ChemPubSoc Europe

DOI: 10.1002/chem.201504306

CHEMISTRY A European Journal Full Paper

Synthetic Methods |*Hot Paper*|

Decarboxylative Trifluoromethylating Reagent $[Cu(O_2CCF_3)(phen)]$ and Difluorocarbene Precursor $[Cu(phen)_2][O_2CCF_2Cl]$

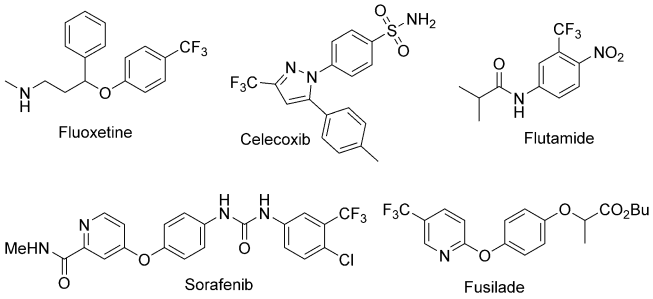
Xiaoxi Lin[+], Chuanqi Hou[+], Haohong Li, and Zhiqiang Weng*[a]

Abstract: This article describes the new economic decarboxylative trifluoromethylating reagent $[Cu(phen)(O_2CCF_3)]$ (**1**; phen = 1,10-phenanthroline) and the efficient difluorocarbene precursor $[Cu(phen)_2][O_2CCF_2Cl]$ (**2**). Treatment of copper *tert*-butoxide with phen and subsequent addition of trifluoroacetic acid or chlorodifluoroacetic acid afforded air-stable complexes **1** and **2**, respectively, which were characterized by X-ray crystallography. The copper(I) ion in **1** is coordinated by a bidentate phen ligand, a monodentate trifluoroacetate group, and a molecule of CH_3CN in a distorted tetrahedral coordination geometry. The molecular structure of **2** adopts an ionic form that consists of a $[Cu(phen)_2]^+$ cation and a chlorodifluoroacetate anion. Complex **1** reacted with a variety of aryl and heteroaryl halides to form trifluoromethyl (hetero)arenes in good yields. The corresponding Hammett plot exhibited a linear relationship and a reaction parameter (ρ) = +0.56 ± 0.02, which indicated that the trifluoromethylation reaction proceeded via a nucleophilic reactive species. Complex **2** reacts with phenols to produce aryl difluoromethyl ethers in modest-to-excellent yields. Mechanistic investigations revealed that the difluoromethylation reaction proceeds by initial copper-mediated formation of difluorocarbene and subsequent concerted addition of difluorocarbene to the phenol to form a three-center transition state.

Introduction

The synthesis of trifluoromethyl-containing aromatic compounds is of general interest because this motif is present in many commercial agrochemicals, pharmaceuticals, and functional materials.[1,2] It is well-recognized that the introduction of trifluoromethyl groups into bioactive molecules frequently has a dramatic impact on their physical and chemical properties, which leads to increased biological activity and significantly improved lipophilicity and metabolic stability.[3] Consequently, the incorporation of a trifluoromethyl group into bioactive molecules has become a powerful tool in drug design and discovery. Well-known examples of commercially meaningful trifluoromethyl arenes (Scheme 1) include the antidepressant Fluoxetine, the arthritis drug Celecoxib, Sorafenib and Flutamide (used for the treatment of kidney and prostate cancer, respectively), as well as a number of herbicides (e.g., fluazifop-butyl (Fusilade)).

Given the prevalence of the trifluoromethyl group in biologically active compounds, designing efficient methods to access trifluoromethylated arenes is of high value. A variety of trifluoromethylation strategies have been developed in recent decades.[4,5]



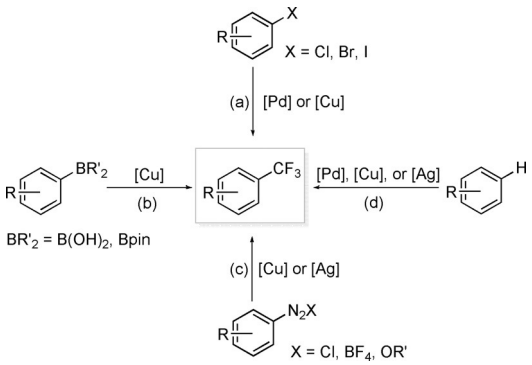
Scheme 1. Selected examples of trifluoromethylated phamaceutical and agrochemical compounds.

Traditionally, $ArCF_3$ compounds have been prepared by Swarts-type reactions, which involve treatment of benzotrichloride or benzoic acid derivatives with anhydrous HF, SbF_5, or SF_4.[6] However, such harsh conditions and limited substrate scope have been the main limitations for Swarts-type reactions. Recently, transition-metal-promoted trifluoromethylation reactions of arenes have been demonstrated to provide convenient methods for the facile formation of trifluoromethylated arenes (Scheme 2).[7–10] These include palladium- and copper-catalyzed/mediated trifluoromethylation of aryl chlorides[12]/iodides[11] (Scheme 2a), copper-catalyzed/mediated trifluoromethylation of aryl boronic acids[13] and boronates[14] (Scheme 2b), copper-[15] and silver-mediated[16] trifluoromethylation of aryl-

[a] X. Lin,[+] C. Hou,[+] Dr. H. Li, Prof. Dr. Z. Weng
State Key Laboratory of Photocatalysis on Energy and Environment College of Chemistry, Fuzhou University
Fuzhou, 350108 (China)
E-mail: zweng@fzu.edu.cn

[+] These authors contributed equally to this work.

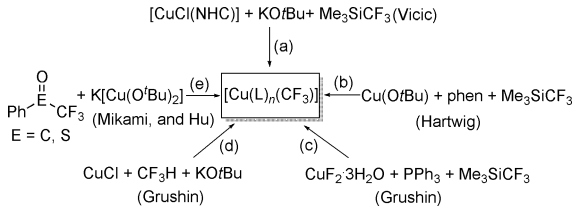
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201504306.



Scheme 2. Strategies for the synthesis of trifluoromethylarenes (pin = pinacolato).

diazonium salts (Scheme 2c), and palladium-,[17] copper-,[18] and silver-catalyzed[19]/mediated[20] trifluoromethylation of aromatic C–H bonds (Scheme 2d).

In addition, the use of copper reagents in trifluoromethylation reactions has attracted much interest due to their good reactivity, low toxicity, and good regiospecificity.[21] Since the pioneering work of McLoughlin and Thrower in 1969 related to the reductive coupling of aryl halides with perfluoroalkyl iodides in the presence of copper metal,[22] $CuCF_3$ reagents have been extensively studied and applied in stoichiometric trifluoromethylation reactions of aryl halides.[23] For example, Vicic and co-workers reported the first thermally stable and well-defined complexes of the type $[Cu(CF_3)(NHC)]$ (NHC = N-heterocyclic carbene), which were obtained from the reaction of [CuCl(NHC)] with KO*t*Bu followed by treatment with Me_3SiCF_3 at room temperature (Scheme 3a).[24] Hartwig and co-workers



Scheme 3. Methods for the synthesis of copper trifluoromethylating reagents.

prepared the 1,10-phenanthroline (phen) ligated complex $[Cu(CF_3)(phen)]$ by the reaction of copper *tert*-butoxide and phen with Me_3SiCF_3 in benzene (Scheme 3b).[25] Grushin and co-workers obtained the triphenylphosphine-coordinated complex $[Cu(CF_3)(Ph_3P)_3]$ by heating a solution of $CuF_2{\cdot}3H_2O$ and Ph_3P in methanol at reflux temperature, followed by reaction with Me_3SiCF_3 in THF (Scheme 3c);[26] they subsequently reported the synthesis of $CuCF_3$ derivatives from the reaction of CuCl and KO*t*Bu with fluoroform (Scheme 3d).[27] Mikami and Hu also independently reported direct synthesis of the $CuCF_3$ reagent from cuprate and trifluoromethyl ketone derivatives[28] or phenyl trifluoromethyl sulfones, respectively[29] (Scheme 3e). These copper reagents reacted with aryl iodides, bromides, boronic acids, and boronate esters to give benzotrifluorides. Despite these notable advances, most strategies rely upon using the costly Me_3SiCF_3 reagent or gaseous HCF_3, which is hard to handle in most academic laboratories, and $Et_3N{\cdot}3HF$ or $Et_3N{\cdot}HCl$ to stabilize the $CuCF_3$ reagent.

