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Communication

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

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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 trifluorovinylation 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 molecules[4] 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*-difluoroalkenes[7] and mono/*gem*-difluorocyclopropanes.[4c,d,8] Moreover, many approaches toward the synthesis of various fluoroalkyl-substituted alkenes[9] and cyclopropanes[10] 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 trifluoroalkenes[11] with two fluorinated carbon atoms (C_2) and, in particular, of pentafluorocyclopropanes[12] 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 tetrafluorocyclopropanation (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 $TMSCF_2CF_2TMS$, 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 trifluorovinylation 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 ($TMSCF_2CF_2TMS$) 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 $TMSCF_2CF_2TMS$. The reaction provided 40% yield of $TMSCF_2CF_2TMS$ in the

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Scheme 1. $TMSCF_2Br$-Enabled CFCE Strategy for the Synthesis of Fluoroalkenes and Fluorocyclopropanes

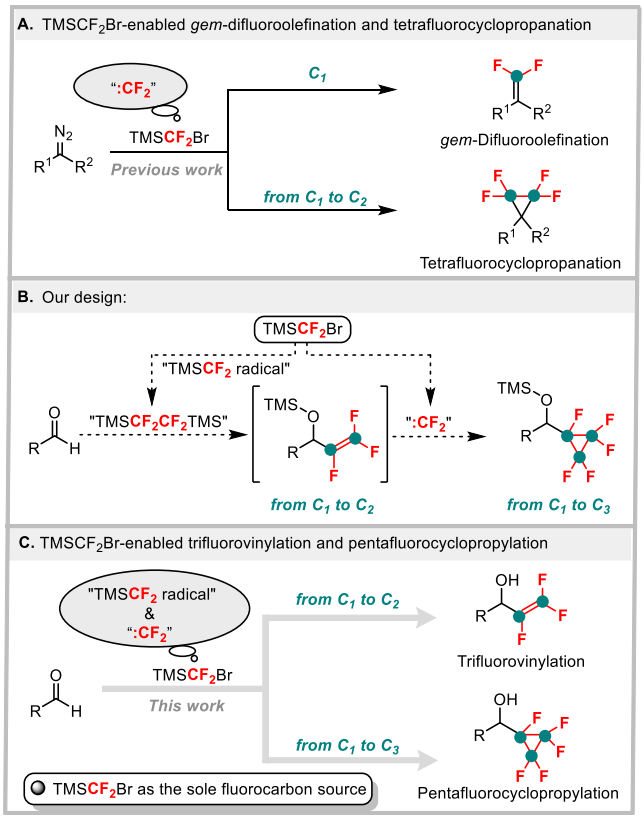
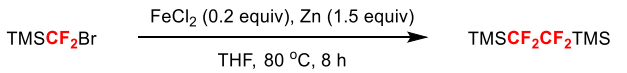


Table 1. Optimization of Reaction Conditions for the Homocoupling Reaction of $TMSCF_2Br$[a]



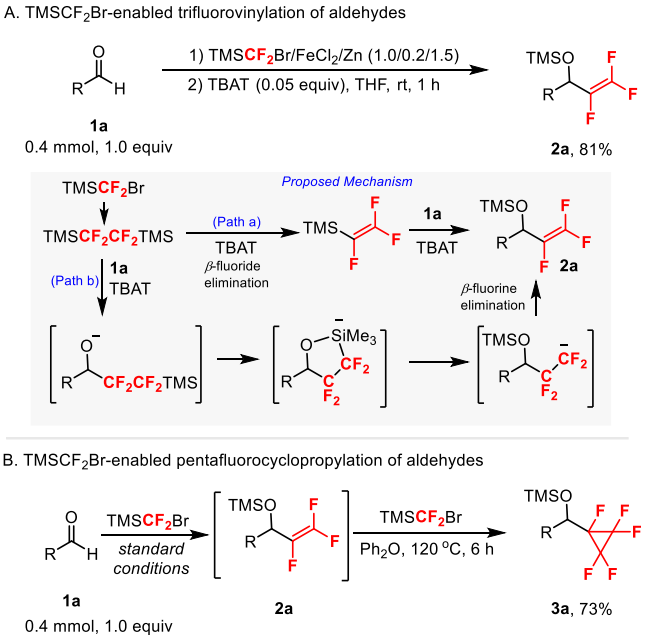
entry	deviation from standard conditions	yield (%)[b]
1	none	94
2	no $FeCl_2$	40
3	no Zn	n.d.[d]
4	50 °C	65
5	0.1 equiv of $FeCl_2$	68
6	DMF as solvent	43
7[c]	scaled up to 100 mmol	89

