Ethyl α-Fluoro Silyl Enol Ether: Stereoselective Synthesis and Its Aldol Reaction with Aldehydes and Ketones

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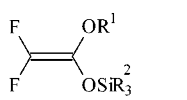
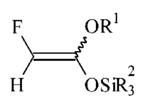
Ethyl α-fluoro silyl enol ether is stereoselectively synthesized in high yield from inexpensive chlorofluoroacetate and Mg (or Zn) in DMF (or HMPA). Lewis acid promoted aldol reaction of this enol ether with aldehydes and ketones gives α-fluoro-*β*-hydroxy esters in good to excellent yields.

Introduction

The Mukaiyama aldol reaction is one of the most important means for C−C bond formation. Silyl enol ethers react with aldehydes in the presence of Lewis acids to give *β*-hydroxy carboxylates. Recently, using chiral catalysts, not only various enatioselective Mukaiyama[1] and vinylogous Mukaiyama[2] aldol reactions have been developed but also asymmetric reactions of α,α-difluoro silyl enol ethers (**1**) with carbonyl compounds have been reported.[3] The utilization of **1** was further demonstrated in fluorinated sugars and amino acid syntheses.[4] Compared with difluoro derivatives (e.g., **1**), surprisingly, much less attention was paid on the synthesis and stereochemistry of α-fluoro-substituted enolates or α-fluoro silyl enol ethers (**2**) and their uses. The only report by Welch in 1984 was the stereoselective synthesis of α-fluoro enolates, α-fluorosilyl enol, and their reactions with aldehydes.[5] However, the enolates were generated from extremely poisonous ethyl fluoroacetates, and the silyl enol ether formed from α-fluoroacetate was an *E*/*Z* mixture that was liable to decompose above 50 °C. Therefore,it is very desirable to find a convenient, economic method for stereoselective synthesis of silyl enol ether. In this paper, we present the synthesis of *E*-configured ethyl α-fluoro silyl enol ether from inexpensive chlorofluoroacetate and its use in the direct aldol reaction.



a, a-difluoro silyl enol ethers
1



a-fluoro silyl enol ethers
2 (*E*/*Z*)

(1) For general reviews, see: (a) Noyori, T. Asymmetric catalysis via chiral complex: selected examples. *Asymmetric Catalysis in Organic Synthesis*; John Wiley: New York 1994; Chapter 4. (b) Sawamura, M.; Ito, Y. Asymmetric aldol reactions. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH Publishers: New York, 1993; Chapter 7.2.

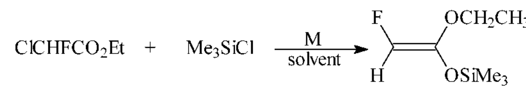
(2) Bluet, G.; Campagne, J.-M. *J. Org. Chem.* **2001**, *66*, 4293.

(3) (a) Iseki, K.; Kuroki, Y.; Asada, D.; Kobayashi, Y. *Tetrahedron Lett.* **1997**, *38*, 1447. (b) Iseki, K.; Kuroki, Y.; Asada, D.; Takahashi, M.; Kishimoto, S.; Kobayashi, Y. *Tetrhedron* **1997**, *53*, 10271.

(4) Kukhar, V. P., Soloshonok, V. A., Eds. *Fluorine-containing Amino Acids Synthesis and Properties*; John Wiley & Sons: New York, 1995.

(5) Welch, J. T.; Seper, K.; Eswarakrishman, S.; Samartino, J. *J. Org. Chem.* **1984**, *49*, 4720.

Scheme 1



3 **4** **5**

Results and Discussion

1. Stereoselective Synthesis of Ethyl α-Fluoro Silyl Enol Ether. It is known that difluoro silyl enol ethers (**1**) are readily prepared by successive treatment of α-halo-α,α-difluoroacetates with activated zinc metal and trialkylchlorosilane in THF and then applied to the synthesis of some useful racemates including α,α-difluoro *β*-hydroxy esters.[3,6] However, when we treated ethyl chlorofluoroacetate (**3**) under the similar conditions, no expected product, ethyl α-fluoro silyl enol ether (**5**), was obtained. But, interestingly, in DMF or HMPA, **5** was, indeed, formed in high yield from **3** (Scheme 1). The results are listed in Table 1.

It was noted from Table 1 that the solvent plays a very important role in this reaction. Moreover, only *E*-configured ethyl α-fluoro silyl enol ether **5** was obtained in high yield with Zn/HMPA or Mg/DMF. The configuration of **5** was specified by ^{1}H-NOESY. The alkenyl-H had an NOE effect with the H of $-SiMe_3$ but no NOE effect with the H of $-OCH_2CH_3$.

