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Direct Synthesis of a Trifluoromethyl Copper Reagent from Trifluoromethyl Ketones: Application to Trifluoromethylation

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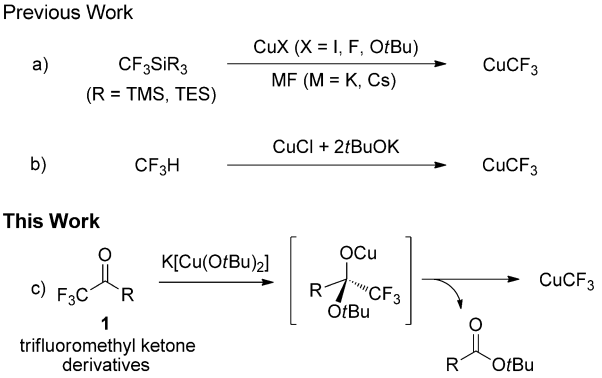
Trifluoromethyl compounds have attracted much attention in the pharmaceutical and agrochemical industries due to the unique properties of the trifluoromethyl group.[1,2] Various synthetic methods for such compounds have so far been developed by the use of trifluoromethyl organometallic (MCF_3) reagents.[3] However, hard lithium and magnesium cations cannot be employed for such reagents, because these MCF_3 reagents are unstable even at low temperature and readily decompose to metal fluoride (MF) and singlet difluoromethylene ($:CF_2$) by means of α-fluoride elimination.[3] In sharp contrast to hard metal cations, soft counterparts are useful as MCF_3 reagents for many types of trifluoromethylation.[3,4] Among the soft MCF_3 reagents, $CuCF_3$ reagents are relatively stable, but maintain their high reactivity. Intensive studies have thus been focused on efficient synthetic protocols for $CuCF_3$ reagents and their application to various trifluoromethylations.[5,6] In particular, the Ruppert–Prakash reagents (CF_3SiR_3)[7] are highly versatile as a stable CF_3^- source, and can readily generate $CuCF_3$ reagents by treatment with a Cu^I salt and metal fluoride; however, this process is still cost-prohibitive for large scale operations (Scheme 1a).[6] Therefore, fluoroform (CF_3H),[8] a large-volume by-product of Teflon® (DuPont) manufacturing, as the cheapest and atom-economical CF_3^- source[9] was utilized with the aim of preparing $CuCF_3$ reagents.[10] Normant reported the preparation of $CuCF_3$ by adding a Cu^I salt to trifluoromethylated hemiaminolate $[CF_3CH(O)NMe_2]^-$, which can be produced by the deprotonation of fluoroform using a strong base followed by the addition to dimethylformamide (DMF); however, the yield of $CuCF_3$ was insufficient.[10a] Recently, Grushin succeeded in achieving a highly efficient preparation of $CuCF_3$ by direct cupration of fluoroform (Scheme 1b).[10b] The fundamental drawback of these methods is that fluoroform, a low boiling point gas (−83 °C) is hard to handle in many synthetic laboratories. Therefore, a more practical synthetic method for the preparation of $CuCF_3$ reagents using low-cost and operationally easy CF_3^- sources in addition to fluoroform is strongly desired. Herein, we describe the practical synthesis of a $CuCF_3$ reagent from one of the most economical and efficient CF_3^- sources, that is, trifluoromethyl ketone derivatives, which are low-cost liquid and easy to handle (Scheme 1c). Moreover, the $CuCF_3$ reagent thus prepared in excellent yield can be utilized to a variety of trifluoromethylations with terminal alkynes, arylbronic acids, and aryl iodides under mild reaction conditions, and thus in late-stage functionalizations.



Scheme 1. Synthetic methods for the preparation of trifluoromethyl copper reagents.

