Radical Carbofluorination of Unactivated Alkenes with Fluoride Ion

Zhonglin Liu, He Chen, Ying Lv, Xinqiang Tan, Haigen Shen, Haizhu Yu, and Chaozhong Li

J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/jacs.8b03077 • Publication Date (Web): 25 Apr 2018

Radical Carbofluorination of Unactivated Alkenes with Fluoride Ion

Zhonglin Liu,[a] He Chen,[a] Ying Lv,[b] Xinqiang Tan,[a] Haigen Shen,[a] Hai-Zhu Yu,*[, b] and Chaozhong Li*[, a, c]

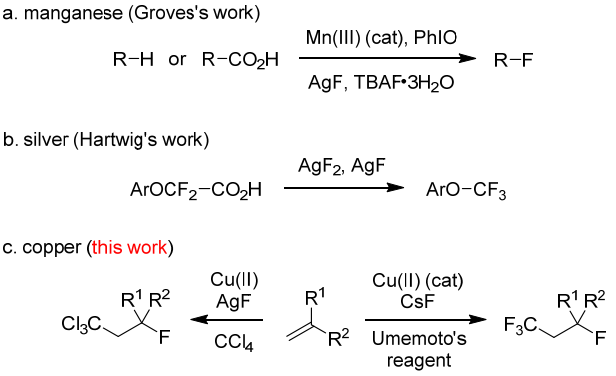
[a] Key Laboratory of Organofluorine Chemistry, Center for Excellence in Molecular Synthesis, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, P. R. China. [b] AnHui Province Key Laboratory of Chemistry for Inorganic/Organic Hybrid Functionalized Materials, Anhui University, Hefei, Anhui 230601, P. R. China. [c] School of Materials and Chemical Engineering, Ningbo University of Technology, No. 201 Fenghua Road, Ningbo 315211, P. R. China

ABSTRACT: The copper-assisted radical carbofluorination of unactivated alkenes with fluoride ion is described. With [Cu(**L3**)F_2]H_2O (**L3** = 4,4'-di(methoxycarbonyl)-2,2'-bipyridine) as the fluorine source and [Ag(DMPhen)(MeCN)]BF_4 (DMPhen = 2,9-dimethyl-1,10-phenanthroline) as the chloride scavenger, the reaction of unactivated alkenes with CCl_4 in acetonitrile provided the corresponding carbofluorination products in satisfactory yields. The protocol exhibited a wide functional group compatibility and broad substrate scope, and could be extended to the use of a variety of activated alkyl chlorides other than CCl_4. A copper-catalyzed fluorotrifluoromethylation of unactivated alkenes was then successfully developed with CsF as the fluorine source and Umemoto's reagent as the trifluoromethylating agent. A mechanism involving the fluorine atom transfer from Cu(II)–F complexes to alkyl radicals is proposed.

INTRODUCTION

Fluorine is a key element in pharmaceuticals, agrochemicals and materials owing to its profound effect on properties such as lipophilicity, permeability and metabolic stability.[1] Moreover, ^{18}F-labeled organic compounds are clinically used as contrast agents for positron emission tomography.[2] As a consequence, the introduction of fluorine atoms into organic molecules via C–F bond formation has received a considerable attention and a significant progress has been achieved in this area in the past decade.[3] In particular, the carbofluorination of alkenes allows the concomitant formation of a C–F bond and a C–C bond, thus rendering it a highly valuable method in organic synthesis.[4–11] For example, Dilman et al[4] reported the electrophilic fluorocyanation of enamines with *N*-fluorobis(benzene-sulfonyl)imide (NSFI)[12] or 1-chloromethyl-4-fluorodiazo-niabicyclo[2,2,2]-octane bis(tetrafluoroborate) (Selectfluor).[13] Asymmetric electrophilic fluorocarbocyclization of alkenes was nicely developed by the groups of Gouverneur, Gagne, Alexakis and Ma.[5, 6b] The palladium-catalyzed carbofluorination of allenes led to the synthesis of a variety of allyl fluorides, as reported by Doyle et al.[7] Furthermore, the palladium-catalyzed enantioselective fluoroarylation of styrenes was successfully developed by the Toste group.[8, 9] Nevertheless, the above methods are mainly restricted to activated alkenes such as enamines, styrenes and allenes. As a comparison, the recently developed silver-catalyzed radical carbofluorination with Selectfluor allows the use of unactivated alkenes, providing a series of functionalized alkyl fluorides.[10, 11] However, almost all the above carbofluorination reactions require the use of expensive N–F reagents (such as NFSI and Selectfluor) or highly toxic XeF_2 as the fluorine source. The only exception is the carbofluorination of allenes with AgF, as reported by Doyle et al.[7] Given that fluoride ion is abundant and the cheapest fluorine source, it is certainly highly desirable to develop new carbofluorination methods with fluoride ion that allow the use of unactivated alkenes. Herein we report the copper-assisted radical carbofluorination of unactivated alkenes with fluoride ion.

Scheme 1. Transition-Metal-Assisted F-Transfer Radical Reactions with Fluoride Ion



Transition metal-assisted Cl- or Br-transfer radical processes are well documented.[14] In contrast, the analogous transition metal-assisted F-transfer processes with fluoride ion are rare

(Scheme 1), despite the recent significant progress in radical fluorination.[3c, 15, 16] Groves and coworkers nicely introduced the manganese-catalyzed oxidative aliphatic C–H fluorination and fluorodecarboxylation with fluoride ion, in which the fluorine-atom-transfer from Mn(IV)–F to an alkyl radical is proposed (Scheme 1a).[17] Hartwig et al reported the synthesis of aryl trifluoromethyl ethers via AgF_2-mediated decarboxylative fluorination, in which the fluorine atom transfer is likely to take place between an alkyl radical and AgF_2 or AgF (Scheme 1b).[18, 19] This mechanism coincides with our proposal in silver-catalyzed radical fluorination reactions with Selectfluor.[16b, 20, 21] These pioneer works urged us to investigate the possibility of copper-assisted F-transfer radical processes.[22] The use of copper as an earth-abundant and cheap metal in combination with fluoride ion as the cheapest fluorine source should render the fluorination method of higher practical value. In this Article, the copper-promoted radical carbofluorination of unactivated alkenes with CCl_4 and fluoride ion is developed. Furthermore, the copper-catalyzed radical fluorotrifluoromethylation of unactivated alkenes with Umemoto's reagent and CsF is successfully implemented (Scheme 1c). The scope and limitation of these methods are explored and the combination of mechanistic experiments with theoretical calculations provides a clear understanding on the copper-assisted fluorine atom transfer processes.

