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Nucleophilic and electrophilic substitutions of difluoropropargyl bromides

Gerald B. Hammond *

Department of Chemistry, University of Louisville, Louisville, KY 40292, USA

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Abstract

Fundamental organic reactions like nucleophilic and electrophilic substitutions have seldom been studied on fluorinated propargyl or allenyl modules, when the carbon atom undergoing substitution is bonded to two fluorine atoms. Herein we report a practical synthesis of difluoropropargyl bromides from substituted acetylenes and dibromodifluorometane using a wide variety of alkyl, aryl or silyl substrates. The synthesis of *O*-, *S*- and carboxylic acid derivatives of difluoropropargyl bromide is also described. These compounds are suitable starting materials for the synthesis of electrophilically substituted difluoropropargyl derivatives via magnesium and fluoride promoted reactions. An indium-mediated reaction of silyldifluoropropargyl bromide, followed by electrophilic trapping with bromine led to a very useful bromoallene, which was then used in reactions with nucleophiles (C, O, N, P, S, Hal) to yield a de facto bimolecular nucleophilic substitution of a difluoropropargyl bromide.

Keywords: Difluoropropargyl; Fluorinated allenes; Nucleophilic substitution; Electrophilic substitution; Indium; Magnesium; TIPS

1. Introduction

It is well known that alkynes and allenes are of paramount importance in organic chemistry, both as synthetic building blocks, and targets [1–4]. Conceptually, the substitution of two fluorine atoms on an allenic or propargylic carbons could lead to the discovery of novel reactions and provide potential targets of biological importance [5]. Traditional synthetic approaches to functionalized allenes or alkynes involve S_N and S_E substitutions. However, even though these types of reactions are essential part of the arsenal of organic reactions, they have seldom been studied on fluorinated propargyl or allenyl modules, when the carbon atom undergoing substitution is bonded to fluorine atoms. Indeed, R–C≡C–CF_2Nu (**3**) cannot be synthesized from R–C≡C–CF_2Br (**1**) under normal conditions using S_N2-type reactions. This lack of reactivity is attributed to the shielding of the carbon atom by the surrounding fluorine atoms [6]. Another synthetic challenge is the preparation of substituted difluoroallene **5** through a organometallic S_N2'displacement (e.g. Grignard reaction). In this case, the initial bromine–magnesium exchange would lead to a magnesium carbenoid intermediate [7], which then undergoes a facile loss of fluorine through α-elimination, thus forming complex mixtures. In this paper we will examine the effects of fluorine activation on S_N2', S_E2 and S_E2' reactions, that is, the substitution of a bromine in **1** by a nucleophile or an electrophile, namely **3** or **2**; and the preparation of an electrophilically substituted allene **4** (Scheme 1).

2. Results and discussion

2.1. Synthesis of substituted difluoropropargyl bromide *1*

The starting material used in this work, difluoropropargyl bromide **1**, has been utilized by other workers in the synthesis of difluorosugars [8], substituted fluorofurans, [9], fluorinated diynes [10], intermediates in the preparation of HIV proteins inhibitors [11], difluorohomopropargyl alcohols [12], and difluoroaldonic acids [13]. Wakselman and coworkers [14], reported the first preparation of **1**, which consisted in alkynylation of a lithium acetylide derived from **6** with CF_2Br_2 (Eq. (1)). Both, ionic [10,14] and SET [15] mechanisms have

* Tel.: +1 502 852 5998.
E-mail address: gb.hammond@louisville.edu.

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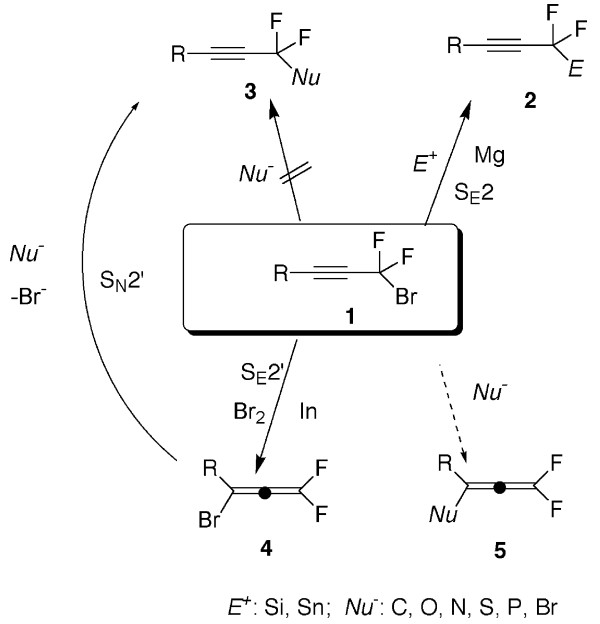
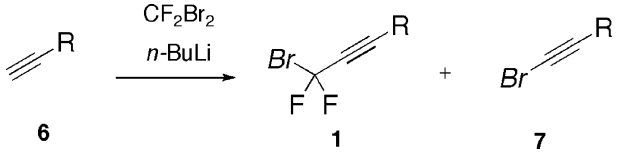


Scheme 1. Transformation of **1** using nucleophilic and electrophilic substitutions.

been postulated for this reaction. The major side product in the preparation of **1** is bromoalkyne **7** (Eq. (1)). A new method for preparing aryl derivatives of **1** (R = Ar) in two steps from $CBrF_2$–$CBrF_2$ was reported recently [16]. However, the yields were not significantly better. For example, for Ar = *p*-Cl–C_6H_4, *p*-MeO–C_6H_4, *p*-Br–C_6H_4, *o*-Cl–C_6H_4, and *o*,*p*-diCl–C_6H_3, the yields ranged between 15 and 35%. In view of the low yields and scarce diversity of substituents on the acetylenic carbon of **1** reported thus far, we set out to develop a more efficient protocol, the results of which have been recently published [17].

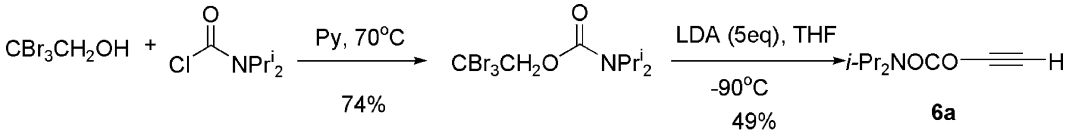


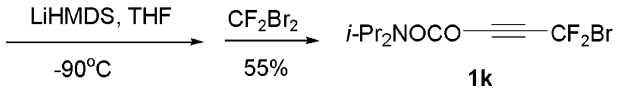
(1)

In stark contrast to the modest yields described above, we obtained the silyl substituted **1a** (R = TIPS) in 82% yield [18]. We surmised that this high yield was associated with the distinctive properties of the TIPS group [19]. Similar results were obtained with other bulky silyl substituents [20]. However, with R = TMS the yield was disappointingly low (19%) under the same conditions. By reducing the number of equivalents of CF_2Br_2, *n*-butyllithium, and the concentration of the solution, and at the same time controlling the temperature of the reaction mixture (rather than the cooling bath), we increased the yields significantly (Table 1).

The TIPS substituent produced the highest yield of **1** (entry 1). The triethylsilyl (TES) group in **1d** was a better alternative to the TMS group (compare entries 2 and 4). The yield of the phenyl analog **1c** (entry 3) was higher than substituted benzenes (compare with entries 5 and 6). An electron-withdrawing substituent on the benzene ring increased the yield of **1** in comparison with an electron-donating substituent (compare entries 7 and 8). Notably, our procedure proved highly effective for the synthesis of alkyl substituents **1i** and **1j** (entries 9 and 10). These reactions were conducted at submolar scale. In our experience, large-scale reactions tend to give better yields of **1** because of diminished losses associated with the column hold up of the distillation apparatus.

We also investigated the feasibility of synthesizing heteroatom substituted difluoropropargyl bromides **1k**, **1l**, **1m** and the carboxylic acid derivative **1n**. The preparation of *S*- and *O*-substituted difluoropropargyl precursors **1k** (Eq. (2)) and **1l** (Eq. (3)) involved multi-step syntheses of the corresponding precursors **6a** and **6b**:





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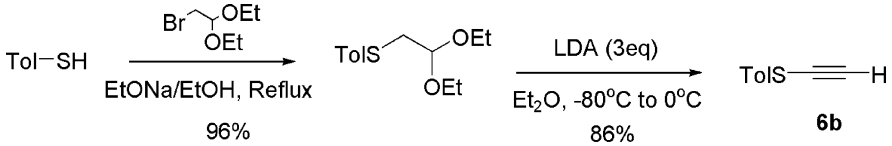
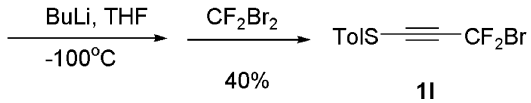
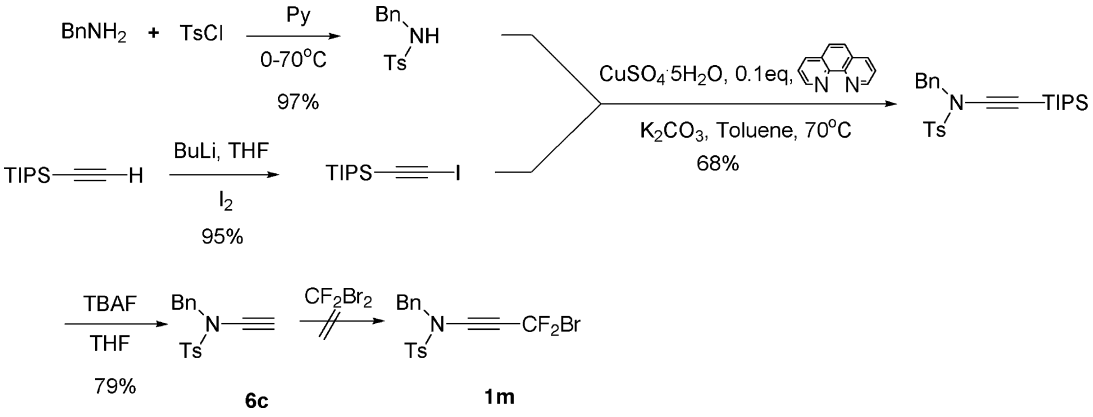




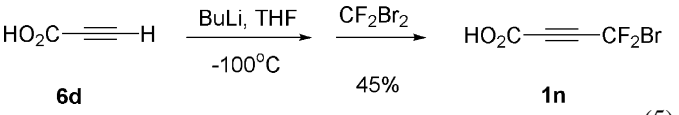
(3)