[a]Standard conditions: $TMSCF_2Br$ (0.8 mmol, 1.0 equiv), $FeCl_2$ (0.2 equiv), Zn (1.5 equiv) in THF (2 mL), 80 °C, 8 h. [b]Yields were determined by ^{19}F NMR using $PhCF_3$ as an internal standard. [c]Reaction was performed on a 100 mmol scale. [d]n.d. = not detected.

absence of $FeCl_2$ (Table 1, entry 2), and no yield of $TMSCF_2CF_2TMS$ was observed in the absence of zinc dust (Table 1, entry 3).[20] Lower temperatures, reduced usage of $FeCl_2$, and solvent changes led to lower yields of $TMSCF_2CF_2TMS$ (Table 1, entries 4–6). $TMSCF_2CF_2TMS$ 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 $TMSCF_2CF_2TMS$ for trifluorovinylation 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. Trifluorovinylation and Pentafluorocyclopropylation of 1a with $TMSCF_2Br$ Under the Optimized Conditions[a]



[a]Conditions for **2a** (R = 4-Ph−C_6H_4): $TMSCF_2Br$ (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 $TMSCF_2CF_2TMS$ (used after aqueous washing). **1a** (0.4 mmol, 1.0 equiv), TBAT (0.02 mmol, 0.05 equiv), the THF solution of $TMSCF_2CF_2TMS$ (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, $TMSCF_2Br$ (1.2 mmol, 3.0 equiv), Ph_2O (0.5 mL), 120 °C, 6 h. Yields were determined by ^{19}F NMR using 1-fluoronaphthalene or $PhCF_3$ as an internal standard.

$TMSCF_2CF_2TMS$ inhibited the desired trifluorovinylation 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 $TMSCF_2CF_2TMS$, and the obtained solution of $TMSCF_2CF_2TMS$ could smoothly react with aldehyde (**1a**) to afford the desired trifluorovinylation product (**2a**) in 81% yield. In accordance with the results reported by Prakash[19c] and Fuchikami,[11g] the trifluorovinylation 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 $TMSCF_2CF_2TMS$. After confirming the formation of trifluoroalkene (**2a**) generated from aldehyde (**1a**) and $TMSCF_2Br$, we further performed the [2 + 1] cycloaddition of the unseparated trifluoroalkene (**2a**) with difluorocarbene (generated from $TMSCF_2Br$) 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 trifluorovinylation could also serve as the initiator of the subsequent [2 + 1] cycloaddition reaction. The unseparated trifluoroalkene (**2a**) obtained from aldehydes (**1a**) and $TMSCF_2Br$ could, without