RESULTS AND DISCUSSION

Our idea originated from the well-established copper-assisted chlorine-atom-transfer radical addition processes.[14] The chlorine-atom-transfer radical addition (Cl-ATRA) of CCl_4 onto alkenes is among the earliest examples of atom transfer reactions.[23] In the meantime, the copper-catalyzed version of the reaction is the most extensively studied example, providing product **B** via chlorine-atom-transfer (CAT) from Cu(II)–Cl to adduct radical **A** (Figure 1). We envisioned that, when a Cu(I)–F complex was used in the reaction, the analogous fluorine-atom-transfer (FAT) leading to carbofluorination product **C** might become possible. However, this was a challenging task because the CAT was demonstrated to be a fast and highly efficient process under the catalysis of copper complexes. The success of FAT thus hinged on the effective inhibition of the competing CAT process.

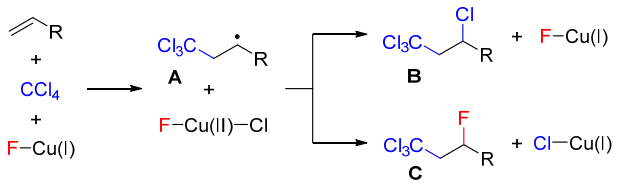
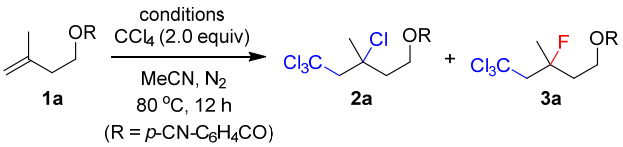
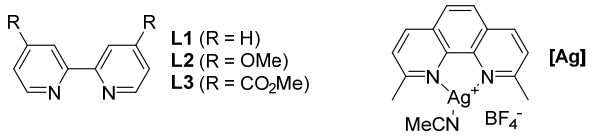


Figure 1. FAT versus CAT.

As a start, we chose 3-methylbut-3-en-1-yl 4-cyanobenzoate (**1a**) as the model substrate to test our idea (Table 1). The choice of 1,1-disubstituted alkene rather than monosubstituted one was to eliminate the possibility of the unwanted halogen-exchange fluorination (e.g., from **B** to **C**).[22a, 24] With 2,2'-bipyridine (**L1**) as the ligand, the reaction of **1a**, CCl_4 and $Cu(OTf)_2$/CsF or CuF_2 in acetonitrile at reflux afforded only a small amount of the CAT product **2a** while no FAT product **3a** could be detected (entries 1 and 2, Table 1). To inhibit the CAT process, Ag(I) salts were introduced as chloride scavengers. However, the direct addition of AgF (2 equiv) showed no improvement (entry 3, Table 1). This might be attributed to the stronger binding of the ligand **L1** to Ag(I) than to Cu(II), leaving little copper complex to initiate the reaction. Indeed, increasing the amount of **L1** from 0.7 to 2.7 equivalents resulted in the formation of **3a** in 20% yield (entry 4, Table 1). To improve the reaction efficiency, the commercially available silver complex $[Ag(DMPhen)(MeCN)]BF_4$ (**[Ag]**, DMPhen = 2,9-dimethyl-1,10-phenanthroline) was then used as the chloride scavenger. Pleasingly, the reaction mixture of **1a**, CCl_4, **[Ag]**, $Cu(OTf)_2$, **L1** and CsF provided **2a** (27%) and **3a** (52%) in a combined yield of 78% (entry 5, Table 1). Switching the ligand **L1** to the more electron-rich 4,4'-dimethoxy-2,2'-bipyridine (**L2**) lowered the yield of **3a** (entry 6, Table 1). In contrast, the use of the more electron-deficient ligand 4,4'-di(methoxycarbonyl)-2,2'-bipyridine (**L3**) increased the yield of **3a** to 63% (entry 7, Table 1). Interestingly, when the amounts of $Cu(OTf)_2$ and **L3** were both increased, **3a** was obtained in a lower yield but **2a** in a higher yield (entry 8, Table 1). We reasoned that this phenomenon might be ascribed to the relatively slow in-situ formation of Cu(II)–F complex required for FAT. We then prepared the copper complex $[Cu(\mathbf{L3})F_2]\cdot H_2O$ and used it in place of $Cu(OTf)_2$/**L3**/CsF. Gratifyingly, the desired fluorination product **3a** was obtained in 71% yield (entry 9, Table 1). When a slight excess of $[Cu(\mathbf{L3})F_2]\cdot H_2O$ was used, **3a** was isolated in 77% yield while only a trace amount of the CAT product **2a** could be observed (entry 10, Table 1). Control experiments revealed that both the copper complex and **[Ag]** were required for the reaction (entries 11–13, Table 1).

