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COMMUNICATION

Difluoromethylene Insertion into Fluoroalkyl Copper Complexes: Elongation of the Perfluoroalkyl Bridge

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Herein, we report the insertion of a difluoromethylene into 1,1,2,2-tetrafluoro-2-arylethyl copper complexes to synthesize extended perfluoroalkyl-bridged compounds that have various functional groups on each edge ($ArCF_2CF_2(CF_2)_nR$, R = arenes, halogens, alkyl, alkenyl, and benzyloxycarbonyl). Further, the one-pot syntheses of perfluoroalkyl-bridged compounds from aryl boronic acid esters were carried out.

The perfluoroalkyl group is ubiquitous in pharmaceuticals, agrochemicals, and other organic materials. C−F bonds are strong owing to the considerably high electronegativity of fluorine atoms, and the C−F bonds are commonly employed to design functionalized molecules. Particularly, the dissociation energies of the C−F bonds in the perfluoroalkyl group are higher than those in monofluoroalkane because of the highly polarized character of a C−F bond.[1] The strong demand for the incorporation of the perfluoroalkyl group has accelerated synthetic chemistry research (Figure 1A). In fact, trifluoromethylation is a matured technology today.[2–9]

Most perfluoroalkyl groups are attached to a molecule as a dangler. In other words, efficient synthetic methods that produce perfluoroalkyl chains with two terminals, particularly with relatively long perfluoroalkyl bridges, have been lacking (Figure 1B). The synthetic methods of difluoromethylene compounds are relatively abundant, including the deoxyfluorination of ketones[10], the nucleophilic transformation of difluoroenolates[11–13] and related nucleophiles,[14,15] regioselective difluoroallylation,[16–20] the addition of difluoroalkyl radical,[21–23] and the transfer of difluorocarbene.[24,25] The synthesis of tetrafluoroethylene bridged compounds has been achieved by the double deoxyfluorination of 1,2-diketone species; however, the reaction requires a large amount of corrosive fluorination reagents.[26] Some organofluorine building blocks contain a tetrafluoroethylene unit.[27] Our group has previously reported the preparation of a 1,1,2,2-tetrafluoroalkyl copper complex via the carbocupration of tetrafluoroethylene (TFE), an organofluorine feedstock molecule.[28,29] Thus, the coupling reaction of the generated fluoroalkyl copper with electrophiles furnishes a variety of tetrafluoroethylene bridged molecules having two different terminal groups. We and Hu's group have developed related oxycupration[30,31] and azacupration,[32] which expanded the scope of this methodology. In contrast to difluoromethylene and tetrafluoroethylene bridges, the installation of relatively long perfluoroalkyl linkers is still under development. The limitation of the classical McLoughlin–Thrower reaction of diiodides, such as hexafluoro-1,3-diiodopropane, is the lack of control of selectivity for mono- and disubstitution reactions.[33] Vicic and co-workers developed unique dizinc reagents prepared from corresponding diiodides.[34] These complexes were applied to annulation and symmetric diarylation. The intrinsic difficulty of installing different functional groups on each edge of diiodides, which are poorly available, hampers the detailed investigation of this class of molecules.

We aim to approach this unexplored chemical space using the homologation reaction of a fluoroalkyl copper complex derived from TFE by the insertion of difluorocarbene(s) into a Cu−C bond. Burton and co-workers report the preparation of $CuCF_2CF_3$ via CF_2 carbene insertion into $CuCF_3$ (Scheme 1b).[35] The copper difluorocarbene ($Cu{=}CF_2$), recently characterized by designed nitrogen-based ligands,[36] was suggested as the key intermediate. Additionally, the double CF_2 insertion reactions in C_6F_5Cu and (*Z*)-$CF_3CF{=}CFCu$ were observed to afford $C_6F_5CF_2CF_2Cu$ and (*E*)-$CF_3CF{=}CFCF_2CF_2Cu$.[37] Further elongation was observed in the report by Chen and co-workers.[38] Hu and co-workers reported the CF_2 insertion reaction using $CuCF_3$, which was prepared using CuCl, trimethylsilyl(trifluoromethyl)silane ($TMSCF_3$), and KF.[39,40] Recently, they achieved the double insertion of CF_2 into $CuCF_2H$ using $TMSCF_2Br$, which afforded hexafluoropropane derivatives with a proton and an aryl group on each edge.[41]

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These precedent works inspired us to develop the homologation reaction of a fluoroalkyl copper reagent derived from TFE. The resulting elongated fluoroalkyl copper complex enabled the construction of a fluoroalkyl bridge longer than CF_2CF_2 containing two different termini.

