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Synthesis and application of well-defined $[\text{Ph}_4\text{P}]^+[\text{Cu}(\text{CF}_2\text{CF}_3)_2]^-$ complex as a versatile pentafluoroethylating reagent†

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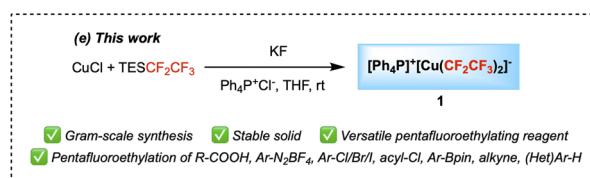
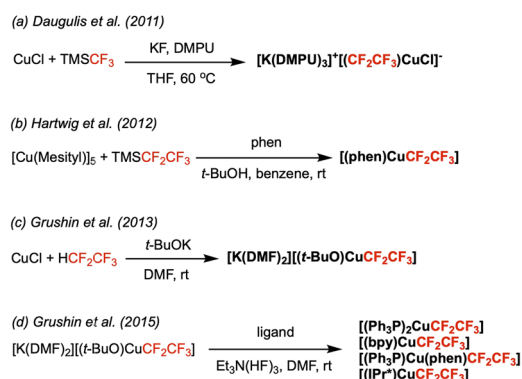
We herein describe the preparation and application of a new bis(pentafluoroethylated) organocuprate $[\text{Ph}_4\text{P}]^+[\text{Cu}(\text{CF}_2\text{CF}_3)_2]^-$. This complex has demonstrated a remarkable range of reactivities towards carboxylic acids, diazonium salts, organic halides, boronic esters, terminal alkynes and (hetero)arenes as a versatile pentafluoroethylating reagent. The construction of $\text{C}(\text{sp}^3)\text{-C}(\text{sp}^2)\text{-C}(\text{sp})\text{-CF}_2\text{CF}_3$ bonds can therefore be achieved using a single reagent.

Introduction

Perfluoroalkylated molecules represent a significant portion of existing pharmaceutical compounds or drug candidates owing to their desirable biological and chemophysical properties.¹ Consequently, methods for introducing perfluoroalkyl groups into organic molecules have become increasingly important.² Trifluoromethylation, the introduction of the smallest perfluoroalkyl group CF_3 , has reached a certain level of maturity.³ In contrast, the development of analogous *pentafluoroethylation* for introducing the CF_2CF_3 group has been lagging drastically behind.⁴ Biologically active compounds containing the pentafluoroethyl group do exist including the angiotensin II receptor antagonist DuP 532,^{5a} antihypertensive potassium channel opener KC-515 (ref. 5b) and fulvestrant for treating breast cancer.^{5c} The number of marketed drugs containing CF_2CF_3 , however, is much lower than that of the CF_3 -containing drugs, despite some evidence pointing to the superior biological activities of the pentafluoroethylated congeners.⁶ Thus, new methods for synthesizing pentafluoroethylated molecules with diverse structures will be crucial for their future applications as therapeutic agents.⁷

The identification of accessible and easy-to-handle pentafluoroethylating reagents has been the bottleneck for developing pentafluoroethylation reactions. In this regard, pioneering works on the preparation and applications of transition-metal-based reagents (MCF_2CF_3 ; $\text{M} = \text{Cu}$,⁸ Zn ,⁹ Ag ,¹⁰

Pd ,¹¹ Ir^{12}) have significantly broadened the reaction scope. Yet, with few exceptions, many of these reagents were not well-characterized and often *in situ* generated. For instance, Hu *et al.*^{8i,j,n,p} and Ogoshi *et al.*^{8k} reported the *in situ* generation of CuCF_2CF_3 using TMSCF_3 and tetrafluoroethylene (TFE), respectively, and studied their reactions with aryl iodides. In terms of well-defined CuCF_2CF_3 complexes, several examples can be found in the literature (Scheme 1). Daugulis *et al.* first described the synthesis of $[\text{K}(\text{DMPU})_3]^+[(\text{CF}_2\text{CF}_3)\text{CuCl}]^-$ from CuCl , KF and TMSCF_3 in DMPU/THF (14% yield), which was characterized by NMR spectroscopy and X-ray crystallography (Scheme 1a).^{8q} This anionic complex was a temperature and moisture sensitive solid that decomposed at room temperature

Scheme 1 Preparation of well-defined $[\text{CuCF}_2\text{CF}_3]$ complexes.

