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Direct Cupration of Fluoroform

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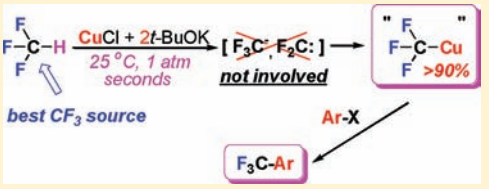
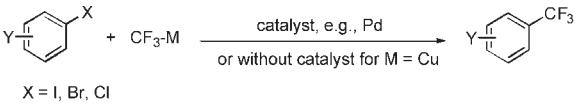
Supporting Information

ABSTRACT: We have found the first reaction of direct cupration of fluoroform, the most attractive CF_3 source for the introduction of the trifluoromethyl group into organic molecules. Treatment of CuX (X = Cl, Br, I) with 2 equiv of MOR (M = K, Na) in DMF or NMP produces novel alkoxycuprates that readily react with CF_3H at room temperature and atmospheric pressure to give $CuCF_3$ derivatives. The CuCl and *t*-BuOK (1:2) combination provides best results, furnishing the $CuCF_3$ product within seconds in nearly quantitative yield. As demonstrated, neither CF_3^- nor CF_2 mediate the Cu−CF_3 bond formation, which accounts for its remarkably high selectivity. The fluoroform-derived $CuCF_3$ solutions can be efficiently stabilized with TREAT HF to produce $CuCF_3$ reagents that readily trifluoromethylate organic and inorganic electrophiles in the absence of additional ligands such as phenanthroline. A series of novel Cu(I) complexes have been structurally characterized, including $K(DMF)[Cu(OBu\text{-}t)_2]$ (**1**), $Na(DMF)_2[Cu(OBu\text{-}t)_2]$ (**2**), $[K_8Cu_6(OBu\text{-}t)_{12}(DMF)_8(I)]^+ I^-$ (**3**), and $[Cu_4(CF_3)_2(C(OBu\text{-}t)_2)_2(\mu^3\text{-}OBu\text{-}t)_2]$ (**7**).



INTRODUCTION

Organic derivatives bearing a trifluoromethyl group on an aromatic ring are widely used as active ingredients of numerous modern drugs and highly efficient crop protection agents.[1−8] Trifluoromethylated aromatic building blocks that are needed for these and other applications, such as in materials,[9] are currently manufactured via a Swarts-type process that involves exhaustive chlorination of a methyl group on the ring with subsequent Cl/F exchange.[10] This process has a number of limitations, including low functional group tolerance, and is environmentally unfriendly because it generates large amounts of chlorine waste. Efficient metal-catalyzed or -mediated cross-coupling of electrophiles with a nucleophilic CF_3 source (eq 1) is a promising alternative to the Swarts reaction.[8] Since the groundbreaking discovery of the Cu-promoted perfluoroalkylation of iodoarenes by McLoughlin and Thrower[11] in the mid-1960s and further developments by Kumadaki et al.[12] and others, considerable progress has been made in the area. Recent advancements in the field include the first Cu-catalyzed trifluoromethylation reactions of iodoarenes,[13] the synthesis of well-defined Cu(I) trifluoromethylating agents,[14] the discovery of previously inconceivable Ph−CF_3 reductive elimination from Pd(II),[15] and the development of the first Pd-catalyzed aromatic trifluoromethylation reactions.[16,17]



(1)

In spite of these important recent accomplishments, the problem of Ar−CF_3 coupling (eq 1) is far from being solved. One of the key challenges in the area is the development of low-cost CF_3-transferring nucleophilic reagents for reaction 1.[8] Numerous polyfluoromethanes that could be used to prepare CF_3 derivatives of Zn, Cd, and Cu (CF_3Cl, CF_3Br, CF_2Cl_2, CF_2ClBr, etc.) are on the Montreal Protocol list of substances that deplete the ozone layer, and CF_3I is available only in limited quantities and also costly. Ruppert-type reagents, CF_3SiR_3, are versatile and highly efficient, yet too expensive for larger scale operations. Low-cost CF_3CO_2M (M = K, Na) must be used in a large excess in order to produce $CuCF_3$ species in good yield via high-temperature (ca. 160 °C) decarboxylation. Although $FSO_2CF_2CO_2Me$ decarboxylates at lower temperatures, it is much more expensive and releases 1 equiv of SO_2 per each equiv of $CuCF_3$ generated.

Fluoroform (trifluoromethane; CF_3H; HFC-23; bp = ∼−82 °C),[18] a side-product of Teflon manufacturing, is cheap, available in large quantities, nontoxic, and not ozone-depleting. It is unsurprising therefore, that CF_3H has long been viewed as an ideal source to prepare stable CF_3 metal derivatives.[8] Although fluoroform (pK_a = 27 in water)[19] can be deprotonated by strong bases such as $KCH_2S(O)Me$, the CF_3^- generated is notorious for exceedingly facile decomposition to difluorocarbene at room temperature and even below. This decomposition can be avoided by deprotonating CF_3H at −20 to −40 °C in DMF that instantly adds the resultant CF_3^- carbanion to give $[Me_2NCH(O)CF_3]^-$.[20,21] Although this hemiaminaloate adduct still quickly decomposes at room temperature, it is stable at −20 °C for at least a few hours and can be used for CF_3 transfer to Cu(I) and subsequent aromatic trifluoromethylation. This strategy was first reported by Folleas, Marek, Normant, and Saint-Jalmes[20] in 2000 and is described in Scheme 1. In the first step, deprotonation of CF_3H in DMF at −25 °C with dimsyl potassium produced potassium hemiaminolate **A** that was detected by ^{19}F NMR.

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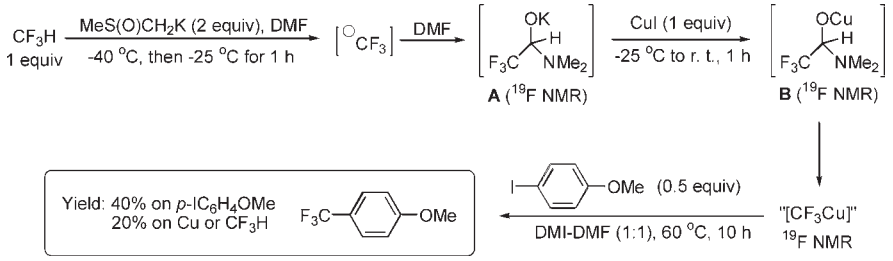
Scheme 1



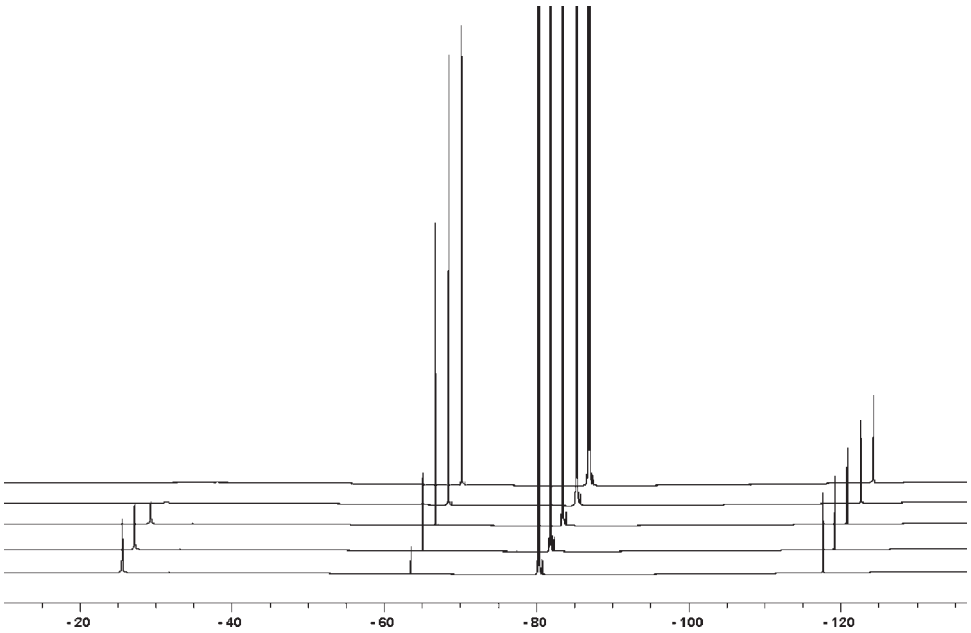


Figure 1. ^{19}F NMR monitoring of the reaction of CF_3H with CuCl, *t*-BuOK, phen (1:1:1) and PhI in DMF (bottom to top: 1, 2, 6, 24, and 36 h after the addition of CF_3H). The signals at −25.6 (s), −63.5 (s), −80.3 (d, J_{F-H} = 79.5 Hz), and −117.7 (m) ppm are from $CuCF_3$, $PhCF_3$, CF_3H (used in excess), and 4,4′-difluorobiphenyl (internal standard), respectively.

The addition of CuI to the thus pregenerated solution of **A** induced ligand exchange leading to Cu(I) hemiaminolate **B** and, eventually, to $CuCF_3$ (^{19}F NMR). The solution containing both **B** and $CuCF_3$ was then stabilized by DMI and heated with *p*-iodoanisole to give *p*-methoxybenzotrifluoride.[20]

Numerous attempts have been made to metalate rather than deprotonate CF_3H in order to directly obtain stable CF_3Cu derivatives in one step instead of via the multistep route shown in Scheme 1. It has been communicated,[20] however, that basic organocopper derivatives including *n*-Bu_2CuLi, *n*-$Bu_2CuCNLi_2$, *n*-$Bu_3CuCNLi_3$, and *tert*-$Bu_2CuCNLi_2$ fail to produce CF_3Cu under a variety of conditions. It is also noteworthy that Et_2Zn, *n*-Bu_3ZnLi, and allylzinc bromide did not give rise to trifluoromethylzinc derivatives on contact with CF_3H, either.[20] Most recently, the formation of zinc perfluoroalkyls from 1*H*-perfluoroalkanes (R_fH) and zinc bis-2,2,6,6-tetramethylpiperidide was described.[13d] The R_fZn derivative was then used for in situ R_f transfer to Cu(I) that was employed as a catalyst for perfluoroalkylation of iodoarenes. Direct cupration of fluoroform has not been reported.

