

Controllable Fluorocarbon Chain Elongation: TMSCF_2Br -Enabled Trifluorovinylolation and Pentafluorocyclopropylation of Aldehydes

An Liu, Xianghong Zhang, Feng Zhao, Chuanfa Ni, and Jinbo Hu*

Cite This: *J. Am. Chem. Soc.* 2024, 146, 1806–1812

Read Online

ACCESS |



Metrics & More



Article Recommendations



Supporting Information

ABSTRACT: Controllable fluorocarbon chain elongation (CFCE) is a promising yet underdeveloped strategy for the well-defined synthesis of structurally novel polyfluorinated compounds. Herein, the direct and efficient trifluorovinylolation and pentafluorocyclopropylation of aldehydes are described by using TMSCF_2Br (TMS = trimethylsilyl) as the sole fluorocarbon source, accomplishing the goals of CFCE from C_1 to C_2 and from C_1 to C_3 , respectively. The key to the success of these CFCE processes lies in the unique and diversified chemical reactivity of TMSCF_2Br , which can serve as two different precursors, namely, a TMSCF_2 radical precursor and a difluorocarbene precursor. Various functional groups are amenable to this new synthetic protocol, providing streamlined access to a broad range of alcohols containing trifluorovinyl or pentafluorocyclopropyl moieties from abundantly available aldehydes. The potential utility of these methods is further demonstrated by the gram-scale synthesis, derivatization, and measurement of log P values of the products.

The unique properties of fluorine have opened up tantalizing opportunities for the advancement of pharmaceuticals, agrochemicals, and materials,¹ thus triggering a boom in the synthesis of various fluorine-containing molecules.² For instance, fluoroalkenes and fluorocyclopropanes have attracted particular interest due to their combined features of fluorine and unsaturated bonds (including “banana bonds” with properties similar to unsaturated double bonds).³ Indeed, many of fluoroalkenes and fluorocyclopropanes have been utilized as functional molecules⁴ or valuable synthons.⁵ Additionally, the easily transformable characters (involving unsaturated bonds) of these compounds may also provide chances for biodegradation, without the concerns about PFAS (per- and polyfluoroalkyl substances) issues.⁶ The past decades have witnessed tremendous developments in the synthesis of mono/*gem*-difluoroalkenes⁷ and mono/*gem*-difluorocyclopropanes.^{4c,d,8} Moreover, many approaches toward the synthesis of various fluoroalkyl-substituted alkenes⁹ and cyclopropanes¹⁰ have also been well-documented. However, all of these established methods mainly focused on the synthesis of fluorine-containing alkenes or cyclopropanes with a single fluorinated carbon atom (C_1). Convenient procedures for the synthesis of trifluoroalkenes¹¹ with two fluorinated carbon atoms (C_2) and, in particular, of pentafluorocyclopropanes¹² with three fluorinated carbon atoms (C_3) are scarce.

The controllable fluorocarbon chain elongation (CFCE) reaction has been considered as a powerful strategy for the selective construction of various structurally diverse polyfluorinated compounds (especially difficult-to-prepare structures by traditional methods) from simple fluorocarbon sources.¹³ TMSCF_2Br (TMS = trimethylsilyl), a commercially available difluorocarbene reagent developed in our group,¹⁴ can serve as one of the choices of fluorocarbon sources owing to its mild and broadly applicable conditions.^{13b,c,14–16} In 2015, we reported *gem*-difluoroolefination (C_1) and tetra-

fluorocyclopropanation (C_2) of diazo compounds with TMSCF_2Br under transition-metal-free conditions, in which the use of TMSCF_2Br as the sole fluorocarbon source realized the controllable incorporation of one and two fluorinated carbon atoms (Scheme 1A).¹⁷ As part of our ongoing studies of CFCE chemistry (Scheme 1B), we postulated that TMSCF_2Br could serve as a TMSCF_2 radical precursor and undergo the homocoupling reaction to form $\text{TMSCF}_2\text{CF}_2\text{TMS}$, which reacts with aldehydes in one pot to give the desired trifluoroalkenes (C_2). Then, the use of TMSCF_2Br as a difluorocarbene precursor enables the [2 + 1] cycloaddition of in situ generated trifluoroalkenes with difluorocarbene, resulting in the formation of the desired pentafluorocyclopropanes (C_3). The overall process can be regarded as TMSCF_2Br -enabled trifluorovinylolation and pentafluorocyclopropylation of aldehydes, which accomplishes the goals of CFCE from C_1 to C_2 and from C_1 to C_3 by using TMSCF_2Br as the sole fluorocarbon source (Scheme 1C).

The homocoupling reaction of TMSCF_2Br was initially explored with the selection of inexpensive commercial zinc dust as a reductant (Table 1).^{18,19} We found that the homocoupling product ($\text{TMSCF}_2\text{CF}_2\text{TMS}$) was observed in 94% yield by using FeCl_2 as a catalyst and zinc dust as a reductant (Table 1, entry 1). The control experiments demonstrated that the combination of FeCl_2 and zinc dust was crucial for the efficient generation of $\text{TMSCF}_2\text{CF}_2\text{TMS}$. The reaction provided 40% yield of $\text{TMSCF}_2\text{CF}_2\text{TMS}$ in the

Received: November 17, 2023

Revised: December 31, 2023

Accepted: January 4, 2024

Published: January 9, 2024



Scheme 1. TMSCF₂Br-Enabled CFCE Strategy for the Synthesis of Fluoroalkenes and Fluorocyclopropanes

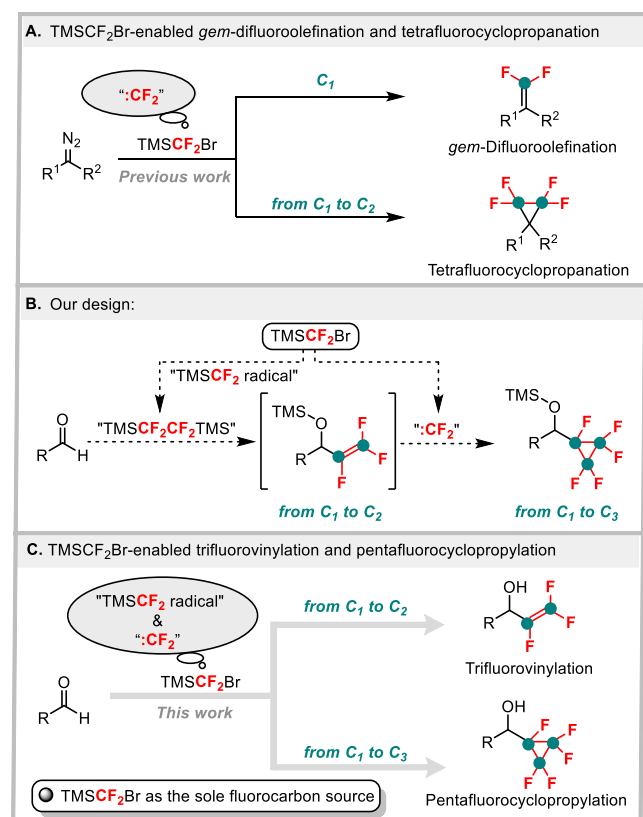


Table 1. Optimization of Reaction Conditions for the Homocoupling Reaction of TMSCF₂Br^a

entry	deviation from standard conditions	yield (%) ^b
1	none	94
2	no FeCl ₂	40
3	no Zn	n.d. ^d
4	50 °C	65
5	0.1 equiv of FeCl ₂	68
6	DMF as solvent	43
7 ^c	scaled up to 100 mmol	89