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under argon over few hours. Subsequently, Hartwig *et al.* reported the preparation of $[(\text{phen})\text{CuCF}_2\text{CF}_3]$ from $[\text{Cu}(\text{Mesityl})]_5$, *t*-BuOH, 1,10-phenanthroline (phen) and $\text{TMSCF}_2\text{CF}_3$ (Scheme 1b).^{8b} This complex was effective for the pentafluoroethylation of arylboronate esters and heteroaryl bromides.^{8e} Grushin *et al.* described the cupration of pentafluoroethane (HCF_2CF_3) gas with $[\text{K}(\text{DMF})][(\text{t-BuO})_2\text{Cu}]$ to generate the $[\text{K}(\text{DMF})][(\text{t-BuO})\text{CuCF}_2\text{CF}_3]$ complex with X-ray structural proof (Scheme 1c).^{8c} A broad scope of pentafluoroethylation of aryl/vinyl iodides and bromides was demonstrated with this complex.^{8g} Moreover, the same group prepared four $[\text{L}_n\text{CuCF}_2\text{CF}_3]$ complexes bearing different ligands (L) using $[\text{K}(\text{DMF})_2][(\text{t-BuO})\text{CuCF}_2\text{CF}_3]$ and obtained their X-ray crystal structures (Scheme 1d).^{8f} The $[(\text{Ph}_3\text{P})\text{Cu}(\text{phen})\text{CF}_2\text{CF}_3]$ complex was shown to be useful for the pentafluoroethylation of acid chlorides.

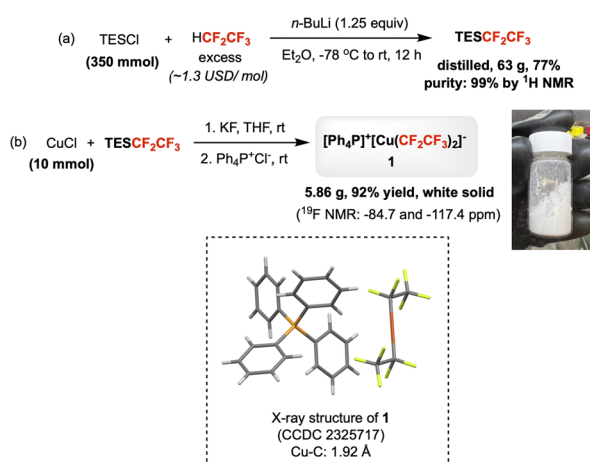
We herein describe the synthesis of a novel bispentafluoroethylated organocuprate $[\text{Ph}_4\text{P}]^+[\text{Cu}(\text{CF}_2\text{CF}_3)_2]^-$ **1** (Scheme 1e). This complex can be prepared on gram-scale and is a stable solid at room temperature under argon for months. More importantly, **1** has demonstrated a broad spectrum of reactivity as a versatile pentafluoroethylating reagent that is superior than previous CuCF_2CF_3 complexes. For instance, **1** was highly reactive towards not only aryl diazonium salts and iodides, but also difficult substrates such as aryl bromides and chlorides. In addition, **1** could be applied in challenging decarboxylative pentafluoroethylation, oxidative pentafluoroethylation of aryl pinacol boronic esters/alkynes, or even direct C–H bond pentafluoroethylation.

Results and discussion

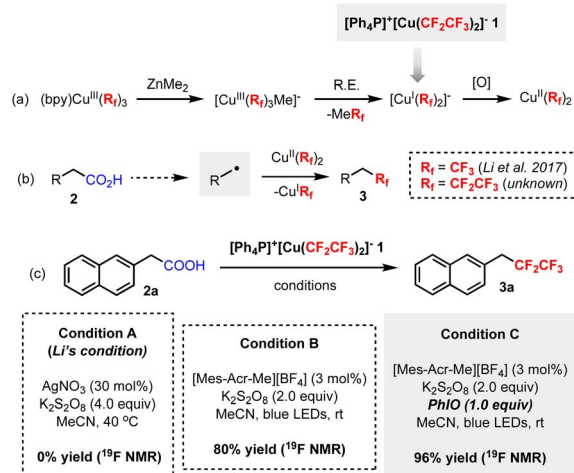
We have recently reported the first preparation of $[\text{Ph}_4\text{P}]^+[\text{Cu}(\text{CF}_3)_2]^-$ complex^{13a} from TMSCF_3 and its usage in trifluoromethylation of organic halides with detailed mechanistic investigation.^{13b,c} Subsequently, $[\text{Ph}_4\text{P}]^+[\text{Cu}(\text{CF}_2\text{H})_2]^-$ was synthesized using TMSCF_2H and proved to be a powerful difluoromethylating reagent.¹⁴ However, the

