An Efficient Preparation of TIPS−Halofluoropropyne and Its Application to the Diastereoselective Synthesis of Propargylic Fluorohydrins

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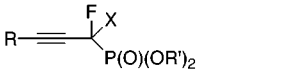
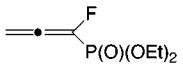
Introduction

The replacement of CH_2 by CHF—an area of much research activity[2]—has been fueled by the continuous expansion of the role played by fluorine in fields as diverse as pharmaceuticals, molecular imaging, and polymers.[3] The increased repertoire of asymmetric fluorination reactions[4] and improvements in the design of fluorine-containing building block,[5] are examples of a synthetic response to new and challenging demands for site-specific fluorine substitution. α-Fluorophosphonates are important mimics of biological phosphates.[6] Our earlier work focused on developing highly functional monofluorophosphonate building blocks. This resulted in the synthesis of α-fluoropropargyl phosphonates **1**[7−8] and α-fluoroallene phosphonate **2**.[8] The latter was used to generate a cascade of diastereospecific reactions leading to unsaturated α-fluorophosphononucleosides and α-fluoroenaminophosphonates. In addition, the Diels−Alder cyclization of **2** provided a diastereoselective route to exocyclic α-fluoromethylidene phosphonates.[9]



1a: R=TIPS, X=H, R'=Et
1b: R=TMS, alkyl, aryl; X=H, F, alkyl
R'=alkyl



2

With the exception of enynes and enediynes—obtained from **1** via HWE olefination—the sluggish reactivity of the phosphonyl group in **1** and **2** will circumscribe their usefulness mainly to the synthesis of other α-fluorophosphonates. To enhance the building block potential of the α-fluoropropargyl motif present in **1**, we sought the substitution of the phosphorus atom with a halogen. This paper reports an efficient one-step synthesis of **3** from halofluoromethane and the diastereoselective synthesis of propargylic fluorohydrins **6** via a Zn-mediated propargylation of aldehydes and acetone.

Results and Discussion

Despite its synthetic potential, only a single previous report of the γ-silyl-α-fluorohalopropargyl synthon exists. Krantz and Castelhano[10] prepared the TMS analogue of **3a** in moderate yields (40−50%) by the reaction of $CHFCl_2$ with the requisite acetylide in THF, at very low temperatures (−100 to −70 °C). The preparation of **3a**,**b** followed our recently discovered synthesis of 1-TIPS-3-bromo-3,3-difluoropropyne.[11] Chloride **3a** was assembled by the alkylation of $CHFCl_2$ with lithium TIPS-acetylide in 76% after distillation (Scheme 1).

The only byproduct detected in this reaction was TIPS−C≡C−$CHCl_2$ according to the GC−MS of the reaction mixture. Substitution of chlorine by bromine in the starting halofluoromethane led to **3b** in slightly lower yield (64%). Reaction byproducts included TIPS−C≡C−Br (GC−MS analysis) and TIPS−C≡C−CFH_2. An attempted S_N2 displacement of chloride from **3a** using KBr in refluxing methyl ethyl ketone (MEK) failed to produce the desired **3b**. The starting material remained unchanged. However, nucleophilic substitution of **3a** or **3b** using NaI in refluxing MEK (reaction time was 40 h in the case of **3a**, and 1 h in the case of **3b**) produced the iodo analogue **3c** quantitatively, according to the ^{19}F NMR spectrum of the crude product. The purification of **3c** was hampered by its gradual decomposition (even under darkness) at room temperature to give TIPS−C≡C−CHO. Dechlorination of **3a** using tri(*n*-butyl)tin hydride[12] (1.0 equiv) with a radical initiator, in refluxing toluene, afforded TIPS-fluoropropyne **4a** in 60−70% yield. This compound could also be prepared, albeit in lower yield (37%), using Zn (1 equiv) in DMF at 100 °C.

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(2) Selected recent examples include: Bainbridge, J. M.; Corr, S.; Kanai, M.; Percy, J. M. *Tetrahedron Lett.* **2000**, *41*, 971−974. Huang, X.; He, P.; Shi, G. *J. Org. Chem.* **2000**, *65*, 627−629. Funabiki, K.; Fukushima, Y.; Matsui, M.; Shibata, K. *J. Org. Chem.* **2000**, *65*, 606−609. Shimizu, M.; Hata, T.; Hiyama, T. *Tetrahedron Lett.* **1999**, *40*, 7375−7378. Narisano, E.; Riva, R. *Tetrahedron*: *Asymmetry* **1999**, *10*, 1223−1242. Narisano, E.; Riva, R. *Tetrahedron*: *Asymmetry* **1999**, *10*, 1223−1242. Laue, K. W.; Haufe, G. *Synthesis* **1998**, 1453−1456. Davis, F. A.; Kasu, P. V. N.; Sundarababu, G.; Qi, H. *J. Org. Chem.* **1997**, *62*, 7546−7547.