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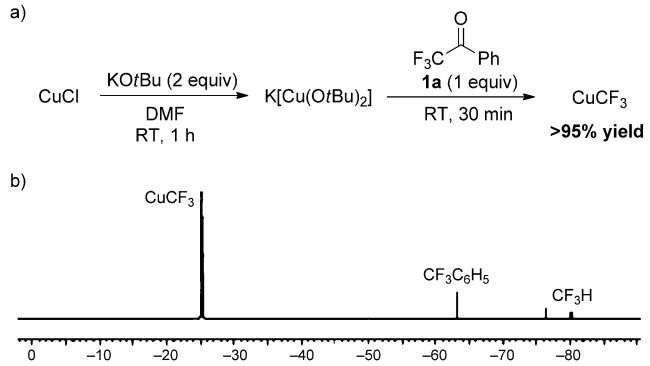
Two methods to employ trifluoromethyl ketone derivatives as CF_3^- sources have been reported up to now. One is decarboxylation,[11] which is accomplished by heating with catalytic or stoichiometric amounts of a Cu^I salt and alkali metal trifluoroacetate and generates $CuCF_3$. The reaction, however, occurs under harsh conditions (ca. 160 °C), and hence it is difficult to efficiently produce $CuCF_3$ reagents that are unstable under the high-temperature conditions. The other method is via tetrahedral intermediates prepared from trifluoromethyl ketone or trifluoroacetic acid derivatives and appropriate nucleophiles.[12] Langlois and Billard reported that trifluoromethyl ketone derivatives could be employed as a CF_3^- source is such reactions—addition of KO*t*Bu, and trifluoromethylation to ketones without acidic α-proton proceeded smoothly.[12a] However, $CuCF_3$ reagents have never been prepared successfully by this route. Therefore, we envisioned a practical method for the preparation of $CuCF_3$ reagents through the formation of tetrahedral intermediates from trifluoromethyl ketone derivative and appropriate nucleophiles.

Initially, the preparation of the $CuCF_3$ reagent by treatment with 2,2,2-trifluoroacetophenone (**1a**) and CuO*t*Bu

generated from CuCl (1 equiv) and KO*t*Bu (1 equiv) as a nucleophile was examined, but $CuCF_3$ was not obtained. This result implied that CuO*t*Bu is not nucleophilic enough to provide the tetrahedral intermediate, hence its cuprate was used as a higher nucleophilic reagent. After $K[Cu(OtBu)_2]$ was prepared from the reaction of CuCl (1 equiv) and KO*t*Bu (2 equiv) in DMF at room temperature for 1 h, the addition of **1a** to the resulting DMF solution led to the formation of $CuCF_3$ in >95% yield within 30 min (Scheme 2a).



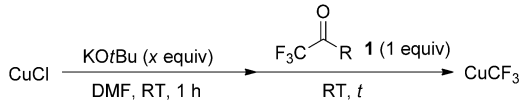
Scheme 2. Preparation of trifluoromethyl copper reagent from cuprate and 2,2,2-trifluoroacetophenone. a) Conditions: After treatment of CuCl (0.5 mmol) and KO*t*Bu (1.0 mmol) in DMF (1.5 mL) at room temperature for 1 h, **1a** (0.5 mmol) was added to the DMF solution at the same temperature. Yield was determined by ^{19}F NMR analysis using benzotrifluoride as an internal standard. b) ^{19}F NMR spectrum (282 MHz, $[D_7]$DMF) of reaction mixture containing $CuCF_3$ species (−25.2 ppm) obtained in >95% yield.

The ^{19}F NMR and ^{13}C NMR data of $CuCF_3$ thus obtained matched well with the data of $CuCF_3$ reported by Grushin (Scheme 2b).[10b]

In addition, the preparation of the $CuCF_3$ reagent from various trifluoromethyl ketones and esters was surveyed by using the cuprate (Table 1). Even with ketones **1b–d** bearing not only electron-donating and -withdrawing groups (entries 1–2), but also a sterically more demanding group (entry 3), excellent yields (>95% yield) were maintained under the same reaction conditions. Unfortunately, the use of trifluoroacetates **1e**,**f** resulted in severely decreased yields, probably because of the lower electrophilicity of **1e**,**f** and higher stability of the tetrahedral intermediate by chelation between potassium and oxygen atoms (entries 4 and 6). However, by employing three equivalents of KO*t*Bu and prolonged reaction times (6 h), it was found that $CuCF_3$ could be obtained in more than 60% yield (entries 5 and 7). *tert*-Butyl trifluoroacetate (**1g**) and ethyl trifluoropyruvate (**1h**) gave low yields (entries 8 and 9), and the formation of $CuCF_3$ was not observed from potassium trifluoroacetate (**1i**) at all (entry 10).

