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Fluorine Chemistry

Transition-Metal-Free Controllable Single and Double Difluoromethylene Formal Insertions into C–H Bonds of Aldehydes with $TMSCF_2Br$

*An Liu, Chuanfa Ni, Qiqiang Xie, and Jinbo Hu**

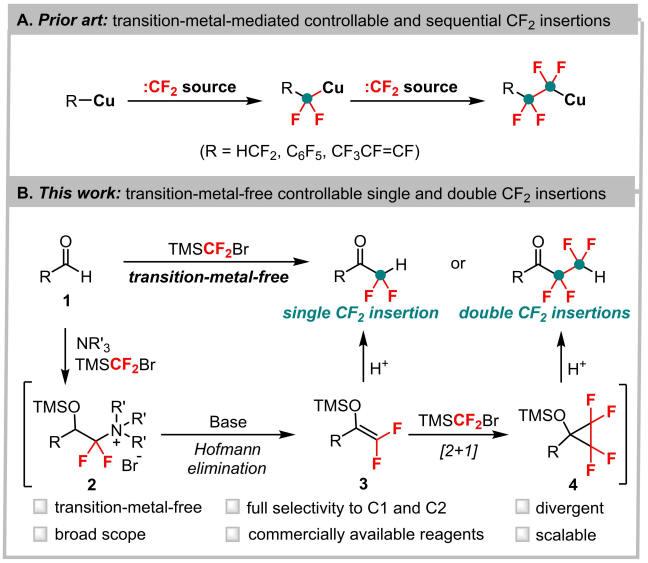
Abstract: We have developed a new strategy for controllable single and double difluoromethylene (CF_2) formal insertions into C–H bonds of aldehydes with nearly full selectivity under transition-metal-free conditions. The key to the success of controllable CF_2 insertions lies in the well-defined formation of 2,2-difluoroenolsilyl ether and 2,2,3,3-tetrafluorocyclopropanolsilyl ether intermediates using difluorocarbene reagent $TMSCF_2Br$ (TMS = trimethylsilyl). These two intermediates can react with various electrophiles including proton sources and various halogenation reagents, allowing for the access to diverse arrays of ketones containing difluoromethylene (CF_2) and tetrafluoroethylene (CF_2CF_2) units. The first synthesis of relatively stable 2,2,3,3-tetrafluorocyclopropanolsilyl ethers has been achieved, which offers a new platform to explore other unknown chemical space.

Introduction

The selective installation of difluoromethylene (CF_2) and tetrafluoroethylene (CF_2CF_2) units into organic molecules has been recognized as a particularly useful approach to modify various properties of molecules for the new design of pharmaceuticals, agrochemicals and materials.[1] For instance, the CF_2 group has been used as a bioisostere of various polar functional groups,[2] and its homologous CF_2CF_2 group has played crucial roles in liquid crystal materials.[3] Additionally, since the difluoromethyl (CF_2H) and tetrafluoroethyl (CF_2CF_2H) groups possess slightly acidic terminal hydrogen atoms, they can serve as lipophilic hydrogen bond donors.[4] Importantly, the terminal C–H bonds in CF_2H and CF_2CF_2H groups also provide sites for biodegrading,[5] which make these functional groups more environmentally friendly (especially when compared with their perfluoroalkyl analogs).[6] However, their synthetic methods are limited.[7,8] In particular, the synthesis of CF_2CF_2 units relies primarily on the deoxyfluorination of 1,2-dicarbonyls (requiring harsh conditions), or transformations of CF_2CF_2 fragments (commonly derived from the ozone-depleting 1,2-dibromotetrafluoroethane or the explosive tetrafluoroethylene).[8]

The use of difluorocarbene as a CF_2 unit for controllable CF_2 insertions is an ideal route toward the molecular architectures containing CF_2, CF_2CF_2 or even $[(CF_2)_n]$ units.[9] However, this strategy has shown unique challenges on the controlled insertions of more than one CF_2 units.[10] To the best of our knowledge, only a few examples have achieved sequential CF_2 insertions into R–Cu bonds in a highly selective manner (Scheme 1A).[11,12] And the direct sequential CF_2 insertion into other bonds (such as C–H, O–H, C–C, etc.) under transition-metal-free conditions for fluorocarbon chain elongation is difficult.[9]

Recently, we developed a multicomponent protocol for the synthesis of α-fluoroamides through sequential transformations of the TMS-protected difluorinated quaternary ammonium salts (**2**) generated in situ from aldehydes (**1**), tertiary amines and the difluorocarbene reagent $TMSCF_2Br$.[13] Inspired by this work, we envisioned that such pivotal intermediates **2** could undergo Hofman elimination under basic conditions to afford synthetically versa-



Scheme 1. Controllable single and double CF_2 insertions.

