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PAPER

A new entry to the construction of a quaternary carbon center having a fluorine atom – S_N2' reaction of γ-fluoroallylic alcohol derivatives with various cyanocuprates†

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Treatment of γ-fluoroallylic phosphate with various lower-ordered cyanocuprates derived from Grignard reagents, organolithium, and organozincs gave the corresponding S_N2' products having a fluorine atom at a quaternary carbon center in excellent yields. This system could be successfully extended to the chiral version, enantiomerically pure fluorine-containing materials also being obtained in high yield.

Introduction

It has been well recognized that the substitution of hydrogen with fluorine can bring about a profound effect on the biological activity, metabolism, solubility, hydrophobicity, and bulk properties of organic substances.[1] Consequently, fluorine-containing materials are extremely important as pharmaceuticals, imaging agents, fine chemicals, materials, and so on.

Among such fluorinated molecules, the compounds having a fluorine atom at a quaternary carbon center **1** (Fig. 1) have recently been attracting much attention, due to their unique properties,[2] and convenient synthetic methods for the preparation of such molecules have been reported in the laboratories of Togni,[3] Shibata,[4] Cahard,[5] Sodeoka,[6] Kim,[7] Nakamura,[8] Barbas III,[9] Jørgensen,[10] Jun–An–Ma,[11] Shibatomi,[12] Maruoka,[13] and so on.[14] Herein is described a new entry to **1** *via* the highly regioselective S_N2' reaction of the γ-fluoroallylic phosphate **2** with lower-ordered organocuprates.[15] In addition, we wish to disclose a highly stereoselective S_N2' reaction of the chiral γ-fluoroallylic phosphate, which enables us to afford an enantiomerically pure fluorine-containing substance.

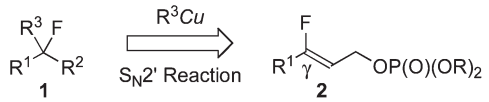

Fig. 1 Intended program.

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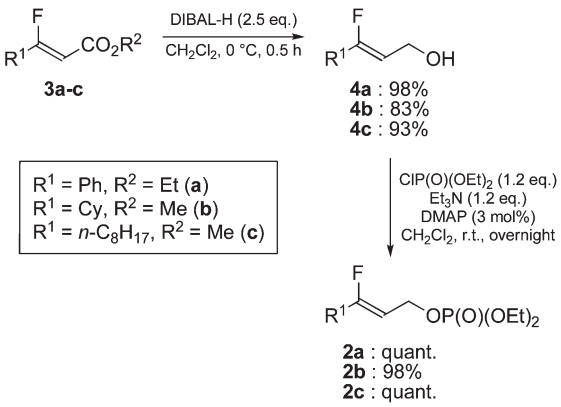
Results and discussion

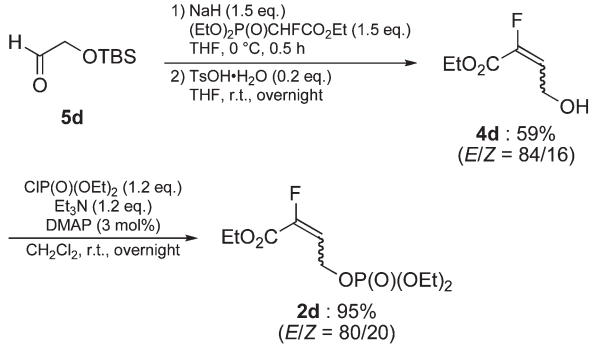
The starting γ-fluoroallylic phosphates could be easily prepared as follows (Schemes 1 and 2). Thus, treatment of (*Z*)-β-fluoro-α,β-unsaturated esters **3a–c**, which could be prepared according to the literature,[16] with an excess amount of DIBAL-H, followed by the usual phosphorylation,[17] gave the corresponding phosphates **2a–c**. On the other hand, α-silyloxyacetaldehyde **5d**[18] underwent a sequential Horner–Wadsworth–Emmons reaction and the acid hydrolysis to afford the corresponding allylic alcohol **4d**. Then the phosphorylation of **4d** provided the desired γ-fluoroallylic phosphate **2d** as a diastereomeric mixture.

With the substrates in hand, we first investigated S_N2' reaction using γ-fluoroallylic phosphate **2a** as described in Table 1.

Thus, treatment of **2a** with 1.1 equiv. of lower-ordered cyanocuprate, prepared from 1.1 equiv. each of CuCN and *n*-BuMgBr, in THF at −78 °C for 0.5 h did not give any desired product at all (entry 1). The reaction at −40 °C, on the other hand, took place to afford the γ-product **γ-1a** in 45% yield, together with

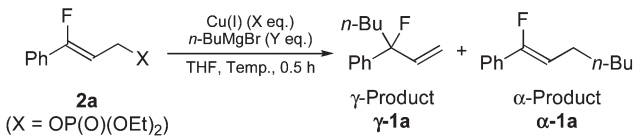


Scheme 1 Preparation of the substrates **2a–c**.



Scheme 2 Preparation of the substrate **2d**.

Table 1 Investigation of the reaction conditions



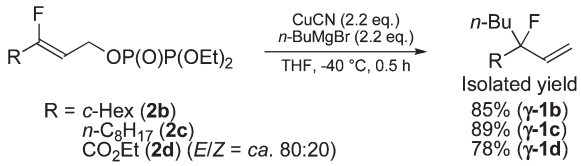
Entry	Cu(I) X/ equiv.	Y/ equiv.	Temp./ °C	Yield[a]/% of **γ-1** + **α-1**	Ratio[a] (γ:α)	Recovery[a]/ % of **2a**
1	CuCN/1.1	1.1	−78	0	—	100
2	CuCN/1.1	1.1	−40	45	100 : 0	55
3[b]	CuCN/1.1	1.1	−40	58	100 : 0	39
4	CuCN/1.1	1.1	0	27	100 : 0	71
5	CuCN/2.2	2.2	−40	100 (50)[c]	97 : 3	0
6	CuCN/0.2	2.2	−40	43	19 : 81	40
7	CuI/2.2	4.4	−40	27	0 : 100	0
8	CuBr/2.2	4.4	−40	27	0 : 100	0
9	CuBr/0.2	2.2	−40	29	0 : 100	0

[a] Determined by ^{19}F NMR. The value in parentheses is of isolated yield. [b] Carried out for 4 h. [c] The product was partially decomposed in silica gel column chromatography.

55% recovery of the starting material (entry 2). In this case, **γ-1a** was obtained exclusively and no **α-1a** was detected at all. As shown in entries 3 and 4, the prolonged reaction time or higher temperature did not lead to satisfactory results. The use of 2.2 equiv. of cyanocuprate caused a significant improvement of the yield, **γ-1a** being afforded in 97% yield, along with a small amount of the α-product (3%) as shown in entry 5. In this case, the product was found to be somewhat unstable for silica gel, the product being obtained in only 50% isolated yield. Unfortunately, the copper-catalyzed attempt led to a decrease of the yield as well as the preferential formation of the α-product (entry 6). As described in entries 7 and 8, other copper salts, such as CuI and CuBr, brought about a significant change in the regioselectivity, the α-product being obtained exclusively, though the yield was only 27%. CuBr-catalyzed reaction also gave **α-1a** exclusively, and no **γ-1a** was detected at all (entry 9).

With the optimized reaction conditions, we next examined the reaction using various γ-fluoroallylic phosphates **2b–d** as summarized in Scheme 3.

Various substrates having cyclohexyl, n-C_8H_{17}, or ethoxycarbonyl groups could participate in the S_N2' reaction very well



Scheme 3 Reaction using various γ-fluoroallylic phosphates.

to give the corresponding adducts **γ-1b–d** in high yields. In all cases, the corresponding α-adducts were not detected at all.