(3) Hudlicky, M.; Pavlath, A. E. *Chemistry of Organic Fluorine Compounds II*; American Chemical Society: Washington, DC, 1995. *Fluorine-containing Molecules. Structure, Reactivity, Synthesis, and Applications*; Liebman, J. F., Greenberg, A., Dolbier, W. R., Eds.; VCH Publishers: New York, 1988. *Fluoroorganic Chemistry: Synthetic Challenges and Biomedicinal Rewards*; Resnati, G., Soloshonok, V. A., Eds.; Tetrahedron Symposia-In-Print No. 58, Elsevier: Amsterdam, 1996; pp1−330. Ojima, I.; McCarthy, J. R.; Welch, J. T. *Biomedical Frontiers of Fluorine Chemistry*; Ojima, I., McCarthy, J. R., Welch, J. T., Eds.; American Chemical Society: Washington, DC, 1996; Vol. 639, p 356. *Fluorine-Containing Amino Acids: Synthesis and Properties*; Kukhar, V. P.; Soloshonok, V. A., Ed.; Wiley: Chichester, 1994. *Biomedicinal Aspects of Fluorine Chemistry*; Filler, R., Kobayashi, Y., Yagupolskii, L. M. Eds; Elsevier: Amsterdam, 1993. *Organofluorine Chemistry. Principles and Commercial Applications*; Banks, R. E., Smart, B. E., Tatlow, J. C., Eds.; Plenum Press: New York, 1994; p 644. For a comprehensive list, up to 1993, of books and reviews on fluoroorganic chemistry see: Resnati, G. *Tetrahedron* **1993**, *49*, 9385−9445.

(4) *Enantiocontrolled Synthesis of Fluoro-Organic Compounds*; Soloshonok, V. A., Ed.; Wiley & Sons: West Sussex, 1999,

(5) For an excellent review and an updated compilation of references, see: Percy, J. M. *Top. Curr. Chem.* **1997**, *193*, 131−195.

(6) Recent review: O'Hagan, D.; Rzepa, H. S. *J. Chem. Soc., Chem. Commun.* **1997**, 645−652.

(7) Benayoud, F.; deMendonca, D. J.; Digits, C. A.; Moniz, G. A.; Sanders, T. C.; Hammond, G. B. *J. Org. Chem.* **1996**, *61*, 5159−5164. Benayoud, F.; Hammond, G. B. *J. C. S. Chem. Commun.* **1996**, 1447−1448.

(8) Zapata, A.; Gu, Y.; Hammond, G. B. *J. Org. Chem.* **2000**, *65*, 227−234.

(9) Gu, Y.; Hama, T.; Hammond, G. B. *J. Chem. Soc., Chem. Commun.* **2000**, 395−396.

(10) Castelhano, A. L.; Krantz, A. *J. Am. Chem. Soc.* **1987**, *109*, 3491−3493.

(11) Wang, Z.; Hammond, G. B. *J. Chem. Soc., Chem. Commun.* **1999**, 2545−2546.

(12) Reviews: Curran, D. P. *Synthesis* **1988**, 417−439. Neumann, W. P. *Synthesis* **1987**, 665−683.

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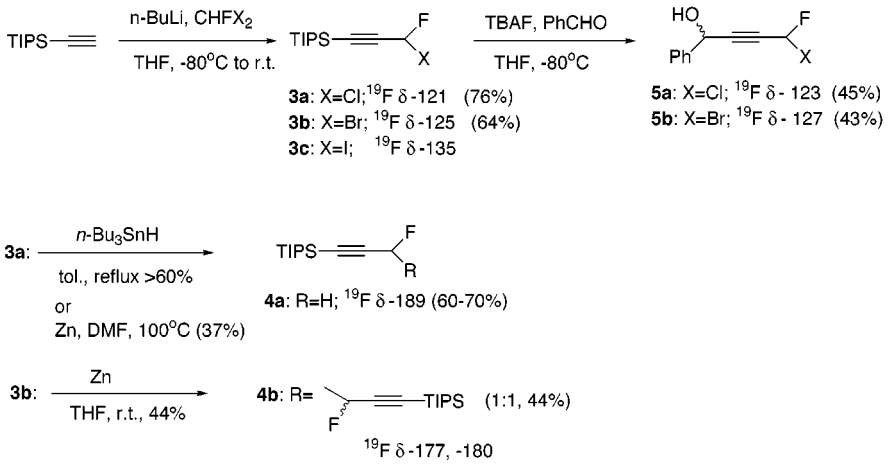
Scheme 1



