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A Novel Diastereoselective Synthesis of (*Z*)-Fluoroalkenes via a Nozaki−Hiyama−Kishi-Type Reaction

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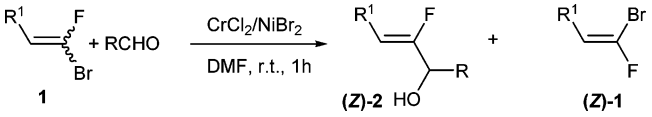

A highly diastereoselective and straightforward synthesis for (*Z*)-2-fluoroallylic alcohols via a Nozaki−Hiyama−Kishi-type reaction with the corresponding bromofluoroolefins was developed, providing an easy access to highly interesting fluorinated synthons.

Fluoroorganic compounds have exhibited increased interest as pharmaceutical[1a,b] and agrochemical[1c] agents in recent years since it has been found that fluorine modifies biological activity by altering the physicochemical properties of organic compounds.[2] For this reason, fluorinated olefins have attracted much attention, for example in the pharmaceutical area as potential enzyme inhibitors[3] and in the peptide field as a mimic of the amide bond.[4] Numerous syntheses for fluoroalkenes were developed. Among them, the Horner−Wadsworth−Emmons reaction with 2-fluoro-2-diethylphosphonoacetic acid methylester,[5] the Peterson olefination,[6] and the Stille or Suzuki palladium coupling reaction[7] are the more commonly used methods to form fluoroolefins. However, a broadly applicable and concise approach for the stereoselective synthesis of fluoroalkenes remains a challenging goal. Herein, we want to report the organometallic reaction of 1-bromo-1-fluoroolefins with aldehydes as a novel access to 2-fluoroallylic alcohols (Scheme 1).

Recently we have reported a novel and convenient method for the synthesis of 1-bromo-1-fluoroolefins via a Et_2Zn-promoted Wittig-type reaction of CBr_3F and PPh_3 with aldehydes or ketones.[8] When aldehydes are used, yields are excellent; in the case of ketones yields are still good to moderate, even with nonactivated ones (Scheme 2). Furthermore, the stereoselective decomposition of one or the other isomer gave us an exclusive access to either the *Z*- or *E*-stereoisomer.[8]

Up to now, except of palladium-catalyzed coupling reactions,[7] only few papers concerning the organometallic reaction of aldehyde-derived bromofluoroolefins have been published. At the beginning of that program, we tried to use organolithium carbenoid species. To our surprise, despite the number of publications in that field,[9] there was very few examples for the formation of an organolithium species, derived from 1-bromo-1-fluoro-2-monosubstituted olefins, and their reaction with aldehydes.[10]

In our hands, the in situ generation of lithium carbenoids from various 1-bromo-1-fluoro-2-monosubstituted ethenes, followed by their addition to aldehydes never led to the formation of the corresponding fluoroolefins even at −130 °C (Scheme 3). We always isolated the nonfluorinated alkyne derivatives, coming from an elimination of HX (X = Br or F depending on which is the first step: elimination or lithium/halogen exchange).

Formation of lithium carbenoids, followed by quenching with D_2O led to nonhalogenated 1-deuterioalkynes. Other organometallic carbenoids were reported to be more stable, such as organotin or organozinc compounds. We tried to generate the zinc carbenoid from bromofluoroalkenes, but all our attempts were unsuccessful (recovery of the unchanged starting materials). Further investigations have been carried out by using other transition metals such as organoindium, organosamarium, organocopper, and organochromium carbenoids, but only the Nozaki−Hiyama−Kishi-type[11] reaction gave us promising results.

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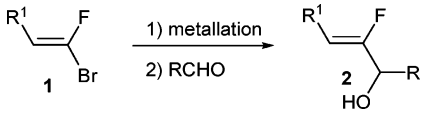
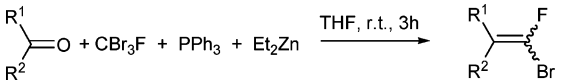
SCHEME 1. Organometallic Reaction of 1-Bromo-1-fluoroolefins with Aldehydes



SCHEME 2. Synthesis of Bromofluoroolefins



SCHEME 3. Reaction through Lithium Carbenoids

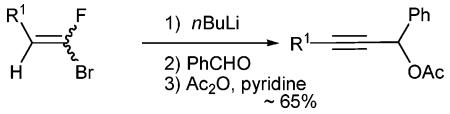
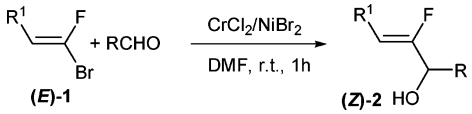


TABLE 1. Fluoroolefins Obtained through the N−H−K Reaction



entry	product	R^1	R	yield, %
1	**2a**	4-MeO-C_6H_4	Ph	78
2	**2b**	4-MeO-C_6H_4	4-MeO-C_6H_4	78
3	**2c**	4-MeO-C_6H_4	4-F-C_6H_4	72
4	**2d**	4-MeO-C_6H_4	4-MeO_2C-C_6H_4	23
5	**2e**	4-MeO-C_6H_4	4-NO_2-C_6H_4	0
6	**2f**	4-MeO-C_6H_4	$PhCH_2CH_2$	65
7	**2g**	4-MeO-C_6H_4	Et	94
8	**2h**	4-MeO-C_6H_4	Me_2CH	59
9	**2i**	4-MeO-C_6H_4	$PhCH_2$	60
10	**2j**	TBDPSO-CH_2CH_2	Me_2CH	48
11	**2k**	TBDPSO-CH_2CH_2	$PhCH_2$	39
12	**2*l***	TBDPSO-CH_2CH_2	Ph	37
13	**2m**	4-F-C_6H_4	Ph	34
14	**2n**	4-MeO_2C-C_6H_4	Ph	20
15	**2o**	4-NO_2-C_6H_4	Ph	0
16	**2p**	2-naphthyl	Ph	53
17	**2q**	$PhCH_2CH_2$	Ph	45