Herein we describe the first example of direct cupration of fluoroform, leading to valuable CF_3Cu reagents in one step. Unlike deprotonation of CF_3H that is conducted at −25 to −40 °C to avoid decomposition to CF_2,[20,21] our cupration reaction occurs at room temperature to furnish the CF_3Cu product directly in high yield of up to >90%. A brief preliminary description of part of this work has been presented in the Latest Developments section of a recent review article.[8]

RESULTS AND DISCUSSION

Originally we found that adding CF_3H to a mixture of CuCl, *t*-BuOK, and 1,10-phenanthroline (phen) in a 1:1:1 molar ratio in DMF containing 3 equiv of PhI at room temperature, triggered a remarkably clean transformation leading to $PhCF_3$ (eq 2). Monitoring the reaction by ^{19}F NMR (Figure 1) showed that a $CuCF_3$ species (δ = −25.6 ppm) was quickly formed, which reacted with PhI to give $PhCF_3$ at full conversion after 36 h at 25 °C. Although the reaction was highly selective, exhibiting no ^{19}F NMR-observable side products, the yield of $PhCF_3$ was only 45−50%. Moreover, the yield of $PhCF_3$ was always around 50% in a number of highly reproducible repeats of this experiment. GC-MS analysis of the reaction mixture revealed the presence of *t*-BuOPh and unreacted PhI. No or little reaction (<5% $CuCF_3$) was observed in the absence of phen.

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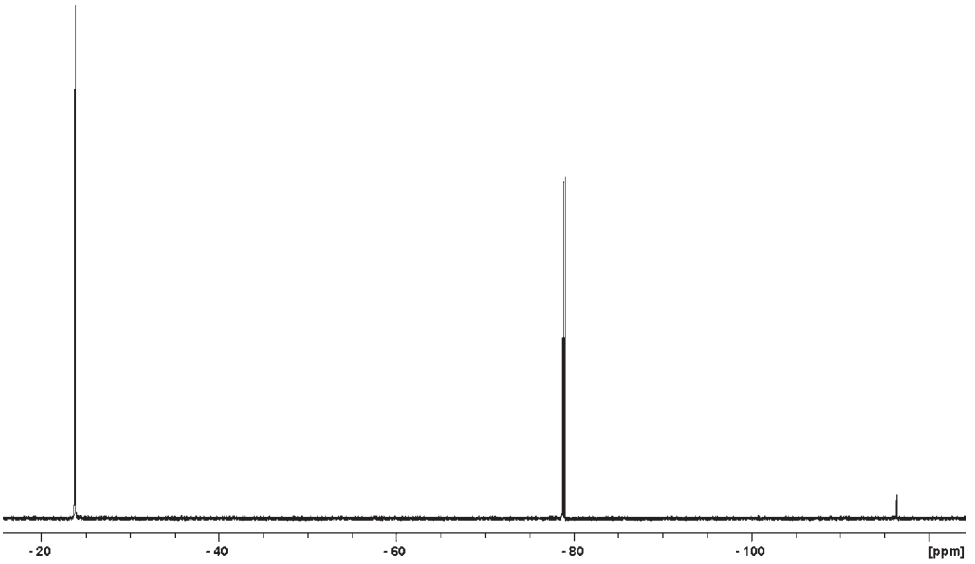
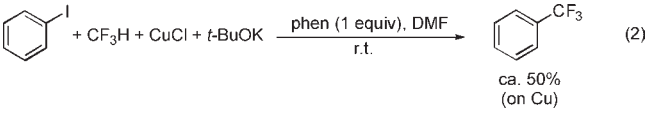


Figure 2. ^{19}F NMR spectrum of a reaction mixture containing the $CuCF_3$ product (−24.0 ppm) formed in 95% yield on addition of CF_3H (−79.0 ppm, d, J_{F-H} = 79.3 Hz) in excess to CuCl ([Cu] = 0.5 M) and *t*-BuOK (1:2) in DMF at room temperature. The signal at −116.4 ppm (m) is from 4,4′-difluorobiphenyl (internal standard).



(2)

It was then found that CF_3H smoothly reacted with CuCl and *t*-BuOK in a 1:2 molar ratio in DMF or NMP to produce a $CuCF_3$ derivative in nearly quantitative yield *in the absence* of phen. This finding prompted our detailed studies of the reaction, the cuprating reagent involved, and the trifluoromethyl copper product.

Cupration of CF_3H with 1:2 CuCl−*t*-BuOK. Addition of CF_3H to a 1:2 mixture of CuCl and *t*-BuOK in DMF ([Cu] = 0.5 M) at room temperature resulted in a quick reaction. The reaction was complete within seconds, giving rise to a $CuCF_3$ derivative in up to >95% yield and no ^{19}F NMR-detectable side-products (Figure 2).

Importantly, the reaction did not give rise to observable quantities of $[CF_3CH(O)NMe_2]^-$ (^{19}F NMR: −78.8 ppm)[20,21] that is well-known to form when CF_3^- is generated in DMF. Performing the cupration in the presence of 2 equiv of styrene or α-methylstyrene did not produce *gem*-difluorocyclopropanes (^{19}F NMR),[22] indicating that the reaction is not mediated by CF_3^- or CF_2. Therefore, deprotonation of CF_3H leading to CF_3^- is not involved in the cupration process.

When the *t*-BuOK to CuCl ratio was increased to 3:1, the formation of $CuCF_3$ also occurred in nearly quantitative yield. In this experiment, however, side products were detected (^{19}F NMR), apparently from the generation of CF_3^-/CF_2 upon slower deprotonation of CF_3H with the extra equivalent of *tert*-butoxide.[21] Repeating the cupration with a 1:1.5 ratio of *t*-BuOK to CuCl gave $CuCF_3$ in only ca. 20% yield. Therefore, the required stoichiometry of CuCl and *t*-BuOK for the generation of an efficient cuprating reagent is 1:2.

The cupration reaction was then carried out in DMF-d_7 for studies by ^{1}H and ^{13}C NMR. The ^{1}H NMR spectrum displayed, in addition to residual solvent peaks and a quartet at 7.6 ppm (J_{F-H} = 79.3 Hz) from CF_3H (excess), only two singlets, one at 6.05 ppm ($\Delta\nu_{1/2}$ = 5 Hz) and one at 1.2 ppm ($\Delta\nu_{1/2}$ = 12 Hz) that integrated in ca. 1:19 (Figure 3). The signal at 6.05 ppm is assigned to the OH of *t*-BuOH that is released upon displacement of the hydrogen of CF_3H with Cu and that is apparently in exchange with the remaining 1 equiv of *tert*-butoxide. This assignment is fully consistent with the observed integral ratio (∼1:19) vs the theoretical value of 1:18.

The ^{13}C NMR spectrum (Figure 4) exhibited, apart from a quartet at 117.4 ppm (J_{C-F} = 277 Hz) from CF_3H and DMF-d_7 solvent peaks, a quartet at 152.3 ppm (J_{C-F} = 350 Hz) from $CuCF_3$, and two sets of broadened resonances from two different types of *tert*-butoxy groups. Line-shape analysis produced the rate of ∼62.5 s^{-1} and $\Delta G^{\neq}$ = 15 kcal mol^{-1} for the exchange of the two *t*-BuO groups at 25 °C.[23] These figures are inconsistent with exchange between *t*-BuOK and *t*-BuOH via proton transfer that is much faster.[24] Indeed, ^{1}H and ^{13}C NMR spectra of an anhydrous DMF-d_7 solution of *t*-BuOK and *t*-BuOH (1:1) exhibited only one set of resonances for the *t*-BuO-group. Therefore, the ^{13}C NMR data not only confirmed the formation of the $CuCF_3$ species observed by ^{19}F NMR, but also indicated that after the cupration the *tert*-butoxide was coordinated to Cu and also involved in exchange with *t*-BuOH.[23,25]

Cuprating Reagents. The reaction of alkali metal *tert*-butoxides with CuCl (1:1) has long been known[26−31] to produce copper(I) tert-butoxide, a tetramer in the solid state[28−30] and a strong base that metalates C−H acids such as terminal acetylenes and cyclopentadiene,[26] 1,3-dinitrobenzene,[31] coordinated phosphines,[29] carboranes,[32] some nonclassical hydrides,[33] and M−H bonds of certain main group element compounds.[34,35] We found, however, that $[t\text{-BuOCu}]_4$, prepared as reported in the literature[26] or generated in situ from CuCl and *t*-BuOK (1:1) in DMF, was poorly reactive toward CF_3H at 20−60 °C, giving only small quantities of CF_3Cu species (<10% by ^{19}F NMR), if any at all. In sharp contrast, the reaction of CF_3H with 1:2 mixtures of CuCl and *t*-BuOK or *t*-BuONa in DMF occurred within seconds at room temperature, yielding CF_3Cu derivatives. Apparently, a different, more reactive alkoxide species was generated on treatment of CuCl with 2 equiv of *t*-BuOM (M = K, Na).