Changing the solvent (THF instead of DMF), and sonicating a mixture of activated zinc[13] and bromide **3b** at room temperature, furnished dimer **4b**, as a 1:1 mixture of diastereoisomers. This reaction also produced small amounts of **4a** and TIPS−C≡C−CH_3. Chloride **3a** failed to undergo a similar reaction. Dimer **4b** could also be obtained by the reaction of triethyl phosphite with **3a** or **3b**.[14]

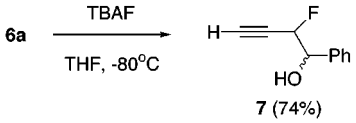
The alkynylsilane moiety present in **3** is a convenient handle for new C−C bond formation. With this in mind, we probed the deprotection of the TIPS group with TBAF and in situ trapping with an electrophile (benzaldehyde). The reaction afforded the desired propargyl alcohol **5a**,**b**, in moderate isolated yields (45%). Substituting the halogen atom before TBAF deprotection greatly improved the yield of desilylated product (see eq 1 below).

The published preparation of **1a** is relatively laborious.[8] Our synthesis of **3** offered an opportunity to synthesize **1a** in one step provided suitable conditions for the phosphorus substitution of the halide in either **3a**, **3b**, or **3c** could be found. Unfortunately, our attempts, using a nucleophilic or electrophilic phosphorus reagent, did not provide the desired result (see ref 14).

We have recently reported the synthesis of α,α-difluorohomopropargylic alcohols starting from TIPS−C≡C−CF_2Br, via a Zn-mediated propargylation of aldehydes and ketones.[15] Propargylic fluorohydrin **6** can be regarded as a monofluoro counterpart to α,α-difluorohomopropargylic alcohols, with the potential to deliver a −CHF− group into an organic compound, by way of a silyl propargyl scaffold. To our surprise, with the exception of 13-fluoro-14-hydroxyhexadec-11-ynyl acetate,[16] propargylic fluorohydrins have not been reported in the literature. Premixing the aldehyde in THF with activated zinc dust and **3b** (sonication at room temperature, or reflux) carried out the synthesis of **6** in yields ranging from 60% to 90% (Table 1). The only byproduct detected in this reaction was dimer **4b** (10−20% according to GC−MS), easily removed during chromatography due to its low polarity.

The yield of **6** appeared to increase with the electrophilic character of the carbonyl compound (e.g., entry b). Furthermore, this reaction favored the preferential formation of the erythro diastereomer. The diastereomeric ratio was determined by ^1H and/or ^{19}F NMR spectroscopy in the crude mixture. The erythro and threo isomers were identified by their $^3J_{HH}$ coupling constants (Table 2).[17] This ratio appears to be dependent on steric hindrance, at least in the case of aliphatic aldehydes (compare entry f vs entry e in Table 1). The preference for the erythro isomer in Zn-mediated additions to aldehydes has also been reported by Chemla and co-workers.[18]

When needed, the TIPS-protecting group in **6** can be easily removed using TBAF, as demonstrated by the conversion of **6a** to **7** (eq 1), under mild conditions and in good yield.



This result may allow access to allylic fluorohydrins as well as α-fluorocarbonyl compounds, after hydrogenation of the triple bond, and oxidation of the alcohol, respectively. These and other organometallic applications of **3** are under investigation.

Experimental Section

All moisture-sensitive reactions were done using flame-dried glassware flushed with argon, magnetic stirring, and dry, freshly distilled solvents. THF was distilled from Na/benzophenone. Toluene was distilled from calcium hydride. Other solvents were HPLC grade and were used without purification. $CHFCl_2$ (HCFC-21, 97%) and $CHFBr_2$ (Halon 1102, 98%) were purchased from SynQuest Laboratories, Inc. (Alachua, FL) and used without further purification. Other commercial reagents were purchased from Aldrich and used as received. All reactions were

(13) For a zinc activation procedure, see: Brandänge, S.; Dahlman, O.; Mörch, L. *J. Am. Chem. Soc.* **1981**, *103*, 4452−4458.

(14) An Arbuzov reaction with triethyl phosphite (Bhattacharya, A. K.; Thyagarajan, G. *Chem. Rev.* **1981**, *81*, 415−430) accompanied by either *n*-Bu_4NI or $(NH_4)_2Ce(NO_3]_6$ (Kottmann, H.; Skarzewski, J.; Effenberger, F. *Synthesis* **1987**, *1987*, 797−801) produced a mixture of **4b**, and TIPS−C≡C−CHO. Use of *n*-BuLi in **3a**, or **b**, followed by the addition of diethyl chlorophosphate or diethyl chlorophosphite led to complex mixtures or unreacted starting material.