^aStandard conditions: TMSCF₂Br (0.8 mmol, 1.0 equiv), FeCl₂ (0.2 equiv), Zn (1.5 equiv) in THF (2 mL), 80 °C, 8 h. ^bYields were determined by ¹⁹F NMR using PhCF₃ as an internal standard. ^cReaction was performed on a 100 mmol scale. ^dn.d. = not detected.

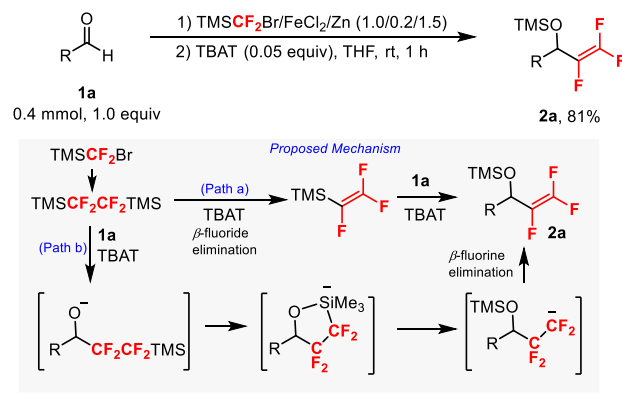
absence of FeCl₂ (Table 1, entry 2), and no yield of TMSCF₂CF₂TMS was observed in the absence of zinc dust (Table 1, entry 3).²⁰ Lower temperatures, reduced usage of FeCl₂, and solvent changes led to lower yields of TMSCF₂CF₂TMS (Table 1, entries 4–6). TMSCF₂CF₂TMS can be isolated by recrystallization at −20 °C (for details, see the Supporting Information).^{19c} It is worth noting that this reaction was successfully scaled up to 100 mmol without much loss of efficiency (Table 1, entry 7).

Subsequently, we explored the application of the unseparated homocoupling product TMSCF₂CF₂TMS for trifluorovinylolation of aldehydes in one pot, and a catalytic amount of tetrabutylammonium triphenyldifluorosilicate (TBAT) was

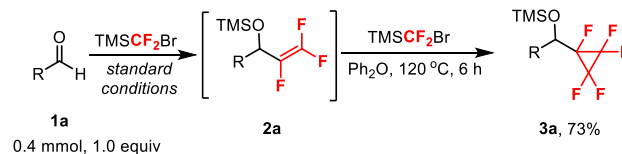
used as an initiator (Scheme 2A). However, the existence of metal salts (such as zinc bromide) in the solution of

Scheme 2. Trifluorovinylolation and Pentafluorocyclopropylation of 1a with TMSCF₂Br Under the Optimized Conditions^a