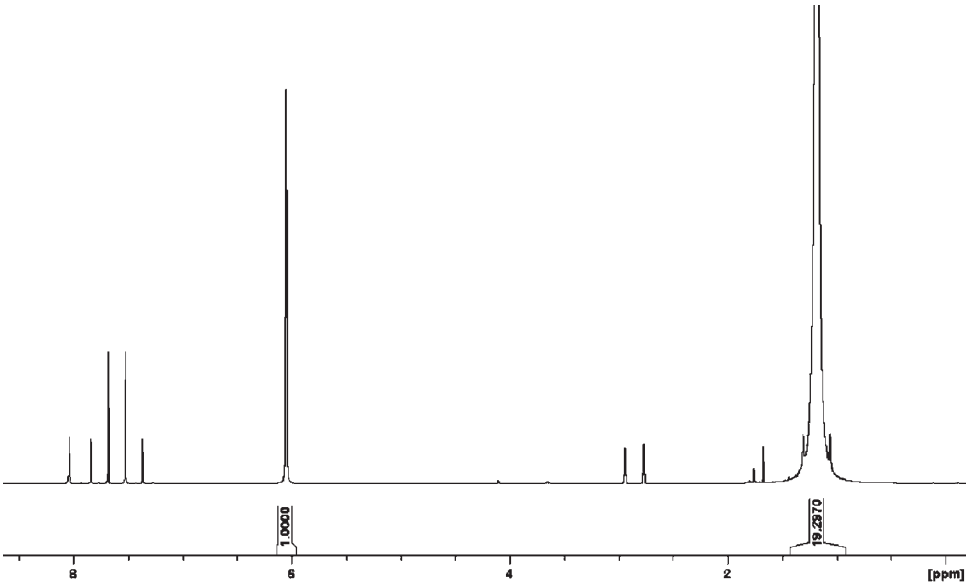


Figure 3. ^{1}H NMR spectrum of a reaction mixture obtained upon addition of CF_3H in excess to CuCl and *t*-BuOK (1:2) in DMF-d_7 (see text).

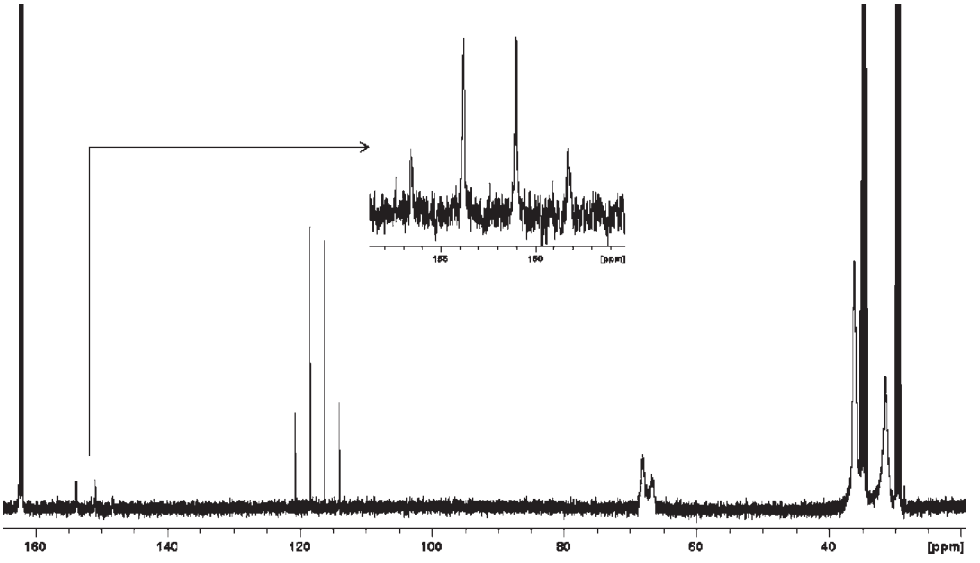


Figure 4. ^{13}C NMR spectrum of a reaction mixture obtained upon addition of CF_3H in excess to CuCl and *t*-BuOK (1:2) in DMF-d_7 (see text).

On addition of a DMF solution containing 2 equiv of *t*-BuOK to a stirred sample of CuCl, the copper salt quickly dissolved and a cloudy solution was produced. Separation of the solid by filtration and analysis by powder X-ray diffraction indicated that KCl was formed quantitatively. Cooling the colorless filtrate gave uniformly shaped, very air- and moisture-sensitive thin white needles, whose structure was determined by single-crystal X-ray diffraction. The established structure K(DMF)[Cu(OBu-*t*)$_2$] (**1**) is shown in Figure 5. This novel dialkoxycuprate crystallizes as a polymer with each K atom coordinated to the oxygen atom of one DMF molecule and three oxygen atoms of three [Cu(OBu-*t*)$_2$] units.

When the experiment was repeated with *t*-BuONa, CuCl also quickly dissolved. However, a large amount of white crystals precipitated out within less than 1 min, resulting in a thick suspension. Gentle heating of this mixture to ~50−60 °C and quick filtration produced a clear, solid-free filtrate that deposited needle-shaped crystals on cooling to room temperature. Although the crystals were also extremely air- and moisture sensitive and very thin, a single-crystal X-ray crystallographic study was possible (Figure 6). This sodium cuprate also crystallized as a polymer, yet appeared to have a different composition, Na(DMF)$_2$[Cu(OBu-*t*)$_2$] (**2**). Each sodium ion in this structure is bonded to two DMF molecules through their oxygen atoms and two oxygen atoms of two adjacent Cu(OBu-*t*)$_2$ links.

Treatment of CuBr with 2 equiv of *t*-BuOM (M = K, Na) in DMF under similar conditions, also resulted in precipitation of alkali metal bromide, even though KBr and NaBr are slightly more easily soluble in DMF than KCl and NaCl. However, no precipitation took place when CuI was dissolved in DMF

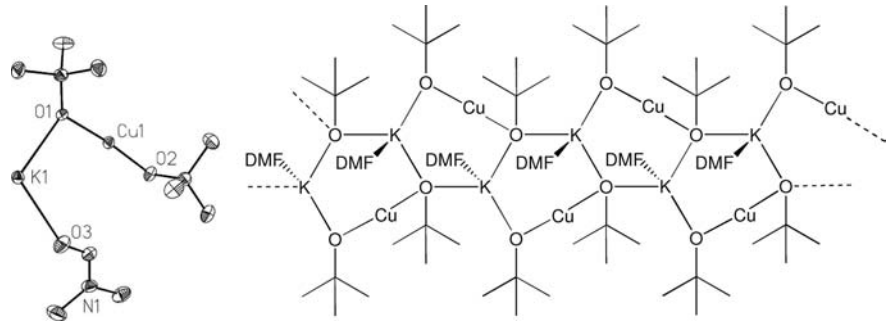


Figure 5. Structure and ORTEP drawing of the structural unit K(DMF)[Cu(OBu-*t*)$_2$] (**1**) with thermal ellipsoids drawn to the 50% probability level.

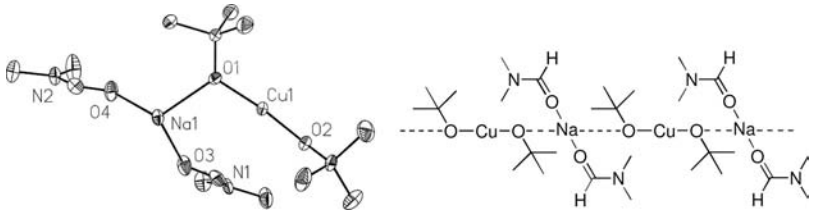


Figure 6. Structure and ORTEP drawing of the structural unit Na(DMF)$_2$[Cu(OBu-*t*)$_2$] (**2**) with thermal ellipsoids drawn to the 50% probability level.

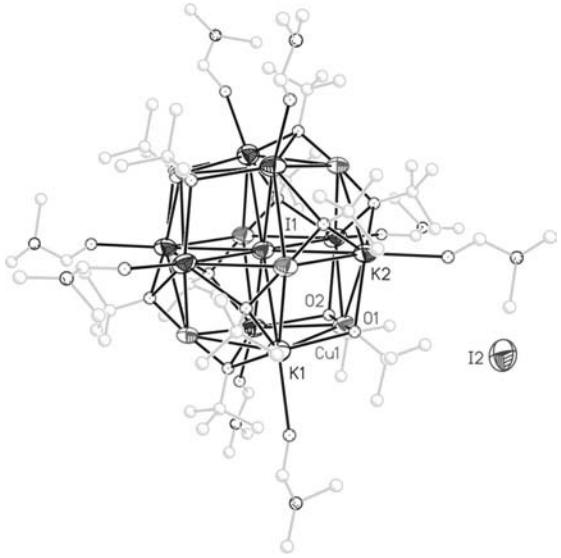


Figure 7. ORTEP drawing of $[K_8Cu_6(OBu\text{-}t)_{12}(DMF)_8(I)]^+ I^-$ (**3**) with thermal ellipsoids drawn to the 50% probability level and all H atoms omitted for clarity.

containing 2 equiv of *t*-BuOM (M = K, Na), in accord with the fact that unlike potassium and sodium chlorides and bromides, NaI and KI are easily soluble in DMF at room temperature.[36] Although all of the combinations of CuX (X = Cl, Br I) with *t*-BuOM (M = K, Na) in a 1:2 molar ratio were found to be reactive toward CF_3H (see below), we suspected that the high solubility of KI and NaI in DMF might influence the structure of the cuprating species. Indeed, cooling a solution obtained by dissolving CuI and *t*-BuOK (1:2) in DMF at room temperature prompted crystallization of a remarkable cationic cluster $[K_8Cu_6(OBu\text{-}t)_{12}(DMF)_8(I)]^+ I^-$ (**3**; Figure 7). This high-symmetry cation crystallizes in the hexagonal space group *R*-$\bar{3}$c (167)

Table 1. Cu−O Bond Distances (Å) and O−Cu−O Bond Angles (deg) in 1−3 and Two Previously Reported Cuprates

	1	**2**	**3**	$[Cu(OC_6H_3\text{-}Me_2\text{-}2,6)_2]^-$ (ref 38)	$[Cu(OPh)_2]^-$ (ref 39)
Cu−O	1.815(2)	1.816(2)	1.827(4)	1.806(6)	1.816(4)
	1.825(2)	1.819(2)	1.832(4)	1.798(8)	1.787(4)
O−Cu−O	173.10(10)	171.50(10)	175.0(2)	169.8(3)	177.8(2)

with an iodine atom in the center of the cluster on a $\bar{3}$ axis. The cluster bears a charge of +1 that is balanced by the outer sphere iodide anion (−1) disordered in three positions around another $\bar{3}$ axis. The eight K atoms form a cube that is body-centered by the iodine atom and face-centered by six copper atoms, each bonded to two *t*-BuO groups. All of the *t*-BuO ligands are μ^3, capping one Cu and two K atoms of two different types. The potassium atoms of both types are five-coordinate, being bonded to the iodine in the center of the cluster, three *t*-BuO groups, and one terminal DMF ligand. The two different DMF molecules attached to K1 and K2 are disordered in different orientations surrounding the iodide anion. This structure is distinct and different from those reported[37] for the neutral polynuclear Cu(I) alkoxides $[M_nCu_4(OCR_3)_8]$ (M = Li, *n* = 4, R = Me; M = Na, *n* = 4, R = Et; M = Ba, *n* = 2, R = Et).