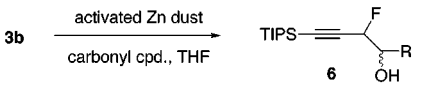
(15) Wang, Z.; Hammond, G. B. *Tetrahedron Lett.* **2000**, *41*, 2339−2342.

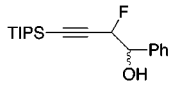
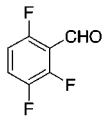
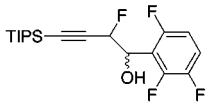
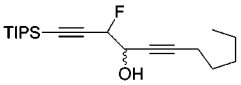
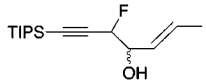
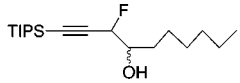
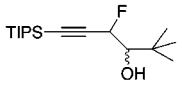
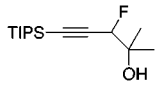
(16) This compound, prepared in low yield after several steps, was an intermediate in a pheromone synthesis: Camps, F.; Fabrias, G.; Guerrero, A. *Tetrahedron* **1986**, *42*, 3623−3629.

(17) Al-Badri, H.; About-Jaudet, E.; Collignon, N. *Synthesis* **1994**, 1072−1078. Buss, A. D.; Cruse, W. B.; Kennard, O.; Warren, S. *J. Chem. Soc., Perkin Trans. 1* **1984**, 243−247.

(18) Chemla, F.; Hebbe, V.; Normant, J. F. *Tetrahedron Lett.* **1999**, *40*, 8093−8096. Chemla, F.; Bernard, N.; Normant, J. F. *Tetrahedron Lett.* **1999**, *40*, 75−78.

Table 1



entry	Carbonyl cpd.	Conditions	6	yield %[a]	*erythro*:*threo*[b]
a	PhCHO	r.t., 2 h		76	4:1
b		r.t., 2 h		90	1:1
c	$H_3C(H_2C)_4C{\equiv}CCHO$	reflux, 6 h		69	2:1
d	*trans*$H_3CHC{=}CHCHO$	0°C to r.t., overnight		56	3:1
e	$CH_3(CH_2)_5CHO$	0°C to r.t., overnight		70	2:1
f	$(CH_3)_3CCHO$	40°C, 2 h		72	5:1
g	$(CH_3)_2CO$	reflux, 2 h[c]		67	--

[a] Isolated yields of pure product after chromatography. [b] Determined by ^1H and/or ^{19}F NMR spectroscopy in the crude product. [c] Acetone was used as solvent.

monitored using one of the following techniques: TLC, GC−MS, and/or ^{19}F NMR. Analytical TLC was performed using Macherey-Nagel Polygram Sil G/UV$_{254}$ precoated plastic plates and visualized using phosphomolybdic acid (5% in methanol). Flash chromatography was performed using silica gel 230−400 mesh, 40−63 μm (Lagand Chemicals). ^1H, ^{19}F, and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300, 282, and 75 MHz, respectively. ^{19}F NMR spectra were referenced against external $CFCl_3$. ^{19}F NMR spectra were broadband decoupled from hydrogen nuclei. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA.

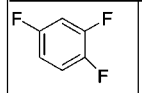
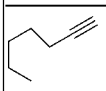
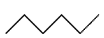
General Procedure for the Synthesis of 1-(Triisopropylsilyl)-3-chloro-3-fluoropropyne 3a. To a solution of (triisopropylsilyl)acetylene[19] (8.480 g, 46.6 mmol) in THF (35 mL) at −80 °C was added *n*-BuLi (1.6M in hexane, 32 mL, 51.2 mmol), and then the mixture was warmed to room temperature and stirred for 30 min. At −80 °C, dichlorofluoromethane (d^{25} = 1.366, 5 mL, 6.83 g, 66.4 mmol) was added dropwise by cannula. The dark brown solution was stirred at 0 °C for 1 h and quenched with saturated NH_4Cl. THF was removed in vacuo, and the residue was extracted by diethyl ether and washed with saturated NH_4Cl and brine. The combined organic layers were dried ($MgSO_4$) and concentrated. Vacuum distillation afforded **3a** (50−52 °C/0.1 mmHg, 8.806 g, 76%): ^1H NMR δ 1.11 (s, 21H), 6.56 (d, 1H, $^2J_{HF}$ = 50.6 Hz); ^{13}C NMR δ 11.2, 18.2, 85.8 (d, $^1J_{CF}$ = 236 Hz), 94.4 (d, $^3J_{CF}$ = 4 Hz), 99.0 (d, $^2J_{CF}$ = 27 Hz); ^{19}F NMR δ −121. Anal. Calcd for $C_{12}H_{22}ClFSi$: C, 57.92; H, 8.91. Found: C, 57.70; H, 8.83.