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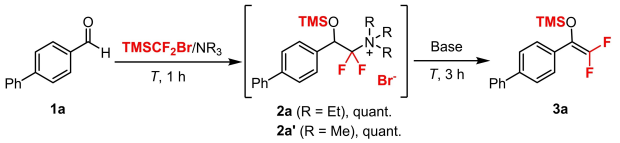
tile 2,2-difluoroenolsilyl ethers (**3**),[14] which then could react with difluorocarbene to deliver potentially valuable 2,2,3,3-tetrafluorocyclopropanolsilyl ethers (**4**).[15] Subsequently, the protonation of **3** and **4** could provide an opportunity to selectively access a range of functionalized difluoromethyl (CF_2H) and tetrafluoroethyl (CF_2CF_2H) ketones, respectively.[12e,16] The overall process can be viewed as transition-metal-free controllable single and double CF_2 insertions into the C–H bonds of aldehydes (Scheme 1B). However, to achieve this new synthetic strategy, several issues have to be considered. Firstly, although methods for the synthesis of **3** by *β*-elimination have been well established, using Hofman elimination to efficiently obtain **3** is still unexplored.[14a] Secondly, it has been known that the difluoromethylenation of C–C multiple bonds with difluorocarbene relies on relatively high temperatures,[17] which might likely cause competitive [2+2] cycloaddition and decomposition of **3**.[18] Finally, compared with nonfluorinated cyclopropanols, the ring-opening reactions of **4** may be hindered because multiple fluorine substitutions typically increase C–C bond strength.[19] Herein, we report our success in the develpoment of controllable single and double difluoromethylene formal insertions into C–H bonds of aldehydes under transition-metal-free conditions. It features nearly full selectivity towards C1 (single CF_2 insertion) and C2 (double CF_2 insertions), which is difficult to accomplish by transition-metal-mediated approaches.[11,12] It is noteworthy that the first synthesis of relatively stable compounds **4** offers a new platform to explore other unknown chemical space.[20]

Results and Discussion

Our study commenced with the examination of the Hofman elimination of the TMS-protected difluorinated quaternary ammonium salt intermediates **2** under various basic conditions (Table 1). Compound **2a** (or **2a′**) can be quantitatively prepared in situ by three-component reaction of *p*-phenylbenzaldehyde (**1a**), triethylamine (or trimethylamine) and the difluorocarbene reagent ($TMSCF_2Br$) according to our previous report.[13] When **2a** was treated with LiHMDS, the formation of the desired 2,2-difluoroenolsilyl ether (**3a**) was observed by ^{19}F NMR in 63 % yield (Table 1, entry 3). Considering that the undesired Hofman elimination involving the ethyl group (when R = Et) might compete with the desired Hofman elimination involving benzylic C–H bond in **2a**, we replaced **2a** (R = Et) by **2a′** (R = Me) and were delighted to find that **3a** was successfully formed in 94 % yield (Table 1, entry 5). In addition, this transformation could also be carried out at room temperature albeit with a slightly decreased yield (Table 1, entry 6).

Encouraged by the above results, we sought to probe the [2+1] cycloaddition of 2,2-difluoroenolsilyl ether intermediate **3a** with difluorocarbene (Table 2). Taking into account the concerns we mentioned above, the difluorocarbene reagent $TMSCF_2Br$, introduced by us in 2011,[21,22] might be a good choice to release difluorocarbene at milder conditions for avoiding other side reactions of unstable intermediate **3a** arising from high temperature. When 3.0 equivalents of $TMSCF_2Br$ and HMPA (the activator for $TMSCF_2Br$ to generate difluorocarbene) were added to **3a** (generated in situ from *p*-phenylbenzaldehyde (**1a**) and $TMSCF_2Br$ under the optimized conditions in Table 1) and the mixture reacted at room temperature for 4 hours, the desired **4a** was obtained in 15 % yield (Table 2, entry 1). Due to excess LiHMDS which perhaps causes unnecessary consumption of $TMSCF_2Br$, the addition of TMSCl to quench residual LiHMDS resulted in a slightly increased yield and more unreacted **3a** (71 %) was observed (Table 2,

