficial effect on both the conversion and yield.

To make the trifluoromethylation reaction potentially practicable, it was critical to find conditions for high conversion (≥95%) of the iodoarene substrate with a minimal amount of the $CuCF_3$ reagent. The results of our effort toward this goal are summarized in Table 1. Note that in most of the previous studies,[2] either the ArI substrate or the CF_3 source had to be used in considerable excess in order to obtain the desired benzotrifluoride products in good yield.

As can be seen from Table 1, a broad variety of aryl iodides could be efficiently trifluoromethylated in up to 99% yield at >99% conversion with only 1.1−2.0 equiv of $CuCF_3$. To our

Scheme 4

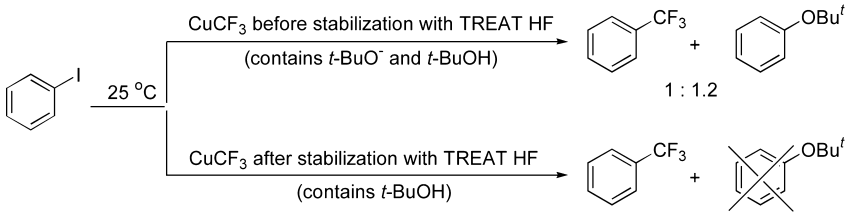


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Table 1. Trifluoromethylation of Aryl and Heteroaryl Iodides with Fluoroform-Derived $CuCF_3$

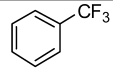
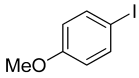
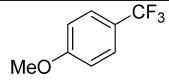
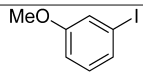
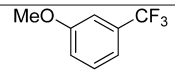
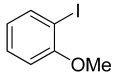
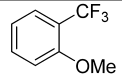
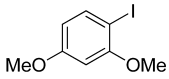
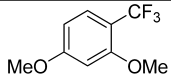
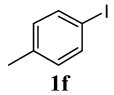
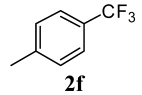
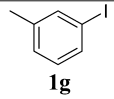
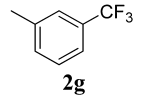
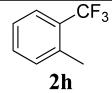
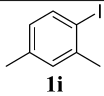
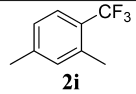
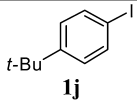
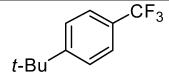
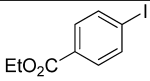
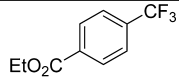
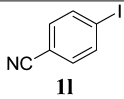
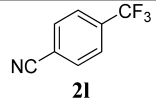
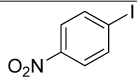
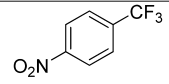
Entry	Substrate	$CuCF_3$, equiv	$Et_3N{\cdot}3HF$, equiv (per 1 equiv of $CuCF_3$)	T, °C (t, h)	Product	Conversion, %		Yield, % ^{19}F NMR (isolated) (scale)
						ArI[a]	$CuCF_3$[b]	
1	 **1a**	1.5	0.53	50 (18)	 **2a**	99	98	95
2		1.5	0.53	23 (24) 50 (18)		>99	>99	96
3	 **1b**	1.5	0.53	23 (72)	 **2b**	84	80	88
4		1.5	0.53	23 (24) 50 (18)		96	99	98
5		2.0	0.53	23 (24) 50 (24)		99	98	99 (88) (11 mmol)
6		1.5	0.33	23 (24) 50 (18)		63	>99	70
7		2.0	0.33	23 (24) 50 (18)		72	>99	80
8	 **1c**	1.5	0.53	23 (26)	 **2c**	75	75	80
9		1.5	0.53	23 (24) 50 (18)		99	97	96
10		2.0	0.53	23 (24) 50 (24)		>99	95	97
11	 **1d**	1.5	0.53	23 (24)	 **2d**	>99	80	99
12		1.5	0.53	23 (24) 50 (18)		>99	95	99 (87) (10 mmol)
13	 **1e**	1.5	0.53	23 (72)	 **2e**	>99	80	95 (97) (6 mmol)
14		1.5	0.53	23 (24) 50 (18)		>99	95	97
15	 **1f**	1.5	0.53	23 (24) 50 (18)	 **2f**	97	>99	97
16		2.0	0.53	23 (24) 50 (24)		>99	>99	93
17	 **1g**	1.5	0.53	23 (24) 50 (18)	 **2g**	98	99	98
18		2.0	0.53	23 (24) 50 (24)		>99	>99	99
19	 **1h**	1.5	0.53	23 (24) 50 (18)	 **2h**	>99	>95	94
20	 **1i**	1.5	0.53	23 (24) 50 (18)	 **2i**	>99	95	97
21	 **1j**	1.5	0.53	23 (24) 50 (18)	 **2j**	94	95	90
22		2.0	0.53	23 (24) 50 (24)		99	>95	95
23	 **1k**	1.5	0.53	23 (20)	 **2k**	96	70	97
24		1.5	0.53	23 (24) 50 (18)		>99	95	93 (96) (10 mmol)
25	 **1l**	1.5	0.53	23 (20)	 **2l**	99	85	98
26		1.5	0.53	23 (24) 50 (18)		>99	95	99 (94) (10 mmol)
27	 **1m**	1.5	0.53	23 (20)	 **2m**	>99	85	95 (83) (5 mmol)

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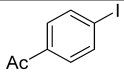
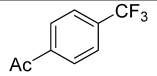
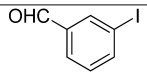
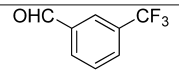
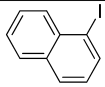
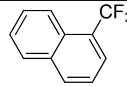
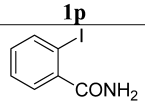
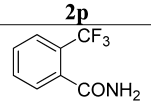
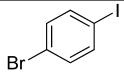
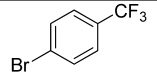
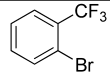
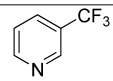
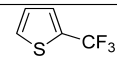
Table 1. continued

Entry	Substrate	$CuCF_3$, equiv	$Et_3N{\cdot}3HF$, equiv (per 1 equiv of $CuCF_3$)	T, °C (t, h)	Product	Conversion, %		Yield, % ^{19}F NMR (isolated) (scale)
						ArI[a]	$CuCF_3$[b]	
28	 **1n**	1.5	0.53	23 (18)	 **2n**	95	75	95
29		1.5	0.53	23 (24) 50 (18)		>99	95	95
30	 **1o**	1.5	0.53	23 (18)	 **2o**	82	70	85
31		1.5	0.53	23 (24) 50 (18)		>99	95	99
32	 **1p**	1.5	0.53	23 (20)	 **2p**	97	80	98
33		1.5	0.53	23 (24) 50 (18)		>99	96	96 (98) (20 mmol)
34	 **1q**	1.1	0.53	23 (0.25)	 **2q**	>99	95	87 (81) (10 mmol)
35	 **1r**	1.5	0.53	23 (24) 50 (18)	 **2r**	>99	97	96[c]
36	 **1s**	1.5	0.53	23 (24) 50 (18)	 **2s**	>99	96	86[d]
37		1.3	0.53	23 (24) 50 (18)		>99	>99	95[e]
38	 **1t**	1.5	0.53	23 (24) 50 (24)	 **2t**	97	>99	73
39		2.0	0.53	23 (24) 50 (24)		96	>99	86
40	 **1u**	1.5	0.53	50 (18)	 **2u**	>99	>95	87[f]

[a]Determined by GC–MS. [b]Determined by ^{19}F NMR. [c]1,4-$(CF_3)_2C_6H_4$ (4%) was produced. [d]1,2-$(CF_3)_2C_6H_4$ (9%) was produced. [e]1,2-$(CF_3)_2C_6H_4$ (3%) was produced. [f]Thiophene (7%, GC–MS) was produced.

delight, almost none of these reactions gave rise to arenes, biaryls, and pentafluoroethyl derivatives that are commonly side-produced in Cu-mediated trifluoromethylation of aryl halides.[2] The only exception was the reaction of 2-iodothiophene **1u** that produced 7% of thiophene as a side product.

Most of the optimization work was performed on **1b**, a more challenging substrate bearing a strongly electron-donating methoxy group in the para-position. For electron-deficient (**1k–o,q**) and most of the ortho-substituted (**1d,e,p,q**) iodoarenes, nearly quantitative conversions could be achieved within 24 h at room temperature. *o*-Iodobenzamide (**1q**) was particularly reactive, undergoing trifluoromethylation of the C–I bond in >99% conversion within 15 min at 23 °C with only 1.1 equiv of $CuCF_3$ (entry 34). This enhanced reactivity likely reflects the ortho-effect that is discussed below. For less reactive aryl iodides bearing electron-donating groups in the meta or para positions, heating at 50 °C for additional 18–24 h was required in order to achieve >95% conversion. Various substituents on the ring were easily tolerated, including not only simple alkyls but also OMe, CO_2R, CN, NO_2, Ac, CHO, $CONH_2$, and Br. The latter, however, was noticed to undergo partial displacement in the reaction, albeit to a minor extent (3–9%; entries 35–37).

While there have been a number of reports on Cu-promoted trifluoromethylation of aryl halides,[2,4–12,14,15] the products have been seldom isolated but rather identified and quantified by ^{19}F NMR and/or GC techniques. It is hard to find a literature procedure describing in sufficient detail not only reaction conditions but also the way a targeted benzotrifluoride was isolated pure on a ≥0.5 g scale and adequately characterized. The particularly meticulous Cottet–Schlosser[35] procedures for the preparation of multigram quantities of some trifluoromethylated naphthalenes and pyridines from the corresponding iodo derivatives are truly exceptional in terms of both high quality and considerable reaction scale. In the current work, isolation of pure products in high yield was demonstrated for a number of reactions (Table 1), and in several cases these were performed on a 10–11-mmol scale to give, for example, **2b** (1.71 g; 88%), **2d** (1.53 g; 87%), **2k** (2.09 g; 96%), **2l** (1.62 g; 94%), and **2q** (1.53 g; 81%). In one 20-mmol scale-up, nearly 4 g of pure 1-trifluoromethylnaphthalene **2p** was prepared (98% yield).

Trifluoromethylation of Aryl Bromides and Chlorides. While being less costly and more readily available, bromo- and chloroarenes are considerably less reactive toward Cu(I) coupling partners than their iodo congeners.[36] Trifluoromethylation of bromoarenes with copper reagents is an extremely challenging and rare transformation[2] that usually occurs only with electron-deficient substrates even in the presence of stabilizing ligands such as NHC[14b] and phen.[12c] A handful of publications mention isolated yields of trifluoromethylated aromatics produced from the corresponding aryl bromides (see Table 3 in ref 2). None of these reports, however, includes a particular procedure for trifluoromethylation of an aryl bromide and isolation and adequate characterization of the product. Only

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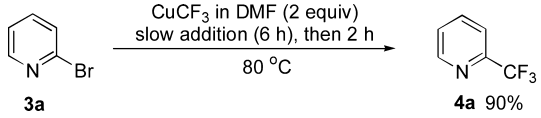
one article[37] provides such procedures for the synthesis of four trifluoromethylated heterocycles from the corresponding bromides, 2,4-dimethoxy-5-(trifluoromethyl)pyrimidine, 2,4-dimethoxy-6-(trifluoromethyl)pyrimidine, 3′,5′-di-*O*-acetyl-8-(trifluoromethyl)-2′-deoxyadenosine, and 2′,3′,5′-tri-*O*-acetyl-8-(trifluoromethyl)inosine in 42, 31, 64, and 42% yield, respectively. To reach these yields, 11−25 equiv of CF_3I and 20−39 equiv of Cu in HMPA were used.

We have preliminarily communicated[30] the formation of 2-trifluoromethylpyridine in 30% ^{19}F NMR yield from the reaction of 2-bromopyridine (**3a**) with fluoroform-derived $CuCF_3$ used as a limiting reagent. In this work, we first focused on **3a** as a substrate because trifluoromethylated pyridines, while being particularly important in the preparation of biologically active compounds, cannot be efficiently made from the corresponding picolines (eq 1) without chlorination of the pyridine ring.

Optimization of the reaction of 2-bromopyridine with the $CuCF_3$ reagent led to an increase in the yield of the desired product, 2-trifluoromethylpyridine (**4a**), to 90% at full conversion (eq 3). Herein, we present only a succinct summary of the optimization studies that included over 60 runs. First, it was established that, like in the case of iodoarenes (see above), the reaction benefits from additional amounts of TREAT HF. The best yields were obtained using $CuCF_3$ stabilized with 1.6 equiv of HF in the form of TREAT HF. Lower yields were observed with $Py(HF)_n$ as the stabilizer. At 50−60 °C, yields of up to 60% at 75% conversion and 80% at >90% conversion could be obtained with 1.0 and 1.5 equiv of $CuCF_3$, respectively. To reach full conversion, however, 2.0 equiv of $CuCF_3$ appeared to be needed. While adding the copper reagent in two portions resulted in further improvements, the best yield of **4a** was obtained when the copper reagent solution was added slowly, over a period of 6 h, to **3a** at 80 °C and the mixture was then agitated for additional 2 h (eq 3). A number of additives were tested. Neither $[Bu_4N]^+ I^-$ nor NEt_3 (1 equiv) had a noticeable effect on the reaction, although in the presence of 10 equiv of NEt_3, **4a** was formed in a slightly higher yield. On deliberate addition of water (1.5 equiv), the yield of **4a** dropped considerably because of decomposition of the $CuCF_3$ reagent.



3a **4a** 90% (3)

After successful optimization of the synthesis of **4a** from **3a**, we proceeded to explore trifluoromethylation reactions of a broad variety of heteroaryl and aryl bromides (Table 2).[38] All isomeric monomethylated 2-bromopyridines **3b−e** were trifluoromethylated in 73−88% yield at 91−99% conversion after 33 h at 50 °C (entries 2−5). In these experiments, the $CuCF_3$ reagent was added in two portions, 1 equiv at the beginning of the reaction and 1 equiv 15 h later, after which the reaction was continued for additional 18 h. More reactive 2-bromoquinoline **3f** underwent smooth trifluoromethylation under milder conditions, 23−50 °C, to give 2-trifluoromethylquinoline **4f** in up to 91% yield at >98% conversion (entries 6 and 7). 2-Bromopyridines bearing electron-deficient substituents, CO_2Me, CHO, and NO_2, were even more reactive, undergoing trifluoromethylation in 88−98% yield at >99% conversion with only 1.5 equiv of $CuCF_3$ after 12−15 h at room temperature (entries 8−11). As expected, the intrinsically less electrophilic 3-bromopyridines reacted more sluggishly to give rise to the corresponding trifluoromethylated derivatives in only ca. 10−30% yield. This reactivity pattern accords with the nearly quantitative yields of 2-trifluoromethylpyrimidine **4n** (95%) and 2,5-bis(trifluoromethyl)pyrazine **4p** (94%), yet only 24% yield of 4-trifluoromethylpyrimidine **4o** from the corresponding mono- and dibromo substrates (entries 15−17). Remarkably, a CH_3 group in an adjacent position (2 or 4) of the 3-brominated pyridine ring enhanced noticeably the reactivity of the C−Br bond (**3l** and **3m** vs **3k**). 2-Bromothiazole **3q** and its 5-nitro derivative **3r** were trifluoromethylated in only ca. 20% yield under such conditions, apparently because of decomposition by the reagent. In order to reach higher yields of **4q** (35%) and **4r** (55%), only 1 equiv of $CuCF_3$ stabilized with 0.33 equiv of TREAT HF should be used (entries 18 and 19). 4-Bromopyridine, commercially available as its hydrochloride, was trifluoromethylated in 74% yield (entry 20). In this case, 3 equiv of $CuCF_3$ were needed because, like other strong acids (HBr),[32] the HCl present in the starting material partially decomposes the organocopper reagent.