1-(Triisopropylsilyl)-3-bromo-3-fluoropropyne 3b. Dibromofluoromethane (5.230 g, 27.26 mmol) was added to TIPS-acetylene (4.536 g, 24.92 mmol) in THF according to the above general procedure. The ratio of the reagents was as follows: TIPS-acetylene/*n*-BuLi/$CHBr_2F$ = 1:1.1:1.1. Vacuum distillation provided **3b** (bp 67 °C/0.1 mmHg, 4.661 g, 64%): ^1H NMR δ 1.11 (s, 21H), 6.79 (d, 1H, $^2J_{HF}$ = 51.5 Hz); ^{13}C NMR δ 11.0, 18.4, 73.5 (d, $^1J_{CF}$ = 246 Hz), 96.7 (d, $^3J_{CF}$ = 6 Hz), 99.5 (d, $^2J_{CF}$ = 26 Hz); ^{19}F NMR δ −125. Anal. Calcd for $C_{12}H_{22}BrFSi$: C, 49.14; H, 7.56. Found: C, 48.64; H, 7.42.

1-(Triisopropylsilyl)-3-fluoropropyne 4a. A mixture of 1,1′-azobis(cyclohexanecarbonitrile) (0.0432 g, 0.177 mmol), tributyltin hydride (0.515 g, 1.77 mmol), and TIPS-chlorofluoropropyne **3a** (0.438 g, 1.77 mmol) was refluxed in toluene for 1 h. After cooling, the solvent was removed in vacuo. The residue was dissolved in diethyl ether and then treated with 1 g/mL of KF solution. After the mixture was stirred 30 min, the white precipitate of *n*-Bu_3SnF was filtrated off at reduced pressure, the ethereal filtrate was dried ($MgSO_4$) and concentrated. Flash column chromatography on silica gel (hexane/CH_2Cl_2 = 98:2) yielded **4a** (0.265 g, 70%): ^1H NMR δ 1.08 (s, 21H), 5.98 (d, 2H, $^2J_{HF}$ = 47.5 Hz); ^{13}C NMR δ 11.0, 18.3, 71.0 (d, $^1J_{CF}$ = 165 Hz), 91.9 (d, $^3J_{CF}$ = 10 Hz), 100.5 (d, $^2J_{CF}$ = 21 Hz); ^{19}F NMR δ −189. Anal. Calcd for $C_{12}H_{23}FSi$: C, 67.23; H, 10.81. Found: C, 67.15; H, 10.74.

(19) TIPS−C≡C−H was purchased from GFS Chemicals, Inc. (Columbus, OH). The company assay showed that 70% contained TIPS-acetylene. The impurities present corresponded to propyl isomers of TIPS: diisopropylpropylsilylacetylene (17%) and diisopropylpropenylsilylacetylene (12%). Fractional distillation failed to separate the TIPS isomers but this did not affect the outcome of the reactions.

Table 2

	Erythro-**6**						*Threo*-**6**					
R	δ ^{19}F	δ C*H*F	δ C*H*OH	$^{2}J_{HF}$	$^{3}J_{HF}$	$^{3}J_{HAHB}$[a]	δ ^{19}F	δ C*H*F	δ C*H*OH	$^{2}J_{HF}$	$^{3}J_{HF}$	$^{3}J_{HAHB}$[a]
Ph	-177.9	5.23 (dd)	4.97 (dd)	48	13	4	-176.6	5.11 (dd)	4.87 (dd)	50	12	8
	-182.8	5.43 (dd)[b]	5.26 (dd)[b]	49	17	5	-176.8	5.54 (dd)[b]	5.32 (dd)[b]	49	13	9
	-180.9	5.14 (dd)	4.54 (m)	48	--[c]	3	-177.7	5.01 (dd)	4.57 (m)	49	--[c]	7
	-183.2	5.08 (dd)	4.32 (m)	49	--[c]	4	-179.6	4.89 (dd)	4.27 (m)	50	--[c]	7
	-183.5	5.06 (dd)	3.82 (m)	48	--[c]	4	-181.6	4.90 (dd)	3.82 (m)	50	--[c]	7
	-172.3	5.20 (dd)	3.53 (dd)	48	16	4	-185.8	--[d]	3.42 (dd)	--[c]	22	4

[a] Coupling between the two protons (H_A and H_B), on the main carbon skeleton, is greater for the threo than for the erythro isomers. See ref 17. The only exception was **6f**. [b] Further signal splitting due to long-range coupling with aromatic fluorines was observed. [c] Unable to determine. [d] Degenerate erythro and threo signals.

