Ethyl 3-Fluoro-3-(tributylstannyl)-2-methoxyacrylate: Preparation and Palladium/Copper-Cocatalyzed Cross-Coupling Reactions as a Novel Route to β-Fluoro-α-keto Acid Derivatives

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α-Keto acid derivatives are not only useful in organic synthesis, e.g., as precursors of amino acids and heterocycles, but also of unabated interest for studies of various biological processes as well as in the development of enzyme inhibitors and drugs.[1] On the basis of the well-known feature that fluorine may confer to biologically active molecules,[2] the introduction of a fluorine atom into the β-position of α-keto acid derivatives may bring about significant biological consequences. Moreover, from a synthetic point of view, β-fluoro-α-keto acids are particularly valuable precursors of the corresponding β-fluoro-α-amino acids which are currently of great interest in the design of potential enzyme inhibitors and therapeutic agents.[2b,3]

The synthesis of β-fluoro-α-keto acids or their derivatives is not trivial. Direct fluorination of enol-type α-keto esters with molecular fluorine had been previously developed.[4] However, due to the extraordinarily high reactivity of molecular fluorine, this method is only applicable to a very limited number of substrates that should be devoid of other potentially reactive functionalities. The alternative method of preparing β-fluoro-α-hydroxy esters from the ring opening of glycidic esters with HF/pyridine and subsequent oxidation to β-fluoro-α-keto esters[5] has also been of limited utility. This is because of the low regioselectivity in the ring-opening step and the necessity to use a strong oxidant, which cannot be tolerated by many other functional groups. In order to develop an efficient and convenient method for the synthesis of β-fluoro-α-keto acid derivatives, we have focused our attention on the development of a convenient reagent which made use of readily available fluorinated starting materials as a source of fluorine. Previously, a number of building blocks and synthons have been discovered for the synthesis of α-keto acid derivatives;[1,6] however, none of them appeared to be adaptable for the synthesis of β-fluorinated analogs. Herein we wish to report that the fluorinated organostannane **1** can be easily prepared from readily available starting material and employed as a synthetic equivalent of 3-fluoropyruvate enolate **2** for the synthesis of β-fluoro-α-keto acid derivatives (Chart 1).

By using our general method recently developed for the synthesis of β,β-difluoro-α-allyloxyacrylates en route to β,β-difluoro-α-keto esters,[7] β,β-difluoro-α-methoxyacrylate **5** has been readily prepared from ethyl trifluoropyruvate (**3**) as shown in Scheme 1. Thus, treatment of the hemiketal formed between ethyl trifluoropyruvate (**3**) and methanol with $SOCl_2$ and pyridine afforded the α-chloro ether **4** in 75% yield. Subsequent reductive dehalogenation of **4** with zinc powder in DMF provided **5** in 85% yield. As a very reactive Michael acceptor, compound **5** cleanly reacted with $(Bu_3Sn)_2CuLi$ to furnish the desired reagent **1** via an addition–elimination mechanism. The organostannane **1** thus obtained consisted of only one isomer. Based on the stereospecificity observed in the analogous addition of $(Bu_3Sn)_2CuLi$ to β-chloroacrylate[8] and propiolate,[9] we tentatively assigned the stereochemistry of **1** as depicted in Scheme 1, which was further proved by examining the stereochemistry of the cross-coupling products (*vide infra*).

With a convenient route to the fluorine-containing organostannane **1**, we decided to establish the feasibility of using **1** in cross-coupling reactions. In general, palladium-catalyzed coupling reactions of organostannanes with organic halides and sulfonates (known as Stille coupling) have already been established as an efficient method for the construction of carbon–carbon bonds.[10] As one of the commonly used organostannanes, simple unsubstituted alkyl β-stannylacrylate has been successfully employed in the cross-coupling reactions with several types of organic substrates.[11] However, the preparation and synthetic utility of β-stannylacrylate bearing additional substituents at an α- or β-position have not been explored. Gratifyingly, when the coupling reactions of **1** with a variety of organic substrates were conducted in DMF at ambient temperature using $Pd(PPh_3)_4$ and CuI as the cocatalyst (Scheme 2), fairly rapid reactions occurred, affording the desired coupling products **7** in satisfactory yield. The results obtained with a variety of organic iodides and triflates are summarized in Table 1.