The new complexes **1**−**3** are extremely rare examples of dialkoxycuprates. We are aware of only two structurally characterized salts of $[Cu(OR)_2]^-$, both being aromatic derivatives where R = 2,6-$Me_2C_6H_3$[38] and Ph.[39] The Cu−O bond lengths and O−Cu−O bond angles in **1**−**3** and the two literature compounds are collected in Table 1. Although **1** and **2** crystallize in the polymeric form and **3** is a cluster, the Cu−O bond distances in **1**-**3** are either similar or slightly longer, by 0.02−0.04 Å, than in the monomeric diaryloxycuprates. The O−Cu−O bond angles are nearly linear in all of the complexes.[40]

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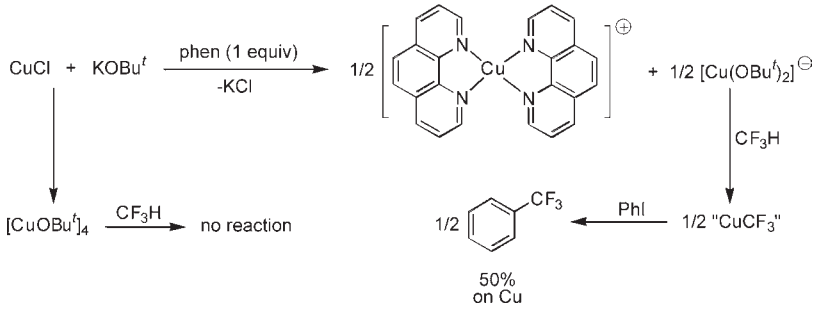
Scheme 2



The data presented above account for the ca. 50% yield of $PhCF_3$ consistently observed in reaction 2. As shown in Scheme 2, the reaction of CuCl with 1 equiv of *t*-BuOK produces $[t\text{-BuOCu}]_4$ that is unreactive or poorly reactive toward CF_3H. In the presence of 1 equiv of phen, however, one-half of the Cu(I) is sequestered in the form of the bis-chelate $[Cu(phen)_2]^+$. This changes the molar ratio of CuCl to *t*-BuOK in the system to 1:2, leading to the formation of the dialkoxycuprate that is reactive toward fluoroform. However, the amount of the CF_3Cu species generated and consequently the yield of the trifluoromethylated product ($PhCF_3$) of its reaction with PhI theoretically cannot exceed 50%, as calculated on the basis of the total quantity of Cu(I) used for the reaction.

Cuprating Reagents Based on CuCl, CuBr, CuI, and Various MOR (M = K, Na). Stability of the CF_3H-Derived $CuCF_3$ Reagents. All possible combinations of CuX (X = Cl, Br, I) with 2 equiv of MOR (M = K, Na; R = Me, Et, *t*-Bu) in DMF and NMP at [Cu] = 0.5 M were studied in order to identify the most efficient reagent for the cupration. Potassium alkoxides were found to be superior in terms of both the yield of the $CuCF_3$ product and its stability. For instance, the 2MeONa-CuCl system gave only small quantities of $CuCF_3$ on reaction with fluoroform, whereas use of KOMe under similar conditions furnished the desired $CuCF_3$ product in 60−65% yield. The yield was much lower however (ca. 10%), when KOMe was replaced with KOEt. Although $Na(DMF)_2[Cu(OBu\text{-}t)_2]$ generated in situ from CuCl and *t*-BuONa in DMF (see above) smoothly reacted with CF_3H, the $CuCF_3$ complex produced was less stable, decomposing quickly at room temperature.

The best results were obtained with the originally discovered CuCl-*t*-BuOK (1:2) system that consistently produced the $CuCF_3$ species in >90% yield on treatment with CF_3H in DMF or NMP. Slightly lower yields (75−90%) were achieved when CuBr was used under identical conditions. With CuI as a Cu(I) source, the yields were in the range of 40−85%, and the resultant $CuCF_3$ solutions were decomposing faster than the ones derived from CuBr and CuCl. Even faster decomposition was observed when the reaction of CF_3H with CuI-*t*-BuOK (1:2) in NMP was carried out in the presence of 2 equiv of KI.

The stability of the CF_3Cu generated from CF_3H and CuCl-*t*-BuOK (1:2) in DMF with [Cu] = 0.5 M at room temperature was studied by measuring ^{19}F NMR spectra of the freshly prepared reaction solutions containing $PhCF_3$ as an internal standard (Table 2). As can be seen from this table, the yield of the CF_3Cu, as determined 5−10 min after its formation (95%), dropped to approximately 80%, 75%, and 65% after 2, 4, and 18 h, respectively. After that, no significant further decomposition was observed. Similar results were obtained in NMP: the originally measured 96% yield of the CF_3Cu product dropped to 76% after 4 h and further to 68% after 14 h, at which point the decomposition ceased. Addition of DMI (20% by volume) to DMF before the cupration did not provide significant stabilization to the CF_3Cu product.[41]

Table 2. Spontaneous Decomposition of $CuCF_3$ Species Generated from CF_3H and CuCl-*t*-BuOK (1:2) in DMF with [Cu] = 0.5M at 22−25 °C

experiment 1[a]		experiment 2[a]	
time, h	$CuCF_3$ yield, %	time, h	$CuCF_3$ yield, %
0.1	95	0.1	94
0.7	87	0.5	89
1.2	84	1.0	85
1.7	80	1.5	81
2.5	77	2.3	78
3.1	76	2.9	76
4.0	74	3.4	75
4.2	72	4.2	72
17.7	64	17.5	65
23.5	64	23.4	65
42.5	61	42.3	63

[a] Results of two similar experiments are presented to demonstrate reproducibility.

A series of studies of the decomposition of the CF_3Cu solutions in DMF resulted in the following important observations:

1. A well-pronounced concentration effect on stability of the $CuCF_3$ product was observed. At [Cu] = 0.75 and 1.0 M the measured yields were lower (ca. 70−85%) than at the standard 0.5 M concentration of Cu(I). Also, at higher [Cu], the $CuCF_3$ product decayed more rapidly, suggesting that the decomposition is unlikely to be a unimolecular process.
2. Freshly prepared $CuCF_3$ solutions reacted with PhI to produce both $PhCF_3$ and *t*-BuOPh. In contrast, the addition of excess PhI to the $CuCF_3$ solutions after ca. one-third of the organocopper complex had decomposed and the decomposition ceased (see Table 2) led to the formation of $PhCF_3$ and, at most, only trace quantities of the ether.
3. The decomposition process was accompanied by precipitation of KF (identified by powder X-ray diffraction), which ceased when the decomposition stopped.
4. As a result of numerous attempts to isolate the $CuCF_3$ species produced in the cupration reaction, four structures were determined by single-crystal X-ray diffraction: $[Cu_2(C(OBu\text{-}t)_2)_2(\mu\text{-}Cl)_2]$ (**4**), $[Cu_2(C(OBu\text{-}t)_2)_2(\mu\text{-}Br)_2]$ (**5**),

dx.doi.org/10.1021/ja2081026 |*J. Am. Chem. Soc.* 2011, 133, 20901–20913

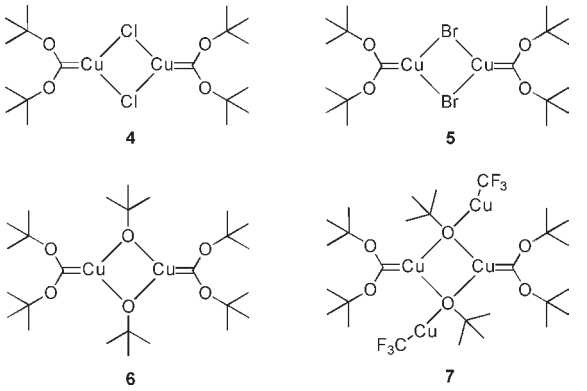


Figure 8. Structures of crystallographically characterized complexes **4**−**7**.

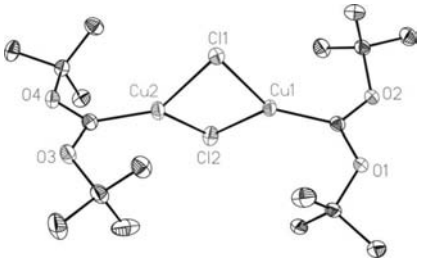


Figure 9. ORTEP drawing of $[Cu_2(C(OBu\text{-}t)_2)_2(\mu\text{-}Cl)_2]$ (**4**) with thermal ellipsoids drawn to the 50% probability level and all H atoms omitted for clarity.