TMS-OTf-Promoted Aldol Reaction of Ethyl α-Fluoro Silyl Enol Ether (5) with Aromatic Aldehydes in CH_2Cl_2. α,α-Difluoro silyl enol ethers (**1**) show high reactivity toward aldehydes. For example, **1** reacts with benzaldehyde in the absence of Lewis acid in dichloromethane at −78 °C to give aldol adducts in 20% yield,[3b] while at 40 °C, in 82% yield. Unexpectedly, we found that alkene **5** is very inert. From −78 °C to room temperature, in CH_2Cl_2 or CH_3CN, its aldol reaction with benzaldehyde did not take place in the presence of nearly all kinds of ordinary Lewis acids (such as $SnCl_4$, $TiCl_4$, $AlCl_3$, $BF_3\cdot OEt_2$, TMS-OTf, $Cu(OTf)_2$, and $ZnCl_2$, etc.). Fortunately, when refluxed in CH_2Cl_2 and catalyzed by TMS-OTf, **5**

(6) (a) Kitagawa, O.; Taguchi, T.; Kobayashi, Y. *Tetrahedron Lett.* **1988**, *29*, 1803. (b) Taguchi, T.; Kitagawa, O.; Suda, Y.; Ohkawa, S.; Hashimoto, A.; Iitaka, Y.; Kobayashi, Y. *Tetrahedron Lett.* **1988**, *25*, 5291. (c) Burton, D. J.; Easdon, J. C. *J. Fluorine Chem.* **1988**, *38*, 125. (d) Kitagawa, O.; Hashimoto, A.; Kobayashi, Y.; Taguchi, T. *Chem. Lett.* **1990**, 1307. (e) Britton; Thomas, C. *US 5618951*, **1997**. (f) Uneyama, K.; Mizutani, G.; Maeda, K., Kato, T. *J. Org. Chem.* **1999**, *64*, 6717.

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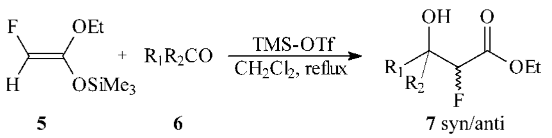
Table 1. Stereoselective Synthesis of Ethyl α-Fluoro Silyl Enol Ether

entry	M[a]	solvent (v/v)	**3**/M/**4**	*T* (°C)	time (h)	convn[b] (%)	yield[c] (%)
1	Zn	THF	1:1.1:1.1	40	4	0	0
2	Zn	HMPA	1:1.1:1.2	25	1.5	100	80
3	Zn	DMF	1:1.1:1.2	50	3	50	
4	Zn	CH3CN	1:1.1:1.2	50	8	0	0
5	Zn	DMF/HMPA = 3:1	1:1.1:1.2	40	6	50	
6	Mg	DMF	1:8:16	25	3	100	82
7	Mg	DMF	1:1.1:1.3	25	5	100	trace

[a] Zinc powder was activated; magnesium was untreated. [b] The conversion of **3**. [c] Isolated yield of **5**.

Scheme 2



R_1 = H

R_2 = Ph(**6a**), 4-CF_3-C_6H_4(**6b**), 3-CF_3-C_6H_4(**6c**), 4-NO_2-C_6H_4(**6d**), 3-NO_2-C_6H_4(**6e**), 2-NO_2-C_6H_4(**6f**), 4-CH_3-C_6H_4(**6g**), 3-CH_3-C_6H_4(**6h**), 4-F-C_6H_4(**6i**), 4-Cl-C_6H_4(**6j**), 4-Br-C_6H_4(**6k**), 3-HO-C_6H_4(**6l**), 4-$CH_3OC_6H_4$(**6m**), $CH_3CH_2CH_2$(**6n**)

Table 2. TMS-OTf-Catalyzed Aldol Reaction of Ethyl α-Fluoro Silyl Enol Ether[a]

entry	R_1R_2CO	time (h)	convn[b] (%)	products	**7** yield[c] (%)	**7** syn/anti[d]
1	**6a**	4	100	**7a**	81	53:47
2	**6b**	4	100	**7b**	85	54:46
3	**6c**	4	100	**7c**	80	50:50
4	**6d**	4	100	**7d**	87	56:44
5	**6e**	4	100	**7e**	80	50:50
6	**6f**	4	100	**7f**	83	52:48
7	**6g**	5	100	**7g**	60	44:56
8	**6h**	5	100	**7h**	72	50:50
9	**6i**	4	100	**7i**	78	44:56
10	**6j**	5	100	**7j**	75	50:50
11	**6k**	5	100	**7k**	74	50:50
12	**6l**	4	100	**7l**	65	50:50
13	**6m**	5	70			
14	**6n**	5	60			