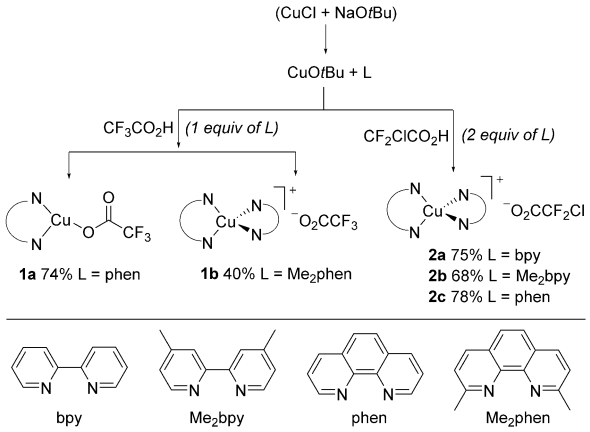
The use of readily available, convenient, and inexpensive alternatives, such as trifluoroacetic acid (TFA) and its derivatives,[4b,30–32] as the trifluoromethyl source for the preparation of trifluoromethylarenes is an attractive prospect. Trifluoromethylation of aryl iodides with $CuCF_3$ formed by decarboxylation of methyl trifluoroacetate has been reported.[12e,33] Vicic and co-workers also reported the preparation of (NHC)–copper–trifluoroacetate complexes for decarboxylative trifluoromethylation of aryl halides.[34] However, despite their economically benign nature, the reaction suffers from some disadvantages, such as high operating temperatures (160–180 °C), lack of practicability, and poor substrate scope. Very recently, Zhang and co-workers reported an Ag-catalyzed radical C–H trifluoromethylation of arenes with TFA as the trifluoromethylating reagent.[35] This method avoids prefunctionalization of the substrate, but has low regioselectivity and limited functional-group compatibility. Therefore, to match the increasing scientific and practical demands, it is still of continued interest and great importance to develop convenient and efficient methods for arene trifluoromethylation. In this context, our group recently developed an efficient copper-catalyzed trifluoromethylation of aryl iodides by using Me_3SiCF_3[36] and related copper reagents for the synthesis of fluorinated organic compounds.[37] Herein, we report the synthesis of complexes $[Cu(O_2CCF_3)(phen)]$ and $[Cu(phen)_2][O_2CCF_2Cl]$ and their successful application to the trifluoromethylation and difluoromethylation of (hetero)aryl halides and phenols to furnish trifluoromethylarenes and (hetero)aryl difluoromethyl ethers, respectively, in good yields.

Results and Discussion

Synthesis and structural studies

The reactions of copper *tert*-butoxide (prepared in situ from CuCl and NaO*t*Bu) with diimine ligand (1–2 equiv) and subsequent addition of TFA or chlorodifluoroacetic acid in THF at room temperature afforded neutral copper–trifluoroacetate complex $[Cu(O_2CCF_3)(phen)]$ (**1a**), ionic complex $[Cu(Me_2phen)_2][(O_2CCF_3)]$ (**1b**), or chlorodifluoroacetate complexes $[Cu(L)_2][O_2CCF_2Cl]$ (**2a–c**; L = bpy, Me_2bpy, and phen, respectively) (Scheme 4). All these complexes were air stable in solution and in the solid state for several hours. These complexes are soluble in DMF, CH_3CN, and CH_2Cl_2, but insoluble in benzene and toluene. Furthermore, these new trifluoroacetato and chlorodifluoroacetato complexes are amenable to large-scale synthesis ($\geq$3 g).

Complexes **1a**, **1b**, and **2a–c** were characterized by ^1H, ^{13}C, and ^{19}F NMR spectroscopy, IR spectroscopy, and elemental analysis. The IR spectrum of the crystalline product **1a** shows intense bands at $\tilde{\nu}$ = 1674 (C=O) and 1434 cm^{-1} (C–O), which indicates η^1-O monodentate coordination to the copper center. Complex **1a** exhibits a diagnostic resonance in the ^{19}F NMR



Scheme 4. Synthesis of copper–trifluoroacetate and copper–chlorodifluoroacetate complexes **1** and **2**.

spectrum in CD_3CN at $\delta = -74.3$ ppm. Complexes **2a**–**c** show signals in the ^{19}F NMR spectra at $\delta \approx -57$ ppm (chlorodifluoroacetate groups).

To support the spectroscopic evidence, single crystals of **1a**, obtained by solvent diffusion (Et_2O/CH_3CN), were subjected to X-ray structural analysis. As shown in Figure 1, the copper

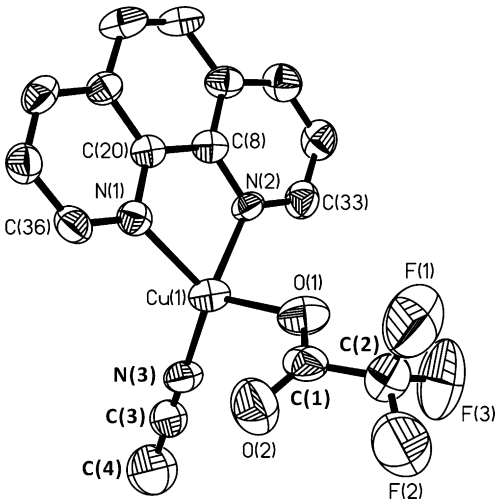


Figure 1. ORTEP drawing of complex **1a**. Thermal ellipsoids are drawn at 40% probability, hydrogen atoms are omitted for clarity.

center is bound by two N atoms from phen, one O atom from the trifluoroacetato ligand, and one N atom from CH_3CN in a distorted-tetrahedral geometry. An interesting feature is the monodentate coordination of the trifluoroacetato ligand, which confirms the indications of the IR spectrum.

The substantially different values of the Cu(1)–O(1) (2.080(7) Å) and Cu(1)–O(2) (3.243(7) Å) bond lengths in **1a** clearly imply monodentate coordination of the trifluoroacetato ligand to the central copper(I) ion. In addition, the Cu(1)–O(1) bond length is significantly longer than in [Cu(SIMes)(trifluoroacetate)] (1.842(4) Å; SIMes = 1,3-dimesitylimidazolin-2-ylidene),[34] which is probably due to the tetrahedral geometry in **1a**. The two Cu–N(phen) bond lengths are almost identical (2.048(6) and 2.073(6) Å), and they are comparable to the corresponding lengths in [Cu(bathophenanthroline)CF_3] (2.024(8) and 2.096(8) Å).[36] The Cu–N(CH_3CN) bond length was 1.886(7) Å, which is slightly longer than in three-coordinate copper(I) complexes [Cu(CH_3CN)(Me_2phen)][X] (X = ClO_4, PF_6, and BF_4; 1.850–1.856 Å).[38] The monodentate coordination mode of the trifluoroacetate group is further characterized by the different C(1)–O(1) (1.170(10) Å) and C(1)–O(2) (1.226(10) Å) bond lengths.

Crystals of **1b** (co-crystallizes with adventitious CF_3CO_2H) suitable for X-ray diffraction were grown by recrystallization from a solution in CH_3CN layered with Et_2O. In contrast to **1a**, the structure of **1b** contains a cationic tetrahedral copper(I) center ligated by two Me_2phen ligands and a free, unligated trifluoroacetate anion (Figure 2). The range of Cu–N bond

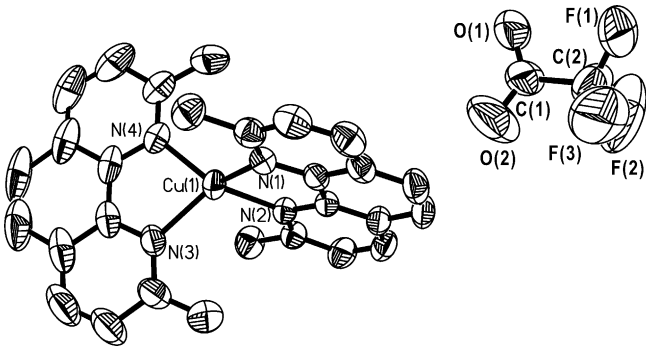


Figure 2. ORTEP drawing of **1b**·CF_3CO_2H. Thermal ellipsoids are drawn at 40% probability, CF_3CO_2H and hydrogen atoms are omitted for clarity.

lengths observed in the $[Cu(Me_2phen)_2]^+$ portion are 2.017(3)–2.050(3) Å, which are similar to those in neutral **1a**. The O(1)-C(1)-O(2) angle (124.3(6)°) of the uncoordinated trifluoroacetate anion is significantly smaller than the angle in **1a** (133.1(12)°).