A. TMSCF₂Br-enabled trifluorovinylolation of aldehydes

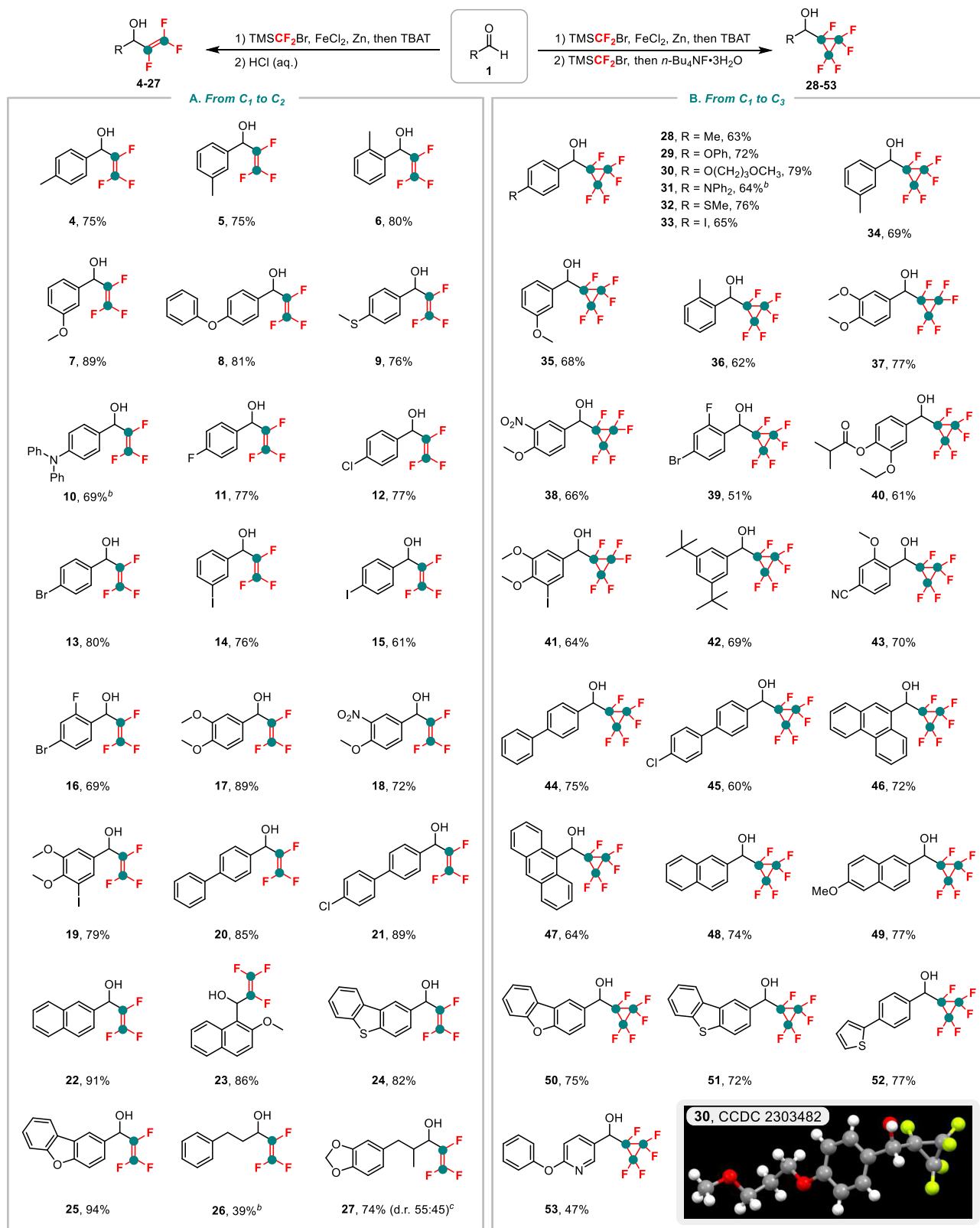


B. TMSCF₂Br-enabled pentafluorocyclopropylation of aldehydes

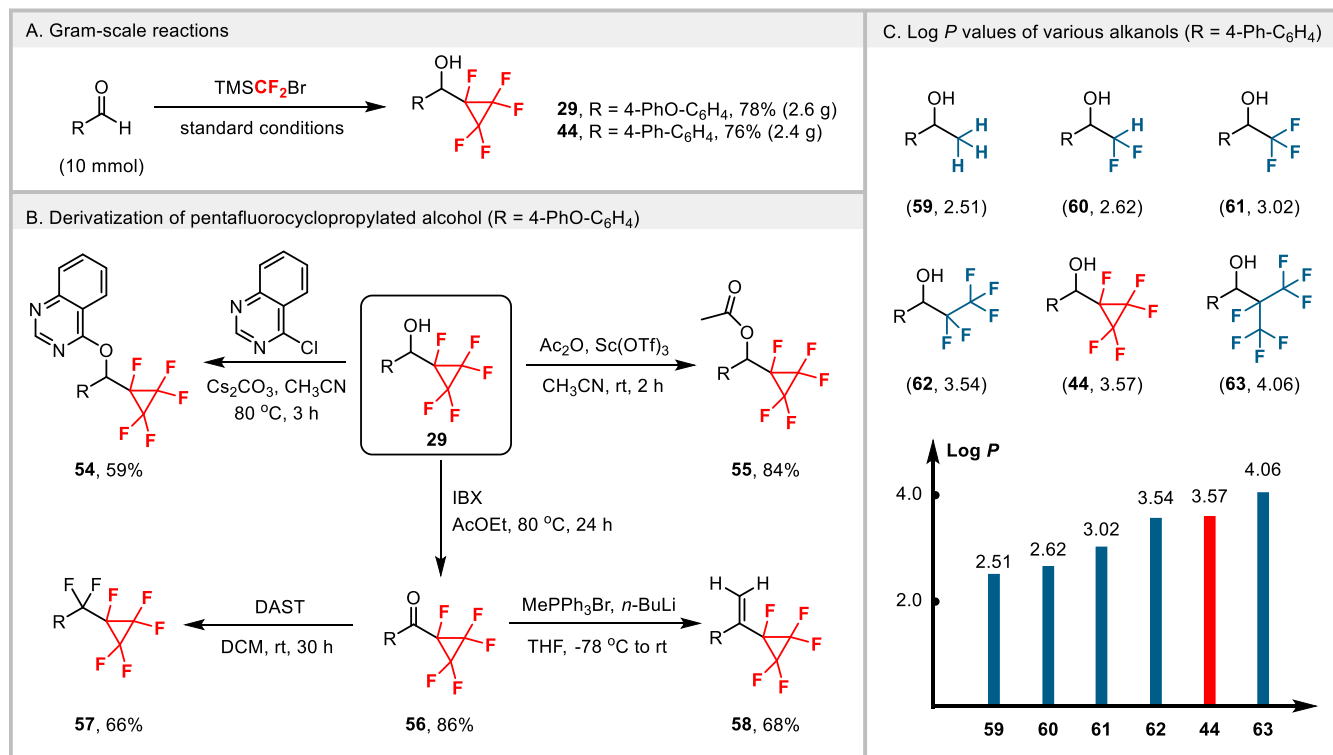


^aConditions for 2a (R = 4-Ph-C₆H₄): TMSCF₂Br (100.0 mmol), FeCl₂ (0.2 equiv), Zn (1.5 equiv) in THF (50 mL), 80 °C, 8 h, to give the THF solution of TMSCF₂CF₂TMS (used after aqueous washing). 1a (0.4 mmol, 1.0 equiv), TBAT (0.02 mmol, 0.05 equiv), the THF solution of TMSCF₂CF₂TMS (0.48 mmol, 1.2 equiv), rt, 1 h. Conditions for 3a: 2a generated from 1a (0.4 mmol, 1.0 equiv) under above conditions, TMSCF₂Br (1.2 mmol, 3.0 equiv), Ph₂O (0.5 mL), 120 °C, 6 h. Yields were determined by ¹⁹F NMR using 1-fluoronaphthalene or PhCF₃ as an internal standard.

TMSCF₂CF₂TMS inhibited the desired trifluorovinylolation reaction since metal salts could consume the fluorine ions (released from the initiator) to form the strong M–F bond (M = metal). We found that simple aqueous washing could effectively remove the metal salts from the solution of TMSCF₂CF₂TMS, and the obtained solution of TMSCF₂CF₂TMS could smoothly react with aldehyde (1a) to afford the desired trifluorovinylolation product (2a) in 81% yield. In accordance with the results reported by Prakash^{19c} and Fuchikami,^{11g} the trifluorovinylolation product can be explained through two possible paths, as shown in Scheme 2A. β-Fluorine ion elimination results in the formation of the trifluorovinyl group from TMSCF₂CF₂TMS. After confirming the formation of trifluoroalkene (2a) generated from aldehyde (1a) and TMSCF₂Br, we further performed the [2 + 1] cycloaddition of the unseparated trifluoroalkene (2a) with difluorocarbene (generated from TMSCF₂Br) to deliver desired pentafluorocyclopropylation product 3a (Scheme 2B). A careful screening of the initiator and solvents, the ratio of reagents, and reaction temperatures brought about the optimized conditions. Interestingly, we found that a catalytic amount of TBAT utilized in the process of trifluorovinylolation could also serve as the initiator of the subsequent [2 + 1] cycloaddition reaction. The unseparated trifluoroalkene (2a) obtained from aldehydes (1a) and TMSCF₂Br could, without

Scheme 3. Substrate Scopes for Trifluorovinylolation and Pentafluorocyclopropylation of Aldehydes with $\text{TMSCF}_2\text{Br}^a$ 