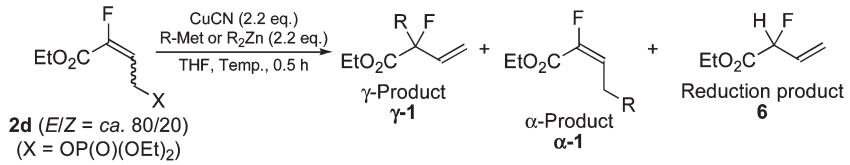
Next, our attention was directed toward the S_N2' reaction with various organometallics, by using the substrate **2d**. The results are collected in Table 2.

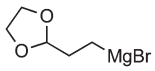
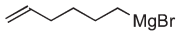
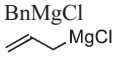
As shown in entries 1–5, various primary Grignard reagents, such as MeMgBr, n-BuMgBr, 3-phenylpropylMgBr, 1,3-dioxolane-2-ethylMgBr, and 5-pentenylMgBr, were found to be good reagents for the present reaction, the desired S_N2' products **γ-1** being exclusively obtained in high to excellent yields. On the other hand, BnMgCl is somewhat less reactive, the desired product being afforded in only 55% yield, together with 6% of the reduction product **6** (entry 6). In the case of allylMgCl, **6** was also obtained in 31% yield, and no γ-product was detected at all (entry 7). The reaction of secondary alkyl Grignard reagents, such as i-PrMgBr and c-HexMgBr, took place smoothly to give the S_N2' products in good yields, though a slight decrease of the regioselectivity was observed and a small amount of the starting allylic phosphate remained unreacted (entries 8 and 9). Surprisingly, the use of a tertiary alkyl Grignard reagent, such as t-BuMgBr, caused a significant change in the regioselectivity, the α-product being obtained exclusively (entry 10). As described in entry 11, PhMgBr could not be applied for the S_N2' reaction, only reduction product **6** was afforded. Additionally, the increase of the amount of PhMgBr did not lead to a satisfactory result (entry 12).

We also examined the S_N2' reaction using organolithium and organozinc reagents. As shown in entry 13, the reaction of cyanocuprate derived from MeLi and CuCN proceeded sluggishly, the desired S_N2' product being obtained in only 32% yield. The use of n-BuLi led to an exclusive formation of the S_N2' product in 80% yield (entry 14), however, PhLi was found to be less reactive, similar to PhMgBr, no desired product being afforded at all (entry 15). As described in entries 16 and 17, the reaction with Et_2Zn or $(i\text{-Pr})_2Zn$ in the presence of CuCN as well as LiCl took place smoothly to give the corresponding S_N2' products in good to high yields, whereas the use of Ph_2Zn did not bring about a fruitful result (entry 18).

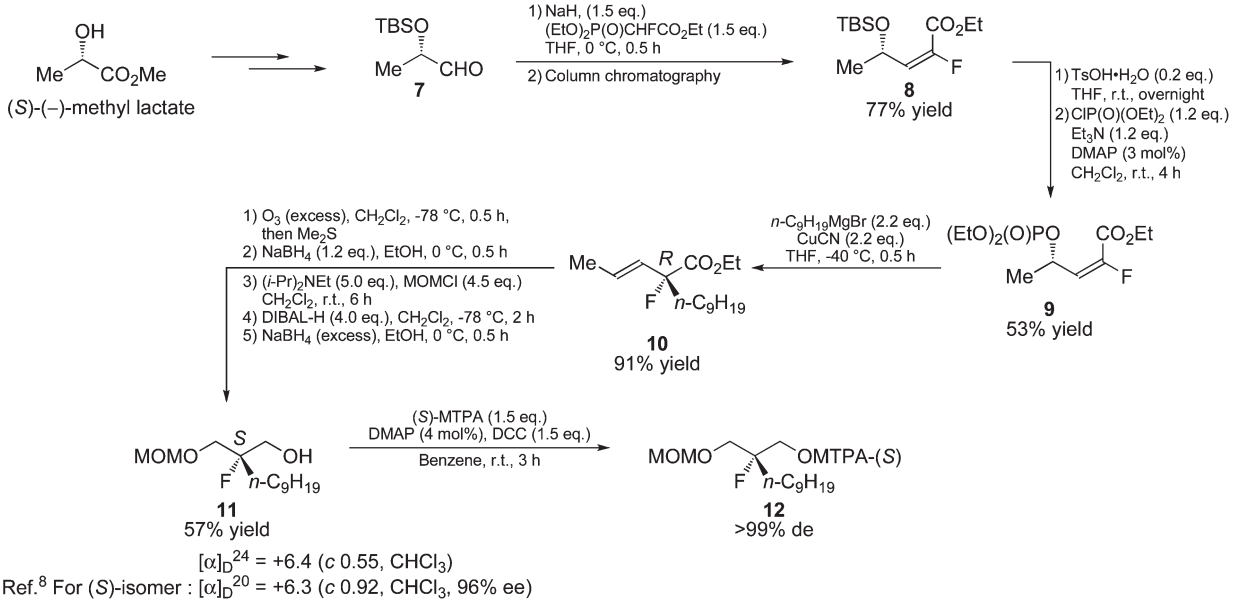
Finally, we attempted the S_N2' reaction using the chiral allylic substrate (Scheme 4). Thus, optically pure α-silyloxypropanal **7**,[19] prepared readily from commercially available S-(−)-methyl lactate in two steps, was subjected to the Horner–Wadsworth–Emmons reaction, followed by a silica gel column separation of the isomeric mixture, giving the corresponding (*E*)-α,β-unsaturated ester **8** in 77% yield. Deprotection and the subsequent phosphorylation gave the enantiomerically pure substrate **9** in 53% yield. Then treatment of **9** with 2.2 equiv. of $(n\text{-}C_9H_{19})$Cu(CN)MgBr in THF at −40 °C for 0.5 h afforded the corresponding S_N2' adduct **10** in 91% yield.

Table 2 S_N2' Reaction using various organometallics



Entry	R-Met or R_2Zn	Temp./°C	Yield[a]/% of **γ-1** + **α-1**		Ratio[a] (γ:α)	Recovery[a]/% of **2d**
1	MeMgBr	−40	85	(±**1e**)	100 : 0	0
2	*n*-BuMgBr	−40	86 (78)	(±**1d**)	100 : 0	4
3	Ph–(CH2)3–MgBr	−40	98 (97)	(±**1f**)	100 : 0	0
4		−40	98 (92)	(±**1g**)	100 : 0	2
5		−40	97 (93)	(±**1h**)	100 : 0	0
6[b]	BnMgCl	−40	55 (53)	(±**1i**)	100 : 0	0
7[c]		−40	0	—	—	0
8	*i*-PrMgBr	−40	67 (53)	(±**1j**)	94 : 6	11
9	*c*-HexMgBr	−40	88 (78)	(±**1k**)	93 : 7	7
10	*t*-BuMgBr	−40	84[d] (78)	(±**1l**)	0 : 100	0
11[e]	PhMgBr	−40	0	—	—	0
12[f,g]	PhMgBr	−40	0	—	—	0
13	MeLi	−20	32	(±**1e**)	100 : 0	0
14	*n*-BuLi	−20	80 (78)	(±**1d**)	100 : 0	0
15	PhLi	−20	0	—	—	0
16[h]	Et_2Zn	0	76 (68)	(±**1m**)	100 : 0	0
17[h]	*i*-Pr_2Zn	0	57 (55)	(±**1j**)	100 : 0	0
18[h]	Ph_2Zn	0	0	—	—	0

[a] Determined by ^{19}F NMR. Values in parentheses are of isolated yields. [b] The reduction product **6** was obtained in 6% yield. [c] The reduction product **6** was obtained in 31% yield. [d] *E*/*Z* = 74/26. [e] The reduction product **6** was obtained in 67% yield. [f] 4.4 equiv. of PhMgBr was used. [g] The reduction product **6** was obtained in 46% yield. [h] 4.4 equiv. of LiCl was used as an additive.



