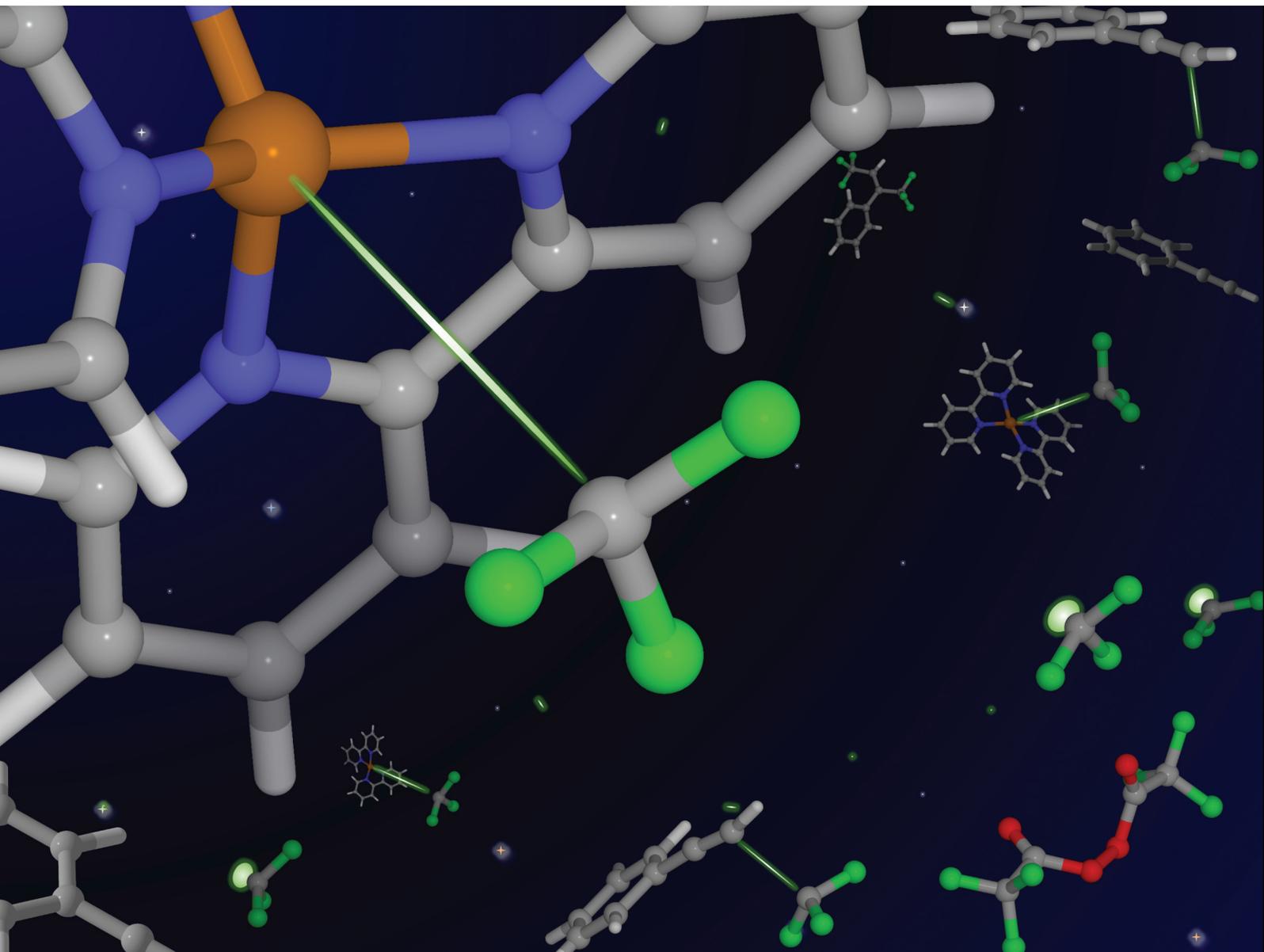


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1,2-Bis-perfluoroalkylations of alkenes and alkynes with perfluorocarboxylic anhydrides *via* the formation of perfluoroalkylcopper intermediates†