^aConditions for **4–27**: TMSCF_2Br (100.0 mmol), FeCl_2 (0.2 equiv), Zn (1.5 equiv) in THF (50 mL), 80 °C, 8 h, to give the THF solution of $\text{TMSCF}_2\text{CF}_2\text{TMS}$ (used after aqueous washing). **1** (0.4 mmol, 1.0 equiv), TBAT (0.02 mmol, 0.05 equiv), the THF solution of $\text{TMSCF}_2\text{CF}_2\text{TMS}$ (0.48 mmol, 1.2 equiv), rt, 1 h. HCl (3 M, 2 mL), rt, 0.5 h. Conditions for **28–53**: Trifluorovinylated silyl ethers generated from **1** (0.4 mmol, 1.0 equiv) under above conditions, TMSCF_2Br (1.2 mmol, 3.0 equiv), Ph_2O (0.5 mL), 120 °C, 6 h. Then, $n\text{-Bu}_4\text{NF}\cdot 3\text{H}_2\text{O}$ (2.0 mmol, 5.0 equiv), rt, 0.5 h. ^bYields were determined by ^{19}F NMR using 1-fluoronaphthalene or PhCF_3 as an internal standard. ^cThe diastereoisomer ratio (d.r.) was determined by ^{19}F NMR spectroscopy analysis.

Scheme 4. Synthetic Applications^a

^aFor reaction details, see the Supporting Information.

extra addition of an initiator, directly react with TMSCF_2Br in Ph_2O at $120\text{ } ^\circ\text{C}$ for 6 h to give the targeted pentafluorocyclopropane (**3a**) in 73% yield. Notably, trifluoroalkene (**2a**) was completely consumed, which indicates that trifluoroalkene (**2a**) has a high reactivity toward difluorocarbene.

After the establishment of these optimized conditions, we next evaluated the substrate scope of the trifluorovinylolation reaction enabled by TMSCF_2Br (Scheme 3A). Trifluorovinylated silyl ethers were converted into the corresponding alcohols (for the sake of easy purification) by treatment with an aqueous HCl solution. An array of structurally diverse aromatic aldehydes proved to be appropriate substrates for this reaction, and the desired trifluorovinylated alcohols were obtained in good yields (4–27). Benzaldehydes bearing *para*-/ *meta*-/ *ortho*-methyl groups could undergo this transformation with the formation of the targeted products (4–6) in similar yields, even though *ortho*-substituents have more steric hindrance than *meta*- and *para*-substituents. Under the standard conditions, this reaction tolerated diverse functional groups well, including electron-donating groups containing oxygen/sulfur/nitrogen atoms (7–10) and weak electron-withdrawing groups containing various halogens (11–15). Relatively complex aromatic aldehydes featuring two and three substituents at the different positions of aryl rings performed well in this reaction, affording the corresponding products (16–19) in 69–89% yields. A variety of aromatic and heteroaromatic aldehydes with π -extended systems were also smoothly transformed into the corresponding trifluorovinylated alcohols (20–25) in high yields. The transformation of the primary aliphatic aldehyde was found to be inefficient (**26**), but the secondary alkyl aldehyde such as helional (a widely used flavor compound) was an appropriate substrate for this

transformation, affording the desired product (**27**) in 74% yield.

Having confirmed the good compatibility of the trifluorovinylolation reaction involving a C₁ to C₂ process, we turned our attention to investigate the substrate versatility of the unprecedented pentafluorocyclopropylation of aldehydes involving a C₁ to C₃ process (Scheme 3B). $n\text{-Bu}_4\text{NF}\cdot 3\text{H}_2\text{O}$ instead of an aqueous HCl solution was utilized for more efficient desilylations of pentafluorocyclopropylated silyl ethers. A wide range of electron-donating and almost electron-neutral substituents on the phenyl rings of aromatic aldehydes, including alkyl (**28**, **34**, **36**), ethers (**29**, **30**, **35**), amine (**31**), thioether (**32**), and halogen (**33**), were found to be compatible with the standard conditions, as demonstrated by the good yields of targeted pentafluorocyclopropylated alcohols **28**–**36**. Some common strong electron-withdrawing substituents (such as nitro (**38**), ester (**40**), and cyano (**43**)) on the phenyl rings of multisubstituted aromatic aldehydes could also be tolerated well under the reaction conditions. The position of the substituents did not have much influence on the product yields, as demonstrated by the examples (**28**–**43**). A range of aromatic and heteroaromatic aldehydes with π -extended systems could yield target products **44**–**53** in moderate to good yields. In addition, the single crystal structure of product **30** was successfully characterized (CCDC 2303482), thus confirming the unprecedented structure of pentafluorocyclopropylated alcohol **30**.

Considering that no method for the preparation of pentafluorocyclopropylated alcohols from abundant aldehydes has been yet reported, we then illustrated the synthetic applications of the pentafluorocyclopropylated alcohols obtained by our new pentafluorocyclopropylation reaction (Scheme 4). First, the gram-scale synthesis of pentafluor-

ocyclopropylated alcohols (**29** and **44**) was successfully accomplished under the standard conditions (Scheme 4A). Subsequently, we utilized the obtained pentafluorocyclopropylated alcohol (**29**) to carry out a variety of derivatization reactions (Scheme 4B). **29** could react with 4-chloroquinazoline under basic conditions to give the nucleophilic aromatic substitution product 4-alkoxy quinazoline (**54**) in 59% yield. **29** was also readily converted into the corresponding ester (**55**) in the presence of acetic anhydride (Ac_2O). In addition, the oxidation of **29** was accomplished by selecting 2-iodoxybenzoic acid (IBX) as an oxidant, furnishing pentafluorocyclopropylated ketone (**56**) in 86% yield. The deoxyfluorination and witting olefination of **56** were successfully achieved, giving corresponding products **57** and **58** in good yields, respectively.

The modulation of the lipophilicity ($\log P$) of bioactive molecules plays a vital role in pharmaceutical and agrochemical discovery, and the appropriate incorporation of fluorine has been utilized as a common strategy for the optimization of lipophilicity.²¹ Thus, we measured the $\log P$ values of a series of alkanols (**44**, **59**–**63**) containing various fluorinated groups by C_{18} reverse phase HPLC (Scheme 4C),²² which indicated that the lipophilicity of the pentafluorocyclopropyl group (**44**) is slightly higher than the pentafluoroethyl group (**62**) possessing the same number of fluorine atoms (3.57 vs 3.54) and yet lower than the heptafluoroisopropyl group (**63**) possessing the same number of fluorinated carbon atoms (3.57 vs 4.06).