To our disappointment, the synthesis of the acetylenic amine analog **1m** could not be accomplished despite repeated attempts using various basic conditions (Eq. (4)):



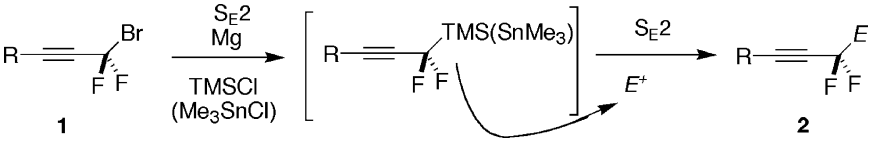
(4)

The carboxylic acid derivative **1n** could be obtained in one step from the commercially available propiolic acid **6d**, albeit in moderate yield (Eq. (5)):



(5)

2.2. S_E2 substitution of gem-difluoropropargyl bromide **1** via Mg(0)-promoted debromometalation (Eq. (6))



(6)

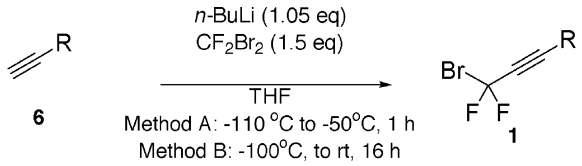
The *gem*-difluoromethylene group (–CF_2–), where the carbon atom is sp^3 hybridized, has received much attention for its protease inhibition, phosphate mimicry, or metabolic oxidation blocking properties, and as enzyme inactivator when substituted on the β-position of aminoacids [21–23]. Similarly, the *gem*-difluoroethylidene group (CF_2=C<), with a sp^2 hybridized carbon-bearing fluorine, is a well known synthetic building block, whose carbonyl mimicking property has aroused interest recently, because of the apparent reversal effect in the regioselectivity of NAD(P)H-dependent hydride transfer in sugars [24]. Methods for the introduction of fluorine in –CF_2– include electrophilic and nucleophilic fluorinating agents [22] or building blocks [25].

We recently reported [26] a practical S_E2 synthesis of *gem*-difluoropropargylsilanes **2a–g** and *gem*-difluoropropargyl stannane **2h** using a Mg(0)-promoted reductive debromometalation of 3-bromo-3,3-difluoropropyne **1** (Eq. (6) and Table 2). As shown in Table 2, the procedure for the selective formation of **2** works well for a diverse group of aromatic and aliphatic alkynes.

Neither over-reduction nor C–F bond cleavage were observed. In the case of aromatic alkynes, the reactions were completed within 30 min at 0 °C in THF (entries 1–4). Also, an aliphatic alkyne reacts smoothly to give the corresponding silylated difluoroalkyne at 0 °C in THF (entry 5), as compared with aliphatic ketones and imines which required DMF as a solvent and high temperature. Moreover, silylated alkynes **1a**, **1d** generally give good yields (entries 6, 7). Using the same protocol, **1c** reacted with trimethylstannyl chloride to give the stannane **2h** in 75% (entry 8). Silylated or stannylated *gem*-difluoropropargyl **2** could act as key intermediates in the synthesis of *gem*-difluoromethylene containing modules because of the rich chemistry of acetylenes. To demonstrate their synthetic utility, we reacted **2d** with benzaldehyde to give **8a** in excellent yield (Scheme 2). Allylation and benzylation produced **8b** and **8c**, respectively, in satisfactory yields.

During our investigations on the preparation of silylated or stannylated *gem*-difluoropropargyl synthons, RC≡C–CF_2Si(Sn), we noticed that the analysis of **2** using mass spectrometry did not yield the expected $M+1$ peak under conditions of methane chemical ionization (methane-CI). When methane-CI ionization was employed, all *gem*-difluoropropargyl synthons produced ions at $[M-19]^+$. These presented as base peaks in the CI spectra of all compounds in which the opposing alkyne substituent was aromatic. Taken together, the CI spectra of *gem*-difluoropropargyl compounds indicate cleavage of the C–F bond is a likely event under conditions of methane chemical ionization. However such C–F bond cleavage is not common in spectra of fluorinated carbon structures due to the strength of the C–F bond. Consequently,

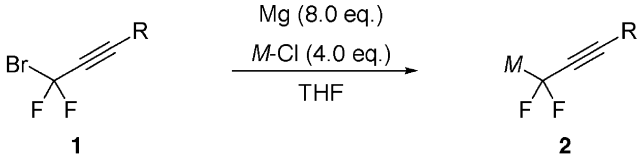
Table 1
An efficient synthesis of difluoropropargyl bromide **1**



Entry	R	Method	% yield of **2**[a]
1	TIPS (**1a**)	B	92
2	TMS (**1b**)	A	52
3	phenyl (**1c**)	B	82
4	TES (**1d**)	B	74
5	*p*-MeC_6H_4 (**1e**)	B	61
6	*o*-MeC_6H_4 (**1f**)	B	42
7	*p*-$MeOC_6H_4$ (**1g**)	B	53
8	*p*-$CF_3C_6H_4$ (**1h**)	B	78
9	hexyl (**1i**)	A	81[b]
10	(3-Me)butyl (**1j**)	A	71

[a] Yield after distillation.
[b] The only other reported yield of an alkyl substituted derivative (pentyl) is 46%.

Table 2
Mg(0)-promoted debromometalation of difluorobromoalkyne **1**[a]



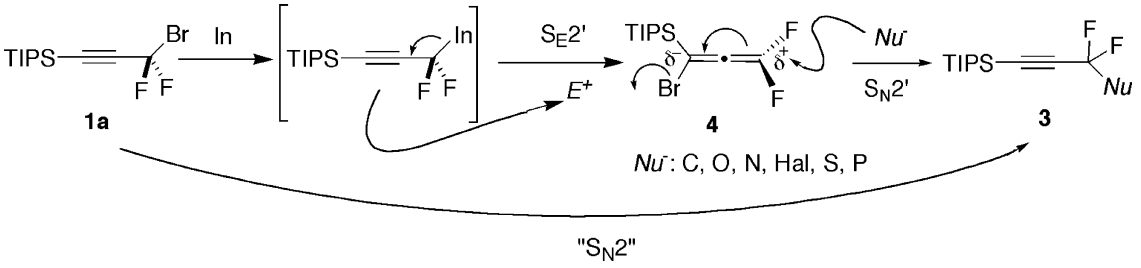
Entry	R	M-CI	Conditions	% yield of **2**[b]
1	*p*-MeP_6H_4	TMSCl	0 °C, 30 min	81 (**2a**)
2	*o*-MeC_6H_4	TMSCl	0 °C, 30 min	77 (**2b**)
3	*p*-$MeOC_6H_4$	TMSCl	0 °C, 30 min	90 (**2c**)
4	Ph	TMSCl	0 °C, 30 min	51 (**2d**)
5	Hex	TMSCl	0 °C, 30 min	63 (**2e**)
6	TIPS	TMSCl	0 °C, 30 min	82 (**2f**)
7	TES	TMSCl	0 °C, 30 min	93 (**2g**)
8	Ph	Me_3SnCl	0 °C 1 h	75 (**2h**)

[a] The reaction was carried out by the procedure shown in experimental section.
[b] Isolated yield.

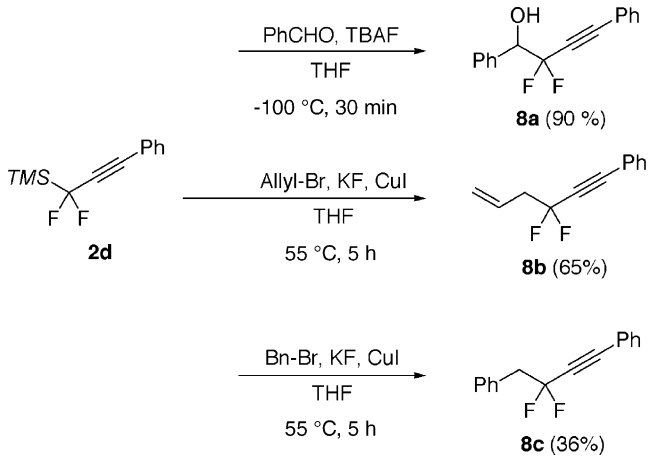
these $[M-19]^+$ ions offer reliable information with respect to the molecular weights of these *gem*-difluoropropargyl structures. The phenomenon of C–F bond cleavage under methane-CI conditions has recently been disclosed by us [27].

2.3. *De facto* S_N2 substitution of difluoropropargyl bromide **1** using a sequence of S_E2' and S_N2' reactions (Eq. (7))

Whereas potent methodologies exist for S_E2-type electrophilic substitution using a difluoromethylene dianion equivalent [28], the shielding of carbon by the surrounding fluorine atoms impedes substitution by a nucleophile, except under exceptional circumstances [10,15]. In principle, RCF_2Nu could be synthesized by a nucleophilic reaction on *gem*-difluoroolefins (Scheme 3a), taking advantage of the preferential attack of nucleophiles at the terminal sp^2 difluoromethylene carbon. However, this approach usually yields addition–



(7)

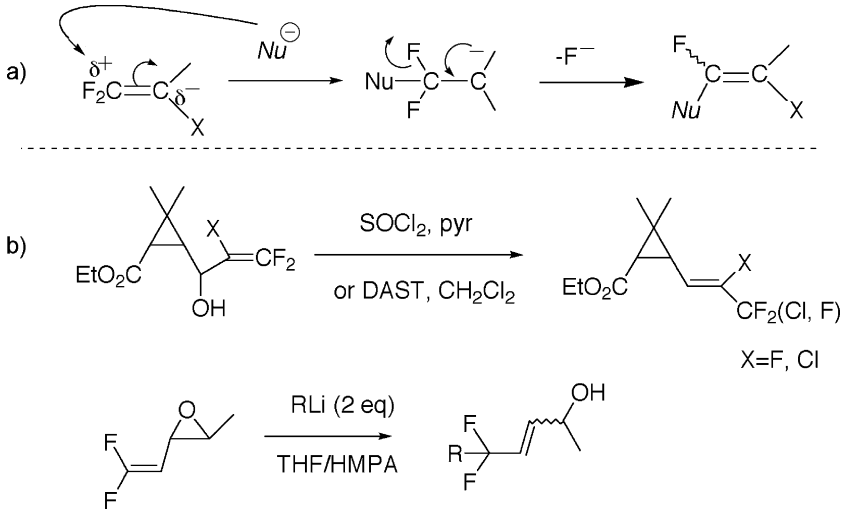


Scheme 2. Synthetic utility of **2d** as a nucleophilic 3-C synthon.

elimination products arising from the facile β-elimination of fluoride ion. The elimination of fluoride has been avoided only in exceptional cases (Scheme 3b) [29,30].