The following points derived from the present work are noteworthy: (1) The recourse of using the copper cocata-

(1) For a review on the syntheses and properties of α-keto acid derivatives, see: Cooper, A. J. L.; Ginos, J. Z.; Meister, A. *Chem. Rev.* **1983**, *83*, 321.

(2) (a) Filler, R., Kobayashi, Y., Eds. *Biomedicinal Aspects of Fluorine Chemistry*; Elsevier: Amsterdam, 1982. (b) Welch, J. T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*; John Wiley & Sons: New York, 1990. (c) Filler, R., Kobayashi, Y., Yagupolski, L. M., Eds. *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*; Elsevier Science: Amsterdam, 1993.

(3) (a) Kollonitsh, J.; Perkins, L. M.; Patchett, A. A.; Doldouras, G. A.; Marburg, S.; Duggan, D. E.; Maycock, A. L.; Aster, S. D. *Nature* **1978**, *274*, 906. (b) Walsh, C. *Tetrahedron* **1982**, *38*, 871. (c) Bey, P. *Ann. Chim. Fr.* **1984**, *9*, 695. (c) Kollonitsh, J. *Israel J. Chem.* **1978**, *17*, 53. (d) Kawada, K.; Tsushima, T. *Kagaku Kogyo* **1987**, *38*, 164; *Chem. Abstr.* **1987**, *107*, R97067. (e) Kukhar, V. P. *J. Fluorine Chem.* **1994**, *69*, 199.

(4) (a) Tsushima, T.; Kawada, K.; Tsuji, T. *J. Org. Chem.* **1982**, *47*, 1107. (b) Tsushima, T.; Kawada, K.; Nishikawa, J.; Sato, T.; Tori, K.; Tsuji, T. *J. Org. Chem.* **1984**, *49*, 1163.

(5) (a) Ayi, A. I.; Remli, M. R.; Condom, R.; Geudj, R. *J. Fluorine Chem.* **1981**, *17*, 565. (b) Remli, M.; Ayi, A. I.; Guedj, R. *J. Fluorine Chem.* **1982**, *20*, 677.

(6) Recent findings: (a) Reetz, M. T.; Heimbach, H.; Schwellnus, K. *Tetrahedron Lett.* **1984**, *25*, 511. (b) Horne, D.; Gaudino, J.; Thompson, W. J. *Tetrahedron Lett.* **1984**, *25*, 3529. (c) Tanaka, M.; Kobayashi, T.; Sakakura, T. *J. Chem. Soc., Chem. Commun.* **1985**, 837. (d) Cacchi, S.; Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1987**, *28*, 3039. (e) Mikolajczyk, M.; Midura, W. H. *Synlett* **1991**, 245. (f) Sagimura, H.; Yoshida, K. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 3209. (g) Barton, D. H. R.; Chern, C.-Y.; Jaszberenyi, J. Cs. *Tetrahedron* **1995**, *51*, 1867.

(7) Shi, G.-Q.; Cai, W.-L. Submitted for publication.

(8) Piers, E.; Wong, T.; Ellis, K. A. *Can. J. Chem.* **1992**, *70*, 2058.

(9) Seitz, D. E.; Lee, S.-H. *Tetrahedron Lett.* **1981**, *22*, 4909.

(10) Reviews: (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. (b) Mitchell, T. N. *Synthesis* **1992**, 803.

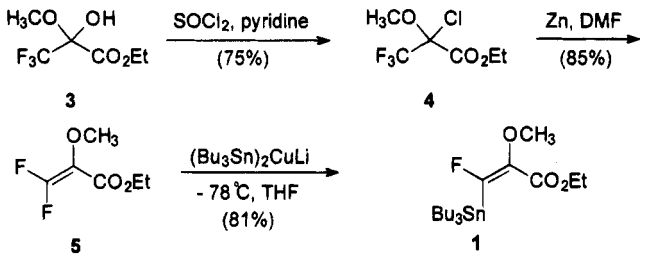
(11) For representative examples, see: (a) Labadie, J. W.; Tueting, D.; Stille, J. K. *J. Org. Chem.* **1983**, *48*, 4634. (b) Stille, J. K.; Groh, B. L. *J. Org. Chem.* **1987**, *109*, 813. (c) Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1988**, *110*, 1557. (d) Houpis, I. N.; DiMichele, L.; Molina, A. *Synlett* **1993**, 365. (e) Lai, M.-T.; Li, D.; Oh, E.; Liu, H.-W. *J. Am. Chem. Soc.* **1993**, *115*, 1619.

