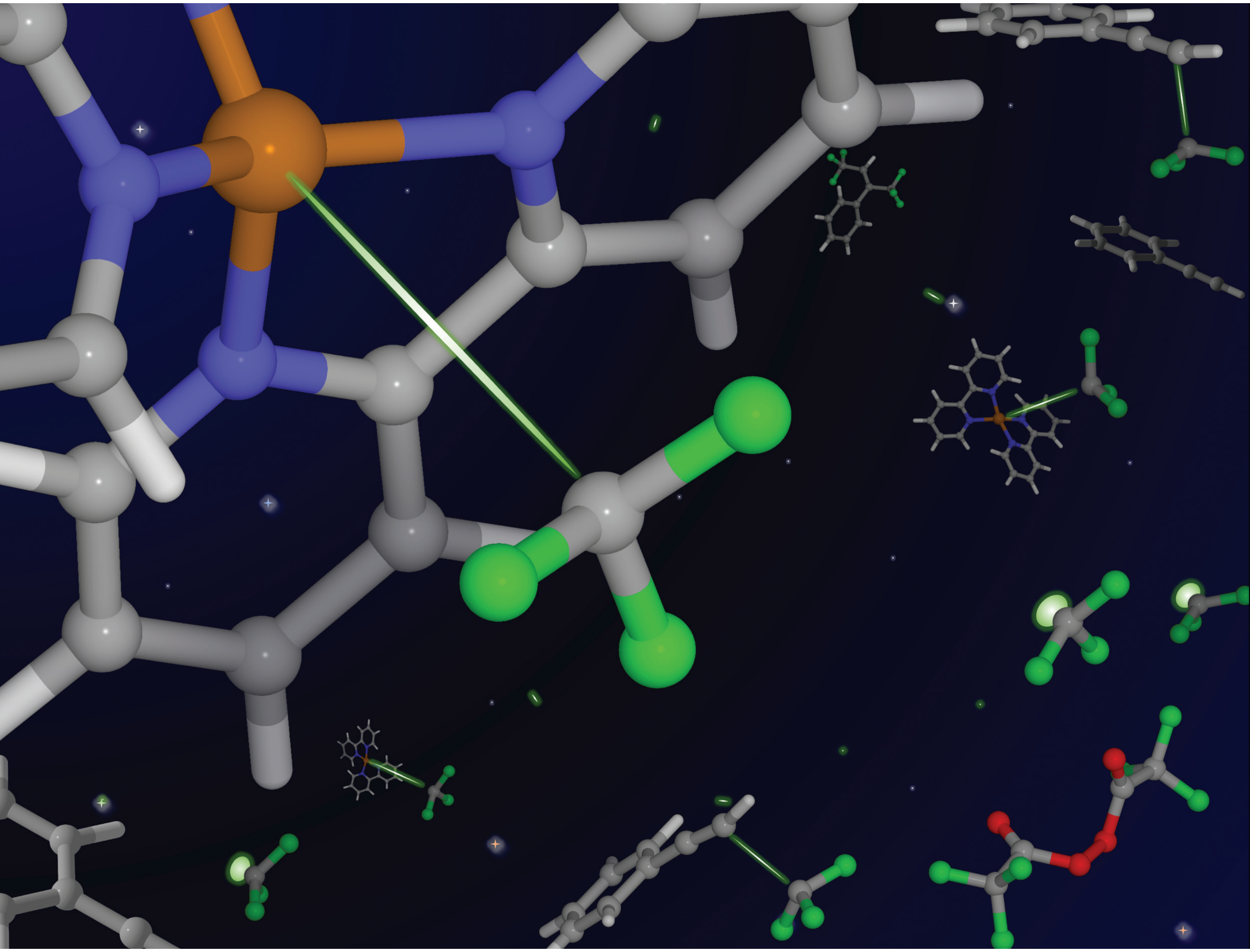
Volume 19
Number 42
14 November 2021
Pages 9085-9328