Table 1. Optimization of Conditions for the Synthesis of 3a



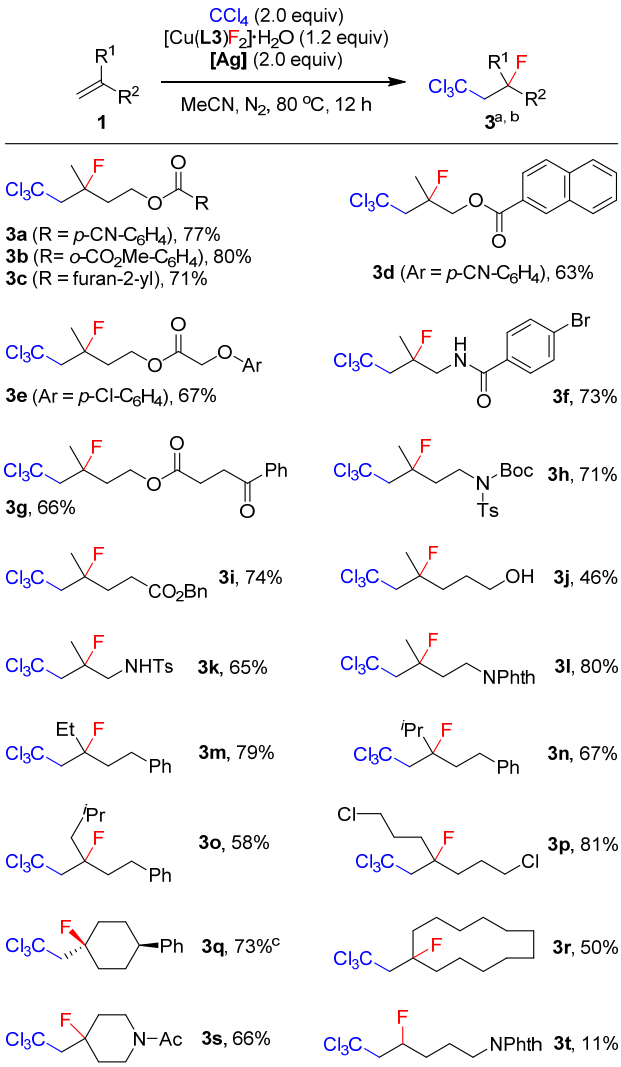


entry[a]	reagents (equiv)	Yield (%)[b] 2a	3a
1	$Cu(OTf)_2$ (0.3), **L1** (0.3), CsF (2.0)	< 5	0
2	CuF_2 (0.7), **L1** (0.7)	5	0
3	$Cu(OTf)_2$ (0.7), **L1** (0.7), AgF (2.0)	7	1
4	$Cu(OTf)_2$ (0.7), **L1** (2.7), AgF (2.0)	4	20
5	$Cu(OTf)_2$ (0.7), **L1** (0.7), CsF (2.0), **[Ag]** (2.0)	27	52
6	$Cu(OTf)_2$ (0.7), **L2** (0.7), CsF (2.0), **[Ag]** (2.0)	15	8
7	$Cu(OTf)_2$ (0.7), **L3** (0.7), CsF (2.0), **[Ag]** (2.0)	24	63
8	$Cu(OTf)_2$ (1.0), **L3** (1.0), CsF (2.0), **[Ag]** (2.0)	30	57
9	$[Cu(\mathbf{L3})F_2]\cdot H_2O$ (1.0), **[Ag]** (2.0)	10	71
10	$[Cu(\mathbf{L3})F_2]\cdot H_2O$ (1.2), **[Ag]** (2.0)	< 5	77
11	$[Cu(\mathbf{L3})F_2]\cdot H_2O$ (1.0)	55	0

12	$[Cu(\mathbf{L3})F_2]\cdot H_2O$ (1.0), $AgBF_4$ (2.0)	7	14
13	**[Ag]** (2.0)	0	0

[a] Reaction conditions: **1a** (0.20 mmol), CCl_4 (0.40 mmol), MeCN (4.0 mL), 80 °C, 12 h. [b] Isolated yield based on **1a**.

Scheme 2. Fluorotrichloromethylation of Alkenes

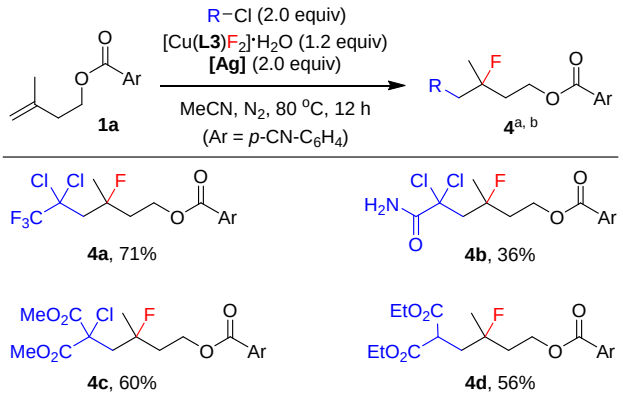


[a] Conditions: **1** (0.20 mmol), CCl_4 (0.40 mmol), $[Cu(\mathbf{L3})F_2]\cdot H_2O$ (0.24 mmol), **[Ag]** (0.40 mmol), MeCN (4.0 mL), 80 °C, 12 h. [b] Isolated yield based on **1**. [c] dr = 95:5 determined by crude ^{1}H NMR (400 MHz).

Having established the optimized conditions for the carbofluorination, we aimed to define the scope of the method. As can be seen in Scheme 2, linear alkenes with a representative selection of substitution patterns all underwent fluorotrichloromethylation smoothly providing the fluorides **3a–3p** in satisfactory yield. Notably, alkenes **1m–1p** with a relatively high steric hindrance around the internal vinylic carbon also participated in the carbofluorination nicely, indicating that the method is insensitive to steric factors. Methylenecycloalkanes were also suitable substrates for the fluorotrichloromethylation, as exemplified by the synthesis of **3q–3s**. Interestingly, a high degree (95:5) of stereoselectivity was observed in the reaction of 4-phenyl-1-methylenecyclohexane (to give **3q**). In addition, the presence of a wide range of functional groups was tolerated by the process. For example, ethers, esters, ketones, nitriles, amides, imides, sulfonamides, carbamates, alkyl chlorides and free alkyl alcohols all proved to be compatible with the reaction. In all the cases with 1,1-disubstituted alkenes, the competing Cl-ATRA processes were effectively inhibited and the Cl-ATRA products (similar to **2a**) were either negligible (< 5%) or not observed. In contrast, the Cl-ATRA prevailed in the case of monosubstituted alkene **1t**, and the carbofluorination product **3t** was obtained in a low yield. This might be attributed to the joint operation of the following two effects: (1) The Cl-ATRA is faster for secondary alkyl radicals than for tertiary alkyl radicals,[14] but (2) the FAT is slower for secondary alkyl radicals than for tertiary alkyl radicals (vide infra).