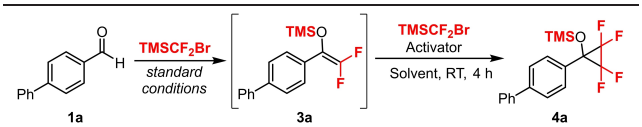
Table 1: Optimization of reaction conditions for **3a**.[a]



Entry	Base	NR_3	*T* [°C]	Yield of **3a** [%][b]
1	KO*t*Bu	NEt_3	−78 to −10	–
2	LiO*t*Bu	NEt_3	−78 to −10	–
3	LiHMDS	NEt_3	−78 to −10	63
4	LDA	NEt_3	−78 to −10	–
5	LiHMDS	NMe_3	−78 to −10	**94**
6	LiHMDS	NMe_3	RT	75

[a] Unless otherwise noted, reactions were performed using **1a** (0.2 mmol, 1.0 equiv), $TMSCF_2Br$ (0.26 mmol, 1.3 equiv), NR_3 (0.4 mmol, 2.0 equiv), THF (2 mL), *T*, 1 h; then base (0.5 mmol, 2.5 equiv), *T*, 3 h. [b] Determined by ^{19}F NMR using 1-fluoronaphthalene as an internal standard. THF = tetrahydrofuran.

Table 2: Optimization of reaction conditions for **4a**.[a]



Entry	Solvent	Activator for $TMSCF_2Br$	Yield of **4a** [%][b]	Yield of unreacted **3a** [%][b]
1	THF	HMPA	15	50
2[c]	THF	HMPA	21	71
3[c]	DCM	HMPA	**87**	0
4[c]	CH_3CN	HMPA	69	18
5[c]	DMF	HMPA	0	71
6[c]	$PhCH_3$	HMPA	3	79
7[c,d]	$PhCH_3$	TBAB	–	–
8[c]	DCM	DMPU	0	84

[a] Unless otherwise noted, reactions were performed using **3a** generated in situ from **1a** (0.2 mmol, 1.0 equiv) under the optimized conditions in Table 1, $TMSCF_2Br$ (3.0 equiv), activator (3.0 equiv), solvent (2 mL), RT, 4 h. [b] Determined by ^{19}F NMR using 1-fluoronaphthalene as an internal standard. [c] TMSCl (0.4 mmol, 2.0 equiv) was added into in situ generated **3a**, RT, 1 h; then $TMSCF_2Br$ (3.0 equiv) and activator (3.0 equiv) were added after switching solvents and filtration, RT, 4 h (for details, see the Supporting Information). [d] TBAB (0.04 mmol, 0.2 equiv), $PhCH_3$ (5 mL), 110 °C, 4 h. HMPA = hexamethylphosphoramide; TBAB = tetrabutylammonium bromide; DMPU = *N,N′*-dimethylpropyleneurea; DCM = dichloromethane; DMF = *N,N*-dimethylformamide.