pentafluoroethylated analogue remained unknown. We decided to use $\text{TESCF}_2\text{CF}_3$ as a potential pentafluoroethyl source for the synthesis of CuCF_2CF_3 complex (Scheme 2). The $\text{TESCF}_2\text{CF}_3$ was conveniently prepared from the low-cost pentafluoroethane (HFC-125, fire suppression agent/ozon-friendly refrigerant) and triethylchlorosilane on 350 mmol scale (Scheme 2a).¹⁵ When initially applying the original protocol for the preparation of $[\text{Ph}_4\text{P}]^+[\text{Cu}(\text{CF}_3)_2]^-$ complex^{13a} using $\text{TESCF}_2\text{CF}_3$, only trace product was detected. By increasing the equivalents of $\text{TESCF}_2\text{CF}_3$ and KF with prolonged reaction time, the product formation was significantly improved. Thus, a two-step procedure was followed (Scheme 2b): (1) reacting CuCl with $\text{TESCF}_2\text{CF}_3$ (4.0 equiv.) and KF (8.0 equiv.) in THF at room temperature overnight; (2) adding tetraphenylphosphonium chloride $\text{Ph}_4\text{P}^+\text{Cl}^-$ (1.0 equiv.) at room temperature and stirring for 2 h. To our delight, the $[\text{Ph}_4\text{P}]^+[\text{Cu}(\text{CF}_2\text{CF}_3)_2]^-$ complex **1** was successfully isolated in 92% yield (5.86 g, white solid) on 10 mmol scale. This complex was fully characterized by ^1H , ^{19}F and ^{31}P NMR spectroscopy as well as high-resolution mass spectrometry. The structure was unambiguously confirmed by X-ray crystallography.

Carboxylic acids are naturally abundant materials that are readily available, inexpensive and stable. As a result, decarboxylative cross-coupling of carboxylic acids has drawn tremendous attention in the synthetic community in recent years.¹⁶ The conversion of CO_2H group to CF_3 *via* decarboxylative trifluoromethylation has emerged as a viable perfluoroalkylation strategy.¹⁷ To the best of our knowledge, decarboxylative pentafluoroethylation remains unknown. Li *et al.* pioneered the decarboxylative trifluoromethylation of aliphatic carboxylic acids using a $\text{Cu}(\text{III})$ complex $(\text{bpy})\text{Cu}(\text{CF}_3)_3$ as the reagent.^{17a} In their proposed mechanism, $(\text{bpy})\text{Cu}(\text{CF}_3)_3$ reacts with ZnMe_2 to generate the $[\text{Cu}(\text{CF}_3)_3\text{Me}]^-$ anion, which undergoes reductive elimination to form the key $[\text{Cu}(\text{CF}_3)_2]^-$ anion (Scheme 3a). In the presence of an oxidant, $[\text{Cu}^{\text{I}}(\text{CF}_3)_2]^-$ anion becomes $\text{Cu}^{\text{II}}(\text{CF}_3)_2$. Decarboxylation of carboxylic acid **2** would lead to the alkyl radical, in Li's report a silver(II) salt was



Scheme 2 Synthesis of bispentafluoroethylated organocuprate $[\text{Ph}_4\text{P}]^+[\text{Cu}(\text{CF}_2\text{CF}_3)_2]^-$ **1**.



Scheme 3 Initial investigation of decarboxylative pentafluoroethylation of aliphatic carboxylic acids using **1**.



employed for this purpose. This radical can react with the $\text{Cu}^{\text{II}}(\text{CF}_3)_2$ species to generate product **3** with the formation of a C–CF₃ bond (Scheme 3b). We envisioned that our Cu(I) complex $[\text{Ph}_4\text{P}]^+[\text{Cu}(\text{CF}_2\text{CF}_3)_2]^-$ 1 can intercept this reaction pathway bypassing the reductive elimination from the Cu(III) anion to achieve decarboxylative pentafluoroethylation. However, the reactivity and compatibility of this complex in the decarboxylation conditions were unclear to us at the outset.