0022-3263/95/1960-6608$09.00/0

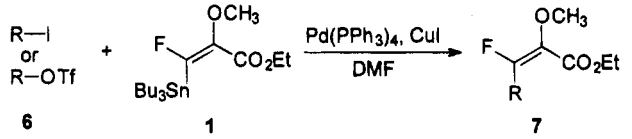
Chart 1

1 2

Scheme 1

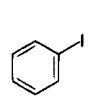
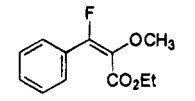
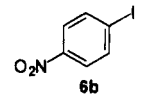
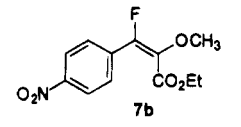
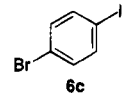
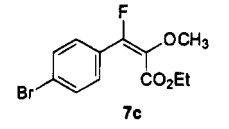
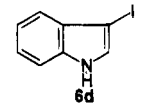
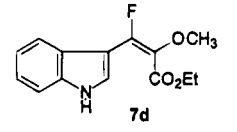
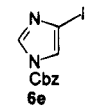
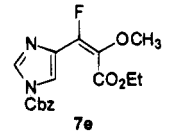
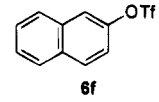
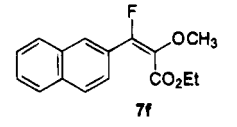
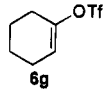
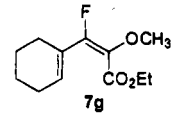


Scheme 2



lyst was dictated by the very limited success of the initial attempt at using $Pd(PPh_3)_4$ or $PhCH_2PdCl(PPh_3)_2$ alone as the catalyst. In fact, in the absence of CuI, no appreciable reactions were observed at room temperature, whereas at elevated temperature the reaction led to the formation of a substantial amount of homocoupling product, $[EtO_2C(H_3CO)C{=}CF-]_2$ (**8**), and consequently the yield of the desired product was rather unsatisfactory. This indicated a decreased reactivity of the organostannane **1** relative to the simple unsubstituted β-stannylacrylate and represents one more example of the beneficial effect of cocatalytic Cu(I) on sluggish or otherwise unsuccessful cross-coupling reactions.[12] (2) In contrast to the fairly rapid reaction observed with aryl and heteroaryl iodide, the cross-coupling of **1** with an aryl bromide using the same cocatalytic system in DMF was found to be rather sluggish even at an elevated temperature of 80 °C. Consequently, the formation of homocoupling product **8** began to compete effectively with the slower cross-coupling reaction. (3) Both aryl and vinyl triflates reacted as successfully as the iodides under the same cocatalytic reaction conditions. In the case of the aryl triflate (Table 1, entry 6), it was necessary to add 1.0 equiv of LiCl[13] in order to obtain a good yield of the desired coupling product. The role[14] of LiCl is considered to accelerate the rate of product formation relative to the rate of formation of **8**. This notion was further supported by the coupling reaction with the vinyl triflate (Table 1, entry 7), where the reaction was extremely fast and consequently no LiCl was required. (4) While unprotected indolyl iodide can be used as the substrate (Table 1, entry 4), only protected iodoimidazole underwent the desired cross-coupling reaction (Table 1, entry 5) presumably because imidazole is more acidic than indole.

Table 1. Palladium/Copper-Cocatalyzed Cross-Coupling of Fluorinated Organostannane 6 with Organic Iodides and Triflates[a]

entry	R-I or R-OTf	time	product	yield[b], %
1	 **6a**	10 min	 **7a**	95
2	 **6b**	30 min	 **7b**	88
3	 **6c**	75 min	 **7c**	92
4	 **6d**	60 min	 **7d**	50
5	 **6e**	60 min	 **7e**	90
6	 **6f**	6 h[c]	 **7f**	80
7	 **6g**	10 min	 **7g**	85

[a] All reactions were performed in DMF at room temperature on a 1.0 mmol scale for 1.0 equiv of organostannane using 10 mol % of $Pd[PPh_3]_4$ and 75 mol % of CuI as the catalysts. [b] Yield of isolated product. [c] This reaction was performed in the presence of 1.0 equiv of LiCl.