Organic & Biomolecular Chemistry

rsc.li/obc



ISSN 1477-0520

ROYAL SOCIETY OF **CHEMISTRY**

COMMUNICATION
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Organic & Biomolecular Chemistry

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: Org. Biomol. Chem., 2021, 19, 9148

Received 4th August 2021, Accepted 28th August 2021

DOI: 10.1039/d1ob01529j

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1,2-Bis-perfluoroalkylations of alkenes and alkynes with perfluorocarboxylic anhydrides *via* the formation of perfluoroalkylcopper intermediates†

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A novel, Cu-mediated protocol toward the 1,2-bis-perfluoroalkylation of alkenes/alkynes was developed. The method proceeded with perfluorocarboxylic anhydrides as inexpensive and readily available perfluoroalkyl sources. Diacyl peroxide was generated *in situ* from the perfluorocarboxylic anhydrides and H_2O_2. The key step in this reaction is the formation of a stable perfluoroalkylcopper intermediate that is achieved with the aid of a bipyridyl ligand. Subsequent reaction of the intermediate with perfluoroalkyl-containing alkyl or vinyl radicals affords the desired products.

Introduction

Perfluoroalkyl-containing organic molecules are of interest as pharmaceuticals[1] and organic functional materials[2] because of their improved physical, chemical, and biological properties derived from their fluorine atoms. Among perfluoroalkyl molecules, alkanes and alkenes bearing two perfluoroalkyl groups on their vicinal carbons are expected to exhibit unique functions;[3] thus methods toward the 1,2-bis-perfluoroalkyaltion of alkenes and alkynes have been actively studied for nearly 50 years.[4–12] Recently, various 1,2-bis-trifluoromethylations have been reported due to the availability of sophisticated trifluoromethylating reagents such as Langlois,[8] Umemoto,[9] and Togni[10] reagents, and trifluoromethylcopper complexes.[11,12] However, such reagents for 1,2-bis-perfluoroalkylations are not as accessible. Thus, to the best of our knowledge, novel 1,2-bis-perfluoroalkylations that can introduce long perfluoroalkyl chains have not been reported in the last two decades, and the substrate scopes of these processes are still very limited.[6a,d,f]

In an attempt to remedy this disadvantage of perfluoroalkylation reactions, our group has been investigating the use of perfluorocarboxylic anhydrides as inexpensive and readily available perfluoroalkyl sources for these processes.[13,14] We have realised the efficient radical perfluoroalkylation of alkenes by the *in situ* generation of diacyl peroxides from the reaction of the acid anhydrides and urea·H_2O_2 (Scheme 1a). The key step in successfully conducting these reactions was the taming of a highly reactive alkyl radical intermediate containing a perfluoroalkyl group, which was transformed into the corresponding carbocation by single-electron transfer (SET) with a Cu(II) species. As part of our interest in perfluoroalkylations driven by perfluorocarboxylic anhydrides, we envisaged a novel protocol for the 1,2-bis-perfluoroalkylation of alkenes and alkynes using perfluorocarboxylic anhydrides (Scheme 1b), which is described herein.

According to recent literature,[9–12] a similar process, 1,2-bis-trifluoromethylation, requires not only electrophilic CF_3 reagents but also CF_3 nucleophiles or CF_3–Cu(II) coupling partners to introduce a second CF_3 group. In 2019, Han and Lee achieved the 1,2-bis-trifluoromethylation of alkenes using the Umemoto reagent and CF_3SiMe_3 as the electrophilic and nucleophilic reagents, respectively, in the presence of a copper catalyst and a stoichiometric amount of silver fluoride.[9] Zhu and Li performed the 1,2-bis-trifluoromethylation of alkynes using the Togni reagent and (bpy)Zn$(CF_3)_2$ (bpy = 2,2′-bipyridine) with a copper catalyst in 2020.[10] Tsui developed a protocol for the 1,2-bis-trifluoromethylation of arynes with Cu(I)CF_3 in the presence of an oxidant to afford unique 1,2-bis-trifluoromethylarenes.[11] In this reaction, a CF_3–Cu(II) intermediate was postulated to be formed and was thought to be responsible for the formation of CF_3-containing aryl radicals; a second equivalent of CF_3–Cu(II) then reacts with these radicals and affords the products. Cook developed an elegant method for the 1,2-bis-trifluoromethylation of terminal alkynes with