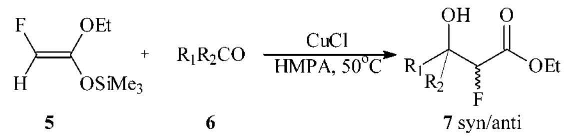
[a] TMS-OTf was catalytic amount (2%). [b] The conversion was based on **5** by ^{19}F NMR. [c] Isolated yields of **7** in addition to a trace of HCF_2CO_2Et. [d] The ratio was determined by ^{19}F NMR.

did react with benzaldehydes to give the aldol adducts **7** in good yields (Scheme 2).[7] The results are listed in Table 2.

The data in Table 2 show that **5** could react well with electron-deficient aromatic aldehydes, but not so well with electron-rich aromatic ones and not at all with aliphatic aldehydes.

3. CuCl-Promoted Aldol Reaction of Ethyl α-Fluoro Silyl Enol Ether (5) with Electron-Rich Aromatic Aldehydes, Aliphatic Aldehydes, and Ketones in HMPA. After several attempts, it was found that with HMPA as a solvent, CuCl can promote the aldol reaction of **5** with electron-rich aromatic aldehydes [such as 4-$MeOC_6H_4CHO$ (**6m**), 4-$Me_2NC_6H_4CHO$ (**6p**)], aliphatic aldehydes [such as butanal (**6n**), but-2-enal (**6o**)], and even ketones [such as cyclohexanone (**6q**) and acetophenone (**6r**)].[8]

Scheme 3



6m: R_1 = H, R_2 = 4-$CH_3OC_6H_4$
6n: R_1 = H, R_2 = $CH_3CH_2CH_2$
6o: R_1 = H, R_2 = CH_3CH=CH
6p: R_1 = H, R_2 = 4-$Me_2NC_6H_4$
6q: R_1R_2 = -$[CH_2]_5$-
6r: R_1 = CH_3, R_2 = Ph

Table 3. CuCl-Catalyzed Aldol Reaction of Ethyl α-Fluoro Silyl Enol Ether[a]

entry	R_1R_2CO	time (h)	convn[b] (%)	products	**7** yields[c] (%)	**7**[d] syn/anti
1	**6m**	10	100	**7m**	84	53:47
2[e]	**6m**	10	100	**7m**	55	
3	**6n**	8	100	**7n**	82	62:38
4	**6o**	7	100	**7o**	80	48:52
5	**6p**	8	100	**7p**	75	56:44
6	**6q**	7	100	**7q**	76	/
7	**6r**	8	100	**7r**	72	44:56

[a] **5**/CuCl = 1:1.10. [b] The conversion was based on **5** by ^{19}F NMR. [c] Isolated yields **7** in addition to a trace of HCF_2CO_2Et. [d] The ratio was determined by ^{19}F NMR. [e] The reaction was performed without CuCl.

It is important to note that the solvent, HMPA, is essential for this reaction, as its absence results in failure. The addition of CuCl to the reaction mixture improves the yields of the products. For example, in the reaction of **6m** with **5**, the yield of **7m** was 84% in the presence of 110 mol % of CuCl, while only 55% in its absence (Scheme 3). The results are listed in Table 3.

In conclusion, we present here a convenient method for stereoselective synthesis of ethyl α-fluoro silyl enol ether from unexpensive chlorofluoroacetate. The successful Mukaiyama aldol reaction of ethyl α-fluoro silyl enol ether gives α-fluoro β-hydroxy esters in good to excellent yields. The study on the asymmetric aldol reaction of **5** with aldehydes or ketones is in progress.

Experimental Section

^{1}H NMR spectra were recorded with TMS as an internal standard (positive for upfield). ^{19}F NMR spectra were recorded using CF_3COOH as an external standard (positive for upfield). The solvent for NMR measurement was $CDCl_3$ or CD_3COCD_3. Caution: HMPA is carcinogenic.