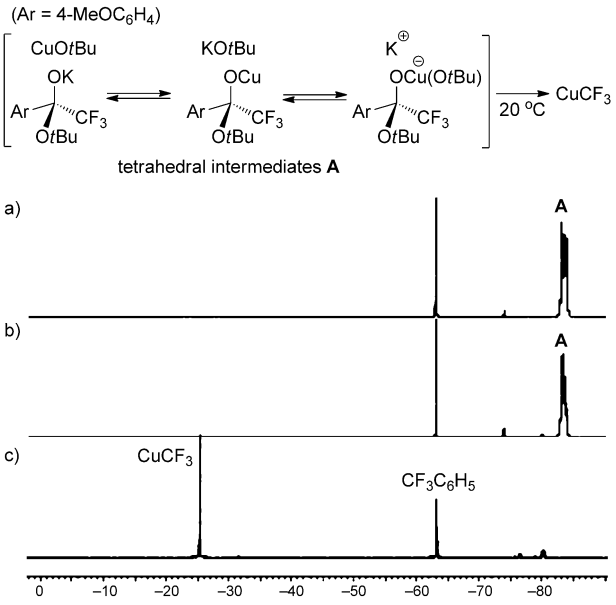
Next, the ^{19}F NMR analysis was performed to gain an insight into tetrahedral intermediate **A** prepared with cuprate and **1b** as the CF_3 source (Scheme 3).[10a] At −30 °C, three peaks (−84.2, −83.9, and −83.4 ppm) were observed in ^{19}F NMR spectrum (Scheme 3a). After the mixture was

Table 1. Preparation of trifluoromethyl coper reagent using various trifluoromethyl sources.[a]



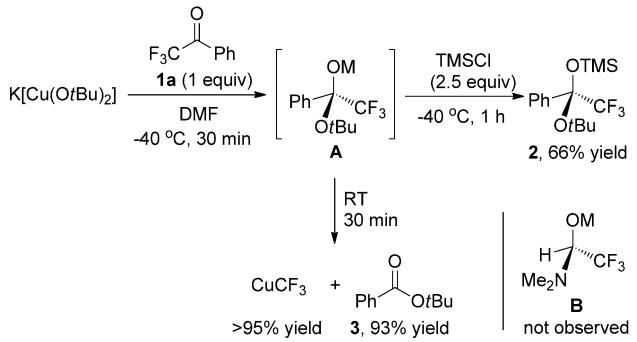
Entry	R	*x*	*t* [h]	Yield [%][b]
1	*p*-$MeOC_6H_4$ (**1b**)	2	0.5	>95
2	*p*-ClC_6H_4 (**1c**)	2	0.5	>95
3	2,4,6,-$Me_3C_6H_2$ (**1d**)	2	0.5	>95
4	OMe (**1e**)	2	6	33
5	OMe (**1e**)	3	6	66
6	OEt (**1f**)	2	6	29
7	OEt (**1f**)	3	6	64
8	O*t*Bu (**1g**)	3	6	2
9	CO_2Et (**1h**)	3	6	21
10	OK (**1i**)	3	6	0

[a] Conditions: After treatment of CuCl (0.5 mmol) and KO*t*Bu (0.5× *x* mmol) in DMF (1.5 mL) at room temperature for 1 h, trifluoromethyl sources **1** (0.5 mmol) were added to the DMF solution at the same temperature. [b] Yield was determined by ^{19}F NMR analysis using benzotrifluoride as an internal standard.



Scheme 3. Top: Plausible structures of tetrahedral intermediates. Bottom: ^{19}F NMR spectra of a reaction mixture containing CuCl (1 equiv), KO*t*Bu (2 equiv), and 4′-methoxy-2,2,2-trifluoroacetophenone (**1b**; 1 equiv) in $[D_7]$DMF. The single peaks of −25.2 and −63.2 ppm are from $CuCF_3$ and benzotrifluoride (internal standard); the ^{19}F NMR spectra were obtained at a) −30, b) −10, and c) 20 °C; $CuCF_3$ was obtained in >95% yield.

gradually warmed up, the peaks began to broaden at −10 °C (Scheme 3b), and the generation of the $CuCF_3$ species was subsequently observed at around room temperature (20 °C) (Scheme 3c). It was proposed that the three peaks, which are in equilibrium at −30 °C, correspond to those of tetrahedral intermediates **A** of the potassium salt, the copper salt, and the cuprate.