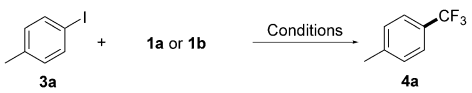
The structures of **2b** and **2c** contain a tetrahedral copper(I) cation ligated by two Me_2bpy or phen ligands, respectively, and a free, unligated anionic chlorodifluoroacetate group (see the Supporting Information). This is in contrast to the X-ray crystal structure of [Cu(O_2CCF_2Cl)(SI*i*Pr)] (SI*i*Pr = 1,3-diisopropylimidazolin-2-ylidene), in which the chlorodifluoroacetate ion is monodentately coordinated to the copper center to form a neutral molecule.[34] The Cu–N bond lengths observed in **2b** (1.9958–2.0521 Å) are similar to those found in **2c** (1.9983–2.0693 Å). The two C–O bond lengths in the carboxylate group are nearly identical (1.233(3) Å and 1.235(3) Å for **2b**; 1.234(2) Å and 1.221(2) Å for **2c**), which together with the planar geometry of the O(1)-O(2)-C(1)-C(2) unit indicates a delocalized structure for the $-CO_2$ moiety. The C–Cl bond lengths in **2b** and **2c** (1.767(2) and 1.768(3) Å, respectively) fall in the

normal range of 1.755–1.849 Å,[39] and the average C–F bond length of 1.342(3) Å in both **2b** and **2c** lies within the normal range of 1.319–1.431 Å.[39] Additionally, the O-C-O angles in **2b** and **2c** are identical (130.5(2)°) and similar to that in $[Cu(O_2CCF_2Cl)(SI\mathit{i}Pr)]$ (130.0(9)°).[34]

Trifluoromethylation reactions

To assess the potential of trifluoroacetate complexes **1a** and **1b** as trifluomethylation reagents, we investigated their reactivity with 4-iodotoluene (**3a**). The results are summarized in Table 1.

Table 1. Optimization of the trifluoromethylation reaction of **3a**.[a]

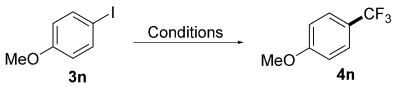


Entry	[Cu]	Additive	Solvent	Yield [%][b]
1	**1a**	NaF	DMF	83
2	**1b**	NaF	DMF	56
3	**1a**	NaF	DMAc	46
4	**1a**	NaF	diglyme	43
5	**1a**	NaF	NMP	54
6	**1a**	NaF	xylene	0
7	**1a**	NaF	DMSO	0
8	**1a**	–	DMF	56

[a] Conditions: **1** (0.15 mmol), **3a** (0.10 mmol), NaF (0.30 mmol), solvent (1.5 mL), N_2 atmosphere, 140 °C, 8 h. [b] Yields were determined by ^{19}F NMR spectroscopic analysis of the crude reaction mixture with an internal standard.

Treatment of **1a** and **1b** with **3a** in the presence of NaF (3 equiv) as an additive in DMF at 140 °C for 8 h resulted in clean formation of 4-methylbenzotrifluoride (**4a**) in modest-to-good yields (Table 1, entries 1 and 2). The phen-ligated reagent **1a** was particularly effective and afforded **4a** in 83% yield (Table 1, entry 1). DMF was found to be a more-effective solvent than *N*,*N*-dimethylacetamide (DMAc), diglyme, or *N*-methylpyrrolidone (NMP) (Table 1, entries 3–5). Other solvents, such as xylene and DMSO, were completely unsatisfactory (Table 1, entries 6 and 7). The role of the additive was then investigated. A moderate yield of **4a** (56%) was obtained when the reaction was conducted in the absence of NaF (Table 1, entry 8). A comparable yield of **4a** (80%) was obtained when LiF was used as the additive (see the Supporting Information). Other additives, such as KF, AgF, $n\mathrm{Bu_4NF}$, and $(HF)_3NEt_3$, were ineffective or farless effective (see the Supporting Information). Prolonging the reaction time to 15 h did not affect the result severely. Moreover, performing the reaction at a lower temperature (120 °C) furnished a lower yield of **4a**, thus the reaction temperature of 140 °C was essential to overcome the energy barrier for decarboxylation of the copper trifluoroacetate reagent. It should be noted that previous reports on copper-mediated decarboxylative trifluoromethylation with $Na[O_2CCF_3]$ noted higher temperatures (typically above 160 °C) to facilitate efficient reactions of (hetero)aryl halides.[4b,30]

Table 2. Comparison of the copper-mediated trifluoromethylation reactions of 1-iodo-4-methoxybenzene (**3n**).



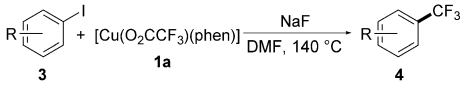
Entry	Conditions	Yield [%]
1	**1a** (2.0 equiv), NaF (3.0 equiv), DMF, 140 °C	83[a]
2	$[Cu(CF_3)(phen)]$ (1.2–1.5 equiv), DMF, 50 °C	96[a,b]
3	$[Cu(CF_3)(PPh_3)_3]$ (0.9 equiv), *t*Bubpy[c] (1.0 equiv), toluene, 80 °C	70–75[a,d]
4	$Na[O_2CCF_3]$ (4.0 equiv), CuI (2.0 equiv), NMP, 160 °C	59[e,f]
5	MeO_2CCF_3 (4 equiv), CuI (20 mol%), CsF (1.2 equiv), DMF, 160 °C	84[g,h]

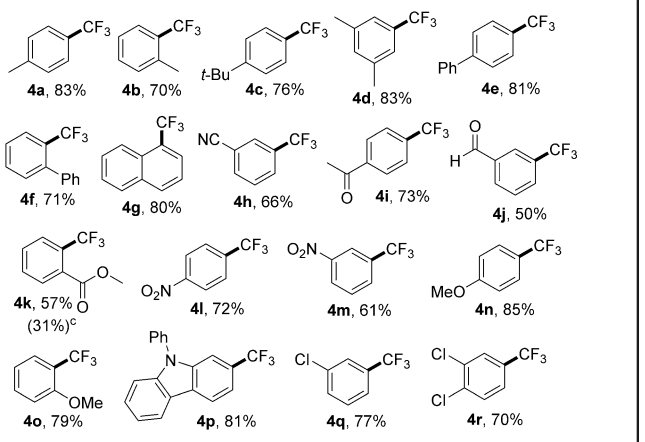
[a] Yields were determined by ^{19}F NMR spectroscopy. [b] See ref. [25a]. [c] *t*Bubpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine. [d] See ref. [26]. [e] Yields were determined by GLC. [f] See ref. [23c]. [g] Yields were determined by GC. [h] See ref. [12e].

Subsequently, a comparison of the reactivity in the copper-mediated trifluoromethylation reaction of 1-iodo-4-methoxybenzene (**3n**) with other trifluoromethylation reagents was performed (Table 2). The results clearly demonstrate that the reactivity of **1a** is comparable to reported reagents. It is also noteworthy that the new reagent **1a** is prepared from readily available and inexpensive starting materials.

Having identified optimal conditions for the trifluoromethylation of **3a**, we explored the scope and generality of the procedure (Table 3). Aryl iodides **3a**–**r**, with different electronic properties, were investigated. Methyl-, *tert*-butyl-, or phenyl-

Table 3. Scope of the trifluoromethylation of aryl iodides by **1a**.[a,b]



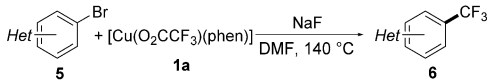


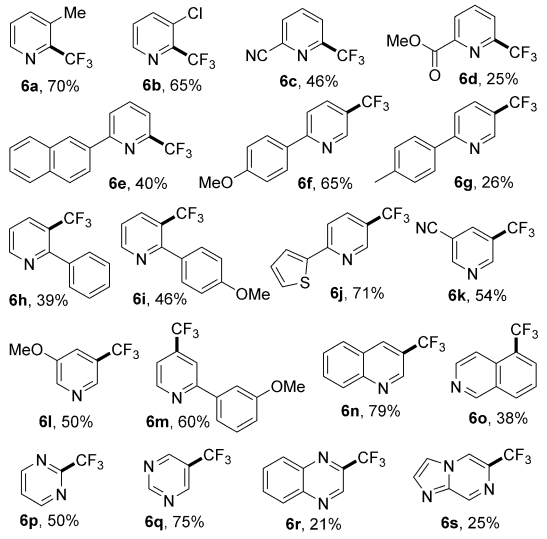
[a] Conditions: **1a** (0.45 mmol), **3** (0.30 mmol), NaF (0.90 mmol), DMF (4.0 mL), 140 °C, 8 h, N_2 atmosphere. [b] Yields were determined by ^{19}F NMR spectroscopic analysis of the crude reaction mixture with an internal standard. [c] Aryl bromide (**4k′**) was used.

substituted aryl iodides **3a**–**f**, and 1-iodonaphthalene (**3g**) provided the desired products **4a**–**g** in good yields (70–83%). Moreover, aryl iodides **3h**–**m**, which contained nitrile, ketone, aldehyde, ester, or nitro functionalities, were successfully reacted with **1a** to give the corresponding products **4h**–**m** in acceptable yields (50–73%). Remarkably, aryl iodides **3n** and **3o** substituted with a deactivating methoxy group provided the desired products **4n** and **4o** in 85 and 79% yield, respectively. Similarly, 3-iodo-*N*-phenylcarbazole (**3p**) also reacted under the standard reaction conditions to give the desired product **4p** in 81% yield. Furthermore, chloro-substituted aryl iodides **3q** and **3r** were trifluoromethylated with high efficiency and afforded the corresponding products **4q** and **4r** in 77 and 70% yield, respectively. When aryl bromide **3k**′ was utilized the desired product **4k** was formed in 31% yield.