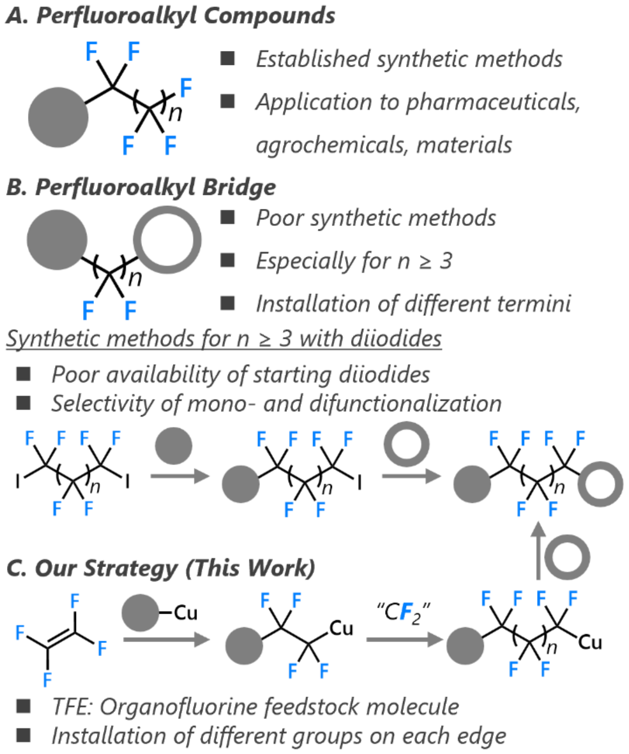
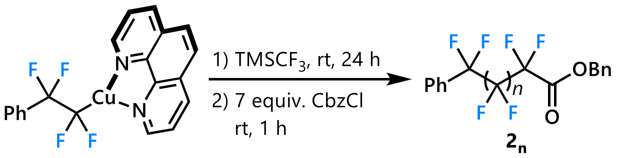


Figure 1. The background of this work

Following the procedure reported by Hu and co-workers, we treated fluoroalkyl copper complex **1** with KF and $TMSCF_3$ in tetrahydrofuran (THF). The reaction was evaluated by ^{19}F nuclear magnetic resonance (NMR) after the addition of excess CbzCl, which transformed fluoroalkyl copper complexes into corresponding benzyl esters. Otherwise the analysis was complicated since the fluoroalkyl copper complexes exhibited poor solubility and dynamic equilibrium between neutral and ionic forms. The reaction afforded the desired homologated product, $\mathbf{2}_1$ (the subscripted integer corresponds with the number of elongated CF_2, as described in Table 1). However, the yield was considerably low and compound $\mathbf{2}_0$ derived from complex **1** was a major product (entry 1). Interestingly, when we performed the reaction without additives, the yield of $\mathbf{2}_1$ increased to 54% with the generation of homolog $\mathbf{2}_2$ in a 5% yield (entry 2). Thereafter, we tested some solvents and found that the mixed solvents of THF and dimethylformamide (DMF) (3:1) afforded compound $\mathbf{2}_1$ in good yield (entries 3–7). When we performed the reaction with 1.2 equiv. of $TMSCF_3$, the yield of $\mathbf{2}_1$ slightly increased to 75%. Although the yield of **2** slightly decreased, the reaction at 0.6 mmol scale led to the full conversion of the starting material as judged by the absence of $\mathbf{2}_0$ (entry 9).

With the optimized reaction condition for preparing elongated fluoroalkyl copper complexes, we investigated the other coupling partner apart from benzyl chloroformate. After **1** was treated with $TMSCF_3$, iodoarene was added and the reaction mixture was heated at 60 °C to afford fluoroalkyl bridged arenes. Various functional groups tolerated our reaction conditions. Electron-withdrawing groups, such as trifluoromethyl (**3a**), cyano (**3b**), formyl (**3c**), and ethoxycarbonyl (**3d**) groups, afforded the corresponding fluoroalkyl compounds in good yields. Furthermore, the unprotected amino (**3f**) group, which can be found in various biologically active molecules, was introduced without a tedious protection/deprotection sequence. Some aromatic hydrocarbons, such as biphenyl (**3g**), 1-naphthyl (**3h**), and fluorene (**3i**), reacted with elongated fluoroalkyl copper reagents. Bromine and chlorine were attached to the benzene ring (**3j**), and they remained intact, affording potential sites for further functionalization by cross-coupling reactions. Treatment with 3-Iodopyridine (**3k**) afforded the desired products. Iodoalkene (**3l**), and benzyl bromide (**3m**) reacted with our elongated fluoroalkyl copper complexes. Note that in some cases such as **3h**, **3l**, and **3m**, we failed to isolate the double insertion product of which existence in the crude reaction mixture was evident by analysis of ^{19}F NMR and HRMS.