The stereochemistry of the coupling products has been examined, although it is of no consequence if conversion to keto acids was desired. It was clear from an examination of both high field ^1H and ^{19}F NMR spectra that the the coupling products were generated exclusively as a single stereoisomer. However, spectroscopic techniques were not able to provide an unambiguous stereochemical assignment.[15] A single crystal X-ray structure determination[16] of the acid **9** obtained by hydrolysis of the coupling product **7a** (Scheme 3) allowed a straightforward assignment of a *Z* configuration. Consideration of the uniformity of the coupling mechanism[10] led us to assume a *Z* configuration for anlogous coupling products and, as a corollary, an *E* configuration for the tin reagent **1**.

(12) Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S. *J. Org. Chem.* **1994**, *59*, 5905 and references cited therein.

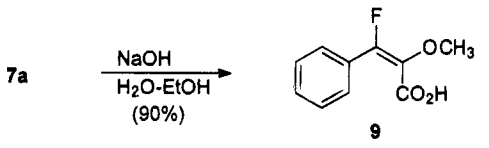
(13) (a) Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 5478. (b) Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033. (c) Scott, W. J.; Crisp, G. T.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4630.

(14) Farina, V.; Krishnan, B.; Marshall, D. R.; Roth, G. P. *J. Org. Chem.* **1993**, *58*, 5434.

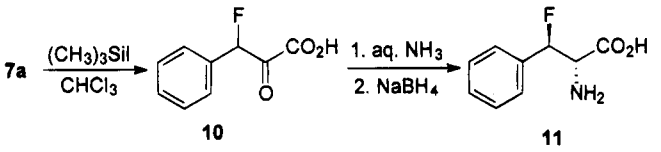
(15) The coupling constant between the fluorine and the carbonyl carbon ($^3J_{F-C(=O)}$) for compound **7a** is 10 Hz which may be considered to be indicative of a trans relationship between the two nuclei. For reference, see: Ichikawa, J.; Yokota, N.; Kobayashi, M.; Minami, T. *Synlett* **1993**, 186.

(16) The authors have deposited the atomic coordinates for **9** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

Scheme 3



Scheme 4



Finally, the synthetic equivalence between the coupling products and β-fluoro-α-keto acids has been demonstrated. Thus, clean conversion of **7a** to β-fluoro-α-keto acid **10** was achieved readily on treatment of **7a** with 2 equiv of Me_3SiI.[17] However, simple acid hydrolysis of **7a** did not provide a satisfactory yield of the desired product **10** due to loss of fluorine. Following the same protocol described by Tsushima, compound **10** was stereoselectively converted to the known β-fluorophenylalanine (**11**) (Scheme 4).[4a]

In summary, organostannane **1** has been conveniently prepared in high yield by addition of $(Bu_3Sn)_2CuLi$ to the readily attainable β,β-difluoro-α-methoxyacrylate **5**. Palladium/copper-cocatalyzed cross-coupling reaction of **1** with a variety of organic iodides and triflates provided a novel route to β-fluoro-α-keto acid derivatives.

Experimental Section

^1H NMR spectra were recorded on a 300 or 90 MHz spectrometer with Me_4Si as internal standard. ^{19}F NMR spectra were obtained on a 60 MHz spectrometer using trifluoroacetic acid as external standard, downfield shifts being designated as negative. Mass spectra were obtained using EI ionization at 70 eV. All reactions were routinely monitored with the aid of TLC or ^{19}F NMR spectroscopy.

THF was distilled from sodium benzophenone ketyl, and DMF was freshly distilled from CaH_2. Pyridine and $SOCl_2$ were distilled prior to use. CuI was purified by a literature procedure.[18] Commercial zinc powder was activated by a standard method.[19] Ethyl trifluoropyruvate was prepared by the method of Knunyants.[20]

Ethyl 2-Chloro-3,3,3-trifluoro-2-methoxypropanoate (4). Freshly distilled ethyl trifluoropyruvate (10.2 g, 60 mmol) and methanol (2.5 mL, 60 mmol) were mixed in dry benzene (100 mL). To the resulting solution cooled with an ice bath was added pyridine (14.4 mL, 180 mmol), followed by $SOCl_2$ (6.5 mL, 90 mmol) added dropwise over 10 min. After being stirred at 0 °C for 30 min, the reaction mixture was poured into ice–water (100 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic phase was washed successively with water (100 mL), saturated $NaHCO_3$ solution (2 × 100 mL), and brine (100 mL) and then dried over Na_2SO_4. Distillation under reduced pressure gave 9.8 g (75%) of **4** as a colorless liquid: bp 60 °C/23 mmHg; ^1H NMR (CCl_4) δ 4.3 (q, J = 7.1 Hz, 2H), 3.62 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H); ^{19}F NMR (CCl_4) δ −0.3 (s); MS (EI, m/z) 185 (M^+ − Cl, 13), 147 (100), 69 (90), 43 (56), 149 (49). Anal. Calcd for $C_6H_8F_3ClO_3$: C, 32.67; H, 3.66. Found: C, 32.86; H, 3.60.