Optimization of the reaction conditions with the *E*-isomer showed that best results for this N−H−K reaction were obtained when adding the bromofluoroolefin and the aldehyde at room temperature to a solution of chromium(II) chloride and nickel(II) bromide in DMF (1.0/1.0/3.0/0.1 ratio). To the best of our knowledge, this constitutes the first N−H−K reaction on terminal dihalogenated alkenes.

We then examined the substrate scope for this N−H−K-type reaction by using different aldehydes (Table 1; entries 1−12) and by varying the nature of the substituent R^1 at the C-2 position of the (*E*)-bromofluoroolefins (Table 1; entries 1 and 12−17). The reaction appeared to be versatile. Indeed, for aromatic and even for aliphatic substituents, the yields were always moderate to good, ranging from 34% to 94%. Functional groups are tolerated except of the reductible ones. With nitro or ester groups on the corresponding aldehydes or bromofluoroolefins (Table 1; entries 4−5, 14−15), the yields of the N−H−K coupling reactions were very low. In accordance with literature precedent,[11c,12] the reactions never proceeded on addition to ketones (acetone or cyclohexanone), and even after 2 days at 100 °C, we could never isolate the desired allylic tertiary alcohol. It is important to note that whatever the substituents were, the reaction always occurred totally stereoselectively with retention of configuration. Starting from (*E*)-1-bromo-1-fluoro-2-monosubstituted olefins, we always ended with (*Z*)-2-fluoroallylic alcohol.

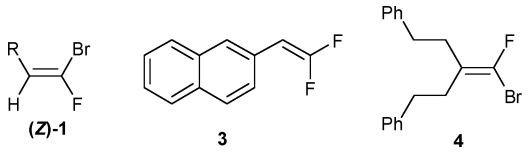


FIGURE 1. Other fluoroolefins used in the N−H−K reaction

We then decided to test (*Z*)-bromofluoroolefin (*Z*)-**1** (Figure 1) together with aldehydes in this N−H−K coupling reaction. In the literature, it is well-known that reactions are difficult when halogen has a substituant in the cis position and isomerization often occurred.[11b,c,12] In our case, under standard conditions with (*Z*)-**1**, degradations were observed and we could never isolate the desired 2-fluoroallylic alcohol. Moreover, the starting material totally disappeared, and no fluorine-containing organic compounds were detected.

On bromofluoroolefins, the N−H−K reaction proceeded exclusively with the halogen in the trans position. So, we decided to engage difluoroolefin **3** (Figure 1) in a N−H−K reaction to assess this assumption. Unfortunately, in that case no reaction occurred. Furthermore, under the N−H−K coupling reaction conditions, tetrasubstituted bromofluoroolefins were relatively unreactive. The best result was observed with compound **4** (Figure 1), and corresponding allylic alcohol **5** was obtained in 10% yield (this is in accordance with known N−H−K reactions of tetrasubstituted olefins[11c]). These two results confirm that the intermediate chromium species in the N−H−K reaction was more difficult to form and less stable when chromium was in the cis position of a substituent and led to rapid decomposition.

We could use this feature to avoid the separation step of the two isomers of the bromoolefins after the Wittig-type reaction. Indeed, on the basis of the difference of reactivity between the two isomers, a 1/1 mixture of bromofluoroolefin **1a** was subjected to our standard N−H−K conditions. The expected (*Z*)-fluoroolefin (*Z*)-**2a** could be isolated from a complexe mixture in 92% yield (based on the *E*-isomer) as a single diastereoisomer, and the unreacted (*Z*)-bromofluoroolefin (*Z*)-**1a** could be recovered in 62% yield (Scheme 4).

In conclusion, we have developed a general, practical, and straightforward method to obtain exclusively (*Z*)-2-fluoroallylic alcohols from the corresponding bromofluoroolefins (even from a mixture of *Z* and *E* stereoisomers) via a Nozaki−Hiyama−Kishi-type reaction. The reaction conditions are mild enough to accept a wide range of substituents on the aldehyde and on the bromofluoroalkene. Moreover, this method is highly diastereoselective, only the (*E*)-bromofluoroolefin reactants yielding the

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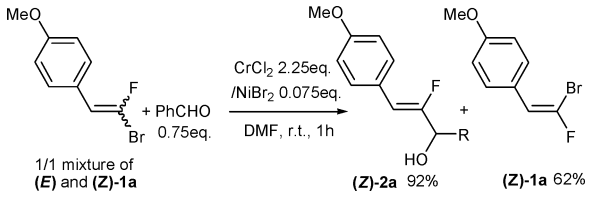
SCHEME 4. N-H−K Reaction on a *Z,E* Mixture of Isomer



(*Z*)-fluoroolefin in moderate to good yields, giving an easy access to highly interesting fluorinated synthons.