$[Cu_2(C(OBu\text{-}t)_2)_2(\mu\text{-}OBu\text{-}t)_2]$ (**6**), and $[Cu_4(CF_3)_2(C(OBu\text{-}t)_2)_2(\mu^3\text{-}OBu\text{-}t)_2]$ (**7**).[42] Figures 8−12 display structures and ORTEP drawings of **4**-**7** that are all bis(*t*-butoxy)-carbene Cu(I) species and rare examples of alkoxycarbene derivatives of copper.[43]

The results described above indicate unambiguously that the $CuCF_3$ decomposition is governed by the formation of a Cu(I) difluorocarbene species that undergo extremely facile[44] nucleophilic displacement of the fluorines with *t*-butoxide. The alkali metal cation present in the solution apparently plays a crucial role in the decomposition process by binding to the fluoride to form thermodynamically stable MF (Scheme 3). This scheme also readily accounts for the aforementioned fact that the $CuCF_3$ products made with NaOR are noticeably less stable than those derived from KOR because "harder" Na^+ has a higher affinity for fluoride than K^+ and is therefore more electrophilic toward the $CuCF_3$ complex. Furthermore, the decomposition stops after all of the potassium cations are consumed and precipitated out in the form of KF. As can be seen from the stoichiometry shown in Scheme 3, three potassium cations decompose one $CuCF_3$ moiety, which accords with the cessation of the decomposition after the originally observed nearly quantitative yield of the $CuCF_3$ drops by one-third to ca. 65% (Table 2). At this point, *t*-butoxide is no longer available for the Cu-promoted reaction with PhI to give *t*-BuOPh. Scheme 3 also explains the faster $CuCF_3$ decomposition at higher concentrations that speed up the abstraction of fluoride by the alkali metal cation.

A comment is due on the structure of **7** bearing a $CuCF_3$ fragment (Figure 12). The Cu−CF_3 bond in **7** (1.8908(16) Å) is one of the shortest ever reported for a structurally characterized

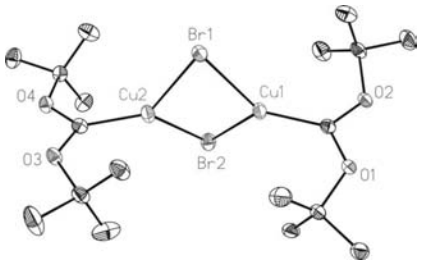


Figure 10. ORTEP drawing of $[Cu_2(C(OBu\text{-}t)_2)_2(\mu\text{-}Br)_2]$(**5**) with thermal ellipsoids drawn to the 50% probability level and all H atoms omitted for clarity.

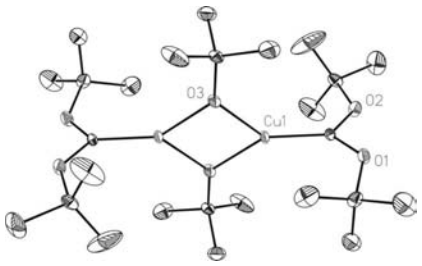


Figure 11. ORTEP drawing of $[Cu_2(C(OBu\text{-}t)_2)_2(\mu\text{-}OBu\text{-}t)_2]$ (**6**) with thermal ellipsoids drawn to the 50% probability level and all H atoms omitted for clarity.

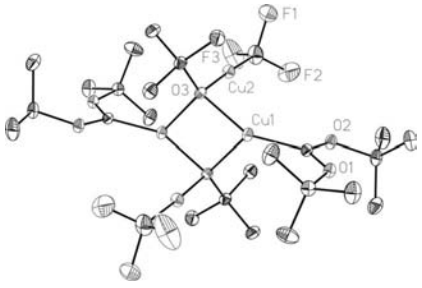
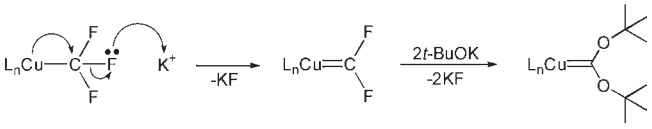


Figure 12. ORTEP drawing of $[Cu_4(CF_3)_2(C(OBu\text{-}t)_2)_2(\mu^3\text{-}OBu\text{-}t)_2]$ (**7**) with thermal ellipsoids drawn to the 50% probability level and all H atoms omitted for clarity.

Scheme 3



$CF_3Cu(I)$ complex. This bond length is comparable to that in [(bathophenanthroline)Cu(CF_3)] (1.907(9) Å)[13e] and much shorter than in [(TMS-IPr)Cu(CF_3)] (1.967(6) Å),[14a] [(SI*i*Pr)Cu(CF_3)] (2.022(4) Å),[14a] [(Ph_3P)$_3$Cu(CF_3)] (2.018(7), 2.025(7), and 2.031(10) Å),[14d] and [(phen)Cu(PPh_3)(CF_3)] (1.985(1) Å).[14d] This trend suggests that the μ^3-OBu-*t* ligand stabilizing the $CuCF_3$ fragment in **7** is, quite predictably, a considerably weaker electron donor than any of the ligands in the other structurally characterized $CuCF_3$ complexes. In spite of the lack of strongly donating ligands, however, our fluoroform-derived

$CuCF_3$ compounds are efficient trifluoromethylating reagents (see below).

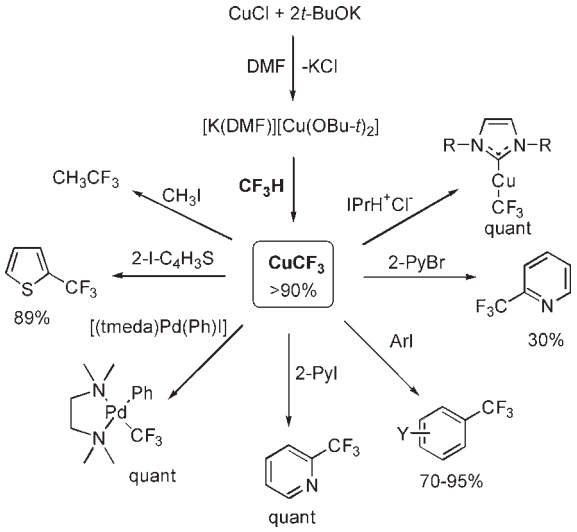
Stabilization of the $CuCF_3$ Reagents. We reasoned that the spontaneous $CuCF_3$ decomposition might be minimized or suppressed altogether by treatment of the freshly prepared solution with an acid HX that would react with the formally present "one extra equivalent of *t*-BuOK" to give *t*-BuOH and KX. Precipitation of the latter would remove from the solution the potassium ions that abstract fluorines from the CF_3 ligand on Cu (Scheme 3). As a result of a series of tests using various acidic compounds, it was found that $Et_3N\cdot 3HF$ (TREAT HF)[45] and $Py\cdot nHF$ (70% HF) provide excellent stabilization to the $CuCF_3$ solutions. Addition of TREAT HF in the amount of 1/3 mol per 1 mol of Cu after the cupration step resulted in precipitation of KF and produced stable solutions of the $CuCF_3$ reagent. Upon treatment with $Et_3N\cdot 3HF$, the ^{19}F NMR signal from the $CuCF_3$ shifted slightly upfield to −26.3 ppm from its original value of −24.2 ppm, and a new minor singlet resonance appeared in the $CuCF_3$ region at −30.4 ppm, which is assigned to $[Cu(CF_3)_2]^-$ on the basis of the literature data.[8,14,41b] In the ^{13}C NMR spectrum of a solution similarly prepared and stabilized with TREAT HF in DMF-d_7, the CF_3 ligand on Cu of the main $CuCF_3$ species resonated as a quartet at 150.7 ppm (J_{C-F} = 350 Hz).

In a typical experiment, TREAT HF was added within 5−15 min after the cupration. Precipitation of KF began instantaneously. Quantitative ^{19}F NMR analysis of the resultant solution showed that the total yield of the trifluoromethylcopper species produced was 95%. This yield was calculated on the basis of the Cu−CF_3 bonds formed, with 85% contribution from a mono-CF_3-ligated Cu species (−26.3 ppm) and 10% from $[Cu(CF_3)_2]^-$ (−30.4 ppm). The molar percentage of the $[Cu(CF_3)_2]^-$ was, however, 5% because the Cu atom in this anion bears two CF_3 groups. On storage of the solution at room temperature, a minor drop in the original yield of 95% to 93% and 91% was detected after 24 h and 3 days, respectively. An aliquot of the same solution that was stored at −35 °C for 8 days showed no sign of decomposition. Characterization of "ligandless" $CuCF_3$ compounds, that is, those lacking ligands such as NHCs,[14a,b] phen[14c,d] and its derivatives,[13e] or Ph_3P,[14d] is nontrivial.[8] As Wiemers and Burton[46] concluded in their classical study, $CuCF_3$ is "an elusive and complex species". Nonetheless, as shown below, our CF_3H-derived $CuCF_3$ can be used as an efficacious trifluoromethylating reagent.

Trifluoromethylation Reactions with CF_3H-Derived $CuCF_3$. The subject of this paper is the new reaction of direct cupration of fluoroform. A detailed description of various trifluoromethylation reactions with our $CuCF_3$ reagents, as well as our studies of their structure and the mechanism of the cupration, are beyond the scope of this publication and will be reported separately. However, to demonstrate the efficiency and versatility of the reagents, a summary of selected trifluoromethylation reactions using our fluoroform-derived $CuCF_3$ solutions is presented in Scheme 4.