Electron-rich bromoarenes are known[2] to react with various $CuCF_3$ species only at elevated temperatures that also cause quick decomposition of the copper reagent. As a result, the yields of the trifluoromethylated products are low. More reactive aryl bromides bearing electron-withdrawing groups on the ring can be trifluoromethylated in much higher yields (Table 2, entries 21−33). Like in the above-described trifluoromethylation of iodoarenes, the reactions of aryl bromides were not complicated by side processes leading to arenes, biaryls, and pentafluoroethyl derivatives.[39] In sharp contrast, the $CuCF_3$ generated in the widely known $Cu−CF_2Br_2−DMAC$ system has been reported[40] to produce mainly biaryls on attempted trifluoromethylation of aryl bromides and iodides.

The previously observed[40] and recently reviewed[11e] promoting effect of a nitro group in the ortho position was also seen in the reactions of isomeric nitrobromobenzenes **3t−v** with fluoroform-derived $CuCF_3$. *o*-Nitrobromobenzene **3t** underwent remarkably fast and clean trifluoromethylation to give *o*-nitrobenzotrifluoride quantitatively within 18 h at room temperature with only 1.3 equiv of $CuCF_3$. In contrast, the reactions of the meta (**3u**) and para (**3v**) isomers required longer times at 50−80 °C and a larger excess of $CuCF_3$, while furnishing the corresponding products **4u** and **4v** in only 22% and 60% yield, respectively. The ortho and para isomers of bromobenzonitrile, however, exhibited identical moderate reactivity toward $CuCF_3$ (entries 25 and 26).

Strikingly, carbonyl-containing groups COOMe, COOH, CHO, and COMe ortho to the bromine atom had a tremendously strong accelerating effect on the trifluoromethylation (entries 27−33). Unmatched reactivity was observed for the acids **3z**, **3aa**, and **3ee** that underwent complete trifluoromethylation with only 1.1 equiv of $CuCF_3$ within 10−15 min at room temperature.[41] Although 2-bromobenzaldehyde **3cc** (entry 31), 2-bromoacetophenone **3dd** (entry 32), and methyl 2-bromobenzoate **3y** (entry 27) were slightly less reactive, the corresponding trifluoromethylated products **4cc**, **4dd**, and **4y** were still obtained in 83, 96, and 98% yield, respectively. A number of aryl and heteroaryl bromides were trifluoromethylated on a preparative 1−10 mmol scale, and the corresponding products (**4f,g,i,j,t,y,z,aa,dd**) were successfully isolated pure in high yield (Table 2).

Chloroarenes are even more challenging substrates[42] for carbon−halogen bond activation, particularly with copper.[36] Unsurprisingly, 2-chloro-3-picoline and 2-chloro-pyridine-3-

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Table 2. Trifluoromethylation of Aryl and Heteroaryl Bromides with Fluoroform-Derived $CuCF_3$ Stabilized with TREAT HF (0.53 equiv)

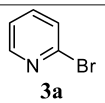
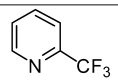
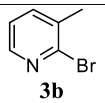
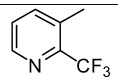
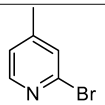
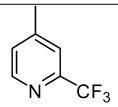
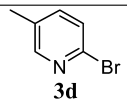
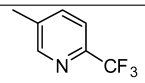
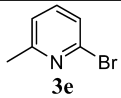
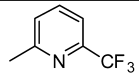
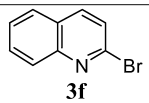
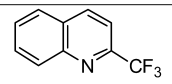
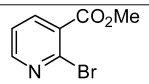
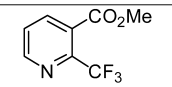
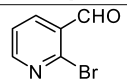
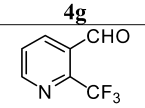
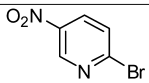
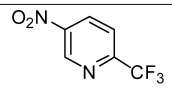
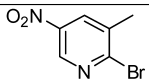
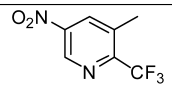
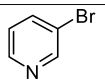
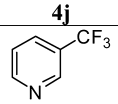
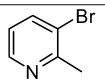
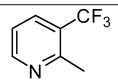
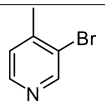
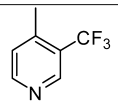
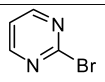
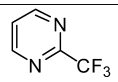
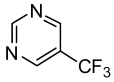
Entry	Substrate	$CuCF_3$, equiv	t, h	T, °C	Product	Conversion, %		Yield, % ^{19}F NMR (isolated) (scale)
						ArBr[a]	$CuCF_3$[b]	
1	 **3a**	2.0	6 + 2[c]	80	 **4a**	>99	>99	90
2	 **3b**	1.0 + 1.0	15 + 18	50	 **4b**	>99	>99	88
3	 **3c**	1.0 + 1.0	15 + 18	50	 **4c**	98	>99	80
4	 **3d**	1.0 + 1.0	15 + 18	50	 **4d**	96	>99	77
5	 **3e**	1.0 + 1.0	15 + 18	50	 **4e**	91	>99	73
6	 **3f**	1.5	18 + 18[d]	23, 50[d]	 **4f**	>98	>99	91
7		1.5	48	23		>99	90	85 (80) (5 mmol)
8	 **3g**	1.5	12	23	 **4g**	>99	85	88 (91) (3 mmol)
9	 **3h**	1.5	12	23	 **4h**	>99	95	94
10	 **3i**	1.5	15	23	 **4i**	>99	95	99 (91) (6 mmol)
11	 **3j**	1.5	15	23	 **4j**	>99	85	98 (92) (3 mmol)
12	 **3k**	1.5	15	60	 **4k**	<20	>99	8
13	 **3l**	1.5	15	60	 **4l**	30	>99	20
14	 **3m**	1.5	15	60	 **4m**	35	>99	17
15	 **3n**	1.5	18	23	 **4n**	99	85	95
16	 **3o**	1.5	18	50	 **4o**	ND[e]	>99	24

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Table 2. continued

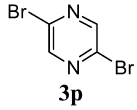
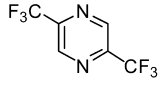
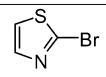
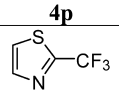
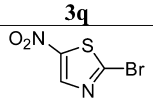
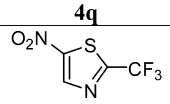
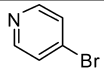
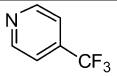
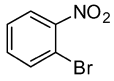
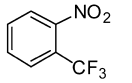
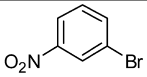
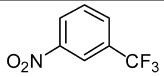
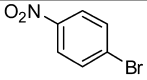
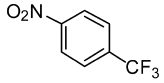
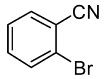
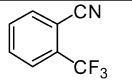
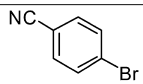
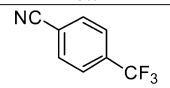
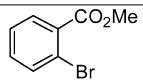
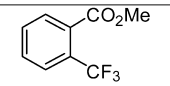
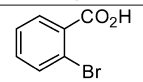
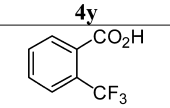
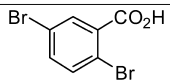
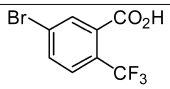
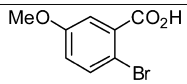
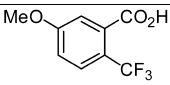
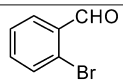
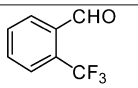
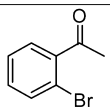
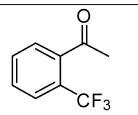
Entry	Substrate	$CuCF_3$, equiv	t, h	T, °C	Product	Conversion, %		Yield, % ^{19}F NMR (isolated) (scale)
						ArBr[a]	$CuCF_3$[b]	
17	 **3p**	3.0	24	23	 **4p**	>99	90	94
18	 **3q**	1[f]	24 + 15[g]	23, 50[g]	 **4q**	>80	>99	35
19	 **3r**	1[f]	12 + 6[h]	50	 **4r**	>99	>99	55
20	 **3s**[i]	3.0	24 + 15[g]	23, 50[g]	 **4s**	85	>99	74
21	 **3t**	1.3	18	23	 **4t**	>99	90	92 (88) (10 mmol)
22	 **3u**	1.5	24 + 24[j]	23, 50[j]	 **4u**	20	>95	22
23	 **3v**	1.5	24 + 24[j]	23, 50[j]	 **4v**	49	>99	48
24		2	4 + 2[k]	80		61	>99	60
25	 **3w**	1.5	72	23	 **4w**	27	60	30
26	 **3x**	1.5	72	23	 **4x**	27	65	31
27	 **3y**	2.0	24 + 24[j]	23, 50[j]	 **4y**	99	99	98 (95) (10 mmol)
28	 **3z**	1.1	0.25	23	 **4z**	>99	95	82 (77)[l] (1 mmol)
29	 **3aa**	1.1	0.20	23	 **4aa**	>99	95	81 (82)[l] (10 mmol)
30	 **3bb**	1.1	0.20	23	 **4bb**	ND[e]	90	79[l]
31	 **3cc**	2	24 + 24[j]	23, 50[j]	 **4cc**	94	>99	83[m]
32	 **3dd**	1.3	18	23	 **4dd**	>99	90	96 (92) (10 mmol)

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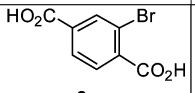
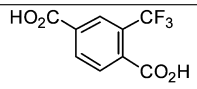
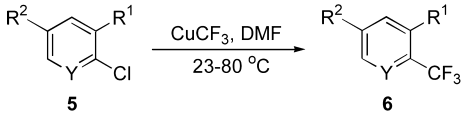
Table 2. continued

Entry	Substrate	$CuCF_3$, equiv	t, h	T, °C	Product	Conversion, %		Yield, % ^{19}F NMR (isolated) (scale)
						ArBr[a]	$CuCF_3$[b]	
33	 **3ee**	1.1	0.3	23	 **4ee**	ND[e]	>90	60

[a]Determined by GC–MS. [b]Determined by ^{19}F NMR. [c]$CuCF_3$ in DMF was added during 6 h, and then the reaction was continued for an additional 2 h. [d]18 h at 23 °C, then 18 h at 50 °C. [e]ND = not determined. [f]$CuCF_3$ without extra TREAT HF. [g]24 h at 23 °C, then 15 h at 50 °C. [h]$CuCF_3$ in DMF was added during 12 h, and then the reaction was continued for an additional 6 h. [i]In the form of hydrochloride. [j]24 h at 23 °C, then 24 h at 50 °C. [k]$CuCF_3$ in DMF was added during 4 h, and then the reaction was continued for an additional 2 h. [l]Approximately 10% of the corresponding phenol was side-produced (^{1}H NMR). The isolated yields are given for pure products. [m]Approximately 2% of benzaldehyde was side-produced (GC–MS).

carbonitrile failed to react with $CuCF_3$ and even more electron-deficient 5-nitro-2-chloro-3-picoline (**5e**) was trifluoromethylated in only ca. 20% yield. The above-described ortho-effect was observed in the reactions of $CuCF_3$ with 2-chloronicotinic acid (**5a**), its ethyl ester (**5b**), 2-chlorobenzoic acid (**5c**), and 2,3-dichloronitrobenzene (**5d**) that gave the corresponding trifluoromethyl derivatives in 30–60% yield (Scheme 5). Remarkably, the reaction of 2-chloronicotinic acid

Scheme 5



5 **6**

6a: Y = N; R^1 = COOH; R^2 = H; Yield = 60% (58%)
6b: Y = N; R^1 = $COOC_2H_5$; R^2 = H; Yield = 30%
6c: Y = CH; R^1 = COOH; R^2 = H; Yield = 35%
6d: Y = CNO_2; R^1 = Cl; R^2 = H; Yield = 58%
6e: Y = N; R^1 = CH_3; R^2 = NO_2; Yield = 20%

5a occurred at as low as room temperature, thereby attesting to the strong ortho-effect of the carboxylic acid functionality. This trifluoromethylation reaction was performed on a 5 mmol scale and the product, 2-trifluoromethylnicotinic acid **6a**, was isolated in 58% yield.

If the reaction mixtures from the trifluoromethylation of 2-bromobenzoic acid and 2-chloronicotinic acid were not worked up quickly but rather allowed to stand at room temperature under argon for several hours (overnight), green-blue crystals and copper metal slowly precipitated out. X-ray analysis of these crystals revealed the structures $[Cu_2(\mu\text{-}O_2CAr)_4(DMF)_2]$ (Ar = 2-$CF_3C_6H_4$, 2-$CF_3C_5H_3N$), as shown in Figures 1 and 2. Apparently, the Cu(I) byproduct of the reactions slowly disproportionated in the presence of the trifluoromethylated acid produced in the reaction to give Cu(0) and the stable Cu(II) dimer. A number of paddlewheel dinuclear Cu(II) carboxylates of the type $[Cu_2(\mu\text{-}O_2CR)_4(L)_2]$ where L is a monodentate ligand such as H_2O, THF, DMF, Py, etc. have been reported in the literature.[43,44]

CuX Byproduct Effect. Copper-mediated coupling reactions of aryl halides sometimes display interesting features that are not always mechanistically understood.[36,45] In the course of our studies, we found an unpredicted effect of the CuX (X = I, Br, Cl) byproduct of the trifluoromethylation reaction on the $CuCF_3$ reagent during the process. A series of experiments indicated that the trifluoromethylation of 2-bromopyridine was not affected in any way when it was performed in the presence of

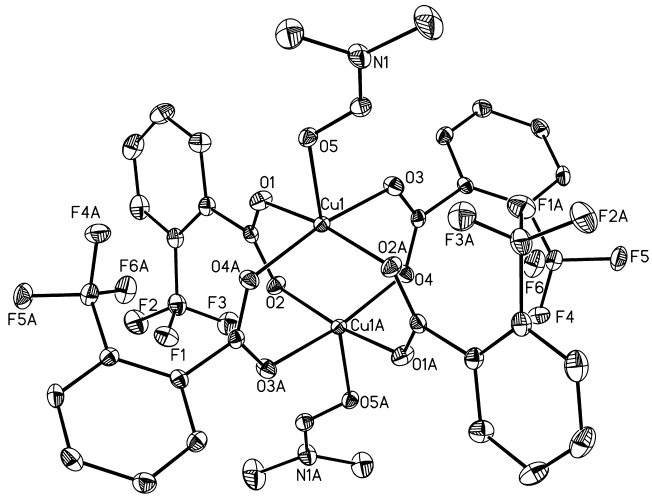


Figure 1. ORTEP drawing of $[Cu_2(\mu\text{-}O_2CC_6H_4CF_3\text{-}2)_4(DMF)_2]$ with thermal ellipsoids drawn to the 50% probability level and all H atoms omitted for clarity. [Symmetry code: $-x + 1, -y + 1, -z$].

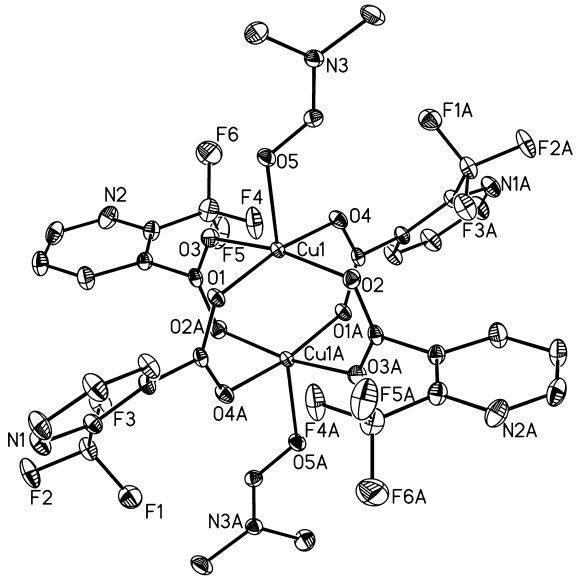


Figure 2. ORTEP drawing of $[Cu_2(\mu\text{-}3\text{-}O_2CC_5H_3NCF_3\text{-}2)_4(DMF)_2]$ with thermal ellipsoids drawn to the 50% probability level and all H atoms omitted for clarity. [Symmetry code: $-x + 1, -y + 2, -z$].