Scheme 4 Synthesis of an enantiomerically pure compound having a fluorine atom at an asymmetric quaternary carbon center.

The stereochemical assignment of **10** was made as follows. The ozonolysis of **10** produced crude α-fluoroaldehyde, which was immediately reduced with an excess amount of $NaBH_4$ to give the corresponding alcohol. MOM protection and the subsequent reduction gave the known compound **11**.[20] The comparison of the observed optical rotation of **11** with its literature value

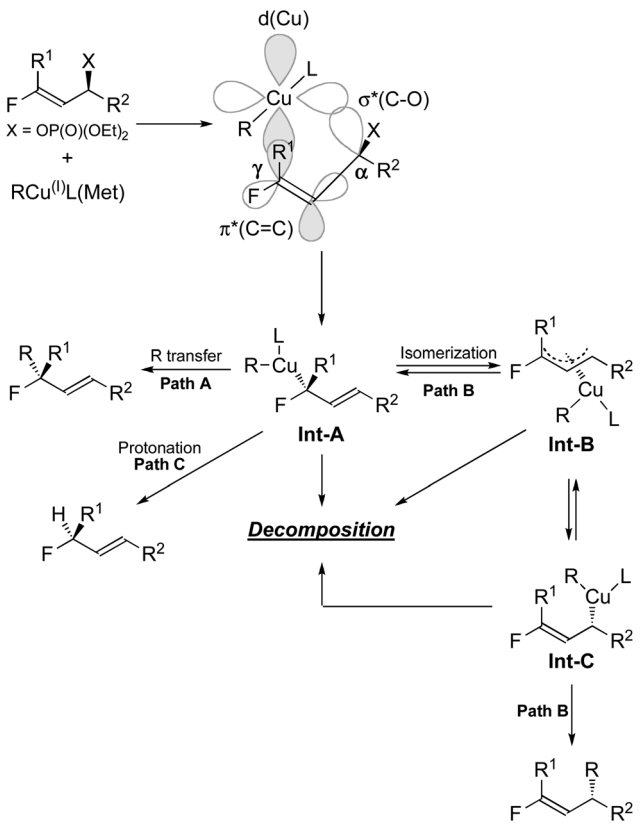
made it possible to determine the absolute configuration of **10** as *R*. Additionally, **11** was treated with (*S*)-MTPA and DCC in the presence of a catalytic amount of DMAP to give the corresponding MTPA ester **12**, whose diastereomeric excess was determined by ^{19}F NMR. It was found that the ester **12** had >99% diastereomeric excess. Accordingly, these results strongly suggest that the S_N2' reaction proceeded in a complete *anti* selective fashion.

Mechanism

Based on the results of the stereochemical assignment, the proposed mechanism for the present S_N2' reaction is outlined in Scheme 5. Thus, when copper reagents coordinate on the double bond of allylphosphate, oxidative addition of the phosphate to $Cu^{(I)}$ takes place to form the intermediate **Int-A**. In this case, a copper d orbital may interact with π* at the γ carbon as well as σ* at the backside of the α carbon, resulting in the high *anti* stereoselectivity.[21]

An exclusive formation of the S_N2' product in the case of primary alkyl organometallic reagents is probably because the primary alkyl group is less hindered and has the highly potent transfer ability as a ligand (Path A). Though the secondary alkyl group is bulkier than the primary alkyl group, the rate of the alkyl transfer may be still fast, resulting in a high γ-regioselectivity. However, the sterically bulkiest tertiary alkyl group rendered **Int-A** much more congested and less stable, which may isomerise easily to form σ-allyl copper intermediate **Int-C** *via* π-allyl copper intermediate **Int-B**, then leading to an exclusive formation of the α-product *via* reductive elimination at the less hindered α-carbon (Path B).

On the other hand, it has been well known that the transfer ability of aryl groups is much lower than alkyl groups.[22] Thus, the reductive elimination of **Int-A**, **B** or **C** may proceed much more slowly, while the oxidative addition of the substrates to $Cu^{(I)}$ may take place smoothly. Consequently, decomposition or protonation (Path C) of **Int-A**, **B**, **C**, instead of reductive elimination, may proceed predominantly.



Scheme 5 A plausible reaction mechanism.

Conclusions

In summary, we have demonstrated the S_N2' reaction of γ-fluoroallylic phosphates with various organocuprates. The reaction proceeded in a highly regioselective manner to give the corresponding γ-adducts in high yields. This system could be also applied for the chiral substrate, affording the desired compound having a fluorine atom at an asymmetric quaternary carbon center in an optically pure form.

Experimental

General methods

Infrared spectra (IR) were determined in a liquid film on a NaCl plate with a JASCO FT/IR-4100 type A spectrometer. ^1H and ^{13}C NMR spectra were measured with a JEOL JNM-AL 400 NMR spectrometer in a chloroform-d ($CDCl_3$) solution with tetramethylsilane (Me_4Si) as an internal reference. A JEOL JNM-AL 400 NMR spectrometer was used for determining the yield of the products with hexafluorobenzene (C_6F_6). ^{19}F NMR (376.05 MHz) spectra were measured with a JEOL JNM-AL 400 NMR spectrometer in a chloroform-d ($CDCl_3$) solution with trichlorofluoromethane ($CFCl_3$) as an internal standard. High-resolution mass spectra (HRMS) were taken on a JEOL JMS-700MS spectrometer by electron impact (EI), chemical ionization (CI), and fast atom bombardment (FAB) methods.

All chemicals were of reagent grade and, if necessary, were purified in the usual manner prior to use. Thin-layer chromatography (TLC) was done with Merck silica gel 60 F_{254} plates, and column chromatography was carried out using Wako gel C-200 as an adsorbent.

General procedure for the preparation of γ-fluoroallylic alcohol

β-Fluoro-α,β-unsaturated ester (3.42 mmol) in CH_2Cl_2 (6.84 mL, 0.5 M) was placed in a three-necked flask under an argon atmosphere. To the mixture was added a solution of diisobutylaluminum hydride in *n*-hexane (0.98 M, 8.72 mL, 8.55 mmol) at 0 °C. After stirring for 30 min at 0 °C, a solution of 10% HCl was added. The resulting mixture was extracted with CH_2Cl_2, and the organic layers were dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The resulting mixture was purified by silica gel column chromatography.

(*Z*)-3-Fluoro-3-phenyl-2-propen-1-ol (4a)

Yield: 98%; ^{1}H NMR ($CDCl_3$) δ 1.47 (1H, br s), 4.46 (2H, br s), 5.67 (1H, dt, J = 36.77, 6.79 Hz), 7.34–7.41 (3H, m), 7.52–7.55 (2H, m) ppm; ^{13}C NMR ($CDCl_3$) δ 56.01 (d, J = 7.43 Hz), 104.75 (d, J = 14.96 Hz), 124.36 (d, J = 7.43 Hz), 128.48 (d, J = 2.41 Hz), 129.26, 131.69 (d, J = 28.92 Hz), 158.01 (d, J = 250.50 Hz) ppm; ^{19}F NMR ($CDCl_3$) δ −117.71 (1F, d, J = 36.77 Hz) ppm; IR (neat) 3339, 2885, 1679, 1496, 1449, 1282, 1101, 1036, 1015 cm^{-1}; HRMS (FAB) calcd for C_9H_9FO (M^+) 152.0637, found 152.0641.