Our reagents can be used to synthesize other $CuCF_3$ complexes and CF_3-derivatives of other metals. For instance, addition of $[IPrH]^+ Cl^-$ (1 equiv) to a freshly prepared $CuCF_3$ solution in DMF resulted in instantaneous formation of $[(IPr)Cu(CF_3)]$[14a] in quantitative yield. An important starting material for the synthesis of trifluoromethyl palladium(II) aryls, $[(tmeda)Pd(Ph)(CF_3)]$,[15b] was produced quantitatively in the reaction of the TREAT HF-stabilized $CuCF_3$ reagent with $[(tmeda)Pd(Ph)(I)]$. Organic electrophiles can also be trifluoromethylated with our reagents. 1,1,1-trifluoroethane was formed from MeI and the $CuCF_3$ at room temperature. A series of aryl iodides bearing electron-donating and electron-withdrawing substituents on the ring underwent smooth trifluoromethylation with the stabilized $CuCF_3$ reagent at 50 °C in 70−99% yield. Even 2-bromopyridine was converted to 2-trifluoromethylpyridine under these conditions, albeit in 30% yield. Importantly, these reactions neither require promotion with additional costly ligands such as phenanthroline, nor produce C_2F_5-derivatives as side products that most frequently emerge from decomposition of various $CuCF_3$ species to difluorocarbene.[1−8]

Scheme 4



CONCLUSIONS

We have discovered direct cupration of fluoroform, the most attractive CF_3 source for trifluoromethylation reactions. The cupration reaction employs only readily available and inexpensive reagents, CuCl and *t*-BuOK in a 1:2 ratio, and furnishes valuable $CuCF_3$ compounds in nearly quantitative yield. The cupration occurs within seconds at room temperature and is not mediated by CF_3^- or CF_2, which accounts for its remarkably high selectivity. After the formation, the $CuCF_3$ solutions can be efficiently stabilized with TREAT HF to produce $CuCF_3$ reagents that do not decay significantly for at least 1−2 days at room temperature. These reagents can be used for a variety of reactions to transfer the CF_3 group to another metal/element and for trifluoromethylation of organic electrophiles.

Our method compares favorably with the one employing zincation.[13d] The zincation reaction employs a more costly metalating agent, zinc bis-2,2,6,6-tetramethylpiperidide, and is efficient for higher 1*H*-perfluoroalkane substrates but considerably less so for CF_3H. At the temperatures required for R_f transfer from Zn to Cu (60−90 °C), the just formed CF_3Cu partially decomposes to give C_2F_5Cu. As a result, the organic trifluoromethylated product is contaminated with the pentafluoroethyl derivative and needs to be isolated and purified by unconventional means. In the single trifluoromethylation example reported in that work,[13d] preparative HPLC was required to obtain the product in pure form (51% yield).

It is also worth noting that our method generates much less inorganic byproducts than the Swarts-type process[8,10] that consumes 3 equiv of Cl_2 and coproduces 6 equiv of HCl (chlorine waste) per each equivalent of $ArCF_3$ made. For larger scale

applications of our method, dialkoxycuprate solutions made from CuCl and *t*-BuOK could be filtered prior to the cupration step in order to remove and recycle the precipitated KCl. After the cupration and stabilization with an HF source, the KF produced could also be separated by filtration and recycled. We also believe that a continuous process might be possible on the basis of our technology. Importantly, trifluoromethylation reactions with our $CuCF_3$ reagents readily occur in the absence of additional ligands such as phenanthroline and are not complicated by side-formation of C_2F_5 derivatives.

EXPERIMENTAL SECTION

All chemicals were purchased from Aldrich (CuCl, CuBr, MeONa, MeOK, EtOK, EtONa, *t*-BuONa, TREAT HF, Py·*n*HF (70% HF)), Alfa Aesar (CuI, *t*-BuOK), and Apollo Scientific (CF_3H). All manipulations were performed under argon in a glovebox, unless noted otherwise. Anhydrous DMF (Alfa Aesar or from an MBraun SPS) and NMP (Alfa Aesar) were used without additional purification. Benzene, toluene, hexanes, ether, and THF were distilled from $Na/OCPh_2$. All solvents, internal standards for quantitative ^{19}F NMR analysis, and liquid organic halide reagents were stored over activated 4 Å molecular sieves in a glovebox. Glass pressure reaction vessels (Fischer−Porter tubes) were purchased from Andrews Glass Co., Inc. ^1H, ^{13}C, and ^{19}F NMR spectra were recorded on Bruker Avance 400 Ultrashield and Bruker Avance 500 Ultrashield NMR spectrometers. Quantitative ^{19}F NMR analyses were carried out with D1 = 5 s. X-ray powder diffraction analysis was performed on a Bruker D8 Advance powder diffractometer using a transmission configuration. An Agilent Technologies 7890A chromatograph equipped with a 5975C MSD unit was used for GC-MS analysis.

Reaction of CF_3H with CuCl, *t*-BuOK, phen (1:1:1), and PhI in DMF. A mixture of CuCl (33 mg; 0.33 mmol), anhydrous 1,10-phenanthroline (60 mg; 0.33 mmol), potassium t-butoxide (39 mg; 0.35 mmol), and DMF (2 mL) was stirred for 1 h. 4,4′-difluorobiphenyl (16.5 mg; 0.09 mmol) was added as an internal standard and a 0.6 mL aliquot of the resultant cloudy solution was placed in a standard 5-mm glass NMR tube. The tube was sealed with a rubber septum and CF_3H (20 mL; 0.89 mmol) was bubbled through the solution via a syringe needle. After the addition of CHF_3 iodobenzene (100 μL; 0.90 mmol) was added and the tube was placed in the probe of an NMR spectrometer for monitoring at 25 °C. The results are summarized in Figure 1, displaying the formation of a $CuCF_3$ species and its transformation to $PhCF_3$ in ∼45−50% yield, as calculated on the amount of CuCl used.

Cupration Experiments in NMR Tubes. (a) A mixture of CuCl (50 mg; 0.51 mmol), *t*-BuOK (118 mg; 1.05 mmol), DMF (1 mL), and PhF (50 μL; 0.53 mmol; internal standard) was stirred for 30 min. A 0.6 mL aliquot of the resultant cloudy solution was placed in a 5-mm NMR tube that was then capped with a rubber septum and brought out. Fluoroform gas (15 mL; 0.67 mmol) was bubbled through the solution via a syringe needle. The reaction was complete within seconds. ^{19}F NMR analysis of the sample 10−15 min after the reaction indicated that a $CuCF_3$ species (−24.0 ppm) was produced in 90−95% yield (e.g., see Figure 2). No other ^{19}F NMR-detectable products were observed. (b) Similar results were obtained in NMP. (c) Repeating the experiment with CuCl in the presence of styrene (2 equiv) produced identical results; neither *gem*-difluorophenylcyclopropane nor any other side products were detected. (d) No formation of 1,1-difluoro-2-methyl-2-phenylcyclopropane was observed in a repeat using CuI as the Cu(I) source and α-methylstyrene (2 equiv) as a CF_2 trap.

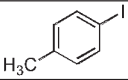
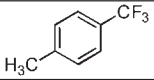
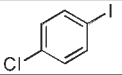
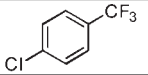
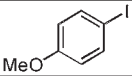
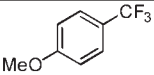
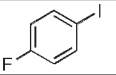
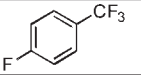
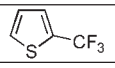
Preparation of $CuCF_3$ from Fluoroform in DMF. Stability Studies. A 3-oz Fischer−Porter tube equipped with a pressure gauge, a needle valve, and a Teflon-coated magnetic stir-bar was charged with CuCl (0.50 g; 5.05 mmol), *t*-BuOK (1.19 g; 10.62 mmol), DMF (10 mL), and $PhCF_3$ (123 μL; 1.00 mmol; internal standard). After the mixture was stirred for 30 min at room temperature, the sealed tube was brought out and evacuated on a vacuum line to ∼1 mmHg.[47] At vigorous stirring, fluoroform was introduced to ∼50 psi, after which the pressure dropped to 5−10 psi within a few seconds. ^{19}F NMR analysis of the sample 10−15 min after the reaction indicated that a $CuCF_3$ species (−24.2 ppm) was produced in 95% yield. Decomposition of the product was monitored by ^{19}F NMR (Table 2). As the decomposition occurred, the singlet ^{19}F NMR signal from $CuCF_3$ was slightly shifting upfield from −24.2 to −25.6 ppm. Note that the cupration reaction may be performed in a standard flask by bubbling CF_3H through the dialkoxycuprate solution. However, the developed procedure in Fischer−Porter tubes provides better protection of the reagents and products from accidental exposure to air.

Synthesis and Isolation of K(DMF)[Cu(OBu-*t*)$_2$] (1). A mixture of CuCl (0.50 g; 5.05 mmol) and *t*-BuOK (1.18 g; 10.54 mmol) in DMF (5 mL) was vigorously stirred for 30 min at room temperature. Filtration of the mixture produced solid KCl that was identified by powder X-ray diffraction after washing with ether (5 mL). The ether washing and the filtrate were combined and kept at −35 °C for 20 h. The white needle-shaped crystals were separated by filtration, washed with cold ether (2 × 0.5 mL), and dried under vacuum. The yield was 1.043 g (64%). The structure of K(DMF)[Cu(OBu-*t*)$_2$] was established by single-crystal X-ray diffraction. Elemental analysis could not be performed because of the extreme air- and moisture-sensitivity of the compound. ^1H NMR (C_6D_6, 25 °C), δ: 7.70 (s, 1H, DMF), 2.41 (s, 3H, DMF), 1.94 (s, 3H, DMF), 1.60 (s, 18H, *t*-Bu). ^{13}C NMR (C_6D_6, 25 °C), δ: 162.9 (s, CH, DMF), 69.5 (s, C, *t*-Bu), 37.3 (s, CH_3, *t*-Bu), 35.7 (s, CH_3, DMF), 31.3 (s, CH_3, DMF).