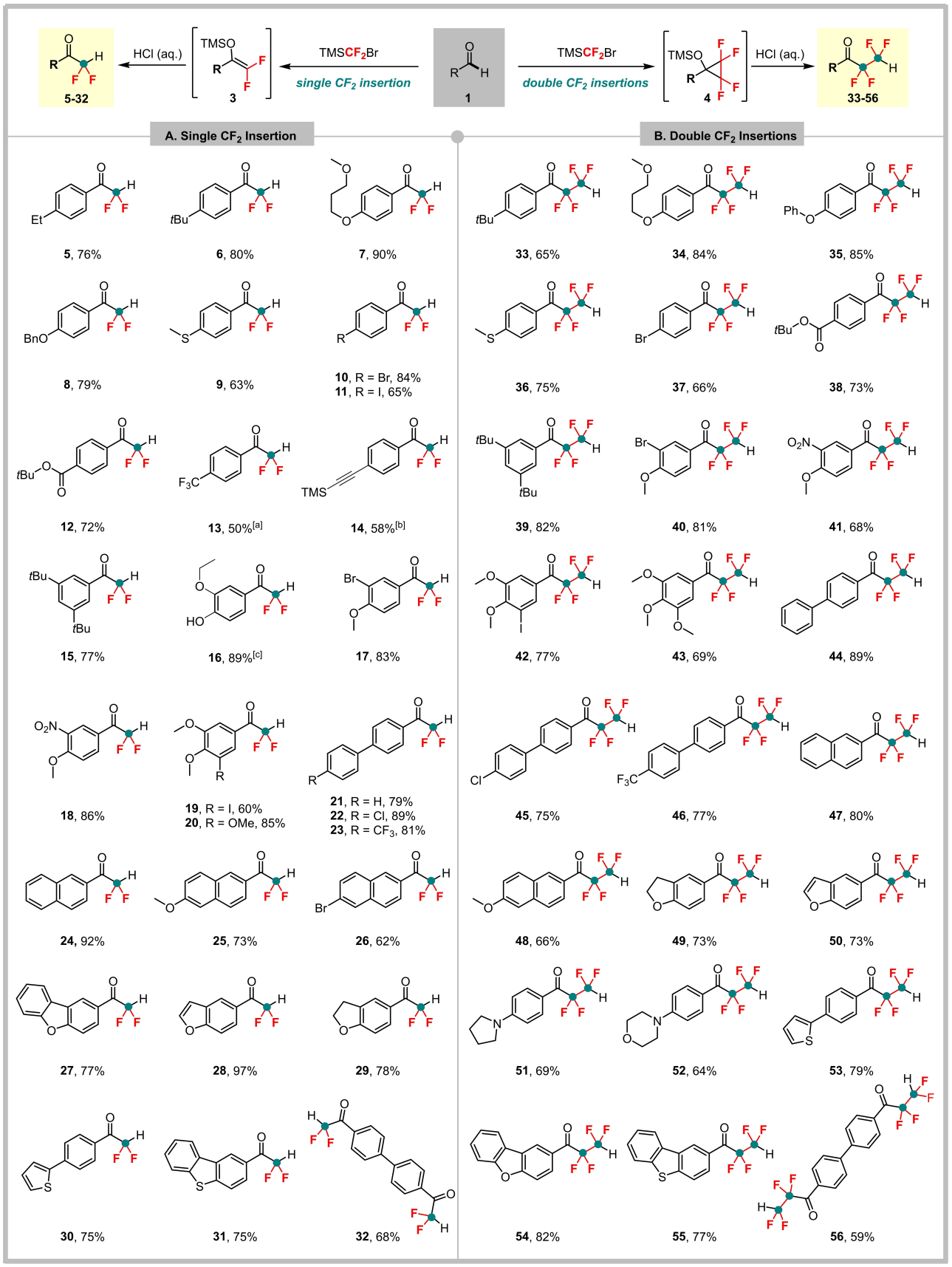
entry 2). Then, we found that switching the solvent from THF to dichloromethane (DCM) followed by filtration resulted in a significant yield increase of **4a** (87 %, Table 2, entry 3). It was remarkable that no residual 2,2-difluoroenolsilyl ether intermediate **3a** was observed by ^{19}F NMR, which alleviated our concern that unconverted **3a** could cause severe separation problems due to the simultaneous generation of the single and double CF_2 insertion products. This observation also indicates that nearly full selectivity towards C1 and C2 can be realized via this strategy, which is difficult to accomplish by the previously reported transition-metal-mediated methods. Solvent screening showed that when the reaction was carried out in CH_3CN, both **4a** (69 %) and unreacted **3a** (18 %) were observed by ^{19}F NMR (Table 2, entry 4). When DMF or $PhCH_3$ was used as solvent, little to no **4a** was produced (Table 2, entries 5–6). Other initiators such as DMPU and TBAB were also evaluated, and it showed that HMPA was the optimal choice for the present [2+1] cycloaddition reaction (Table 2, entry 7–8).