1. Stereoselective Synthesis of Ethyl α-Fluoro Silyl Enol Ether in HMPA. To a mixture of activated zinc dust (14.3 g, 0.24 mol) and HMPA (80 mL), stirred at 25 °C, under nitrogen, was added chlorotrimethylsilane (32 mL, 0.24 mol). The mixture was stirred at 25 °C for 90 min and cooled to 5 °C. Ethyl chlorofluoroacetate (**3**) (28.0 g, 0.20 mol) was added dropwise. The cooling bath was removed, and the reaction was allowed to a temperature of 30−40 °C for 5 h and 50 °C for an additional 1 h. ^{19}F NMR showed the conversion of chlorofluoroacetate was 100%. After the mixture was cooled, the precipitate was filtered off and the product was extracted with ether. The combined ether layer was washed with water and

(7) Here we describe the products having the syn or anti configuration according to ref 5; i.e., when two substituents, fluorine and hydroxyl, are on the same side of the molecule plane in a zigzig main chain, the molecule is denoted as having a syn relationship, whereas on the opposite side of this plane it is denoted as possessing an anti relationship.

(8) Ito, H.; Ishizuka, T.; Tateiwa, J.; Hosomi, A. *Tetrahedron Lett.* **1998**, *39*, 6295.

dried over anhydrous Na_2SO_4. After the ether was removed, the crude product was distilled under reduced pressure to give **5** as a colorless oil (28.4 g, yield 80%), bp 83−85 °C/37 mmHg.

Ethyl α-fluoro silyl enol ether (5) (*E*-configuration): colorless oil; IR (film) (cm^{-1}) 2966, 1752, 1720, 1369, 1254, 1203, 1051, 853; ^1H NMR δ 0.18 (s, 9H), 1.28 (t, J = 7.2 Hz, 3H), 4.23 (q, J = 7.2 Hz, 2H), 4.95 (d, J = 48 Hz, 1H); ^{19}F NMR δ 150.2 (d, J = 48 Hz, 1F); MS *m/z* (relative intensity) 178 (M^+, 5.73), 135 (17.96), 79 (26.43), 73 (100.00), 45 (16.43); HRMS calcd for $C_7H_{15}FO_2Si$ 178.0825, found 178.0834.

2. Stereoselective Synthesis of Ethyl α-Fluoro Silyl Enol Ether in DMF. To a mixture of magnesium (3.9 g, 0.16 mol) and chlorotrimethylsilane (34.7 g, 0.32 mol) in distilled DMF (200 mL), cooled to 0 °C, under nitrogen, was added **3** (2.8 g, 20 mmol) dropwise. Then the mixture was stirred for an additional 6 h at 25 °C. After removal of the excessive chlorotrifluorosilane in a vacuum and of the residue magnesium by decantation, the product was extracted with ether. The combined ether layer was washed with ice-cold water and then dried over Na_2SO_4. After the ether was removed, the crude product was distilled under reduced pressure to give **5** as a colorless oil (2.9 g, 82%).

3. General Procedure for TMS-OTf-Promoted Aldol Reaction of Ethyl α-Fluoro Silyl Enol Ether (5) with Aldehydes in CH_2Cl_2. To a solution of **6a** (212 mg, 2 mmol) and TMS-OTf (8 μL) in dry CH_2Cl_2 (5 mL) at room temperature was added **5** (356 mg, 2 mmol). The mixture was refluxed for 4 h. ^{19}F NMR showed the conversion of **5** was 100%. The product was extracted with ether and dried over Na_2SO_4. After removal of the ether, the residue was subjected to column chromatography, using petroleum ether and ethyl acetate (5:1) as eluant, to give **7a** as a colorless oil (339 mg, 81%).

Ethyl 2-fluoro-3-hydroxy-3-phenylpropanoate (7a):[9] colorless oil; 81% yield; IR (film) (cm^{-1}) 3474, 2986, 1747, 1376, 1301, 1214, 1106, 1028; ^1H NMR δ 1.19 (t, J = 7.1 Hz, 3H), 1.96 and 3.07 (s, 1H), 4.05 and 4.15 (q, J = 7.0 Hz, 2H), 5.02−5.18 (m, 2H), 7.29−7.48 (m, 5H); ^{19}F NMR δ 117.4 (dd, J = 50.0, 19.5 Hz, 0.53F), 122.8 (dd, J = 47.5, 24.8 Hz, 0.47F); MS *m/z* (relative intensity) 213 (M^+ + 1, 3.80), 212 (M^+, 1.24), 195 (66.81), 151 (17.41), 123 (21.08), 107 (100.00), 91 (15.50), 79 (48.19).