Ethyl 3,3-Difluoro-2-methoxypropenoate (5). A mixture of **4** (11.0 g, 50 mmol), freshly activated zinc powder (12.8 g, 0.20 mol), and a small amount of CuI (ca. 50 mg) in DMF (100 mL) was vigorously stirred at 25 °C under nitrogen. After the heat evolution ceased, the reaction mixture was diluted with ether (100 mL) and filtered. The filtrate was washed with water (2 × 50 mL) and dried over Na_2SO_4. Distillation under reduced pressure afforded 7.1 g (85%) of **5** as a colorless liquid: bp 52 °C/24 mmHg; ^1H NMR (CCl_4) δ 4.25 (q, J = 7.2 Hz, 2H), 3.65 (s, 3H), 1.31 (t, J = 7.2 Hz, 3H); ^{19}F NMR (CCl_4) δ 5.3 (d, J = 3.0 Hz), 9.8 (d, J = 3.0 Hz); MS (EI, m/z) 167 (M^+ + 1, 100), 166 (M^+, 61), 59 (13), 121 (99), 113 (54). Anal. Calcd for $C_6H_8F_2O_3$: C, 43.38; H, 4.85. Found: C, 43.18; H, 4.78.

Ethyl (*E*)-3-Fluoro-2-methoxy-3-(tributylstannyl)propenoate (1). Bu_3SnH (2.7 mL, 10 mmol) was added to solution of LDA in THF prepared by mixing diisopropylamine (1.3 mL, 10 mmol) and a hexane solution of BuLi (1.5 M, 7.0 mL) in THF (15 mL) at 0 °C. After 10 min at 0 °C, the reaction mixture was cooled to −15 °C and CuI (1.0 g, 5.0 mmoL) was added. The resulting suspension was stirred at −15 °C for 30 min and then cooled to −78 °C. A THF solution (2.0 mL) of **5** (0.84 g, 5.0 mmol) was added over 2 min. After 30 min at −78 °C, the reaction was quenched with a saturated NH_4Cl solution (60 mL) and extracted with diethyl ether. The combined ethereal extracts were washed with water (2 × 30 mL), dried over Na_2SO_4, and concentrated. The residue was purified by chromatography on silica gel eluting with a 1:9 mixture of ethyl acetate and petroleum ether to afford 3.5 g (80%) of **1** as a colorless oil: ^1H NMR ($CDCl_3$) δ 4.25 (q, J = 7.1 Hz, 2H), 3.78 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H), 1.05–1.72 (m, 18H), 0.89 (t, J = 7.1 Hz, 9H); ^{19}F NMR ($CDCl_3$) δ 31.0 (s); MS (EI, m/z) 437 (M^+, 5), 381 (100), 353 (54), 267 (25), 239 (19), 177 (14). Anal. Calcd for $C_{18}H_{35}FO_3Sn$: C, 49.45; H, 8.07. Found: C, 49.86; H, 8.36.

General Procedure for the Cross-Coupling Reactions Exemplified by the Reaction of 1 with Iodobenzene. Organostannane **1** (0.44 g, 1.0 mmol) and iodobenzene (0.20 g, 1.0 mmol) were dissolved in DMF (10 mL) under nitrogen at room temperature. $Pd(PPh_3)_4$ (0.12 g, 0.10 mmol) and purified CuI (0.14 g, 0.75 mmol) were then added. The mixture was stirred at room temperature and monitored by TLC (SiO_2) for the disappearance of the starting organostannane. The reaction mixture was diluted with diethyl ether (20 mL), filtered, and washed with water (2 × 20 mL). The ethereal phase was stirred with 20% aqueous KF (10%) for 30 min before being dried and concentrated. The residue was purified by column chromatography on silica gel, eluting with a 1:9 mixture of ethyl acetate and petroleum ether to afford 0.20 g (95%) of the coupling product **7a** as a colorless oil: ^1H NMR ($CDCl_3$) δ 7.37 (s, 5H), 4.14 (q, J = 7.0 Hz, 2H), 3.81 (s, 3H), 1.07 (t, J = 7.0 Hz, 3H); ^{19}F NMR ($CDCl_3$) δ 23.0 (s); MS (EI, m/z) 224 (M^+, 100), 205 (90), 179 (34), 125 (72), 105 (90). Anal. Calcd for $C_{12}H_{13}FO_3$: C, 64.28; H, 5.84. Found: C, 64.17; H, 5.83.