1 equiv of the deliberately added product, 2-(trifluoromethyl)-pyridine. In contrast, CuBr, the reaction byproduct, was found to destabilize the $CuCF_3$ reagent, causing its partial decom-

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position.[46] In line with these observations, dilution of the reaction mixture with additional DMF led to an increase in stability of the $CuCF_3$, while also slowing down the trifluoromethylation. This negative effect of CuBr on the stability of $CuCF_3$ was unexpected. It is noteworthy that the reaction medium contains triethylamine that comes from the TREAT HF stabilizer and that is known[47] to react with CuX (X = Cl, Br, I) to give cubane-type complexes $[Cu_4(NEt_3)_4X_4]$. Indeed, $[Cu_4(NEt_3)_4Br_4]$ was isolated from the room-temperature reaction of **3g** and structurally characterized (Figure 3).[48] However, complexes of the type $[Cu_4(NEt_3)_4X_4]$ are quite labile,[47] easily releasing CuX under the reaction conditions.

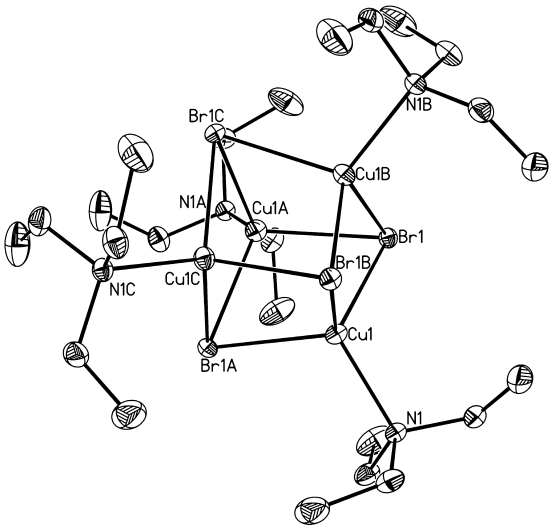
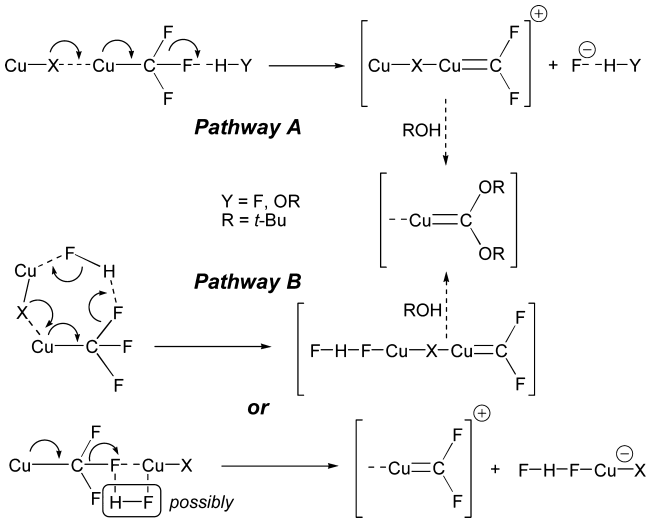


Figure 3. ORTEP drawing of $[Cu_4(NEt_3)_4Br_4]$ with thermal ellipsoids drawn to the 50% probability level and all H atoms omitted for clarity. [Symmetry codes: (A) $-x + 2, y, z + 2$; (B) $-x + 2, -y-2, z$; (C) $x, -y + 2, -z + 2$].

Two distinct mechanisms might be operational in the CuX-induced decomposition of $CuCF_3$ (Scheme 6). One (pathway A) involves coordination (nucleophilic attack) of the halide of CuX to the Cu atom of the ligand-deficient $CuCF_3$, prompting the formation of an X bridge between the two metals. This dinuclear intermediate then undergoes α-fluoride elimination that is facilitated by hydrogen bonding to the leaving fluoride ion. In the other mechanism (pathway B), CuX acts as a Lewis acid rather than a nucleophile. Lewis acids are well-known[49] to promote α-fluoride elimination from CF_3 metal derivatives. Although strong coordination of the copper atom of CuX to a fluorine atom of the CF_3 ligand is unlikely, it cannot be ruled out. A more likely possibility is HF-mediated interaction as shown in Scheme 6 (pathway B). The proposed structures presented in Scheme 6 are aimed only at portraying the general concept of the two mechanistic possibilities and, in all likelihood, are far from the real, probably very complex, strongly H-bonded system involving DMF, HF, *t*-BuOH, and Et_3N (see below). One way or another, the decomposition of the $CuCF_3$ species involves α-fluoride elimination with subsequent facile[49] nucleophilic displacement of the fluorines of the difluorocarbene ligand with *t*-butoxy groups. Bis(*tert*-butoxy)carbene Cu(I) complexes have been isolated from partially decomposed $CuCF_3$ solutions and structurally characterized.[30] Pertaining to the F−H−F-Cu(I) species proposed in Scheme 6, structurally

Scheme 6



characterized cuprous bifluoride complexes have been recently reported.[50]

To distinguish between the two conceptually distinct mechanisms shown in Scheme 6, we studied the decomposition of $CuCF_3$ during its reaction with 4-iodofluorobenzene in the presence of deliberately added CuI, CuBr, and CuCl. These experiments demonstrated that (i) larger quantities of CuCl cause more decomposition (Table 3) and (ii) the ability of CuX

Table 3. Trifluoromethylation of 4-FC_6H_4I (1 equiv) with Fluoroform-Derived $CuCF_3$ (1.5 equiv) in DMF in the Presence of Various Amounts of CuCl at 100 °C (0.5 h)

CuCl (equiv)	^{19}F NMR yield of 4-$FC_6H_4CF_3$ (%)
0	85
0.1	82
0.5	69
1.0	34

Table 4. Trifluoromethylation of 4-FC_6H_4I (1.5 equiv) with Fluoroform-Derived $CuCF_3$ (1 equiv) in DMF in the Presence of CuX (1 equiv) at 80 °C (12 h)

CuX	^{19}F NMR yield of 4-$FC_6H_4CF_3$ (%)
CuCl	25
CuBr	39
CuI	62

to decompose $CuCF_3$ increases in the order X = I < Br < Cl (Table 4), which correlates with the Lewis acidity[51] rather than nucleophilicity of Cu(I) halides. Furthermore, if pathway A was operational, nucleophiles with a strong affinity for Cu(I), such as iodide, might also make $CuCF_3$ more prone to α-fluoride elimination. That, however, was not observed. On addition of 1 equiv of $[Bu_4N]^+ I^-$ to $Et_3N{\cdot}3HF$-stabilized $CuCF_3$ in DMF, the population of the mono-CF_3 Cu species (^{19}F NMR: δ = ca. −26 ppm) decreased and that of $[Cu(CF_3)_2]^-$ (^{19}F NMR: δ = ca. −31 ppm) increased with no change in the overall integral intensity of the sum of the two CF_3 resonances. This observation indicated that a fraction of the $CuCF_3$ was converted to CuI, likely in the form of $[Cu_4(NEt_3)_4I_4]$ (see above), and $[Cu(CF_3)_2]^-$ via I/CF_3 ligand exchange and CF_3 redistribution. Importantly however, the treatment with

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$[Bu_4N]^+ I^-$ resulted in overall higher stability of the $CuCF_3$ species and their lower reactivity toward haloarenes. It has been reported[14b] that $[Cu(CF_3)_2]^-$ is less reactive toward ArX than mono-CF_3 Cu(I) complexes. As follows from the above, the side-decomposition of $CuCF_3$ during the trifluoromethylation of ArX is controlled primarily by the Lewis acidity of the Cu(I) halide byproduct rather than by its donating ability.

The above-described results show that as the trifluoromethylation of ArX occurs, CuX is released that destabilizes $CuCF_3$. The latter is consequently involved in two competing processes, (i) the desired trifluoromethylation of the ArX substrate and (ii) undesired decomposition that competes more efficiently toward the end of the reaction when the concentration of the ArX is lower and that of the by-produced CuX is higher.

DISCUSSION

Reactivity of Fluoroform-Derived $CuCF_3$ and Selectivity of Its Coupling with Aryl Halides. The fluoroform-derived $CuCF_3$ is highly reactive toward aryl halides. A comparison of the data described above with those reported in the literature suggests that our $CuCF_3$ is one of the most, if not the most, reactive copper-based species/systems for trifluoromethylation of haloarenes. Under optimized conditions, the trifluoromethylation reactions of aryl iodides occur in excellent, usually nearly quantitative yield and selectivity at as low as 23−50 °C (Table 1). Although more cost-attractive bromoarenes are much less reactive, we have succeeded in trifluoromethylating an unprecedented number of various aryl and heteroaryl bromides with our $CuCF_3$ in modest to excellent yield (Table 2). Scale-up experiments and isolation of the desired pure products on a gram scale attest to the synthetic value of the fluoroform-derived $CuCF_3$ reagent.

Importantly, the trifluoromethylation reactions with fluoroform-derived $CuCF_3$ readily occur in the absence of additional ligands. Moreover, deliberately adding ligands such as phenanthroline, tertiary phosphines, and pyridine at the beginning of the reaction does not result in improvement but rather the opposite. As can be seen from eq 4, after the cupration of fluoroform in DMF and stabilization with 1 equiv of HF in the form of $Et_3N{\cdot}3HF$ (TREAT HF), the resultant solution formally contains ca. 1 equiv of "$CuCF_3$", 2 equiv of *t*-BuOH, and $^1/_3$ equiv of Et_3N. With additional TREAT HF used in this work (see above), the solution comprises of DMF, *t*-BuOH, Et_3N, and HF that most likely form a 3D hydrogen-bonded network. The Cu(I) center in this seemingly simple yet very complex environment must be stabilized by weak ligation to the donor atoms of DMF, *t*-BuOH, NEt_3, and, possibly,[50] even HF. The exceptional reactivity of the $CuCF_3$ in such a medium suggests that limited coordinative saturation of the Cu center is imperative for binding to the aromatic substrate as a key step of the overall transformation. This conclusion is supported by the previously observed[12d] well-pronounced inhibition of the aromatic trifluoromethylation with $[(Ph_3P)_3CuCF_3]$ by extra phosphine R_3P (R = Ph, *n*-Bu, *t*-Bu).

$$[K(DMF)][Cu(OBu\text{-}t)_2] \xrightarrow[\text{2. } 1/3Et_3N(HF)_3]{\text{1. } CHF_3} \text{"}CuCF_3\text{"} + 2t\text{-BuOH} + 1/3Et_3N \quad (4)$$

(in DMF); -KF

In addition to being highly reactive, the fluoroform-derived $CuCF_3$ trifluoromethylates haloarenes in a remarkably selective manner. Unlike radical trifluoromethylation of aromatic C−H bonds that lacks positional selectivity,[52] Cu-mediated Ar−CF_3 coupling is usually regiospecific.[2] Our trifluoromethylation reactions are no exception, i.e. the substitution occurs exclusively at the halogen site. Much more surprising, and pleasantly so, is the remarkable chemoselectivity of the reactions of aryl halides with fluoroform-derived $CuCF_3$. These reactions are not complicated by the side formation of biaryls, arenes, and C_2F_5 and higher R_f derivatives that are conventionally produced in many reported analogous transformations.[2] The higher perfluoroalkyl side products emerge from the generation of difluorocarbene that inserts into the Cu−CF_3 bond to give $Cu(CF_2)_nCF_3$ ($n > 0$) which then fluoroalkylates the substrate. Separation of the coformed $Ar(CF_2)_nCF_3$ from the desired trifloromethylated compound is extremely difficult, if not impossible. This problem is nonexistent in the reactions of fluoroform-derived $CuCF_3$.

Mechanistic Considerations and the Ortho-Effect. As the Ar−CF_3 coupling occurs, CuX is coproduced, that destabilizes the $CuCF_3$ reagent, acting as a Lewis acid. This side reaction can be minimized, however, by performing the trifluoromethylation at a higher dilution. The $S_{RN}1$ and S_NAr routes that may govern[53] some Cu-promoted or catalyzed transformations of haloarenes are unlikely involved in our trifluoromethylation reactions. The lack of formation of arenes and biaryls as side-products indicates that $S_{RN}1$ may not be operational to a considerable extent. Moreover, the formation of only small quantities of the bis-trifluoromethylated products from *p*- and *o*-BrC_6H_4I **1r** and **1s** (Table 1) is inconsistent with the $S_{RN}1$ mechanism.[54,55] An independent competition experiment was performed to determine that *p*-nitroiodobenzene is only 22 times more reactive toward the $CuCF_3$ than iodobenzene. This small difference in reactivity rules out the classical S_NAr pathway.[56,57]

The enhanced reactivity of many ortho-substituted haloarene substrates toward the $CuCF_3$ observed in the current work is characteristic of Cu-mediated/catalyzed aromatic substitution reactions in general. This so-called ortho-effect,[58] originally discovered by Ullmann himself[59] 110 years ago and recognized by others[60] in the 1930s, was thoroughly studied[61] by the methods of physical organic chemistry in the 1960s and reviewed in the 1970s.[62−64] The accelerating effect of the nitro group in the ortho position reported by Clark[40] for the Cl/CF_3 exchange (see above) is yet another example of the general reactivity pattern that has received little study and virtually no understanding in the chemistry of aromatic trifluoromethylation. Clark also reported that this effect was absent in the case of cyano-substituted chloroarenes and therefore concluded that "the correct transition state geometry" was required for the ortho-effect to take place (Figure 4). Only weak activation of the C−Cl bond was observed in Clark's work for carbonyl-containing ortho-functionalities CHO, COMe, and CO_2Me.

The ortho-effect could not be explored for ArX (X = Br, I) in Clark's studies because bromoarenes and iodoarenes produced

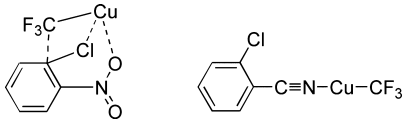

Figure 4. Proposed[40] "correct" (*o*-NO_2) and "incorrect" (*o*-CN) geometries of the transitions states in Cu-promoted trifluoromethylation of ortho-substituted chloroarenes.

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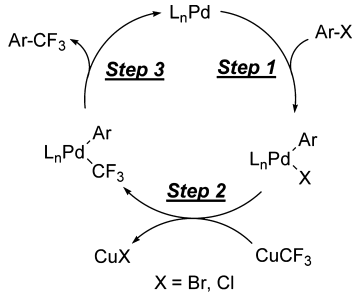
biaryls rather than CF_3 derivatives on treatment with $CuCF_3$ generated from Cu and CF_2Br_2 in DMAC.[40] In our work, the ortho-effect was observed for both aryl iodides and bromides. In accord with Clark's data, *o*-bromonitrobenzene was considerably more reactive than its meta and para isomers (Table 2, entries 21−23), while *o*- and *p*-bromobenzonitriles exhibited similar reactivity toward $CuCF_3$.

The strong ortho-effect of the carbonyl-containing substituents COOMe, COOH, CHO, and COMe found in our studies could be accounted for by coordination of the oxygen atoms of these groups to the Cu atom that would facilitate the reaction in the same manner as the nitro group (Figure 4). As *o*-iodoanisole **1d** is more reactive toward $CuCF_3$ than its meta (**1c**) and para (**1b**) isomers (Table 1), the methoxy group also exhibits the ortho effect. Furthermore, even a methyl group ortho to the carbon−halogen bond promotes the trifluoromethylation. In the 3-bromopyridine series, the reactivity of the C−Br bond is noticeably enhanced by the CH_3 group in the 2 or 4 position (Table 2, **3l** and **3m** vs **3k**; entries 12−14). We have also established and quantified the ortho-effect of the methyl group for the benzene series by measuring the rate constant ratio k_R/k_H = 3.5 for the reactions of ortho-bromotoluene (R = 2-CH_3) and bromobenzene with $CuCF_3$. While one might picture, with some stretch of imagination, the proposed chelation (Figure 4) for the methoxy group, it is hard to see how this mechanism can account for the activating effect of the methyl group that is neither an electron-acceptor[65] nor a lone electron pair donor. This minor, yet real reaction rate enhancement by the methyl substituent points to the general complexity of the ortho-effect that is currently being studied in our laboratories.