Ethyl 2-fluoro-3-hydroxy-3-(4-trifluoromethylphenyl)-propanoate (7b): white solid; 85% yield; IR (KBr) (cm^{-1}) 3461, 2990, 1751, 1338, 1131, 1116, 859. ^1H NMR δ 1.16 and 1.22 (t, J = 7.1 Hz, 3H), 2.84 (s, 1H), 4.18 (m, 2H), 5.12−5.41 (m, 2H), 7.69 (m, 4H); ^{19}F NMR δ −19.3 (s, 3F), 117.2 (dd, J = 48.5, 19.0 Hz, 0.54F), 124.5 (dd, J = 47.8, 26.1 Hz, 0.46F); MS *m/z* (relative intensity) 281 (M^+ + 1, 11.97), 263 (55.04), 219 (60.85), 191 (42.09), 175 (67.25), 127 (100.00), 106 (55.10), 78 (58.37); HRMS calcd for $C_{12}H_{10}F_4O_2$ 262.0616, found 262.0600.

Ethyl 2-fluoro-3-hydroxy-3-(3-trifluoromethylphenyl)-propanoate (7c): colorless oil; 80% yield; IR (film) (cm^{-1}) 3480, 2989, 1749, 1331, 1168, 1127, 1075, 807, 703; ^1H NMR δ 1.15 and 1.20 (t, J = 7.1 Hz, 3H), 1.96 and 3.04 (s, 1H), 4.04−4.21 (m, 2H), 5.15−5.30 (m, 2H), 7.57−7.85 (m, 4H); ^{19}F NMR δ −19.2 (s, 3F), 117.3 (dd, J = 46.8, 20.0 Hz, 0.5F), 124.5 (dd, J = 47.4, 26.0 Hz, 0.5F); MS *m/z* (relative intensity) 281 (M^+ + 1, 22.72), 263 (94.21), 219 (100.00), 191 (52.69), 171 (43.84), 127 (59.26); HRMS calcd for $C_{12}H_{12}F_4O_3$ 280.0722, found 280.0683.

Ethyl 2-fluoro-3-hydroxy-3-(4-nitrophenyl)propanoate (7d): colorless oil; 87% yield; IR (film) (cm^{-1}) 3502, 2987, 1759, 1608, 1524, 1350, 1217, 1108, 1015, 857, 724; ^1H NMR δ 1.16 and 1.24 (t, J = 7.1 Hz, 3H), 2.05 and 3.10 (s, 1H), 4.16 (m, 2H), 5.17−5.36 (m, 2H), 7.72−8.26 (m, 4H); ^{19}F NMR δ 116.7 (dd, J = 47.9, 19.5 Hz, 0.56F), 124.9 (dd, J = 47.7, 26.1 Hz, 0.44F); MS *m/z* (relative intensity) 258 (M^+ + 1, 5.18), 240 (5.16), 152 (63.67), 106 (100.00), 78 (89.71), 43 (52.33); HRMS calcd for $C_{11}H_{10}FNO_4$ 239.0593, found 239.0587.

Ethyl 2-fluoro-3-hydroxy-3-(3-nitrophenyl)propanoate (7e): colorless oil; 80% yield; IR (film) (cm^{-1}) 3485, 2987, 1748, 1533, 1353, 1219, 1097, 724; ^1H NMR δ 1.16 and 1.25 (t, J = 7.1 Hz, 3H), 2.90 (s, 1H), 4.19 (m, 2H), 5.19−5.61 (m, 2H), 7.66−8.35 (m, 4H); ^{19}F NMR δ 117.7 (dd, J = 50.1, 18.7 Hz, 0.5F), 123.6 (dd, J = 47.8, 26.0 Hz, 0.5F); MS *m/z* (relative intensity) 257 (M^+, 0.09), 152 (58.09), 106 (100.00), 78 (76.41), 29 (8.61); HRMS calcd for $C_{11}H_{12}FNO_5$ 257.0699, found 257.0735.

Ethyl 2-fluoro-3-hydroxy-3-(2-nitrophenyl)propanoate (7f): white solid; 83% yield; IR (KBr) (cm^{-1}) 3466, 2999, 1743, 1525, 1378, 1345, 1217, 1060, 861, 794, 717; ^1H NMR δ 1.17 and 1.28 (t, J = 7.2 Hz, 3H), 2.11 and 3.28 (s, 1H), 4.14 and 4.26 (q, J = 7.2 Hz, 2H), 5.25 (td, J = 44.5, 3.0 Hz, 1H), 5.83 (m, 1H), 7.60−8.08 (m, 4H); ^{19}F NMR δ 110.6 (dd, J = 47.6, 16.0 Hz, 0.52F), 126.4 (dd, J = 47.6, 25.8 Hz, 0.48F); MS *m/z* (relative intensity) 239 (M^+ − 18, 0.91), 152 (100.00), 134 (53.51), 104 (54.86), 78 (43.63), 29 (9.43); HRMS calcd for $C_{11}H_{10}FNO_4$ 239.0593, found 239.0590.