On the basis of ab initio calculations we postulated that a vinylogous *gem*-difluoroolefin, such as fluoroallene **4** (Fig. 1), would be ideally suited to the task of acting as a difluoromethylene cation-equivalent because of the opposite NBO (natural bond orbital) charges in **4** (+0.765 versus −0.449).

This charge distribution would favor a S_N2' nucleophile attack on the CF_2 center, with concomitant bromide elimination, the driving force being the favorable allene to propargyl isomerization. Conversely, its non-fluorinated counterpart has the electronic charge concentrated on both carbon termini, a deterrent towards nucleophilic attack. To synthesize **4** we relied on a procedure reported by our group a few years ago [32],



Scheme 3. (a) Nucleophilic substitution on a sp^2 fluorinated carbon. (b) Synthesis of fluorinated pyrethroids and propargyl alcohols through nucleophilic addition to a sp^2 CF_2 group.

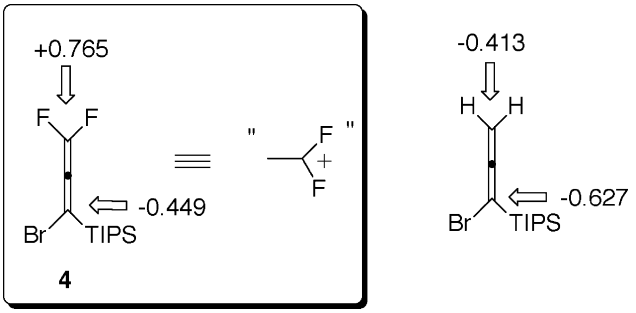
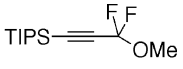
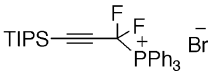
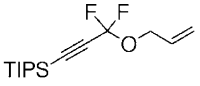
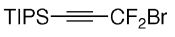
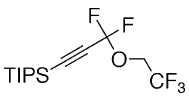
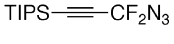
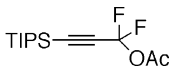
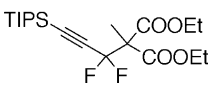
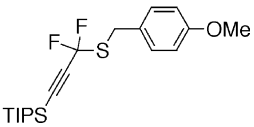
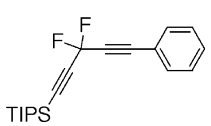


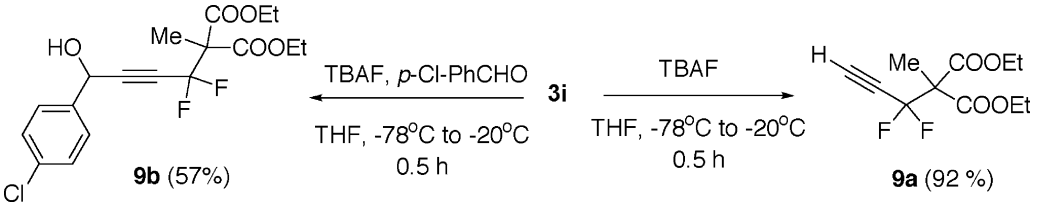
Fig. 1. Ab initio calculation of *gem*-difluorinated allene **4** and its non-fluorinated counterpart. Numbers refer to NBO (natural bond order) charge densities. Computational analysis was carried out using Gaussian 03, Revision C.02 at the HF/6-311++g level of theory [31].

whereby a preformed indium propargyl complex reacted with a reactive electrophile such as aqueous formaldehyde, to furnish a fluoroallenyl alcohol. A similar reaction with a reactive electrophile such as Br_2 should produce the desired γ-bromodifluoroallene **4**. Indeed, the indium-mediated S_E2' bromide substitution converted **1a** to **4** in 81% yield (Eq. (7)). To our satisfaction, **4** reacted easily with a wide range of weak and strong nucleophiles (P, O, S, C, N, Br), in a S_N2' manner, producing **3** in good to excellent yields (Table 3) [33].

Although the reaction of amines with **4** produced complex mixtures, this problem was circumvented by using sodium azide as a nitrogen nucleophile. This reaction produced a stable propargyl difluoroazide **3h** in close to 70% yield. Notably, our new methodology also allowed the synthesis of hydrofluoroether **3c** using trifluoroethanol as the nucleophile under very mild

Table 3
S_N2 synthesis of difluoropropargyl **3** from difluoroallene **4**

Nucleophile/conditions		Entry (yield)[3]	Nucleophile/conditions		Entry (yield)[3]
MeOH, K_2CO_3 0°C, 3h		**3a** (61%)	PPh_3, ether rt, 12h		**3f** (92%)
OH K_2CO_3, 0°C, 4h		**3b** (70%)	NaBr, DMF rt, 12 h		**3g** (78%)
F_3COH K_2CO_3, 0°C, 4h		**3c** (68%)	NaN_3, CH_3CN rt, 12 h		**3h** (68%)
AcOH/AgOAc rt, 12h		**3d** (70%)	Me(COOEt)$_2$ THF, NaH, 0°C 4 h		**3i** (70%)
MeO, SH n-BuLi, THF, -78°C to 0°C		**3e** (53%)	H n-BuLi, THF, -78°C to 0°C		**3j** (55%)



Scheme 4. Deprotection and functionalization of **3i** using TBAF.

conditions, in 68% yield. Prior to our disclosure, the synthesis of hydrofluoroethers could only be achieved under strongly basic conditions – that led to vinyl ether by-products – or through the very recently reported [34] Pd(0)-catalyzed hydroalkoxylation of hexafluoropropene. In addition to the alkyne functionality present in **3**, the TIPS group is also a useful synthetic handle. It can be cleaved in excellent yield, without loss of fluorine, to yield **9a**, using TBAF. Alternatively, it can be further functionalized using an electrophilic trap, such as *p*-chlorobenzaldehyde, to produce **9b**, as demonstrated in Scheme 4.

3. Conclusion

We have found a practical preparation of difluoropropargyl bromide and have used this compound in wide-ranging nucleophilic and electrophilic substitutions (S_E2, S_E2' and S_N2') that led to the synthesis of novel CF_2-substituted-alkynes and -allenes. In addition, we have discovered a sequence of S_E2' and S_N2' substitutions that accomplished a de facto S_N2 displacement of bromide. Overall, these results have increased our understanding on the effects of two fluorine atoms on a carbon undergoing nucleophilic or electrophilic substitutions—two benchmark organic reactions. Synthetic applications are ongoing in our laboratory.

4. Experimental

4.1. General

^1H, ^{13}C and ^{19}F NMR spectra were recorded on Varian Inova 500 instrument at 500, 126 and 470 MHz, respectively, using $CDCl_3$ as a solvent. The chemical shifts are reported in δ (ppm) values relative to $CHCl_3$ (δ 7.26 ppm for ^1H NMR and δ 77.0 ppm for ^{13}C NMR) and $CFCl_3$ (δ 0 ppm for ^{19}F NMR). Coupling constants are reported in hertz (Hz). GC/MS analyses were performed on a Varian Saturn 2000 system. Infrared spectra were recorded using either a Mattson Infinity Series FTIR or Mattson Galaxy Series FTIR 5000 spectrometer. All air and/or moisture sensitive reactions were carried out under argon atmosphere. Solvents (tetrahydrofuran, ether, dichloromethane and DMF) were dried using a PureSolv PS-400-4 purification system (Innovative Technology, Inc.). All other commercial reagents were obtained from Sigma–Aldrich Chemical Co. Progress of the reactions was monitored by ^{19}F NMR and the mixture yield was obtained using α,α,α-trifluoromethylbenzene as internal reference. The percentage purity of the isolated product was determined by comparing the integration of the ^{19}F NMR signal corresponding to a measured amount of the product with the signal integration corresponding to a 0.3 equivalent of α,α,α-trifluoromethylbenzene, used as internal reference. Products were purified using a Biotage flash+ system or Chromatotron apparatus. Column chromatography was performed using #R12030B, SiliaFlash® P60, 40–63 μm obtained from SiliCycle Inc. TLC was developed on Merck silica gel 60 F254 Aluminum sheets. Prep. TLC was conducted on DC-fertigplatten SIL RP-18W/UV_{254} by Alltech associates Inc. Elemental analysis was performed at Atlantic Microlabs Inc., Norcross, Georgia 30091. Accurate mass determinations were performed either at the Nebraska Center for Mass Spectrometry, University of Nebraska-Lincoln, Nebraska 68588 or Mass Spectrometry & Proteomics Facility, Ohio State University, Columbus, OH 43210.

4.2. Method A (for the synthesis of TMS and alkyl difluoropropargyl bromides **1b**, **1i** and **1j**)

To a solution of trimethylsilylacetylene (4.91 g, 50 mmol) in dry THF (250 mL), a 2.5 M hexane solution of *n*-butyllithium (20 mL, 50 mmol) was added dropwise at approximately −90 °C (liquid N_2/EtOH bath) under an argon atmosphere. After the reaction mixture was stirred for 30 min at that temperature, the reaction mixture was cooled to −110 °C (because the solvent along the wall of reaction flask froze at −110 °C, it is important to maintain good stirring throughout). Cold dibromodifluoromethane (−78 °C) (5.5 mL, 60 mmol) was added to the mixture by cannulation. The temperature of the reaction mixture has to be controlled very carefully during the addition of CF_2Br_2 using a thermometer immersed in the reaction mixture (very important!). The reaction temperature may raise to −90 °C or even higher even if CF_2Br_2 is introduced slowly. After the addition is completed, the mixture is allowed to warm up to −50 °C with stirring during the course of 1 h and quenched with sat. aq. NH_4Cl (50 mL). The aqueous layer was extracted with ether (100 mL) and the organic layer was washed by water (3× 100 mL). The organic layer was dried over Na_2SO_4. After evaporation of the solvent, the crude product was purified by distillation (110–125 °C/760 mmHg) to afford **1b** (7.0 g, 52%, >92% purity) as a colorless oil.

IR (neat) 2193 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$), δ: 0.26 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$), δ: −1.13, 95.0 (t, J = 36.0 Hz), 97.0 (t, J = 4.3 Hz), 100.9 (t, J = 290 Hz); ^{19}F NMR (470 MHz, $CDCl_3$), δ: −33.8 (s, 2F). Satisfactory elemental analysis could not be obtained due to slight contamination with **7** which co-eluted and co-distilled with **1b**.