In conclusion, we developed a new controllable fluorocarbon chain elongation (CFCE) strategy enabling trifluorovinylation and pentafluorocyclopropylation of aldehydes with TMSCF_2Br . The reaction started with the highly efficient formation of $\text{TMSCF}_2\text{CF}_2\text{TMS}$ via FeCl_2 -catalyzed homocoupling of TMSCF_2Br with inexpensive zinc dust as a reductant. In this process, TMSCF_2Br was utilized as a TMSCF_2 radical precursor. And trifluorovinylation of aldehydes with the unseparated $\text{TMSCF}_2\text{CF}_2\text{TMS}$ brought about the desired trifluoroalkenes with the CFCE from C_1 to C_2 . More importantly, the use of TMSCF_2Br as a difluorocarbene precursor enabled $[2 + 1]$ cycloaddition of the unseparated trifluoroalkenes with difluorocarbene, affording another desired pentafluorocyclopropylated products with the CFCE from C_1 to C_3 . Notably, the current pentafluorocyclopropylation method represents the first example of CFCE from C_1 to C_3 by the use of TMSCF_2Br as the sole fluorocarbon source.^{13b,c,17} Gram-scale synthesis, derivatization, and measurement of $\log P$ values further enhanced the synthetic potential of our methods. Further exploration of the CFCE strategy in the synthesis of fluorinated functional molecules (especially compounds containing more than three fluorinated carbon atoms) is currently underway in our laboratory.

■ ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/jacs.3c12919>.

Experimental details, optimization of the reaction conditions, the procedures for the synthesis of substrates and products, X-ray structure of compound **30** (CCDC 2303482), and the spectroscopic data of the corresponding compounds are included in the Supporting Information (PDF)

Accession Codes

CCDC 2303482 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

Jinbo Hu – Key Laboratory of Fluorine and Nitrogen Chemistry and Advanced Materials, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, Shanghai 200032, China; orcid.org/0000-0003-3537-0207; Email: jinbohu@sioc.ac.cn

Authors

An Liu – Key Laboratory of Fluorine and Nitrogen Chemistry and Advanced Materials, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, Shanghai 200032, China

Xianghong Zhang – Key Laboratory of Fluorine and Nitrogen Chemistry and Advanced Materials, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, Shanghai 200032, China

Feng Zhao – Key Laboratory of Fluorine and Nitrogen Chemistry and Advanced Materials, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, Shanghai 200032, China

Chuanfa Ni – Key Laboratory of Fluorine and Nitrogen Chemistry and Advanced Materials, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, Shanghai 200032, China

Complete contact information is available at:

<https://pubs.acs.org/10.1021/jacs.3c12919>

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the National Key Research and Development Program of China (2021YFF0701700), the National Natural Science Foundation of China (22271299 and 22261132514), the National Science Foundation of Shandong Province (ZR2023LFG003), and the Shandong Dongyue Polymer Materials Co. Ltd.

■ REFERENCES

- (1) (a) Sheikhi, N.; Bahraminejad, M.; Saeedi, M.; Mirfazli, S. S. A review: FDA-approved fluorine-containing small molecules from 2015 to 2022. *Eur. J. Med. Chem.* **2023**, 260, No. 115758. (b) Inoue, M.; Sumii, Y.; Shibata, N. Contribution of Organofluorine Compounds to Pharmaceuticals. *ACS Omega* **2020**, 5, 10633–10640. (c) Ogawa, Y.; Tokunaga, E.; Kobayashi, O.; Hirai, K.; Shibata, N. Current Contributions of Organofluorine Compounds to the Agrochemical Industry. *iScience* **2020**, 23, No. 101467. (d) Guo, Z.; Yu, Q.; Chen, Y.; Liu, J.; Li, T.; Peng, Y.; Yi, W. Fluorine-Containing Functional Group-Based Energetic Materials. *Chem. Rec.* **2023**, 23, No. e202300108. (e) Zhang, C.; Yan, K.; Fu, C.; Peng, H.; Hawker, C. J.; Whittaker, A. K. Biological Utility of Fluorinated

Compounds: from Materials Design to Molecular Imaging, Therapeutics and Environmental Remediation. *Chem. Rev.* **2022**, *122*, 167–208.

(2) (a) Britton, R.; Gouverneur, V.; Lin, J.-H.; Meanwell, M.; Ni, C.; Pupo, G.; Xiao, J.-C.; Hu, J. Contemporary synthetic strategies in organofluorine chemistry. *Nat. Rev. Methods Primers* **2021**, *1*, 47. (b) Liang, T.; Neumann, C. N.; Ritter, T. Introduction of fluorine and fluorine-containing functional groups. *Angew. Chem., Int. Ed.* **2013**, *52*, 8214–8264.

(3) Palke, W. E. Double bonds are bent equivalent hybrid (banana) bonds. *J. Am. Chem. Soc.* **1986**, *108*, 6543–6544.

(4) (a) Couve-Bonnaire, S.; Cahard, D.; Pannecoucke, X. Chiral dipeptide mimics possessing a fluoroolefin moiety: a relevant tool for conformational and medicinal studies. *Org. Biomol. Chem.* **2007**, *5*, 1151–1157. (b) Morand, S.; Jubault, P.; Bouillon, J. P.; Couve-Bonnaire, S. *gem*-Heteroatom-Substituted Fluoroalkenes as Mimics of Amide Derivatives or Phosphates: A Comprehensive Review. *Chem. - Eur. J.* **2021**, *27*, 17273–17292. (c) David, E.; Milanole, G.; Ivashkin, P.; Couve-Bonnaire, S.; Jubault, P.; Pannecoucke, X. Syntheses and applications of monofluorinated cyclopropanes. *Chem. - Eur. J.* **2012**, *18*, 14904–14917. (d) Jubault, P.; Pons, A.; Poisson, T.; Pannecoucke, X.; Charette, A. Synthesis and Applications of Fluorocyclopropanes. *Synthesis* **2016**, *48*, 4060–4071.

(5) (a) Altman, R. A.; Sorrentino, J. P. Fluorine-Retentive Strategies for the Functionalization of *gem*-Difluoroalkenes. *Synthesis* **2021**, *53*, 3935–3950. (b) Lu, M.-Z.; Goh, J.; Maraswami, M.; Jia, Z.; Tian, J.-S.; Loh, T.-P. Recent Advances in Alkenyl sp^2 C–H and C–F Bond Functionalizations: Scope, Mechanism, and Applications. *Chem. Rev.* **2022**, *122*, 17479–17646. (c) Liu, C.; Zeng, H.; Zhu, C.; Jiang, H. Recent advances in three-component difunctionalization of *gem*-difluoroalkenes. *Chem. Commun.* **2020**, *56*, 10442–10452. (d) Wang, J.; Gao, H.; Shi, C.; Chen, G.; Tan, X.; Chen, X.; Xu, L.; Cai, X.; Huang, B.; Li, H. Recent advances in radical-based C–F bond activation of polyfluoroarenes and *gem*-difluoroalkenes. *Chem. Commun.* **2021**, *57*, 12203–12217. (e) Zhang, J.; Geng, S.; Feng, Z. Advances in silylation and borylation of fluoroarenes and *gem*-difluoroalkenes via C–F bond cleavage. *Chem. Commun.* **2021**, *57*, 11922–11934. (f) Babudri, F.; Cardone, A.; Farinola, G. M.; Martinelli, C.; Mendichi, R.; Naso, F.; Striccoli, M. Synthesis of Poly(arylenevinylene)s with Fluorinated Vinylene Units. *Eur. J. Org. Chem.* **2008**, *2008*, 1977–1982. (g) Souzy, R.; Ameduri, B.; Boutevin, B. Synthesis and (co)polymerization of monofluoro, difluoro, trifluorostyrene and ((trifluorovinyl)oxy)benzene. *Prog. Polym. Sci.* **2004**, *29*, 75–106. (h) Song, X.; Xu, C.; Wang, M. Transformations based on ring-opening of *gem*-difluorocyclopropanes. *Tetrahedron Lett.* **2017**, *58*, 1806–1816.