Experimental Section

General Procedure of the N−H−K Reaction. To a mixture of anhydrous $CrCl_2$ (3.0 equiv of commercial source), anhydrous $NiBr_2$ (0.1 equiv), and freshly distilled oxygen free DMF (3 mL/mmol of $CrCl_2$) was added a solution of the corresponding bromofluoroolefin (1.0 equiv) and the appropriate aldehyde (1.0 equiv) in DMF (20 mL/mmol of bromofluoroolefin) at room temperature under Ar. The mixture was stirred at room temperature for 1 h. After the reaction was completed, controlled by monitoring the ^{19}F NMR signal of the reaction mixture, an aqueous solution of ethylenediamine[13] (12.6 M, 1 mL/mmol of bromofluoroolefin) was added to the green mixture with stirring over 15 min, until the reaction mixture turned dark purple. The solution was then poured into water (150 mL/mmol) and extracted with AcOEt (3 × 80 mL/mmol), washed with HCl (aq ,2 M, 80 mL/mmol) and brine (80 mL/mmol). The organic phase was then dried by $MgSO_4$. After filtration and concentration, the residue was purified by column chromatography (cyclohexane/AcOEt) to afford desired 2-fluoro allylic alcohol **2**.

For the NMR peak assignments, the atoms are numbered (see the Supporting Information).

2a: (*Z*)-2-Fluoro-3-(4-methoxyphenyl)-1-phenylprop-2-en-1-ol. Yellow syrup (cyclohexane/AcOEt (4/1), R_f 0.3). ^1H NMR (300 MHz, $CDCl_3$) δ 7.4−7.1 (m, 7H, $H_{4,10,11,12}$), 6.8 (d, J = 8.7 Hz, 2H, H_5), 5.7 (d, $^3J^{trans}_{H-F}$ = 39.5 Hz, 1H, H_2), 5.2 (dd, $^3J_{H-F}$ = 12.8 Hz, ^3J = 4.0 Hz,1H, H_8), 3.6 (s, 3H, H_7), 3.1−2.9 (b, 1H, OH). ^{19}F NMR (282.5 MHz, $CDCl_3$) δ −118.3 (dd, $^3J^{trans}_{H-F}$ = 39.5 Hz, $^3J_{H-F}$ = 12.8 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 158.5 (d, J = 266 Hz, C_1), 159.2 (d, J = 3 Hz, C_6), 140.0 (C_9), 130.6 (d, J = 8 Hz, C_{10}), 129.1 (C_{11}), 128.9 (C_{12}), 127.3 (C_4), 125.9 (d, J = 3 Hz, C_3), 114.4 (C_5), 107.1 (d, J = 6 Hz, C_2), 73.5 (d, J = 32 Hz, C_8), 55.7 (C_7). MS (EI) 258 (M^+), 243 ($M^+ - CH_3$), 237 (M^+ − MeO), 121. IR (KBr) 3369, 2974, 2897, 1655, 1608, 1513, 1454, 1251, 1180, 1089, 1048, 880, 701 cm^{-1}. Anal. Calcd for $C_{16}H_{15}FO_2$: C, 74.40; H, 5.85. Found: C, 74.38; H, 5.91.

2b: (*Z*)-2-Fluoro-1,3-bis(4-methoxyphenyl)prop-2-en-1-ol. Pale yellow solid (mp 97 °C, cyclohexane/AcOEt (4/1), R_f =0.2). ^1H NMR (300 MHz, $CDCl_3$) δ 7.4−7.3 (m, 4H, $H_{4,10}$), 6.9−6.8 (m, 4H, $H_{5,11}$), 5.8 (d, $^3J^{trans}_{H-F}$ = 39.7 Hz, 1H, H_2), 5.2 (d, $^3J_{H-F}$ = 11.8 Hz, 1H, H_8), 3.72 (s, 3H, H_7), 3.71 (s, 3H, H_{13}), 2.4 (b, 1H, OH). ^{19}F NMR (282.5 MHz, $CDCl_3$) δ −118.2 (dd, $^3J^{trans}_{H-F}$ = 39.7 Hz, $^3J_{H-F}$ = 11.8 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) 158.6 (d, J = 265 Hz, C_1), 160.1 (C_6), 159.1 (C_{12}), 132.2 (C_3), 130.5 (d, J = 7 Hz, C_4), 128.5 (C_{10}), 125.9 (d, J = 3 Hz, C_9), 114.4−114.3 ($C_{5,11}$), 106.7 (d, J = 6 Hz, C_2), 73.2 (d, J = 32 Hz, C_8), 55.7−55.6 ($C_{7,13}$). MS (EI) δ 288 (M^+), 272 ($M^+ - H_2O$), 237, 163, 135, 121, 44. IR (KBr) 3479, 3060, 2890 2835, 1682, 1609, 1513, 1463, 1244, 1183, 1151, 1039, 1018, 851, 768, 532 cm^{-1}. Anal. Calcd for $C_{17}H_{17}FO_3$: C, 70.82; H, 5.94. Found: C, 70.79; H, 5.78.