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†Electronic supplementary information (ESI) available: Supplementary data, experimental procedures, NMR spectra, computational details. See DOI: 10.1039/d1ob01529j

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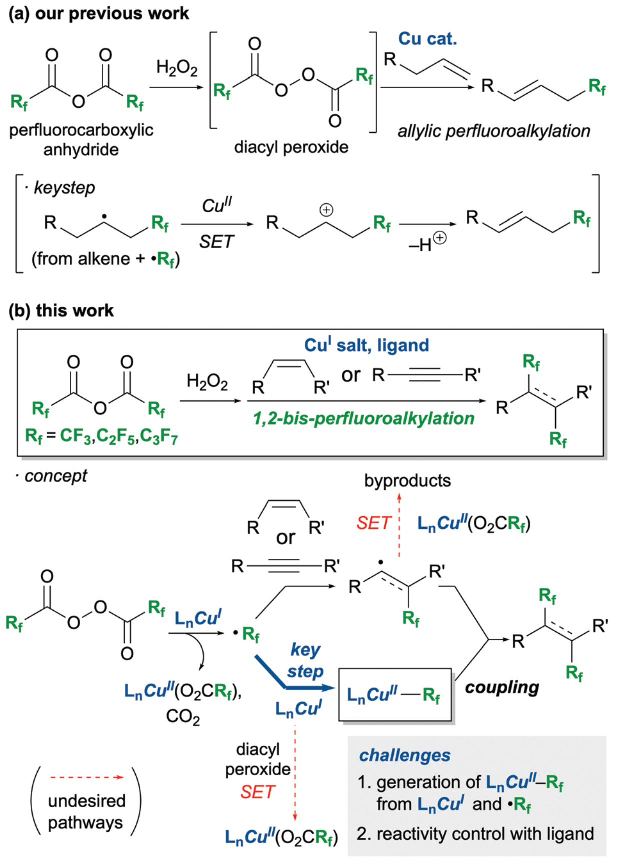


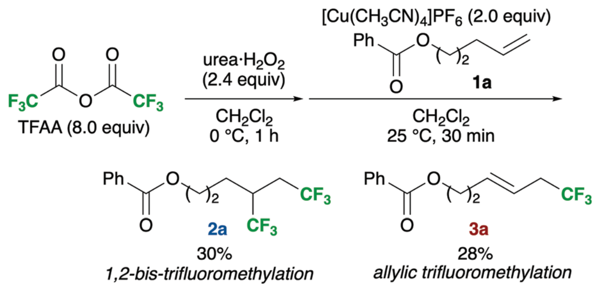
Scheme 1 Perfluoroalkylation by using perfluorocarboxylic anhydrides (a) previous work (b) this work.

(bpy)Cu(III)(CF_3)$_3$, where the photolysis of the latter simultaneously generated a CF_3 radical and a CF_3–Cu(II) intermediate.[12] Inspired by these previous works, we designed a methodology for the Cu-mediated 1,2-bis-perfluoroalkylation of alkenes and alkynes with perfluorodiacyl peroxides. This unprecedented approach involves the generation of a perfluoroalkylcopper(II) intermediate (R_f–Cu(II)) that occurs through the capturing of perfluoroalkyl radicals with a Cu(I) salt (Scheme 1b, concept).[15] However, there are a few, formidable challenges to this approach. First, the same Cu(I) species must contribute to two different processes simultaneously: the formation of perfluoroalkyl radicals with diacyl peroxide by SET and the formation of the R_f–Cu(II) intermediate through the capturing of the perfluoroalkyl radical. The second disadvantage of the proposed method is that the concentration balance between the R_f–Cu(II) and alkyl/vinyl radical intermediates, generated from perfluoroalkyl radicals reacting with the alkene/alkyne, must be precisely tuned to introduce a second perfluoroalkyl group. This balance is required because in the absence of the R_f–Cu(II) intermediate the alkyl/vinyl radicals, which are highly reactive, can participate in undesirable side reactions. To solve these issues, we envisioned the use of a ligand to control the reactivity and stability of the copper species.