Palladium Catalysis. An obvious idea to overcome the problem of the intrinsically low reactivity of less activated aryl bromides and especially chlorides toward $CuCF_3$ would be to apply palladium catalysis. As proposed in Scheme 7, the catalytic

Scheme 7



loop would then include Ar−X bond activation via oxidative addition to Pd(0) (step 1), followed by transmetalation with $CuCF_3$ (step 2), and Ar−CF_3 reductive elimination (step 3). We have performed a number of experiments toward the development of such a process, albeit only limited turnover numbers have been achieved.[66] There are at least a few major problems with the catalytic loop presented in Scheme 7. One is the extremely difficult Ar−CF_3 reductive elimination from Pd(II). Since the discovery of the first example of this transformation with Xantphos in 2006,[13] only BrettPhos and RuPhos have been found[16] to effect this type of coupling, in spite of high research activity in the area. Another serious impediment to Pd-catalyzed trifluoromethylation of aryl halides with $CuCF_3$ is facile transfer of the stabilizing phosphine ligand on Pd to Cu and the irreversible poly trifluoromethylation of the Pd(II) center.[13,67] Finally, the enhanced reactivity of Pd complexes bearing a CF_3 ligand toward transmetalation[13] can lead to a quick loss of catalytic activity. The reaction between [$L_nPd(Ar)(X)$] and [$L_nPd(CF_3)(Ar)$] involved in the catalytic loop (Scheme 7) produces catalytically inactive [$L_nPd(CF_3)(X)$] and [$L_nPd(Ar)_2$]. This pathway for catalyst deactivation via transmetalation has been confirmed experimentally[13a] and discussed in more detail in our previous reports.[13d,68]

Cupration vs Deprotonation for Fluoroform Activation. There is a fundamental difference between the long known[18−22,26−28] deprotonation methodology and our new cupration reaction for activation and utilization of fluoroform. One would be mistaken to view these two as similar processes, despite the fact that the F_3C−H bond is cleaved in both cases. The mechanism of the reaction of fluoroform with strong bases evidently involves deprotonation that leads to CF_3^- carbanionic species that easily eliminate fluoride to produce difluorocarbene. As discussed in the Introduction, to avoid this decomposition, the deprotonation reactions must be run at a low temperature. The cupration reaction is not mediated by free CF_3^- but rather leads directly to the formation of the covalent Cu−CF_3 bond.[30] As a result, the cupration can be carried out at room temperature without the risk of CF_2 formation.

Another clear demonstration of the difference between the two methodologies is the vastly distinct reactivity of the CF_3 species produced by the two types of reactions. The trifluoromethyl anion generated on deprotonation of fluoroform readily adds to the C=O bond,[18−22,26−28] whereas the $CuCF_3$ is unreactive toward carbonyl functionalities, as can be clearly seen from the above-described results and our previous publications.[30−32] A particularly convincing manifestation of this point is the regiospecific trifluoromethylation of the carbon−halogen bond of α-haloketones that is effected by the $CuCF_3$ reagent[32] but is inconceivable for the deprotonation methods. Obviously, the direct cupration of fluoroform and its deprotonation constitute two distinct synthetic methodologies that complement each other rather than compete.[69]

■ CONCLUSIONS

Fluoroform-derived $CuCF_3$ has been found to exhibit remarkably high reactivity toward aryl and heteroaryl halides, performing most efficiently in the absence of any added ligands. With a broad variety of iodoarene substrates, these reactions occur under mild conditions (23−50 °C) and exhibit high chemoselectivity to furnish the desired trifluoromethylated products in consistently high, most often nearly quantitative yield (86−99%). Vastly less reactive aryl and heteroaryl bromides can be trifluoromethylated as well. Although the scope is narrower in this case, a considerable number of brominated pyridine, pyrimidine, pyrazine, and thiazole derivatives as well as aryl bromides bearing electron-withdrawing groups and/or ortho substituents have been trifluoromethylated in up to 99% yield. Trifluoromethylation of the aromatic C−Cl bond has been demonstrated only for the most electrophilic substrates such as 2-chloronicotinic acid (60% yield).

Another key feature of the aromatic trifluoromethylation reactions with fluoroform-derived $CuCF_3$ is their exceptionally high chemoselectivity. The side-formation of biaryls and C_2F_5 derivatives that is characteristic of many reported analogous transformations is not observed in the reactions of fluoroform-derived $CuCF_3$. Consequently, nearly 20 trifluoromethylated

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aromatic compounds have been isolated pure in high yield on a gram scale (up to 20 mmol) from the reactions of various ArX with fluoroform-derived $CuCF_3$.

Additional studies have revealed that (i) the by-produced Cu(I) halide destabilizes the $CuCF_3$ reagent, the magnitude of the effect varying directly with the Lewis acidity of the copper halide byproduct CuCl > CuBr > CuI; (ii) classical S_NAr and $S_{RN}1$ mechanisms are unlikely operational; and (iii) the reactions exhibit an ortho effect, i.e. the enhanced reactivity of o-substituted aryl halides 2-RC_6H_4X toward $CuCF_3$. Interestingly, this ortho-effect is observed for R = NO_2, COOH, CHO, COOEt, $COCH_3$, OCH_3, and even CH_3, but not for R = CN. The nature of the ortho-effect and the mechanism of the reaction of $CuCF_3$ with aryl halides are currently being studied in our laboratories.

The fluoroform-derived $CuCF_3$ reagent and its reactions with haloarenes provide an unmatched combination of reactivity, selectivity, and low cost. This set of properties along with the established substrate scope and reactivity patterns revealed in our studies offer opportunities for practicable developments of the method. Such developments, in turn, may allow us "to kill two birds with one stone" by utilizing the environmentally hazardous fluoroform waste streams as a chemical feedstock for making valuable fluorinated compounds.

EXPERIMENTAL SECTION

Anhydrous DMF was stored over freshly calcined 4 Å molecular sieves in a glovebox. NMR spectra were recorded on 400 and 500 MHz NMR spectrometers. Quantitative ^{19}F NMR analyses were carried out with D1 = 5 s.

Preparation of $CuCF_3$ from Fluoroform. Fluoroform-derived $CuCF_3$ reagents in DMF were prepared and stabilized with TREAT HF (1 equiv HF per Cu) following the literature procedure.[30] A summary of particular reagent solutions used in this work is presented in Table S1 of the Supporting Information. The reaction on a 0.1 mol scale was carried out as follows. In a glovebox, CuCl (purity 99%; 10 g; 100 mmol) was added to a solution of *t*-BuOK (purity 97%; 23.6 g; 204 mmol) in DMF (170 mL), and the reaction mixture was vigorously stirred for 30 min at room temperature. The precipitated KCl was filtered off and washed on the filter with DMF (30 mL). The combined filtrate and the washings were placed in a 12-oz Fischer–Porter vessel equipped with a pressure gauge, a needle valve, and a Teflon-coated magnetic stir-bar. The vessel was sealed, brought out, and evacuated on a vacuum line to ca. 1 mmHg, as previously described.[30] At vigorous stirring and additional cooling in an ice bath (to prevent overheating), fluoroform was introduced at ca. 50 psi over approximately 5 min until gas absorption ceased. A solution of TREAT HF (ca. 37% HF; 5.5 mL; 33 mmol) in DMF (15 mL) was then added at agitation under argon. The vessel was brought back to the glovebox and the solution of $CuCF_3$ (232–233 mL) together with the suspended KF produced in the stabilization step was transferred to a glass bottle for storage. For the determination of the yield of $CuCF_3$ and its concentration, to an aliquot of the solution (1 mL) was added 1,3-bis(trifluoromethyl)benzene as an internal standard (20 μL; 0.129 mmol), and the resultant sample was analyzed by ^{19}F NMR.

$CuCF_3$ reagents with extra TREAT HF (0.2 mol of extra TREAT HF per mol of stabilized $CuCF_3$) were prepared as follows. To a portion of the solid free supernatant of the stabilized $CuCF_3$ reagent (120 mL) was added, with vigorous stirring, TREAT HF (1.7 mL, 10.2 mmol). After ca. 1 h, the clear $CuCF_3$ solution over the produced and settled solid was used for trifluoromethylation reactions immediately or stored at −30 °C in the glovebox for further use.

(Trifluoromethyl)benzene (2a). In a glovebox, to iodobenzene (**1a**; purity >99%; 14 μL; 0.125 mmol) in an NMR tube was added at room temperature $CuCF_3$ containing an extra 0.2 equiv of TREAT HF (0.37 M; 0.51 mL; 1.5 equiv) and 1,3-bis(trifluoromethyl)benzene (internal standard; 9.7 μL). The NMR tube was sealed with a septum, brought out of the glovebox, and kept at room temperature for 24 h and then at 50 °C (oil bath) for 18 h. Quantitative ^{19}F NMR analysis of the reaction mixture indicated that **2a** was produced in 96% yield (<0.01 equiv of $CuCF_3$ remained in solution). After dilution with ether (2 mL) and washing with water (5 mL), the organic layer was filtered through a short silica gel plug and analyzed by GC–MS to determine the conversion of **1a** (>99%). Characterization of **2a** in reaction solution: m/z = 146 (GC–MS; EI); ^{19}F NMR (unlocked): δ = −61.9 (s).[13a]

1-Methoxy-4-(trifluoromethyl)benzene (2b). To 1-iodo-4-methoxybenzene (**1b**; purity 98%; 2.63 g; 11 mmol) was added under argon at room temperature $CuCF_3$ in DMF (0.38 M; 58 mL; 2 equiv) containing an extra 0.2 equiv of TREAT HF, and the mixture was stirred for 24 h at room temperature and then for 24 h at 50 °C. Ether (100 mL), water (300 mL) and aqueous NH_3 (33%; 8 mL) were added at agitation in air. The organic layer was separated and the aqueous layer was washed with ether (2 × 50 mL). The combined ether solutions were washed with brine (2 × 100 mL), dried over $MgSO_4$, filtered, and evaporated (25 °C; 100 mbar). The residue was dissolved in pentane, the solution was filtered through a short silica gel column, and evaporated (25 °C; 50 mbar) to give **2b** as a slightly yellowish oil (1.71 g; 88%). m/z = 176 (GC–MS; EI). ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.63 − 7.50 (m, 2H), 7.03–6.92 (m, 2H), 3.85 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 162.2 (q, $^5J_{C-F}$ = 1.2 Hz), 127.0 (q, $^3J_{C-F}$ = 3.8 Hz), 124.7 (q, $^1J_{C-F}$ = 271.0 Hz), 123.0 (q, $^2J_{C-F}$ = 32.7 Hz), 114.1, 55.5. ^{19}F NMR ($CDCl_3$, 376 MHz): δ = −61.6 (s).[12c]

1-Methoxy-3-(trifluoromethyl)benzene (2c). In a glovebox, to 1-iodo-3-methoxybenzene (**1c**; purity 98%; 16.5 μL; 0.125 mmol) in an NMR tube was added at room temperature $CuCF_3$ containing an extra 0.2 equiv of TREAT HF (0.38 M; 0.49 mL; 1.5 equiv) and 1,3-bis(trifluoromethyl)benzene (internal standard; 9.7 μL). The NMR tube was sealed with a septum, brought out of the glovebox, and kept at room temperature for 24 h and then at 50 °C (oil bath) for 18 h. Quantitative ^{19}F NMR analysis of the reaction mixture indicated that **2c** was produced in 96% yield (0.04 equiv of $CuCF_3$ remained unreacted). After dilution with ether (2 mL) and extraction with water (5 mL), the organic layer was filtered through a short silica gel plug and analyzed by GC–MS to determine the conversion of **1c** (99%). Characterization of **2c** in the reaction solution: m/z = 176 (GC–MS; EI); ^{19}F NMR (unlocked): δ = −61.9 (s).[31]

1-Methoxy-2-(trifluoromethyl)benzene (2d). To 1-iodo-2-methoxybenzene (**1d**; purity 98%; 1.33 mL; 10 mmol) was added under argon at room temperature $CuCF_3$ in DMF (0.37 M; 40.5 mL; 1.5 equiv) containing an extra 0.2 equiv of TREAT HF, and the mixture was stirred for 24 h at room temperature and then for 18 h at 50 °C. Ether (100 mL), water (200 mL), and aqueous NH_3 (33%; 5 mL) were added at agitation in air. The organic layer was separated and the aqueous layer was washed with ether (2 × 50 mL). The combined ether solutions were washed with brine (2 × 100 mL), dried over $MgSO_4$, filtered, and evaporated (25 °C; 100 mbar). The residue was filtered through a short silica gel plug in pentane and the filtrate was evaporated (25 °C; 50 mbar) to give **2d** as a colorless oil (1.53 g; 87%). m/z = 176 (GC–MS; EI). ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.61–7.54 (m, 1H), 7.53–7.46 (m, 1H), 7.05–6.97 (m, 2H), 3.91 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 157.7, 133.5, 127.1 (q, $^3J_{C-F}$ = 5.3 Hz), 124.1 (q, $^1J_{C-F}$ = 272.0 Hz), 120.1, 118.8 (q, $^2J_{C-F}$ = 30.7 Hz), 112.1, 55.7. ^{19}F NMR ($CDCl_3$, 376 MHz): δ = −62.5 (s).[70]

2,4-Dimethoxy-1-(trifluoromethyl)benzene (2e). To 1-iodo-2,4-dimethoxybenzene (**1e**; purity 97%; 1.63 g; 6 mmol) was added under argon at room temperature $CuCF_3$ in DMF (0.37 M; 24 mL; 1.5 equiv) containing an extra 0.2 equiv of TREAT HF, and the mixture was stirred for 72 h at room temperature. Ether (60 mL), water (120 mL), and aqueous NH_3 (33%; 3 mL) were added at agitation in air. The organic layer was separated and the aqueous layer was washed with ether (2 × 30 mL). The combined ether solutions were washed with brine (2 × 60 mL), dried over $MgSO_4$, filtered, and evaporated (25 °C, 50 mbar). A solution of the residue in pentane was filtered through a short silica gel plug and evaporated (25 °C, 20 mbar) to give **2e** as a slightly yellowish oil (1.20 g; 97%). m/z = 206 (GC–MS; EI). ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.47 (d, J = 8.6 Hz, 1H), 6.52 (d, J = 2.0 Hz, 1H), 6.48 (dd, J = 8.6, 2.0 Hz, 1H), 3.87 (s, 3H), 3.83 (s, 3H). ^{13}C

NMR ($CDCl_3$, 100 MHz): δ = 163.9, 159.0 (q, $^3J_{C-F}$ = 1.6 Hz), 128.3 (q, $^3J_{C-F}$ = 5.3 Hz), 124.2 (q, $^1J_{C-F}$ = 270.9 Hz), 111.6 (q, $^2J_{C-F}$ = 31.3 Hz), 103.9, 99.4, 55.8, 55.5. ^{19}F NMR ($CDCl_3$, 376 MHz): δ = −61.3 (s).[17l]