(*Z*)-3-Cyclohexyl-3-fluoro-2-propen-1-ol (4b)

Yield: 83%; ^{1}H NMR ($CDCl_3$) δ 1.15–1.31 (6H, m), 1.67–1.70 (1H, m), 1.76–1.87 (4H, m), 2.04–2.13 (1H, m), 4.20–4.23 (2H, m), 4.80 (1H, dt, J = 35.35, 6.39 Hz) ppm; ^{13}C NMR ($CDCl_3$) δ 25.71, 25.88, 29.63 (d, J = 2.51 Hz), 40.30 (d, J = 24.80 Hz), 55.64 (d, J = 8.23 Hz), 102.36 (d, J = 14.06 Hz), 165.88 (d, J = 259.53 Hz) ppm; ^{19}F NMR ($CDCl_3$) δ −109.95 (1F, dd, J = 35.35, 14.67 Hz) ppm; IR (neat) 3330, 2930, 2856, 1702, 1451, 1313, 1284, 1161, 1014 cm^{-1}; HRMS (FAB) calcd for $C_9H_{15}FO$ (M^+) 158.1107, found 158.1114.

(*Z*)-3-Fluoro-2-undecen-1-ol (4c)

Yield: 93%; ^{1}H NMR ($CDCl_3$) δ 0.88 (3H, t, J = 6.19 Hz), 1.27–1.29 (11H, m), 1.46–1.53 (2H, m), 2.17 (2H, dt, J = 17.58, 8.09 Hz), 4.22 (2H, br s), 4.83(1H, dt, J = 36.63, 7.19 Hz) ppm; ^{13}C NMR ($CDCl_3$) δ 14.03, 22.61, 25.91, 25.92, 28.90, 29.18 (d, J = 11.55 Hz), 31.79, 31.84 (d, J = 26.41 Hz), 55.62 (d, J = 8.23 Hz), 104.44 (d, J = 14.06 Hz), 162.13 (d, J = 258.73 Hz) ppm; ^{19}F NMR ($CDCl_3$) δ −105.31 (1F, dt, J = 36.63, 17.58 Hz) ppm; IR (neat) 3324, 2927, 2856, 1707, 1466, 1432, 1378, 1310, 1242, 1158, 1112, 1082, 1010 cm^{-1}; HRMS (FAB) calcd for $C_9H_{15}FO$ (M^+) 158.1107, found 158.1114.

Synthetic procedure for the preparation of γ-hydroxy-α-fluoroesters

To a suspension of sodium hydride (60% in oil, 0.06 g, 1.5 mmol) in THF (4 mL) at 0 °C was added triethyl 2-fluoro-2-phosphonoacetate (0.31 mL, 1.5 mmol). After stirring for 30 min at 0 °C, a solution of α-(*tert*-butyldimethylsilyloxy)acetaldehyde (0.17 g, 1.0 mmol) in THF (1 mL) was added. After stirring the resulting solution for 30 min at 0 °C, the solution was quenched with an aqueous saturated NH_4Cl solution and extracted with ethyl acetate. The organic layers were dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The resulting mixture was purified by silica gel column chromatography to give the corresponding adduct (0.19 g, 0.74 mol, 74%).

To a solution of the adduct (0.19 g, 0.74 mmol) in THF (7 mL) at room temperature was added $TsOH{\cdot}H_2O$ (28 mg, 0.15 mmol) in water (0.5 mL). After stirring overnight at room temperature, the solution was quenched with an aqueous saturated $NaHCO_3$ solution and extracted with ethyl acetate. The organic layers were dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The resulting mixture was purified by silica gel column chromatography to afford the corresponding γ-fluoro-allylic alcohol (87 mg, 0.59 mmol, 80%).

Ethyl 2-fluoro-4-hydroxy-2-butenoate (4d)

Combined yield: 59% (*E*/*Z* = 84/16).

***E* isomer.** ^{1}H NMR ($CDCl_3$) δ 1.36 (3H, t, J = 6.99 Hz), 1.64 (1H, m), 4.29 (2H, q, J = 6.99 Hz), 6.27 (1H, dt, J = 19.98, 6.39 Hz) ppm; ^{19}F NMR ($CDCl_3$) δ −121.22 (1F, d, J = 19.98 Hz) ppm.

***Z* isomer.** ^{1}H NMR ($CDCl_3$) δ 1.33 (3H, t, J = 6.99 Hz), 2.55 (1H, br s), 4.33 (2H, q, J = 6.99 Hz), 6.16 (1H, dt, J = 32.77, 6.39 Hz) ppm; ^{19}F NMR ($CDCl_3$) δ −126.73 (1F, d, J = 32.77 Hz) ppm.

General procedure for the preparation of allylic phosphates

Allylic alcohol (1.09 mmol) in CH_2Cl_2 (2.2 mL) was placed in a three-necked flask under an argon atmosphere where at 0 °C was added DMAP (4 mg, 0.033 mmol), diethyl chlorophosphate (0.19 mL, 1.31 mmol) followed by addition of triethylamine (0.18 mL, 1.31 mmol). The reaction mixture was allowed to warm to room temperature and stirred overnight. The solution was quenched with water and after separation of the two layers, the aqueous solution was washed with CH_2Cl_2 twice and the combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The resulting mixture was purified by silica gel column chromatography.

(*Z*)-Diethyl 3-fluoro-3-phenyl-2-propenyl phosphate (2a)

Yield: quant.; ^{1}H NMR ($CDCl_3$) δ 1.35 (6H, dt, J = 1.20, 7.19 Hz), 4.13 (2H, q, J = 7.19 Hz), 4.14 (4H, dq, J = 7.19, 7.19 Hz), 5.67 (1H, dt, J = 34.77, 7.59 Hz), 7.37–7.39 (3H, m), 7.54–7.57 (2H, m) ppm; ^{13}C NMR ($CDCl_3$) δ 16.04 (d, J = 7.43 Hz), 60.40 (dd, J = 8.33, 5.82 Hz), 63.78 (d, J = 5.72 Hz), 100.59 (dd, J = 14.86, 6.63 Hz), 124.56 (d, J = 7.43 Hz), 128.52, 129.71, 131.09 (d, J = 34.24 Hz), 159.34 (d, J = 254.51 Hz) ppm; ^{19}F NMR ($CDCl_3$) δ −115.02 (1F, d, J = 34.77 Hz) ppm; ^{31}P NMR ($CDCl_3$) δ −1.41 (1P, s) ppm; IR (neat) 3062, 2984, 2910, 1683, 1496, 1448, 1392, 1268, 1035 cm^{-1}; HRMS (FAB) calcd for $C_{13}H_{18}FNaO_4P$ (M + Na) 311.0824, found 311.0835.

(*Z*)-Diethyl 3-cyclohexyl-3-fluoro-2-propenyl phosphate (2b)

Yield: 98%; ^{1}H NMR ($CDCl_3$) δ 1.15–1.36 (11H, m), 1.67–1.90 (5H, m), 2.04–2.12 (1H, m), 4.11 (4H, dq, J = 7.29, 7.29 Hz), 4.59–4.64 (2H, m), 4.80 (1H, dt, J = 35.57, 7.19 Hz) ppm; ^{13}C NMR ($CDCl_3$) δ 16.03 (d, J = 6.62 Hz), 25.76, 25.58, 29.41 (d, J = 2.41 Hz), 40.24 (d, J = 23.90 Hz), 60.25 (dd, J = 9.94, 5.82 Hz), 63.61 (d, J = 5.72 Hz), 98.60 (dd, J = 13.15, 6.53 Hz), 167.28 (d, J = 263.65 Hz) ppm; ^{19}F NMR ($CDCl_3$) δ −106.95 (1F, dd, J = 35.57, 14.67 Hz) ppm; ^{31}P NMR ($CDCl_3$) δ −1.48 (1P, s) ppm; IR (neat) 2983, 2932, 2857, 1703, 1451, 1392, 1273, 1168, 1030 cm^{-1}; HRMS (FAB) calcd for $C_{13}H_{25}FO_4P$ (M + H) 295.1474, found 295.1481.