*4.2.1. 1-Bromo-1,1-difluoronon-2-yne (**1i**)*

Colorless oil; 81% yield; bp. 67–70 °C/8 mmHg; this compound was contaminated by 7% compound **3**. IR (neat) 2242 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$), δ: 0.92 (t, J = 7.0 Hz, 3H), 1.27–1.37 (m, 4H), 1.42–1.45(m, 2H), 1.54–1.63(m, 2H), 2.34–2.38(m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$), δ: 14.13, 18.69, 22.64, 27.43, 28.61, 31.34, 74.17 (t, J = 38.1 Hz), 93.36 (t, J = 5.8 Hz), 101.69 (t, J = 287 Hz); ^{19}F NMR (470 MHz, $CDCl_3$), δ: −30.4 (s, 2F); GC/MS (EI) *m/z*: 177, 159, 139, 117, 97, 79.

*4.2.2. 1-Bromo-1,1-difluoro-6-methylhept-2-yne (**1j**)*

Colorless oil; 71% yield; bp. 65–70 °C/10 mmHg; this compound was contaminated by 5% compound **3**. IR (neat) 2252 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$), δ: 0.93 (d, J = 7.0 Hz, 6H), 1.49 (q, J = 7.0 Hz, 2H), 1.67–1.71(m, 1H), 2.34–2.39(m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$), δ: 16.72, 22.16, 27.50, 36.26, 74.05 (t, J = 37.3 Hz), 93.42 (t, J = 5.7 Hz), 101.68 (t, J = 287 Hz); ^{19}F NMR (470 MHz, $CDCl_3$), δ: −30.4 (s, 2F); GC/MS (EI) *m/z*: 189, 163, 125, 79, 57. Satisfactory elemental analysis could not be obtained for **1i**, and **1j** due to slight contamination with **7** which co-eluted and co-distilled with the product.

*4.3. Method B (for the synthesis of 3,3-difluoropropargyl bromides **1a**, **1c–h**)*

To a solution of 4-ethynyltoluene (1.6 g, 14.6 mmol) in dry THF (30 mL), a 2.5 M hexane solution of *n*-butyllithium (6.1 mL, 15.3 mmol) was added dropwise at −78 °C under an argon atmosphere. After the reaction mixture was stirred for 30 min at −78 °C, cold (−78 °C) dibromodifluoromethane (4.6 g, 21.9 mmol) was added to the reaction mixture at −100 °C. After stirring for 16 h at rt., the THF solution was washed with sat. aq. NH_4Cl (10 mL). The aqueous layer was extracted with hexane (2× 20 mL) and the combined organic layer was dried over Na_2SO_4. After evaporation of the solvent, the crude product was purified by distillation under reduced pressure (75 °C/4.4 mmHg) to afford **1e** (2.2 g, 61%) as a colorless oil. *Note*: the spectral data of **1a** [18] and **1c** [10] have been previously published.

*4.3.1. 3-Bromo-3,3-difluoro-1-triethylsilylpropyne (**1d**)*

Colorless oil; 74% yield; bp. 60 °C/4.8 mmHg; IR (neat) 2191 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$), δ: 0.69 (q, J = 8.0 Hz, 6H), 1.02 (t, J = 8.0 Hz, 9H); ^{13}C NMR (126 MHz, $CDCl_3$), δ: 3.6, 7.2 95.6 (t, J = 4.8 Hz), 96.2 (t, J = 36.5 Hz), 100.7 (t, J = 290 Hz); ^{19}F NMR (470 MHz, $CDCl_3$), δ: −33.5 (s, 2F); Anal. Calcd. for $C_9H_{15}BrF_2Si$: C, 40.15; H, 5.62. Found: C, 40.46; H, 6.04.

*4.3.2. 3-Bromo-3,3-difluoro-1-(4-methyl)phenylpropyne (**1e**)*

IR (neat) 2223, 2247 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$), δ: 2.40 (s, 3H), 7.20 (d, J = 7.5 Hz, 2H), 7.44 (d, J = 7.5 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$), δ: 21.7, 80.5 (t, J = 38.4 Hz), 90.4 (t, J = 5.8 Hz), 102.1 (t, J = 290 Hz), 115.7, 129.4, 129.6, 132.1, 141.4; ^{19}F NMR (470 MHz, $CDCl_3$), δ: −32.1 (s, 2F); HRMS (EI) *m/z* calcd. for $C_{10}H_7F_2Br$, 243.9699. Found: 243.9690.

*4.3.3. 3-Bromo-3,3-difluoro-1-(2-methyl)phenylpropyne (**1f**)*

Colorless oil; 42% yield; bp. 75 °C/4.4 mmHg; IR (neat) 2224, 2247 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$), δ: 2.47 (s, 3H), 7.19–7.50 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$), δ: 20.3, 84.6 (t, J = 38.6 Hz), 89.4 (t, J = 5.8 Hz), 102.1 (t, J = 290 Hz), 118.6, 125.8, 129.9, 130.8, 132.5, 141.7; ^{19}F NMR (470 MHz, $CDCl_3$), δ: −32.2 (s, 2F); HRMS (EI) *m/z* calcd. for $C_{10}H_7F_2Br$, 243.9699. Found: 243.9696.

*4.3.4. 3-Bromo-3,3-difluoro-1-(4-methoxy)phenylpropyne (**1g**)*

Yellow oil; 53% yield; bp. 105 °C/2.2 mmHg; IR (neat) 2218, 2252 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$), δ: 3.84 (s, 3H), 6.90 (d, J = 8.0 Hz, 2H), 7.48 (d, J = 8.0 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$), δ: 55.4, 80.2 (t, J = 37.4 Hz), 90.6 (t, J = 5.8 Hz), 102.2 (t, J = 289 Hz), 110.6, 114.3, 134.0, 161.5; ^{19}F NMR (470 MHz), δ: −33.5 (s, 2F); Anal. Calcd. for $C_{10}H_7BrF_2O$: C, 64.01; H, 2.70. Found: C, 64.02; H, 2.66.

*4.3.5. 3-Bromo-3,3-difluoro-1-(4-trifluoromethyl) phenylpropyne (**1h**)*

Colorless oil; 78% yield; bp. 68 °C/3.8 mmHg; IR (neat) 2225, 2263 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$), δ: 7.67 (s, 4H); ^{13}C NMR (126 MHz, $CDCl_3$), δ: 82.5 (t, J = 38.6 Hz), 87.7 (t, J = 5.7 Hz), 101.7 (t, J = 291 Hz), 122.6, 123.4 (q, J = 273 Hz), 125.6 (q, J = 3.8 Hz), 132.6, 132.5 (q, J = 16.5 Hz); ^{19}F NMR (470 MHz, $CDCl_3$), δ: −64.4 (s, 3F), −33.8 (s, 2F); HRMS (EI) *m/z* calcd. for $C_{10}H_4BrF_5$, 247.9417. Found: 247.9414.

*4.3.6. 3-Bromo-3,3-difluoroprop-1-ynyl diisopropylcarbamate (**1k**)*

2,2,2-Tribromoethanol (5.66 g, 20 mmol) and carbamoyl chloride **2** (4 g, 24 mmol) in pyridine (20 mL) were heated to 70 °C for 16 h under argon. After cooling, HCl and ether were added, the mixture was extracted with ether (3× 50 mL) and the combined organic phase was washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$). After concentrated in vacuo, the crude product was purified by flash column chromatography (20/1 hexane/ethyl acetate) to afford product 2,2,2-tribromoethyl diisopropylcarbamate (6.08 g, 74%) as a white solid. An aliquot (2.05 g, 5 mmol) was dissolved in THF (50 mL), and LDA (14 mL, 1.8 M in THF, 25 mmol) was added to the solution at −85 °C. The mixture was stirred for another 4 h. MeOH (2 mL) was added and stirred for another 2 h, and then warmed to rt. Afterwards, H_2O (30 mL) were added and the mixture was extracted with ether. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by flash column chromatography (30/1 hexane/ethyl acetate) to afford ethynyl diisopropylcarbamate **6a** (414 mg, 49%) as a yellow solid. To a solution of **6a** (85 mg, 0.5 mmol) in THF (3 mL), LiHMDS (1 M in THF, 0.6 mL) was added slowly at −90 °C and stirred for 15 min. CF_2Br_2 was

added to the mixture and stirred for 1 h then warmed to rt. Saturated aqueous NH_4Cl was added and the mixture was extracted with ether. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Flash column chromatography afforded **1k** (78 mg, 55%). ^1H NMR (500 MHz, $CDCl_3$): 3.69 (s, 1H), 1.10–1.03 (m, 14H); ^{19}F NMR (470 MHz, $CDCl_3$): −53.97; GC/MS: 298/300.

*4.3.7. 3-Bromo-3,3-difluoroprop-1-ynyl-p-tolylsulfide (**1l**)*

A mixture of 4-methylbenzenethiol (6.2 g, 50 mmol), 2-bromo-1,1-diethoxyethane (10.8 g, 55 mmol), and sodium ethoxide (3.74 g, 55 mmol) in ethanol (50 mL) was refluxed for 5 h. Saturated aqueous NH_4Cl was added to the mixture then extracted with ethyl acetate (3× 80 mL). The organic phase was dried ($MgSO_4$). After removal of the solvent, distillation (110 °C) afforded 2-*p*-tolylsulfinyl-1,1-diethoxyethane (11.5 g, 96%). To a solution of diisopropylamine (8.4 mL, 60 mmol) in ether (100 mL), butyl lithium (2.5 M in hexane, 24 mL, 60 mmol) was added at −80 °C. After stirring for 30 min at 0 °C, the reaction mixture was cooled down to −80 °C and 2-*p*-tolylsulfinyl-1,1-diethoxyethane was syringed into the mixture. A milky solution was observed as the reaction was warmed to 0 °C. After stirring for 15 min the reaction was quenched with saturated aqueous NH_4Cl and neutralized with 1 M HCl. The aqueous phase was extracted (ether, 2× 100 mL) and the combined organic phase was dried ($MgSO_4$), concentrated in vacuo to afford **6b** (2.55 g, 86%). To a solution of **6b** (2.37 g, 16 mmol) in THF (100 mL) butyl lithium (2.5 M in hexane, 7.2 mL, 18 mmol) was added dropwise at −100 °C and stirred for 0.5 h. CF_2Br_2 (6.72 g, 32 mmol) was added and warmed to −70 °C for 0.5 h. Saturated aqueous NH_4Cl was added and the mixture was extracted (ether, 3× 80 mL). The combined organic phase was washed with water (3× 100 mL) and dried ($MgSO_4$). After concentrated in vacuo, the crude product was purified by column chromatography to afford **1l** (1.77 g, 40%) as yellow liquid. The product was unstable even if kept in a refrigerator. ^1H NMR (500 MHz, $CDCl_3$): 7.36–7.34 (m, 2H), 7.23–7.21 (m, 2H), 2.38 (s, 3H); ^{19}F NMR (470 MHz, $CDCl_3$): −31.71 (s, 2F).