1-Methyl-4-(trifluoromethyl)benzene (2f). In a glovebox, to 1-iodo-4-methylbenzene (**1f**; purity 99%; 27 mg; 0.125 mmol) in an NMR tube was added at room temperature $CuCF_3$ in DMF containing an extra 0.2 equiv of TREAT HF (0.38 M; 0.66 mL; 2 equiv) and 1,3-bis(trifluoromethyl)benzene (internal standard; 9.7 μL). The NMR tube was sealed with a septum, brought out of the glovebox, and kept at room temperature for 24 h and then at 50 °C (oil bath) for 24 h. Quantitative ^{19}F NMR analysis of the reaction mixture indicated that **2f** was produced in 93% yield (<0.01 equiv of $CuCF_3$ remained unreacted). After dilution with ether (2 mL) and extraction with water (5 mL), the organic layer was filtered through a short silica gel plug and analyzed by GC−MS to determine the conversion (>99%). Characterization of **2f** in reaction solution: m/z = 160 (GC−MS; EI); ^{19}F NMR (unlocked): δ = −61.5 (s).[70]

1-Methyl-3-(trifluoromethyl)benzene (2g). In a glovebox, to 1-iodo-3-methylbenzene (**1g**; purity 99%; 16 μL; 0.125 mmol) in an NMR tube was added at room temperature $CuCF_3$ in DMF containing an extra 0.2 equiv of TREAT HF (0.38 M; 0.66 mL; 2 equiv) and 1,3-bis(trifluoromethyl)benzene (internal standard; 9.7 μL). The NMR tube was sealed with a septum, brought out of the glovebox, and kept at room temperature for 24 h and then at 50 °C (oil bath) for 24 h. Quantitative ^{19}F NMR analysis of the reaction mixture indicated that **2g** was produced in 99% yield (<0.01 equiv of $CuCF_3$ remained unreacted). After dilution with ether (2 mL) and extraction with water (5 mL), the organic layer was filtered through a short silica gel plug and analyzed by GC−MS to determine the conversion (>99%). Characterization of **2g** in reaction solution: m/z = 160 (GC−MS; EI); ^{19}F NMR (unlocked): δ = −61.8 (s).[70]

1-Methyl-2-(trifluoromethyl)benzene (2h). In a glovebox, to 1-iodo-2-methylbenzene (**1h**; purity 98%; 16 μL; 0.125 mmol) in an NMR tube was added at room temperature $CuCF_3$ in DMF containing an extra 0.2 equiv of TREAT HF (0.38 M; 0.49 mL; 1.5 equiv) and 1,3-bis(trifluoromethyl)benzene (internal standard; 9.7 μL). The NMR tube was sealed with a septum, brought out of the glovebox, and kept at room temperature for 24 h and then at 50 °C (oil bath) for 18 h. Quantitative ^{19}F NMR analysis of the reaction mixture indicated that **2h** was produced in 94% yield (<0.05 equiv of $CuCF_3$ remained unreacted). After dilution with ether (2 mL) and extraction with water (5 mL), the organic layer was filtered through a short silica gel plug and analyzed by GC−MS to determine the conversion (>99%). Characterization of **2h** in reaction solution: m/z = 160 (GC−MS; EI); ^{19}F NMR (unlocked): δ = −60.7 (s).[70]

2,4-Dimethyl-1-(trifluoromethyl)benzene (2i). In a glovebox, to 1-iodo-2,4-dimethylbenzene (**1i**; purity 97%; 18 μL; 0.125 mmol) in an NMR tube was added at room temperature $CuCF_3$ in DMF containing an extra 0.2 equiv of TREAT HF (0.38 M; 0.49 mL; 1.5 equiv) and 1,3-bis(trifluoromethyl)benzene (internal standard; 9.7 μL). The NMR tube was sealed with a septum, brought out of the glovebox, and kept at room temperature for 24 h and then at 50 °C (oil bath) for 18 h. Quantitative ^{19}F NMR analysis of the reaction mixture indicated that **2i** was produced in 97% yield (0.07 equiv of $CuCF_3$ remained unreacted). After dilution with ether (2 mL) and extraction with water (5 mL), the organic layer was filtered through a short silica gel plug and analyzed by GC−MS to determine the conversion (>99%). Characterization of **2i** in reaction solution: m/z = 174 (GC−MS; EI); ^{19}F NMR (unlocked): δ = −60.2 (s).[71]

1-(*tert*-Butyl)-4-(trifluoromethyl)benzene (2j). In a glovebox, to 1-(*tert*-butyl)-4-iodobenzene (**1j**; purity 95%; 22 μL; 0.125 mmol) in an NMR tube was added at room temperature $CuCF_3$ in DMF containing an extra 0.2 equiv of TREAT HF (0.38 M; 0.66 mL; 2 equiv) and 1,3-bis(trifluoromethyl)benzene (internal standard; 9.7 μL). The NMR tube was sealed with a septum, brought out of the glovebox, and kept at room temperature for 24 h and then at 50 °C (oil bath) for 24 h. Quantitative ^{19}F NMR analysis of the reaction mixture indicated that **2j** was produced in 95% yield (0.05 equiv of $CuCF_3$ remained unreacted). After dilution with ether (2 mL) and extraction with water (5 mL), the organic layer was filtered through a short silica gel plug and analyzed by GC−MS to determine the conversion (99%). Characterization of **2j** in reaction solution: m/z = 202 (GC−MS; EI); ^{19}F NMR (unlocked): δ = −61.5 (s).[17a]

Ethyl 4-(Trifluoromethyl)benzoate (2k). To ethyl 4-iodobenzoate (**1k**; purity 97%; 1.71 mL; 10 mmol) was added under argon at room temperature $CuCF_3$ in DMF (0.37 M; 40.5 mL; 1.5 equiv) containing an extra 0.2 equiv of TREAT HF, and the mixture was stirred for 24 h at room temperature and then for 18 h at 50 °C. Ether (100 mL), water (200 mL), and aqueous NH_3 (33%; 5 mL) were added at agitation in air. The organic layer was separated and the aqueous layer was washed with ether (2 × 50 mL). The combined ether solutions were washed with brine (2 × 100 mL), dried over $MgSO_4$, filtered, and evaporated (25 °C; 100 mbar). A solution of the residue in pentane was filtered through a short silica gel plug and evaporated (25 °C; 20 mbar) to give **2k** as a yellowish oil (2.09 g; 96%). m/z = 218 (GC−MS; EI). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.20−8.12 (m, 2H), 7.74−7.66 (m, 2H), 4.42 (q, J = 7.1 Hz, 2H), 1.41 (t, J = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 165.3, 134.3 (q, $^2J_{C-F}$ = 32.7 Hz), 133.8, 130.0, 125.3, 123.8 (q, $^1J_{C-F}$ = 272.6 Hz), 61.5, 14.2. ^{19}F NMR ($CDCl_3$, 376 MHz): δ = −63.2 (s).[12c]

4-(Trifluoromethyl)benzonitrile (2l). To 4-iodobenzonitrile (**1l**; purity 99%; 2.31 g; 10 mmol) was added under argon at room temperature $CuCF_3$ in DMF (0.37 M; 40.5 mL; 1.5 equiv) containing an extra 0.2 equiv of TREAT HF, and the mixture was stirred for 24 h at room temperature and then for 18 h at 50 °C. Ether (100 mL), water (200 mL), and aqueous NH_3 (33%; 5 mL) were added at agitation in air. The organic layer was separated and the aqueous layer was washed with ether (2 × 50 mL). The combined ether solutions were washed with brine (2 × 100 mL), dried over $MgSO_4$, filtered, and evaporated (25 °C, 50 mbar). The residue was dissolved in pentane/dichloromethane (2:1 v/v) and the solution was filtered through a short silica gel plug. The filtrate was evaporated (25 °C, 10 mbar) to afford **2l** as a light tan solid (1.62 g, 94%). m/z = 171 (GC−MS; EI). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.81 (d, J = 8.3 Hz, 2H), 7.76 (d, J = 8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 134.2 (q, $^2J_{C-F}$ = 33.3 Hz), 132.6, 126.0 (q, $^3J_{C-F}$ = 3.8 Hz), 123.0 (q, $^1J_{C-F}$ = 272.8 Hz), 117.3, 116.0 (q, $^5J_{C-F}$ = 1.5 Hz). ^{19}F NMR ($CDCl_3$, 471 MHz): δ = −63.6 (s).[70]

1-Nitro-4-(trifluoromethyl)benzene (2m). To 1-iodo-4-nitrobenzene (**1m**; purity 98%; 1.27 g; 5 mmol) was added under argon at room temperature $CuCF_3$ in DMF (0.38 M; 20 mL; 1.5 equiv) containing an extra 0.2 equiv of TREAT HF, and the mixture was stirred for 24 h at room temperature. Ether (50 mL), water (100 mL), and aqueous NH_3 (33%; 3 mL) were added at agitation in air. The organic layer was separated and the aqueous layer was washed with ether (2 × 25 mL). The combined ether solutions were washed with brine (2 × 50 mL), dried over $MgSO_4$, filtered, and evaporated (40 °C, 50 mbar). The residue was dissolved in pentane/dichloromethane (2:1 v/v) and the solution was filtered through a short silica gel plug. Evaporation of the filtrate (40 °C; 5 mbar; partial sublimation of the product was observed) gave **2m** as a white solid (0.80 g; 83%). m/z = 191 (GC−MS; EI). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.37−8.31 (m, 2H), 7.86−7.80 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 150.2, 136.1 (q, $^2J_{C-F}$ = 33.3 Hz), 126.9 (q, $^3J_{C-F}$ = 3.7 Hz), 124.2, 123.1 (q, $^1J_{C-F}$ = 273.0 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz): δ = −63.5 (s).[70]

1-(4-(Trifluoromethyl)phenyl)ethanone (2n). In a glovebox, to 1-(4-iodophenyl)ethanone (**1n**; purity 98%; 31 mg; 0.125 mmol) in an NMR tube was added at room temperature $CuCF_3$ in DMF containing an extra 0.2 equiv of TREAT HF (0.38 M; 0.49 mL; 1.5 equiv) and 1,3-bis(trifluoromethyl)benzene (internal standard; 9.7 μL). The NMR tube was sealed with a septum, brought out of the glovebox, and kept at room temperature for 24 h and then at 50 °C (oil bath) for 18 h. Quantitative ^{19}F NMR analysis of the reaction mixture indicated that **2n** was produced in 95% yield (0.1 equiv of $CuCF_3$ remained unreacted). After dilution with ether (2 mL) and washing with water (5 mL), the organic phase was filtered through a short silica gel plug and analyzed by GC−MS to determine the conversion (>99%). Characterization of **2n** in reaction solution: m/z = 188 (GC−MS; EI); ^{19}F NMR (unlocked): δ = −62.2 (s).[17a]

3-(Trifluoromethyl)benzaldehyde (2o). In a glovebox, to 3-iodobenzaldehyde (**1o**; purity 95%; 30 mg; 0.125 mmol) in an NMR tube was added at room temperature $CuCF_3$ in DMF containing an extra 0.2 equiv of TREAT HF (0.38 M; 0.49 mL; 1.5 equiv) and 1,3-bis(trifluoromethyl)benzene (internal standard; 9.7 μL). The NMR tube was sealed with a septum, brought out of the glovebox, and kept at room temperature for 24 h and then at 50 °C (oil bath) for 18 h. Quantitative ^{19}F NMR analysis of the reaction mixture indicated that **2o** was produced in 99% yield (0.07 equiv of $CuCF_3$ remained unreacted). After dilution with ether (2 mL) and extraction with water (5 mL), the organic layer was filtered through a short silica gel plug and analyzed by GC−MS to determine the conversion (>99%). Characterization of **2o** in reaction solution: m/z = 174 (GC−MS; EI); ^{19}F NMR (unlocked): δ = −62.2 (s). Lit.[72]

1-(Trifluoromethyl)naphthalene (2p). To 1-iodonaphthalene (**1p**; purity >98%; 3.0 mL; 20 mmol) was added under argon at room temperature $CuCF_3$ in DMF (0.37 M; 81 mL; 1.5 equiv) containing an extra 0.2 equiv of TREAT HF, and the mixture was stirred for 24 h at room temperature and then for 18 h at 50 °C. Ether (100 mL), water (400 mL) and aqueous NH_3 (33%; 10 mL) were added at agitation in air. The organic layer was separated and the aqueous layer was washed with ether (2 × 50 mL). The combined ether solutions were washed with brine (2 × 100 mL), dried over $MgSO_4$, filtered, and evaporated (25 °C; 50 mbar). The residue was dissolved in pentane and the solution was filtered through a short silica gel plug. Evaporation of the filtrate (25 °C; 10 mbar) gave **2p** as a colorless oil (3.9 g; 98%). m/z = 196 (GC−MS; EI). ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.37−8.27 (m, 1H), 8.03 (d, J = 8.3 Hz, 1H), 7.98−7.90 (m, 2H), 7.73−7.63 (m, 1H), 7.66−7.57 (m, 1H), 7.56−7.46 (m, 1H). ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 134.1, 132.9, 129.1 (q, $^4J_{C-F}$ = 1.2 Hz), 128.9, 127.8, 126.7, 126.2 (q, $^2J_{C-F}$ = 29.9 Hz), 125.0 (q, $^1J_{C-F}$ = 273.4 Hz), 124.8 (q, $^3J_{C-F}$ = 6.0 Hz), 124.4 (q, $^3J_{C-F}$ = 2.3 Hz), 124.2. ^{19}F NMR ($CDCl_3$, 376 MHz): δ = −59.7 (s).[70]

2-(Trifluoromethyl)benzamide (2q). To 2-iodobenzamide (**1q**; purity 98%; 2.52 g; 10 mmol) was added under argon at room temperature $CuCF_3$ in DMF (0.37 M; 30 mL; 1.1 equiv) containing an extra 0.2 equiv of TREAT HF, and the mixture was stirred for 15 min at room temperature. Ether (150 mL), water (150 mL), and aqueous NH_3 (33%; 5 mL) were added at agitation in air. The organic layer was separated and the aqueous layer was washed with ether (2 × 150 mL). The combined ether solutions were washed with brine (50 mL), dried over $MgSO_4$, filtered, and evaporated (40 °C, 20 mbar). The residue was crystallized from acetone/hexane (ca. 1:10 v/v) to give **2q** as a white solid (1.53 g; 81%). m/z = 189 (GC−MS; EI). ^1H NMR (acetone-d_6, 400 MHz): δ = 7.78−7.73 (m, 1H), 7.72−7.66 (m, 1H), 7.66−7.62 (m, 1H), 7.62−7.57 (m, 1H), 7.31 (bs, 1H), 7.02 (bs, 1H). ^{13}C NMR (acetone-d_6, 100 MHz): δ = 170.1, 137.8 (q, $^3J_{C-F}$ = 2.1 Hz), 133.0 (q, $^4J_{C-F}$ = 1.1 Hz), 130.4, 129.2, 127.6 (q, $^2J_{C-F}$ = 31.8 Hz), 127.1 (q, $^3J_{C-F}$ = 5.1 Hz), 124.9 (q, $^1J_{C-F}$ = 273.0 Hz). ^{19}F NMR (acetone-d_6, 376 MHz): δ = −59.7 (s). Anal. Calcd for $C_8H_6F_3NO$: C, 50.8; H, 3.2; N, 7.4. Found: C, 50.7; H, 3.2; N, 7.5. Lit.[73]

1-Bromo-4-(trifluoromethyl)benzene (2r). In a glovebox, to 1-bromo-4-iodobenzene (**1r**; purity 98%; 36 mg; 0.125 mmol) in an NMR tube was added at room temperature $CuCF_3$ in DMF containing an extra 0.2 equiv of TREAT HF (0.38 M; 0.49 mL; 1.5 equiv) and 1,3-bis(trifluoromethyl)benzene (internal standard; 9.7 μL). The NMR tube was sealed with a septum, brought out of the glovebox, and kept at room temperature for 24 h and then at 50 °C (oil bath) for 18 h. Quantitative ^{19}F NMR analysis of the reaction mixture indicated that **2r** was produced in 96% yield. The solution also contained ca. 4% of 1,4-$(CF_3)_2C_6H_4$ and 0.05 equiv of unreacted $CuCF_3$. After dilution with ether (2 mL) and extraction with water (5 mL), the organic layer was filtered through a short silica gel plug and analyzed by GC−MS to determine the conversion (>99%). Characterization of **2r** in reaction solution: m/z = 224, 226 (GC−MS; EI); ^{19}F NMR (unlocked): δ = −61.9 (s).[70]