2c: (*Z*)-2-Fluoro-1-(4-fluorophenyl)-3-(4-methoxyphenyl-)prop-2-en-1-ol. Yellow oil (cyclohexane/AcOEt (10/1), R_f 0.1). ^1H NMR (300 MHz, $CDCl_3$) δ 7.4−7.2 (m, 4H, $H_{4,11}$), 7.0 (t, $^3J_{H-F}$ = 8.7 Hz, 2H, H_{10}), 6.7 (d, J = 9.0 Hz, 2H, H_5), 5.7 (d, $^3J^{trans}_{H-F}$ = 39.4 Hz, 1H, H_2), 5.2 (d, $^3J_{H-F}$ = 12.8 Hz, 1H, H_8), 3.6 (s, 3H, H_7), 3.1 (b,1H, OH). ^{19}F NMR (282.5 MHz, $CDCl_3$) δ −118.8 (dd, $^3J^{trans}_{H-F}$ = 39.4 Hz, $^3J_{H-F}$ = 12.8 Hz, F_1), −114.0 (tt, $^3J_{H-F}$ = 8.6 Hz, $^4J_{H-F}$ = 4.3 Hz, F_{12}). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 163.0 (d, ^1J = 247 Hz, C_{12}), 159.3 (d, J = 3 Hz, C_6), 158.2 (d, ^1J = 266 Hz, C_1), 135.8 (d, J = 3 Hz, C_9), 130.6 (d, J = 8 Hz, C_4), 129.0 (d, J = 8 Hz, C_{10}), 125.7 (d, J = 3 Hz, C_3), 115.9 (d, ^2J = 22 Hz, C_{11}), 114.4 (C_5), 107.2 (d, ^2J = 6 Hz, C_2), 73.0 (d, J = 32 Hz, C_8), 55.6 (C_7). HRMS (EI) calcd for $C_{16}H_{14}F_2O_2$ 276.0962, found 276.0963.

2d: (*Z*)-4-[2-Fluoro-1-hydroxy-3-(4-fluorophenyl)allyl]-benzoic Acid Methyl Ester. White solid (mp 84 °C, cyclohexane/AcOEt (4/1), R_f 0.2). ^1H NMR (300 MHz, $CDCl_3$) δ 8.1 (d, J = 8 Hz, 2H, H_{11}), 7.6 (d, J = 8 Hz, 2H, H_{10}), 7.5 (d, J = 8.7 Hz, 2H, H_4), 6.9 (d, J = 8.7 Hz, 2H, H_5), 5.8 (d, $^3J^{trans}_{H-F}$ = 39.4 Hz, 1H, H_2), 5.4 (d, $^3J_{H-F}$ = 13.8 Hz, 1H, H_8), 3.9 (s, 3H, H_{14}), 3.8 (s, 3H, H_7), 2.9 (b, 1H, OH). ^{19}F NMR (282.5 MHz, $CDCl_3$) −119.3 (dd, $^3J^{trans}_{H-F}$ = 41.6 Hz, $^3J_{H-F}$ = 14.3 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 167 (C_{13}), 159.5 (C_6), 157.7 (d, J = 262 Hz, C_1), 144.9 (C_9), 130.6 (d, J = 7 Hz, C_4), 130.4 (C_{11}), 130.3 (C_{10}), 127.1 (C_{12}), 125.5 (C_3), 114.3 (C_5), 107.7 (d, $^2J^{trans}$ = 14 Hz, C_2), 73.4 (d, ^2J = 31 Hz, C_8), 55.7 (C_{14}), 52.6 (C_7). HRMS (EI) calcd for $C_{18}H_{17}FO_4$ 316.1111, found 316.1114.

2f: (*Z*)-2-Fluoro-1-(4-methoxyphenyl)-5-phenylpent-1-en-3-ol. Yellow solid (mp 60 °C, (cyclohexane/AcOEt (4/1), R_f 0.3). ^1H NMR (300 MHz, $CDCl_3$) δ 7.4 (d, J = 8.7 Hz, 2H, H_4), 7.3−7.0 (m, 5H, $H_{12,13,14}$), 6.8 (d, J = 8.7 Hz, 2H, H_5), 5.6 (d, $^3J^{trans}_{H-F}$ = 39.9 Hz, 1H, H_2), 4.2−4.0 (m, 1H, H_8), 3.7 (s, 3H, H_7), 2.8−2.6 (m, 2H, H_9), 2.1−1.9 (m, 3H, H_{10}, OH). ^{19}F NMR (282.5 MHz, $CDCl_3$) δ −121.8 (dd, $^3J_{H-F}$ = 16.6 Hz, $^3J^{trans}_{H-F}$ = 39.9 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 159.1 (d, ^1J = 267 Hz, C_1), 159.2 (C_6), 141.7 (C_{11}), 130.4 (C_{13}), 129.0 (d, J = 7 Hz, C_4), 128.9 ($C_{12\ 14}$), 126.5 (C_3), 114.4 (C_5), 106.6 (d, ^2J = 8 Hz, C_2), 71.1 (d, J = 30 Hz, C_8), 55.7 (C_7), 35.9 (C_9), 32.0 (C_{10}). MS (EI) 287 (M^+), 268 ($M^+ - H_2O$), 181 ($M^+ - CH_2CH_2Ph$), 121, 91 ($^+CH_2Ph$), 77 (Ph^+). IR (KBr) 3390, 3062, 3027, 2934, 2862, 2837, 1693, 1666, 1607, 1513, 1454, 1299, 1251, 1179, 860, 825, 749, 700, 532 cm^{-1}. Anal. Calcd for $C_{18}H_{19}FO_2$: C, 75.50; H, 6.69. Found: C, 75.71; H, 6.85.