*4.3.8. 4-Bromo-4,4-difluorobut-2-ynoic acid (**1n**)*

To a solution of propiolic acid **6d** (1.35 g, 19.3 mmol) in THF (100 mL) was added butyl lithium (2.5 M in hexane, 16 mL, 40 mmol) slowly at −100 °C and stirred for 0.5 h. CF_2Br_2 (5 mL, dissolved in 10 mL THF) was cannulated to the mixture. After warming to rt. for 1 h, the reaction mixture was quenched with saturated aqueous NH_4Cl and acidified with HCl. The aqueous phase was extracted with ether (3× 80 mL) and the combined organic phase was washed with 1 M HCl (do not use water to wash!) and dried ($MgSO_4$). After removal of the solvent, distillation gave **1n** (1.725 g, 45%). ^{19}F NMR (470 MHz, $CDCl_3$): −37.35; GC/MS: 198/200.

Note: treatment of ethyl ester of **6d** with LDA followed by CF_2Br_2; or **6d** with LDA followed by CF_2Br_2 failed.

*4.3.9. Attempted synthesis of **1m***

Tosyl chloride (20 g, 0.105 mol) was added to a solution of benzylamine (11 mL, 0.1 mol) in pyridine (35 mL) at 0 °C, and the mixture was warmed to rt. for 2 h and heated to 70 °C for 4 h. After cooling down to rt., the mixture was poured onto 1 M HCl. The aqueous phase was extracted with ethyl acetate and washed with 1 M HCl (2× 80 mL), water (3× 80 mL) and dried ($MgSO_4$). Removal of the solvent afforded *N*-benzyl-*N*-tosylamine (25.4 g, 97%). To a solution of ethynyltriisopropylsilane (3.64 g, 20 mmol) in THF (30 mL) butyl lithium (2.5 M in hexane, 10 mL, 25 mmol) was syringed in at −80 °C. After stirring for 0.5 h, iodine (5.59 g, 22 mmol) was added to quench the reaction. Ether (100 mL) was added to dilute the mixture and the organic phase was washed with water (3× 50 mL). After drying ($MgSO_4$) and solvent removal, the crude product was purified by flash column chromatography (hexane) to afford 1-iodo-2-trisopropylsilyethyne (5.87 g, 95%) as a yellow liquid. A mixture of *N*-benzyl-*N*-tosylamine (1.148 g, 4.4 mmol), potassium carbonate (1.104 g, 8 mmol), $CuSO_4{\cdot}5H_2O$ (100 mg, 0.4 mmol), phenanthrene (148 mg, 0.8 mmol), 1-iodo-2-trisopropylsilyethyne (1.232 g, 4 mmol) in toluene (10 mL), was heated to 70 °C for 24 h. After cooling down the mixture was diluted with ether (20 mL) and filtered. Flash column chromatography afforded *N*-benzyl-2-(triisopropylsilyl)-*N*-tosylethynamine (720 mg, 68%). An aliquot of *N*-benzyl-2-(triisopropylsilyl)-*N*-tosylethynamine (220 mg, 0.5 mmol) was dissolved in THF (2 mL), and cooled to −80 °C. TBAF was added slowly. After stirring for 5 min, saturated aqueous NH_4Cl was added to the mixture. The aqueous phase was extracted with ether (2× 30 mL) and dried ($MgSO_4$). The crude product was purified by flash column chromatography to afford product **6c** (112 mg, 79%) as a white solid. Treatment of **6c** with strong bases such as *n*-BuLi, LDA, LiHMDS, or NaHMDS followed by reaction with CF_2Br_2 failed to produce **1m**.

*4.3.10. A typical procedure for the synthesis of 3,3-difluoropropargylsilanes (**2**)*

To the mixture of Mg (194 mg, 8.0 mmol) and chlorotrimethylsilane (0.51 mL, 4.0 mmol) in dry THF (10 mL), 3-bromo-3,3-difluoro-1-(4-methylphenyl)propyne (**1e**) (245 mg, 1.0 mmol) was added dropwise at 0 °C under an argon atmosphere. The reaction mixture was stirred for 30 min at 0 °C. The residual Mg was removed by decantation, the THF solution was washed with H_2O (5 mL). The aqueous layer was extracted with hexane (2× 5 mL) and the combined organic layer was dried over Na_2SO_4. After evaporation of the solvent, the crude product was purified by silica gel treated with Et_3N/hexane = 1/9 column chromatography (hexane) to afford **2a** (193 mg, 81%) as a colorless oil.

*4.3.11. 3,3-Difluoro-1-(4-methyl)phenyl-3-trimethylsilylpropyne (**2a**)*

IR (neat) 2225 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$), δ: 0.29 (s, 9H), 2.37 (s, 3H), 7.16 (d, J = 7.0 Hz, 2H), 7.38 (d, J = 7.0 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$), δ: −4.9, 21.6, 81.6 (t, J = 30.6 Hz), 91.4 (t, J = 9.6 Hz), 111.7, 120.6 (t, J = 254 Hz), 129.2, 131.9, 140.0; ^{19}F NMR (470 MHz, $CDCl_3$, C_6F_6 as an internal standard), δ: 56.8 (s, 2F); Anal. Calcd. for $C_{13}H_{16}F_2Si$: C, 65.51; H, 6.77. Found: C, 65.24; H, 6.94.

*4.3.12. 3,3-Difluoro-1-(2-methyl)phenyl-3-trimethylsilylpropyne (**2b**)*

Colorless oil; 77% yield; IR (neat) 2222 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$), δ: 0.29 (s, 9H), 2.38 (s, 3H), 7.16 (d, J = 7.5 Hz, 2H), 7.39 (d, J = 8.5 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$), δ: −5.0, 21.5, 81.6 (t, J = 31.8 Hz), 91.4 (t, J = 9.7 Hz), 111.7, 120.6 (t, J = 255 Hz), 129.2, 131.9, 140.0; ^{19}F NMR (470 MHz, $CDCl_3$, C_6F_6 as an internal standard), δ: 57.5 (s, 2F); Anal. Calcd. for $C_{13}H_{16}F_2Si$: C, 65.51; H, 6.77. Found: C, 65.52; H, 6.69.

*4.3.13. 3,3-Difluoro-1-(4-methoxy)phenyl-3-trimethylsilyl-1-propyne (**2c**)*

Yellow oil; 90% yield; IR (neat) 2221 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$), δ: 0.28 (s, 9H), 3.83 (s, 3H), 6.87 (d, J = 8.5 Hz, 2H), 7.43 (d, J = 8.5 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$), δ: −4.9, 55.3, 81.0 (t, J = 31.8 Hz), 91.3 (t, J = 9.6 Hz), 122.8, 114.1, 120.7 (t, J = 254 Hz), 133.6, 160.6; ^{19}F NMR (470 MHz, $CDCl_3$, C_6F_6 as an internal standard), δ: 57.8 (s, 2F); Anal. Calcd. for $C_{13}H_{16}F_2OSi$: C, 61.39; H, 6.34. Found: C, 61.31; H, 6.25.

*4.3.14. 3,3-Difluoro-1-phenyl-3-trimethylsilylpropyne (**2d**)*

Colorless oil; 51% yield; IR (neat) 2225 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$), δ: 0.29 (s, 9H), 7.34–7.50 (m, 5H); ^{13}C NMR (126 MHz, $CDCl_3$), δ: −5.0, 82.2 (t, J = 31.8 Hz), 91.0 (t, J = 9.6 Hz), 120.5 (t, J = 255 Hz), 120.8 (t, J = 3.5 Hz), 128.4, 129.6 132.0; ^{19}F NMR (470 MHz, $CDCl_3$, C_6F_6 as an internal standard), δ: 57.1 (s, 2F); Anal. Calcd. for $C_{12}H_{14}F_2Si$: C, 64.25; H, 6.29. Found: C, 64.60; H, 6.23.

*4.3.15. 1,1-Difluoro-1-trimethylsilyl-2-nonyne (**2e**)*

Colorless oil; 63% yield; IR (neat) 2234 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$), δ: 0.22 (s, 9H), 0.89 (t, J = 7.0 Hz, 3H), 1.26–1.33 (m, 4H), 1.40 (q, J = 7.0 Hz, 2H), 1.55 (q, J = 7.0 Hz, 2H), 2.31 (q, J = 7.0 H, 2H); ^{13}C NMR (126 MHz, $CDCl_3$), δ: −5.1, 14.0, 18.7, 22.5, 28.0, 28,4, 31.2, 74.4 (t, J = 31.8 Hz), 93.0 (t, J = 8.7 Hz), 120.4 (t, J = 253 Hz); ^{19}F NMR (470 MHz, $CDCl_3$, C_6F_6 as an internal standard), δ: 58.8 (t, J = 7.0 Hz, 2F); Anal. Calcd. for $C_{12}H_{22}F_2Si$: C, 62.02; H, 9.54. Found: C, 62.40; H, 9.44.

*4.3.16. 3,3-Difluoro-1-triisopropylsilyl-3-trimethylsilylpropyne (**2f**)*

Colorless oil; 82% yield; IR (neat) 1863 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$), δ: 0.24 (s, 9H), 1.08–1.11 (m, 21H); ^{13}C NMR (126 MHz, $CDCl_3$), δ: −5.0, 11.0, 18.5, 94.0 (t, J = 7.1 Hz), 99.8 (t, J = 28.9 Hz), 119.8 (t, J = 254 Hz); ^{19}F NMR (470 MHz, $CDCl_3$, C_6F_6 as an internal standard), δ: 56.7 (s, 2F); Anal. Calcd. for $C_{15}H_{30}F_2Si_2$: C, 59.15; H, 9.93. Found: C, 59.22; H, 10.09.

*4.3.17. 3,3-Difluoro-1-trietylsilyl-3-trimethylsilyl-1-propyne (**2g**)*

Yellow oil; 93% yield; IR (neat) 1884 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$), δ: 0.23 (s, 9H), 0.65 (q, J = 8.0 Hz, 6H), 1.01 (t, J = 8.0 Hz, 9H); ^{13}C NMR (126 MHz, $CDCl_3$), δ: −5.1, 3.98, 7.29, 95.3 (t, J = 7.7 Hz) 98.9 (t, J = 29.7 Hz), 119.8 (t, J = 255 Hz); ^{19}F NMR (470 MHz, $CDCl_3$, C_6F_6 as an internal standard), δ: 56.7 (s, 2F); Anal. Calcd. for $C_{12}H_{24}F_2Si_2$: C, 54.91; H, 9.22. Found: C, 55.18; H, 9.31.