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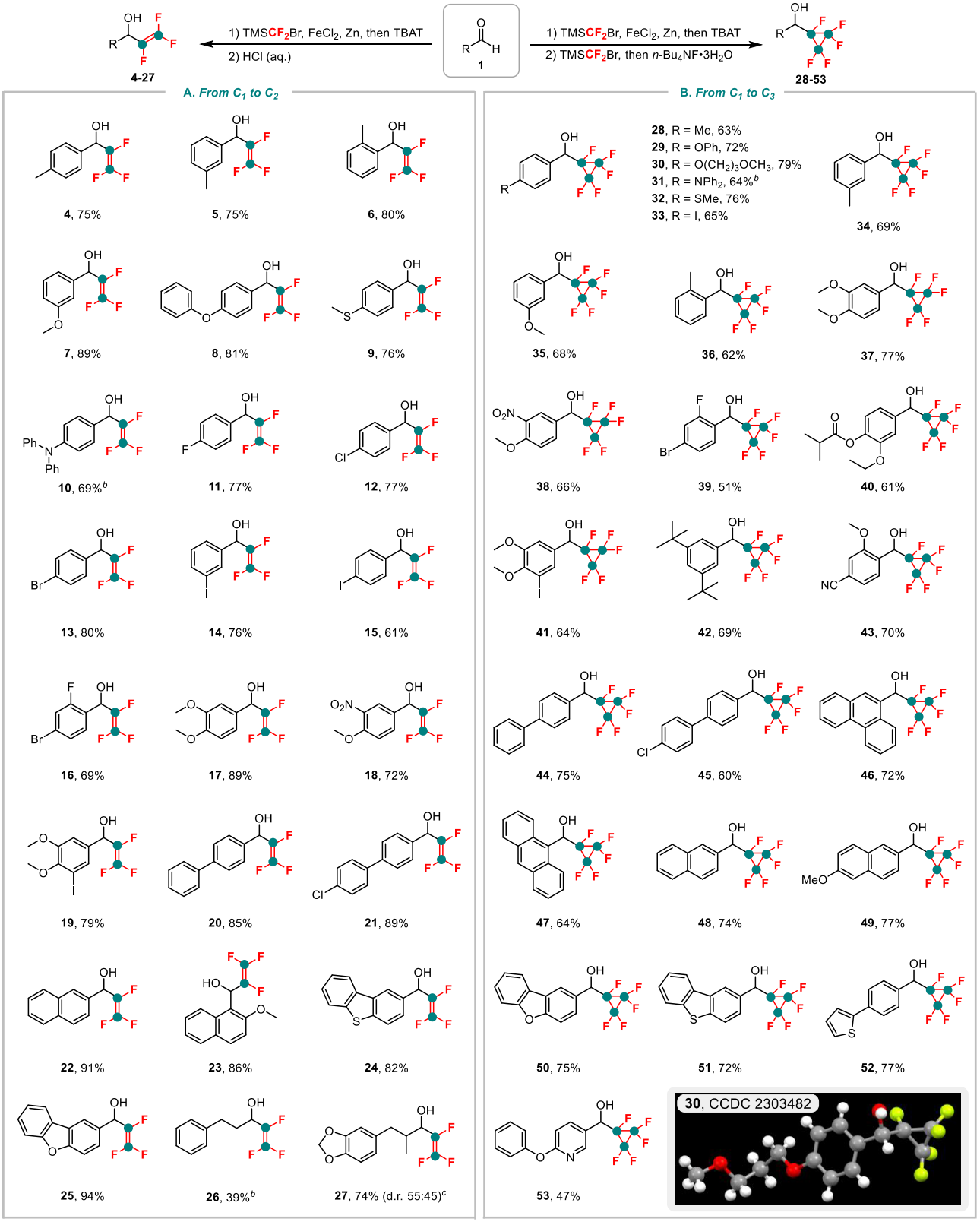
Scheme 3. Substrate Scopes for Trifluorovinylation and Pentafluorocyclopropylation of Aldehydes with $TMSCF_2Br$[a]



[a]Conditions 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 $TMSCF_2CF_2TMS$ (used after aqueous washing). **1** (0.4 mmol, 1.0 equiv), TBAT (0.02 mmol, 0.05 equiv), the THF solution of $TMSCF_2CF_2TMS$ (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*-$Bu_4NF{\cdot}3H_2O$ (2.0 mmol, 5.0 equiv), rt, 0.5 h. [b]Yields were determined by ^{19}F NMR using 1-fluoronaphthalene or $PhCF_3$ as an internal standard. [c]The diastereoisomer ratio (d.r.) was determined by ^{19}F NMR spectroscopy analysis.