2g: (*Z*)-2-Fluoro-1-(4-methoxyphenyl)pent-1-en-3-ol. Pale yellow oil (cyclohexane/AcOEt (4/1), R_f 0.2). ^1H NMR (300 MHz, $CDCl_3$) δ 7.5 (d, J = 8.7 Hz, 2H, H_4), 6.9 (d, J = 8.7 Hz, 2H, H_5), 5.7 (d, $^3J^{trans}_{H-F}$ = 40.2 Hz, 1H, H_2), 4.1 (dt, $^3J_{H-H}$ = 6.7 Hz, $^3J_{H-F}$ = 16.7 Hz, 1H, H_8), 3.8 (s, 3H, H_7), 2.9−2.7 (b, 1H, OH), 1.9−1.6 (m, 2H, H_9), 0.9 (t, J = 7.4 Hz, 3H, H_{10}). ^{19}F NMR (282.5 MHz, $CDCl_3$) δ −121.5 (dd, $^3J^{trans}_{H-F}$ = 40.2 Hz, $^3J_{H-F}$ = 16.7 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 159.3 (d, ^1J = 267 Hz, C_1), 159.0 (d, J = 3 Hz, C_6), 130.3 (d, J = 7 Hz, C_4), 126.1 (d, J = 2 Hz, C_3), 114.3 (C_5), 106.4 (d, ^2J = 8 Hz, C_2), 73.1 (d, J = 29 Hz, C_8), 55.6 (C_7), 27.5 (C_9), 10.1 (C_{10}). MS (EI) 210 (M^+), 192 ($M^+ - H_2O$), 181 (M^+ − Et), 177. IR (KBr) 3343, 2970, 1609, 1513, 1254, 1181, 1032, 860, 530 cm^{-1}. Anal. Calcd for $C_{12}H_{15}FO_2$: C, 68.55; H, 7.19. Found: C, 68.64; H, 6.99.

2h: (*Z*)-2-Fluoro-1-(4-methoxyphenyl)-4-methylpent-1-en-3-ol. Yellow oil (cyclohexane/AcOEt (9/1), R_f 0.3). ^1H NMR (300 MHz, $CDCl_3$) δ 7.4 (d, J = 8.7 Hz, 2H, H_4), 6.8 (d, J = 8.7 Hz, 2H, H_5), 5.6 (d, $^3J^{trans}_{H-F}$ = 40.2 Hz, 1H, H_2), 3.9−3.8 (m, 1H, H_8), 3.7 (s, 3H, H_7), 2.0−1.9 (m, 1H, H_9), 1.8 (d, J = 5.6 Hz, 1H, OH), 1.0 (d, J = 6.8 Hz, 3H, H_{10}), 0.9 (d, J = 6.8 Hz, 3H, H_{10}). ^{19}F NMR (282.5 MHz, $CDCl_3$) δ −120.6 (dd, $^3J^{trans}_{H-F}$ = 41.4 Hz, $^3J_{H-F}$ = 13.3 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 158.9 (d, J = 267 Hz, C_1), 159.1 (C_6), 130.1 (d, J = 7 Hz, C_4), 126.0 (C_3), 114.3 (C_5), 107.2 (d, $^2J^{trans}$ = 6 Hz, C_2), 76.9 (d, ^2J = 29 Hz, C_8), 55.7 (C_7), 32.0 (C_9), 19.3 (C_{10}), 18.3 (C_{10}). MS (EI) 225 (M^+), 206 ($M^+ - H_2O$), 194 (M^+ − MeO), 181 ($M^+ - {}^iPr$), 44 ($^iPr^+$). IR (KBr) 3410, 2961, 1608, 1512, 1250,1179, 1032, 860, 826, 532 cm^{-1}. Anal. Calcd for $C_{13}H_{16}FO_2$: C, 69.62; H, 7.64. Found: C, 69.56; H, 7.77.

2i: (*Z*)-3-Fluoro-4-(4-methoxyphenyl)-1-phenylbut-3-en-2-ol. Yellow solid (mp <44 °C, cyclohexane/AcOEt (4/1), R_f 0.3). ^1H NMR (300 MHz, $CDCl_3$) δ 7.4 (d, J = 8.7 Hz, 2H, H_4), 7.2−7.0 (m, 5H, $H_{11,12,13}$), 6.8 (d, J = 8.7 Hz, 2H, H_5), 5.6 (d, $^3J^{trans}_{H-F}$ = 40.1 Hz, 1H, H_2), 4.4−4.3 (m, 1H, H_8), 3.7 (s, 3H, H_7), 3.1 (dd, $^2J_{H-H}$ = 5.2 Hz, $^3J_{H-F}$ = 13.8 Hz, 1H, H_9), 2.8 (dd, $^2J_{H-H}$ = 7.9 Hz, $^3J_{H-F}$ = 13.8 Hz, 1H, H_9), 2.1 (b, 1H, OH). ^{19}F NMR (282.5

(13) (a) Stamos, D. P.; Sheng, X. C.; Kishi, Y. *Tetrahedron Lett*. **1997**, *38*, 6355. (b) Taylor, R. E.; Ciavarri, J. P. *Org. Lett*. **1999**, *1*, 467.