(6) (a) Evich, M. G.; Davis, M. J. B.; McCord, J. P.; Acrey, B.; Awkerman, J. A.; Knappe, D. R. U.; Lindstrom, A. B.; Speth, T. F.; Tebes-Stevens, C.; Strynar, M. J.; et al. Per- and polyfluoroalkyl substances in the environment. *Science* **2022**, *375*, No. eabg9065. (b) Trang, B.; Li, Y.; Xue, X. S.; Ateia, M.; Houk, K. N.; Dichtel, W. R. Low-temperature mineralization of perfluorocarboxylic acids. *Science* **2022**, *377*, 839–845.

(7) (a) Fujita, T.; Fuchibe, K.; Ichikawa, J. Transition-Metal-Mediated and -Catalyzed C–F Bond Activation by Fluorine Elimination. *Angew. Chem., Int. Ed.* **2019**, *58*, 390–402. (b) Paquin, J.-F.; Drouin, M.; Hamel, J.-D. Synthesis of Monofluoroalkenes: A Leap Forward. *Synthesis* **2018**, *50*, 881–955. (c) Yanai, H.; Taguchi, T. Synthetic Methods for Fluorinated Olefins. *Eur. J. Org. Chem.* **2011**, *2011*, 5939–5954. (d) Luo, Q.; Wang, X.; Hu, J. Synthesis of fluoroalkenes via Julia and Julia-Kocienski olefination reactions. *Tetrahedron* **2022**, *113*, No. 132694. (e) Zhang, X.-J.; Cheng, Y.-M.; Zhao, X.-W.; Cao, Z.-Y.; Xiao, X.; Xu, Y. Catalytic asymmetric synthesis of monofluoroalkenes and *gem*-difluoroalkenes: advances and perspectives. *Org. Chem. Front.* **2021**, *8*, 2315–2327. (f) Chelucci, G. Synthesis and Metal-Catalyzed Reactions of *gem*-Dihalovinyl Systems. *Chem. Rev.* **2012**, *112*, 1344–1462.

(8) (a) Taguchi, T.; Okada, M. Fluorinated cyclopropanes. *J. Fluorine Chem.* **2000**, *105*, 279–283. (b) Thankachan, A. P.; Sindhu,

K. S.; Krishnan, K. K.; Anilkumar, G. Recent advances in the syntheses, transformations and applications of 1,1-dihalocyclopropanes. *Org. Biomol. Chem.* **2015**, *13*, 8780–8802.

(9) For selected examples, see (a) Chang, D.; Gu, Y.; Shen, Q. Pd-Catalyzed Difluoromethylation of Vinyl Bromides, Triflates, Tosylates, and Nonaflates. *Chem. - Eur. J.* **2015**, *21*, 6074–6078. (b) Xue, C.; Jiang, X.; Fu, C.; Ma, S. C–F bond formation with fluoride anions – highly selective iodofluorination of simple allenes. *Chem. Commun.* **2013**, *49*, S651–S653. (c) Fier, P. S.; Hartwig, J. F. Copper-Mediated Difluoromethylation of Aryl and Vinyl Iodides. *J. Am. Chem. Soc.* **2012**, *134*, 5524–5527. (d) Prakash, G. K. S.; Ganesh, S. K.; Jones, J.-P.; Kulkarni, A.; Masood, K.; Swabeck, J. K.; Olah, G. A. Copper-Mediated Difluoromethylation of (Hetero)aryl Iodides and β -Styryl Halides with Tributyl(difluoromethyl)stannane. *Angew. Chem., Int. Ed.* **2012**, *51*, 12090–12094. (e) Li, S.; Yang, W.; Shi, J.; Dan, T.; Han, Y.; Cao, Z.-C.; Yang, M. Synthesis of Trifluoromethyl-Substituted Allenols via Catalytic Trifluoromethylbenzoxylation of 1,3-Enynes. *ACS Catal.* **2023**, *13*, 2142–2148. (f) Storozhenko, O. A.; Festa, A. A.; Zolotareva, V. A.; Rybakov, V. B.; Varlamov, A. V.; Voskressensky, L. G. Photoredox-Catalyzed Chlorotrifluoromethylation of Arylallenes: Synthesis of a Trifluoromethyl Building Block. *Org. Lett.* **2023**, *25*, 438–442.

(10) For selected reviews, see (a) Bos, M.; Poisson, T.; Pannecoucke, X.; Charette, A. B.; Jubault, P. Recent Progress Toward the Synthesis of Trifluoromethyl- and Difluoromethyl-Substituted Cyclopropanes. *Chem. - Eur. J.* **2017**, *23*, 4950–4961. (b) Decaens, J.; Couve-Bonnaire, S.; Charette, A. B.; Poisson, T.; Jubault, P. Synthesis of Fluoro-, Monofluoromethyl-, Difluoromethyl-, and Trifluoromethyl-Substituted Three-Membered Rings. *Chem. - Eur. J.* **2021**, *27*, 2935–2962. (c) Pons, A.; Delion, L.; Poisson, T.; Charette, A. B.; Jubault, P. Asymmetric Synthesis of Fluoro, Fluoromethyl, Difluoromethyl, and Trifluoromethylcyclopropanes. *Acc. Chem. Res.* **2021**, *54*, 2969–2990. (d) Wu, W. F.; Lin, J. H.; Xiao, J. C.; Cao, Y. C.; Ma, Y. Recent Advances in the Synthesis of CF_3 - or HCF_2 -Substituted Cyclopropanes. *Asian J. Org. Chem.* **2021**, *10*, 485–495.