*4.3.18. 3,3-Difluoro-1-phenyl-3-trimethylstannylpropyne (**2h**)*

To the mixture of Mg (194 mg, 8.0 mmol) and chlorotrimethyltin (4.0 mL of 1.0 M solution) in dry THF (10 mL), **1c** (231 mg, 1.0 mmol) was added dropwise at 0 °C under an argon atmosphere. The reaction mixture was stirred for 1 h at 0 °C. The residual Mg was removed by decantation. After evaporation of the solvent and removal of excess amount of chrolotrimethyltin in vacuo (<0.1 mmHg, rt.), the hexane solution was washed with H_2O (5 mL), aqueous layer was extracted with hexane (2× 5 mL) and combined organic layer was dried over Na_2SO_4. The crude product was chromatographed on silica gel (hexane) treated with Et_3N/hexane = 1/9 to afford **2h** (236 mg, 75%) as a colorless oil.

IR (neat) 2223 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$), δ: 0.41 (s, 9H), 7.33–7.49 (m, 5H); ^{13}C NMR (126 MHz, $CDCl_3$), δ: −9.5, 83.9 (t, J = 27.8 Hz), 92.5 (t, J = 10.6 Hz), 121.0, 124.0 (t, J = 279 Hz), 128.4, 129.5, 131.8; ^{19}F NMR (470 MHz, $CDCl_3$, C_6F_6 as an internal standard), δ: 68.0 (s, 2F); Anal. Calcd. for $C_{12}H_{14}F_2Sn$: C, 45.76; H, 4.48. Found: C, 46.24; H, 4.42.

*4.3.19. Fluoride ion promoted addition of **2d** to benzaldehyde*

To a solution of **2d** (224 mg, 1.0 mmol) and benzaldehyde (1.09 mg, 1.5 mmol) in THF (1.5 mL) at −78 °C was added TBAF (1.0 mL of 1.0 M solution in THF) dropwise under an argon atmosphere. After the mixture was stirred for 1 h at −78 °C, the reaction mixture was washed with water (5 mL). The aqueous layer was extracted with EtOAc (2× 5 mL). The combined organic layer was dried over $MgSO_4$. After removal of solvent, the crude product was purified by silica gel column chromatography (ether/hexane = 1/9) to furnish **8a** [8] (232 mg, 90%) as a colorless oil.

*4.3.20. 4,4-Difluoro-6-phenyl-1-hexen-5-yne (**8b**)*

A solution of **2d** (224 mg, 1.0 mmol), allyl bromide (605 mg, 5.0 mmol), KF (70 mg, 1.2 mmol), and CuI (286 mg, 1.5 mmol) in DMF (1.5 mL) under an argon atmosphere was stirred for 5 h at 55 °C. The usual workup procedure of the mixture provided the crude product. The crude mixture was chromatographed on silica gel (hexane) to give **8b** (125 mg, 65%) as a colorless oil.

IR (neat) 2243, 1230 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$), δ: 2.87–2.94 (m, 2H), 5.30–5.33 (m, 2H), 5.85–5.94 (m, 1H), 7.34–7.51 (m, 5H); ^{13}C NMR (126 MHz, $CDCl_3$), δ: 44.1 (t, J = 27.8 Hz), 81.4(t, J = 40.6 Hz), 87.3 (t, J = 6.7 Hz), 114.0 (t, J = 234 Hz), 120.2, 121.1, 128.5, 129.9, 132.1; ^{19}F NMR (470 MHz, $CDCl_3$, C_6F_6 as an internal standard), δ: 79.1 (t, J = 15.5 Hz, 2F); HRMS (EI) m/z calcd. for $C_{10}H_{10}F_2$, 192.0751. Found: 192.0744.

*4.3.21. 3,3-Difluoro-1,4-diphenylbutyne (**8c**)*

A solution of **2d** (224 mg, 1.0 mmol), benzylbromide (513 mg, 3.0 mmol), KF (70 mg, 1.2 mmol), and CuI (286 mg, 1.5 mmol) in DMF (1.5 mL) under an argon atmosphere was stirred for 8 h at 70 °C. The usual workup procedure of the mixture provided the crude product. The crude mixture was chromatographed on silica gel (hexane) to give **8c** (87 mg, 36%) as a colorless oil.

IR (neat) 2244 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$), δ: 3.44 (t, J = 14.0 Hz, 2H), 7.33–7.42 (m, 10H); ^{13}C NMR (126 MHz, $CDCl_3$), δ: 45.8 (t, J = 27.0 Hz), 81.4 (t, J = 40.3 Hz) 88.0 (t, J = 6.7 Hz), 114.2 (t, J = 235 Hz), 120.2, 127.7, 128.3, 128.4, 129.8, 130.7, 132.0, 132.1; ^{19}F NMR (470 MHz, $CDCl_3$, C_6F_6 as an internal standard), δ: 79.9 (t, J = 14.0 Hz, 2F); HRMS (EI) m/z calcd. for $C_{10}H_{12}F_2$, 242.0907. Found: 242.0905.

*4.3.22. Synthesis of (1-bromo-3,3-difluoropropa-1,2-dienyl)triisopropylsilane **4***

To a 0.15 M solution of (3-bromo-3,3-difluoroprop-1-ynyl)triisopropylsilane **1a** in a mixture of 2% NH_4Cl aqueous solution and THF (4:1) is added indium (1 equiv.). This mixture was sonicated at 5–10 °C for 6–8 h. The temperature in the ultrasound bath was adjusted by addition of ice periodically. An aliquot was analyzed in $CDCl_3$ by ^{19}F NMR to monitor the completion of the reaction. After the starting material was consumed, the reaction mixture was extracted by ether and the organic layer was washed by brine and dried over $MgSO_4$. Then the most solvent was removed in reduced pressure to give the crude indium complex. (Not evaporation to complete dryness, because the indium complex is not stable when solvent was removed completely.) The crude indium complex was used in next step directly without further purification. Although this indium complex can be kept in freezer for several days, using of the complex for next step immediately give better yield. The freshly prepared indium complex (prepared from compound **1a** (3.20 g, 9.7 mmol)) was dissolved in THF (50 ml), then reaction mixture was cooled to −78 °C, then a solution of Br_2 (3.10 g, 19.4 mmol) in THF (10 mL) was added dropwise to the reaction mixture under stirring. The reaction mixture was warmed to −20 °C and was stirring for another 0.5 h at −20 °C. Then saturated $Na_2S_2O_3$ solution (10 mL) was added to quench the reaction. After stirring for 5 min at about 0 °C, the resulting aqueous mixture was extracted with ether (three times); the extract washed with brine (three times) and then dried over Na_2SO_4. The solvent was removed by rotavapor, and the crude product was purified by flash silica gel chromatography (pure hexane) to give **4** (2.44 g, 76%) as colorless oil. The yield varied from 67 to 81%, the obtained fluoroallene **4** is not stable in solution, but neat **4** can be stored in freezer for more than 1 month.

IR (neat) 2947, 2869, 1986, 1716, 1397, 1218, 1114, 882 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$), δ: 1.08–1.13 (m, 18H), 1.29–1.34 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$), δ: 11.39, 18.11, 111.80, 154.40 (t, J = 268 Hz), 179.14 (t, J = 36 Hz); ^{19}F NMR (470 MHz, $CDCl_3$), δ: −97.9 (s); Anal. Calcd. for $C_{12}H_{21}F_2Si$: C, 46.30; H, 6.80. Found: C, 48.88; H, 7.36. (Satisfactory EA and MS data couldn't be obtained because of the unstable nature of difluoroallene for long periods at room temperature that prevent it from being shipped.)

*4.3.23. (3,3-Difluoro-3-methoxyprop-1-ynyl)triisopropylsilane (**3a**)*

At 0 °C, to a mixture of K_2CO_3 (212 mg, 2 mmol) and MeOH (2 mL), the solution of bromoallene **4** (311 mg, 1 mmol) in 1 mL THF was introduced through a syringe, the reaction mixture was stirred for 3 h at 0 °C. Then 10 ml saturated NH_4Cl solution was added to quench the reaction. After stirring for 5 min at about 0 °C, the resulting aqueous mixture was extracted with ether (three times); the extract washed with brine (three times) and then dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was purified by flash silica gel chromatography (pure hexane to 10% ethyl acetate in hexane) to give **3a** (158 mg, 61%) as a colorless oil.

IR (neat) 2846, 2868, 1463, 1265, 1172, 1026, 882, 679 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$), δ: 1.04–1.14 (m, 21H), 3.16 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$), δ: 11.08, 18.53, 52.40, 88.63, 95.36 (t, J = 51 Hz), 114.14 (t, J = 241 Hz); ^{19}F NMR (470 MHz, $CDCl_3$), δ: −57.9 (s); GC/MS (EI) m/z: 243 (M^+ − F), 219, 191, 163, 81; Anal. Calcd. for $C_{13}H_{24}F_2OSi$: C, 59.50; H, 9.22. Found: C, 59.31; H, 9.21.

*4.3.24. (3-(Allyloxy)-3,3-difluoroprop-1-ynyl)triisopropylsilane (**3b**)*

At 0 °C, to a mixture of K_2CO_3 (212 mg, 2 mmol) and allylic alcohol (2 mL), the solution of bromoallene **4** (311 mg, 1 mmol) in THF (1 mL) was introduced through a syringe, the reaction mixture was stirred for 4 h at 0 °C. Then saturated NH_4Cl solution (10 ml) was added to quench the reaction. After stirring for 5 min at about 0 °C, the resulting aqueous mixture was extracted with ether (three times); the extract washed with brine (three times) and then dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was purified by flash silica gel chromatography (pure hexane to 10% ethyl acetate in hexane) to give **3b** (200 mg, 70%) as a colorless oil.

IR (neat) 2946, 2868, 1463, 1256, 1162, 1025, 882 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$), δ: 1.07–1.19 (m, 21H), 4.41–4.43 (m, 2H), 5.26 (d, J = 10 Hz, 1H), 5.38 (d, J = 17 Hz, 1H), 5.91–5.97 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$), δ: 11.09, 18.58, 66.68, 88.61 (t, J = 5.3 Hz), 95.60 (t, J = 52 Hz), 113.84 (t, J = 242 Hz), 118.62, 132.15; ^{19}F NMR (470 MHz, $CDCl_3$), δ: −55.0 (s); GC/MS (EI) m/z: 269 (M^+ − F), 227, 209, 185, 93; Anal. Calcd. for $C_{15}H_{26}F_2OSi$: C, 62.46; H, 9.09. Found: C, 62.44; H, 9.20.