Scheme 4. Isolation of *O*-silylated tetrahedral intermediate **2** and *tert*-butyl benzoate **3**.

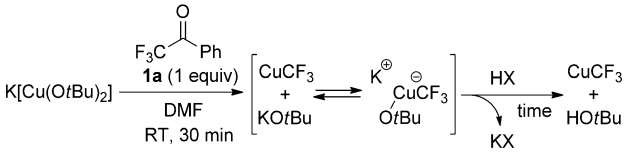
On the other hand, the addition of TMSCl to tetrahedral intermediate **A** provided the *O*-silylated product **2** as the tetrahedral intermediate trapped in 66% yield (Scheme 4). *tert*-Butyl benzoate (**3**) was also isolated in 93% yield by warming up to room temperature. Significantly, the dimethylformamide (DMF)-adduct **B**, formed by addition to DMF solution of free CF_3^- ions as reported by Normant,[10a] was not totally observed in ^{19}F NMR spectroscopy. Even in the presence of electron-rich alkenes (2 equiv), such as α-methylstyrene, the reaction did not give the *gem*-difluorocyclopropane, which can be produced by difluoromethylene species via the decomposition of free CF_3^- ion. These results strongly indicate that $CuCF_3$ is directly formed from the tetrahedral intermediate **A**.

The stability of $CuCF_3$ in DMF at room temperature was investigated by monitoring the ^{19}F NMR spectrum (Table 2). It was found that the yield of $CuCF_3$ decreased from 97 to 69% after 48 h, but further decomposition did not take place even after prolonged time. These results agreed with the report by Grushin.[10b] It was proposed that such decomposition was caused by the potassium cation of remaining KO*t*Bu, which would strongly interact with fluorine atom of the $CuCF_3$ species prepared. To solve this problem, we tried to suppress the decomposition through neutralization of remaining KO*t*Bu with appropriate acids (HX) to precipitate potassium salt (KX) in the solution. Grushin has already succeeded in minimizing the decomposition by neutralization with $Et_3N{\cdot}3HF$ (TREAT HF).[10b] Therefore, various acids, for example $Et_3N{\cdot}3HF$, $Et_3N{\cdot}HCl$, and HCl in Et_2O (1.0 M solution) were used for the stabilization of the $CuCF_3$ reagent (Table 2).[13] With all acids, the ^{19}F NMR signal of $CuCF_3$ shifted upfield to −27.4 from −25.2 ppm due to exchange from *tert*-butoxide to *tert*-butanol, and the precipitation of KF or KCl was observed. Even after one day, $Et_3N{\cdot}3HF$ and $Et_3N{\cdot}HCl$ could retard the decomposition of $CuCF_3$, compared with the conditions without acids. With HCl in Et_2O, the stability was equal to that with $Et_3N{\cdot}3HF$, but $CuCF_3$ decomposed up to 89% at an initial stage, likely due to the heat of neutralization.

We then focused our attention to employ the $CuCF_3$ reagent that can be directly prepared from 2,2,2-trifluoro acetophenone (**1a**) for a variety of trifluoromethylation reactions. Initially, we attempted the oxidative trifluoromethylation of terminal alkynes as a coupling reaction at the sp-carbon, because the products obtained are useful as CF_3-containing building blocks (Scheme 5).[6c,j] After the optimization of the reaction conditions,[13] it was found to be efficient to use tetramethylethylenediamine (TMEDA) and $Et_3N{\cdot}HCl$ as the ligand and acid, respectively, in the presence of the $CuCF_3$ reagent (2 equiv) at room temperature in air. The slow addition of alkynes **4** through a syringe pump was also the key for enhancing the yield. The reaction with not only electron-rich and -deficient aromatic but also aliphatic alkynes **4a–i** proceeded in more than 88% yield under much milder conditions, compared with previous results.[6c,j] Aliphatic alkyne **4j**, with a steroidal backbone, also led to the corresponding product **5j** in 91% yield.