The scope of the trifluoromethylation reaction was further explored by using heteroaryl bromides (Table 4). A variety of heteroaryl bromides were investigated and showed excellent tolerance for nitrogen-containing aromatic compounds. For example, 2-bromopyridines **5a**–**e** were suitable substrates and provided the corresponding products **6a**–**c** and **6e** in moderate-to-good yields; **6d** was obtained in a low yield. Likewise, 3-bromopyridines **5f**–**k** and 4-bromopyridine **5m** afforded the corresponding trifluoromethylated products **6f**–**m** in acceptable yields. The scope of the reaction was extended to the trifluoromethylation of other brominated nitrogen heterocycles. 3-Bromoquinoline (**5n**) yielded **6n** in 79% yield, whereas 5-bromoisoquinoline (**5o**) afforded **6o** in 38% yield. In addition, the use of 2- and 5-bromopyrimidine (**5p**, **5q**) was tolerated under the optimized conditions, and the corresponding products **6p** and **6q** were obtained in 50 and 75% yield, respectively. In comparison, the trifluoromethylation of 2-bromoquinoxaline (**5r**) and 6-bromoimidazo[1,2-*a*]pyrazine (**5s**) proved more challenging and afforded corresponding products **6r** and **6s** in lower yields (21 and 25%, respectively).

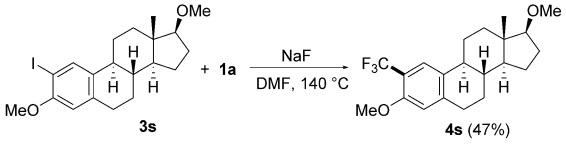
Table 4. Scope of the trifluoromethylation of heteroaryl bromides by **1a**.[a,b]





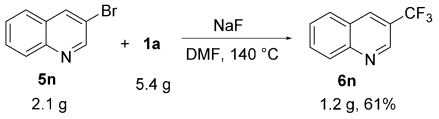
[a] Conditions: **1a** (0.45 mmol), **5** (0.30 mmol), NaF (0.90 mmol), DMF (4.0 mL), 140 °C, 8 h, N_2 atmosphere. [b] Yields were determined by ^{19}F NMR spectroscopic analysis of the crude reaction mixture with an internal standard.

To further test and refine this methodology, we performed a late-stage trifluoromethylation of an estradiol derivative (Scheme 5). The reaction of **3s** with **1a** provided a 47% isolated yield of **4s**. This result demonstrates that our protocol can be extended to other pharmaceutically relevant molecules.



Scheme 5. Late-stage trifluoromethylation of estradiol derivative **3s**.

To demonstrate the scalability of the protocol, a gram-scale reaction was performed with **5n** and **1a** under the standard conditions. After 12 h in DMF at 140 °C, the trifluoromethylated product **6n** was isolated in 61% yield (Scheme 6).



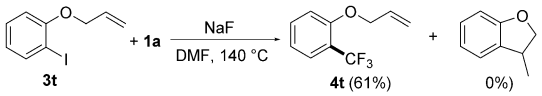
Scheme 6. Scalability of the trifluoromethylation reaction of **5n**.

Radical-probe experiment

To probe for possible radical intermediates in this transformation, a series of experiments were rationally designed and performed. Trifluoromethylation of **3a** with **1a** was carried out in the presence of radical scavenger 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO). The trifluoromethylated product **4a** was obtained in 40% yield (determined by ^{19}F NMR spectroscopic analysis). The addition of TEMPO did not completely suppress the reaction, and no TEMPO–CF_3 adduct was formed (see the Supporting Information). Therefore, it is unlikely that a CF_3 radical is formed during the trifluoromethylation reaction.

Similarly, the reaction proceeds cleanly in the presence of 1,9-dihydroanthracene—a known radical scavenger—to afford the desired product **4a** in 76% yield (see the Supporting Information). These results indicate that the trifluoromethylation reaction does not involve a radical-mediated mechanism.

Furthermore, the reaction of **1a** with 1-(allyloxy)-2-iodobenzene (**3t**) was conducted. The corresponding aryl radical has been reported to undergo rapid cyclization to form a [3-(2,3-dihydrobenzofuran)]-methyl radical with a rate constant of $9.6\times10^9\ s^{-1}$ en route to 3-methyl-2,3-dihydrobenzofuran.[40] The re-



Scheme 7. Test for an aryl-radical intermediate.

action of **3t** in DMF at 140 °C for 12 h gave the trifluoromethylated product **4t** as the sole product in 61% yield (Scheme 7). No cyclization product was detected, thus this result also suggests that the trifluoromethylation reaction does not proceed via a free aryl-radical pathway.

Hammett plots

The electronics of the reactive species were investigated by using a Hammett correlation plot. Competition experiments between *para*-substituted iodobenzene derivatives and iodobenzene were examined by reacting both iodoarenes (10 equiv each), **1a** (1 equiv), and NaF (3 equiv) in DMF at 140 °C for 6 h. The product ratios were determined by ^{19}F NMR spectroscopy. Using the relative rates determined from each competition experiment, a Hammett plot of $\log(k_R/k_H)$ versus $\sigma\rho$ was constructed (R is the *para* substituent of the iodoarene analogue (Figure 3). This plot gave a ρ value of $+0.56$ ($R^2 =$ 0.99). On the basis of these Hammett studies, we propose that the reactive species involved in the trifluoromethylation reaction is nucleophilic in character.[30]

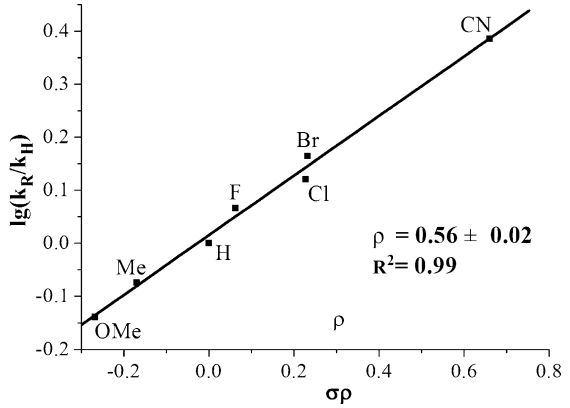
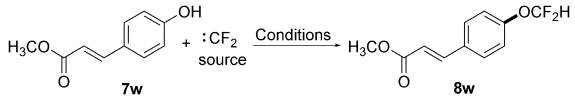


Figure 3. Hammett plots for the reactions of *p*-RC_6H_4I with **1a** in DMF. Conditions: [**1a**] = 0.033 mM, [PhI] = 0.33 mM, [aryl iodide] = 0.33 mM, [NaF] = 0.10 mM, DMF (1.5 mL), 140 °C, 6 h. Each point is the average of two experiments.

Difluoromethylation reactions

Aryl difluoromethyl ethers are important structural motifs in a range of compounds with biological or medicinal relevance.[2b] There is a continued strong demand for efficient and selective synthetic routes to these versatile scaffolds.[4f,41] In recent years, developments in methodology have achieved this target by the use of non-ODS-based difluorocarbene reagents (ODS = ozone-depleting substance).[42–44]

Table 5. Optimization of the difluoromethylation of **7w**.[a]



Entry	:CF_2 source	Solvent	Yield [%][b]
1	**2a**	DMF	45
2	**2b**	DMF	77
3	**2c**	DMF	99
4	$Na[ClCF_2CO_2]$	DMF	35
5	**2c**	CH_3CN	33
6	**2c**	DMSO	28
7	**2c**	NMP	33
8	**2c**	diglyme	0
9	**2c**	dioxane	0
10	**2c**	toluene	0

[a] Conditions: difluorocarbene source (0.15 mmol), **7w** (0.10 mmol), NaOH (0.45 mmol), solvent (1.5 mL), 75 °C, 4 h, N_2 atmosphere. [b] Yields were determined by ^{19}F NMR spectroscopic analysis of the crude reaction mixture with an internal standard.

After isolation and full characterization of the copper–chlorodifluoroacetate complexes **2a–c**, we evaluated the potential of these complexes to serve as difluorocarbene precursors in copper-mediated difluoromethylation of phenolic substrates.