(11) For selected examples, see (a) Kikushima, K.; Etou, Y.; Kamura, R.; Takeda, I.; Ito, H.; Ohashi, M.; Ogoshi, S. Direct Transformation of Tetrafluoroethylene to Trifluorovinylzinc via sp^2 C–F Bond Activation. *Org. Lett.* **2020**, *22*, 8167–8172. (b) Zhang, Y.; Wu, D.; Weng, Z. Synthesis of 1,2,2-trifluorovinyl sulphides and selenides from trifluorovinylolation of organic thiocyanates and selenocyanates. *Org. Chem. Front.* **2017**, *4*, 2226–2229. (c) Levin, V. V.; Dilman, A. D.; Belyakov, P. A.; Struchkova, M. I.; Tartakovsky, V. A. Nucleophilic trifluoromethylation with organoboron reagents. *Tetrahedron Lett.* **2011**, *52*, 281–284. (d) Kirij, N. V.; Dontsova, D. A.; Pavlenko, N. V.; Yagupolskii, Y. L.; Scherer, H.; Tyrra, W.; Naumann, D. Insight into the Reactions of Trifluorovinylsilanes with Aromatic Aldehydes. *Eur. J. Org. Chem.* **2008**, *2008*, 2267–2272. (e) Raghavanpillai, A.; Burton, D. J. Room Temperature Preparation of Trifluoroethenylzinc Reagent by Metalation of the Readily Available Halocarbon HFC-134a and an Efficient, Economically Viable Synthesis of 1,2,2-Trifluorostyrenes. *J. Org. Chem.* **2004**, *69*, 7083–7091. (f) Funabiki, K.; Sawa, K.-i.; Shibata, K.; Matsui, M. CFC- or HFC-Free Approach to α -Substituted β,γ,γ -Trifluoroalkyl Alcohols by the Reaction of β -Fluoro- β -trifluoromethylated Enol Tosylate with Grignard Reagents. *Synlett* **2002**, *2002*, 1134–1136. (g) Hagiwara, T.; Fuchikami, T. 1,2-Bis(dimethylphenylsilyl)tetrafluoroethane. Application to the Trifluorovinylolation and Tetrafluoroethylenation of Carbonyl Compounds. *Chem. Lett.* **1997**, *26*, 787–788.

(12) (a) Feng, Z.; Riemann, L.; Guo, Z.; Herrero, D.; Simon, M.; Golz, C.; Mata, R. A.; Alcarazo, M. Pentafluorocyclopropanation of (Hetero)arenes Using Sulfonium Salts: Applications in Late-Stage Functionalization. *Angew. Chem., Int. Ed.* **2023**, *135*, No. e202306764. (b) Liu, R.; Hu, J. Synthesis of Aryl Perfluorocyclopropyl Ethers via [2 + 1] Cyclopropanation Using $TMSCF_2Br$ Reagent. *Org. Lett.* **2022**, *24*, 3589–3593. (c) Yang, Z. Y. Preparation of highly fluorinated cyclopropanes and ring-opening reactions with halogens. *J. Org. Chem.* **2003**, *68*, 4410–4416.