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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 H₂O₂. 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 pharmaceuticals¹ and organic functional materials² 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-perfluoroalkylation 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 Togni¹⁰ 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-H₂O₂ (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 CF₃ reagents but also CF₃ nucleophiles or CF₃-Cu(II) coupling partners to introduce a second CF₃ group. In 2019, Han and Lee achieved the 1,2-bis-trifluoromethylation of alkenes using the Umemoto reagent and CF₃SiMe₃ 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(CF₃)₂ (bpy = 2,2'-bipyridine) with a copper catalyst in 2020.¹⁰ Tsui developed a protocol for the 1,2-bis-trifluoromethylation of alkynes with Cu(I)CF₃ in the presence of an oxidant to afford unique 1,2-bis-trifluoromethylarenes.¹¹ In this reaction, a CF₃-Cu(II) intermediate was postulated to be formed and was thought to be responsible for the formation of CF₃-containing aryl radicals; a second equivalent of CF₃-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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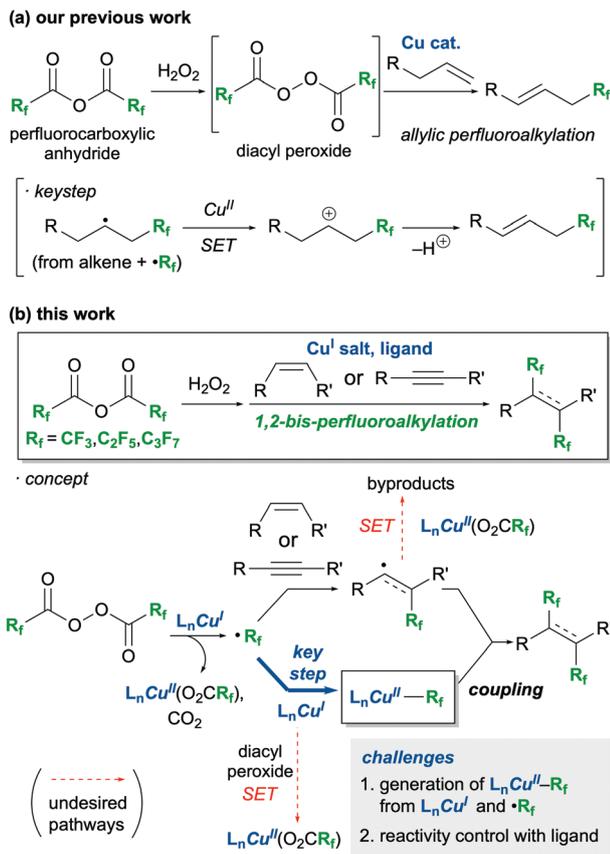
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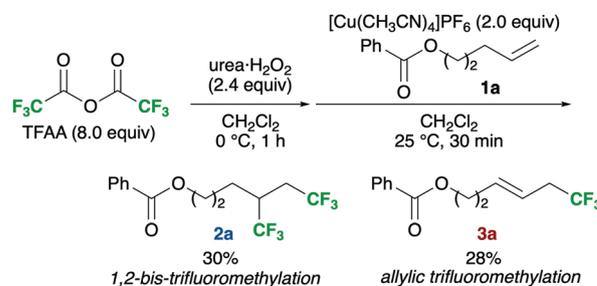
Scheme 1 Perfluoroalkylation by using perfluorocarboxylic anhydrides (a) previous work (b) this work.

(bpy)Cu(II)(CF₃)₃, where the photolysis of the latter simultaneously generated a CF₃ radical and a CF₃-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-H₂O₂ in the presence of 2.0 equiv. of [Cu(CH₃CN)₄]PF₆ (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**),



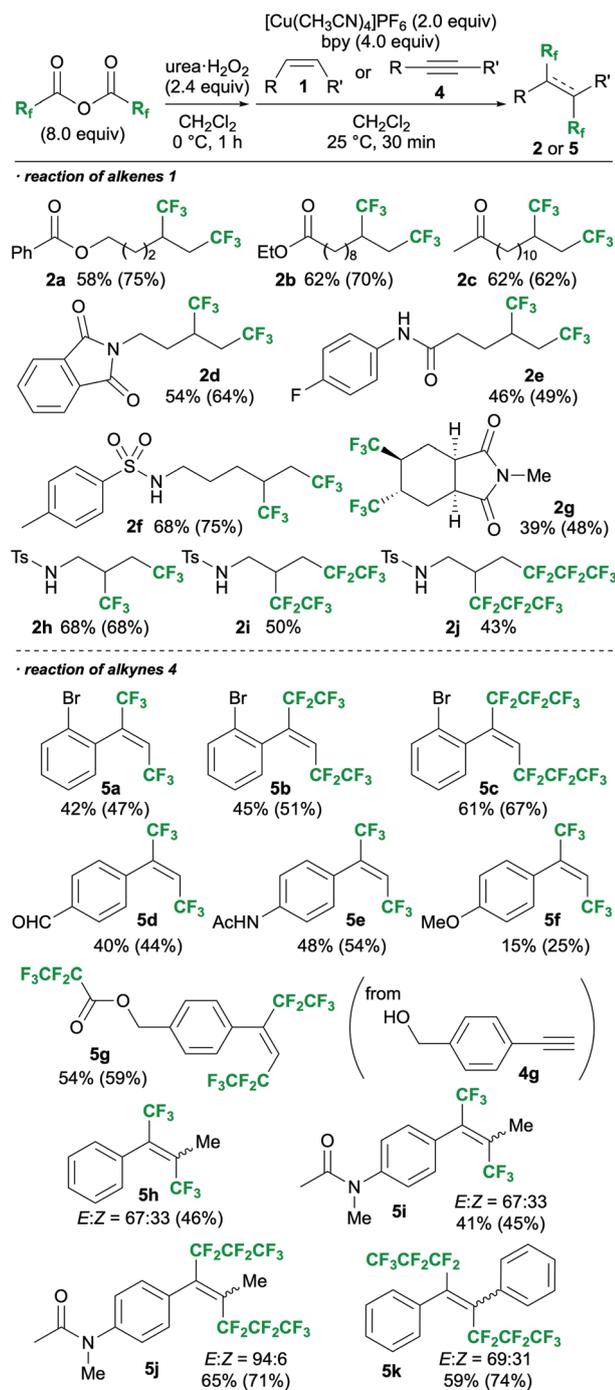
Scheme 2 A preliminary result of the reaction using a simple Cu(I) salt.