MHz, $CDCl_3$) δ −120.9 (dd, $^3J^{trans}_{H-F}$ = 41.1 Hz, $^3J_{H-F}$ = 13.7 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 157.1 (d, J = 265 Hz, C_1), 157.7 (C_6), 135.9 (C_{10}), 129.0 (C_{13}), 128.5 (C_{11}), 127.6 (C_4), 125.8 (C_{12}), 124.4 (C_3), 112.9 (C_5), 105.2 (d, $^2J^{trans}$ = 7 Hz, C_2), 71.1 (d, ^2J = 31 Hz, C_8), 54.2 (C_7), 39.8 (C_9). MS (EI) 273 (M^+), 254 ($M^+ - H_2O$), 181 ($M^+ - CH_2Ph$), 44. IR (KBr) 3417, 3028, 2933, 2837, 1693, 1607, 1512, 1250, 1180, 1032, 860, 748, 701, 504 cm^{-1}. Anal. Calcd for $C_{17}H_{17}FO_2$: C, 74.98; H, 6.29. Found: C, 74.89; H, 6.43.

2j: (*Z*)-7-(*tert*-Butyldiphenylsilanyloxy)-4-fluoro-2-methylhept-4-en-3-ol. Yellow oil (cyclohexane/AcOEt (10/1), R_f 0.4). ^1H NMR (300 MHz, $CDCl_3$) δ 7.7−7.5 (m, 4H, H_7), 7.4−7.1 (m, 6H, $H_{6,8}$), 4.8 (dt, $^3J^{trans}_{H-F}$ = 37.9 Hz, $^3J_{H-H}$ = 7.4 Hz, 1H, H_2), 3.7 (t, J = 6.7 Hz, 2H, H_4), 3.6−3.5 (m, 1H, H_{11}), 2.3−2.2 (m, 2H, H_3), 1.9−1.8 (m, 2H, H_{12}, OH), 1.0 (s, 9H, H_{10}), 0.9 (dd′, J = 6.8 Hz, J' = 6.8 Hz, 6H, $H_{13,14}$). ^{19}F NMR (282.5 MHz, $CDCl_3$) δ −124.3 (dd, $^3J^{trans}_{H-F}$ = 37.9 Hz, $^3J_{H-F}$ = 18.3 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 160.1 (d, ^1J = 258 Hz, C_1), 136.0 (C_6), 134.3 (C_5), 130.1 (C_8), 128.1 (C_7), 104.4 (d, $^2J^{trans}$ = 14 Hz, C_2), 76.8 (d, ^2J = 29 Hz, C_{11}), 63.6 (d, J = 3 Hz, C_4), 31.7 (C_{12}), 27.4 (C_3), 27.3 (C_{10}), 19.6 (C_6), 19.4−18.3 ($C_{13,\ 14}$). HRMS (EI) calcd for $C_{24}H_{33}FO_2Si$ 400.2234, found 400.2226.

2k: (*Z*)-6-(*tert*-Butyldiphenylsilanyloxy)-3-fluoro-1-phenylhex-3-en-2-ol. Yellow oil (cyclohexane/AcOEt (10/1), R_f 0.2).^1H NMR (300 MHz, $CDCl_3$) δ 7.8−7.5 (m, 4H, H_7), 7.5−7.0 (m, 11H, $H_{6,8,14,15,16}$), 4.8 (dt, $^3J^{trans}_{H-F}$ = 38.0 Hz, $^3J_{H-H}$ = 7.5 Hz, 1H, H_2), 4.3−4.1 (m, 1H, H_{11}), 3.6 (t, J = 6.6 Hz, 2H, H_4), 3.0−2.7 (m, 2H, H_{12}), 2.4−2.2 (m, 2H, H_3), 1.9−1.7 (b,1H, OH), 1.0 (s, 9H, H_{10}). ^{19}F NMR (282.5 MHz, $CDCl_3$) δ −124.4 (dd, $^3J^{trans}_{H-F}$ = 37.9 Hz, $^3J_{H-F}$ = 14.9 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 159.9 (d, $^1J^{trans}$ = 257 Hz, C_1), 137.5 (C_{13}), 136.0 (C_6), 134.2 (C_5), 130.1 (C_8), 129.9−128.9 ($C_{14,\ 15}$), 128.1 (C_7), 127.2 (C_{16}), 109.9 (d, $^2J^{trans}$ = 13 Hz, C_2), 72.0 (d, ^2J = 31 Hz, C_{11}), 63.5 (C_4), 41.0 (C_{12}), 27.4 (C_3), 27.3 (C10), 19.6 (C_9). MS (EI) 449 (M^+), 229, 199, 173, 155, 91 (CH_2Ph^+). IR (KBr) 3415, 3070, 2956, 2858, 1709, 1495, 1472, 1427, 1390, 1111, 1030, 938, 823, 740, 701, 613, 506 cm^{-1}. Anal. Calcd for $C_{28}H_{33}FO_2Si$: C, 74.96; H, 7.41. Found: C, 74.81; H, 7.64.