Table 1. Reaction condition screening



1, 0.02 mmol

Entry	Solvent	$TMSCF_3$ (equiv.)	NMR yield (%)[a]		
			$\mathbf{2}_0$	$\mathbf{2}_1$	$\mathbf{2}_2$
1[b]	THF	1 equiv.	84	7	n.d.
2	THF	1 equiv.	30	54	5
3	DMF	1 equiv.	21	49	5
4	1,4-dioxane	1 equiv.	17	54	11
5	THF/DMF (1:1)	1 equiv.	21	59	3
6	THF/DMF (3:1)	1 equiv.	16	73	5
7	THF/DMF (5:1)	1 equiv.	14	68	5
8[c]	THF/DMF (3:1)	1.2 equiv.	6	75	9
9[d]	THF/DMF (3:1)	1.2 equiv.	n.d.	52	19

a) Yields were determined by the ^{19}F NMR analysis of crude using $PhCF_3$ as an internal standard, n.d. = not detected; b) 1 equiv. of KF was added; c) 0.1 mmol scale; d) 0.6 mmol scale.

Next, we investigated the substrate scope of the fluoroalkyl copper complexes. To circumvent the laborious isolation procedure of fluoroalkyl copper reagent, we established the consecutive procedure consisting of the carbocupration of TFE and the subsequent CF_2 insertion reaction (Figure 3). We mixed 4-methoxyphenyl boronic acid neopentyl glycol ester with Cu*Ot*Bu and Phen in THF. Thereafter, the solution was pressurized with TFE. After stirring and removing TFE, we added $TMSCF_3$ and DMF to generate an elongated fluoroalkyl copper. The treatment of this solution with 4-(trifluoromethyl)iodobenzene afforded **3n** in good yield. Thereafter, we investigated the scope of aryl boronic esters using this method. The reaction using aryl boronic acid esters bearing fluorine (**3o**), chlorine (**3p**), and bromine (**3q**) proceeded without the elimination of these halogens. While the reaction using 2-naphthyl boronic ester afforded the desired products (**3r**) in good yield, the reaction of 1-naphthyl boronic ester required a long time to complete the insertion step (**3s**), probably due to the steric hindrance of the 1-naphthyl boronic acid ester. Taking advantage of the high molecular weight of a naphthalene ring than a phenyl one, which typically affords volatile products, we attempted the halogenation of the copper complexes. The addition of *p*-toluenesulfonyl chloride (TsCl), *N*-bromosuccinimide (NBS), and molecular iodine facilitated the incorporation of chlorine (**4a**), bromine (**4b**), and iodine (**4c**) at the edge of the fluoroalkyl chain.