*4.3.25. (3,3-Difluoro-3-(2,2,2-trifluoroethoxy)prop-1-ynyl)triisopropylsilane (**3c**)*

At 0 °C, to a mixture of K_2CO_3 (212 mg, 2 mmol) and trifluoroethanol (2 mL), the solution of bromoallene **4** (311 mg, 1 mmol) in 1 mL THF was introduced through a syringe, the reaction mixture was stirred for 4 h at 0 °C. Then saturated NH_4Cl (10 mL) solution was added to quench the reaction. After stirring for 5 min at about 0 °C, the resulting aqueous

mixture was extracted with ether (three times); the extract washed with brine (three times) and then dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was purified by flash silica gel chromatography (pure hexane) to give **3c** (224 mg, 68%) as colorless oil.

IR (neat) 2948, 2871, 2200, 1463, 1294, 1257, 1172, 883 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$), δ: 1.08–1.18 (m, 21H), 4.22 (q, J = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$), δ: 11.02, 18.50, 62.24 (q, J = 37.0 Hz), 90.96 (t, J = 5.7 Hz), 93.77 (t, J = 49.6 Hz), 113.19 (t, J = 246 Hz), 122.60 (t, J = 276 Hz); ^{19}F NMR (470 MHz, $CDCl_3$), δ: −56.69 (s, 2F), −74.75 (t, J = 8 Hz, 3F); GC/MS (EI) m/z: 330 (M^+), 204, 177, 131, 111, 91; Anal. Calcd. for $C_{14}H_{23}F_5OSi$: C, 50.89; H, 7.02. Found: C, 51.38; H, 7.20.

*4.3.26. 1,1-Difluoro-3-(triisopropylsilyl)prop-2-ynyl acetate (**3d**)*

At room temperature, to a mixture of AgOAc (334 mg, 2 mmol) and acetic acid (2 mL), the solution of bromoallene **4** (311mg, 1 mmol) in 1 mL acetic acid was introduced through a syringe, the reaction mixture was stirred for 12 h at room temperature. Then saturated NH_4Cl solution (10 ml) was added to quench the reaction. After stirring for 5 min at rt., the reaction mixture was filtered and the solid collected was washed by ether. The resulting filtrate was extracted with ether (three times); the extract was washed by brine (three times) and then dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was purified by flash silica gel chromatography (pure hexane to 10% ethyl acetate in hexane) to give **3d** (188 mg, 70%) as a colorless oil.

IR (neat) 2946, 2868, 2193, 1799, 1464, 1131, 882 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$), δ: 1.09–1.12 (m, 21H), 2.17 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$), δ: 11.04, 18.53, 21.18, 91.24, 93.98 (t, J = 46 Hz), 110.38 (t, J = 246 Hz), 165.02; ^{19}F NMR (470 MHz, $CDCl_3$), δ: −56.6 (s); GC/MS (EI) m/z: 247 (M^+ − AcO), 209, 173, 149, 81; HRMS (EI): calcd. for $C_{15}H_{26}F_2OSi$ (M^+): 290.1514. Found: 290.1513.

*4.3.27. (3-(4-Methoxybenzylthio)-3,3-difluoroprop-1-ynyl)triisopropylsilane (**3e**)*

At −78 °C, to a solution of (4-methoxyphenyl)methanethiol (308 mg, 278 μL, 2 mmol) in THF (2 mL), 2.5 M solution of butyllithium in hexane (0.64 mL, 1.6 mmol) was added under argon, the reaction mixture was stirred for about 0.5 h at −78 °C, and then the solution of bromoallene **4** (311 mg, 1 mmol) in THF (1 mL) was introduced through a syringe, the reaction mixture was allow to be warmed to 0 °C slowly. Then saturated NH_4Cl solution (10 mL) was added to quench the reaction. After stirring for 5 min at about 0 °C, the resulting aqueous mixture was extracted with ether (three times); the extract washed with brine (three times) and then dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was purified by flash silica gel chromatography (hexane to 10% ethyl acetate in hexane) to give **3e** (202 mg, 53%) as a colorless oil.

IR (neat) 2945, 2866, 1513, 1463, 1250, 1154 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$), δ: 1.13–1.19 (m, 21H), 3.82 (s, 3H), 4.16 (s, 2H), 6.88 (d, J = 6.5 Hz, 2H), 7.29 (d, J = 6.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$), δ: 11.16, 18.68, 34.31, 55.48, 94.01, 97.03 (t, J = 38 Hz), 114.42, 117.43 (t, J = 263 Hz), 127.62, 130.55, 159.40; ^{19}F NMR (470 MHz, $CDCl_3$), δ: −59.8 (s); GC/MS (EI) m/z: 383 (M^+ − H), 341, 121; Anal. Calcd. for $C_{20}H_{30}F_2OSSi$: C, 62.46; H, 7.86. Found: C, 62.52; H, 7.97.

*4.3.28. (1,1-Difluoro-3-(triisopropylsilyl)prop-2-ynyl)triphenylphosphonium bromide (**3f**)*

At room temperature, to a mixture of PPh_3 (394 mg, 1.5 mmol) in ether (4 mL), the solution of bromoallene **4** (311 mg, 1 mmol) in 1 mL ether was introduced through a syringe, the reaction mixture was stirred for 12 h at room temperature. Then reaction mixture was filtered and the solid was washed with ether, and the white solid obtained was dried in vacuum (526 mg, 92%).

IR ($CHCl_3$ solution) 2946, 2866, 2166, 1584, 1438, 1158, 1108, 730, 686 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$), δ: 0.83–0.95 (m, 21H), 7.71–7.74 (m, 2H), 7.79–7.83 (m, 2H), 7.87–8.01 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$), δ: 10.81, 18.38, 92.52–92.68 (m), 107.68, 108.58–112.79 (m), 112.00 (d, J = 84 Hz), 131.60 (t, J = 13 Hz), 134.85 (t, J = 10 Hz), 137.87; ^{19}F NMR (470 MHz, $CDCl_3$), δ: −82.2 (d, J = 102 Hz); Anal. Calcd. for $C_{30}H_{36}BrF_2PSi$: C, 62.82; H, 6.33. Found: C, 62.71; H, 6.63.

*4.3.29. (3-Bromo-3,3-difluoroprop-1-ynyl)triisopropylsilane (**3g**)*

At 0 °C, to a mixture of NaBr (212 mg, 2 mmol) and DMF 2 mL, the solution of bromoallene **4** (311 mg, 1 mmol) in DMF (1 mL) was introduced through a syringe, the reaction mixture was stirred for 12 h at room temperature. Then saturated NH_4Cl solution (10 mL) was added to quench the reaction. After stirring for 5 min at about 0 °C the resulting aqueous mixture was extracted with ether (three times); the extract washed with brine (three times) and then dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was purified by flash silica gel chromatography (pure hexane) to give **3g** (242 mg, 78%) as colorless oil. The spectral data is the same as **1a**.

*4.3.30. (3-Azido-3,3-difluoroprop-1-ynyl)triisopropylsilane (**3h**)*

At 0 °C, to a mixture of NaN_3 (130 mg, 2 mmol) and CH_3CN (2 mL), the solution of bromoallene **4** (311 mg, 1 mmol) in CH_3CN (1 mL) was introduced through a syringe, the reaction mixture was stirred for 12 h at room temperature. Then 10 mL saturated NH_4Cl solution was added to quench the reaction. After stirring for 5 min at rt., the reaction mixture was extracted with ether (three times); the extract washed with brine (three times) and then dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was purified by flash silica gel chromatography (pure hexane to 10% ethyl acetate in hexane) to give **3h** (212 mg, 68%) as a colorless oil.

IR (neat) 2948, 2869, 2148, 1465, 1247, 1207, 1045, 883 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$), δ: 1.11–1.13 (m, 21H);

^{13}C NMR (125 MHz, $CDCl_3$), δ: 10.99, 18.50, 93.13 (t, J = 47 Hz), 93.79 (s), 111.93 (t, J = 239 Hz); ^{19}F NMR (470 MHz, $CDCl_3$), δ: −58.18 (s); GC/MS (EI) *m/z*: 193, 178, 166, 151, 126, 97, 82, 67, 55;

*4.3.31. Diethyl 2-(1,1-difluoro-3-(triisopropylsilyl)prop-2-ynyl)-2-methylmalonate (**3i**)*

At 0 °C, to a solution of methyl diethyl malonate (348 mg, 2 mmol) in THF (2 mL), NaH (60% suspension in mineral oil) (72 mg, 1.8 mmol) was added under argon, the reaction mixture was stirred for about 0.5 h at 0 °C, and then the solution of bromoallene **4** (311 mg, 1 mmol) in THF (1 mL) was introduced through a syringe, the reaction mixture was stirred for 4 h at 0 °C. Then saturated NH_4Cl solution (10 mL) was added to quench the reaction. After stirring for 5 min at about 0 °C, the resulting aqueous mixture was extracted with ether (three times); the extract washed with brine (three times) and then dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was purified by flash silica gel chromatography (10% ethyl acetate in hexane to 50% ethyl acetate in hexane) to give **3i** (282 mg, 70%) as a colorless oil.

IR (neat) 2954, 2866, 1745, 1463, 1271, 1046, 883, 679 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$), δ: 1.08–1.10 (m, 21H), 1.27 (t, J = 7.1 Hz, 6H), 1.69 (s, 3H), 4.24 (q, J = 7.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$), δ: 11.10, 14.05, 17.50, 18.56, 61.97 (t, J = 25 Hz), 62.30, 92.31, 96.82 (t, J = 38 Hz), 111.64 (t, J = 240 Hz), 52.40, 88.63, 95.36 (t, J = 51 Hz), 114.14 (t, J = 241 Hz); ^{19}F NMR (470 MHz, $CDCl_3$), δ: −87.6 (s); GC/MS (EI) *m/z*: 404 (M^+), 385, 361, 269, 241, 225; Anal. Calcd. for $C_{20}H_{34}F_2O_4Si$: C, 59.38; H, 8.47. Found: C, 59.11; H, 8.48.

*4.3.32. (3,3-Difluoro-5-phenylpenta-1,4-diynyl)triisopropylsilane (**3j**)*

At −78 °C, to a solution of 1-ethynylbenzene (204 mg, 2 mmol) in THF (2 mL), a 2.5 M solution of butyllithium in hexane (0.64 mL, 1.6 mmol) was added under argon, the reaction mixture was stirred for about 0.5 h at −78 °C, and then the solution of bromoallene **4** (311 mg, 1 mmol) in THF (1 mL) was introduced through a syringe, the reaction mixture was allow to be warmed to 0 °C slowly. Then saturated NH_4Cl solution (10 ml) was added to quench the reaction. After stirring for 5 min at about 0 °C, the resulting aqueous mixture was extracted with ether (three times); the extract washed with brine (three times) and then dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was purified by flash silica gel chromatography (hexane) to give **3j** (183 mg, 55%) as colorless oil.