Similarly, our copper-mediated transformation was also shown to be compatible with a variety of activated alkyl chlorides (Scheme 3). For example, the use of CF_3CCl_3 in place of CCl_4 gave rise to the corresponding trifluoromethylated product **4a** in 71% yield. Trichloroacetamide also participated in the carbofluorination to afford γ-fluorinated amide **4b**. Dimethyl 2,2-dichloromalonate also proved to be an effective coupling partner and furnished product **4c** in 60% yield. Furthermore, monochlorinated malonate could also be employed for the reaction, leading to the synthesis of fluorinated malonate **4d** in satisfactory yield. It is worth mentioning that all the above products (**3** and **4**) are inaccessible by previous carbofluorination methods. For example, our previous investigation indicated that the silver-catalyzed reaction of alkenes, malonate and Selectfluor failed to give any carbofluorination products such as **4d**.[10a] Therefore, this copper-mediated method nicely complements the literature precedents.

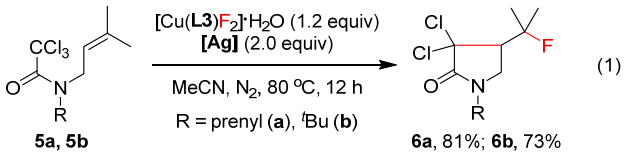
Scheme 3. Carbofluorination of 1a with Alkyl Chlorides

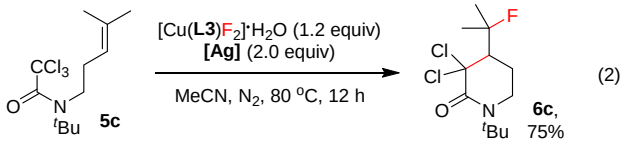


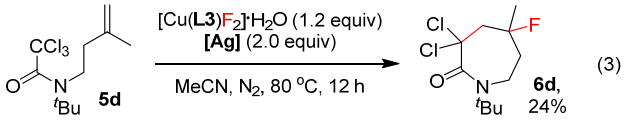
[a] Conditions: **1a** (0.20 mmol), RCl (0.40 mmol), $[Cu(\mathbf{L3})F_2]\cdot H_2O$ (0.24 mmol), **[Ag]** (0.40 mmol), MeCN (4.0 mL), 80 °C, 12 h. [b] Isolated yield based on **1a**.

The above protocol could also be extended to intramolecular carbofluorination reactions. As depicted in Eq. 1, the reaction of *N*-prenyltrichloroacetamide **5a** or **5b** under the above optimized conditions provided fluorinated γ-lactams **6a** or **6b** in high yield. *N*-Butenyl-substituted trichloroacetamide **5c** underwent smooth 6-*exo* cyclization

furnishing fluorinated δ-lactam **6c** in 75% yield (Eq. 2). Furthermore, fluorinated caprolactam **6d** could also be achieved via 7-*endo* cyclization of unsaturated amide **5d** (Eq 3). These examples also served as further evidence supporting the radical mechanism of carbofluorination.





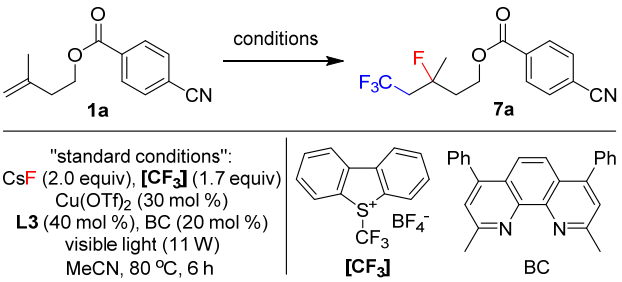


The above results clearly demonstrated the feasibility of FAT from Cu(II)–F complexes to alkyl radicals. Nevertheless, in the carbofluorination with alkyl chlorides, a stoichiometric amount of Cu(II)–F complex was required in order to compete with the undesired Cl-ATRA or copper-assisted CAT processes. Without the interference of Cl-ATRA or CAT, FAT processes that are catalytic in terms of copper should be possible. To prove the viewpoint, we carried out the copper-catalyzed fluorotrifluoromethylation of unactivated alkenes with fluoride ion as the fluorine source.

Much as fluorine atom, CF_3 group also plays a prominent role in pharmaceuticals and agrochemicals. The fluorotrifluoromethylation of alkenes allows the concurrent introduction of a F atom and a CF_3 group and is highly desirable in view of the increasing demand for fluorinated compounds in various research fields. Zupan and Gregorcic first reported the fluorotrifluoromethylation of styrene with XeF_2 and CF_3CO_2H in a low efficiency.[25] Very recently, Qing and coworkers developed the silver-mediated fluorotrifluoromethylation of unactivated alkenes.[11] However, the method required excess AgOTf and an additional oxidant di(acetoxy)iodobenzene in addition to the use of Selectfluor as the fluorine source.

Taking advantage of the above results in carbofluorination with CCl_4, we conducted an extensive screening of experimental conditions for the fluorotrifluoromethylation of alkene **1a** (Table 2, also see Table S1 in the Supporting Information for details). We were pleased to find that, with CsF (2 equiv) as the fluorine source, $Cu(OTf)_2$ (30 mol%) as the catalyst, **L3** (40 mol %) and bathocuproine (BC, 20 mol %) as the ligands, the reaction of alkene **1a** with Umemoto's reagent[26] (*S*-(trifluoromethyl)dibenzothiophenium tetrafluoroborate, **[CF_3]**, 1.7 equiv) in acetonitrile at 80 °C under visible light irradiation furnished the expected product **7a** in 81% yield (entry 1, Table 2). The product yield decreased to 31% when the reaction was performed in the dark (entry 2, Table 2). The effect of visible light might be attributed to its acceleration on the single electron transfer between Cu(I) intermediate and Umemoto's reagent.[27] Both **L3** and BC were required in order to achieve a high yield of **7a** (entries 3–6, Table 2). The role of BC was more likely to promote the disproportionation of Cu(II) to give Cu(I) intermediate, which in turn initiated the reaction. This was supported by our UV-vis spectroscopic experiments (see Figure S1 in SI for details). It was also supported by the fact that almost no reaction occurred in the dark without the presence of BC (entries 7 and 8, Table 2). On the other hand, **L3** proved to be a better ligand than BC in promoting the FAT from Cu(II)–F complexes to alkyl radicals (vide supra). The results in Table 2 also indicated the synergistic effect of visible light, **L3** and BC. Finally, the control experiment demonstrated the role of Cu(II) as the catalyst (entry 9, Table 2).