Results and discussion

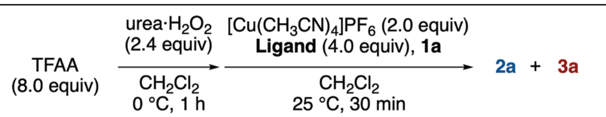
We preliminarily examined a model reaction of alkene **1a** with trifluoroacetic anhydride (TFAA)/urea·H_2O_2 in the presence of 2.0 equiv. of [Cu(CH_3CN)$_4$]PF_6 (Scheme 2). The desired product (**2a**) was obtained in 30% yield; however, it was accompanied by the formation of allylic trifluoromethylation product **3a**,[13a] which was obtained in almost the same yield (28%). Next, the ligands of the Cu salt were screened to alter the reactivity of the complex (Table 1; see also Table S1 in ESI†). As a result, bipyridyl-type ligands were found to enhance the selectivity and yield of **2a** (entries 2–4). Among them, bpy gave the best results (entry 2). In contrast, reactions employing pyridine or aliphatic, multidentate amine ligands preferentially provided **3a** (entries 1, 5, and 6), whereas those conducted with phosphine ligands suppressed the reaction (entries 7 and 8).

With the optimal conditions (Table 1, entry 2) in hand, the substrate scope was then investigated, as shown in Scheme 3.[16,17] The functional group tolerance was confirmed by the reaction of several alkenes, which afforded the desired products bearing esters (**2a,b**), ketones (**2c**), phthalimides (**2d**),



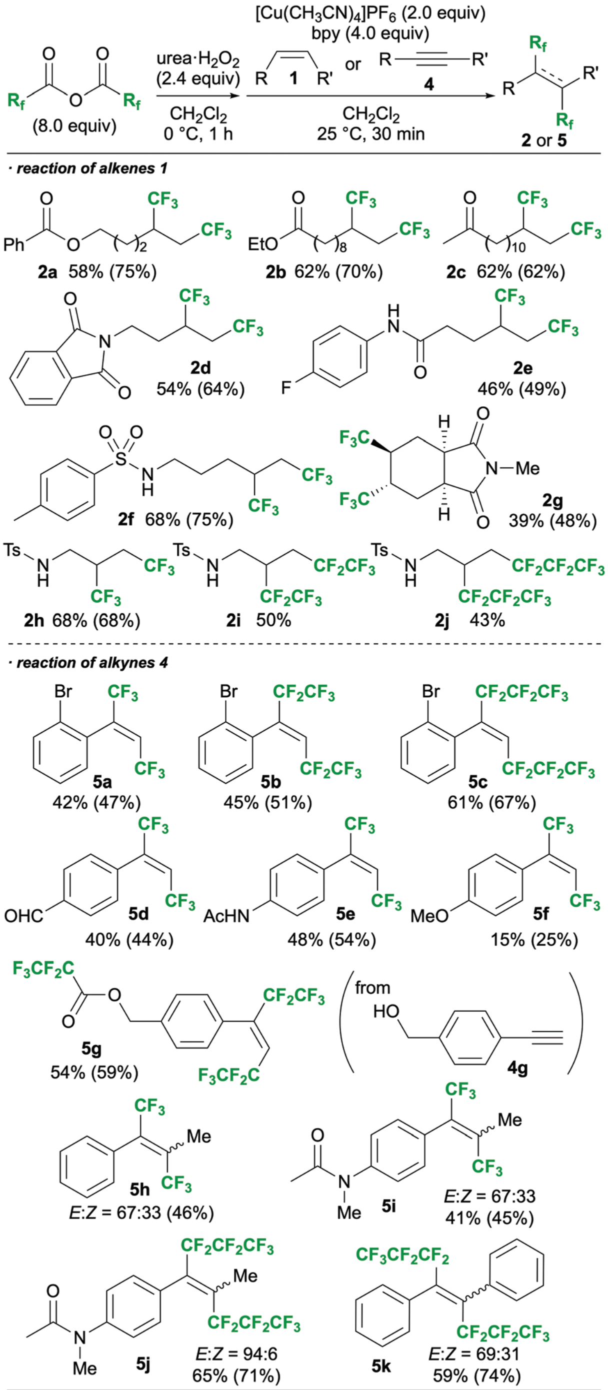
Scheme 2 A preliminary result of the reaction using a simple Cu(I) salt.