(*Z*)-Diethyl 3-fluoro-2-undecenyl phosphate (2c)

Yield: quant.; ^{1}H NMR ($CDCl_3$) δ 0.88 (3H, t, J = 6.59 Hz), 1.27–1.36 (16H, m), 1.46–1.54 (2H, m), 2.18 (2H, dt, J = 17.58, 7.99 Hz), 4.07–4.15 (4H, m), 4.61 (2H, dd, J = 7.79, 7.79 Hz), 4.86 (1H, dt, J = 35.17, 7.79 Hz) ppm; ^{13}C NMR ($CDCl_3$) δ 14.00, 16.05 (d, J = 6.63 Hz), 22.57, 25.70, 25.71, 28.81, 29.13 (d, J = 9.93 Hz), 31.75, 31.78 (d, J = 26.51 Hz), 60.16 (dd, J = 9.04, 5.72 Hz), 63.64 (d, J = 5.72 Hz), 100.62 (dd, J = 13.15, 6.58 Hz), 163.67 (d, J = 262.85 Hz) ppm; ^{19}F NMR ($CDCl_3$) δ −102.25 (1F, dt, J = 35.17, 17.58 Hz) ppm; ^{31}P NMR ($CDCl_3$) δ −1.40 (1P, s) ppm; IR (neat) 2929, 2857, 1709, 1467, 1392, 1277, 1166, 1098, 1034 cm^{-1}; HRMS (FAB) calcd for $C_{15}H_{30}FO_4P$ (M^+) 324.1866, found 324.1875.

Ethyl 4-[(diethoxyphosphinyl)oxy]-2-fluoro-2-butenoate (2d)

Combined yield: 95% (*E*/*Z* = 80/20).

***E* isomer.** ^{1}H NMR ($CDCl_3$) δ 1.36 (9H, dt, J = 3.60, 7.19 Hz), 4.14 (4H, dq, J = 7.19, 7.19 Hz), 4.33 (2H, q, J = 7.19 Hz), 5.04 (2H, ddd, J = 8.79, 5.99, 2.80 Hz), 6.08 (1H, dt, J = 17.98, 5.99 Hz) ppm; ^{19}F NMR ($CDCl_3$) δ −120.27 (1F, d, J = 17.98 Hz) ppm.

***Z* isomer.** ^{1}H NMR ($CDCl_3$) δ 1.34 (9H, dt, J = 3.60, 7.19 Hz), 4.14 (4H, dq, J = 7.19, 7.19 Hz), 4.31 (2H, q, J = 6.79 Hz), 4.78 (2H, ddd, J = 8.79, 6.79, 2.40 Hz), 6.28 (1H, dt, J = 31.57, 6.79 Hz) ppm; ^{19}F NMR ($CDCl_3$) δ −123.81 (1F, d, J = 31.57 Hz) ppm.

General procedure for the reaction of γ-fluoroallylic phosphate with various cuprates derived from Grignard reagent

To a suspension of CuCN (0.059 g, 0.66 mmol) in anhydrous THF (2 mL) was added dropwise a THF solution of Grignard reagent (0.66 mmol, prepared from RBr and magnesium) at −78 °C under an argon atmosphere. After stirring for 10 min, the mixture was warmed to −10 °C, then stirred for 10 min. The reaction mixture was again cooled to −40 °C, and to this mixture was added dropwise a solution of γ-fluoroallylic phosphate (0.3 mmol) in anhydrous THF (2 mL). After 30 min, the reaction was quenched with an aqueous saturated NH_4Cl solution and the whole was extracted with diethyl ether. The combined organic layers were dried over anhydrous Na_2SO_4, concentrated *in vacuo*. The residue was purified by silica gel column chromatography.

General procedure for the reaction of γ-fluoroallylic phosphate with cuprate derived from organolithium reagents

To a suspension of CuCN (0.059 g, 0.66 mmol) in anhydrous THF (2 mL) was added dropwise a hexane solution of organolithium (0.66 mmol) at −78 °C under an argon atmosphere. After stirring for 10 min, the mixture was warmed to −20 °C, then stirred for 15 min. Then, a solution of γ-fluoroallylic phosphate (0.3 mmol) in anhydrous THF (2 mL) was dropwise added. After 30 min, the reaction was quenched with an aqueous saturated NH_4Cl solution and the whole was extracted with diethyl ether. The combined organic layers were dried over anhydrous Na_2SO_4, concentrated *in vacuo*. The residue was purified by silica gel column chromatography.

General procedure for the reaction of γ-fluoroallylic phosphate with cuprate derived from organozinc reagents

To a suspension of CuCN–2LiCl (0.059 g, 0.66 mmol) in anhydrous THF (2 mL) was added dropwise a hexane solution of Et_2Zn (1.6 M, 0.41 mL, 0.66 mmol) at −78 °C under an argon atmosphere. After stirring for 10 min, the mixture was warmed to 0 °C, then stirred for 10 min. The reaction mixture was again cooled to 0 °C, and to this mixture was added dropwise a solution of γ-fluoroallylic phosphate (0.3 mmol) in anhydrous THF (2 mL). After 24 h, the reaction was quenched with an aqueous saturated NH_4Cl solution and the whole was extracted with diethyl ether. The combined organic layers were dried over anhydrous Na_2SO_4, concentrated *in vacuo*. The residue was purified by silica gel column chromatography.

3-Fluoro-3-phenyl-1-heptene (±1a)

Yield: 50%; ^{1}H NMR ($CDCl_3$) δ 0.87 (3H, t, J = 7.59 Hz), 1.20–1.41 (4H, m), 1.96–2.05 (2H, m), 5.19 (1H, d, J = 11.19 Hz), 5.32 (1H, dt, J = 17.18, 1.60 Hz), 6.11 (1H, ddd, J = 17.18, 17.18, 11.19 Hz), 7.26–7.31 (1H, m), 7.34–7.36 (4H, m) ppm; ^{13}C NMR ($CDCl_3$) δ 13.92, 22.80 (d, J = 0.80 Hz), 25.34 (d, J = 3.31 Hz), 39.78 (d, J = 24.00 Hz), 98.06 (d, J = 176.00 Hz), 113.96 (d, J = 11.55 Hz), 124.69 (d, J = 9.04 Hz), 127.25 (d, J = 11.71 Hz), 128.21 (d, J = 1.71 Hz), 140.30 (d, J = 23.09 Hz), 142.67 (d, J = 23.19 Hz) ppm; ^{19}F NMR ($CDCl_3$) δ −158.10 (1F, dt, J = 17.18, 21.81 Hz) ppm; IR (neat) 3062, 3030, 2958, 2872, 1603, 1495, 1448, 1409, 1380, 1226, 1102, 1071 cm^{-1}; HRMS (FAB) calcd for $C_{13}H_{17}F$ (M^+) 192.1314, found 192.1315.

3-Cyclohexyl-3-fluoro-1-heptene (±1b)

Yield: 85%; ^{1}H NMR ($CDCl_3$) δ 0.90 (3H, t, J = 7.19 Hz), 0.99–1.34 (9H, m), 1.52–1.83 (8H, m), 5.15 (1H, ddd, J = 11.19, 2.00, 2.00 Hz), 5.22 (1H, dd, J = 16.99, 2.00 Hz), 5.72 (1H, ddd, J = 22.10, 16.99, 11.19 Hz) ppm; ^{13}C NMR ($CDCl_3$) δ 14.03, 23.05, 25.11 (d, J = 4.12 Hz), 26.24, 26.39, 26.51 (d, J = 5.82 Hz), 35.89 (d, J = 23.09 Hz), 45.57 (d, J = 22.29 Hz), 100.07 (d, J = 176.90 Hz), 113.82 (d, J = 12.35 Hz), 138.21 (d, J = 22.29 Hz) ppm; ^{19}F NMR ($CDCl_3$) δ −166.41 (1F, ddt, J = 29.33, 22.10, 14.67 Hz) ppm; IR (neat) 2931, 2855, 1451, 1411, 1379, 1141 cm^{-1}; HRMS (FAB) calcd for $C_{13}H_{23}F$ (M^+) 198.1784, found 198.1787.