Synthesis and Isolation of Na(DMF)$_2$[Cu(OBu-*t*)$_2$] (2). (a) DMF (2 mL) was added, at stirring, to a mixture of CuCl (51 mg; 0.51 mmol) and *t*-BuOK (109 mg; 1.13 mmol). The copper salt quickly dissolved and a large amount of needle-shaped crystals precipitated out within 5−10 s to produce a thick suspension. Gently heating the mixture to ∼50−55 °C resulted in dissolution of the white needles. The cloudy solution was filtered warm to remove insoluble NaCl. The solid-free, colorless filtrate produced uniformly shaped, very thin and extremely air- and moisture sensitive white needle crystals on cooling to room temperature. The structure of the product Na(DMF)$_2$[Cu(OBu-*t*)$_2$] was established by single-crystal X-ray diffraction. (b) A mixture of CuCl (253 mg; 2.56 mmol), *t*-BuOK (508 mg; 5.29 mmol), and DMF (10 mL) was stirred at 50−55 °C for 30 min and filtered warm. The solid NaCl was washed with ether (5 mL). The ether washing and the filtrate were combined and kept at −35 °C for 1.5 h. The white solid was separated by filtration, washed with ether (0.5 mL), hexanes (15 mL), and dried under vacuum. The yield was 883 mg (91% if calculated for Na(DMF)$_2$[Cu(OBu-*t*)$_2$]). However, ^1H NMR indicated that the DMF to *t*-BuO ratio in the solid was <1. ^1H NMR (THF-d_8, 25 °C), δ: 7.92 (s, 1.5H, DMF), 2.88 (s, 4.5H, DMF), 2.77 (s, 4.5H, DMF), 1.18 (s, 18H, *t*-Bu). ^{13}C NMR (THF-d_8, 25 °C), δ: 162.6 (s, CH, DMF), 68.8 (s, C, *t*-Bu), 36.9 (br s, CH_3, *t*-Bu), 36.1 (s, CH_3, DMF), 31.2 (s, CH_3, DMF).

Preparation of $CuCF_3$ from Fluoroform in NMP. Stabilization Effect. A 3-oz Fischer−Porter tube equipped with a pressure gauge, a needle valve, and a Teflon-coated magnetic stir-bar was charged with CuCl (0.50 g; 5.05 mmol), *t*-BuOK (1.20 g; 10.71 mmol), NMP (10 mL), and PhF (187 μL; 2.00 mmol; internal standard). After the mixture was stirred for 30 min at room temperature, the sealed tube was brought out and quickly evacuated on a vacuum line to ∼1 mmHg.[47] At vigorous stirring, fluoroform was introduced to ∼50 psi, after which the pressure dropped to 5−10 psi within a few seconds. ^{19}F NMR analysis of the sample 10−15 min after the reaction indicated that a $CuCF_3$ species (−24.9 ppm) was produced in 96% yield. Within 5−10 min, a 5-mL aliquot of this solution was withdrawn and treated with TREAT HF (135.5 μL; 0.83 mmol). Decomposition of the $CuCF_3$ in the unstabilized and stabilized solutions was monitored by ^{19}F NMR. Without the stabilization, the yield of $CuCF_3$ dropped to 76% and 68% after 4 and 14 h,

Table 3. Aromatic Trifluoromethylation Reactions with CF_3H-Derived $CuCF_3$ Reagents at 50 °C[a]

substrate	reaction time, h	product	^{19}F NMR conversion of $CuCF_3$, %	^{19}F NMR yield, %
	25		>95	80-85
	25		>99	75-80
	25		>95	90-95
	25		>99	70-75
	25		>95	75
	16		>99	95-99
	16		>99	30
	25		>99	85-90

[a] See the Experimental Section for specifics.

respectively. In contrast, the total yield of $CuCF_3$ (−26.9 ppm) including 3% of $[Cu(CF_3)_2]^-$ (−31.0 ppm) in the stabilized solution after 4 and 14 h was 92% and 90%, respectively.

Preparation of $CuCF_3$ from Fluoroform in DMF. Stabilization Effect. A 3-oz Fischer−Porter tube equipped with a pressure gauge, a needle valve, and a Teflon-coated magnetic stir-bar was charged with CuCl (0.50 g; 5.05 mmol), *t*-BuOK (1.18 g; 10.54 mmol), DMF (10 mL), and PhF (187 μL; 2.00 mmol; internal standard). After the mixture was stirred for 30 min at room temperature, the sealed tube was brought out and quickly evacuated on a vacuum line to ∼1 mmHg.[47] At vigorous stirring, fluoroform was introduced to ∼50 psi, after which the pressure dropped to 5−10 psi within a few seconds. After 5 min, a solution of TREAT HF (272 μL; 1.67 mmol) in DMF (1 mL) was added. A 1-mL aliquot was withdrawn and placed in a freezer at −35 °C. By ^{19}F NMR, the yield of the $CuCF_3$ in the stabilized solution stored at room temperature under argon was 94%, 92%, 90%, and 89% (including 5% of $[Cu(CF_3)_2]^-$, −30.4 ppm) after 0.2, 13, 60, and 80 h, respectively. In the 1-mL sample of the same stabilized solution stored at −35 °C the yield was 93% after 80 h.

Stabilization of the $CuCF_3$ Reagent with TREAT HF in Excess. A 3-oz Fischer−Porter tube equipped with a pressure gauge, a needle valve, and a Teflon-coated magnetic stir-bar was charged with CuCl (0.50 g; 5.05 mmol), *t*-BuOK (1.18 g; 10.54 mmol), DMF (10 mL), and PhF (187 μL; 2.00 mmol; internal standard). After the mixture was stirred for 30 min at room temperature, the sealed tube was brought out and quickly evacuated on a vacuum line to ca. 1 mmHg.[47] At vigorous stirring, fluoroform was introduced to ∼50 psi, after which the pressure dropped to 5−10 psi within a few seconds. After 5 min, a solution of TREAT HF (326 μL; 2.00 mmol) in DMF (1 mL) was added. By ^{19}F NMR, the yield of the $CuCF_3$ in the stabilized solution stored at room temperature under argon was 97%, 92%, and 89% (including 3% of $[Cu(CF_3)_2]^-$, −30.4 ppm) after 0.2, 10, and 38 h, respectively. This experiment shows that use of TREAT HF in 20% excess provides neither extra stabilization, nor destabilization to the $CuCF_3$ reagent.

Trifluoromethylation Reactions with Stabilized $CuCF_3$ Reagents Derived from CF_3H. A 3-oz Fischer−Porter tube equipped with a pressure gauge, a needle valve, and a Teflon-coated magnetic stir-bar was charged with CuCl (0.50 g; 5.05 mmol), *t*-BuOK (1.18 g; 10.54 mmol), DMF (10 mL), and PhF (187 μL; 2.00 mmol; internal standard). After the mixture was stirred for 30 min at room temperature, the sealed tube was brought out and quickly evacuated on a vacuum line to ∼1 mmHg.[47] At vigorous stirring, fluoroform was introduced to ∼50 psi, after which the pressure dropped to 5−10 psi within a few seconds. After 15 min, a solution of TREAT HF (272 μL; 1.67 mmol) in DMF (1 mL) was added. By ^{19}F NMR, the yield of the $CuCF_3$ in the stabilized solution was 98% (including 3% of $[Cu(CF_3)_2]^-$; −31.0 ppm). This solution was used in a series of trifluoromethylation reactions. For each aromatic trifluoromethylation reaction, to 0.6 mL of this solution (0.21 mmol of $CuCF_3$) placed in a 5-mm NMR tube was added an organic halide (0.32 mmol) and the mixture was heated at 50 °C (oil bath). Results of these experiments are summarized in Table 3. In another experiment, 0.1 mL of this solution (0.035 mmol of $CuCF_3$) was added to [(tmeda)Pd(Ph)(I)] (15 mg; 0.035 mmol) in DMF (0.5 mL). After 5.5 h at room temperature, full conversion to [(tmeda)Pd(Ph)(CF_3)][15b] was observed by ^{19}F NMR ($\delta = -19.8$ ppm). In another experiment, to 0.6 mL of the $CuCF_3$ solution (0.21 mmol) was added CH_3I (80 μL, 6-fold excess). After 1.5 days at room temperature, full conversion of the $CuCF_3$ reagent was observed by ^{19}F NMR. The yield of CF_3CH_3 (−59.6 ppm, q, $J_{F-H} = 13$ Hz) present in the liquid phase was 28%. The total yield could not be determined because of the distribution of the 1,1,1-trifluoroethane product (bp = −47 °C) between the solution and the gas phase.