Table 1 Ligand screening for the proposed method[a]



Entry	Ligand[b]	Yield[c] (%) 2a	3a (*E*/*Z*)	2a : 3a
1	Pyridine (8 equiv.)	2	27 (90/10)	7/93
2	2,2′-Bipyridine (bpy)	75[d]	4 (91/9)	94/6
3	4,4′-Dimethyl-2,2′-bipyridine	64	7 (91/9)	90/10
4	1,10-Phenanthroline	51	1 (n.d.)	98/2
5	TMEDA	5	36 (88/12)	12/88
6	PMDTA[e]	1	5 (88/12)	17/83
7	PPh_3 (8.0 equiv.)	n.d.	n.d.	—
8	DPPE	n.d.	n.d.	—

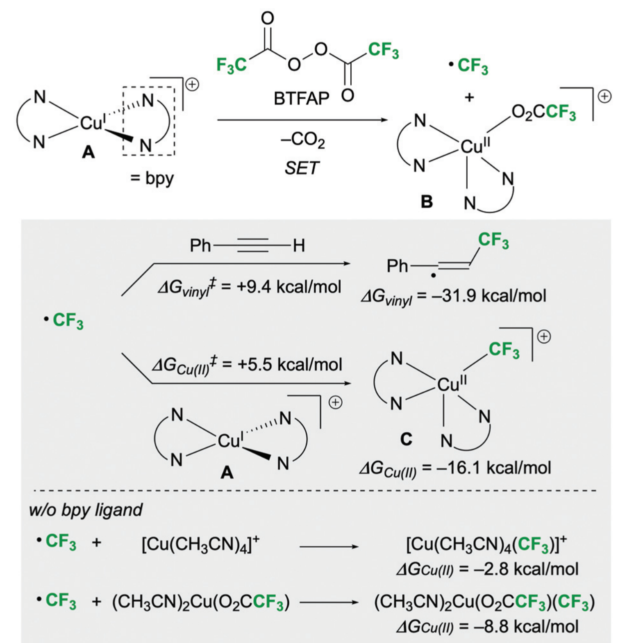
[a] Run on a 0.2 mmol scale. [b] 4.0 equiv. of ligand were used unless otherwise noted. [c] The yields were determined by NMR analysis. [d] Isolated yield was 58% yield. [e] PMDTA = *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine.



Scheme 3 Substrate scope of the proposed method (NMR yields are shown in parentheses).

amides (**2e**), and sulphonamides (**2f**). A cyclic internal alkene could also be employed in the reaction, and the corresponding product (**2g**) was obtained. *N*-Tosyl allylamine, which was found to induce intramolecular amino- and carbo-trifluoromethylations in our previous work,[13b] successfully provided the 1,2-bis-trifluoromethylated product **2h** in the present study. Perfluorocarboxylic anhydrides bearing longer alkyl chains were also employed in place of TFAA, providing the corresponding 1,2-bis-perfluoroalkylated molecules **2i** and **2j**. In addition, the reactions of terminal alkynes (**4**) smoothly proceeded to give 1,2-bis-perfluoroalkylated alkenes **5a–g** with complete *E*-selectivity. The reaction also showed sufficient reactivity toward internal alkynes, affording the corresponding tetrasubstituted alkenes (**5h–5k**). To the best of our knowledge, the only other example of a 1,2-bis-perfluoroalkylation of an internal alkyne is that of arynes reported by Tsui's group.[11] In all cases of the present study, *E*-selectivity was preferred; however, both the type of perfluoroalkyl group and the substituents on the triple bond of the alkyne were found to affect the stereoselectivity.