With these optimized conditions in hand, the protonation of 2,2-difluoroenolsilyl ether intermediates **3** by aqueous HCl solution to access diverse single CF_2 insertion products was first investigated (Scheme 2A). A wide range of aldehydes could serve as efficient substrates to afford the corresponding difluoromethyl ketones (**5**–**32**). Aromatic aldehydes bearing both electron-donating groups (such as alkyl (**5**–**6**), ethers (**7**–**8**) and methylthiol (**9**)) and electron-withdrawing groups (such as halogen (**10**–**11**), ester (**12**) and trifluoromethyl (**13**)) could undergo desired transformations, affording the corresponding products in 50 % to 90 % yields. Interestingly, terminal alkyne in 4-ethynylbenzaldehyde could also be deprotonated by LiHMDS to generate alkynyl carbanion, which reacted with excess $TMSCF_2Br$ to form **14** in 58 % yield. 3,5-Di-*tert*-butylbenzaldehyde was found to be a suitable substrate (**15**), but *ortho*-methylbenzaldehyde failed to undergo Hofman elimination. In addition, benzaldehydes with diverse substitution patterns (such as possessing single or multiple substituents at the *para*- and *meta*-position of aryl rings) were also well compatible with the reaction conditions, giving corresponding products in good yields (**16**–**20**). When aromatic aldehyde containing isobutyrate was subject to standard conditions, product **16** bearing OH group was obtained in 89 % yield due to the hydrolysis of the isobutyrate under acidic conditions. Notably, halogenated substrates, which could serve as a useful functional handle for further derivatizations but are known to be easily overreduced by the reported reduction methods,[23] were also successfully applied in the reaction (**10**, **11**, **17**, **19**, and **26**). A selection of extended π-systems was also demonstrated to be compatible with the reaction, including *p*-phenylbenzaldehydes (**21**–**23**) and naphthaldehydes (**24**–**26**). In addition, the reactions with oxygen- and sulfur-containing heteroaromatic aldehydes also gave the corresponding products **27**–**31** in good to excellent yields. Remarkably, [1,1′-biphenyl]-4,4′-dicarbaldehyde was able to undergo double-site CF_2-insertion reaction via the current strategy, affording product **32** in 68 % yield.

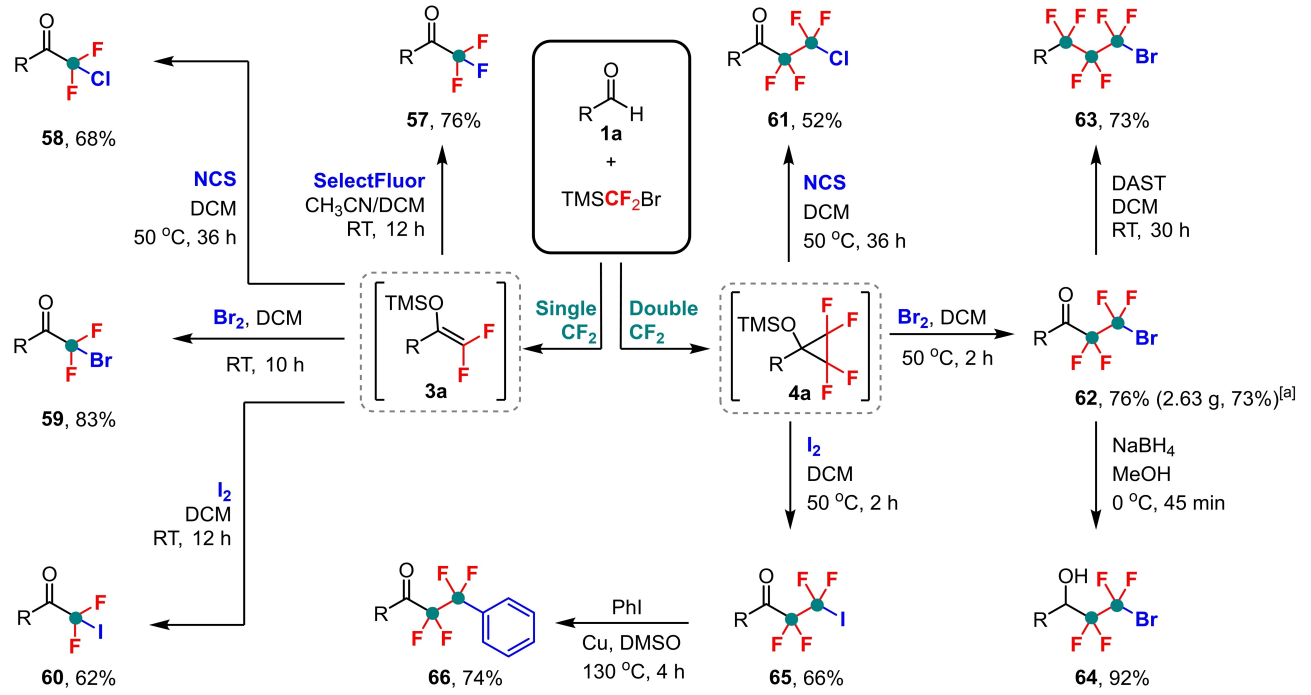
Subsequently, the substrate scope of controllable double CF_2 insertion products via an unprecedented protonation of in situ generated 2,2,3,3-tetrafluorocyclopropanolsilyl ether intermediates **4** was also examined (Scheme 2B). Notably, this novel transition-metal-free method showed nearly full C2 selectivity and was compatible with a diverse set of both electron-rich and electron-deficient aldehydes. A wide array of functional groups, such as *tert*-butyl (**33**), alkyl and aryl ethers (**34**–**35**), thioether (**36**), bromine (**37**, **40**), ester (**38**), nitro (**41**), iodine (**42**), chlorine (**45**), trifluoromethyl (**46**), and amine (**51**–**52**) were well tolerated under standard conditions. Varying the substitution patterns of aldehydes at the *para*- and *meta*-position of aryl rings did not affect the yields, as demonstrated by the examples of **39**–**43**. The reactions with aldehydes bearding polyaromatic rings (such as biphenyl (**44**–**46**) and naphthalene (**47**–**48**)) were able to provide corresponding products in 66–89 % yields. The reactions with heteroaryl aldehydes containing dihydrobenzofuran, benzofuran, pyrrolidine, morpholine, thiophene, dibenzo[*b*,*d*]furane, and dibenzo[*b*,*d*]thiophene groups were also examined, and the corresponding products **49**–**55** were obtained in moderate to good yields. It was also found that double-site CF_2-insertion reaction proceeded smoothly to give **56** in 59 % yield.