3-Butyl-3-fluoro-1-undecene (±1c)

Yield: 89%; ^{1}H NMR ($CDCl_3$) δ 0.88 (3H, t, J = 6.79 Hz), 0.89 (3H, t, J = 6.79 Hz), 1.26–1.33 (16H, m), 1.54–1.70 (4H, m), 5.13 (1H, ddd, J = 11.19, 1.60, 1.60 Hz), 5.23 (1H, dd, J = 17.58, 1.60 Hz), 5.75 (1H, ddd, J = 20.38, 17.58, 11.19 Hz) ppm; ^{13}C NMR ($CDCl_3$) δ 14.00, 14.09, 22.67, 22.99, 23.23 (d, J = 4.12 Hz), 25.41 (d, J = 5.02 Hz), 29.28, 29.51, 29.63,

31.89, 38.50 (d, J = 23.19 Hz), 38.78 (d, J = 23.09 Hz), 98.22 (d, J = 173.59 Hz), 113.88 (d, J = 12.45 Hz), 139.75 (d, J = 22.29 Hz) ppm; ^{19}F NMR ($CDCl_3$) δ −159.49 to −159.68 (1F, m) ppm; IR (neat) 3095, 2928, 2857, 1647, 1467, 1412, 1379, 1340, 1260, 1132, 1075 cm^{-1}; HRMS (FAB) calcd for $C_{15}H_{29}F$ (M^+) 228.2253, found 228.2248.

Ethyl 2-ethenyl-2-fluoro-3-hexanoate (±1d)

Yield: 78% (in both cases of *n*-BuMgBr and *n*-BuLi); ^{1}H NMR ($CDCl_3$) δ 0.90 (3H, t, J = 6.99 Hz), 1.22–1.48 (7H, m), 1.77–2.06 (2H, m), 4.25 (2H, q, J = 7.19 Hz), 5.25–5.28 (1H, m), 5.47 (1H, d, J = 17.58 Hz), 5.97 (1H, ddd, J = 19.98, 17.58, 10.99 Hz) ppm; ^{13}C NMR ($CDCl_3$) δ 13.81, 14.11, 22.47, 24.97 (d, J = 2.51 Hz), 37.17 (d, J = 22.29 Hz), 61.69, 96.06 (d, J = 190.06 Hz), 115.86 (d, J = 11.55 Hz), 134.59 (d, J = 21.49 Hz), 170.26 (d, J = 26.51 Hz) ppm; ^{19}F NMR ($CDCl_3$) δ −169.56 (1F, dt, J = 19.98, 27.08 Hz) ppm; IR (neat) 2960, 2873, 1762, 1737, 1467, 1408, 1370, 1274, 1206, 1136, 1035 cm^{-1}; HRMS (FAB) calcd for $C_{10}H_{17}FO_2$ (M^+) 188.1213, found 188.1219.

Ethyl 2-fluoro-2-methyl-3-butenoate (±1e)

This product was inseparable from impurities, therefore only the peak that could be assigned was described.

^{1}H NMR ($CDCl_3$) δ 4.25 (2H, q, J = 6.79 Hz), 5.28 (1H, d, J = 10.79 Hz), 5.49 (1H, d, J = 17.58 Hz), 6.03 (1H, ddd, J = 17.58, 17.58, 10.79 Hz) ppm; ^{19}F NMR ($CDCl_3$) δ −157.25 (1F, dq, J = 17.58, 17.58 Hz) ppm; HRMS (FAB) calcd for $C_7H_{12}FO_2$ (M + H) 147.0821, found 147.0819.

Ethyl 2-ethenyl-2-fluoro-5-phenylpentanoate (±1f)

Yield: 97%; ^{1}H NMR ($CDCl_3$) δ 1.29 (3H, t, J = 7.19 Hz), 1.57–2.11 (4H, m), 2.64 (2H, t, J = 7.59 Hz), 4.24 (2H, q, J = 7.19 Hz), 5.27 (1H, m), 5.47 (1H, d, J = 16.79 Hz), 5.88–6.01 (1H, m), 7.16–7.30 (5H, m) ppm; ^{13}C NMR ($CDCl_3$) δ 14.02, 24.53 (d, J = 2.41 Hz), 35.33, 36.77 (d, J = 23.09 Hz), 61.69, 95.87 (d, J = 190.86 Hz), 116.01 (d, J = 11.55 Hz), 134.80 (d, J = 21.49 Hz), 170.01 (d, J = 26.51 Hz) ppm; ^{19}F NMR ($CDCl_3$) δ −169.54 (1F, dt, J = 19.98, 21.93 Hz) ppm; IR (neat) 3584, 3062, 3026, 2937, 2867, 1758, 1735, 1603, 1496, 1454, 1408, 1369, 1263, 1180, 1091, 1024 cm^{-1}; HRMS (FAB) calcd for $C_{15}H_{20}FO_2$ (M + H) 251.1447, found 251.1468.

Ethyl 2-ethenyl-5,5-(ethylenedioxy)-2-fluoro-pentanoate (±1g)

Yield: 92%; ^{1}H NMR ($CDCl_3$) δ 1.31 (3H, t, J = 7.19 Hz), 1.60–2.22 (4H, m), 3.82–3.98 (4H, m), 4.25 (2H, q, J = 7.19 Hz), 4.90 (1H, t, J = 4.40 Hz), 5.29–5.32 (1H, m), 5.50 (1H, d, J = 17.58 Hz), 5.96 (1H, ddd, J = 19.58, 17.58, 10.79 Hz) ppm; ^{13}C NMR ($CDCl_3$) δ 14.04, 27.25 (d, J = 2.41 Hz), 31.22 (d, J = 22.29 Hz), 61.78, 64.88 (2C), 95.39 (d, J = 190.96 Hz), 103.42, 116.40 (d, J = 10.74 Hz), 134.48 (d, J = 21.49 Hz), 169.81 (d, J = 25.60 Hz) ppm; ^{19}F NMR ($CDCl_3$) δ −169.80 (1F, dt, J = 19.58, 21.81 Hz) ppm; IR (neat) 2980, 2886, 1758, 1736, 1643, 1446, 1410, 1370, 1257, 1195, 1142, 1026 cm^{-1}; HRMS (FAB) calcd for $C_{11}H_{18}FO_4$ (M + H) 233.1189, found 233.1188.

Ethyl 2-ethenyl-2-fluoro-7-octenote (±1h)

Yield: 93%; ^{1}H NMR ($CDCl_3$) δ 1.26–1.65 (7H, m), 1.77–2.08 (4H, m), 4.25 (2H, q, J = 6.79 Hz), 4.93–5.02 (2H, m), 5.26–5.29 (1H, m), 5.48 (1H, d, J = 17.18 Hz), 5.78 (1H, m), 5.97 (1H, m) ppm; ^{13}C NMR ($CDCl_3$) δ 14.09, 22.33 (d, J = 2.51 Hz), 28.55, 33.38, 37.24 (d, J = 23.19 Hz), 61.70, 95.98 (d, J = 190.06 Hz), 114.58, 115.93 (d, J = 11.55 Hz), 134.99 (d, J = 21.49 Hz), 138.41, 170.17 (d, J = 26.41 Hz) ppm; ^{19}F NMR ($CDCl_3$) δ −169.59 (1F, dt, J = 26.70, 19.18 Hz) ppm; IR (neat) 3076, 2932, 2858, 1761, 1736, 1641, 1463, 1409, 1370, 1253, 1185, 1027 cm^{-1}; HRMS (FAB) calcd for $C_{12}H_{19}FO_2$ (M^+) 214.1369, found 214.1362.