Methyl 4-hydroxy cinnamate (**7w**) was chosen as a model substrate for the optimization process (Table 5). In the presence of NaOH (4.5 equiv) at 75 °C in DMF for 4 h, difluoromethylation of **7w** with **2a–c** gave the desired product methyl 3-(4-(difluoromethoxy)phenyl)acrylate (**8w**) in moderate-to-excellent yields (Table 5, entries 1–3). Interestingly, the reaction proceeds chemoselectively at the O–H bond but not at the C=C and C=O bonds, which indicates that the O–H bond is more reactive towards difluorocarbene under basic conditions. Additionally, the nitrogen ligands were found to significantly affect the reaction efficiency. Treatment of **7w** with **2a** or **2b**—ligated by bpy and Me_2bpy, respectively—afforded **8w** in 45 or 77% yield, respectively (Table 5, entries 1 and 2), whereas complex **1c**, with a phen ligand, gave **8w** in 99% yield (Table 5, entry 3). Notably, difluoromethylation of **7w** with $Na[ClCF_2CO_2]$ afforded the product in a lower yield (35%) under similar reaction conditions (Table 5, entry 4), which highlights the synthetic utility of this method.

Complex **2c** was selected for further optimization studies after considering the cost and the good yield obtained in the difluoromethylation reaction. The choice of solvent significantly influenced the difluoromethylation yield (Table 5, entries 3 and 5–10); DMF was the optimal reaction medium, presumably due to the excellent solubility of the copper reagent and NaOH. The role of the basic additive was also investigated, and NaOH gave the best result (see the Supporting Information).

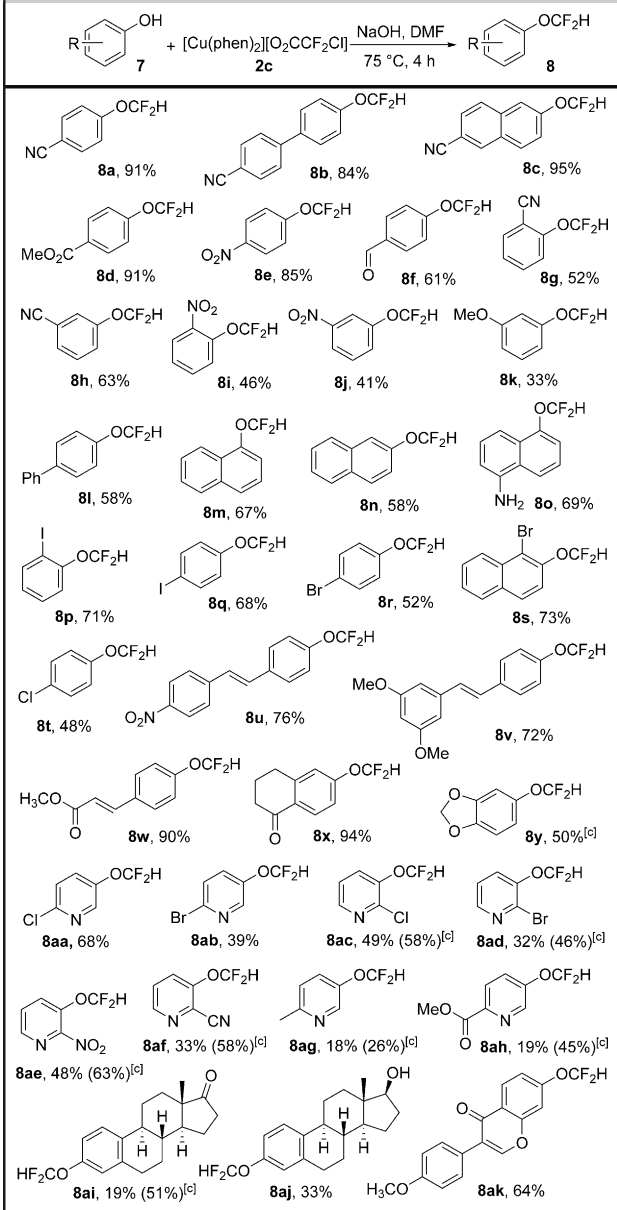
A reaction temperature of 75 °C was essential to achieve a good yield of **8w**; no reaction occurred when the reaction was conducted at 40 °C in DMF (see the Supporting Information). In addition, a reaction time of 4 h was necessary for com-

pletion of the reaction; reducing the reaction time to 1 h lowered the yield of **8w** to 40%. (see the Supporting Information).

Notably, under the current conditions, complex **2c** appears to have a lower barrier for decarboxylation of the copper chlorodifluoroacetate reagent, which enables the reaction to proceed at a reasonably practical reaction temperature of 75 °C. For comparison, previously reported copper-mediated decarboxylative trifluoromethylation reactions with MeO_2CCF_2Cl[31] or $TMSO_2CCF_2Cl$[45] required higher temperatures (typically above 100 °C).

With these optimal reaction conditions in hand, the difluoromethylation reactions of a variety of substituted phenols were examined (Table 6). An assortment of electron-deficient and electron-rich phenols, as well as sterically hindered aromatic phenols were successfully difluoromethylated with **2c**.

Table 6. Difluoromethylation of phenols.[a,b]



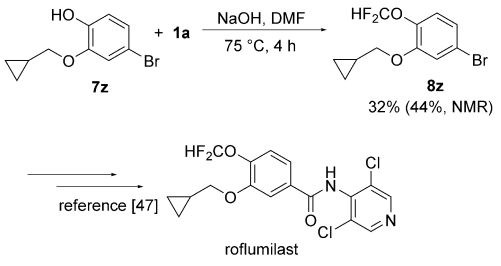
[a] Conditions: **2c** (1.5 mmol), **7** (1.0 mmol), NaOH (4.5 mmol), DMF (15.0 mL), 75 °C, 4 h, N_2 atmosphere. [b] Isolated yields. [c] Yields were determined by ^{19}F NMR spectroscopic analysis of the crude reaction mixture with an internal standard.

Electron-deficient phenols **7a–e** (4-cyanophenol, 4-cyano-4′-hydroxybiphenyl, 6-cyano-2-naphthol, methyl paraben, and 4-nitrophenol) reacted with **2c** to give the corresponding products **8a–e** in good-to-excellent yields, whereas 4-formylphenol (**7f**), 2- and 3-cyanophenol (**7g**, **7h**), and 2- and 3-nitrophenol (**7i**, **7j**) gave products **8f–j** in moderate yields. In addition, phenols with electron-donating groups, such as 3-methoxyphenol (**7k**) reacted with **2c** to furnish the corresponding product **8k** in 33% yield. 4-Phenylphenol (**7l**) reacted to afford the corresponding product **8l** in 58% yield. The reaction could also be carried out with 1- and 2-naphthol (**7m**, **7n**) to produce products **8m** and **8n**, respectively, in moderate yields. Notably, the reaction was compatible with an unprotected NH_2 functionality (**8o**). Similarly, aryl halides were well tolerated, and the desired products **8p–t** were obtained in moderate-to-good yields. The ability to incorporate a halogen moiety into the difluoromethylated products provides opportunities for further functional group manipulation by palladium-mediated transformations. Furthermore, 4-hydroxy-4′-nitrostilbene (**7u**), pterostilbene (**7v**), and methyl 4-hydroxy cinnamate (**7w**) were amenable to the reaction conditions and were difluoromethylated to produce **8u–w** in 76, 72, and 90% yield, respectively. Pleasingly, reaction of **2c** with 6-hydroxy-1-tetralone (**7x**) and sesamol (**7y**) gave the desired products **8x** and **8y** in 94 and 50% yield, respectively.

To demonstrate the scalability of this process, the difluoromethylation of **7v** with **1c** was repeated on a 4 mmol scale and delivered 0.91 g (74% yield) of the difluoromethylated product **8v**. These results clearly imply both the scalability and reliability of the method.

This difluoromethylation reaction was also applicable to hydroxypyridines. Various 3-hydroxypyridines were applied in the reaction and afforded the desired difluoromethylation products in moderate-to-good yields. Furthermore, chloro-, bromo-, nitro-, cyano-, and ester-groups in various positions on the ring were tolerated under the standard conditions. It is noteworthy that the pyridone N-difluoromethylation products were never detected under our reaction conditions.

This facile method makes late-stage difluoromethylation feasible for complex biologically active compounds that contain hydroxyl groups. To this end, estrone (**7ai**), estradiol (**7aj**), and formononetin (**7ak**) were subjected to the optimized difluoro-



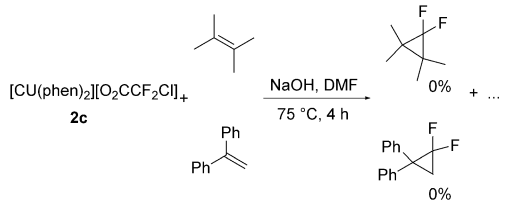
Scheme 8. Synthesis of roflumilast intermediate **8z**.

methylation reaction conditions. The targeted products **8ai**–**8ak** were isolated in moderate-to-good yields. These examples show the high functional-group tolerance and the potential of this protocol for use with complicated biologically active compounds.