2*l*: (*Z*)-5-(*tert*-Butyldiphenylsilanyloxy)-2-fluoro-1-phenylpent-2-en-1-ol. Yellow oil (cyclohexane/AcOEt (9/1), R_f 0.4). ^1H NMR (300 MHz, $CDCl_3$) δ 7.5−7.4 (m, 4H, H_7), 7.3−7.1 (m, 11H, $H_{6,8,13,14,15}$), 5.1−5.0 (m, 1H, H_{11}), 4.8 (dt, $^3J^{trans}_{H-F}$ = 37.1 Hz, $^3J_{H-H}$ = 7.4 Hz, 1H, H_2), 3.5 (t, J = 2.1 Hz, 2H, H_4), 2.2−2.1 (m, 2H, H_3), 2.0 (b, 1H, 0H), 0.8 (s, 9H, H_{10}). ^{19}F NMR (282.5 MHz, $CDCl_3$) δ −122.0 (dd, $^3J^{trans}_{H-F}$ = 37.1 Hz, $^3J_{H-F}$ = 15.4 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 159.9 (d, $^1J^{trans}$ = 257 Hz, C_1), 139.9 (C_{12}), 136.0 (C_6), 134.2 (C_5), 130.0 (C_{13}), 128.9 (C_{14}), 128.7 (C_{15}), 128.0 (C_7), 127.1 (C_8), 105.0 (d, $^2J^{trans}$ = 13 Hz, C_2), 73.2 (d, ^2J = 32 Hz, C_{11}), 63.3 (C_4), 27.4 (C_3), 27.2 (C10), 19.6 (C_9). MS (EI) 435 (M^+), 229, 201, 199, 159, 91. IR (KBr) 3391, 3070, 2957, 2930, 2857, 1709, 1472, 1427, 1111, 823, 738, 701, 613, 505 cm^{-1}. Anal. Calcd for $C_{27}H_{31}FO_2Si$: C, 74.61; H, 7.19. Found: C, 74.52; H, 7.32.

2m: (*Z*)-2-Fluoro-3-(4-fluorophenyl)-1-phenylprop-2-en-1-ol. Pale yellow syrup (cyclohexane/AcOEt (10/1), R_f 0.1). ^1H NMR (300 MHz, $CDCl_3$) δ 7.4−7.1 (m, 7H, $H_{5,9,10,11}$), 7.0−6.8 (m, 2H, H_4), 5.8 (d, $^3J^{trans}_{H-F}$ = 38.9 Hz, 1H, H_2), 5.3 (d, $^3J_{H-F}$ = 11.8 Hz, 1H, H_7), 2.7−2.6 (b, 1H, OH). ^{19}F NMR (282.5 MHz, $CDCl_3$) δ −114.3 (m, 1F, F_6), −116.5 (dd, $^3J^{trans}_{H-F}$ = 38.9 Hz, $^3J_{H-F}$ = 11.8 Hz, 1F, F_1). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 162.7 (dd, ^1J = 248 Hz, J' = 3 Hz, C_6), 159.8 (dd, ^1J = 267 Hz, J' = 2 Hz, C_1), 140.1 (C_8), 131.3 (dd, J = 8 Hz, J' = 8 Hz, C_4), 129.5−127.6 ($C_{9,10}$), 129.4 (C_{11}), 127.2 (C_3), 116.2 (d, J = 22 Hz, C_5), 106.7 (d, ^2J = 6 Hz, C_2), 73.9 (d, J = 32 Hz, C_7). HRMS (EI) calcd for $C_{15}H_{12}F_2O$ 246.0856, found 246.0860.

2n: (*Z*)-4-(2-Fluoro-3-hydroxy-3-phenylpropenyl)benzoic Acid Methyl Ester. Yellow solid (mp 77 °C, cyclohexane/AcOEt (4/1), R_f 0.3). ^1H NMR (300 MHz, $CDCl_3$) δ 8.0 (d, J = 8.5 Hz, 2H, H_5), 7.6 (d, J = 8.5 Hz, 2H, H_4), 7.5−7.3 (m, 5H, $H_{11,12,13}$), 6.0 (d, $^3J^{trans}_{H-F}$ = 38.6 Hz, 1H, H_2), 5.3 (d, J = 10.2 Hz, 1H, H_9), 3.9 (s, 3H, H_8), 3.1−2.9 (b, 1H, OH). ^{19}F NMR (282.5 MHz, $CDCl_3$) δ −110.9 (dd, $^3J^{trans}_{H-F}$ = 38.6 Hz, J = 10.2 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 167.3 (C_7), 161.6 (d, J = 271 Hz, C_1), 139.6 (C_{10}), 137.8 (C_6), 130.1 (C_5), 129.3 (C_{11}), 129.0 (d, J = 8 Hz, C_4), 127.2 (C_{12}), 126.8 (C_{13}), 129.1 (C_3), 106.3 (d, J = 5 Hz, C_2), 73.4 (d, J = 33 Hz, C_9), 52.5 (C_8). MS (EI) 286 (M^+), 251, 207, 105, 91, 77, 51. IR (KBr) 3374, 2951, 1720, 1607, 1437, 1280, 1111, 1016, 874, 766, 698 cm^{-1}. Anal. Calcd for $C_{17}H_{15}FO_3$: C, 71.32; H, 5.28. Found: C, 71.39; H, 5.14.