1-Bromo-2-(trifluoromethyl)benzene (2s). In a glovebox, to 1-bromo-2-iodobenzene (**1s**; purity 95%; 16 μL; 0.125 mmol) in an NMR tube was added at room temperature $CuCF_3$ in DMF containing an extra 0.2 equiv of TREAT HF (0.38 M; 0.43 mL; 1.3 equiv) and 1,3-bis(trifluoromethyl)benzene (internal standard; 9.7 μL). The NMR tube was sealed with a septum, brought out of the glovebox, and kept at room temperature for 24 h and then at 50 °C (oil bath) for 24 h. Quantitative ^{19}F NMR analysis indicated that **2s** was produced in 95% yield. The solution also contained 3% of 1,2-$(CF_3)_2C_6H_4$ and unreacted $CuCF_3$ (<0.01 equiv). After dilution with ether (2 mL) and extraction with water (5 mL), the organic layer was filtered through a short silica gel plug and analyzed by GC−MS to determine the conversion (>99%). Characterization of **2s** in reaction solution: m/z = 224, 226 (GC−MS; EI); ^{19}F NMR (unlocked): δ = −61.6 (s).[74]

3-(Trifluoromethyl)pyridine (2t). In a glovebox, to 3-iodopyridine (**1t**; purity 98%; 26 mg; 0.125 mmol) in an NMR tube was added at room temperature $CuCF_3$ in DMF containing an extra 0.2 equiv of TREAT HF (0.38 M; 0.66 mL; 2 equiv) and 1,3-bis(trifluoromethyl)-benzene (internal standard; 9.7 μL). The NMR tube was sealed with a septum, brought out of the glovebox, and kept at room temperature for 24 h and then at 50 °C (oil bath) for 24 h. Quantitative ^{19}F NMR analysis of the reaction mixture indicated that **2t** was produced in 86% yield (<0.01 equiv of $CuCF_3$ remained unreacted). After dilution with ether (2 mL) and extraction with water (5 mL), the organic layer was filtered through a short silica gel plug and analyzed by GC−MS to determine the conversion (96%). Characterization of **2t** in reaction solution: m/z = 147 (GC−MS; EI); ^{19}F NMR (unlocked): δ = −61.7 (s).[70]

2-(Trifluoromethyl)thiophene (2u). In a glovebox, to 2-iodothiophene (**1u**; purity 98%; 14 μL; 0.125 mmol) in an NMR tube was added at room temperature $CuCF_3$ in DMF containing an extra 0.2 equiv of TREAT HF (0.37 M; 0.51 mL; 1.5 equiv) and 1,3-bis(trifluoromethyl)benzene (internal standard; 9.7 μL). The NMR tube was sealed with a septum, brought out of the glovebox, and kept at 50 °C (oil bath) for 18 h. Quantitative ^{19}F NMR analysis indicated that **2u** was produced in 87% yield (<0.05 equiv of $CuCF_3$ remained unreacted). After dilution with ether (2 mL) and extraction with water (5 mL), the organic layer was filtered through a short silica gel plug and analyzed by GC−MS to determine the conversion (>99%). Thiophene (7%) was also detected. Characterization of **2u** in reaction solution: m/z = 152 (GC−MS; EI); ^{19}F NMR (unlocked): δ = −54.1 (s).[70]

2-(Trifluoromethyl)pyridine (4a). To a solution of 2-bromopyridine (**3a**; 24 μL; 0.25 mmol) in DMF (0.25 mL) placed in an oil bath at 80 °C under argon, was added via a syringe pump over a period of 6 h a solution of $CuCF_3$ in DMF (0.37 M; 1.35 mL; 2 equiv) containing an extra 0.2 equiv of TREAT HF, and the mixture was stirred for additional 2 h at the same temperature. After the reaction mixture was allowed to cool to room temperature, ether (5 mL) and 1,3-bis(trifluoromethyl)benzene (internal standard; 19.4 μL) were added at agitation in air. The resultant suspension was filtered. Quantitative ^{19}F NMR analysis of the filtrate indicated that **4a** was produced in 90% yield. After washing with water (5 mL), the organic layer was filtered through a short silica gel plug and analyzed by GC−MS to determine the conversion of **3a** (>99%). Characterization of **4a** in reaction solution: m/z = 147 (GC−MS; EI); ^{19}F NMR (unlocked): δ = −67.2 (s).[40]

3-Methyl-2-(trifluoromethyl)pyridine (4b). In a glovebox, to 2-bromo-3-methylpyridine (**3b**; purity 95%; 15 μL; 0.125 mmol) in an NMR tube was added at room temperature $CuCF_3$ in DMF containing an extra 0.2 equiv of TREAT HF (0.39 M; 0.32 mL; 1 equiv) and 1,3-bis(trifluoromethyl)benzene (internal standard; 9.7 μL). The NMR tube was sealed with a septum, brought out of the glovebox, and heated at 50 °C (oil bath) for 15 h. After another portion of $CuCF_3$ (1 equiv) was added via syringe, the mixture was heated at 50 °C for additional 18 h. Quantitative ^{19}F NMR analysis of the reaction mixture indicated that **4b** was produced in 88% yield (<0.01 equiv of $CuCF_3$ remained unreacted). After dilution with ether (2 mL) and washing with water (5 mL), the organic layer was filtered through a short silica gel plug and analyzed by GC−MS to determine the conversion (>99%). Characterization of **4b** in reaction solution: m/z = 161 (GC−MS; EI); ^{19}F NMR (unlocked): δ = −64.3 (s). Lit.[75]

4-Methyl-2-(trifluoromethyl)pyridine (4c). In a glovebox, to 2-bromo-4-methylpyridine (**3c**; purity 97%; 14 μL; 0.125 mmol) in an NMR tube was added at room temperature $CuCF_3$ in DMF containing

an extra 0.2 equiv of TREAT HF (0.39 M; 0.32 mL; 1 equiv) and 1,3-bis(trifluoromethyl)benzene (internal standard; 9.7 μL). The NMR tube was sealed with a septum, brought out of the glovebox, and heated at 50 °C (oil bath) for 15 h. Another portion of $CuCF_3$ (1 equiv) was then added *via* syringe and the mixture was heated at 50 °C for additional 18 h. Quantitative ^{19}F NMR analysis indicated that **4c** was produced in 80% yield (<0.01 equiv of $CuCF_3$ remained unreacted). After dilution with ether (2 mL) and extraction with water (5 mL), the organic layer was filtered through a short silica gel plug and analyzed by GC−MS to determine the conversion (98%). Characterization of **4c** in reaction solution: m/z = 161 (GC−MS; EI); ^{19}F NMR (unlocked): δ = −67.2 (s). Lit.[75]

5-Methyl-2-(trifluoromethyl)pyridine (4d). In a glovebox, to 2-bromo-5-methylpyridine (**3d**; purity 98%; 22 mg; 0.125 mmol) in an NMR tube was added at room temperature $CuCF_3$ in DMF containing an extra 0.2 equiv of TREAT HF (0.39 M; 0.32 mL; 1 equiv) and 1,3-bis(trifluoromethyl)benzene (internal standard; 9.7 μL). The NMR tube was sealed with a septum, brought out of the glovebox, and heated at 50 °C (oil bath) for 15 h. Another portion of $CuCF_3$ (1 equiv) was then added *via* syringe and the mixture was heated at 50 °C for additional 18 h. Quantitative ^{19}F NMR analysis of the reaction mixture indicated that **4d** was produced in 77% yield (<0.01 equiv of $CuCF_3$ remained unreacted). After dilution with ether (2 mL) and extraction with water (5 mL), the organic layer was filtered through a short silica gel plug and analyzed by GC−MS to determine the conversion (96%). Characterization of **4d** in reaction solution: m/z = 161 (GC−MS; EI); ^{19}F NMR (unlocked): δ = −66.8 (s). Lit.[75]

6-Methyl-2-(trifluoromethyl)pyridine (4e). In a glovebox, to 2-bromo-6-methylpyridine (**3e**; purity 98%; 14.5 μL; 0.125 mmol) in an NMR tube was added at room temperature $CuCF_3$ in DMF containing an extra 0.2 equiv of TREAT HF (0.39 M; 0.32 mL; 1 equiv) and 1,3-bis(trifluoromethyl)benzene (internal standard; 9.7 μL). The NMR tube was sealed with a septum, brought out of the glovebox, and heated at 50 °C (oil bath) for 15 h. Another portion of $CuCF_3$ (1 equiv) was then added *via* syringe and the mixture was heated at 50 °C for additional 18 h. Quantitative ^{19}F NMR analysis indicated that **4e** was produced in 73% yield (<0.01 equiv of $CuCF_3$ remained unreacted). After dilution with ether (2 mL) and extraction with water (5 mL), the organic layer was filtered through a short silica gel plug and analyzed by GC−MS to determine the conversion (91%). Characterization of **4e** in reaction solution: m/z = 161 (GC−MS; EI); ^{19}F NMR (unlocked): δ = −67.3 (s). Lit.[75]

2-(Trifluoromethyl)quinolone (4f). To 2-bromoquinoline (**3f**; purity 95%; 1.095 g; 5 mmol) was added under argon at room temperature $CuCF_3$ in DMF (0.37 M; 27 mL; 2 equiv) containing an extra 0.2 equiv of TREAT HF, and the mixture was stirred for 48 h at room temperature. Ether (50 mL), water (150 mL), and aqueous NH_3 (33%; 5 mL) were added at agitation in air. The organic layer was separated and the aqueous layer was washed with ether (2 × 50 mL). The combined ether solutions were washed with brine (50 mL), dried over $MgSO_4$, filtered, and evaporated (40 °C, 50 mbar). The residue was dissolved in pentane/dichloromethane (5:1 v/v), the solution was filtered through a short silica gel plug, and evaporated (40 °C; 10 mbar) to give **4f** as a yellowish solid (0.79 g; 80%). m/z = 197 (GC−MS; EI). ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.27 (d, J = 8.5 Hz, 1H), 8.19 (d, J = 8.5 Hz, 1H), 7.83 (d, J = 8.3 Hz, 1H), 7.77 (ddd, J = 8.5, 6.9, 1.5 Hz, 1H), 7.68 (d, J = 8.5 Hz, 1H), 7.62 (ddd, J = 8.1, 7.0, 1.1 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 147.9 (q, $^2J_{C-F}$ = 34.6 Hz), 147.2, 138.2, 130.9, 130.1, 128.9, 128.6, 127.8, 121.7 (q, $^1J_{C-F}$ = 275.2 Hz), 116.8 (q, $^3J_{C-F}$ = 2.1 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz): δ = −67.5 (s).[15a]

Methyl 2-(Trifluoromethyl)nicotinate (4g). To methyl 2-bromonicotinate (**3g**; purity 97%; 668 mg; 3 mmol) was added under argon at room temperature $CuCF_3$ in DMF (0.37 M; 12 mL; 1.5 equiv) containing an extra 0.2 equiv of TREAT HF, and the mixture was stirred for 12 h at room temperature. Ether (60 mL), water (120 mL), and aqueous NH_3 (33%; 2 mL) were added at agitation in air. The organic layer was separated and the aqueous layer was washed with ether (2 × 30 mL). The combined ether solutions were washed with brine (120 mL), dried over $MgSO_4$, filtered, and evaporated (25 °C, 100 mbar). The residue was dissolved in pentane/dichloromethane (1:3 v/v), the solution was filtered through a short silica gel plug, and evaporated (25 °C; 10 mbar) to give **4g** as a colorless oil (0.56 g; 91%). m/z = 205 (GC−MS; EI). ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.74 (dd, J = 4.8, 1.3 Hz, 1H), 8.12−7.99 (m, 1H), 7.54 (dd, J = 7.9, 4.8 Hz, 1H), 3.91 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 165.8, 150.9, 145.6 (q, $^2J_{C-F}$ = 35.2 Hz), 138.3, 127.8 (q, $^3J_{C-F}$ = 1.1 Hz), 126.1, 121.1 (q, $^1J_{C-F}$ = 275.0 Hz), 53.2. ^{19}F NMR ($CDCl_3$, 376 MHz): δ = −64.9 (s). Anal. Calcd for $C_8H_6F_3NO_2$: C, 46.8; H, 3.0; N, 6.8. Found: C, 46.9; H, 3.1; N, 6.9.

2-(Trifluoromethyl)nicotinaldehyde (4h). In a glovebox, to 2-bromonicotinaldehyde (**3h**; 23 mg; 0.125 mmol) in an NMR tube was added at room temperature $CuCF_3$ in DMF containing an extra 0.2 equiv of TREAT HF (0.38 M; 0.49 mL; 1.5 equiv) and 1,3-bis(trifluoromethyl)benzene (internal standard; 9.7 μL). The NMR tube was sealed with a septum, brought out of the glovebox, and kept at room temperature for 12 h. Quantitative ^{19}F NMR analysis of the reaction mixture indicated that **4h** was produced in 94% yield (0.1 equiv of $CuCF_3$ remained unreacted). After dilution with ether (2 mL) and extraction with water (5 mL), the organic layer was filtered through a short silica gel plug and analyzed by GC−MS to determine the conversion (>99%). Characterization of **4h** in reaction solution: m/z = 175 (GC−MS; EI); ^{19}F NMR (unlocked): δ = −60.0 (s). Lit.[76]

5-Nitro-2-(trifluoromethyl)pyridine (4i). To 2-bromo-5-nitropyridine (**3i**; 1.218 g; 6 mmol) was added under argon at room temperature $CuCF_3$ in DMF (0.38 M; 24 mL; 1.5 equiv) containing an extra 0.2 equiv of TREAT HF, and the mixture was stirred for 24 h at room temperature. Ether (50 mL), water (150 mL), and aqueous NH_3 (33%; 5 mL) were added at agitation in air. The organic layer was separated and the aqueous layer was washed with ether (2 × 50 mL). The combined ether solutions were washed with brine (50 mL), dried over $MgSO_4$, filtered, and evaporated (25 °C; 100 mbar). The residue was dissolved in pentane/dichloromethane (4:1 v/v) and the solution was filtered through a short silica gel plug and evaporated (25 °C, 10 mbar) to give **4i** as a yellowish solid (1.05 g; 91%). m/z = 192 (GC−MS; EI). ^1H NMR ($CDCl_3$, 400 MHz): δ = 9.52 (d, J = 2.3 Hz, 1H), 8.69 (ddd, J = 8.6, 2.5, 0.8 Hz, 1H), 7.94 (dd, J = 8.5, 0.7 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 152.8 (q, $^2J_{C-F}$ = 35.9 Hz), 145.6, 145.5, 133.1, 121.4 (q, $^3J_{C-F}$ = 2.7 Hz), 120.6 (q, $^1J_{C-F}$ = 275.0 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz): δ = −68.3 (s).[40] Anal. Calcd for $C_6H_3F_3N_2O_2$: C, 37.5; H, 1.6; N, 14.6. Found: C, 37.7; H, 1.6; N, 14.6.

3-Methyl-5-nitro-2-(trifluoromethyl)pyridine (4j). To 2-bromo-3-methyl-5-nitropyridine (**3j**; 651 mg; 3 mmol) was added under argon at room temperature $CuCF_3$ in DMF (0.37 M; 12 mL; 1.5 equiv) containing an extra 0.2 equiv of TREAT HF, and the mixture was stirred for 24 h at room temperature. Ether (60 mL), water (120 mL), and aqueous NH_3 (33%; 2 mL) were added at agitation in air. The organic layer was separated and the aqueous layer was washed with ether (2 × 30 mL). The combined ether solutions were washed with brine (60 mL), dried over $MgSO_4$, filtered, and evaporated (25 °C, 100 mbar). The residue was dissolved in pentane/dichloromethane (1:4 v/v) and the solution was filtered through a short silica gel plug and evaporated (25 °C, 10 mbar) to give **4j** as a yellowish oil (0.57 g; 92%). m/z = 206 (GC−MS; EI). ^1H NMR ($CDCl_3$, 400 MHz): δ = 9.25 (d, J = 2.4 Hz, 1H), 8.47−8.42 (m, 1H), 2.68−2.61 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 150.6 (q, $^2J_{C-F}$ = 34.0 Hz), 145.3, 141.5, 135.2, 134.5, 121.4 (q, $^1J_{C-F}$ = 276.2 Hz), 18.2 (q, $^3J_{C-F}$ = 2.7 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz): δ = −65.9 (q, $^5J_{H-F}$ = 1.6 Hz). Anal. Calcd for $C_7H_5F_3N_2O_2$: C, 40.8; H, 2.5; N, 13.6. Found: C, 41.2; H, 2.6; N, 13.6.