Table 2. Optimization of Conditions for the Synthesis of 7a



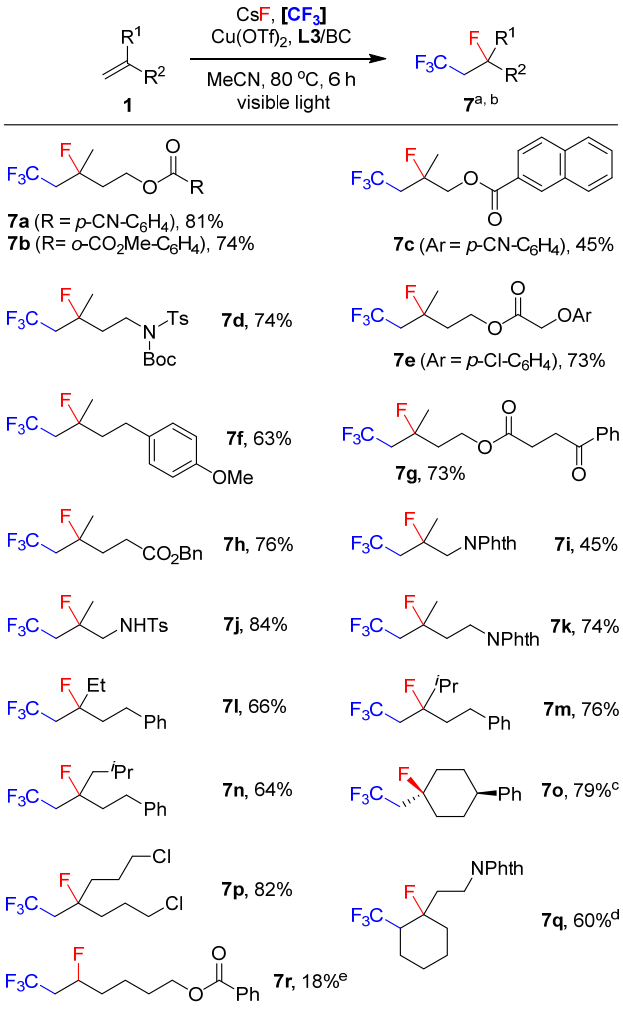
entry[a]	variation from the "standard conditions"	yield (%)[b]
1	none	81
2	without visible light	31
3	**L3** in place of BC	28
4	BC in place of **L3**	45
5	without BC	21
6	without **L3**	37
7	without visible light and BC	0
8	without visible light and **L3**	10
9	without $Cu(OTf)_2$	0

[a] The reaction was carried out in 0.20 mmol scale in MeCN (4.0 mL). [b] Isolated yield based on **1a**.

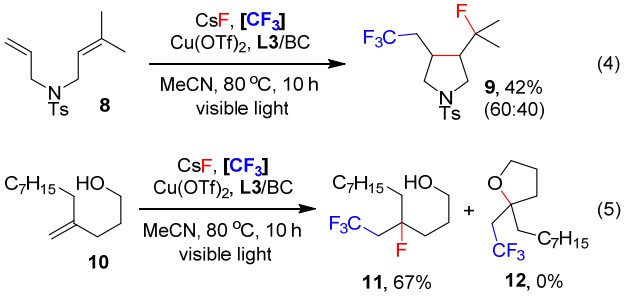
With the optimized conditions in hand, we set out to explore the scope of the method. As shown in Scheme 4, a variety of 1,1-disubsituted alkenes could be converted to the corresponding fluorotrifluoromethylation products **7a–7p** in satisfactory yields, attesting to the broad tolerance of the reaction for functional groups such as ether, ketone, ester, amide, sulfonamide, alkyl chloride, or cyano groups. Again a high degree (95:5) of stereoselectivity was observed in the case of **7o**, whose stereochemistry was unambiguously established by X-ray diffraction analysis. Notably, benzylic C–H bonds (e.g., **7f** and **7l–7o**) that are prone to C–H fluorination with Selectfluor under visible light irradiation[28] or copper catalysis,[16e] remained safe owing to the use of fluoride ion as the fluorine source. The protocol was also applicable to trisubstituted alkenes, as exemplified by the efficient synthesis of **7q**. As a comparison, the reaction of monosubstituted alkenes gave the fluorotrifluoromethylation products such as **7r** in a low yield along with the hydrotrifluoromethylation side-product. These results indicated that secondary alkyl radicals are less reactive towards Cu(II)–F, consistent with our observation in the above fluorotrichloromethylation with CCl_4.

To provide further evidence on the radical mechanism of fluorotrifluoromethylation, mechanistic studies were carried out. The reaction of diene **8** as a radical probe under the above "standard conditions" afforded the cyclized product **9** in 42% yield (Eq. 4). On the other hand, the reaction of pent-4-en-1-ol **10** as a cationic probe produced exclusively the fluorotrifluoromethylation product **11** in 67% yield while tetrahydrofuran product **12** could not be observed at all (Eq. 5). Given that the intramolecular trapping of a carbocation with an alcohol to form a 5-membered ring is much faster than the intermolecular trapping with a fluoride ion, the result in Eq. 5 demonstrated that carbocationic intermediates are unlikely to be involved in the fluorination step.

Scheme 4. Fluorotrifluoromethylation of Alkenes



[a] Conditions: **1** (0.20 mmol), Umemoto's reagent (0.34 mmol), CsF (0.40 mmol), $Cu(OTf)_2$ (0.06 mmol), **L3** (0.08 mmol), BC (0.04 mmol), MeCN (4.0 mL), 80 °C, visible light (11 W), 6 h. [b] Isolated yield based on **1**. [c] dr = 95:5 determined by crude ^{19}F NMR (376 MHz). [d] *Cis*/*trans* = 50:50. [e] The corresponding hydrotrifluoromethylation byproduct was obtained in 35% yield.