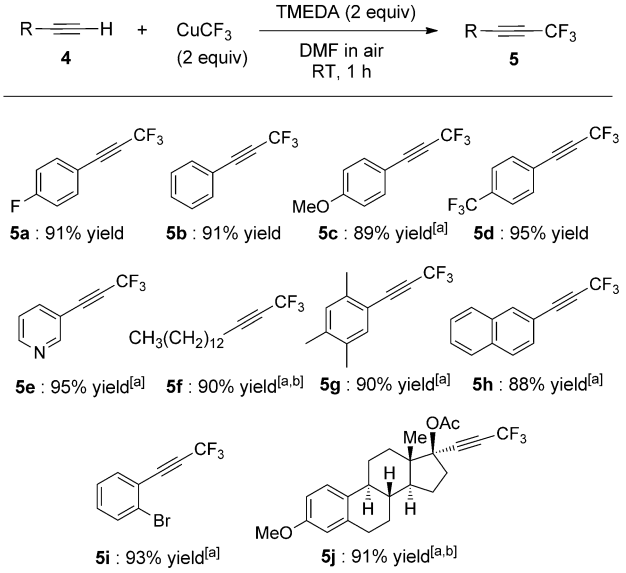
Trifluoromethylation with boronic acids **6** was also scrutinized as an oxidative coupling reaction at an sp^2-carbon (Scheme 6).[3c] The reaction by treatment of boronic acids **6** in the presence of the $CuCF_3$ reagent (2 equiv) proceeded smoothly without any ligands to provide the corresponding products **7** in good-to-excellent yields. In contrast to the oxidative trifluoromethylation of terminal alkynes, toluene was the best solvent. Under the optimized reaction conditions,[13] aromatic boronic acids **6a–i** bearing both electron-withdrawing and -donating substituents showed high yields. While the reaction with **6f** and **6j** resulted in severely decreased yields, which were improved by using DMF instead of toluene and extending the reaction time up to 4 h. The pinacolboronate ester, obtained by iridium-catalyzed C–H activation/borylation of α-tocopherol nicotinate,[6h,i] was also examined to

Table 2. Stability of trifluoromethyl copper reagent.

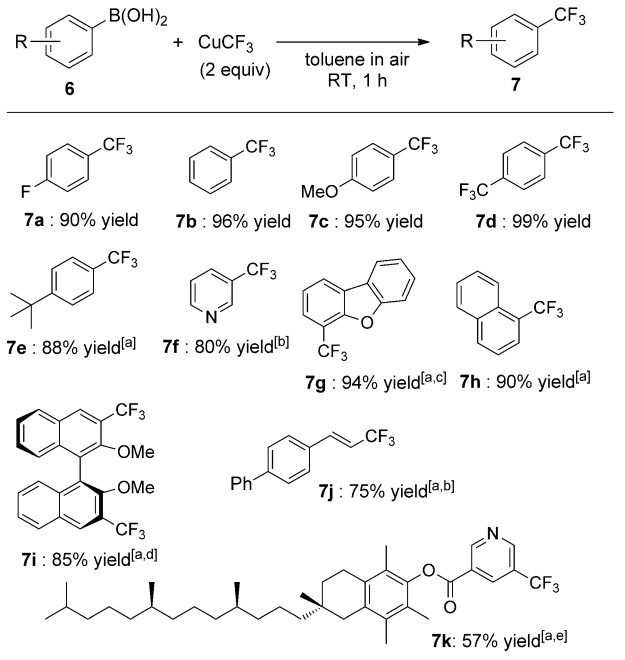


None		$Et_3N{\cdot}3HF$ (1/3 equiv)		$Et_3N{\cdot}HCl$ (1 equiv)		HCl in Et_2O (1 equiv)	
t [h]	$CuCF_3$ [% yield[a]]	*t* [h]	$CuCF_3$ [% yield[a]]	*t* [h]	$CuCF_3$ [% yield[a]]	*t* [h]	$CuCF_3$ [% yield[a]]
0.1	97	0.1	97	0.1	93	0.1	89
1	95	1	95	1	89	1	87
3	89	3	91	3	89	3	86
9	83	6	91	6	88	6	85
21	74	27	89	24	84	20	83
48	69	42	85	45	79	42	81
72	69	72	83	72	74	72	79

[a] Yield was determined by ^{19}F NMR analysis using benzotrifluoride as an internal standard.