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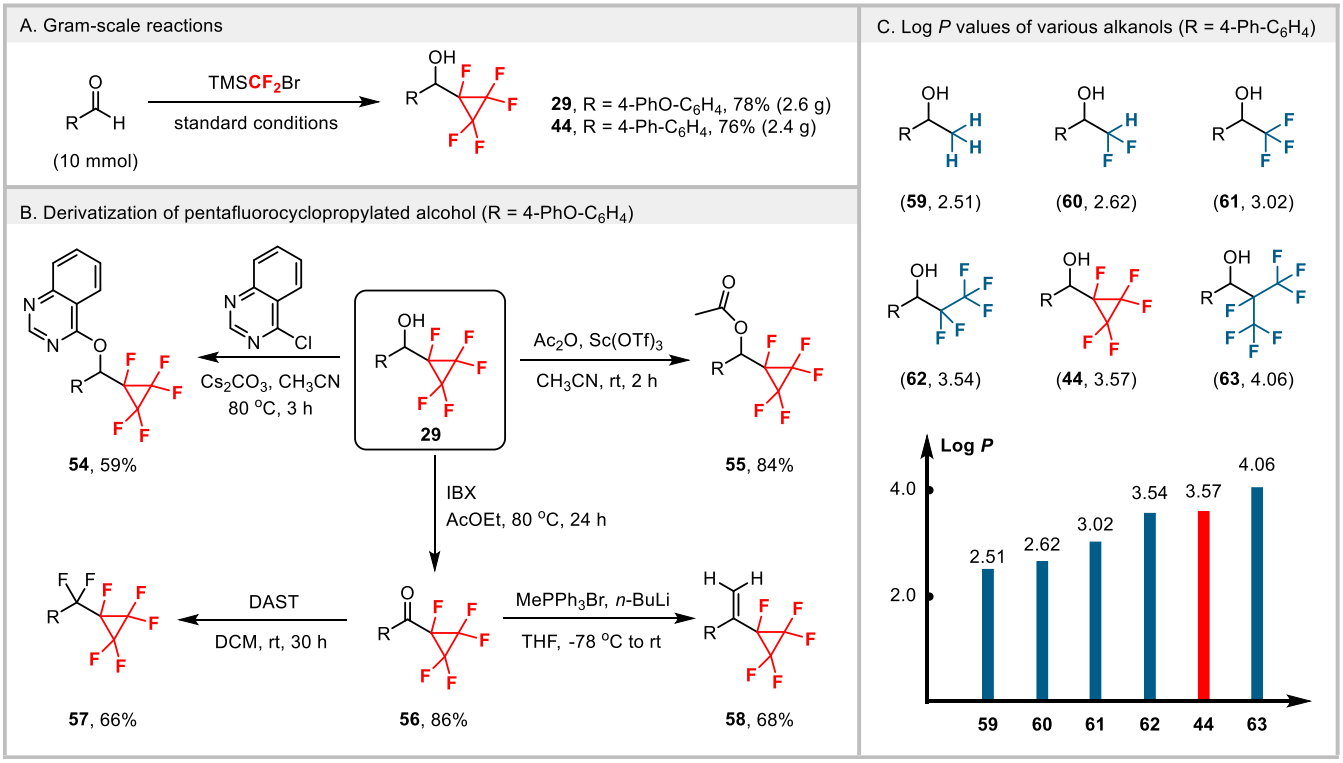
Scheme 4. Synthetic Applications[a]



[a]For reaction details, see the Supporting Information.

extra addition of an initiator, directly react with $TMSCF_2Br$ in Ph_2O at 120 °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 trifluorovinylation 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 trifluorovinylation reaction involving a C_1 to C_2 process, we turned our attention to investigate the substrate versatility of the unprecedented pentafluorocyclopropylation of aldehydes involving a C_1 to C_3 process (Scheme 3B). n-$Bu_4NF{\cdot}3H_2O$ 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-

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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 $TMSCF_2CF_2TMS$ 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 $TMSCF_2CF_2TMS$ 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

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.

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Notes

The authors declare no competing financial interest.

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