Ethyl (*E*)-3-(4-Nitrophenyl)-3-fluoro-2-methoxypropenoate (7b). Reaction of organostannane **1** (0.44 g, 1.0 mmol) and 1-iodo-4-nitrobenzene (0.25 g, 1.0 mmol) for 30 min yielded 2.4 g (88%) of **7b** as colorless crystals after chromatography using a 1:9 mixture of ethyl acetate and petroleum ether as the eluent: mp 32–34 °C; ^1H NMR ($CDCl_3$) δ 8.23 (d, J = 8.6 Hz, 2H), 7.64 (d, J = 8.6 Hz, 2H), 4.13 (q, J = 7.1 Hz, 2H), 3.85 (s, 3h), 1.22 (t, J = 7.1 Hz, 3H); ^{19}F NMR ($CDCl_3$) δ 29.0 (s); MS (EI, m/z) 269 (M^+, 77), 221 (28), 170 (50), 150 (100), 107 (48). Anal. Calcd for $C_{12}H_{12}FNO_5$: C, 53.53; H, 4.49; N, 5.20. Found: C, 53.53; H, 4.16; N, 4.95.

Ethyl (*E*)-3-(4-Bromophenyl)-3-fluoro-2-methoxypropenoate (7c). Reaction of organostannane **1** (0.44 g, 1.0 mmol) and 1-iodo-4-bromobenzene (0.28 g, 1.0 mmol) for 75 min yielded 2.8 g (92%) of **7c** as an oil after chromatography using a 1:9 mixture of ethyl acetate and petroleum ether as the eluent: ^1H NMR ($CDCl_3$) δ 7.58 (d, J = 8.5 Hz, 2H), 7.35 (d, J = 8.5 Hz, 2H), 4.07 (q, J = 7.1 Hz, 2H), 3.75 (s, 3H), 1.13 (t, J = 7.1 Hz, 3H); ^{19}F NMR ($CDCl_3$) 24.3 (s); MS (EI, m/z) 304 (M^+, 96), 259 (22), 203 (89), 183 (86), 107 (100). Anal. Calcd for $C_{12}H_{12}BrFO_3$: C, 47.55; H, 4.65. Found: C, 47.54; H, 4.75.

Ethyl (*Z*)-3-Fluoro-3-(1*H*-indol-3-yl)-2-methoxypropenoate (7d). Reaction of organostannane **1** (0.44 g, 1.0 mmol) and 3-iodo-1*H*-indole (0.24 g, 1.0 mmol) for 60 min yielded 0.13 g (50%) of **7d** as an oil after chromatography using a 3:7 mixture of ethyl acetate and petroleum ether as the eluent: ^1H NMR

(17) Olah, G. A.; Narang, S. C. *Tetrahedron* **1982**, *38*, 2225.
(18) Kauffman, G. B.; Fang, L. Y. *Inorg. Synth.* **1983**, *22*, 101.
(19) Tsuda, K.; Ohki, E.; Nozoe, S. *J. Org. Chem.* **1963**, *28*, 783.
(20) (a) Knunyants, I. L.; Shokina, V. V.; Tyuleneva, V. V. *Dokl. Akad. Nauk. SSSR* **1966**, *169*, 594; *Chem. Abstr.* **1966**, *65*, 15218e. (b) Sianesi, D.; Pasetti, A.; Tarli, F. *J. Org. Chem.* **1966**, *31*, 2312. This compound was also prepared in our laboratory by another convenient method: (a) Francese, C.; Toxdeux, M.; Wakselman, C. *Tetrahedron Lett.* **1988**, *29*, 1029. (b) Shi, G.-q.; Xu, Y.-y. *J. Chem. Soc., Chem. Commun.* **1989**, 607.