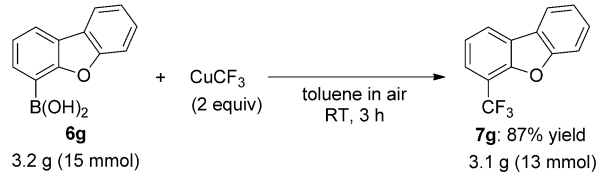
Scheme 5. Trifluoromethylation of terminal alkynes. Conditions; **4** (0.1 mmol), $CuCF_3$ reagent (0.2 mmol), TMEDA (0.2 mmol), air (1 atm) in DMF (1 mL) at room temperature. Alkynes **4** in DMF (0.5 mL) were added over a period of 1 h by using a syringe pump. Yields were determined by ^{19}F NMR analysis using benzotrifluoride as an internal standard. The $CuCF_3$ reagent was neutralized by $Et_3N{\cdot}HCl$ (1 equiv) before being used in the reaction. [a] Isolated yield. [b] 1,10-Phenanthroline (0.2 mmol) was used instead of TMEDA as a ligand, and alkyne (0.1 mmol) was added over 2 h by using a syringe pump under O_2.



Scheme 6. Trifluoromethylation of arylboronic acids. Conditions; **6** (0.1 mmol), $CuCF_3$ reagent (0.2 mmol), air (1 atm) in toluene (1 mL) at room temperature. Yields were determined by ^{19}F NMR analysis using benzotrifluoride as an internal standard. The $CuCF_3$ reagent was neutralized by $Et_3N{\cdot}HCl$ (1 equiv) before being used in the reaction. [a] Isolated yield. [b] DMF was used instead of toluene as a solvent, and reaction time was 4 h. [c] Reaction time was 3 h. [d] $CuCF_3$ reagent of 4 equivalents was used, and DMF was used instead of toluene as a solvent. [e] Pinacolboronate ester (Bpin) was used instead of boronic acid.

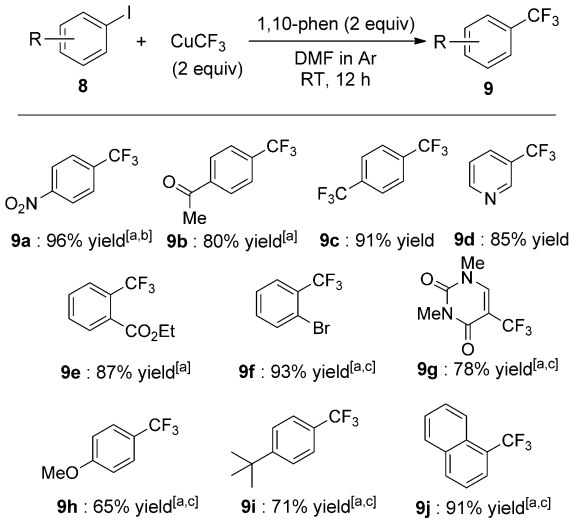
give the trifluoromethylated product **7k** in an overall yield for the two steps of 57%.

We ran a gram-scale reaction for oxidative trifluoromethylation with boronic acid (Scheme 7). Under the optimized reaction conditions, the reaction with **6g** (scale: 3.2 g, 15 mmol) proceeded smoothly and we isolated the corresponding product **7g** in 87% yield (3.1 g, 13 mmol).



Scheme 7. Large-scale operation for trifluoromethylation.

Finally, the $CuCF_3$ reagent prepared by our new method was successfully applied to trifluoromethylation with aryl iodide **8** (Scheme 8).[3c] After surveying a wide range of solvents, oxidants, and ligands, we found that the reaction proceeded smoothly when conducted in DMF with 1,10-phenanthroline, which was more efficient than TMEDA. With the reaction conditions established,[13] the use of the electron-deficient aryl iodides **8a–e** led to the corresponding products **9a–e** in good-to-excellent yields even at room temperature. While decreased yields were found for **8f**, with sterically more demanding *ortho*-substituent, uracil derivative **8g**, and **8h–j**, with increased electron density of aromat-



Scheme 8. Trifluoromethylation of aryl iodides. Conditions; **8** (0.1 mmol), $CuCF_3$ reagent (0.2 mmol), 1,10-phenanthroline (0.2 mmol) in DMF (1 mL) at room temperature. Yields were determined by ^{19}F NMR analysis using benzotrifluoride as an internal standard. $CuCF_3$ reagent neutralized by $Et_3N{\cdot}HCl$ (1 equiv) before being used in the reaction. [a] Isolated yield. [b] 1 equivalent of each of $CuCF_3$ reagent and 1,10-phenanthroline were used. [c] Reaction temperature was 50 °C.

ic ring; however, increasing the reaction temperature up to 50 °C improved the reactivity to give good yields.