3-(Trifluoromethyl)pyridine (4k). In a glovebox, to 3-bromopyridine (**3k**; 12 μL; 0.125 mmol) in an NMR tube was added at room temperature $CuCF_3$ in DMF containing an extra 0.2 equiv of TREAT HF (0.37 M; 0.51 mL; 1.5 equiv) and 1,3-bis(trifluoromethyl)benzene (internal standard; 9.7 μL). The NMR tube was sealed with a septum, brought out of the glovebox, and heated at 60 °C for 15 h. Quantitative ^{19}F NMR analysis indicated that **4k** was produced in 8% yield (<0.01 equiv of $CuCF_3$ remained unreacted). After dilution with ether (2 mL) and extraction with water (5 mL), the organic layer was filtered through a short silica gel plug and analyzed by GC−MS to estimate the conversion (<20%). Characterization of **4k** in reaction solution: m/z = 147 (GC−MS; EI); ^{19}F NMR (unlocked): δ = −61.7 (s).[70]

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2-Methyl-3-(trifluoromethyl)pyridine (4l). In a glovebox, to 3-bromo-2-methylpyridine (**3l**; 14 μL; 0.125 mmol) in an NMR tube was added at room temperature $CuCF_3$ in DMF containing an extra 0.2 equiv of TREAT HF (0.37 M; 0.51 mL; 1.5 equiv) and 1,3-bis(trifluoromethyl)benzene (internal standard; 9.7 μL). The NMR tube was sealed with a septum, brought out of the glovebox, and heated at 60 °C for 15 h. Quantitative ^{19}F NMR analysis indicated that **4l** was produced in 20% yield (<0.01 equiv of $CuCF_3$ remained unreacted). After dilution with ether (2 mL) and extraction with water (5 mL), the organic layer was filtered through a short silica gel plug and analyzed by GC−MS to determine the conversion (30%). Characterization of **4l** in reaction solution: m/z = 161 (GC−MS; EI); ^{19}F NMR (unlocked): δ = −61.5 (s).

4-Methyl-3-(trifluoromethyl)pyridine (4m). In a glovebox, to 3-bromo-4-methylpyridine (**3m**; 14 μL; 0.125 mmol) in an NMR tube was added at room temperature $CuCF_3$ in DMF containing an extra 0.2 equiv of TREAT HF (0.37 M; 0.51 mL; 1.5 equiv) and 1,3-bis(trifluoromethyl)benzene (internal standard; 9.7 μL). The NMR tube was sealed with a septum, brought out of the glovebox, and heated at 60 °C for 15 h. Quantitative ^{19}F NMR analysis of the reaction mixture indicated that **4m** was produced in 17% yield (<0.01 equiv of $CuCF_3$ remained unreacted). After dilution with ether (2 mL) and extraction with water (5 mL), the organic layer was filtered through a short silica gel plug and analyzed by GC−MS to determine the conversion (35%). Characterization of **4m** in reaction solution: m/z = 161 (GC−MS; EI); ^{19}F NMR (unlocked): δ = −60.5 (s).

2-(Trifluoromethyl)pyrimidine (4n). In a glovebox, to 2-bromopyrimidine (**3n**; purity 98%; 20 mg; 0.125 mmol) in an NMR tube was added at room temperature $CuCF_3$ in DMF containing an extra 0.2 equiv of TREAT HF (0.38 M; 0.49 mL; 1.5 equiv) and 1,3-bis(trifluoromethyl)benzene (internal standard; 9.7 μL). The NMR tube was sealed with a septum, brought out of the glovebox, and kept at room temperature for 18 h. Quantitative ^{19}F NMR analysis indicated that **4n** was produced in 95% yield (0.2 equiv of $CuCF_3$ remained unreacted). After dilution with ether (2 mL) and extraction with water (5 mL), the organic layer was filtered through a short silica gel plug and analyzed by GC−MS to determine the conversion (99%). Characterization of **4n** in reaction solution: m/z = 148 (GC−MS; EI); ^{19}F NMR (unlocked): δ = −69.8 (s).[40]

5-(Trifluoromethyl)pyrimidine (4o). In a glovebox, to 5-bromopyrimidine (**3o**; purity 98%; 20 mg; 0.125 mmol) in an NMR tube was added at room temperature $CuCF_3$ in DMF (0.37 M; 0.51 mL; 1.5 equiv) and 1,3-bis(trifluoromethyl)benzene (internal standard; 9.7 μL). The NMR tube was sealed with a septum, brought out of the glovebox, and heated at 50 °C (oil bath) for 18 h. Quantitative ^{19}F NMR analysis of the reaction mixture indicated that **4o** was produced in 24% yield (<0.01 equiv of $CuCF_3$ remained unreacted). Characterization of **4o** in reaction solution: m/z = 148 (GC−MS; EI); ^{19}F NMR (unlocked): δ = −61.8 (s).

2,5-Bis(trifluoromethyl)pyrazine (4p). In a glovebox, to 2,5-dibromopyrazine (**3p**; 30 mg; 0.125 mmol) in an NMR tube was added at room temperature $CuCF_3$ in DMF containing an extra 0.2 equiv of TREAT HF (0.36 M; 1.0 mL; 3 equiv) and 1,3-bis(trifluoromethyl)-benzene (internal standard; 9.7 μL). The NMR tube was sealed with a septum, brought out of the glovebox, and kept at room temperature for 24 h. Quantitative ^{19}F NMR analysis of the reaction mixture indicated that **4p** was produced in 94% yield (0.25 equiv of $CuCF_3$ remained unreacted). After dilution with ether (2 mL) and extraction with water (5 mL), the organic layer was filtered through a short silica gel plug and analyzed by GC−MS to determine the conversion (>99%). Characterization of **4p** in reaction solution: m/z = 216 (GC−MS; EI); ^{19}F NMR (unlocked): δ = −67.1 (s).

2-(Trifluoromethyl)thiazole (4q). In a glovebox, to 2-bromothiazole (**3q**, 11 μL, 0.125 mmol) in an NMR tube was added at room temperature $CuCF_3$ in DMF (0.37 M; 0.34 mL; 1 equiv) and 2-(trifluoromethyl)pyridine **4a** (internal standard; 14 μL). The NMR tube was sealed with a septum, brought out of the glovebox, and kept at room temperature for 24 h and then at 50 °C (oil bath) for 15 h. Quantitative ^{19}F NMR analysis of the reaction mixture indicated that **4q** was produced in 35% yield (<0.01 equiv of $CuCF_3$ remained unreacted). After dilution with ether (2 mL) and extraction with water (5 mL), the organic layer was filtered through a short silica gel plug and analyzed by GC−MS to determine the conversion (>80%). Characterization of **4q** in reaction solution: m/z = 153 (GC−MS; EI); ^{19}F NMR (unlocked): δ = −60.0 (s).

5-Nitro-2-(trifluoromethyl)thiazole (4r). To a solution of 2-bromo-5-nitrothiazole (**3r**; purity 98%; 79 mg; 0.37 mmol) in DMF (0.2 mL) under argon, at 50 °C, was added via a syringe pump, over 12 h $CuCF_3$ in DMF (0.37 M; 1 mL; 1 equiv), and the mixture was stirred for additional 6 h at this temperature. After cooling to room temperature, ether (5 mL) and 2-(trifluoromethyl)pyridine **4a** (internal standard; 43 μL) were added at agitation in air. The resultant suspension was filtered and analyzed by ^{19}F NMR to determine the yield of **4r** (55%). GC−MS analysis showed >99% conversion of **3r**. Characterization of **4r** in reaction solution: m/z = 198 (GC−MS; EI); ^{19}F NMR (unlocked): δ = −61.9 (s).

4-(Trifluoromethyl)pyridine (4s). In a glovebox, to 4-bromopyridine hydrochloride (**3s**; 25 mg; 0.125 mmol) in an NMR tube was added at room temperature $CuCF_3$ in DMF containing an extra 0.2 equiv of TREAT HF (0.37 M; 1.0 mL; 3 equiv) and 1,3-bis(trifluoromethyl)benzene (internal standard; 9.7 μL). The NMR tube was sealed with a septum, brought out of the glovebox, and kept at room temperature for 24 h and then at 50 °C (oil bath) for 15 h. Quantitative ^{19}F NMR analysis indicated that **4s** was produced in 74% yield (<0.01 equiv of $CuCF_3$ remained unreacted). After dilution with ether (2 mL) and extraction with water (5 mL), the organic layer was filtered through a short silica gel plug and analyzed by GC−MS to determine the conversion (85%). Characterization of **4s** in reaction solution: m/z = 147 (GC−MS; EI); ^{19}F NMR (unlocked): δ = −64.0 (s). Lit.[77]

1-Nitro-2-(trifluoromethyl)benzene (4t). To 1-bromo-2-nitrobenzene (**3t**; 2.06 g; 10 mmol) was added under argon at room temperature $CuCF_3$ in DMF (0.37 M; 35 mL; 1.3 equiv) containing an extra 0.2 equiv of TREAT HF, and the mixture was stirred for 12 h at room temperature and then for 6 h at 50 °C. Ether (50 mL), water (250 mL), and aqueous NH_3 (33%; 5 mL) were added at agitation in air. The organic layer was separated and the aqueous layer was washed with ether (2 × 50 mL). The combined ether solutions were washed with brine (2 × 50 mL), dried over $MgSO_4$, filtered, and evaporated (25 °C, 100 mbar). The residue was dissolved in pentane/dichloromethane (4:1 v/v) and the solution was filtered through a short silica gel plug and evaporated (25 °C, 10 mbar) to give **4t** as a yellowish solid (1.685 g; 88%). m/z = 191 (GC−MS; EI). ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.93−7.85 (m, 1H), 7.88−7.81 (m, 1H), 7.78−7.70 (m, 2H). ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 148.1, 133.4, 132.8, 127.9 (q, $^3J_{C-F}$ = 5.2 Hz), 124.9, 123.2 (q, $^2J_{C-F}$ = 33.9 Hz), 122.2 (q, $^1J_{C-F}$ = 273.0 Hz). ^{19}F NMR ($CDCl_3$, 471 MHz): δ = −60.1 (s).[40]

1-Nitro-3-(trifluoromethyl)benzene (4u). In a glovebox, to 1-bromo-3-nitrobenzene (**3u**; 25 mg; 0.125 mmol) in an NMR tube was added at room temperature $CuCF_3$ in DMF containing an extra 0.2 equiv of TREAT HF (0.38 M; 0.49 mL; 1.5 equiv) and 1,3-bis(trifluoromethyl)benzene (internal standard; 9.7 μL). The NMR tube was sealed with a septum, brought out of the glovebox, and kept at room temperature for 24 h and then at 50 °C (oil bath) for 24 h. Quantitative ^{19}F NMR analysis of the reaction mixture indicated that **4u** was produced in 22% yield (<0.05 equiv of $CuCF_3$ remained unreacted). After dilution with ether (2 mL) and extraction with water (5 mL), the organic layer was filtered through a short silica gel plug and analyzed by GC−MS to estimate the conversion (ca. 20%). Characterization of **4u** in reaction solution: m/z = 191 (GC−MS; EI); ^{19}F NMR (unlocked): δ = −62.6 (s).[17a]

1-Nitro-4-(trifluoromethyl)benzene (4v). To a stirring solution of 1-bromo-4-nitrobenzene (**3v**; 51 mg; 0.25 mmol) in DMF (0.25 mL) under argon at 80 °C (oil bath) was added, via a syringe pump over a period of 4 h, $CuCF_3$ in DMF containing an extra 0.2 equiv of TREAT HF (0.36 M; 1.39 mL; 2 equiv). After the addition was finished, the mixture was stirred at 80 °C for additional 2 h. The reaction mixture was allowed to cool to room temperature and treated with ether (5 mL) and 1,3-bis(trifluoromethyl)benzene (internal standard, 19.4 μL) at agitation in air. The resultant suspension was

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filtered. Quantitative ^{19}F NMR analysis of the filtrate indicated that **4v** was produced in 60% yield. After washing with water (5 mL) and subsequent filtration through a short silica gel plug, the organic phase was analyzed by GC−MS to determine the conversion (61%). Characterization of **4v** in reaction solution: m/z = 191 (GC−MS; EI); ^{19}F NMR (unlocked): δ = −62.2 (s).[70]

2-(Trifluoromethyl)benzonitrile (4w). In a glovebox, to 2-bromobenzonitrile (**3w**; purity 98%; 23 mg; 0.125 mmol) in an NMR tube was added at room temperature $CuCF_3$ in DMF containing an extra 0.2 equiv of TREAT HF (0.36 M; 0.52 mL; 1.5 equiv) and 1,3-bis(trifluoromethyl)benzene (internal standard; 9.7 μL). The NMR tube was sealed with a septum, brought out of the glovebox, and kept at room temperature for 72 h. Quantitative ^{19}F NMR analysis of the reaction mixture indicated that **4w** was produced in 30% yield (0.65 equiv of $CuCF_3$ remained unreacted). After dilution with ether (2 mL) and extraction with water (5 mL), the organic layer was filtered through a short silica gel plug and analyzed by GC−MS to determine the conversion (ca. 27%). Characterization of **4w** in reaction solution: m/z = 171 (GC−MS; EI); ^{19}F NMR (unlocked): δ = −61.1 (s). Lit.[73]

4-(Trifluoromethyl)benzonitrile (4x). In a glovebox, to 4-bromobenzonitrile (**3x**; purity 98%; 23 mg; 0.125 mmol) in an NMR tube was added at room temperature $CuCF_3$ in DMF containing an extra 0.2 equiv of TREAT HF (0.36 M; 0.52 mL; 1.5 equiv) and 1,3-bis(trifluoromethyl)benzene (internal standard; 9.7 μL). The NMR tube was sealed with a septum, brought out of the glovebox, and kept at room temperature for 72 h. Quantitative ^{19}F NMR analysis of the reaction mixture indicated that **4x** was produced in 31% yield (0.55 equiv of $CuCF_3$ remained unreacted). After dilution with ether (2 mL) and extraction with water (5 mL), the organic layer was filtered through a short silica gel plug and analyzed by GC−MS to determine the conversion (ca. 27%). Characterization of **4x** in reaction solution: m/z = 171 (GC−MS; EI); ^{19}F NMR (unlocked): δ = −62.6 (s).[70]

Methyl 2-(Trifluoromethyl)benzoate (4y). To methyl 2-bromobenzoate (**3y**; purity 98% 1.43 mL; 10 mmol) was added under argon at room temperature $CuCF_3$ in DMF (0.37 M, 54 mL, 2 equiv) containing an extra 0.2 equiv of TREAT HF, and the mixture was stirred for 24 h at room temperature and then for 24 h at 50 °C. Ether (100 mL), water (300 mL), and aqueous NH_3 (33%; 10 mL) were added at agitation in air. The organic layer was separated and the aqueous layer was washed with ether (2 × 50 mL). The combined ether solutions were washed with brine (2 × 100 mL), dried over $MgSO_4$, filtered, and evaporated (25 °C; 100 mbar). The residue was dissolved in pentane/dichloromethane (4:1 v/v) and the solution was filtered through a short silica gel plug and evaporated (25 °C; 10 mbar) to give **4y** as a slightly yellowish oil (1.94 g; 95%). m/z = 204 (GC−MS; EI). ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.82−7.75 (m, 1H), 7.77−7.71 (m, 1H), 7.65−7.57 (m, 2H), 3.94 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 167.0, 131.7 (q, $^4J_{C-F}$ = 0.8 Hz), 131.1, 131.0 (q, $^3J_{C-F}$ = 2.4 Hz), 130.0, 128.5 (q, $^2J_{C-F}$ = 32.4 Hz), 126.5 (q, $^3J_{C-F}$ = 5.4 Hz), 123.4 (q, $^1J_{C-F}$ = 273.1 Hz), 52.4. ^{19}F NMR ($CDCl_3$, 376 MHz): δ = −59.9 (q, $^5J_{H-F}$ = 1.6 Hz).[70]