An initial attempt using Li's conditions (A)^{17a} with **1** and **2a** failed to provide any products (Scheme 3c). However, we were delighted to find that by using the photocatalyst 9-mesityl-10-methylacridinium tetrafluoroborate $[\text{Mes-Acr-Me}]^+[\text{BF}_4]^-$ under blue light irradiation (condition B), the desired product **3a** could be obtained in 80% yield. Although visible-light-induced decarboxylative functionalization of carboxylic acids has been well-studied,^{18a,c} its application to perfluoroalkylation is limited.^{18b,c} Extensive screening of reaction parameters including photocatalysts, oxidants, additives and solvents was carried out to improve the yield.¹⁹ It was found that adding a hypervalent iodine(III) reagent PhIO (iodosylbenzene)²⁰ could enhance the yield to 96% (condition C).

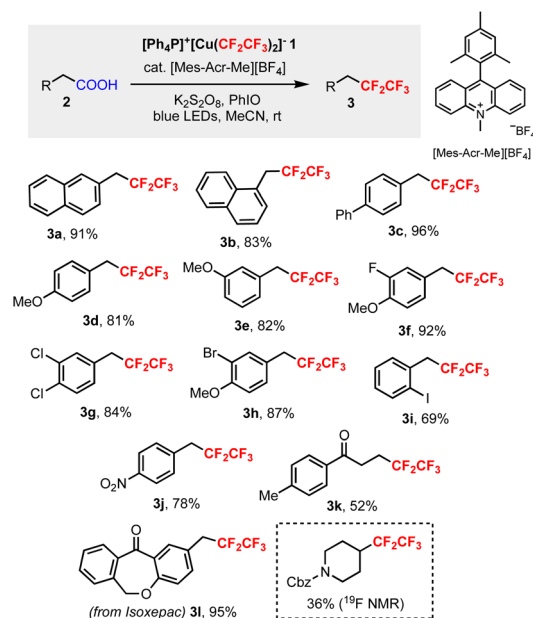
The scope of aliphatic carboxylic acids **2** in the decarboxylative pentafluoroethylation using **1** was subsequently studied (Scheme 4). Under the optimized conditions, a variety of carboxylic acids containing benzylic CO₂H group could be converted to the corresponding pentafluoroethylated products **3a–j**. The reaction tolerated electron-donating (**3d**) and electron-withdrawing (**3j**) aryl substituents. Halogens including fluoro (**3f**), chloro (**3g**), bromo (**3h**) and iodo (**3i**) groups were also compatible. A γ -keto acid was suitable substrate in the reaction (**3k**). Moreover, the anti-inflammatory agent Isoxepac could be

pentafluoroethylated in excellent yield (**3l**). However, a secondary carboxylic acid only gave a low yield.

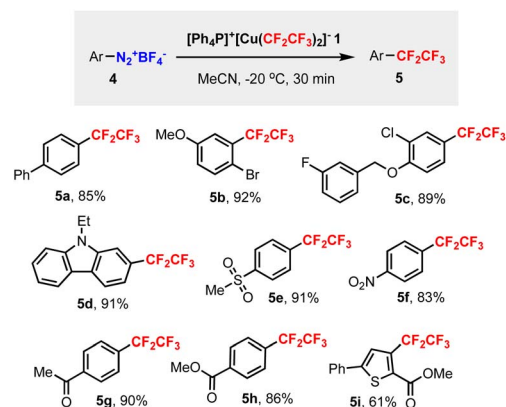
Based on literature evidence,^{18c} the following plausible reaction mechanism is proposed for the decarboxylative pentafluoroethylation of **2** with reagent **1** (see the ESI† for proposed mechanisms and control experiments). The photocatalyst $[\text{Mes-Acr-Me}]^+$ is activated by visible light, which then undergoes single-electron oxidation of carboxylate $\text{R-CH}_2\text{-COO}^-$ (from **2**) to give acyloxyl radical $\text{R-CH}_2\text{-COO}^\bullet$ and generate the $[\text{Mes-Acr-Me}]^\bullet$ species. Decarboxylation of $\text{R-CH}_2\text{-COO}^\bullet$ leads to R-CH_2 alkyl radical. Meanwhile, $[\text{Cu}^{\text{I}}(\text{CF}_2\text{CF}_3)_2]^-$ 1 is oxidized to $\text{Cu}^{\text{II}}(\text{CF}_2\text{CF}_3)_2$ which then reacts with the R-CH_2 radical to form the $\text{R-CH}_2\text{-CF}_2\text{CF}_3$ product **3** (cf. Scheme 3b).^{17a} Finally, $[\text{Mes-Acr-Me}]^\bullet$ is oxidized *via* SET to regenerate the catalyst $[\text{Mes-Acr-Me}]^+$. Adding PhIO can lead to the formation of phenyliodine(III) dicarboxylates $(\text{RCH}_2\text{COO})_2\text{I}^{\text{Ph}}$, which are known to undergo decarboxylation in the presence of copper(I) complexes to generate R-CH_2 alkyl radical.²⁰ It is possible that both pathways contributed to the formation of **3** from **2**.