In summary, we have succeeded in the direct synthesis of the $CuCF_3$ reagent from cuprate and trifluoromethyl ketone derivatives, as a useful trifluoromethyl source. It is notable that all of the reagents are low-cost for large-scale operations, that the operation is simple, and that the yield of $CuCF_3$ is virtually quantitative. Furthermore, it was demonstrated that the $CuCF_3$ reagent obtained from 2,2,2-trifluoroacetophenone (**1a**) can be successfully applied to three types of trifluoromethylations with terminal alkynes, arylbronic acids, and aryl iodides, to provide the corresponding products in good-to-high yields. Development of novel reactions with the "ligandless" $CuCF_3$ reagent prepared by our method is now underway in our laboratory.

Experimental Section

Synthetic procedure of $CuCF_3$ reagent from 2,2,2-trifluoroacetophenone (1a): A mixture of CuCl (50 mg, 0.50 mmol) and KO*t*Bu (112 mg, 1.0 mmol) in DMF or [D_7]DMF (1 mL) was stirred for 1 h at room temperature under argon atmosphere. 2,2,2-Trifluoroacetophenone (**1a**) (68 μL, 0.50 mmol) was added dropwise to the mixture at room temperature. After the reaction mixture was stirred for 30 min, $CuCF_3$ species was observed by ^{19}F NMR analysis using benzotrifluoride as an internal standard (>95% yield).

Typical procedure for trifluoromethylation of terminal alkynes with the $CuCF_3$ reagent: The $CuCF_3$ reagent (DMF solution 0.40–0.50 M, 400–500 μL, 0.2 mmol) neutralized by $Et_3N{\cdot}HCl$ (27 mg, 0.2 mmol) was added to a solution of TMEDA (30 μL, 0.2 mmol) or 1,10-phenanthroline (36 mg, 0.2 mmol) in DMF (1 mL) at room temperature. A solution of terminal alkyne **4** (0.1 mmol) in DMF (0.5 mL) was added to the mixture over 1–2 h by using a syringe pump in air (1 atm). After stirring for 15 min at room temperature, the reaction mixture was quenched by 1 M aqueous HCl (5 mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O (5 mL×3). The organic layers were combined and washed with brine (10 mL), dried over Na_2SO_4, and evaporated. The resulting crude product was purified by silica-gel column chromatography to give the trifluoromethylated products **5**.

Typical procedure for trifluoromethylation of arylboronic acids with the $CuCF_3$ reagent: The $CuCF_3$ reagent (DMF solution 0.40–0.50 M, 400–500 μL, 0.2 mmol) neutralized by $Et_3N{\cdot}HCl$ (27 mg, 0.2 mmol) was added to a solution of arylboronic acid **6** (0.1 mmol) in toluene or DMF (1 mL) at room temperature in air. After stirring for 1–4 h, the reaction mixture was quenched by 1 M aqueous HCl (5 mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O (5 mL×3). The organic layers were combined and washed with brine (10 mL), dried over Na_2SO_4, and evaporated. The resulting crude product was purified by silica-gel column chromatography to give the trifluoromethylated products **7**.

Typical procedure for trifluoromethylation of aryl iodides with the $CuCF_3$ reagent: The $CuCF_3$ reagent (DMF solution 0.40–0.50 M, 400–500 μL, 0.2 mmol) neutralized by $Et_3N{\cdot}HCl$ (27 mg, 0.2 mmol) was added to a solution of aryl iodide **8** (0.1 mmol) and 1,10-phenanthroline (36 mg, 0.2 mmol) in DMF (1 mL) at room temperature under an argon atmosphere. After stirring for 12 h, the reaction mixture was quenched by 1 M aqueous HCl (5 mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O (5 mL×3). The organic layers were combined and washed with brine (10 mL), dried over Na_2SO_4, and evaporated. The resulting crude product was purified by silica-gel column chromatography to give the trifluoromethylated products **9**.

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Keywords: copper · fluorine · ketones · Ruppert–Prakash reagents · trifluoromethylation

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[13] For details, see the Supporting Information.

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