Ethyl 2-benzyl-2-fluoro-3-butenoate (±1i)

Yield: 53%; ^{1}H NMR ($CDCl_3$) δ 1.19 (3H, t, J = 7.39 Hz), 3.14 (1H, dd, J = 19.98, 14.79 Hz), 3.29 (1H, dd, J = 28.77, 14.79 Hz), 4.11–4.19 (2H, m), 5.27–5.30 (1H, m), 5.47 (1H, d, J = 17.18 Hz), 6.06 (1H, ddd, J = 19.18, 17.18, 10.79 Hz), 7.21–7.31 (5H, m) ppm; ^{13}C NMR ($CDCl_3$) δ 13.95, 43.76 (d, J = 22.39 Hz), 61.74, 95.85 (d, J = 194.27 Hz), 116.53 (d, J = 10.74 Hz), 127.14, 128.12, 130.31 (d, J = 1.71 Hz), 134.04, 134.68 (d, J = 21.49 Hz), 169.43 (d, J = 21.49 Hz) ppm; ^{19}F NMR ($CDCl_3$) δ −167.13 (1F, ddd, J = 28.77, 19.98, 19.18 Hz) ppm; IR (neat) 3032, 2983, 1760, 1735, 1605, 1496, 1455, 1408, 1370, 1275, 1195, 1084, 1046, 1000 cm^{-1}; HRMS (FAB) calcd for $C_{13}H_{16}FO_2$ (M + H) 223.1134, found 223.1134.

Ethyl 2-fluoro-2-(1-methylethyl)-3-butenoate (±1j)

Yield: 53% (in the case of *i*-PrMgBr), 55% (in the case of $(i\text{-Pr})_2$Zn); ^{1}H NMR ($CDCl_3$) δ 0.96 (6H, dd, J = 13.59, 6.79 Hz), 1.31 (3H, t, J = 7.19 Hz), 2.21 (1H, dsept, J = 26.78, 6.79 Hz), 4.25 (2H, q, J = 7.19 Hz), 5.28–5.31 (1H, m), 5.47 (1H, d, J = 17.88 Hz), 5.93 (1H, ddd, J = 21.58, 17.88, 10.99 Hz) ppm; ^{13}C NMR ($CDCl_3$) δ 14.11, 15.43 (d, J = 4.12 Hz), 16.44 (d, J = 4.12 Hz), 34.45 (d, J = 22.29 Hz), 61.55, 98.37 (d, J = 195.08 Hz), 116.16 (d, J = 11.55 Hz), 134.40 (d, J = 21.48 Hz), 170.22 (d, J = 26.51 Hz) ppm; ^{19}F NMR ($CDCl_3$) δ −184.22 (1F, dd, J = 26.78, 21.58 Hz) ppm; IR (neat) 2977, 1762, 1737, 1469, 1391, 1371, 1255, 1200, 1135, 1039 cm^{-1}; HRMS (FAB) calcd for $C_9H_{15}FO_2$ (M^+) 174.1056, found 174.1061.

Ethyl 2-cyclohexyl-2-fluoro-3-butenoate (±1k)

Yield: 78%; ^{1}H NMR ($CDCl_3$) δ 1.02–1.37 (8H, m), 1.52–1.67 (2H, m), 1.77–1.93 (4H, m), 4.21–4.30 (2H, m), 5.27–5.30 (1H, m), 5.45 (1H, d, J = 17.18 Hz), 5.91 (1H, ddd, J = 21.58, 17.18, 10.79 Hz) ppm; ^{13}C NMR ($CDCl_3$) δ 14.12, 25.37 (d, J = 2.51 Hz), 25.92, 26.06 (d, J = 3.31 Hz), 43.85 (d, J = 20.68 Hz), 61.51, 98.27 (d, J = 194.27 Hz), 116.01 (d, J = 11.55 Hz), 134.23 (d, J = 21.59 Hz), 170.16 (d, J = 26.41 Hz) ppm; ^{19}F NMR ($CDCl_3$) δ −181.17 (1F, dd, J = 24.44, 21.58 Hz) ppm; IR (neat) 2933, 2856, 1761, 1735, 1451, 1267, 1235, 1198, 1168, 1098, 1056, 1036 cm^{-1}; HRMS (FAB) calcd for $C_{12}H_{19}FO_2$ (M^+) 214.1369, found 214.1376.

Ethyl 2-fluoro-5,5-dimethyl-2-hexenoate (1l)

Combined yield: 78% (*E*/*Z* = 95/5).

***E* isomer.** ^{1}H NMR ($CDCl_3$) δ 0.93 (9H, s), 1.34 (3H, t, J = 7.39 Hz), 2.44 (2H, dd, J = 8.19, 1.60 Hz), 4.29 (2H, q, J = 7.39 Hz), 5.97 (1H, dt, J = 22.78, 8.19 Hz) ppm; ^{19}F NMR ($CDCl_3$) δ −120.74 (1F, d, J = 22.78 Hz) ppm; HRMS (FAB) calcd for $C_{10}H_{18}FO_2$ (M + H) 189.1291, found 189.1298.

***Z* isomer.** ^{1}H NMR ($CDCl_3$) δ 0.93 (9H, s), 1.34 (3H, t, J = 7.39 Hz), 2.13 (2H, dd, J = 8.19, 1.60 Hz), 4.16 (2H, q, J = 7.39 Hz), 6.17 (1H, dt, J = 33.17, 8.19 Hz) ppm; ^{19}F NMR ($CDCl_3$) δ −130.88 (1F, d, J = 33.17 Hz) ppm; HRMS (FAB) calcd for $C_{10}H_{18}FO_2$ (M + H) 189.1291, found 189.1298.

Ethyl 2-ethyl-2-fluoro-3-butenate (1m)

Yield: 68%; ^{1}H NMR ($CDCl_3$) δ 0.96 (3H, t, J = 7.19 Hz), 1.31 (3H, t, J = 6.39 Hz), 1.82–2.11 (2H, m), 4.26 (2H, q, J = 7.19 Hz), 5.27–5.30 (1H, m), 5.49 (1H, d, J = 17.18 Hz), 5.97 (1H, ddd, J = 18.78, 17.18, 10.39 Hz) ppm; ^{13}C NMR ($CDCl_3$) δ 7.16 (d, J = 4.12 Hz), 14.09, 30.62 (d, J = 23.09 Hz), 61.65, 96.28 (d, J = 190.16 Hz), 116.89 (d, J = 11.55 Hz), 134.82 (d, J = 21.49 Hz), 170.16 (d, J = 26.41 Hz) ppm; ^{19}F NMR ($CDCl_3$) δ −170.16 (1F, m) ppm; IR (neat) 2957, 2925, 2854, 1738, 1714, 1647, 1464, 1377, 1261, 1033 cm^{-1}; HRMS (FAB) calcd for $C_8H_{14}FO_2$ (M + H) 161.0978, found 161.0970.

Ethyl 2-fluoro-3-butenoate (6)

This product was inseparable from impurities, therefore only the peak that could be assigned was described.

^{1}H NMR ($CDCl_3$) δ 1.31 (3H, t, J = 7.19 Hz), 4.27 (2H, q, J = 7.19 Hz), 5.29 (1H, ddd, J = 47.96, 5.60, 0.80 Hz), 5.42 (1H, d, J = 10.79 Hz), 5.57 (1H, dd, J = 17.58, 0.80 Hz), 5.99 (1H, dddd, J = 17.58, 16.79, 10.79, 5.60 Hz) ppm; ^{19}F NMR ($CDCl_3$) δ −190.02 (1F, dd, J = 47.96, 16.79 Hz) ppm.

Preparation of the chiral γ-fluoroallylic phosphate 9

To a suspension of sodium hydride (60% in oil, 0.26 g, 6.8 mmol) in THF (22 mL) at 0 °C was added triethyl 2-fluoro-2-phosphonoacetate (1.32 mL, 6.4 mmol). After stirring for 30 min at 0 °C, a solution of the chiral aldehyde **7** (0.81 g, 4.3 mmol) in THF (5 mL) was added. After stirring the resulting solution for 30 min at 0 °C, the solution was quenched with an aqueous saturated NH_4Cl solution and extracted with ethyl acetate. The organic layers were dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The resulting mixture was purified by silica gel column chromatography to give the corresponding adduct (0.89 g, 3.4 mmol, 77% yield).