Arenediazonium salts are useful substrates for Sandmeyer-type trifluoromethylation and can be made from inexpensive aromatic amines.²¹ However, the corresponding pentafluoroethylation is far less explored. One report in the literature by Hu *et al.*⁸ⁿ described the copper-mediated pentafluoroethylation of arenediazonium tetrafluoroborates with *in situ* generated tetrafluoroethylene (TFE) from TMSCF_3 and NaI. By adding CuSCN and CsF to TFE, the " CuCF_2CF_3 " species is formed which can react with the diazonium salt.²² We found that **1** was remarkably reactive with arenediazonium salts **4** even at -20°C (Scheme 5).²³ Within 30 min, various arenediazonium tetrafluoroborates could be converted directly to pentafluoroethyl arenes **5** in good yields. The reaction exhibited good functional group tolerability towards halo (**5b**, **5c**), amine (**5d**), sulfone (**5e**), nitro (**5f**), ketone (**5g**), ester (**5h**) and heteroaryl (**5i**) groups. This protocol was operationally straightforward without the use of separate reagents/additives and the conditions were mild and fast.

(Hetero)aryl halides could be pentafluoroethylated using **1** based on analogous trifluoromethylation conditions^{13a}



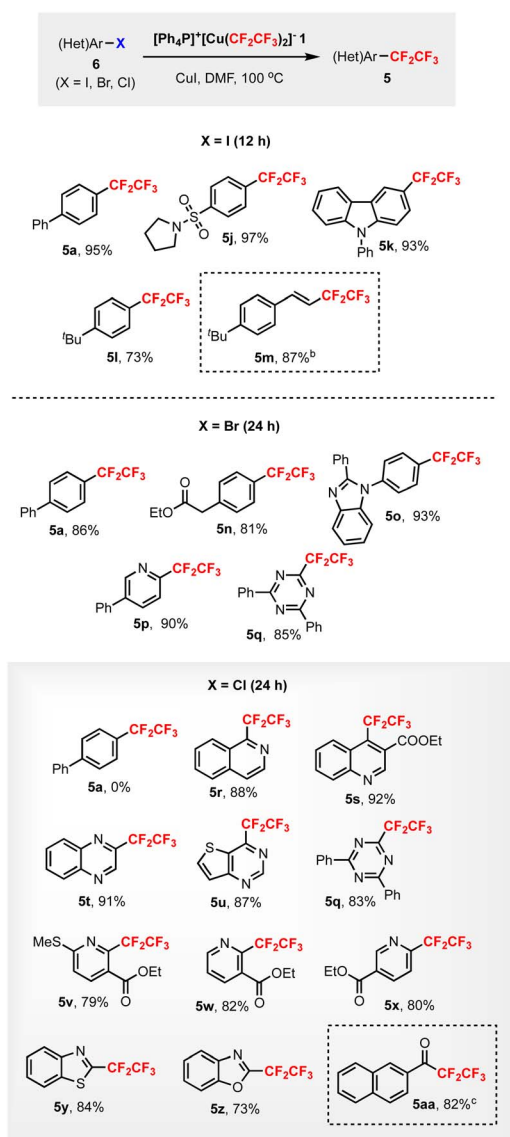
Scheme 4 Scope of decarboxylative pentafluoroethylation using **1**.^a ^aGeneral conditions: **1** (0.2 mmol), **2** (0.4 mmol), $[\text{Mes-Acr-Me}][\text{BF}_4]$ (3 mol%), $\text{K}_2\text{S}_2\text{O}_8$ (0.4 mmol), PhIO (0.2 mmol), MeCN (2.0 mL), blue LEDs, rt for 12 h under argon. Isolated yields based on **1**.