A plausible mechanism for the fluorotrifluoromethylation is shown in Figure 2. Visible light-promoted single electron transfer between Umemoto's reagent and a Cu(I) complex generates trifluoromethyl radical and a Cu(II)–F complex. The addition of electrophilic trifluoromethyl radical to an alkene gives the nucleophilic alkyl radical **D**, which abstracts a fluorine atom from Cu(II)–F complex to provide the fluorotrifluoromethylation product **7** and regenerate the Cu(I) complex.

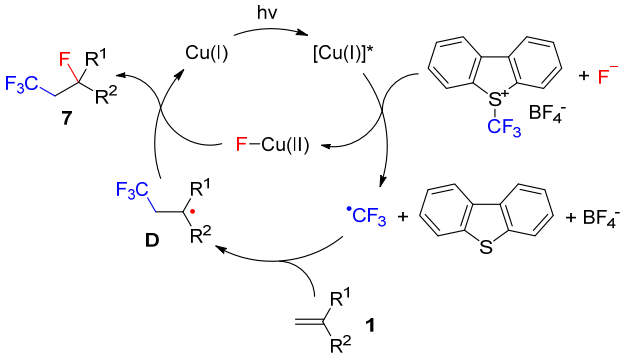
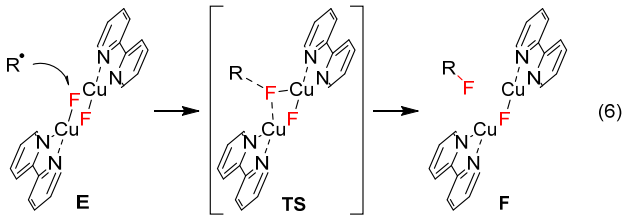


Figure 2. Proposed mechanism of fluorotrifluoromethylation.

As illustrated above, both fluorotrichloromethylation and fluorotrifluoromethylation with fluoride ion made possible by the FAT from Cu(II)–F complexes to alkyl radicals. To gain insight into the copper-assisted FAT process, mechanistic studies were carried out. Complex $[Cu(\mathbf{L3})F_2]\cdot H_2O$ was recrystallized in methanol and then subjected to X-ray diffractional analysis, which revealed that, in the solid state it exists as a binulcear complex bridged by two fluoride ions (see the SI for details). The study by Holm and Lee on Cu(II)F complexes also indicated that these complexes are fluoride-bridged dimers with the Cu_2F_2 unit of square planar geometry both in the solid state and in solution.[29] It is therefore reasonable to assume that the active species responsible for the FAT to alkyl radicals is $[Cu_2(\mathbf{L3})_2F_2]^{2+}$. Such a process (shown in Eq. 6) was then computed by density functional calculations at the B3LYP/6-311+G(d)//B3LYP/6-31G(d) level (with IEFPCM model and MeCN solvent), which has been demonstrated to be a fairly accurate tool in dealing with fluoro-containing models.[30, 31] To reduce the complexity, 2,2'-bipyridine was used in place of **L3** in the calculations (Eq. 6), and *tert*-butyl and isopropyl radicals were used as the models of tertiary and secondary alkyl radicals, respectively. For the reaction of *tert*-butyl radical with $[Cu_2(bpy)_2F_2]^{2+}$ in MeCN

solution, an activation free energy of 13.3 kcal/mol is computed and the whole process (from **E** to **F** with R = *t*-Bu) is exothermic by 7.9 kcal/mol. As a comparison, a higher energy barrier of 16.0 kcal/mol is computed for the reaction of isopropyl radical with $[Cu_2(bpy)_2F_2]^{2+}$. These data indicate that *tert*-butyl radical is more reactive than isopropyl radical towards $[Cu_2(bpy)_2F_2]^{2+}$, in accordance with the above experimental results. Meanwhile, the charge distribution analysis shows that the NBO charge on carbon radical center in the transition state (**TS**) is 0.477 (R = *t*-Bu) or 0.271 (R = *i*-Pr), indicative of the partial oxidation of the carbon radical in the transition state. This calculated result reveals that, during the FAT process (from **E** to **F)** the approaching of alkyl radical to fluoride ion is accompanied and possibly promoted by gradual electron transfer from the alkyl radical to the copper complex. This analysis is supported by the fact that *t*-Bu radical is much easier to be oxidized than *i*-Pr radical. It is also supported by our experimental observation (entries 6 and 7, Table 1) that bipyridine **L3** with electron-withdrawing substituents (CO_2Me) had a much better performance in fluorination than **L2** with electron-donating substituents (OMe), given that electron-withdrawing substitution makes the copper complex a stronger oxidant. Finally, the calculations also illustrate that alkyl radical approaches the fluoride ion in the direction perpendicular to the plane of $[Cu_2(bpy)_2F_2]^{2+}$. This accounts for the insensitivity of the above carbofluorination reactions towards steric factors.



(6)

CONCLUSION

The chemistry detailed above has demonstrated that radical carbofluorination of unactivated alkenes with fluoride ion can be successfully implemented with the aid of Cu(II) catalysts. The use of $[Cu(\mathbf{L3})F_2]\cdot H_2O$ complex readily prepared from $CuF_2\cdot 2H_2O$ enables a variety of activated alkyl chlorides to participate in the carbofluorination of alkenes efficiently. Fluorotrifluoromethylation of alkenes with fluoride ion can be achieved under mild conditions with the catalysis of $Cu(OTf)_2$. These protocols are highly practical in that the procedures are operationally simple, broad in scope, tolerant of sensitive functional groups, and utilize fluoride ion as the cheapest fluorine source and cheap copper complexes as catalysts. Furthermore, the copper-assisted fluorine-atom-transfer mechanism significantly expands the scope of radical fluorination, providing a solid basis for the future development of new fluorination methods.

The significance of the above chemistry is not limited to fluorination reactions. The model of copper-assisted radical fluorination with fluoride ion (Eq. 6) should inspire the functionalization of alkyl radicals (in particular tertiary alkyl radicals) with nucleophiles other than fluoride ion.[32] The research in this direction is currently underway in our laboratory.