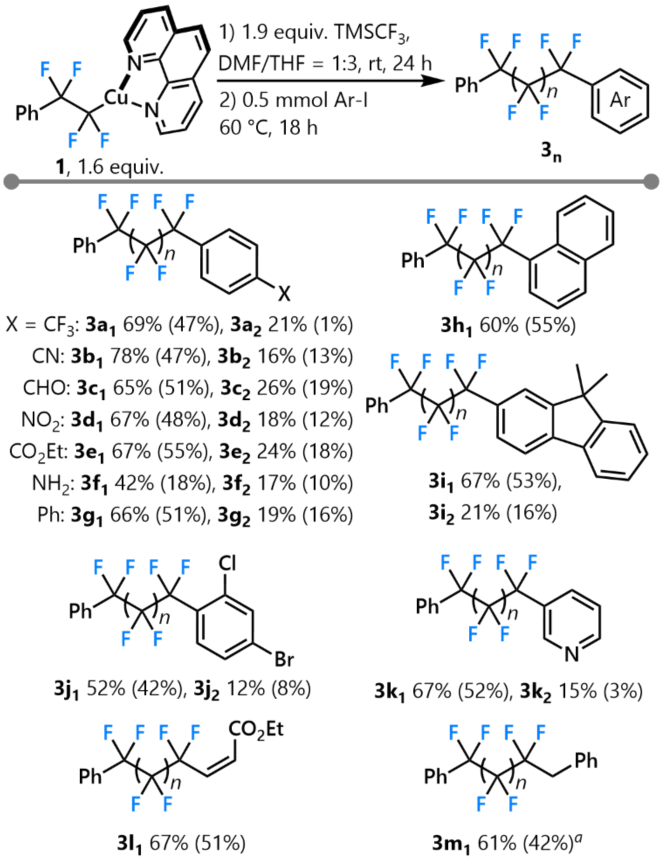


Figure 2. Substrate scope using **1**. The yields of the corresponding fluoroalkyl compounds are determined by ^{19}F NMR spectroscopy using PhCF$_3$ as an internal standard. Isolated yields were described in parenthesis. a) Instead of aryl iodides, benzyl bromide was added. The mixture was heated at 80 °C.

We conducted single crystal X-ray diffraction studies of **3b$_n$** (n = 0, 1, 2)§ to verify the structural impact of the CF$_2$ insertion. While the structure of the fluoroalkyl bridges of **3b$_0$** and **3b$_2$** was zigzag, that of **3b$_1$** was twisted in the crystal lattice (Figure S1A). The difference in the shape of the molecule derived from the orientation of the fluoroalkyl bridge was reflected in the packing of the molecules (Figure S1B). The rod-like **3b$_0$** and **3b$_2$** were laid straight for every dimension. Conversely, **3b$_1$** was crooked, making up a helical structure via hydrogen bonding between CN and the *m*-C–H of a phenyl group with an N–H distance of 2.8 Å. The pitch of the helix was 9.9 Å. The helixes were piled up along the *c*-axis at 6.9 Å intervals with significant overlap (Figure S1C). These arrays of helical structures were laid along the *a*-axis side by side. This comparison demonstrated that CF$_2$ insertion significantly impacted the structure of the fluoroalkyl molecule.

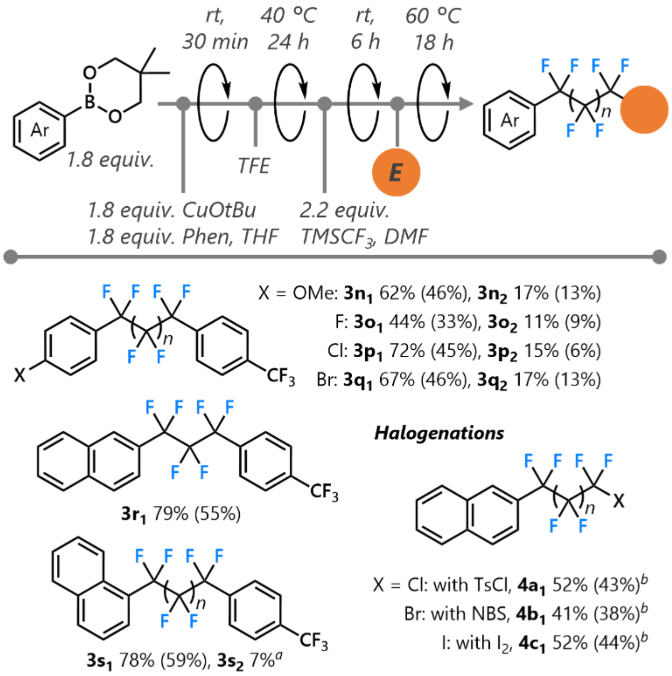


Figure 3. Substrate scope for aryl boronic ester. The yields of the corresponding fluoroalkyl compounds were determined by ^{19}F NMR spectroscopy using PhCF$_3$ as an internal standard. Isolated yields were described in parenthesis. a) The reaction mixture was stirred for 24 h after the addition of TMSCF$_3$. b) The haloganating reagents were added (2 equiv.) to fluoroalkyl copper and stirred at room temperature for 18 h.