Scheme 5 Pentafluoroethylation of arenediazonium tetrafluoroborates using **1**.^a ^aGeneral conditions: **1** (0.2 mmol), **4** (0.2 mmol), MeCN (2.0 mL), under argon. Isolated yields.



(Scheme 6). Aryl iodides were quite reactive within 12 h to provide products **5a**, **5j–l** in good yields. An example of alkenyl iodide in pentafluoroethylation was also demonstrated (**5m**). Aryl and heteroaryl bromides gave products **5a**, **5n–q** in good yields after 24 h. In contrast, aryl chlorides were much less reactive than aryl iodide and aryl bromide, often were inert in previously reported pentafluoroethylation protocols.²⁴ Actually, reaction of unactivated 4-biphenyl chloride with **1** did not generate compound **5a** at all. However, activated heteroaryl chlorides containing isoquinoline (**5r**), quinoline (**5s**), quinoxaline (**5t**), pyrimidine (**5u**), triazine (**5q**), nicotinate (**5v–x**), benzothiazole (**5y**) and benzoxazole (**5z**) cores did react with reagent **1** to afford pentafluoroethylated heteroarenes in 73–92% yields. Intriguingly, an acid chloride (2-naphthoyl chloride)

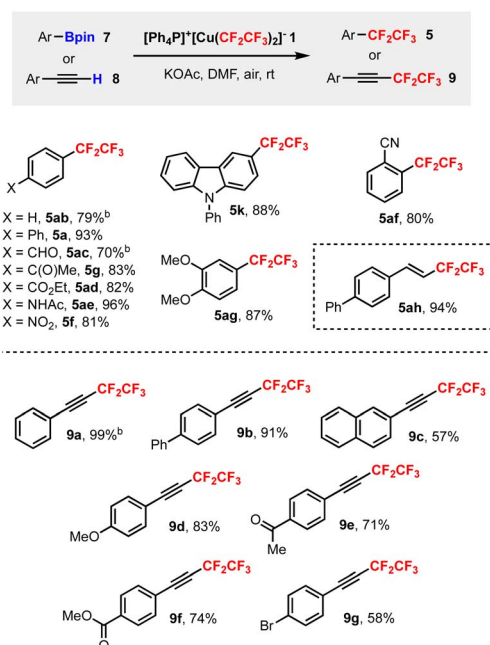


Scheme 6 Pentafluoroethylation of (hetero)aryl halides using **1**.^a
^aGeneral conditions: **1** (0.3 mmol), **6** (0.2 mmol), CuI (0.2 mmol), DMF (2.0 mL), under argon. Isolated yields. ^b*d* = 17 : 1 from starting alkenyl iodide. ^cConditions: 2-naphthoyl chloride (0.2 mmol), **1** (0.3 mmol), THF (2.0 mL), 60 °C for 12 h, under argon.

was able to generate the pentafluoroethylated ketone **5aa** at lower temperature (60 °C) without the CuI additive.^{8f}

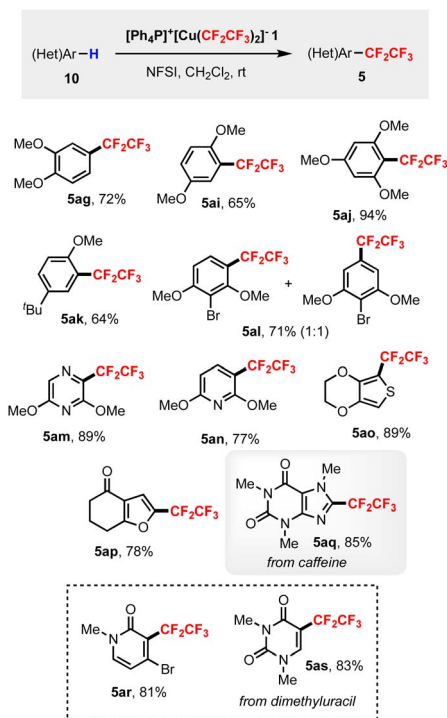
Furthermore, reagent **1** was effective in oxidative pentafluoroethylation of aryl boronic esters **7** and terminal alkynes **8** under mild conditions (Scheme 7).²⁵ Thus, pentafluoroethylated arenes **5** were synthesized from the corresponding aryl-Bpin tolerating aldehyde, ester, amide, nitro and nitrile groups. An alkenyl-Bpin substrate also gave the product (**5ah**). Readily available terminal alkynes were directly converted to pentafluoroethylated internal alkynes **9a–g** showing good functional group tolerance. The simple operations (open to air) and the use of air as a green oxidant were the advantages of these reactions.