To a solution of this adduct in THF (40 mL) at room temperature was added $TsOH{\cdot}H_2O$ (0.13 g, 0.68 mmol) in water (2 mL). After stirring overnight at room temperature, the solution was quenched with an aqueous saturated $NaHCO_3$ solution and extracted with ethyl acetate. The organic layers were dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The resulting mixture was purified by silica gel column chromatography. Subsequently, the obtained alcohol in CH_2Cl_2 (5 mL) was placed in a three-necked flask under an argon atmosphere where at 0 °C was added DMAP (11 mg, 0.091 mmol), diethyl chlorophosphate (0.46 mL, 3.17 mmol) followed by addition of triethylamine (0.44 mL, 3.20 mmol). The reaction mixture was allowed to warm to room temperature and stirred overnight. The solution was quenched with water and after separation of the two layers, the aqueous solution was washed with CH_2Cl_2 twice and the combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The resulting mixture was purified by silica gel column chromatography to give the corresponding γ-fluoroallylic phosphate (0.54 g, 1.8 mmol, 53% yield).

(*S*)-(*E*)-Ethyl 4-[(diethoxyphosphinyl)oxy]-2-fluoro-2-pentenoate (9)

$[\alpha]_D^{27}$ = +43.0 (*c* 1.05, $CDCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.30–1.38 (9H, m), 1.48 (3H, d, J = 5.99 Hz), 4.06–4.13 (4H, m), 4.33 (2H, q, J = 7.19 Hz), 5.85 (1H, m), 5.98 (1H, m) ppm; ^{13}C NMR ($CDCl_3$) δ 13.93, 16.00 (dd, J = 16.57, 1.66 Hz), 22.09 (dd, J = 5.32, 2.91 Hz), 61.97, 63.70 (dd, J = 5.82, 1.61 Hz), 69.58 (dd, J = 8.28, 4.97 Hz), 123.11 (dd, J = 19.43, 5.37 Hz), 146.60 (d, J = 262.04 Hz), 159.99 (d, J = 34.64 Hz) ppm; ^{19}F NMR ($CDCl_3$) δ −121.79 (1F, d, J = 19.18 Hz) ppm; ^{31}P NMR ($CDCl_3$) δ −2.69 (1P, s) ppm; IR (neat) 3482, 2986, 2937, 2911, 1731, 1674, 1447, 1396, 1337, 1332, 1276, 1229, 1151, 1097, 1036 cm^{-1}; HRMS (FAB) calcd for $C_{11}H_{21}FO_6P$ (M + H) 299.1060, found 299.1060.

S_N2' reaction of the chiral γ-fluoroallylic phosphate

To a suspension of CuCN (0.059 g, 0.66 mmol) in anhydrous THF (2 mL) was added dropwise a THF solution of *n*-$C_9H_{19}MgBr$ (0.66 mmol, prepared from *n*-$C_9H_{19}Br$ and magnesium) at −78 °C under an argon atmosphere. After stirring for 10 min, the mixture was warmed to −10 °C, then stirred for 10 min. The reaction mixture was again cooled to −40 °C, and to this mixture was added dropwise a solution of γ-fluoroallylic phosphate (89 mg, 0.30 mmol) in anhydrous THF (2 mL). After 30 min, the reaction was quenched with an aqueous saturated NH_4Cl solution and the whole was extracted with diethyl ether. The combined organic layers were dried over anhydrous Na_2SO_4, concentrated *in vacuo*. The residue was purified by silica gel column chromatography to give the corresponding S_N2' adduct (74 mg, 0.27 mmol, 91% yield).

(*R*)-Ethyl-2-fluoro-2-(1-propenyl)-undecanoate (10)

$[\alpha]_D^{24}$ = +29.6 (*c* 1.15, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.88 (3H, t, J = 6.79 Hz), 1.25–2.04 (22H, m), 4.21–4.28 (2H, m), 5.55–5.64 (1H, m), 5.88 (1H, dq, J = 14.39, 6.49 Hz) ppm; ^{13}C NMR ($CDCl_3$) δ 14.02, 14.09, 17.61, 22.60, 22.85, 22.89, 29.21, 29.30, 29.75 (d, J = 3.31 Hz), 31.80, 37.67 (d, J = 22.29 Hz), 61.47, 95.71 (d, J = 187.65 Hz), 127.44 (d, J = 10.74 Hz), 128.17 (d, J = 20.68 Hz), 170.70 (d, J = 26.41 Hz) ppm; ^{19}F NMR ($CDCl_3$) δ −164.68 (1F, dt, J = 33.49, 18.33 Hz) ppm; IR (neat) 2926, 2855, 1762, 1738, 1406, 1370, 1259, 1136,

1027 cm^{-1}; HRMS (FAB) calcd for $C_{16}H_{30}FO_2$ (M + H) 273.2230, found 273.2229.

Determination of the stereochemistry

The S_N2' product **10** (0.49 g, 1.81 mmol) dissolved in CH_2Cl_2 (5 mL) was cooled to −78 °C and then ozone gas was bubbled into the solution. After the solution turned blue, argon gas was bubbled into the reaction mixture at that temperature. Dimethyl sulfide (0.20 mL, 2.72 mmol) was added to the mixture, which was allowed to warm to room temperature for 1 h. To this solution was added water and after separation of the two layers, the aqueous solution was washed with CH_2Cl_2 and the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under vacuum. The resulting mixture was purified by flash chromatography to give the corresponding α-fluoroaldehyde.

To a solution of the aldehyde in EtOH (15 mL) was added $NaBH_4$ (0.082 g, 2.17 mmol) at 0 °C. After stirring for 30 min at 0 °C, aqueous 10% HCl solution was slowly added to the reaction mixture and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford the corresponding alcohol (0.41 g, 1.58 mmol).

To a solution of this alcohol in CH_2Cl_2 (15 mL) was added DIPEA (1.30 mL, 7.5 mmol) and MOMCl (0.50 mL, 6.75 mmol) successively at room temperature. After the reaction was completed, saturated aqueous NaCl solution was slowly added to the reaction mixture and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford the MOM ether (0.48 g, 1.56 mmol).

To a solution of this MOM ether in CH_2Cl_2 (3 mL) was added a solution of diisobutylaluminum hydride in *n*-hexane (1.02 M, 6.14 mL, 6.24 mmol) at −78 °C. After stirring for 2 h at −78 °C, MeOH was slowly added and then water was added to the reaction mixture. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography to give the corresponding aldehyde.

To a solution of this aldehyde in EtOH (15 mL) was added $NaBH_4$ (0.073 g, 1.93 mmol) at 0 °C. After stirring for 30 min at 0 °C, saturated aqueous 10% HCl solution was slowly added to the reaction mixture and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give the desired compound (0.27 g, 1.03 mmol, 57% yield).

(*S*)-2-Fluoro-2-methoxymethoxymethylundecan-1-ol (11)

Known compound: $[\alpha]_D^{24}$ = +6.4 (*c* 0.55, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.88 (3H, t, J = 6.39 Hz), 1.10–1.45 (14H, m), 1.60–1.80 (2H, m), 2.0–2.1 (1H, m), 3.39 (3H, s), 3.62–3.80 (4H, m), 4.66 (2H, s) ppm; ^{13}C NMR ($CDCl_3$) δ 14.08, 22.64, 22.68, 29.26, 26.45, 26.47, 30.00, 31.84, 32.59 (d, J = 21.28 Hz), 55.43, 64.70 (d, J = 25.60 Hz), 68.38 (d, J = 28.11 Hz), 96.78, 97.37 (d, J = 171.99 Hz) ppm; ^{19}F NMR ($CDCl_3$) δ −170.69 (1F, tt, J = 36.60, 18.30 Hz) ppm.

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