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.



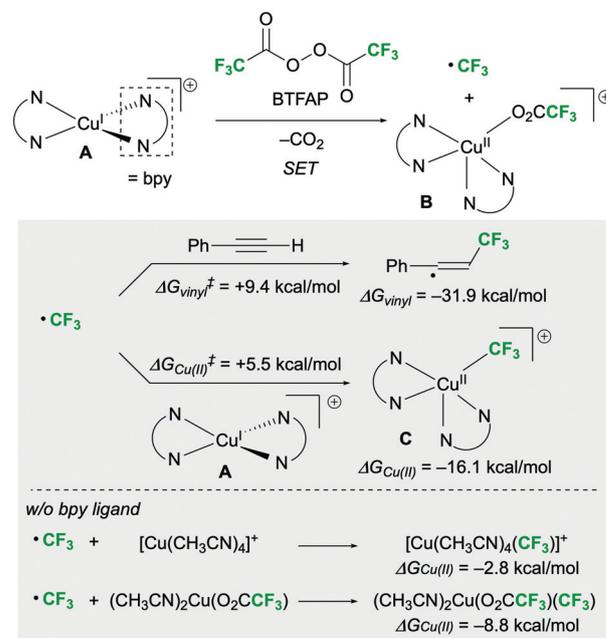


Scheme 3 Substrate scope of the proposed method (NMR yields are shown in parentheses).

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 (BTFAA) and A generates a CF₃ radical and [(bpy)₂Cu(O₂CCF₃)]⁺ (B) (Scheme 4).^{13,20} The CF₃ radicals react with the alkyne to afford a vinyl radical intermediate.²¹ Simultaneously, [(bpy)₂Cu(II)CF₃]⁺ (C) can be formed by the reaction of a CF₃ 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 CF₃ radicals by A is kinetically preferable to vinyl radical formation ($\Delta G_{\text{Cu(II)}}^{\ddagger} = +5.5 \text{ kcal mol}^{-1}$ vs. $\Delta G_{\text{vinyl}}^{\ddagger} = +9.4 \text{ kcal mol}^{-1}$). Furthermore, the bpy ligand was found to remarkably stabilize intermediate C; the free energy change for the formation of intermediate C ($\Delta G_{\text{Cu(II)}}$) was $-16.1 \text{ kcal mol}^{-1}$, whereas the free energy changes for the formation of bpy-free Cu(II)–CF₃



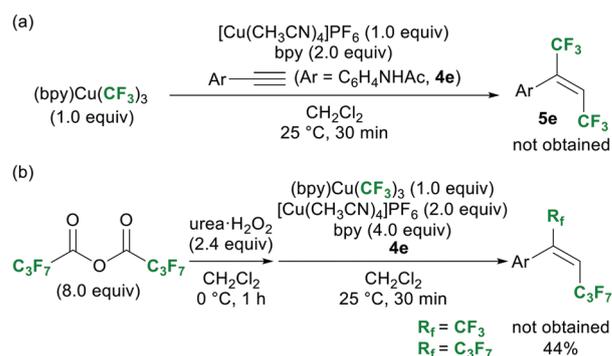
Scheme 4 Proposed pathways of the formations of CF₃–Cu(II) species with CF₃ radicals.



complexes $[\text{Cu}(\text{CH}_3\text{CN})_4(\text{CF}_3)]^+$ and $(\text{CH}_3\text{CN})_2\text{Cu}(\text{O}_2\text{CCF}_3)(\text{CF}_3)$ ($\Delta G_{\text{Cu(II)}}$) 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)-CF₃ species, which is due to the high thermodynamic stability of the former ($\Delta G_{\text{vinyl}}^\ddagger = -31.9$ 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 CF₃-Cu(II) intermediate C, the double addition of two CF₃ 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 CF₃-Cu(II) intermediate C is the predominant pathway.