1,6-Bis(triisopropyl)-3,4-difluoro-1,5-hexadiyne 4b. Freshly activated zinc dust (0.130 g, 1.99 mmol) was added to TIPS-bromofluoropropyne **3b** (0.580 g, 1.99 mmol) in THF. The mixture was sonicated for 30 min and stirred at room temperature until the absence of starting material. Standard workup (saturated NH_4Cl, brine, ether extraction, drying, and concentration) and purification by flash chromatography (pentane/cyclohexane = 1:1) afforded **4b** (0.186 g, 44%). Erythro or threo: ^{1}H NMR δ 1.08 (s, 21H), 5.26 (dm, 2H, $^2J_{HF}$ = 62.5 Hz); ^{13}C NMR δ 11.0, 18.5, 82.5 (dd, $^1J_{CF}$ = 183 Hz, $^2J_{CF}$ = 29 Hz), 93.4 (t, $^3J_{CF}$ = 4.6 Hz), 97.5 (t, $^2J_{CF}$ = 16 Hz); ^{19}F NMR δ −180. Threo or erythro: ^{1}H NMR δ 1.08 (s, 21H), 5.18 (dm, 2H, $^2J_{HF}$ = 58.9 Hz); ^{13}C NMR δ 11.0, 18.5, 82.3 (dd, $^1J_{CF}$ = 184 Hz, $^2J_{CF}$ = 29 Hz), 93.8 (t, $^3J_{CF}$ = 4.7 Hz), 98.0 (t, $^2J_{CF}$ = 16 Hz); ^{19}F NMR δ −177. Anal. Calcd for $C_{24}H_{44}F_2Si_2$: C, 67.54; H, 10.39. Found: C, 67.80; H, 10.39.

4-Chloro-4-fluoro-1-phenyl-2-butyn-1-ol 5a. At −80 °C, TBAF (1.28 mL 1.0 M) was added into the solution of TIPS-chlorofluoropropyne **3a** (0.276 g, 1.11 mmol) in THF mixed with benzaldehyde (0.120 g, 1.11 mmol). The reaction was quenched at −50 °C within 1 h. Standard workup and purification using flash column chromatography on silica gel (hexane/EtOAc = 9:1) gave **5a** (0.100 g, 45%): ^{1}H NMR δ 2.30 (s, 1H), 5.58 (d, 1H, $^5J_{HF}$ = 4.8 Hz), 6.65 (dd, 1H, $^2J_{HF}$ = 50.5 Hz, $^5J_{HH}$ = 1.4 Hz), 7.35−7.5 (m, 5H); ^{13}C NMR δ 64.4, 79.5 (d, $^2J_{CF}$ = 29 Hz), 86.2 (d, $^1J_{CF}$ = 236 Hz), 90.3 (d, $^3J_{CF}$ = 7 Hz), 126.6, 128.9, 129.0, 138.8; ^{19}F NMR δ −123. Anal. Calcd for $C_{10}H_8ClFO$: C, 60.47; H, 4.06. Found: C, 60.71; H, 4.19.

General Procedure for the Preparation of Propargylic Fluorohydrins 6a,b,d,e. Freshly activated zinc dust was added to **3b** in THF mixed with the aldehyde. The mixture was sonicated for 30 min and stirred at room temperature until the absence of starting material was observed in ^{19}F NMR or GC−MS. Standard workup (saturated NH_4Cl, brine, ether extraction, drying, and concentration) and purification by flash chromatography (hexane/EtOAc = 98:2) afforded TIPS-propargylic fluorohydrin.

4-(Triisopropylsilyl-2-fluoro-1-phenyl-3-butyn-1-ol 6a. Zn (0.171 g, 2.62 mmol), **3b** (0.764 g, 2.62 mmol), and benzaldehyde (0.278 g, 2.62 mmol) yielded **6a** (0.636 g, 76%). Erythro*:* ^{1}H NMR δ 1.04 (s, 21H), 2.52 (s, 1H), 4.97 (dd, 1H, $^3J_{HF}$ = 12.3 Hz, $^3J_{HH}$ = 3.8 Hz), 5.23 (dd, 1H, $^2J_{HF}$ = 47.7 Hz, $^3J_{HH}$ = 4.1 Hz), 7.25−7.46 (m, 5H); ^{13}C NMR δ 11.0, 18.5, 75.0 (d, $^2J_{CF}$ = 24 Hz), 86.2 (d, $^1J_{CF}$ = 175 Hz), 93.5 (d, $^3J_{CF}$ = 8 Hz), 99.5 (d, $^2J_{CF}$ = 25 Hz), 126.8, 128.3, 128.4, 137.6; ^{19}F NMR δ −178. Anal. Calcd for $C_{19}H_{29}FSiO$: C, 71.20; H, 9.12. Found: C, 71.26; H, 9.18.