Subsequently, this difluoromethylation protocol was applied to the synthesis of roflumilast, an orally available drug developed by Altana Pharma[46] (Scheme 8). Roflumilast, used for the treatment of chronic obstructive pulmonary disease exacerbations, received approval in 2010 in the European Union and in 2011 in the USA.[3] Difluoromethylation of bromophenol **7z** was successfully performed to provide difluoro derivative **8z** in an isolated yield of 32%. Compound **8z** could be readily transformed into roflumilast by following reported procedures.[47]

Mechanistic observations

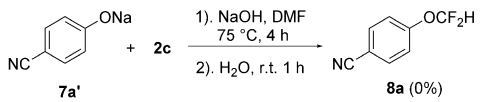
To gain some insight into the reaction mechanism, a series of experiments were designed and performed. To trap difluorocarbene, the reaction of **2c** with tetramethylethylene or 1,1-diphenylethylene—conventional difluorocarbene scavengers—and NaOH was carried out in DMF at 75 °C for 4 h. No difluorocyclopropane products were detected by ^{19}F NMR spectroscopy (Scheme 9). The difluorocarbene intermediate formed undergoes decomposition to an unidentified species. This experiment indicates that difluorocarbene reacts with phenol faster than with tetramethylethylene or 1,1-diphenylethylene.[12l]



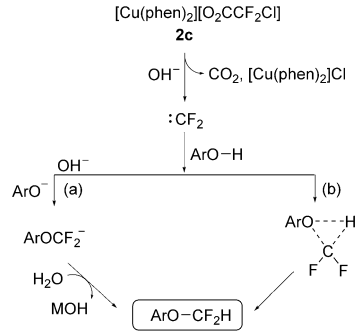
Scheme 9. Mechanistic experiments with difluorocarbene scavengers.

The reaction of sodium phenolate **7a′** with **2c** and subsequent addition of H_2O (1 equiv) under similar reaction conditions did not produce the difluoromethylated product **8a** (Scheme 10). These results suggest that these difluoromethylation reactions with **2c** are unlikely to proceed by an anionic chain reaction[48] that involves addition of difluorocarbene to the phenolate to form a carbanion intermediate (Scheme 11 a).

For the reaction of an optically active silane with difluorocarbene, Sommer and co-workers proposed a concerted mechanism with a three-center transition state, in which difluorocarbene inserted into Si–H bonds.[49] This mechanism was proved



Scheme 10. Difluoromethylation of sodium phenolate **7a′**.



Scheme 11. Proposed mechanism for difluoromethylation of phenols with **2c**; M = Na.

experimentally by chemically induced dynamic nuclear polarization NMR spectroscopy.[50] Gordon and Gano conducted ab initio calculations for the insertion of methylene/silylene into methane/silane at the 3-21G level of theory,[51] and Houk and co-workers investigated the cycloadditions of difluorocarbene with ethylene by using ab initio methods.[52] All these calculations indicate that singlet difluorocarbene, which possesses higher electronic stability, can insert into E–H (E = Si, Ge) bonds in a nucleophilic fashion.

We carried out higher-level calculations to support this mechanism. Geometry optimizations for all compounds without symmetry constraints were performed by using DFT calculations at the B3LYP level.[53] The 6-31G(d) basis set was used for C, H, O, and F atoms. Frequency calculations at the same level of theory were also performed to identify all stationary points as minima (zero imaginary frequency). Intrinsic reaction coordinates (IRC) were also calculated to verify the transition states. All calculations were performed by using the Gauss-

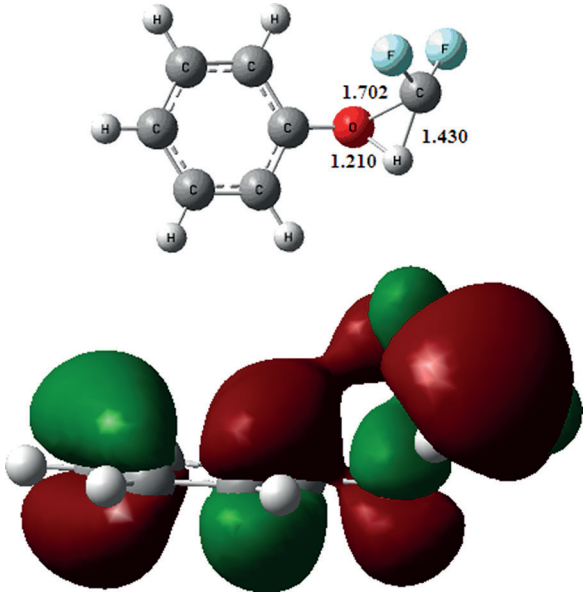


Figure 4. Top: Geometry of three-center transition state of CF_2 carbene insertion reaction (bond lengths in Å). Bottom: HOMO of three-center transition state showing the bonding nature.

ian 03 software package.[54] According to the calculations, the insertion reaction of difluorocarbene into phenol has an energy barrier of 21.52 kcal mol^{-1}, which is comparable to the known activation energy (23.6 kcal mol^{-1}, MP2/3-21G) for addition of difluorocarbene to propene.[48] This result also agrees with experimental observations. The geometry of the three-center transition state for this insertion reaction is shown in Figure 4 (see the Supporting Information for the IRC data). The lower energy barrier can be attributed to the higher electronic stability of difluorocarbene, and bonding between the σ HOMO of difluorocarbene and the σ* LUMO located at the oxygen center is observed (Figure 4). In this transition, the σ orbitals of the two fragments distort greatly to facilitate the bonding process.

Based on the results above, a concerted mechanism involving a three-center transition state is proposed (Scheme 11 b). Initially, the decarboxylative reaction of **2c** with NaOH generates difluorocarbene with byproducts CO_2 and $[Cu(phen)_2]Cl$ byproducts. Electrophilic hydrogen-atom abstraction forms the three-center transition state, which leads to the formation of desired product.

Conclusions

We have synthesized new economic copper reagents $[Cu(O_2CCF_3)(phen)]$ (**1a**) and $[Cu(phen)_2][O_2CCF_2Cl]$ (**2c**) from readily available and inexpensive starting materials. The structures of these compounds were elucidated by X-ray crystallography. Air-stable complexes **1a** and **2c** serve as an efficient trifluoromethylating reagent for decarboxylative trifluoromethylation of (hetero)aryl halides to form trifluoromethyl (hetero)arenes or as a difluorocarbene precursor for difluoromethylation of phenols and hydroxypyridines to form (hetero)aryl difluoromethyl ethers, respectively. Preliminary mechanistic investigations indicated that radical intermediates are unlikely to be involved in the trifluoromethylation reaction. Hammett studies revealed that the copper-mediated decarboxylative trifluoromethylation involves a reactive species with nucleophilic character. A concerted addition of difluorocarbene to phenol to form a three-center transition state is proposed for the difluoromethylation reaction.

Acknowledgements

Financial support from the National Natural Science Foundation of China (NSFC) (grant number 21372044), the Research Fund for the Doctoral Program of Higher Education of China (grant number 20123514110003), and Fuzhou University (grant number 022494) is gratefully acknowledged.

Keywords: aryl difluoromethyl ethers · carbenes · copper · decarboxylation · trifluoromethylation

[1] a) M. Schlosser, *Angew. Chem. Int. Ed.* **2006**, *45*, 5432 – 5446; *Angew. Chem.* **2006**, *118*, 5558 – 5572; b) K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881 – 1886; c) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320 – 330; d) W. K. Hagmann, *J. Med. Chem.* **2008**, *51*, 4359 – 4369.

[2] a) J. H. Clark, D. Wails, T. W. Bastock, *Aromatic Fluorination*, CRC, Boca Raton, **1996**; b) P. Kirsch, *Modern fluoroorganic chemistry: synthesis, reactivity, applications*, Wiley-VCH, Weinheim, **2004**; c) J.-P. Begue, D. Bonnet-Delpon, *Bioorganic and Medicinal Chemistry of Fluorine*, Wiley, Hoboken, **2008**.

[3] J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.* **2014**, *114*, 2432 – 2506.

[4] a) J.-A. Ma, D. Cahard, *J. Fluorine Chem.* **2007**, *128*, 975 – 996; b) S. Roy, B. T. Gregg, G. W. Gribble, V.-D. Le, S. Roy, *Tetrahedron* **2011**, *67*, 2161 – 2195; c) A. Studer, *Angew. Chem. Int. Ed.* **2012**, *51*, 8950 – 8958; *Angew. Chem.* **2012**, *124*, 9082 – 9090; d) D. L. Browne, *Angew. Chem. Int. Ed.* **2014**, *53*, 1482 – 1484; *Angew. Chem.* **2014**, *126*, 1506 – 1508; e) X. Liu, C. Xu, M. Wang, Q. Liu, *Chem. Rev.* **2015**, *115*, 683 – 730; f) C. Ni, M. Hu, J. Hu, *Chem. Rev.* **2015**, *115*, 765 – 825.