The direct conversion of C–H bonds to C–R_f bonds bypassing the requirement of prefunctionalized substrates is a very desirable strategy. Trifluoromethylation of arene C–H bonds has been reported by Zhang *et al.* using a high-valent Cu(III)-CF₃ complex.²⁶ However, to the best of our knowledge, the corresponding pentafluoroethylation using copper-based reagents is unknown. In the literature, the C–H bond pentafluoroethylation has been achieved by employing nickel catalysts,^{27a,b} cobalt complexes^{27c} and photocatalytic methods.^{27d,e} We discovered that our CuCF₂CF₃ complex **1** was capable of pentafluoroethylating arenes and heteroarenes in the presence of an oxidant (Scheme 8). Different oxidants including K₂S₂O₈, PIDA, Selectfluor, Oxone and NFSI were screened and NFSI showed the best reactivity.¹⁹ Thus, at room temperature, aromatic C–H bonds could be converted to C–CF₂CF₃ bonds (**5ag**, **5ai–5al**). Heteroaromatic C–H bonds including pyrazine (**5am**), pyridine



Scheme 7 Aerobic pentafluoroethylation of boronic esters and terminal alkynes using **1**.^a
^aGeneral conditions using boronic esters: **1** (0.3 mmol), **7** (0.2 mmol), KOAc (0.3 mmol), DMF (2.0 mL), open to air, 12 h. Isolated yields. General conditions using terminal alkynes: **1** (0.24 mmol), **8** (0.2 mmol), KOAc (0.3 mmol), DMF (2.0 mL), open to air, 12 h. Isolated yields. ^bYield determined by ¹⁹F NMR using benzotrifluoride as the internal standard.





Scheme 8 Oxidative pentafluoroethylation of (hetero)aromatic C–H bond using **1**.^a General conditions: **1** (0.2 mmol), **10** (1.0 mmol), NFSI (0.6 mmol), CH₂Cl₂ (2.0 mL), under argon, 12 h. Isolated yields.

(**5an**), thiophene (**5ao**) and furan (**5ap**) were also reactive. Interestingly, the C–H bond of *caffeine* could be smoothly functionalized to afford the pentafluoroethylated *caffeine* **5aq**. Moreover, the alkenyl C–H bond pentafluoroethylation was achieved to give compound **5ar** and an uracil derivative **5as**. It was found that the electron-rich arenes were more reactive than the electron-poor ones. In comparison with 1,4-dimethoxybenzene (**5ai**, 65%), 1,4-dibromobenzene (14%) and 1,4-dinitrobenzene (<5%) gave low yields even at elevated temperature (60 °C in DCE). This is likely due to the electrophilic nature of the pentafluoroethyl radical generated *in situ*, which is more reactive towards the electron-rich arenes.

Conclusions

In conclusion, we have synthesized and characterized a novel [Ph₄P]⁺[Cu(CF₂CF₃)₂]⁻ complex **1**. This complex proved to be a highly versatile pentafluoroethylating reagent. A diverse array of pentafluoroethylation reactions of carboxylic acids, diazonium salts, organic halides, boronic esters, terminal alkynes and (hetero)arenes were developed using **1**. Therefore, one reagent was capable of constructing all C(sp³)–, C(sp²) and C(sp)–CF₂CF₃ bonds. It is worth mentioning that the [Ph₄P]⁺[Cu(CF₂CF₃)₂]⁻ complex **1** has demonstrated superior reactivities than its [Ph₄P]⁺[Cu(CF₃)₂]⁻ counterpart.¹⁹ For instance, pentafluoroethylation of carboxylic acid, diazonium salt, arene C–H bond and heteroaryl chloride using **1** gave significantly higher yields than the corresponding trifluoromethylation with

[Ph₄P]⁺[Cu(CF₃)₂]⁻. Further transformations of **1** and studies of reaction mechanisms are ongoing in our laboratories.

Data availability

The data supporting this article have been included as part of the ESI.†

Author contributions

The manuscript was written through the contributions of all authors. All authors have approved the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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