1-(Triisopropylsilyl)-5-ene-3-fluoroheptyn-4-ol 6d. Zn (0.100 g, 1.53 mmol), **3b** (0.447 g, 1.53 mmol) and *trans*-crotonaldehyde (0.107 g, 1.53 mmol) yielded **6d** (0.244 g, 56%). Erythro: ^{1}H NMR δ 1.08 (s, 21H), 1.75 (d, 3H, $^3J_{HH}$ = 6.3 Hz), 2.03 (s, 1H), 4.29 (m, 1H), 5.08 (dd, 1H, $^2J_{HF}$ = 48.5 Hz, $^3J_{HH}$ = 3.6 Hz), 5.57 (m, 1H), 5.87 (m, 1H); ^{13}C NMR δ 11.0, 17.8, 18.5, 74.1 (d, $^2J_{CF}$ = 23 Hz), 85.4 (d, $^1J_{CF}$ = 173 Hz), 92.7 (d, $^3J_{CF}$ = 8 Hz), 100.0 (d, $^2J_{CF}$ = 25 Hz), 127.0 (d, $^3J_{CF}$ = 5 Hz), 130.8; ^{19}F NMR δ −183. Anal. Calcd for $C_{16}H_{29}FSiO$: C, 67.55; H, 10.27. Found: C, 67.46; H, 10.24.

1-(Triisopropylsilyl)-3-fluoro-1-decyn-4-ol 6e. Zn (0.061 g, 0.94 mmol), **3b** (0.274 g, 0.94 mmol), and heptanal (0.107 g, 0.94 mmol) yielded **6e** (0.216 g, 70%). Erythro: ^{1}H NMR δ 0.89 (t, 3H), 1.09 (s, 21H), 1.29 (s, 6H), 1.56 (m, 2H), 1.67 (m, 1H), 1.90 (m, 1H), 3.82 (m, 1H), 5.06 (dd, 1H, $^2J_{HF}$ = 48.3 Hz, $^3J_{HH}$ = 3.8 Hz); ^{13}C NMR δ 11.0, 14.0, 18.5, 22.6, 25.3, 29.1, 31.6, 31.8 ($^3J_{CF}$ = 3 Hz), 73.0 (d, $^2J_{CF}$ = 22 Hz), 86.0 (d, $^1J_{CF}$ = 171 Hz), 92.6 (d, $^3J_{CF}$ = 8 Hz), 100.3 (d, $^2J_{CF}$ = 25 Hz); ^{19}F NMR δ −183. Anal. Calcd for $C_{19}H_{37}FSiO$: C, 69.45; H, 11.35. Found: C, 69.72; H, 11.22.

General Procedure for the Preparation of Propargylic Fluorohydrins 6c,f,g. The mixture of TIPS-bromofluoropropyne, fleshly activated zinc dust, and aldehyde (1:1:1) was vigorously stirred at the refluxing temperature of THF.

1-(Triisopropylsilyl)-3-fluoro-1,5-undecadiyne-4-ol 6c. Zn (0.058 g, 0.89 mmol), **3b** (0.259 g, 0.89 mmol), and 2-octynal (0.110 g, 0.89 mmol) yielded **6c** (0.208 g, 69%). Threo: ^{1}H NMR δ 0.9 (m, 3H), 1.11 (s, 21H), 1.22 (m, 4H), 1.53 (m, 2H), 2.20 (td, 2H, $^3J_{HH}$ = 7.2 Hz, $^5J_{HH}$ = 2.0 Hz), 4.57 (ddt, 1H, $^3J_{HF}$ = 9.2 Hz, $^3J_{HH}$ = 7.1 Hz, $^5J_{HH}$ = 2.1 Hz), 5.01 (dd, 1H, $^2J_{HF}$ = 49.3 Hz, $^3J_{HH}$ = 7.1 Hz); ^{13}C NMR δ 11.0, 13.9, 18.5, 18.7, 22.2, 28.1, 31.0,

65.2 (d, $^2J_{CF}$ = 27 Hz), 75.5 (d, $^3J_{CF}$ = 7 Hz), 84.7 (d, $^1J_{CF}$ = 176 Hz), 88.5, 92.5 (d, $^3J_{CF}$ = 8 Hz), 99.8 (d, $^2J_{CF}$ = 24 Hz); ^{19}F NMR δ −178. Anal. Calcd for $C_{20}H_{35}FSiO$: C, 70.95; H, 10.42. Found: C, 71.18; H, 10.47.