Ethyl 2-fluoro-3-hydroxy-3-(4-methylphenyl)propanoate (7g). colorless oil; 60% yield; IR (film) (cm^{-1}) 3482, 2985, 1748, 1375, 1297, 1210, 1109, 1062, 820, 771; ^1H NMR δ 1.18 (t, J = 7.1 Hz, 3H), 3.04 (s, 1H), 2.31 (s, 3H), 4.05 and 4.15 (q, J = 7.1 Hz, 2H), 5.05 (m, 2H), 7.13−7.35 (m, 4H); ^{19}F NMR δ 117.6 (dd, J = 50.0, 18.0 Hz, 0.44F), 122.5 (dd, J = 47.5, 25.8 Hz, 0.56F); MS *m/z* (relative intensity) 226 (M^+, 0.64), 209 (100.00), 165 (16.85), 121 (65.66), 105 (11.59), 93 (35.81); HRMS calcd for $C_{12}H_{15}FO_3$ 226.1005, found 226.0962.

Ethyl 2-fluoro-3-hydroxy-3-(3-methylphenyl)propanoate (7h): colorless oil; 72% yield; IR (film) (cm^{-1}) 3483, 2985, 1749, 1376, 1301, 1217, 1110, 1062, 754, 715. ^1H NMR δ 1.18 (t, J = 7.1 Hz, 3H), 1.96 and 3.06 (s, 1H), 2.32 (d, J = 3.5 Hz, 3H), 4.05 and 4.16 (q, J = 7.1 Hz, 2H), 5.09 (m, 2H), 7.10−7.28 (m, 4H); ^{19}F NMR δ 117.2 (dd, J = 50.2, 16.6 Hz, 0.5F), 122.5 (dd, J = 48.7, 15.9 Hz, 0.5F); MS *m/z* (relative intensity) 226 (M^+, 1.24), 206 (7.07), 121 (100.00), 105 (12.50), 93 (79.44), 91 (48.66), 77 (27.11); HRMS calcd for $C_{12}H_{15}FO_3$ 226.1005, found 226.0976.

Ethyl 2-fluoro-3-(4-fluorophenyl)-3-hydroxypropanoate (7i):[10] colorless oil; 78% yield; IR (film) (cm^{-1}) 3473, 2987, 1747, 1607, 1513, 1376, 1306, 1224, 1099, 1062, 841, 782. ^1H NMR δ 1.21 (t, J = 7.2 Hz, 3H), 2.86 (s, 1H), 4.18 (q, J = 7.2 Hz, 2H), 5.00−5.18 (m, 2H), 7.12 (m, 2H), 7.50 (m, 2H); ^{19}F NMR δ 34.2 (m, 1F), 117.9 (dd, J = 50.0, 18.5 Hz, 0.44F), 123.0 (dd, J = 47.9, 26.0 Hz, 0.56F); MS *m/z* (relative intensity) 230 (M^+, 3.16), 210 (6.90), 125 (100.00), 109 (10.84), 97 (36.63).

Ethyl 3-(4-chlorophenyl)-2-fluoro-3-hydroxypropanoate (7j):[11] colorless oil; 75% yield; IR (film) (cm^{-1}) 3467, 2986, 1747, 1494, 1376, 1307, 1217, 1093, 833, 745; ^1H NMR δ 1.22 (t, J = 7.1 Hz, 3H), 1.98 and 3.28 (s, 1H), 4.07 and 4.16 (t, J = 7.1 Hz, 2H), 5.04−5.25 (m, 2H), 7.37−7.53 (m, 4H); ^{19}F NMR δ 117.7 (dd, J = 50.0, 19.0 Hz, 0.5F), 124.5 (dd, J = 47.8, 26.0 Hz, 0.5F); MS *m/z* (relative intensity) 246 (M^+, 3.59), 226 (6.55), 141 (100.00), 77 (32.84).