We treated complex **1** with a large amount of TMSCF$_3$ to gain insight into how long the perfluoroalkyl chain can be created. We prepared a solution of complex **1** in THF/DMF solution and repeated the sequence of adding TMSCF$_3$ and stirring for 24 h four times (Figure 4). After the treatment of the resultant mixture with CbzCl, the product was analyzed by GCMS to find peaks that were assigned to **2$_2$**, **2$_3$**, **2$_4$**, and **2$_5$**. In addition to these peaks, high-resolution mass spectroscopy found **2$_6$**, **2$_7$**, and **2$_8$**. The crude reaction mixture contained a large amount of TMSCF$_3$. Considering the full conversion of TMSCF$_3$ under our standard conditions to prepare **2$_1$** (Table 1, entry 8), the remaining TMSCF$_3$ indicated that the reaction retarded as the elongation of the fluoroalkyl chain proceeded.

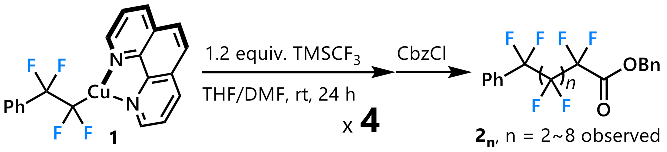


Figure 4. Further elongation of the fluoroalkyl chain

The mechanism of the homologation reaction is still unclear. At this stage, the involvement of free CF$_2$ carbene is unlikely because the addition of excess 1,1-diphenylethylene neither produced any difluorocyclopropane product nor inhibited homologation. Additionally, we could not find TFE or other perfluoroalkyl compounds typically generated as the side products of free CF$_2$ carbene in the crude reaction mixture. Instead, we observed the formation of benzyl trifluoroacetate or pentafluoropropionate after treatment with CbzCl, which was derived from corresponding trifluoromethyl or pentafluoroethyl copper complexes. Though these observations indicated that the CuCF$_3$ generated in situ is a possible source of a CF_2 unit, the reaction of **1** with (phen)$CuCF_3$ did not give $\mathbf{2_1}$ at all.

In summary, we have described the homologation reaction of the fluoroalkyl copper complexes derived from TFE. The reaction enables the construction of relatively long fluoroalkanes that connect two different functional groups. The length of the fluoroalkyl bridge significantly modified the structure of the entire molecule, as shown in the comparison of the X-ray crystallographic studies.

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Conflicts of interest

Y.Z., R.D., and S.O. has a pending patent application (JP2023-055618) related to this work.

Notes and references

§ Crystallographic data is available at CCDC ($\mathbf{2b_0}$: 2277724, $\mathbf{2b_1}$: 2277726, $\mathbf{2b_2}$: 2277725).