2-(Trifluoromethyl)benzoic Acid (4z). To 2-bromobenzoic acid (**3z**; purity 97%; 207 mg; 1 mmol) was added under argon at room temperature $CuCF_3$ in DMF (0.38 M; 2.9 mL; 1.1 equiv) containing an extra 0.2 equiv of TREAT HF, and the mixture was stirred for 15 min at room temperature. Ether (20 mL) and aqueous HCl (2N; 30 mL) were added at agitation in air. The organic layer was separated and the aqueous layer was washed with ether (2 × 10 mL). The combined ether solutions were washed with brine (2 × 10 mL), dried over $MgSO_4$, and filtered. A small amount of silica gel was added to the filtrate and the solvent was removed under reduced pressure. The residue was placed onto a short silica gel column and washed with EtOAc/hexane (1:4 v/v). Evaporation of the eluate gave **4z** as a white solid (147 mg; 77%). m/z = 190 (GC−MS; EI). ^1H NMR (acetone-d_6, 400 MHz): δ = 7.94−7.87 (m, 1H), 7.88−7.82 (m, 1H), 7.82−7.72 (m, 2H), 5.50−2.00 (bs, 1H). ^{13}C NMR (acetone-d_6, 100 MHz): δ = 167.9, 133.2 (q, $^4J_{C-F}$ = 1.1 Hz), 132.7 (q, $^3J_{C-F}$ = 2.2 Hz), 132.2, 131.1, 128.8 (q, $^2J_{C-F}$ = 32.2 Hz), 127.5 (q, $^3J_{C-F}$ = 5.5 Hz), 124.6 (q, $^1J_{C-F}$ = 272.6 Hz). ^{19}F NMR (acetone-d_6, 376 MHz): δ = −59.9 (s). Lit.[78]

5-Bromo-2-(trifluoromethyl)benzoic acid (4aa). To 2,5-dibromobenzoic acid (**3aa**; purity 96%; 2.92 g; 10 mmol) was added under argon at room temperature $CuCF_3$ in DMF (0.37 M; 30 mL; 1.1 equiv) containing an extra 0.2 equiv of TREAT HF, and the mixture was stirred for 10 min at room temperature. Ether (100 mL) and aqueous HCl (2N; 150 mL) were added at agitation in air. The organic layer was separated and the aqueous layer was washed with ether (2 × 50 mL). The combined ether solutions were washed with brine (2 × 50 mL), dried over $MgSO_4$, and filtered. A small amount of silica gel was added to the filtrate and the solvent was removed under reduced pressure. The residue was placed onto a short silica gel column and washed with EtOAc/hexane (1:4 v/v). Evaporation of the eluate gave **4aa** as a white solid (2.20 g; 82%). ^1H NMR (acetone-d_6, 400 MHz): δ = 8.09−8.04 (m, 1H), 8.00−7.92 (m, 1H), 7.81 (d, J = 8.5 Hz, 1H), 4.50−2.00 (bs, 1H). ^{13}C NMR (acetone-d_6, 126 MHz): δ = 166.7, 135.1, 134.0, 133.9, 129.2 (q, $^3J_{C-F}$ = 5.4 Hz), 128.0 (q, $^2J_{C-F}$ = 33.0 Hz), 126.8, 124.0 (q, $^1J_{C-F}$ = 273.0 Hz). ^{19}F NMR (acetone-d_6, 376 MHz): δ = −60.1 (s). Lit.[79]

5-Methoxy-2-(trifluoromethyl)benzoic Acid (4bb). In a glovebox, to 2-bromo-5-methoxybenzoic acid (**3bb**; 25 mg; 0.125 mmol) in an NMR tube was added at room temperature $CuCF_3$ in DMF containing an extra 0.2 equiv of TREAT HF (0.38 M; 0.36 mL; 1.1 equiv) and 1,3-bis(trifluoromethyl)benzene (internal standard; 9.7 μL). The NMR tube was sealed with a septum, brought out of the glovebox, and kept at room temperature. Quantitative ^{19}F NMR analysis of the reaction mixture after 12 min indicated that **4bb** was produced in 79% yield (0.11 equiv of $CuCF_3$ remained unreacted). Characterization of **4bb** in reaction solution: ^{19}F NMR (unlocked): δ = −57.1 (s). Lit.[79]

2-(Trifluoromethyl)benzaldehyde (4cc). In a glovebox, to 2-bromobenzaldehyde (**3cc**; purity 98%; 15 μL; 0.125 mmol) in an NMR tube was added at room temperature $CuCF_3$ in DMF containing an extra 0.2 equiv of TREAT HF (0.37 M; 0.68 mL; 2 equiv) and 1,3-bis(trifluoromethyl)benzene (internal standard; 9.7 μL). The NMR tube was sealed with a septum, brought out of the glovebox, and kept at room temperature for 24 h and then at 50 °C (oil bath) for 24 h. Quantitative ^{19}F NMR analysis of the reaction mixture indicated that **4cc** was produced in 83% yield (<0.01 equiv of $CuCF_3$ remained unreacted). After dilution with ether (2 mL) and extraction with water (5 mL), the organic layer was filtered through a short silica gel plug and analyzed by GC−MS to determine the conversion (96%). Benzaldehyde (ca. 2%) was also detected. Characterization of **4cc** in reaction solution: m/z = 174 (GC−MS; EI); ^{19}F NMR (unlocked): δ = −55.0 (s).[40]

1-(2-(Trifluoromethyl)phenyl)ethanone (4dd). To 1-(2-bromophenyl)ethanone (**3dd**; 1.36 mL; 10 mmol) was added under argon at room temperature $CuCF_3$ in DMF (0.37 M; 35 mL; 1.3 equiv) containing an extra 0.2 equiv of TREAT HF, and the mixture was stirred for 12 h at room temperature and then for 6 h at 50 °C. Ether (50 mL), water (250 mL), and aqueous NH_3 (33%; 5 mL) were added at agitation in air. The organic layer was separated and the aqueous layer was washed with ether (2 × 50 mL). The combined ether solutions were washed with brine (2 × 50 mL), dried over $MgSO_4$, filtered, and evaporated (25 °C, 100 mbar). The residue was dissolved in pentane/dichloromethane (2:1 v/v) and the solution was filtered through a short silica gel plug and evaporated (25 °C; 10 mbar) to give **4dd** as a yellowish oil (1.74 g; 92%). m/z = 188 (GC−MS; EI). ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.74−7.67 (m, 1H), 7.64−7.57 (m, 1H), 7.58−7.51 (m, 1H), 7.45 (d, J = 7.5 Hz, 1H), 2.58 (d, J = 3.3 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 201.7, 140.3 (q, $^3J_{C-F}$ = 1.9 Hz), 131.9 (q, $^4J_{C-F}$ = 0.8 Hz), 130.1, 127.1, 126.6 (q, $^2J_{C-F}$ = 32.3 Hz), 126.6 (q, $^3J_{C-F}$ = 5.1 Hz), 123.7 (q, $^1J_{C-F}$ = 273.4 Hz), 30.3 (q, $^4J_{C-F}$ = 1.6 Hz). ^{19}F NMR ($CDCl_3$, 471 MHz): δ = −58.2 (s).[40]

2-(Trifluoromethyl)terephthalic Acid (4ee). In a glovebox, to 2-bromoterephthalic acid (**3ee**; purity 98%; 31 mg; 0.125 mmol) in an NMR tube was added at room temperature $CuCF_3$ in DMF containing an extra 0.2 equiv of TREAT HF (0.37 M; 0.37 mL; 1.1 equiv) and 1,3-bis(trifluoromethyl)benzene (internal standard; 9.7 μL). The NMR tube was sealed with a septum, brought out of the glovebox, and kept at room temperature. Quantitative ^{19}F NMR analysis of the reaction mixture after 20 min indicated that **4ee** was produced in 60% yield (0.1

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equiv of $CuCF_3$ remained unreacted). Characterization of **4ee** in reaction solution: ^{19}F NMR (unlocked): $\delta = -58.7$ (s).[80]

2-(Trifluoromethyl)nicotinic Acid (6a). To 2-chloronicotinic acid (**5a**; purity 99%; 796 mg; 5 mmol) was added under argon at room temperature $CuCF_3$ in DMF (0.37 M; 20 mL; 1.5 equiv) containing an extra 0.2 equiv of TREAT HF, and the mixture was stirred for 48 h at room temperature. Ether (100 mL) and aqueous HCl (2N; 100 mL) were added at agitation in air. The organic layer was separated and the aqueous layer was washed with ether (3 × 50 mL). The combined ether solutions were washed with brine (50 mL), dried over $MgSO_4$, filtered, and evaporated. The residue was crystallized from isopropanol/hexane to give **6a** as a white solid (556 mg; 58%). ^1H NMR (acetone-d_6, 400 MHz): $\delta = 8.86$ (d, $J = 4.1$ Hz, 1H), 8.35−8.27 (m, 1H), 7.82 (dd, $J = 7.9$, 4.7 Hz, 1H), 4.00−2.00 (bs, 1H). ^{13}C NMR (acetone-d_6, 100 MHz): $\delta = 166.7$, 151.7, 145.4 (q, $^2J_{C-F} = 34.8$ Hz), 139.2, 129.4, 127.7, 122.4 (q, $^1J_{C-F} = 274.2$ Hz). ^{19}F NMR (acetone-d_6, 376 MHz): $\delta = -65.0$ (s).[81]

Ethyl 2-(Trifluoromethyl)nicotinate (6b). In a glovebox, to ethyl 2-chloronicotinate (**5b**; 19 μL; 0.125 mmol) in an NMR tube was added at room temperature $CuCF_3$ in DMF containing an extra 0.2 equiv of TREAT HF (0.37 M; 0.68 mL; 2 equiv) and 1,3-bis(trifluoromethyl)benzene (internal standard; 9.7 μL). The NMR tube was sealed with a septum, brought out of the glovebox, and heated at 60 °C for 4.5 h. Quantitative ^{19}F NMR analysis of the reaction mixture indicated that **6b** was produced in 30% yield (0.35 equiv of $CuCF_3$ remained unreacted). After dilution with ether (2 mL) and extraction with water (5 mL), the organic layer was filtered through a short silica gel plug and analyzed by GC−MS to estimate the conversion at 70%. Characterization of **6b** in reaction solution: $m/z = 219$ (GC−MS; EI); ^{19}F NMR (unlocked): $\delta = -63.4$ (s). Lit.[82]

2-(Trifluoromethyl)benzoic Acid (6c). In a glovebox, to 2-chlorobenzoic acid (**5c**; purity 98%; 20 mg; 0.125 mmol) in an NMR tube was added at room temperature $CuCF_3$ in DMF containing an extra 0.2 equiv of TREAT HF (0.38 M; 0.49 mL; 1.5 equiv) and 1,3-bis(trifluoromethyl)benzene (internal standard; 9.7 μL). The NMR tube was sealed with a septum, brought out of the glovebox, and kept at room temperature for 60 h. Quantitative ^{19}F NMR analysis of the reaction mixture indicated that **6c** was produced in 35% yield (0.03 equiv of $CuCF_3$ remained unreacted). Characterization of **6c** in reaction solution: ^{19}F NMR (unlocked): $\delta = -58.5$ (s). Lit.[78]

1-Chloro-3-nitro-2-(trifluoromethyl)benzene (6d). To a solution of 1,2-dichloro-3-nitrobenzene (**5d**; purity 97%; 25 mg; 0.125 mmol) in DMF (0.13 mL) under argon, at 80 °C, was added over a period of 4 h (syringe pump) $CuCF_3$ in DMF containing an extra 0.2 equiv of TREAT HF (0.38 M, 1.64 mL, 5 equiv) and the mixture was stirred for one more h at this temperature. The reaction mixture was then cooled to room temperature. Ether (5 mL) and 1,3-bis(trifluoromethyl)benzene (internal standard; 9.7 μL) were added at agitation in air and the solution was filtered and analyzed by ^{19}F NMR to determine the yield of **6d** (58%). GC−MS analysis showed 92% conversion of **5d** and the presence of 1-chloro-3-nitrobenzene (ca. 20%). Characterization of **6d** in reaction solution: $m/z = 226$ (GC−MS; EI); ^{19}F NMR (unlocked): $\delta = -57.5$ (s).[40]

3-Methyl-5-nitro-2-(trifluoromethyl)pyridine (6e). In a glovebox, to 2-chloro-3-methyl-5-nitropyridine (**5e**; 22 mg; 0.125 mmol) in an NMR tube was added at room temperature $CuCF_3$ in DMF containing an extra 0.2 equiv of TREAT HF (0.37 M; 0.68 mL; 2 equiv) and 1,3-bis(trifluoromethyl)benzene (internal standard; 9.7 μL). The NMR tube was sealed with a septum, brought out of the glovebox, and heated at 60 °C for 4.5 h. Quantitative ^{19}F NMR analysis of the reaction mixture indicated that **6e** was produced in 20% yield, with 0.25 equiv of $CuCF_3$ still being present. After dilution with ether (2 mL) and extraction with water (5 mL), the organic layer was filtered through a short silica gel plug and analyzed by GC−MS to determine the conversion (56%) and indicate the formation of 2-fluoro-3-methyl-5-nitropyridine (ca. 20%). Characterization of **6e** in reaction solution: $m/z = 206$ (GC−MS; EI); ^{19}F NMR (unlocked): $\delta = -64.6$ (s).

Reactions with Various Quantities of CuCl. Inside a glovebox, to a solution of 1-fluoro-4-iodobenzene (purity 99%; 7.4 μL; 0.06 mmol) in DMF (0.3 mL) in an NMR tube was added at room temperature $CuCF_3$ (0.33 M; 0.3 mL). The NMR tube was sealed with a septum, brought out, and kept at 100 °C (oil bath) for 30 min. Quantitative ^{19}F NMR analysis of the reaction mixture indicated that 1-fluoro-4-(trifluoromethyl)benzene was produced in 85% yield (<0.01 equiv of $CuCF_3$ remained unreacted). This experiment was then repeated in the presence of various quantities of CuCl: 1 mg (0.01 mmol), 5 mg (0.05 mmol), and 10 mg (0.1 mmol). The yields of 1-fluoro-4-(trifluoromethyl)benzene are listed in Table 3.

Reactions with Various CuX (X = Cl, Br, I). Inside a glovebox, to CuCl (21 mg; 0.2 mmol) in an NMR tube were added, at room temperature, $CuCF_3$ (0.33 M; 0.6 mL) and 1-fluoro-4-iodobenzene (purity 99%; 35 μL; 0.3 mmol). The NMR tube was sealed with a septum, brought out of the glovebox, and kept at room temperature for 55 min and then at 80 °C (oil bath) for 12 h. Quantitative ^{19}F NMR analysis of the reaction mixture indicated that 1-fluoro-4-(trifluoromethyl)benzene was produced in 25% yield (<0.01 equiv of $CuCF_3$ remained unreacted). This experiment was repeated with CuBr (32 mg; 0.2 mmol) and then with CuI (38 mg; 0.2 mmol) in place of CuCl. The results of these experiments are presented in Table 4.

■ ASSOCIATED CONTENT

Supporting Information

NMR spectra (PDF) and full details of crystallographic studies (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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