Ethyl 3-(4-bromophenyl)-2-fluoro-3-hydroxypropanoate (7k): colorless oil; 74% yield; IR (film) (cm^{-1}) 3456, 2990, 1754, 1217, 1205, 1099, 1011, 735. ^1H NMR δ 1.12 and 1.22 (t, J = 7.1 Hz, 3H), 3.27 (s, 1H), 4.17 (q, J = 7.1 Hz, 2H), 5.04−5.24 (m, 2H), 7.37−7.57 (m, 4H); ^{19}F NMR δ 117.6 (dd, J = 48.9, 19.0 Hz, 0.5F), 123.7 (dd, J = 47.0, 16.0 Hz, 0.5F); MS *m/z* (relative intensity) 290 (M^+, 4.58), 272 (5.60), 187 (91.57), 185 (100.00), 157 (15.59), 106 (17.37), 78 (38.16); HRMS calcd for $C_{11}H_{12}BrFO_3$ 289.9953, found 289.9969.

Ethyl 2-fluoro-3-hydroxy-3-(3-hydroxyphenyl)propanoate (7l): colorless oil; 65% yield; IR (film) (cm^{-1}): 3402, 2987, 1741, 1594, 1459, 1377, 1226, 1110, 1058, 1021, 861, 769, 721, 698; ^1H NMR δ 1.20 (t, J = 7.1 Hz, 3H), 2.10 and 3.35 (s, 2H), 4.19 (q, J = 7.1 Hz, 2H), 4.98−5.18 (m, 2H), 6.75−7.20 (m, 4H); ^{19}F NMR δ 117.1 (dd, J = 47.8, 21.5 Hz, 0.5F), 122.3 (dd, J = 48.0, 24.1 Hz, 0.5F); MS *m/z* (relative intensity) 228 (M^+, 18.87), 123 (100.00), 95 (75.59), 77 (25.66), 43 (45.03); HRMS calcd for $C_{11}H_{13}FO_4$ 228.0797, found 228.0806.

CuCl-Promoted Aldol Reaction of Ethyl α-Fluoro Silyl Enol Ether in HMPA. To a flask, with CuCl (110 mg, 1.11

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mmol) dissolved in 1 mL of anhydrous HMPA, were added **5** (178 mg, 1 mmol) and **6m** (136 mg, 1 mmol) under nitrogen protection. Then the mixture was stirred at 50 °C for 10 h. ^{19}F NMR showed the conversion of **5** was 100%. The product was extracted with ether and dried over Na_2SO_4. After the removal of the ether, the residue was subjected to column chromatography, using petroleum ether and ethyl acetate (5:1) as eluant, to give **7m** as a colorless oil (205 mg, 84%).

Ethyl 2-fluoro-3-hydroxy-3-(4-methoxyphenyl)propanoate (7m): colorless oil; 84% yield; IR (film) (cm^{-1}) 3477, 2985, 1747, 1614, 1516, 1252, 1105, 1031, 836, 776. ^{1}H NMR δ 1.21 (t, J = 7.3 Hz, 3H), 3.26 (s, 1H), 3.77 (s, 3H), 4.14 (q, J = 7.2 Hz, 2H), 4.92−5.16 (m, 2H), 6.89 (m, 2H), 7.35 (m, 2H); ^{19}F NMR δ 117.9 (dd, J = 50.2, 18.5 Hz, 0.53F), 121.6 (dd, J = 46.7, 24.5 Hz, 0.47F); MS *m/z* (relative intensity) 242 (M$^+$, 6.82), 225 (100.00), 197 (3.58), 137 (26.55), 109 (9.65); HRMS calcd for $C_{12}H_{15}FO_4$ 242.0954, found 242.0947.

Ethyl 2-fluoro-3-hydroxyhexanoate (7n): colorless oil; 82% yield; IR (film) (cm^{-1}) 3455, 2964, 1745, 1376, 1299, 1214, 1073, 1029, 856; ^{1}H NMR δ 0.91 (t, J = 7.0 Hz, 3H), 1.26 (t, J = 7.1 Hz, 3H), 1.37−1.58 (m, 4H), 2.89 (s, 1H), 3.98 (m, 1H), 4.20 (m, 2H), 4.81 and 4.98 (t and d, J = 1.8 and 3.4 Hz, 1H); ^{19}F NMR δ 118.7 (dd, J = 49.5, 21.0 Hz, 0.62F), 127.0 (dd, J = 48.0, 26.2 Hz, 0.38F); MS *m/z* (relative intensity) 179 (M$^+$ + 1, 2.42), 178 (M$^+$, 0.02), 161 (3.14), 107 (24.99), 106 (60.43), 78 (100.00), 55 (51.85), 43 (38.19). Anal. Calcd for $C_8H_{15}FO_3$: C, 53.92; H, 8.48; F, 10.66. Found: C, 53.76; H, 8.70; F, 10.80.