[5] a) Y. Ji, T. Brueckl, R. D. Baxter, Y. Fujiwara, I. B. Seiple, S. Su, D. G. Blackmond, P. S. Baran, *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 14411 – 14415; b) J. C. Fennewald, B. H. Lipshutz, *Green Chem.* **2014**, *16*, 1097 – 1100.

[6] a) F. Swarts, *Bull. Acad. R. Med. Belg.* **1892**, *24*, 309; b) G. A. Boswell, W. C. Ripka, R. M. Scribner, C. W. Tullock in *Organic Reactions*, Wiley, New York, **2004**.

[7] a) R. J. Lundgren, M. Stradiotto, *Angew. Chem. Int. Ed.* **2010**, *49*, 9322 – 9324; *Angew. Chem.* **2010**, *122*, 9510 – 9512; b) T. Furuya, A. S. Kamlet, T. Ritter, *Nature* **2011**, *473*, 470 – 477; c) O. A. Tomashenko, V. V. Grushin, *Chem. Rev.* **2011**, *111*, 4475 – 4521; d) A. J. Hickman, M. S. Sanford, *Nature* **2012**, *484*, 177 – 185; e) T. Besset, C. Schneider, D. Cahard, *Angew. Chem. Int. Ed.* **2012**, *51*, 5048 – 5050; *Angew. Chem.* **2012**, *124*, 5134 – 5136; f) T. Liu, Q. Shen, *Eur. J. Org. Chem.* **2012**, 6679 – 6687; g) L. Chu, F.-L. Qing, *Acc. Chem. Res.* **2014**, *47*, 1513 – 1522.

[8] a) V. V. Grushin, W. J. Marshall, *J. Am. Chem. Soc.* **2006**, *128*, 12644 – 12645; b) N. D. Ball, J. W. Kampf, M. S. Sanford, *J. Am. Chem. Soc.* **2010**, *132*, 2878 – 2879; c) N. D. Ball, J. B. Gary, Y. Ye, M. S. Sanford, *J. Am. Chem. Soc.* **2011**, *133*, 7577 – 7584; d) M. C. Nielsen, K. J. Bonney, F. Schoenebeck, *Angew. Chem. Int. Ed.* **2014**, *53*, 5903 – 5906; *Angew. Chem.* **2014**, *126*, 6013 – 6016; e) M. S. Winston, W. J. Wolf, F. D. Toste, *J. Am. Chem. Soc.* **2014**, *136*, 7777 – 7782; f) N. Nebra, V. V. Grushin, *J. Am. Chem. Soc.* **2014**, *136*, 16998 – 17001.

[9] Y. Zeng, L. Zhang, Y. Zhao, C. Ni, J. Zhao, J. Hu, *J. Am. Chem. Soc.* **2013**, *135*, 2955 – 2958.

[10] a) A. Maleckis, M. S. Sanford, *Organometallics* **2014**, *33*, 2653 – 2660; b) J. Jover, F. M. Miloserdov, J. Benet-Buchholz, V. V. Grushin, F. Maseras, *Organometallics* **2014**, *33*, 6531 – 6543.

[11] E. J. Cho, T. D. Senecal, T. Kinzel, Y. Zhang, D. A. Watson, S. L. Buchwald, *Science* **2010**, *328*, 1679 – 1681.

[12] a) M. Oishi, H. Kondo, H. Amii, *Chem. Commun.* **2009**, 1909 – 1911; b) C.-P. Zhang, Z.-L. Wang, Q.-Y. Chen, C.-T. Zhang, Y.-C. Gu, J.-C. Xiao, *Angew. Chem. Int. Ed.* **2011**, *50*, 1896 – 1900; *Angew. Chem.* **2011**, *123*, 1936 – 1940; c) H. Kondo, M. Oishi, K. Fujikawa, H. Amii, *Adv. Synth. Catal.* **2011**, *353*, 1247 – 1252; d) T. Knauber, F. Arikan, G.-V. Roeschenthaler, L. J. Goossen, *Chem. Eur. J.* **2011**, *17*, 2689 – 2697; e) T. Schareina, X.-F. Wu, A. Zapf, A. Cotté, M. Gotta, M. Beller, *Top. Catal.* **2012**, *55*, 426 – 431; f) Y. Nakamura, M. Fujiu, T. Murase, Y. Itoh, H. Serizawa, K. Aikawa, K. Mikami, *Beilstein J. Org. Chem.* **2013**, *9*, 2404 – 2409; g) Z. Gonda, S. Kovács, C. Wéber, T. Gáti, A. Mészáros, A. Kotschy, Z. Novák, *Org. Lett.* **2014**, *16*, 4268 – 4271; h) K. Aikawa, Y. Nakamura, Y. Yokota, W. Toya, K. Mikami, *Chem. Eur. J.* **2015**, *21*, 96 – 100; i) J. Zheng, J.-H. Lin, X.-Y. Deng, J.-C. Xiao, *Org. Lett.* **2015**, *17*, 532 – 535.

[13] a) L. Chu, F.-L. Qing, *Org. Lett.* **2010**, *12*, 5060 – 5063; b) T. Liu, Q. Shen, *Org. Lett.* **2011**, *13*, 2342 – 2345; c) J. Xu, D. F. Luo, B. Xiao, Z. J. Liu, T. J. Gong, Y. Fu, L. Liu, *Chem. Commun.* **2011**, *47*, 4300 – 4302; d) C.-P. Zhang, J. Cai, C.-B. Zhou, X.-P. Wang, X. Zheng, Y.-C. Gu, J.-C. Xiao, *Chem. Commun.* **2011**, *47*, 9516 – 9518; e) X. Jiang, L. Chu, F.-L. Qing, *J. Org. Chem.* **2012**, *77*, 1251 – 1257; f) Y. Li, L. Wu, H. Neumann, M. Beller, *Chem. Commun.* **2013**, *49*, 2628 – 2630.

[14] a) T. Liu, X. Shao, Y. Wu, Q. Shen, *Angew. Chem. Int. Ed.* **2012**, *51*, 540 – 543; *Angew. Chem.* **2012**, *124*, 555 – 558; b) B. A. Khan, A. E. Buba, L. J. Gooßen, *Chem. Eur. J.* **2012**, *18*, 1577 – 1581.

[15] a) G. Danoun, B. Bayarmagnai, M. F. Grünberg, L. J. Gooßen, *Angew. Chem. Int. Ed.* **2013**, *52*, 7972 – 7975; *Angew. Chem.* **2013**, *125*, 8130 –