6-(Triisopropylsilyl)-4-fluoro-2,2-dimethyl-5-hexyn-3-ol 6f. Zn (0.067 g, 1.03 mmol), **3b** (0.3 g, 1.03 mmol), and trimethylacetaldehyde (0.089 g, 1.03 mmol) yielded **6f** (0.22 g, 72%). Erythro: ^{1}H NMR δ 1.03 (d, 9H), 1.09 (s, 21H), 2.15 (s, 1H), 3.52 (dd, 1H, $^3J_{HF}$ = 16.0 Hz, $^3J_{HH}$ = 4.1 Hz), 5.20 (dd, 1H, $^2J_{HF}$ = 47.5 Hz, $^3J_{HH}$ = 4.2 Hz); ^{13}C NMR δ 11.0, 18.5, 26.2, 26.6, 79.4 (d, $^2J_{CF}$ = 22 Hz), 84.2 (d, $^1J_{CF}$ = 169 Hz), 94.1 (d, $^3J_{CF}$ = 9 Hz), 100.8 (d, $^2J_{CF}$ = 25 Hz); ^{19}F NMR δ −172. Anal. Calcd for $C_{17}H_{33}FSiO$: C, 67.94; H, 11.07. Found: C, 68.39; H, 10.97.

5-(Triisopropylsilyl)-3-fluoro-2-methyl-4-pentyn-2-ol 6g. Zn (0.269 g, 4.11 mmol) and **3b** (1.201 g, 4.11 mmol), refluxing in 5 mL of anhydrous acetone, yielded **6g** (0.753 g, 67%): ^{1}H NMR δ 1.09 (s, 21H), 1.34 (dd, 6H, $^4J_{HF}$ = 10.3 Hz, $^4J_{HH}$ = 1.3 Hz), 2.05 (s, 1H), 4.87 (dd, 1H, $^2J_{HF}$ = 48.9 Hz, $^3J_{HH}$ = 3.3 Hz); ^{13}C NMR δ 11.0, 18.5, 23.9 (d, $^3J_{CF}$ = 2 Hz), 24.4 (d, $^3J_{CF}$ = 2 Hz), 72.6 (d, $^2J_{CF}$ = 21 Hz), 89.0 (d, $^1J_{CF}$ = 175 Hz), 91.9 (d, $^3J_{CF}$ = 8 Hz), 101.0 (d, $^2J_{CF}$ = 24 Hz); ^{19}F NMR δ −182. Anal. Calcd for $C_{15}H_{29}FSiO$: C, 66.12; H, 10.73. Found: C, 66.00; H, 10.78.

2-Fluoro-1-phenyl-3-butyn-1-ol 7. At −80 °C, TBAF (1.13 mL 1.0M in THF) was added to the solution of **6a** (0.36 g, 1.13 mmol) in THF. The reaction was quenched within 1 h. Standard workup and purification using flash column chromatography on silica gel (hexane/EtOAc = 9:1) afforded **7** (0.136 g, 74%). Erythro: ^{1}H NMR δ 2.55 (s, 1H), 2.73 (dd, 1H, $^4J_{HF}$ = 5.6 Hz, $^4J_{HH}$ = 2.2 Hz), 5.00 (dd, 1H, $^3J_{HF}$ = 11.9 Hz, $^3J_{HH}$ = 4.5 Hz), 5.20 (ddd, 1H, $^2J_{HF}$ = 47.2 Hz, $^3J_{HH}$ = 4.4 Hz, $^4J_{HH}$ = 2.2 Hz), 7.34−7.47 (m, 5H); ^{13}C NMR δ 74.7 (d, $^2J_{CF}$ = 24 Hz), 78.9 (d, $^3J_{CF}$ = 9.9 Hz), 85.5 (d, $^1J_{CF}$ = 175 Hz), 126.8, 128.4, 128.6, 137.3; ^{19}F NMR δ −180. Anal. Calcd for $C_{10}H_9FO$: C, 73.16; H, 5.53. Found C, 73.15; H, 5.63. Threo: ^{1}H NMR 2.66 (dd, 1H, $^4J_{HF}$ = 5.8 Hz, $^4J_{HH}$ = 2.1 Hz), δ 2.92 (s, 1H), 4.89 (ddd, 1H, $^3J_{HF}$ = 12.3 Hz, $^3J_{HH}$ = 7.4 Hz), 5.11 (ddd, 1H, $^2J_{HF}$ = 48.7 Hz, $^3J_{HH}$ = 7.3 Hz, $^4J_{HH}$ = 2.1 Hz), 7.36−7.47 (m, 5H); ^{19}F NMR δ −181.

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Supporting Information Available: Mass spectral data for compounds **3a**−**c**, **4a**,**b**, **5a**,**b**, **6a**−**g**, and **7**. NMR data for **3c**, **5b**, and **6b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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