2p: (*Z*)-2-Fluoro-3-naphthalen-2-yl-1-phenylprop-2-en-1-ol. Yellow solid (mp 74 °C, cyclohexane/AcOEt (4/1), R_f 0.3). ^1H NMR (300 MHz, $CDCl_3$) δ 7.9 (s, 1H, H_{12}), 7.7−7.5 (m, 4H, $H_{5,7,10,12}$), 7.4−7.3 (m, 7H, $H_{8,9,15,16,17}$), 6.0 (d, $^3J^{trans}_{H-F}$ = 39.2 Hz, 1H, H_2), 5.3 (d, $^3J_{H-F}$ = 11.8 Hz, 1H, H_{13}), 3.1 (b, 1H, OH). ^{19}F NMR (282.5 MHz, $CDCl_3$) δ −114.5 (dd, $^3J^{trans}_{H-F}$ = 41.1 Hz, $^3J_{H-F}$ = 11.8 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 160.2 (d, J = 269 Hz, C_1), 139.9 (C_6), 133.9 (C_{11}), 133.1 (d, J = 2 Hz, C_3), 130.8 (d, J = 3 Hz, C_{14}), 129.2 ($C_{8,9}$), 129.0 (C_5), 128.6 (C_{16}), 128.5 (C_{12}), 128.0 (C_{17}), 127.4 (C_{15}), 127.1 (C_4), 127.0 (C_7), 126.7 (C_{10}), 107.6 (d, $^2J^{trans}$ = 13 Hz, C_2), 73.6 (d, ^2J = 31 Hz, C_{13}). MS (EI) 278 (M^+), 260 ($M^+ - H_2O$), 257, 183, 105, 77, 51. IR (KBr) 3307, 3055, 1682, 1594, 1494, 1452, 1274, 1157, 1013, 825, 746, 715, 698, 473 cm^{-1}. Anal. Calcd for $C_{19}H_{15}FO$: C, 81.99; H, 5.43. Found: C, 81.93; H, 5.41.

2q: (*Z*)-2-Fluoro-1,5-diphenylpent-2-en-1-ol. Pale yellow syrup (cyclohexane/AcOEt (10/1), R_f 0.2). ^1H NMR (300 MHz, $CDCl_3$) δ 7.5−7.1 (m, 10H, $H_{6,7,8,11,12,13}$), 5.3 (dd, $^3J_{H-F}$ = 12.9 Hz, J' = 3.1 Hz, 1H, H_9), 5.0 (dt, $^3J^{trans}_{H-F}$ = 37.1 Hz, $^3J_{H-H}$ = 7.4 Hz, 1H, H_2), 2.8 (t, J = 7.7 Hz, 2H, H_4), 2.6−2.3 (m, 3H, H_3, OH). ^{19}F NMR (282.5 MHz, $CDCl_3$) δ −122.6 (dd, $^3J^{trans}_{H-F}$ = 37.1 Hz, $^3J_{H-F}$ = 12.9 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 157.0 (d, J = 256 Hz, C_1), 139.6 (C_5), 137.7 (C_{10}), 126.7−126.7−126.6−124.9 ($C_{6,7,10,12}$), 126.5 (C_{13}), 124.2 (C_8), 104.9 (d, J = 13 Hz, C_2), 70.9 (d, J = 31 Hz, C_9), 33.5 (d, J = 2 Hz, C_4), 23.3 (d, J = 4 Hz, C_3). MS (EI) 257 (M^+), 238 ($M^+ - H_2O$), 148, 147, 91 (CH_2Ph^+). IR (KBr) 3390, 3027, 2925, 2859, 1703, 1495, 1453, 1025, 748, 699 cm^{-1}. Anal. Calcd for $C_{17}H_{17}FO$: C, 79.66; H, 6.69. Found: C, 79.81; H, 6.88.

5: 4-Fluoro-2-methyl-5-phenethyl-7-phenylhept-4-en-3-ol. Yellow oil (cyclohexane/AcOEt (10/1), R_f 0.3). ^1H NMR (300 MHz, $CDCl_3$) δ 7.3−7.1 (m, 10H, $H_{6,7,8,12,13,14}$), 5.1 (d, $^3J_{H-F}$ = 9.2 Hz, 1H, OH), 3.8−3.7 (m, 1H, H_{15}), 2.7−2.6 (m, 4H, $H_{4,10}$), 2.3 (m, 4H, $H_{3,9}$), 1.5−1.4 (m, 1H, H_{16}), 0.8 (d, J = 6.6 Hz, 3H, H_{17}), 0.7 (d, J = 6.9 Hz, 3H, H_{18}). ^{19}F NMR (282.5 MHz, $CDCl_3$) δ −129.6 (d, $^3J^{trans}_{H-F}$ = 29.0 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 158.5 (d, J = 284 Hz, C_1), 141.8 ($C_{5,11}$), 128.4 ($C_{6,7,12,13}$), 126.1 ($C_{8,14}$), 107.7 (d, J = 12 Hz, C_2), 72.9 (d, J = 34 Hz, C_{15}), 38.2 ($C_{3/9}$), 34.6 ($C_{4/10}$), 33.9 ($C_{4/10}$), 32.5 ($C_{3/9}$), 19.0 (d, J = 21 Hz, C_{16}), 18.3−18.1 ($C_{17,18}$). HRMS (EI) calcd for $C_{22}H_{27}FO$ 326.2046, found 326.2046.

Supporting Information Available: ^1H, ^{13}C, and ^{19}F NMR spectra with atom numbers for the NMR spectra attribution. This material is available free of charge via the Internet at http://pubs.acs.org.

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