Finally, the reaction mechanism was investigated using the 1,2-bis-trifluoromethylation of alkynes as a model reaction. We assumed that a stable, cationic copper(I) complex ligating two bpy ligands (**A**) is formed under the optimal conditions.[18,19] At the beginning of the reaction, SET between bis(trifluoroacetyl) peroxide (BTFAP) and **A** generates a CF_3 radical and $[(bpy)_2Cu(O_2CCF_3)]^+$ (**B**) (Scheme 4).[13,20] The CF_3 radicals react with the alkyne to afford a vinyl radical intermediate.[21] Simultaneously, $[(bpy)_2Cu(II)CF_3]^+$ (**C**) can be formed by the reaction of a CF_3 radical with **A**. The free energies of activation obtained by density functional theory (DFT) calculations (M06$_{(CPCM = DCM)}$/6-311+G(d,p), SDD for Cu) indicated that the capturing of CF_3 radicals by **A** is kinetically preferable to vinyl radical formation ($\Delta G^{\ddagger}_{Cu(II)}$ = +5.5 kcal mol^{-1} *vs.* $\Delta G^{\ddagger}_{vinyl}$ = +9.4 kcal mol^{-1}). Furthermore, the bpy ligand was found to remarkably stabilize intermediate **C**; the free energy change for the formation of intermediate **C** ($\Delta G_{Cu(II)}$) was −16.1 kcal mol^{-1}, whereas the free energy changes for the formation of bpy-free Cu(II)–CF_3

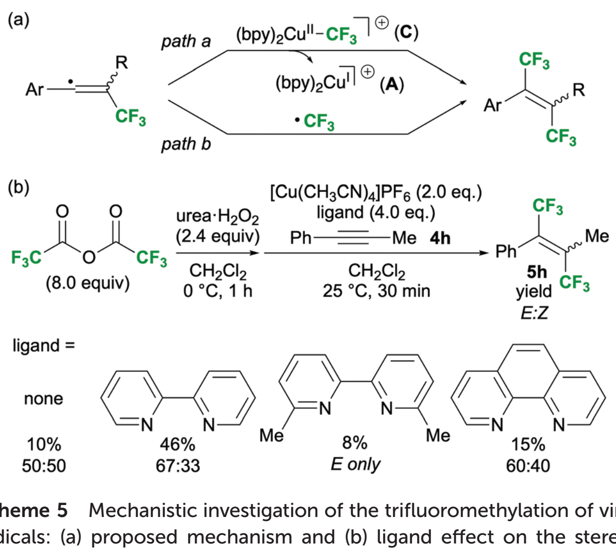


Scheme 4 Proposed pathways of the formations of CF_3–Cu(II) species with CF_3 radicals.

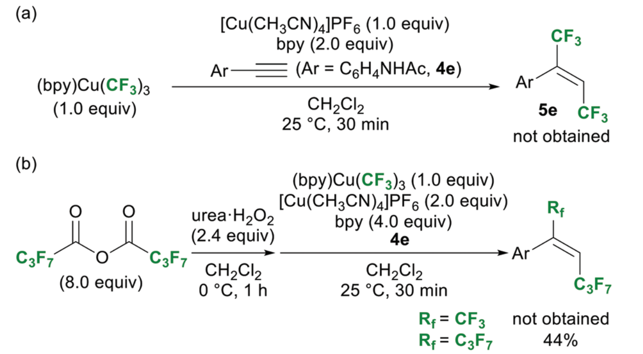
complexes $[Cu(CH_3CN)_4(CF_3)]^+$ and $(CH_3CN)_2Cu(O_2CCF_3)(CF_3)$ ($\Delta G_{Cu(II)}$) were −2.8 and −8.8 kcal mol^{-1}, respectively.[19] The reversibility of this step would lead to an imbalance between the concentrations of the vinyl radical and the Cu(II)–CF_3 species, which is due to the high thermodynamic stability of the former ($\Delta G^{\ddagger}_{vinyl}$ = −31.9 kcal mol^{-1}). Thus, bpy was considered to play a crucial role in controlling the selectivity of the reaction by stabilising intermediate **C** and suppressing this reverse reaction.