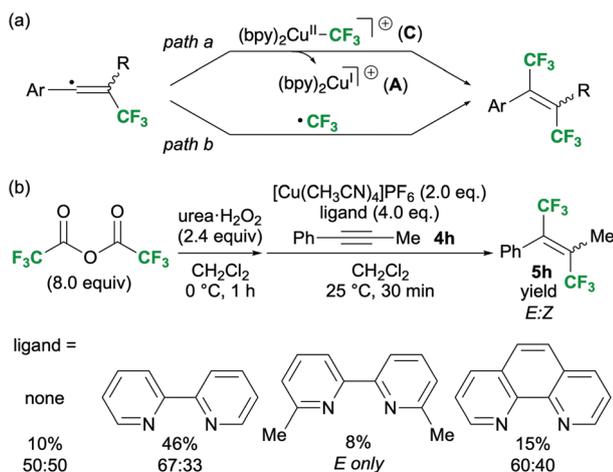
Several attempts were made to detect the CF₃-Cu(II) species *via* spectroscopic analyses of the reaction mixture, but all attempts failed. On the other hand, the ¹⁹F NMR analysis of the crude mixture after workup suggested the formation of (bpy)Cu(CF₃)₃, although its yield (as determined by ¹⁹F NMR analysis) was only 5%.²³ This result strongly suggests the formation of CF₃-Cu species during the reaction. To evaluate the reactivity of (bpy)Cu(CF₃)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



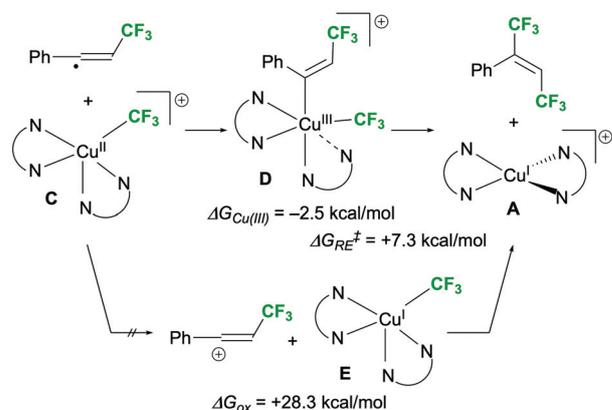
Scheme 6 Examination of the reactivity of (bpy)Cu(CF₃)₃ under the optimal conditions (Table 1, entry 2).

the presence of (bpy)Cu(CF₃)₃ gave only the 1,2-bis-heptafluoropropylation product, proving that (bpy)Cu(CF₃)₃ did not participate in the reaction (Scheme 6b). Stable (bpy)Cu(CF₃)₃ was concluded to be a terminal by-product derived from the reactive CF₃-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(CF₃)₃ proceeds through the capturing of a vinyl radical with (bpy)(L)Cu(II)-CF₃ (L = CF₃ or OSO₃H) 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 CF₃-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 ($\Delta G_{\text{Cu(III)}} = -2.5$ kcal mol $^{-1}$), which is followed by reductive elimination



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



Scheme 7 Possible pathways of the reaction between the vinyl radical and $[(\text{bpy})_2\text{Cu(II)CF}_3]^+$ (C).



($\Delta G_{\text{RE}}^{\ddagger} = +7.3 \text{ kcal mol}^{-1}$). 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 $+28.3 \text{ kcal mol}^{-1}$, 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 $\text{R}_f\text{-Cu(II)}$ intermediate (C for $\text{R}_f = \text{CF}_3$), 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 $\text{R}_f = \text{CF}_3$). DFT studies proved that bpy ligands play a crucial role in stabilising $\text{R}_f\text{-Cu(II)}$ intermediate (C for $\text{R}_f = \text{CF}_3$), 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

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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 CF₃ 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(CH₃CN)₄]PF₆ 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 ¹⁹F NMR signals from the CF₃ 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.
- 24 S. Liu, H. Liu, S. Liu, Z. Liu, C. Lu, X. Leng, Y. Lan and Q. Shen, *J. Am. Chem. Soc.*, 2020, **142**, 9785.