ASSOCIATED CONTENT

Supporting Information

Full experimental details, characterizations of new compounds, copies of ^1H, ^{13}C and ^{19}F NMR spectra, DFT calculation results (PDF), and X-ray crystal structures of complex $Cu(\mathbf{L3})F_2$ and compound **7o** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

clig@mail.sioc.ac.cn (C.L.); yuhaizhu@ahu.edu.cn (H.Z.Y.)

Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

This Project was supported by the National Basic Research Program of China (973 Program) (Grant 2015CB931900), by the National Natural Science Foundation of China (Grants 21421002, 21472220, 21532008, 21602239, and 21672001), and by the Strategic Priority Research Program of the Chinese Academy of Sciences (Grant XDB20020000).

REFERENCES

(1) (a) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881–1886. (b) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308–319. (c) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320–330. (d) Kirk, K. L. *Org. Process Res. Dev.* **2008**, *12*, 305–321.

(2) (a) Miller, P. W.; Long, N. J.; Vilar, R.; Gee, A. D. *Angew. Chem., Int. Ed.* **2008**, *47*, 8998–9033. (b) Ametamey, S. M.; Honer, M.; Schubiger, P. A. *Chem. Rev.* **2008**, *108*, 1501–1516.

(3) For reviews, see: (a) Yerien, D. E.; Bonesi, S.; Postigo, A. *Org. Biomol. Chem.* **2016**, *14*, 9398–9427. (b) Champagne, P. A.; Desroches, J.; Hamel, J.-D.; Vandamme, M.; Paquin, J.-F. *Chem. Rev.* **2015**, *115*, 9073–9174. (c) Chatalova-Sazepin, C.; Hemelaere, R.; Paquin, J.-F.; Sammis, G. M. *Synthesis* **2015**, *47*, 2554–2569. (d) Wu, J. *Tetrahedron Lett.* **2014**, *55*, 4289–4294. (e) Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 8214–8264. (f) Hollingworth, C.; Gouverneur, V. *Chem. Commun.* **2012**, *48*, 2929–2942. (g) Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature* **2011**, *42*, 470–477. (h) Furuya, T.; Klein, J. E. M. N.; Ritter, T. *Synthesis* **2010**, *42*, 1804–1821. (i) Wilkinson, J. A. *Chem. Rev.* **1992**, *92*, 505–519.

(4) Dilman, A. D.; Belyakov, P. A.; Struchkova, M. I.; Arkhipov, D. E.; Korlyukov, A. A.; Tartakovsky, V. A. *J. Org. Chem.* **2010**, *75*, 5367–5370.

(5) (a) Cochrane, N. A.; Nguyen, H.; Gagne, M. R. *J. Am. Chem. Soc.* **2013**, *135*, 628–631. (b) Romanov-Michailidis, F.; Guenee, L.; Alexakis, A. *Angew. Chem., Int. Ed.* **2013**, *52*, 9266–9270. (c) Wolstenhulme, J. R.; Rosenqvist, J.; Lozano, O.; Ilupeju, J.; Wurz, N.; Engle, K. M.; Pidgeon, G. W.; Moore, P. R.; Sanford, G.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2013**, *52*, 9796–9800. (d) Wolstenhulme, J. R.; Gouverneur, V. *Acc. Chem. Res.* **2014**, *47*, 3560–3570.

(6) (a) Yuan, W.; Szabo, K. J. *Angew. Chem., Int. Ed.* **2015**, *54*, 8533–8537. (b) Nie, J.; Zhu, H.-W.; Cui, H.-F.; Hua, M.-Q.; Ma, J.-A. *Org. Lett.* **2007**, *9*, 3053–3056.

(7) Braun, M.-G.; Katcher, M. H.; Doyle, A. G. *Chem. Sci.* **2013**, *4*, 1216–1220.

(8) Talbot, E. P. A.; Fernandes, T. de A.; McKenna, J. M.; Toste, F. D. *J. Am. Chem. Soc.* **2014**, *126*, 4101–4104.

(9) (a) He, Y.; Yang, Z.; Thornbury, R. T.; Toste, F. D. *J. Am. Chem. Soc.* **2015**, *137*, 12207–12210. (b) Miro, J.; del Pozo, C.; Toste, F. D.; Fustero, S. *Angew. Chem., Int. Ed.* **2016**, *55*, 9045–9049.

(10) (a) Zhu, L.; Chen, H.; Wang, Z.; Li, C. *Org. Chem. Front.* **2014**, *1*, 1299–1305. (b) Wang, H.; Guo, L.-N.; Duan, X.-H. *Chem. Commun.* **2014**, *50*, 7382–7384. (c) Kindt, S.; Heinrich, M. R. *Chem. –Eur. J.* **2014**, *20*, 15344–15348. (d) Guo, R.; Yang, H.; Tang, P. *Chem. Commun.* **2015**, *51*, 8829–8832. (e) Chen, H.; Zhu, L.; Li, C. *Org. Chem. Front.* **2017**, *4*, 565–568.

(11) Yu, W.; Xu, X.-H.; Qing, F.-L. *Adv. Synth. Catal.* **2015**, *357*, 2039–2044.

(12) Differding, E.; Ofner, H. *Synlett* **1991**, 187–189.

(13) (a) Banks, R. E.; Mohialdin-Khaffaf, S. N.; Lal, G. S.; Sharif, I.; Syvret, R. G. *J. Chem. Soc., Chem. Commun.* **1992**, 595–596. (b) Singh, R. P.; Shreeve, J. M. *Acc. Chem. Res.* **2004**, *37*, 31–44. (c) Nyffeler, P. T.; Durón, S. G.; Burkart, M. D.; Vincent, S. P.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2005**, *44*, 192–212.

(14) (a) Clark, A. J. *Chem. Soc. Rev.* **2002**, *31*, 1–11. (b) Severin, K. *Curr. Org. Chem.* **2006**, *10*, 217–224. (c) Pintauer, T. *Eur. J. Inorg. Chem.* **2010**, 2449–2460. (d) Li, C. In *Encyclopedia of Radicals in Chemistry, Biology and Materials*; Chatgilialoglu, C., Studer, A., Eds.; Wiley: Chichester, U. K., 2012; pp 943–964.

(15) Sibi, M. P.; Landais, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 3570–3572.