The trifluoromethylation of the vinyl radical was then evaluated and two possible pathways were proposed (Scheme 5a). If SET between Cu(I) intermediate **A** and the diacyl peroxide is the dominant process over the formation of CF_3–Cu(II) intermediate **C**, the double addition of two CF_3 radicals to the triple bond (*path b*) might proceed instead of a coupling process (*path a*).[6,8,22] Further, when the reaction proceeds *via path b*, the stereoselectivity outcome would only depend on the substrate structure. We observed that bipyridyl-type ligands such as bpy, 6,6′-dimethyl-2,2′-bipyridine, and 1,10-phenanthroline increased the *E*-selectivity of the reaction of internal alkyne **4h** (Scheme 5b). In particular, sterically demanding 6,6′-dimethyl-2,2′-bipyridine greatly increased the *E*-selectivity but decreased the product yield. This result confirms that *path a* involving CF_3–Cu(II) intermediate **C** is the predominant pathway.

Several attempts were made to detect the CF_3–Cu(II) species *via* spectroscopic analyses of the reaction mixture, but all attempts failed. On the other hand, the ^{19}F NMR analysis of the crude mixture after workup suggested the formation of (bpy)Cu$(CF_3)_3$, although its yield (as determined by ^{19}F NMR analysis) was only 5%.[23] This result strongly suggests the formation of CF_3–Cu species during the reaction. To evaluate the reactivity of (bpy)Cu$(CF_3)_3$ under the optimal conditions (Table 1, entry 2), it was used as the reagent instead of a diacyl peroxide; however, no reactivity was observed (Scheme 6a). In addition, the reaction with heptafluorobutyric anhydride in



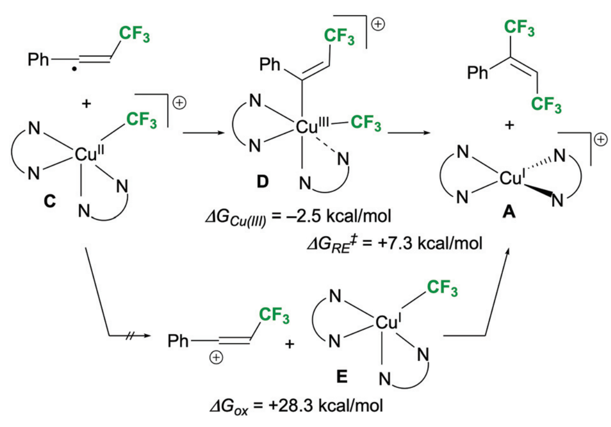
Scheme 5 Mechanistic investigation of the trifluoromethylation of vinyl radicals: (a) proposed mechanism and (b) ligand effect on the stereoselectivity outcome.



Scheme 6 Examination of the reactivity of (bpy)Cu$(CF_3)_3$ under the optimal conditions (Table 1, entry 2).

the presence of (bpy)Cu$(CF_3)_3$ gave only the 1,2-bis-heptafluoropropylation product, proving that (bpy)Cu$(CF_3)_3$ did not participate in the reaction (Scheme 6b). Stable (bpy)Cu$(CF_3)_3$ was concluded to be a terminal by-product derived from the reactive CF_3–Cu(II) intermediate (**C**).[19]