8133; b) J.-J. Dai, C. Fang, B. Xiao, J. Yi, J. Xu, Z.-J. Liu, X. Lu, L. Liu, Y. Fu, *J. Am. Chem. Soc.* **2013**, *135*, 8436 – 8439.
[16] X. Wang, Y. Xu, F. Mo, G. Ji, D. Qiu, J. Feng, Y. Ye, S. Zhang, Y. Zhang, J. Wang, *J. Am. Chem. Soc.* **2013**, *135*, 10330 – 10333.
[17] a) X. Wang, L. Truesdale, J.-Q. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 3648 – 3649; b) X.-G. Zhang, H.-X. Dai, M. Wasa, J.-Q. Yu, *J. Am. Chem. Soc.* **2012**, *134*, 11948 – 11951; c) L.-S. Zhang, K. Chen, G. Chen, B.-J. Li, S. Luo, Q.-Y. Guo, J.-B. Wei, Z.-J. Shi, *Org. Lett.* **2013**, *15*, 10 – 13.
[18] a) L. Chu, F.-L. Qing, *J. Am. Chem. Soc.* **2012**, *134*, 1298 – 1304; b) M. Shang, S.-Z. Sun, H.-L. Wang, B. N. Laforteza, H.-X. Dai, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2014**, *53*, 10439 – 10442; *Angew. Chem.* **2014**, *126*, 10607 – 10610.
[19] S. Seo, J. B. Taylor, M. F. Greaney, *Chem. Commun.* **2013**, *49*, 6385 – 6387.
[20] a) Y. Ye, S. H. Lee, M. S. Sanford, *Org. Lett.* **2011**, *13*, 5464 – 5467; b) A. Hafner, S. Bräse, *Angew. Chem. Int. Ed.* **2012**, *51*, 3713 – 3715; *Angew. Chem.* **2012**, *124*, 3773 – 3775.
[21] a) D. J. Burton, L. Lu, *Top. Curr. Chem.* **1997**, *193*, 46 – 89; b) D. J. Burton, G. A. Hartgraves, *J. Fluorine Chem.* **2007**, *128*, 1198 – 1215.
[22] V. C. R. McLoughlin, J. Thrower, *Tetrahedron* **1969**, *25*, 5921 – 5940.
[23] a) Y. Kobayashi, I. Kumadaki, *Tetrahedron Lett.* **1969**, *10*, 4095 – 4096; b) N. V. Kondratenko, E. P. Vechirko, L. M. Yagupolskii, *Synthesis* **1980**, 932 – 933; c) K. Matsui, E. Tobita, M. Ando, K. Kondo, *Chem. Lett.* **1981**, *10*, 1719 – 1720; d) D. M. Wiemers, D. J. Burton, *J. Am. Chem. Soc.* **1986**, *108*, 832 – 834; e) H. Urata, T. Fuchikami, *Tetrahedron Lett.* **1991**, *32*, 91 – 94; f) F. Cottet, M. Schlosser, *Eur. J. Org. Chem.* **2002**, 327 – 330; g) M. M. Kremlev, A. I. Mushta, W. Tyrra, Y. L. Yagupolskii, D. Naumann, A. Möller, *J. Fluorine Chem.* **2012**, *133*, 67 – 71; h) Q.-Y. Chen, S.-W. Wu, *J. Chem. Soc. Chem. Commun.* **1989**, 705 – 706.
[24] a) G. G. Dubinina, H. Furutachi, D. A. Vicic, *J. Am. Chem. Soc.* **2008**, *130*, 8600 – 8601; b) G. G. Dubinina, J. Ogikubo, D. A. Vicic, *Organometallics* **2008**, *27*, 6233 – 6235; c) H. Wang, D. A. Vicic, *Synlett* **2013**, *24*, 1887 – 1898.
[25] a) H. Morimoto, T. Tsubogo, N. D. Litvinas, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2011**, *50*, 3793 – 3798; *Angew. Chem.* **2011**, *123*, 3877 – 3882; b) N. D. Litvinas, P. S. Fier, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2012**, *51*, 536 – 539; *Angew. Chem.* **2012**, *124*, 551 – 554; c) M. G. Mormino, P. S. Fier, J. F. Hartwig, *Org. Lett.* **2014**, *16*, 1744 – 1747.
[26] O. A. Tomashenko, E. C. Escudero-Adán, M. M. Belmonte, V. V. Grushin, *Angew. Chem. Int. Ed.* **2011**, *50*, 7655 – 7659; *Angew. Chem.* **2011**, *123*, 7797 – 7801.
[27] a) A. Zanardi, M. A. Novikov, E. Martin, J. Benet-Buchholz, V. V. Grushin, *J. Am. Chem. Soc.* **2011**, *133*, 20901 – 20913; b) A. Lishchynskyi, M. A. Novikov, E. Martin, E. C. Escudero-Adán, P. Novák, V. V. Grushin, *J. Org. Chem.* **2013**, *78*, 11126 – 11146; c) A. I. Konovalov, A. Lishchynskyi, V. V. Grushin, *J. Am. Chem. Soc.* **2014**, *136*, 13410 – 13425; d) P. Novák, A. Lishchynskyi, V. V. Grushin, *Angew. Chem. Int. Ed.* **2012**, *51*, 7767 – 7770; *Angew. Chem.* **2012**, *124*, 7887 – 7890.
[28] H. Serizawa, K. Aikawa, K. Mikami, *Chem. Eur. J.* **2013**, *19*, 17692 – 17697.
[29] X. Li, J. Zhao, L. Zhang, M. Hu, L. Wang, J. Hu, *Org. Lett.* **2015**, *17*, 298 – 301.
[30] G. E. Carr, R. D. Chambers, T. F. Holmes, D. G. Parker, *J. Chem. Soc. Perkin Trans. 1* **1988**, 921 – 926.
[31] D.-B. Su, J.-X. Duan, Q.-Y. Chen, *Tetrahedron Lett.* **1991**, *32*, 7689 – 7690.
[32] M. Chen, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2013**, *52*, 11628 – 11631; *Angew. Chem.* **2013**, *125*, 11842 – 11845.
[33] B. R. Langlois, N. Roques, *J. Fluorine Chem.* **2007**, *128*, 1318 – 1325.
[34] K. A. McReynolds, R. S. Lewis, L. K. G. Ackerman, G. G. Dubinina, W. W. Brennessel, D. A. Vicic, *J. Fluorine Chem.* **2010**, *131*, 1108 – 1112.
[35] G. Shi, C. Shao, S. Pan, J. Yu, Y. Zhang, *Org. Lett.* **2015**, *17*, 38 – 41.
[36] Z. Weng, R. Lee, W. Jia, Y. Yuan, W. Wang, X. Feng, K.-W. Huang, *Organometallics* **2011**, *30*, 3229 – 3232.
[37] a) Z. Weng, W. He, C. Chen, R. Lee, D. Tan, Z. Lai, D. Kong, Y. Yuan, K.-W. Huang, *Angew. Chem. Int. Ed.* **2013**, *52*, 1548 – 1552; *Angew. Chem.* **2013**, *125*, 1588 – 1592; b) Y. Liu, C. Chen, H. Li, K.-W. Huang, J. Tan, Z. Weng, *Organometallics* **2013**, *32*, 6587 – 6592; c) C. Chen, L. Ouyang, Q. Lin, Y. Liu, C. Hou, Y. Yuan, Z. Weng, *Chem. Eur. J.* **2014**, *20*, 657 – 661; d) R. Huang, Y. Huang, X. Lin, M. Rong, Z. Weng, *Angew. Chem. Int. Ed.* **2015**, *54*, 5736 – 5739; *Angew. Chem.* **2015**, *127*, 5828 – 5831. Corrigendum: R. Huang, Y. Huang, X. Lin, M. Rong, Z. Weng, *Angew. Chem. Int. Ed.* **2015**, *54*, 8022; *Angew. Chem.* **2015**, *127*, 8134.
[38] a) M. Munakata, M. Maekawa, S. Kitagawa, S. Matsuyama, H. Masuda, *Inorg. Chem.* **1989**, *28*, 4300 – 4302; b) A. J. Blake, P. Hubberstey, W.-S. Li, D. J. Quinlan, C. E. Russell, C. L. Sampson, *J. Chem. Soc. Dalton Trans.* **1999**, 4261 – 4268.
[39] F. H. Allen, O. Kennard, D. G. Watson, L. Brammer, A. G. Orpen, R. Taylor, *J. Chem. Soc. Perkin Trans. 2* **1987**, S1 – S19.
[40] A. Annunziata, C. Galli, M. Marinelli, T. Pau, *Eur. J. Org. Chem.* **2001**, 1323 – 1329.
[41] J. Hu, W. Zhang, F. Wang, *Chem. Commun.* **2009**, 7465 – 7478.
[42] a) D. L. S. Brahms, W. P. Dailey, *Chem. Rev.* **1996**, *96*, 1585 – 1632; b) W. R. Dolbier, M. A. Battiste, *Chem. Rev.* **2003**, *103*, 1071 – 1098.
[43] a) F. Wang, T. Luo, J. Hu, Y. Wang, H. S. Krishnan, P. V. Jog, S. K. Ganesh, G. K. S. Prakash, G. A. Olah, *Angew. Chem. Int. Ed.* **2011**, *50*, 7153 – 7157; *Angew. Chem.* **2011**, *123*, 7291 – 7295; b) F. Wang, W. Zhang, J. Zhu, H. Li, K.-W. Huang, J. Hu, *Chem. Commun.* **2011**, *47*, 2411 – 2413.
[44] a) K. Oshiro, Y. Morimoto, H. Amii, *Synthesis* **2010**, 2080 – 2084; b) C. Ni, J. Hu, *Synthesis* **2014**, *46*, 842 – 863.
[45] X. Zhang, J. Wang, Z. Wan, *Org. Lett.* **2015**, *17*, 2086 – 2089.
[46] H. Amschler, D. Flockerzi, B. Gutterer, A. Hatzelmann, C. Schudt, R. Beume, U. Kilian, H. P. O. Wolf, PCT Int. Appl., WO 9501338A1, **1995**.
[47] E. L. Williams, T.-c. Wu, PCT Int. Appl., WO 2004033430A2, **2004**.
[48] a) F. Wang, W. Huang, J. Hu, *Chin. J. Chem.* **2011**, *29*, 2717 – 2721; b) L. Li, F. Wang, C. Ni, J. Hu, *Angew. Chem. Int. Ed.* **2013**, *52*, 12390 – 12394; *Angew. Chem.* **2013**, *125*, 12616 – 12620.
[49] L. H. Sommer, L. A. Ulland, G. A. Parker, *J. Am. Chem. Soc.* **1972**, *94*, 3469 – 3471.
[50] H. D. Roth, *Acc. Chem. Res.* **1977**, *10*, 85 – 91.
[51] M. S. Gordon, D. R. Gano, *J. Am. Chem. Soc.* **1984**, *106*, 5421 – 5425.
[52] K. N. Houk, N. G. Rondan, J. Mareda, *Tetrahedron* **1985**, *41*, 1555 – 1563.
[53] W. Kohn, A. D. Becke, R. G. Parr, *J. Phys. Chem.* **1996**, *100*, 12974 – 12980.
[54] Gaussian 03, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, Gaussian, Inc., Wallingford CT, **2004**.

Received: October 27, 2015
Published online on January 12, 2016