1 D. O'Hagan, *Chem. Soc. Rev.*, 2008, **37**, 308–319.
2 C. Zhang, *Org. Biomol. Chem.*, 2014, **12**, 6580.
3 C. Zhang, *Adv. Synth. Catal.*, 2014, **356**, 2895–2906.
4 J. Charpentier, N. Früh and A. Togni, *Chem. Rev.*, 2015, **115**, 650–682.
5 W. Zhu, J. Wang, S. Wang, Z. Gu, J. L. Aceña, K. Izawa, H. Liu and V. A. Soloshonok, *J. Fluorine Chem.*, 2014, **167**, 37–54.
6 S. Barata-Vallejo, B. Lantaño and A. Postigo, *Chem. Eur. J.*, 2014, **20**, 16806–16829.
7 O. A. Tomashenko and V. v. Grushin, *Chem. Rev.*, 2011, **111**, 4475–4521.
8 H. Xiao, Z. Zhang, Y. Fang, L. Zhu and C. Li, *Chem. Soc. Rev.*, 2021, **50**, 6308–6319.
9 X. Liu, C. Xu, M. Wang and Q. Liu, *Chem. Rev.*, 2015, **115**, 683–730.
10 G. S. Lal, G. P. Pez, R. J. Pesaresi, F. M. Prozonic and H. Cheng, *J. Org. Chem.*, 1999, **64**, 7048–7054.
11 M. Decostanzi, J.-M. Campagne and E. Leclerc, *Org. Biomol. Chem.*, 2015, **13**, 7351–7380.
12 Y. Gong, J. S. Yu, Y. J. Hao, Y. Zhou and J. Zhou, *Asian J. Org. Chem.*, 2019, **8**, 610–626.
13 X. S. Hu, J. S. Yu and J. Zhou, *Chem. Commun.*, 2019, **55**, 13638–13648.
14 J. B. Geri, M. M. Wade Wolfe and N. K. Szymczak, *J. Am. Chem. Soc.*, 2018, **140**, 9404–9408.
15 M. M. Wade Wolfe, S. Guo, L. S. Yu, T. R. Vogel, J. W. Tucker and N. K. Szymczak, *Chem. Commun.*, 2022, **58**, 11705–11708.
16 S. Sakamoto, T. W. Butcher, J. L. Yang and J. F. Hartwig, *Angew. Chem. Int. Ed.*, 2021, **60**, 25746–25752.
17 X.-Q. Chen, H. Lu, C.-X. Chen, R. Zeng, D.-Y. Wang, C.-Y. Shi and A. Zhang, *J. Org. Chem.*, 2022, **87**, 2935–2946.
18 X. Feng, J. Ren, X. Gao, Q. Min and X. Zhang, *Angew. Chem. Int. Ed.*, 2022, **61**, e202210103.
19 C.-Y. Shi, X.-Q. Chen, R. Zeng, H. Lu, Z. Fan and A. Zhang, *Org. Lett.*, 2023, **25**, 3870–3875.
20 Q.-Q. Min, Z. Yin, Z. Feng, W.-H. Guo and X. Zhang, *J. Am. Chem. Soc.*, 2014, **136**, 1230–1233.
21 C. Luo and J. S. Bandar, *J. Am. Chem. Soc.*, 2019, **141**, 14120–14125.
22 D. B. Vogt, C. P. Seath, H. Wang and N. T. Jui, *J. Am. Chem. Soc.*, 2019, **141**, 13203–13211.
23 C. Liu, N. Shen and R. Shang, *Nat. Commun.*, 2022, **13**, 354.
24 W. Zhang and Y. Wang, *Tetrahedron Lett.*, 2018, **59**, 1301–1308.
25 K. Fuchibe and J. Ichikawa, *Chem. Commun.*, 2023, **59**, 2532–2540.
26 R. P. Singh, U. Majumder and J. M. Shreeve, *J. Org. Chem.*, 2001, **66**, 6263–6267.
27 A. J. Boydell, V. Vinader and B. Linclau, *Angew. Chem. Int. Ed.*, 2004, **43**, 5677–5679.
28 H. Saijo, M. Ohashi and S. Ogoshi, *J. Am. Chem. Soc.*, 2014, **136**, 15158–15161.
29 R. Doi, Y. Zhou and S. Ogoshi, *Synthesis*, 2023, **55**, 857–867.
30 L. Li, C. Ni, Q. Xie, M. Hu, F. Wang and J. Hu, *Angew. Chem. Int. Ed.*, 2017, **129**, 10103–10107.
31 M. Ohashi, T. Adachi, N. Ishida, K. Kikushima and S. Ogoshi, *Angew. Chem. Int. Ed.*, 2017, **129**, 12073–12077.
32 N. Ishida, T. Adachi, H. Iwamoto, M. Ohashi and S. Ogoshi, *Chem. Lett.*, 2021, **50**, 442–444.
33 V. C. R. Mcloughlin and J. Thrower, *Tetrahedron*, 1969, **25**, 5921–5940.
34 P. T. Kaplan, L. Xu, B. Chen, K. R. McGarry, S. Yu, H. Wang and D. A. Vicic, *Organometallics*, 2013, **32**, 7552–7558.
35 D. M. Wiemers and D. J. Burton, *J. Am. Chem. Soc.*, 1986, **108**, 832–834.
36 X. Zeng, Y. Li, Q.-Q. Min, X.-S. Xue and X. Zhang, *Nat. Chem.*, 2023, DOI:10.1038/s41557-023-01236-8.
37 Z. Y. Yang, D. M. Wiemers and D. J. Burton, *J. Am. Chem. Soc.*, 1992, **114**, 4402–4403.
38 D.-B. Su, J.-X. Duan, A.-J. Yu and Q.-Y. Chen, *J. Fluorine Chem.*, 1993, **65**, 11–14.
39 Q. Xie, L. Li, Z. Zhu, R. Zhang, C. Ni and J. Hu, *Angew. Chem. Int. Ed.*, 2018, **57**, 13211–13215.
40 Q. Xie, Z. Zhu, L. Li, C. Ni and J. Hu, *Chem. Sci.*, 2020, **11**, 276–280.
41 X. Wang, S. Pan, Q. Luo, Q. Wang, C. Ni and J. Hu, *J. Am. Chem. Soc.*, 2022, **144**, 12202–12211.