Next, the pathway for the reaction of vinyl radicals with **C** is discussed. Cook *et al.* proposed that their photo-induced 1,2-bis-trifluoromethylation of alkynes with (bpy)Cu$(CF_3)_3$ proceeds through the capturing of a vinyl radical with (bpy)(L)Cu(II)–CF_3 (L = CF_3 or OSO_3H) and subsequent reductive elimination.[12] Thus, as described above, we hypothesized that the coupling process in the present study proceeds in a similar manner: the capturing of the vinyl radical with intermediate **C**, followed by reductive elimination of Cu(III) intermediate **D** (Scheme 7, upper arrow).[24] In addition to this, we also considered another possible mechanism involving SET between the vinyl radical and intermediate **C**, in which the resulting vinyl cation and CF_3–Cu(I) intermediate **E** react *via* nucleophilic addition to give the desired product (Scheme 7, lower arrow).[9] The sufficiently small free energy change obtained by DFT calculations suggested that Cu(III) intermediate **D** is formed by the reaction of **C** with the vinyl radical ($\Delta G_{Cu(III)}$ = −2.5 kcal mol^{-1}), which is followed by reductive elimination



Scheme 7 Possible pathways of the reaction between the vinyl radical and $[(bpy)_2Cu(II)CF_3]^+$ (**C**).

($\Delta G^{\ddagger}_{RE}$ = +7.3 kcal mol^{-1}). Notably, in the second trifluoromethylation step, no positive effects were induced by bpy on the stability of **D** and on the rate of the reductive elimination.[19] On the other hand, the free energy change for vinyl cation formation by SET (ΔG_{ox}) was +28.3 kcal mol^{-1}, suggesting that this process is either very slow or could not proceed.[19]

Conclusions

We have achieved the Cu-mediated 1,2-bis-perfluoroalkylation of alkenes/alkynes using perfluorocarboxylic anhydrides as inexpensive and readily available perfluoroalkyl sources. The addition of the bpy ligand to the Cu salt dramatically improved the yields of the desired products, which allowed us to obtain various 1,2-bis-perfluoroalkylated molecules (**2** and **5**), including unique tetrasubstituted alkenes (**5h–5k**). In this study, we demonstrated an unprecedented approach for generating a key species in perfluoroalkylation, an R_f–Cu(II) intermediate (**C** for $R_f = CF_3$), by the reaction of perfluoroalkyl radicals with a Cu(I) intermediate (**A**). This efficiently introduced a second R_f group onto the perfluoroalkyl-containing alkyl or vinyl radical *via* a Cu(III) intermediate (**D** for $R_f = CF_3$). DFT studies proved that bpy ligands play a crucial role in stabilising R_f–Cu(II) intermediate (**C** for $R_f = CF_3$), allowing for an efficient and selective transformation. We believe that this method is useful for the practical synthesis of 1,2-bis-perfluoroalkylated compounds and will contribute to the development of new bioactive molecules and functional materials. In addition, this methodology can control radical species with copper, which is a process that will contribute to future, new reaction designs.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported by JSPS KAKENHI (No. 21K06489) and the project funding provided by RIKEN. TT is grateful to the SPDR Program in RIKEN. The computational study was conducted on HOKUSAI-GW (RIKEN).

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21 Radical trapping using TEMPO as the additive suggested the formation of vinyl radicals, where the TEMPO adduct of the vinyl radical was detected by ESI-MS analysis. See Scheme S1 in the ESI.†

22 The thermal fragmentation of the diacyl peroxide can generate a CF_3 radical. However, heating the reaction mixture in the absence of the copper salt at a higher temperature (60 °C) did not give **2a**. In addition, reducing the equivalents of $[Cu(CH_3CN)_4]PF_6$ from 2.0 to 1.0 resulted in a significant decrease in yield and selectivity.

23 The complex was identified by comparing the intensities and coupling patterns of the ^{19}F NMR signals from the CF_3 groups at the apical and equatorial positions with those in the literature (see Fig. S1 in ESI):† (*a*) A. M. Romine, N. Nebra, A. I. Konovalov, E. Martin, J. Benet-Buchholz and V. V. Grushin, *Angew. Chem., Int. Ed.*, 2015, **54**, 2745; (*b*) N. Nebra and V. V. Grushin, *J. Am. Chem. Soc.*, 2014, **136**, 16998.

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