To further demonstrate the synthetic potential of the present controllable single and double CF_2-insersion method, the key intermediates **3a** and **4a** were successfully halogenated for the synthesis of other halodifluoromethyl and halotetrafluoroethyl ketones by various halogenation reagents (Scheme 3). It was found that SelectFluor, NCS, Br_2 and I_2 were all suitable electrophiles for in situ formed intermediate **3a**. Halodifluotomethyl ketones (**57**–**60**) were obtained in 62–83 % yields, respectively. The unprecedented halogenations of intermediate **4a** with NCS, Br_2 and I_2 were also realized, giving the corresponding halogenated products in moderate to good yields (**61**, **62** and **65**). It is noteworthy that the gram-scale bromination of intermediate **4a** was also successfully achieved to produce **62** (2.63 g) in 73 % yield without much loss of efficiency. Carbonyls are a class of important motifs for the development of pharmaceuticals and functional materials, which are capable of various transformations. We found that the deoxyfluorination of **62** in the presence of DAST was smoothly proceeded to furnish **63**, which, interestingly, offers an opportunity to access $RCF_2CF_2CF_2$-containing products. Compound **62** was also efficiently reduced by $NaBH_4$ to give **64** in 92 % isolated yield. Finally, copper-mediated cross coupling of **65** with PhI was accomplished to afford **66** in 74 % yield.

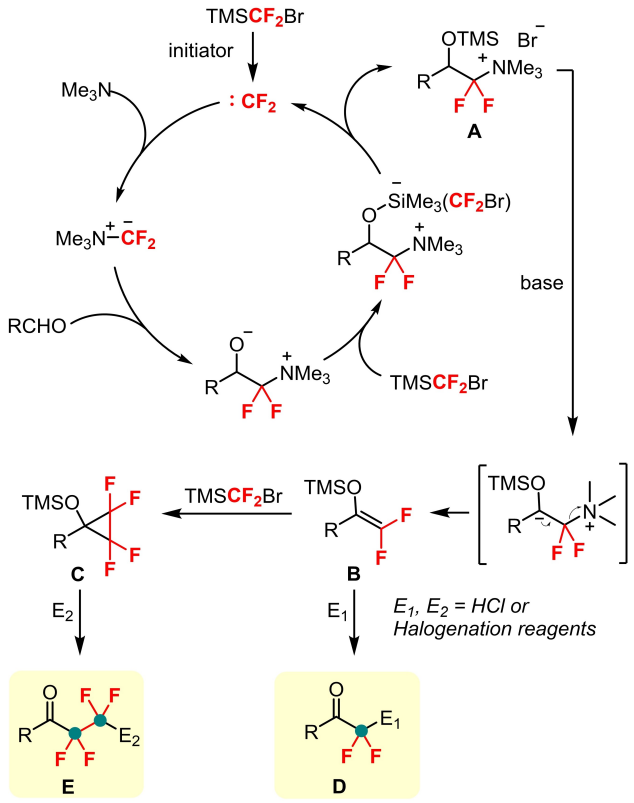
A plausible mechanism is depicted in Scheme 4. According to our previous report, TMS-protected quaternary ammonium salt intermediate **A** can be generated via a difluorocarbene-involved chain reaction pathway.[13] Subsequently, intermediate **A** undergoes Hofman elimination under basic conditions to afford the key intermediate **B** (2,2-difluoroenolsilyl ethers), which then can efficiently react with difluorocarbene to deliver another key intermediate **C** (2,2,3,3-tetrafluorocyclopropanolsilyl ethers) without residue of intermediate **B**. The complete conversion among intermediates **A**, **B** and **C** can be clearly determined by ^{19}F NMR