Ethyl 2-fluoro-3-hydroxy-4(*E*)-hexenoate (7o): colorless oil; 80% yield; IR (film) (cm^{-1}) 3481, 2985, 1756, 1376, 1297, 1212, 1081, 1028, 969; ^{1}H NMR δ 1.26 (t, J = 7.2 Hz, 3H), 1.66 (m, 3H), 3.21 (s, 1H), 4.19 (q, J = 7.1 Hz, 2H), 4.40 (m, 1H), 4.87 (ddd, J = 48.0, 20.8, 3.5 Hz, 1H), 5.58 (m, 1H), 5.72 (m, 1H); ^{19}F NMR δ 120.1 (dd, J = 50.0, 21.9 Hz, 0.48F), 123.6 (dd, J = 48.0, 23.9 Hz, 0.52F); MS *m/z* (relative intensity) 159 (M$^+$ − 17, 3.03), 78 (24.30), 71 (100.00), 69 (16.22), 53 (11.44), 43 (22.80), 41 (20.55); HRMS calcd for $C_8H_{11}FO_2$ 158.0743, found 158.0755.

Ethyl 4-(4-dimethylaminophenyl)-2-fluoro-3-hydroxypropanoate (7p): colorless oil; 75% yield; IR (film) (cm^{-1}) 3480, 2984, 2896, 1749, 1616, 1526, 1351, 1220, 1060, 947, 821, 757; ^{1}H NMR δ 1.20 (t, J = 7.1 Hz, 3H), 2.91 (s, 6H), 3.25 (s, 1H), 4.13 (q, J = 7.0 Hz, 2H), 4.87−5.13 (m, 2H), 6.71 (m, 2H), 7.24 (m, 2H); ^{19}F NMR δ 117.7 (dd, J = 48.8, 20.0 Hz, 0.56F), 120.2 (dd, J = 49.1, 23.0 Hz, 0.44F); MS *m/z* (relative intensity) 255 (M$^+$, 9.90), 237 (0.91), 150 (100.00), 148 (13.83), 122 (14.27), 107 (10.32); HRMS calcd for $C_{13}H_{16}FNO_2$ 237.1165, found 237.1167.

Ethyl fluoro-1-(hydroxycyclohexyl)acetate (7q):[9] colorless oil; 76% yield; IR (film) (cm^{-1}) 3521, 2939, 1745, 1450, 1375, 1304, 1211, 1095, 1033, 858; ^{1}H NMR δ 1.26 (t, J = 7.1 Hz, 3H), 1.48−1.73 (m, 10H), 3.23 (s, 1H), 4.22 (q, J = 7.1 Hz, 2H), 4.70 (d, J = 48.4 Hz, 1H); ^{19}F NMR δ 117.6 (d, J = 48.5 Hz, 1F); MS *m/z* (relative intensity) 204 (M$^+$, 3.12), 185 (10.60), 171 (45.96), 143 (45.99), 91 (89.17), 57 (100.00), 55 (74.32), 43 (59.61), 41 (60.91). Anal. Calcd for $C_{10}H_{17}FO_3$: C, 58.81; H, 8.39; F, 9.30. Found: C, 58.68; H, 8.38; F, 9.23.

Ethyl 2-fluoro-3-hydroxy-3-phenylbutanoate (7r):[5] colorless oil; 72% yield; IR (film) (cm^{-1}) 3501, 2987, 1749, 1449, 1376, 1304, 1209, 1091, 1028, 764, 701; ^{1}H NMR δ 0.99 and 1.08 (t, J = 7.1 Hz, 3H), 3.27 (s, 1H), 3.99 and 4.07 (q, J = 7.1 Hz, 2H), 5.08 (dd, J = 47.9, 7.2 Hz, 1H), 7.24−7.57 (m, 5H); ^{19}F NMR δ 110.6 (d, J = 47.9 Hz, 0.44F), 113.2 (d, J = 48.0 Hz, 0.56F); MS *m/z* (relative intensity) 209 (M$^+$ − 17, 2.22), 121 (100.00), 105 (17.75), 77 (10.51), 43 (53.33).

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Supporting Information Available: ^{1}H NMR and ^{19}F NMR spectra of **5**, **7a**,**b**,**e**,**g**,**i**,**n**,**q**,**r**. This material is available free of charge via the Internet at http://pubs.acs.org.

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