Reaction of CF_3H-Derived $CuCF_3$ with $IPrH^+$ Cl^-. A mixture of CuCl (50 mg; 0.51 mmol), *t*-BuOK (118 mg; 1.05 mmol), DMF-d_7 (1.3 mL), and PhF (187 μL; 2 mmol; internal standard) was stirred for 30 min. A 0.65 mL aliquot of the resultant cloudy solution was placed in a 5-mm NMR tube that was then capped with a rubber septum and brought out. Fluoroform gas (15 mL; 0.67 mmol) was bubbled through the solution via a syringe needle. ^{19}F NMR analysis of the sample 10−15 min after the reaction indicated that a $CuCF_3$ species (−23.0 ppm) was formed in >95% yield. Treatment of this solution with $IPrH^+$ Cl^-

Table 4. Crystallographic Data for Complexes 1−7

	1	2	3	4	5	6	7
Formula	$C_{11}H_{25}Cu_1K_1N_1O_3$	$C_{14}H_{32}Cu_1N_2Na_1O_4$	$C_{72}H_{164}Cu_6I_2K_8N_2O_{20}$	$C_{18}H_{36}Cl_2Cu_2O_4$	$C_{18}H_{36}Br_2Cu_2O_4$	$C_{26}H_{54}Cu_2O_6$	$C_{28}H_{54}Cu_4F_6O_6$
Formula weight	321.96	378.95	2409.95	514.45	603.37	589.77	854.87
Crystal size (mm)	0.30 × 0.03 × 0.03	0.30 × 0.06 × 0.03	0.10 × 0.10 × 0.10	0.30 × 0.20 × 0.10	0.20 × 0.20 × 0.10	0.40 × 0.20 × 0.02	0.40 × 0.30 × 0.30
Crystal color	colorless	colorless	yellow	colorless	colorless	yellow	yellow
Temp (K)	100	100	100	100	100	100	100
Crystal system	monoclinic	monoclinic	trigonal/hexagonal	monoclinic	monoclinic	monoclinic	monoclinic
Space group	$P2_1/n$	$P2_1/c$	$R\bar{3}c$	$P2_1/c$	$P2_1/c$	$P2_1/c$	$P2_1/n$
A (Å)	10.1264(16)	6.202(2)	17.754(2)	11.4005(9)	11.3451(10)	11.8480(10)	11.8758(3)
B (Å)	6.3330(10)	19.855(8)	17.754(2)	21.0308(17)	21.5829(19)	8.5446(7)	10.8214(3)
C (Å)	25.079(4)	16.646(7)	62.184(7)	11.1890(9)	11.1733(10)	16.2194(14)	14.3329(3)
α (deg)	90	90	90	90	90	90	90
β (deg)	96.011(7)	95.483(14)	90	115.130(2)	114.292(4)	109.051(4)	96.8830(10)
γ (deg)	90	90	120	90	90	90	90
V (Å^3)	1599.5(4)	2040.3(13)	16974(4)	2428.8(3)	2493.7(4)	1552.1(2)	1828.69(8)
Z	4	4	6	4	4	2	2
ρ (g/cm^3)	1.337	1.234	1.415	1.407	1.607	1.262	1.553
μ (mm^{-1})	1.623	1.107	2.003	1.989	4.928	1.403	2.360
θ_{max} (deg)	29.93	26.91	24.76	29.99	33.36	33.58	39.57
Reflec. measured	64609	20546	28860	65084	23735	42123	26332
Unique reflections obv.	3987 [R_{int} = 0.0320]	2679 [R_{int} = 0.0887]	2221 [R_{int} = 0.0554]	5937 [R_{int} = 0.0341]	6535 [R_{int} = 0.0523]	5446 [R_{int} = 0.0582]	7677 [R_{int} = 0.0330]
Absorpt. correct.	TWINABS	SADABS	SADABS	SADABS	SADABS	SADABS	SADABS
Trans. min/max	0. 67/1.00	0.81/0.98	0.98/1.00	0. 81/0.98	0.69/1.00	0.82/0.98	0.84/1.00
Parameters	161	209	250	256	247	209	236
R1/wR2 [I>2σ(I)]	0.0450/0.1100	0.0456/0.0785	0.0576/0.1536	0.0266/0.0665	0.0437/0.1005	0.0868/0.2317	0.0362/0.0981
R1/wR2 [all data]	0.0545/0.1148	0.0961/0.0923	0.0872/0.1722	0.0326/0.0700	0.0686/0.1104	0.0945/0.2367	0.0513/0.1078
Goodness-of-fit (F^2)	1.125	1.007	1.016	1.044	1.040	1.225	1.025
Peak/hole (e/Å^3)	0.575/-0.664	0.372/-0.351	1.556/-1.838	0.560/-0.334	1.321/-0.710	1.499/-1.425	1.386/-1.150

(105 mg; 0.25 mmol) in DMF-d_7 (0.3 mL) produced [(IPr)Cu(CF_3)][14a] quantitatively. ^{1}H NMR (DMF-d_7, 25 °C), δ: 7.98 (s, 2H, IPr), 7.60 (t, 2H, J = 7.7 Hz, arom CH), 7.48 (d, 4H, J = 7.7 Hz, arom CH), 2.64 (m, 4H, J = 7.0 Hz, *i*-Pr CH), 1.32 (d, 12H, J = 7.0 Hz, *i*-Pr CH_3), 1.27 (d, 12H, J = 7.0 Hz, *i*-Pr CH_3). Signals from *t*-BuOH were also observed in the ^{1}H NMR spectrum at 4.23 ppm (s, 2H, OH) and at 1.19 ppm (s, 18H, CH_3). ^{19}F NMR (DMF-d_7, 25 °C), δ: −30.7 (s, $CuCF_3$).

Single Crystal X-ray Structure Determination. *Crystal Handling and Mounting.* The extremely air- and moisture-sensitive crystals of **1** and **2** were picked up using 200 μm MiTeGen Capton MicroMounts (M1-L19−200) and mounted on Crystalcap Copper Magnetic holders (Hampton Research) inside a glovebox, then quickly dipped into liquid nitrogen. The crystals were then directly mounted on the goniometer at 100 K using Hampton Research Cryo Tools: a CrystalCap Copper magnetic handling tool, a Crystalwand vial clamp for sample manipulation, and a Cryotong for crystal transfer at cryotemperatures. Air-sensitive crystals of **3**−**7** were coated with perfluoropolyether inside a glovebox for protection from air prior to mounting on the goniometer.

Data Collection. Crystal structures of **1**, **3**, **4**, **5**, and **7** were determined using a Bruker-Nonius diffractometer equipped with an APEX II 4K CCD[48] area detector, a FR591 rotating anode with MoK_α radiation, Montel mirrors as monochromator, a Kappa 4-axis goniometer, and an Oxford Cryosystem Plus low temperature device (T = −173 °C). Crystal structures of **2** and **6** were determined using an APEX DUO Kappa 4-axis goniometer equipped with an APEX II 4K CCD area detector, two Microfocus E025 IμS X-ray sources (Mo$_{K\alpha}$ and Cu$_{K\alpha}$), Quazar MX multilayer optics, and an Oxford Cryosystem Plus low temperature device (T = −173 °C). Full-sphere data collection was used with ω and φ scans. The following programs were used: APEX-2 (data collection),[48a] Bruker Saint V/.60A (data reduction),[48b] and SADABS or TWINABS (absorption correction).[48c]

Structure Solution and Refinement. The structures were solved using direct methods as implemented in SHELXTL[48d] and visualized using the XP program. Missing atoms were subsequently located from difference Fourier synthesis and added to the atom list. Least-squares refinement on F^2 using all measured intensities was carried out using SHELXTL. All non-hydrogen atoms were refined, including anisotropic displacement parameters. A summary of the crystallographic data is presented in Table 4. The twin crystal of **1** was processed with SAINT (simultaneous data processing) and TWINABS for absorption correction. The structure was refined using the overlapping reflections (crystal ratio = 90:10). High-symmetry **3** crystallizes in the trigonal/hexagonal space group $R\bar{3}c$. The center of the cluster (I1) is located on a $\bar{3}$ axis and only 1/6 of the complex was refined and the rest generated by symmetry operations. The outer-sphere iodine with an occupation of 1/6 is disordered in three positions around another $\bar{3}$ axis. Two different DMF molecules attached to the potassium atoms 1 and 2 are disordered in different orientations surrounding the iodide anion. Complexes **4** and **5** are isostructural, except one of the *t*-Bu groups is disordered in two orientations in **4** (ratio of disorder = 70:30). Dimer **6** (monoclinic, space group $P2_1/c$) was refined for a disordered model with two different positions and an occupancy ratio of 87:13. As both disordered positions exhibited *Ci*-symmetry, the corresponding half-molecules were refined. The less occupied position that is shifted in respect to the principal position by 0.5 axis units is likely because of the presence of a second smaller crystal forming a symmetry related twin with the main crystal. This position appeared as an electron density shadow overlapping the main structure. After the refinement using this model, the R1 value lowered from 12.3% to 8.7%. The crystal of **7** had *Ci*-symmetry and the corresponding half molecule was refined. The CF_3 group in **7** is disordered in two positions with occupancy factors of 62% and 38%.

■ ASSOCIATED CONTENT

Supporting Information. Complete ref 41b (PDF) and full details of crystallographic studies for complexes **1**−**7** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(47) To avoid evaporation and losses of the volatile external standard ($PhCF_3$ or PhF) the mixture was kept under vacuum for no longer than 15 s. In a control experiment, a DMF (10 mL) solution was prepared, containing PhF at the concentration used in the cupration reactions and CF_3COOK as a nonvolatile ^{19}F NMR internal standard. The solution was then placed in the Fischer−Porter tube used for the cupration reactions and kept under vacuum (ca. 1 mmHg) for 15 s. No detectable loss of PhF was detected by ^{19}F NMR analysis. After the solution was kept under vacuum on the same line for 10 min, ^{19}F NMR analysis indicated ca. 10% loss of PhF.

(48) (a) *Data collection with APEX II*, versions v1.0-22, v2009.1-0, and v2009.1-02 (2007); Bruker AXS Inc.: Madison, WI, U.S.A. (b) *Data reduction with Bruker SAINT*, versions V.2.10 (2003), V/.60A, and V7.60A (2007); Bruker AXS Inc., Madison, WI, U.S.A. (c) Blessing, R. H. *Acta Cryst. A* 1995, 51, 33; *SADABS*, V.2.10(2003), V2008, and V2008/1 (2001); *TWINABS*, version 2008/4; Bruker AXS Inc.: Madison, WI, U.S.A. (d) Sheldrick, G. M. *Acta Cryst. A* **2008** *A64*, 112; *SHELXTL*, versions V6.12 and 6.14.