Scheme 2. Substrate scopes for controllable single and double CF_2 formal insertions into the C–H bonds of aldehydes. For reaction details, see the Supporting Information. The yield refers to the isolated yield. [a] The yield was determined by ^{19}F NMR using $PhCF_3$ as an internal standard. [b] 4-Ethynylbenzaldehyde was used as the starting substance. [c] 2-Ethoxy-4-formylphenyl isobutyrate was used as the starting substance.



Scheme 3. Halogenation reaction and representative synthetic applications. For reaction details, see the Supporting Information. The yield refers to the isolated yield of products **57**–**66** (R = 4-Ph-C_6H_4). [a] Performed on 10-mmol scale. SelectFluor = 1-ChloroMethyl-4-fluoro-1,4-diazoniabicyclo-[2.2.2]octane bis(tetrafluoroborate); NCS = *N*-Chlorosuccinimide; DAST = diethylaminosulfur trifluoride; DMSO = dimethyl sulfoxide.

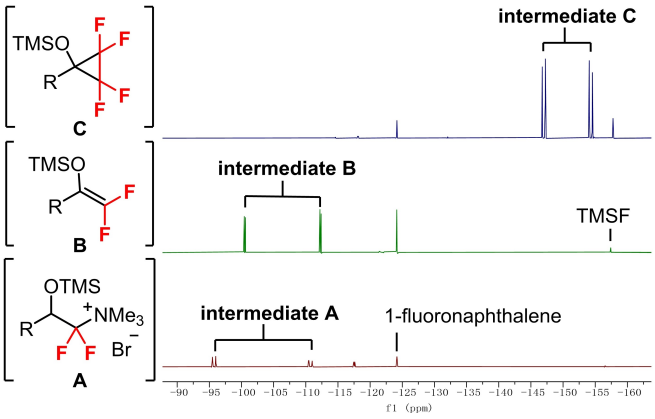


Scheme 4. Proposed mechanism.

(Scheme 5, R = 4-Ph-C_6H_4), which indicates that such controllable single and double CF_2 insertion method features nearly full selectivity toward C1 and C2. Finally, nucleophilic intermediates **B** and **C** can be intercepted by suitable electrophiles to selectively afford desirable single and double CF_2 insertion products (**D**, **E**).

Conclusion

In summary, the unprecedented controllable single and double difluoromethylene formal insertions into C–H bonds of aldehydes under transition-metal-free conditions has been realized, providing a distinct method to the streamlined access to structurally diverse ketones containing CF_2 or CF_2CF_2 units. This new synthetic strategy demonstrates nearly full selectivity of single and double CF_2 insertions, which is difficult to achieve by previously reported transition-metal-mediated methods. Highly selective formation of 2,2-difluoroenolsilyl ethers and 2,2,3,3-tetrafluorocyclopropanolsilyl ethers by the reaction of aldehydes and $TMSCF_2Br$ is the key to the success of this controllable CF_2 insertion reactions. Such two key intermediates were not only protonated by aqueous HCl, but also were successfully halogenated for the synthesis of other halodifluoromethyl and halotetrafluoroethyl ketones. The synthetic potency of this new method has been showcased by its scalability and various product diversifications. Notably, the relatively stable 2,2,3,3-tetrafluorocyclopropanolsilyl ethers were synthesized for the first time, which provide a new platform to explore other unknown chemical space. Further investiga-



Scheme 5. ^{19}F NMR experiment analysis *(Complete Conversion)*.

tions on their unique ring-opening reactivity arising from multiple fluorine substituents are underway in our laboratory.

Experimental Section

The data that support the findings of this study are available in the Supporting Information of this article.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: C–H Bond · Difluorocarbene · Difluoromethylene Insertion · Metal-Free · Selectivity

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