- (13) (a) Wang, Q.; Hu, J. Fluorocarbon Chain Homologation and Elongation Reactions. In *Homologation Reactions*; Pace, V., Ed.; Wiley, 2023; pp 575–594. (b) Liu, A.; Ni, C.; Xie, Q.; Hu, J. Transition-Metal-Free Controllable Single and Double Difluoromethylene Formal Insertions into C–H Bonds of Aldehydes with TMSCF_2Br . *Angew. Chem., Int. Ed.* **2023**, 62, No. e202217088. (c) Wang, X.; Pan, S.; Luo, Q.; Wang, Q.; Ni, C.; Hu, J. Controllable Single and Double Difluoromethylene Insertions into C–Cu Bonds: Copper-Mediated Tetrafluoroethylation and Hexafluoropropylation of Aryl Iodides with TMSCF_2H and TMSCF_2Br . *J. Am. Chem. Soc.* **2022**, 144, 12202–12211. (d) Pan, S.; Xie, Q.; Wang, X.; Wang, Q.; Ni, C.; Hu, J. Copper-mediated pentafluoroethylation of organoboronates and terminal alkynes with TMSCF_3 . *Chem. Commun.* **2022**, 58, 5156–5159. (e) Fu, X. P.; Xue, X. S.; Zhang, X. Y.; Xiao, Y. L.; Zhang, S.; Guo, Y. L.; Leng, X.; Houk, K. N.; Zhang, X. Controllable catalytic difluorocarbene transfer enables access to diversified fluoroalkylated arenes. *Nat. Chem.* **2019**, 11, 948–956. (f) Xie, Q.; Zhu, Z.; Li, L.; Ni, C.; Hu, J. Controllable double CF_2 -insertion into sp^2 C–Cu bond using TMSCF_3 : a facile access to tetrafluoroethylene-bridged structures. *Chem. Sci.* **2020**, 11, 276–280. (g) Xie, Q.; Li, L.; Zhu, Z.; Zhang, R.; Ni, C.; Hu, J. From C_1 to C_2 : TMSCF_3 as a Precursor for Pentafluoroethylation. *Angew. Chem., Int. Ed.* **2018**, 57, 13211–13215. (h) Mestre, J.; Castillon, S.; Boutureira, O. "Ligandless" Pentafluoroethylation of Unactivated (Hetero)aryl and Alkenyl Halides Enabled by the Controlled Self-Condensation of TMSCF_3 -Derived CuCF_3 . *J. Org. Chem.* **2019**, 84, 15087–15097. (i) Yang, Z. Y.; Burton, D. J. A novel double insertion of the difluoromethylene unit from trifluoromethylcopper into the carbon-copper bond of perfluoroaryl- and perfluorovinylcopper reagents: preparation, mechanism and applications of new fluorinated copper reagents. *J. Fluorine Chem.* **2000**, 102, 89–103. (j) Yang, Z. Y.; Wiemers, D. M.; Burton, D. J. Trifluoromethylcopper: a useful difluoromethylene transfer reagent: a novel double insertion of difluoromethylene into pentafluorophenylcopper. *J. Am. Chem. Soc.* **1992**, 114, 4402–4403.
- (14) (a) Wang, F.; Zhang, W.; Zhu, J.; Li, H.; Huang, K. W.; Hu, J. Chloride ion-catalyzed generation of difluorocarbene for efficient preparation of *gem*-difluorinated cyclopropanes and cyclopropanes. *Chem. Commun.* **2011**, 47, 2411–2413. (b) Li, L.; Wang, F.; Ni, C.; Hu, J. Synthesis of *gem*-difluorocyclopropa(n)es and O-, S-, N-, and P-difluoromethylated compounds with TMSCF_2Br . *Angew. Chem., Int. Ed.* **2013**, 52, 12390–12394.
- (15) For selected examples by our group, see (a) Xie, Q.; Ni, C.; Zhang, R.; Li, L.; Rong, J.; Hu, J. Efficient Difluoromethylation of Alcohols Using TMSCF_2Br as a Unique and Practical Difluorocarbene Reagent under Mild Conditions. *Angew. Chem., Int. Ed.* **2017**, 56, 3206–3210. (b) Xie, Q.; Zhu, Z.; Li, L.; Ni, C.; Hu, J. A General Protocol for C–H Difluoromethylation of Carbon Acids with TMSCF_2Br . *Angew. Chem., Int. Ed.* **2019**, 58, 6405–6410. (c) Liu, A.; Ni, C.; Xie, Q.; Hu, J. TMSCF_2Br -Enabled Fluorination-Aminocarbonylation of Aldehydes: Modular Access to α -Fluoroamides. *Angew. Chem., Int. Ed.* **2022**, 61, No. e202115467.
- (16) For recent examples by other groups, see (a) Yuan, W.-J.; Tong, C.-L.; Xu, X.-H.; Qing, F.-L. Copper-Mediated Oxidative Chloro- and Bromodifluoromethylation of Phenols. *J. Am. Chem. Soc.* **2023**, 145, 23899. (b) Trifonov, A. L.; Dilman, A. D. *gem*-Difluoroolefination of Amides. *Chem. - Eur. J.* **2023**, 29, No. e202303144. (c) Mao, Y.; Li, N.; Liu, J.; Jiang, Z.-X.; Yang, Z. TBAF-Mediated [3 + 1] Cycloaddition of Difluorocarbene to Access *gem*-Difluorinated 1,2-Diazetidine Analogues as Potent Anticancer Agents. *Org. Lett.* **2023**, 25, 7567–7572. (d) Hayashi, H.; Katsuyama, H.; Takano, H.; Harabuchi, Y.; Maeda, S.; Mita, T. In silico reaction screening with difluorocarbene for N-difluoroalkylative dearomatization of pyridines. *Nat. Synth.* **2022**, 1, 804–814. (e) Lim, H.; Seong, S.; Kim, Y.; Seo, S.; Han, S. Biopatterned Reorganization of Alkaloids Enabled by Ring-Opening Functionalization of Tertiary Amines. *J. Am. Chem. Soc.* **2021**, 143, 19966–19974.
- (17) Hu, M.; Ni, C.; Li, L.; Han, Y.; Hu, J. *gem*-Difluoroolefination of Diazo Compounds with TMSCF_3 or TMSCF_2Br : Transition-Metal-Free Cross-Coupling of Two Carbene Precursors. *J. Am. Chem. Soc.* **2015**, 137, 14496–14501.
- (18) For selected reviews, see (a) Chen, S.; Zhao, Y. C(sp³)—C(sp³) Bond Formation via Transition-Metal Mediated and Catalyzed Reductive Homocouplings. *Chin. J. Org. Chem.* **2020**, 40, 3078–3093. (b) Koch, A.; Dufrois, Q.; Wirgenings, M.; Görls, H.; Kriek, S.; Etienne, M.; Pohnert, G.; Westerhausen, M. Direct Synthesis of Heavy Grignard Reagents: Challenges, Limitations, and Derivatization. *Chem. - Eur. J.* **2018**, 24, 16840–16850. (c) Stefani, H. A.; Guarezemini, A. S.; Cella, R. Homocoupling reactions of alkynes, alkenes and alkyl compounds. *Tetrahedron* **2010**, 66, 7871–7918.
- (19) For selected examples, see (a) Dilman, A.; Levin, V.; Agababyan, D.; Struchkova, M. Dimerization of Benzyl and Allyl Halides via Photoredox-Mediated Disproportionation of Organozinc Reagents. *Synthesis* **2018**, 50, 2930–2935. (b) Dolbier, W. R., Jr.; Duan, J.-X.; Roche, A. J. A Novel, Non-High-Dilution Method for Preparation of 1,1,2,2,9,9,10,10-Octafluoro[2.2]paracyclophane. *Org. Lett.* **2000**, 2, 1867–1869. (c) Yudin, A. K.; Prakash, G. K. S.; Deffieux, D.; Bradley, M.; Bau, R.; Olah, G. A. Preparation of and Fluoroalkylation with (Chlorodifluoromethyl)trimethylsilane, Difluorobis(trimethylsilyl)methane, and 1,1,2,2-Tetrafluoro-1,2-bis-(trimethylsilyl)ethane. *J. Am. Chem. Soc.* **1997**, 119, 1572–1581. (d) Chen, G. J.; Tamborski, C. Solvents effects in reactions between perfluoroalkyl iodides and cadmium. *J. Fluorine Chem.* **1987**, 36, 123–139. (e) Fuchikami, T.; Ojima, I. Reaction of (bromodifluoromethyl)-phenyldimethylsilane with organometallic reagents. *J. Organomet. Chem.* **1981**, 212, 145–153. (f) Knunyants, I. L.; Dzhi-yuan', L.; Shokina, V. V. Perfluoro α,ω -diolefins and some of their reactions. *Russ. Chem. Bull.* **1961**, 10, 1361–1366. (g) LeGoff, E.; Ulrich, S. E.; Denney, D. B. Studies on the Mechanism of the Wurtz Reaction. The Configurations of 2-Bromoöctane, 3-Methylnonane and 7,8-Dimethyltetradecane. *J. Am. Chem. Soc.* **1958**, 80, 622–625. (h) Wurtz, A. Ueber eine neue Klasse organischer Radicale. *Justus Liebigs Ann. Chem.* **1855**, 96, 364–375.
- (20) Kosobokov, M. D.; Levin, V. V.; Zemtsov, A. A.; Struchkova, M. I.; Korlyukov, A. A.; Arkhipov, D. E.; Dilman, A. D. Geminal silicon/zinc reagent as an equivalent of difluoromethylene bis-carbanion. *Org. Lett.* **2014**, 16, 1438–1441.
- (21) Jeffries, B.; Wang, Z.; Felstead, H. R.; Le Questel, J.-Y.; Scott, J. S.; Chiarpain, E.; Graton, J.; Linclau, B. Systematic Investigation of Lipophilicity Modulation by Aliphatic Fluorination Motifs. *J. Med. Chem.* **2020**, 63, 1002–1031.
- (22) (a) Xu, W. Q.; Xu, X. H.; Qing, F. L. Synthesis and Properties of $\text{CF}_3(\text{OCF}_3)\text{CH}$ -Substituted Arenes and Alkenes. *Chin. J. Chem.* **2020**, 38, 847–854. (b) Thomson, C. J.; Zhang, Q.; Al-Maharik, N.; Buhl, M.; Cordes, D. B.; Slawin, A. M. Z.; O'Hagan, D. Fluorinated cyclopropanes: synthesis and chemistry of the aryl α,β,β -trifluorocyclopropane motif. *Chem. Commun.* **2018**, 54, 8415–8418.