IR (neat) 2945, 2867, 2241, 1463, 1281, 1152, 1106, 1025, 756 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$), δ: 1.14–1.22 (m, 21H), 7.40–7.44(m, 3H), 7.55–7.56 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$), δ: 11.21, 18.66, 81.56 (t, J = 43 Hz), 86.81, 91.58, 98.24 (t, J = 41 Hz), 100.85 (t, J = 222 Hz), 120.06, 128.77, 130.47, 132.50; ^{19}F NMR (470 MHz, $CDCl_3$), δ: −65.3 (s); GC/MS (EI) *m/z*: 312 (M^+ − F), 289, 219, 165, 103; HRMS (EI): calcd. for $C_{20}H_{26}F_2Si$ (M^+): 332.1772. Found: 332.1777.

*4.3.33. Diethyl 2-(1,1-difluoroprop-2-ynyl)-2-methylmalonate (**9a**)*

At −78 °C, to a solution of diethyl 2-(1,1-difluoro-3-(triisopropylsilyl)prop-2-ynyl)-2-methylmalonate **3i** (104 mg, 0.257 mmol) in THF (2.5 mL), 1.0 M solution of TBAF in THF (0.3 mL, 0.3 mmol) was added under argon, the reaction mixture was stirred for about 0.5 h at −78 °C, the reaction mixture was allow to be warmed to −20 °C slowly. Then saturated NH_4Cl solution (10 mL) was added to quench the reaction. After stirring for 5 min at about 0 °C, the resulting aqueous mixture was extracted with ether (three times); the extract washed with brine (three times) and then dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was purified by flash silica gel chromatography (10% AcOEt in hexane) to give **9a** (68 mg, 92%) as colorless oil.

IR (neat) 3264, 2943, 2866, 2133, 1742, 1459, 1275, 1099, 645 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$), δ: 1.26 (t, J = 5.5 Hz, 1H), 4.21–4.28 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$), δ: 14.02, 16.96, 61.72 (t, J = 25 Hz), 62.53, 74.76 (t, J = 38 Hz), 111.89 (t, J = 241 Hz), 166.76; ^{19}F NMR (470 MHz, $CDCl_3$), δ: −89.4 (s); GC/MS (EI) *m/z*: 248 (M^+), 203, 111.

*4.3.34. Diethyl-2-(4-(4-chlorophenyl)-1,1-difluoro-4-hydroxybut-2-ynyl)-2-methylmalonate (**9b**)*

At −78 °C, to a solution of diethyl 2-(1,1-difluoro-3-(triisopropylsilyl)prop-2-ynyl)-2-methylmalonate (104 mg, 0.257 mmol) and *p*-Cl–PhCHO (75.5 mg, 0.514 mmol) in THF (2.5 mL), 1.0 M solution of TBAF in THF (0.257 mL, 0.257 mmol) was added under argon, the reaction mixture was stirred for about 0.5 h at −78 °C, the reaction mixture was allow to be warmed to −20 °C slowly. Then saturated NH_4Cl solution (10 mL) was added to quench the reaction. After stirring for 5 min at about 0 °C, the resulting aqueous mixture was extracted with ether (three times); the extract washed with brine (three times) and then dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was purified by flash silica gel chromatography (10–30% AcOEt in hexane) to give **9b** (56 mg, 57%) as colorless oil.

IR (neat) 3482, 2985, 2258, 1734, 1276, 1054 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$), δ: 1.16 (t, J = 7.5 Hz, 3H), 1.17 (t, J = 7.5 Hz, 3H), 1.60 (s, 3H), 4.14 (q, J = 7.5 Hz, 2H), 4.15 (1, J = 7.5 Hz, 2H), 5.44 (s, 3H), 7.28 (d, J = 8.0 Hz, 2H), 7.38 (d, J = 8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$), δ: 13.79, 16.62, 62.00 (t, J = 25.7 Hz), 62.36, 63.35, 77.75 (t, J = 39.1 Hz), 87.93 (t, J = 6.7 Hz), 111.00 (t, J = 240 Hz), 166.69; ^{19}F NMR (470 MHz, $CDCl_3$), δ: −89.06 (s); GC/MS (EI) *m/z*: 388 (M^+), 370, 321, 295, 267, 249, 225, 176, 139, 111, 75; Anal. Calcd. for $C_{18}H_{19}ClF_2O_5$: C, 55.61; H, 4.93. Found: C, 55.42; H, 5.04.

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References

[1] S.M. Ma, Eur. J. Org. Chem. (2004) 1175–1183.
[2] S. Hashmi, Angew. Chem. Int. Ed. 39 (2000) 3590–3593.
[3] N. Krause, A.S.K. Hashmi (Eds.), Modern Allene Chemistry, Wiley–VCH, Weinheim, 2004.
[4] A. Hoffmann-Roder, N. Krause, Angew. Chem. Int. Ed. 43 (2004) 1196–1216.
[5] Q.L. Shen, G.B. Hammond, J. Am. Chem. Soc. 124 (2002) 6534–6535.
[6] R.D. Chambers, Fluorine in Organic Chemistry, Blackwell Publishing Ltd./CRC Press, Boca Raton, FL, 2004.
[7] M. Pohmakotr, W. Ieawsuwan, P. Tuchinda, P. Kongsaeree, S. Prabpai, V. Reutrakul, Org. Lett. 6 (2004) 4547–4550.
[8] Y. Hanzawa, K. Inazawa, A. Kon, H. Aoki, Y. Kobayashi, Tetrahedron Lett. 28 (1987) 659–662.
[9] H.L. Sham, D.A. Betebenner, N.E. Wideburg, D.J. Kempf, J.J. Plattner, D.W. Norbeck, J. Fluorine Chem. 73 (1995) 221–224.
[10] M.G. Barlow, S. Tajammal, A.E. Tipping, J. Fluorine Chem. 64 (1993) 61–71.
[11] H.L. Sham, D.A. Betebenner, J. Chem. Soc. Chem. Commun. (1991) 1134–1135.
[12] M. Kirihara, T. Takuwa, S. Takizawa, T. Momose, H. Nemoto, Tetrahedron 56 (2000) 8275–8280.
[13] C. Audouard, I. Barsukov, J. Fawcett, G.A. Griffith, J.M. Percy, S. Pintat, C.A. Smith, J. Chem. Soc. Chem. Commun. (2004) 1526–1527.
[14] I. Rico, D. Cantacuzene, C. Wakselman, J. Chem. Soc., Perkin Trans. 1 (1982) 1063–1065.
[15] P.Y. Kwok, F.W. Muellner, C.K. Chen, J. Fried, J. Am. Chem. Soc. 109 (1987) 3684–3692.
[16] V.G. Nenajdenko, G.N. Varseev, V.N. Korotchenko, A.V. Shastin, E.S. Balenkova, J. Fluorine Chem. 125 (2004) 1339.
[17] B. Xu, M. Mae, J.A. Hong, Y. Li, G.B. Hammond, Synthesis (2006) 803–806.
[18] Z.G. Wang, G.B. Hammond, J. Chem. Soc. Chem. Commun. (1999) 2545–2546.
[19] C. Rücker, Chem. Rev. 95 (1995) 1009–1064.
[20] S. Arimitsu, B. Xu, T.L.S. Kishbaugh, L. Griffin, G.B. Hammond, J. Fluorine Chem. 125 (2004) 641–645.
[21] P. Kirsch, Modern Fluoroorganic Chemistry, Wiley–VCH, Weinheim, 2004.
[22] T. Hiyama, Organofluorine Compounds. Chemistry and Applications, Springer-Verlag, Berlin, 2000.
[23] I. Ojima, J.R. McCarthy, J.T. Welch (Eds.), Biomedical Frontiers of Fluorine Chemistry, American Chemical Society, Washington, DC, 1996
[24] C. Leriche, X. He, C. Chang, H. Liu, J. Am. Chem. Soc. 125 (2003) 6348–6349.
[25] V.A. Soloshonok (Ed.), Fluorine-containing Synthons, Oxford University Press/American Chemical Society, Washington, DC, 2005.
[26] M. Mae, J.A. Hong, K. Uneyama, G.B. Hammond, Tetrahedron Lett. 46 (2005) 1787–1789.
[27] H.E. Hurst, M. Mae, J.A. Hong, G.B. Hammond, J. Fluorine Chem. 127 (2006) 126–132.
[28] G.K.S. Prakash, J.B. Hu, W. Ying, G.A. Olah, Angew. Chem. Int. Ed. 43 (2004) 5203–5206.
[29] M. Fujita, T. Hiyama, Tetrahedron Lett. 27 (1986) 3659–3660.
[30] H. Ueki, T. Chiba, T. Yamazaki, T. Kitazume, J. Org. Chem. 69 (2004) 7616–7627.
[31] M.J.T. Frisch, G.W. Truck, H.B.Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, J.A. Montgomery, Jr., T. Vreven, K.N. Kudin, J.C. Burant, J.M. Millam, S.S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G.A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J.E. Knox, H.P. Hratchian, J.B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R.E. Stratmann, O. Yazyev, A.J. Austin, R. Cammi, C. Pomelli, J.W. Ochterski, P.Y. Ayala, K. Morokuma, G.A. Voth, P. Salvador, J.J. Dannenberg, V.G. Zakrzewski, S. Dapprich, A.D. Daniels, M.C. Strain, O. Farkas, D.K. Malick, A.D. Rabuck, K. Raghavachari, J.B. Foresman, J.V. Ortiz, Q. Cui, A.G. Baboul, S. Clifford, J. Cioslowski, B.B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R.L. Martin, D.J. Fox, T. Keith, M.A. Al-Laham, C.Y. Peng, A. Nanayakkara, M. Challacombe, P.M.W. Gill, B. Johnson, W. Chen, M.W. Wong, C. Gonzalez, J.A. Pople, Gaussian, Inc., Wallingford, CT, 2004.
[32] Z.G. Wang, G.B. Hammond, J. Org. Chem. 65 (2000) 6547–6552.
[33] B. Xu, G.B. Hammond, Angew. Chem. Int. Ed. 44 (2005) 7404–7407.
[34] Y. Matsukawa, J. Mizukado, H. Quan, M. Tamura, A. Sekiya, Angew. Chem. Int. Ed. 44 (2005) 1128–1130.