(16) For seminal works in radical fluorination, see: (a) Rueda-Becerril, M.; Sazepin, C. C.; Leung, J. C. T.; Okbinoglu, T.; Kennepohl, P.; Paquin, J.-F.; Sammis, G. M. *J. Am. Chem. Soc.* **2012**, *134*, 4026–4029. (b) Yin, F.; Wang, Z.; Li, Z.; Li, C. *J. Am. Chem. Soc.* **2012**, *134*, 10401–10404. (c) Liu, W.; Huang, X.; Cheng, M.-J.; Nielsen, R. J.; Goddard, W. A., III; Groves, J. T. *Science* **2012**, *337*, 1322–1325. (d) Barker, T. J.; Boger, D. L. *J. Am. Chem. Soc.* **2012**, *134*, 13588. (e) Bloom, S.; Pitts, C. R.; Miller, D. C.; Haselton, N.; Holl, M. G.; Urheim, E.; Lectka, T. *Angew. Chem., Int. Ed.* **2012**, *51*, 10580–10583.

(17) (a) Liu, W.; Groves, J. T. *Angew. Chem., Int. Ed.* **2013**, *52*, 6024–6027. (b) Huang, X.; Liu, W.; Ren, H.; Neelamegam, R.; Hooker, J. M.; Groves, J. T. *J. Am. Chem. Soc.* **2014**, *136*, 6842–6845. (c) Huang, X.; Liu, W.; Hooker, J. M.; Groves, J. T. *Angew. Chem., Int. Ed.* **2015**, *54*, 5241–5245. (d) Liu, W.; Huang, X.; Placzek, M.; Krska, S. W.; McQuade, P.; Hooker, J. M.; Groves, J. T. *Chem. Sci.* **2018**, *9*, 1168–1172. (e) Li, G.; Dilger, A. K.; Cheng, P. T.; Ewing, W. R.; Groves, J. T. *Angew. Chem., Int. Ed.* **2018**, *57*, 1251–1255.

(18) Zhang, Q.-W.; Brusoe, A. T.; Mascitti, V.; Hesp, K. D.; Blakemore, D. C.; Kohrt, J. T.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2016**, *55*, 9758–9762.

(19) Fier, P. S.; Hartwig, J. F. *Science* **2013**, *342*, 956–960.

(20) (a) Li, Z.; Song, L.; Li, C. *J. Am. Chem. Soc.* **2013**, *135*, 4640–4643. (b) Zhang, C.; Li, Z.; Zhu, L.; Yu, L.; Wang, Z.; Li, C. *J. Am. Chem. Soc.* **2013**, *135*, 14082–14085. (c) Li, Z.; Wang, Z.; Zhu, L.; Tan, X.; Li, C. *J. Am. Chem. Soc.* **2014**, *136*, 16439–16443. (d) Dong, Y.; Wang, Z.; Li, C. *Nat. Commun.* **2017**, *8*, 277.

(21) For a different view on the mechanism of silver-catalyzed fluorodecarboxylation with Selectfluor, see: Patel, N. R.; Flowers, R. A., II *J. Org. Chem.* **2015**, *80*, 5834–5841.

(22) Nishikata et al. reported the copper-catalyzed fluorination of α-bromo-*N*-arylamides with CsF. However, this method is not applicable to ordinary tertiary alkyl halides and the mechanism of fluorination remains unclear. See: (a) Nishikata, T.; Ishida, S.; Fujimoto, R. *Angew. Chem., Int. Ed.* **2016**, *55*, 10008–10012. (b) Ishida, S.; Takeuchi, K.; Taniyama, N.; Sunada, Y.; Nishikata, T. *Angew. Chem., Int. Ed.* **2017**, *56*, 11610–11614. (c) Dang, H.; Mailig, M.; Lalic, G. *Angew. Chem., Int. Ed.* **2014**, *53*, 6473–6476.

(23) Kharasch, M. S.; Jenson, E. V.; Urry, W. H. *Science* **1945**, *102*, 128.

(24) Chen, H.; Liu, Z.; Lv, Y.; Tan, X.; Shen, H.; Yu, H.-Z.; Li, C. *Angew. Chem., Int. Ed.* **2017**, *56*, 15411–15415.

(25) Gregorcic, A.; Zupan, M. *J. Org. Chem.* **1979**, *44*, 4120–4122.

(26) Umemoto, T.; Ishihara, S. *J. Am. Chem. Soc.* **1993**, *115*, 2156 - 2164.

(27) For similar discussions, see: (a) Paria, S.; Reiser, O. *ChemCatChem* **2014**, *6*, 2477–2483. (b) Kainz, Q. M.; Matier, C. D.; Bartoszewicz, A.; Zultanski, S. L.; Peters, J. C.; Fu, G. C. *Science* **2016**, *351*, 681–684.

(28) Xia, J.-B.; Zhu, C.; Chen, C. *J. Am. Chem. Soc.* **2013**, *135*, 17494–17500.

(29) Lee, S. C.; Holm, R. H. *Inorg. Chem.* **1993**, *32*, 4745–4753.

(30) Jiang, Y.; Yu, H.; Fu, Y.; Liu, L. *Sci. China Chem.* **2015**, *58*, 673–683.

(31) The possibility of the FAT between alkyl radical and mononuclear copper complex (i.e., Cu(**L3**)F_2) was also examined. However, our calculations indicated that the H-abstraction to form HF and an alkene is more likely to take place. See the SI for details.

(32) For related examples, see: (a) Ahn, J. M.; Peters, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **2017**, *139*, 18101–18106. (b) Matier, C. D.; Schwaben, J.; Peters, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **2017**, *139*, 17707–17710. (c) Ahn, J. M.; Ratani, T. S.; Hannoun, K. I.; Fu, G. C.; Peters, J. C. *J. Am. Chem. Soc.* **2017**, *139*, 12716–12723. (d) Zhao, W.; Wurz, R. P.; Peters, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **2017**, *139*, 12153–12156. (e) Shen, H.; Liu, Z.; Zhang, P.; Tan. X.; Zhang, Z.; Li, C. *J. Am. Chem. Soc.* **2017**, *139*, 9843–9846.

SYNOPSIS TOC