($CDCl_3$) δ 9.56 (br.s, 1H), 7.98 (m, 2H), 7.28–7.52 (m , 3H), 4.40 (q, J = 7.1 Hz, 2H), 3.70 (s, 3H), 1.39 (t, J = 7.1 Hz, 3H); ^{19}F NMR ($CDCl_3$) δ 43.0 (s); MS (EI, *m/z*) 263 (M^+, 100), 248 (78), 218 (12), 192 (31), 164 (48), 147 (63). Anal. Calcd for $C_{14}H_{14}FNO_3$: C, 63.87, H, 5.36; N, 5.32. Found: C, 63.52; H, 5.42; N, 5.13.

Ethyl (*Z*)-3-[1-(Benzyloxycarbonyl)imidazol-4-yl]-3-fluoro-2-methoxypropenoate (7e). Reaction of organostannane **1** (0.44 g, 1.0 mmol) and 1-(benzyloxycarbonyl)-4-iodoimidazole (0.33 g, 1.0 mmol) for 60 min yielded 0.31 g (90%) of **7e** as an oil after chromatography using a 3:7 mixture of ethyl acetate and petroleum ether as the eluent: ^1H NMR ($CDCl_3$) δ 7.83 (s, 1H), 7.63 (s, 1H), 7.20 (s, 5H), 5.21 (s, 2H), 4.05 (q, J = 7.3 Hz, 2H), 3.60 (s, 3H), 1.10 (t, J = 7.3 Hz, 3H); ^{19}F NMR ($CDCl_3$) δ 43.5 (s); MS (EI, *m/z*) 348 (M^+, 17), 305 (54), 259 (8), 91 (63). Anal. Calcd for $C_{17}H_{17}FN_2O_5$: C, 58.62; H, 4.92; N, 8.04. Found: C, 58.26; H, 4.94; N, 7.93.

Ethyl (*Z*)-3-Fluoro-3-(naphth-2-yl)-2-methoxypropenoate (7f). Reaction of organostannane **1** (0.44 g, 1.0 mmol), 2-naphthyl triflate (0.28 g, 1.0 mmol), and LiCl (0.043 g, 1.0 mmol) for 6 h yielded 0.22 g (80%) of **7f** as an oil after chromatography using a 2:8 mixture of ethyl acetate and petroleum ether as the eluent: ^1H NMR ($CDCl_3$) δ 7.28–7.79 (m, 7H), 3.88 (q, J = 7.2 Hz, 2H), 3.69 (s, 3H), 0.81 (t, J = 7.2 Hz, 3H); ^{19}F NMR ($CDCl_3$) δ 24.0 (s); MS (EI, *m/z*) 274 (M^+, 100), 259 (4), 229 (8), 175 (55), 155 (50). Anal. Calcd for $C_{16}H_{15}FO_3$: C, 70.96; H, 5.45. Found: C, 70.86; H, 5.45.

Ethyl (*Z*)-3-(1-Cyclohexenyl)-3-fluoro-2-methoxypropenoate (7g). Reaction of organostannane **1** (0.44 g, 1.0 mmol) and 1-cyclohexenyl triflate (0.23 g, 1.0 mmol) for 10 min yielded 0.19 g (85%) of **7g** as an oil after chromatography using a 2:8 mixture of ethyl acetate and petroleum ether as the eluent: ^1H NMR ($CDCl_3$) δ 5.85 (m, 1H), 4.05 (q, J = 7.1 Hz, 2H), 3.48 (s, 3H), 2.05 (m, 4H), 1.55 (m, 4H), 1.16 (t, J = 7.1 Hz, 3H); ^{19}F ($CDCl_3$) δ 29.0 (s); MS (EI, *m/z*) 228 (M^+, 48), 212 (36), 199 (29), 170 (59), 139 (100), 109 (21). Anal. Calcd for $C_{12}H_{17}FO_3$: C, 63.14; H, 7.51. Found: C, 62.81; H, 7.28.

Diethyl (2*Z*,4*Z*)-3,4-Difluoro-2,5-dimethoxy-2,4-hexadiene-1,6-dioate (8). ^1H NMR ($CDCl_3$) δ 4.17 (q, J = 7.2 Hz, 4H), 3.79 (s, 6H), 1.26 (t, J = 7.2 Hz, 6H); ^{19}F NMR ($CDCl_3$) δ 38.1-(s); MS (EI, *m/z*) 294 (M^+, 14), 275 (23), 221 (100), 193 (72), 165 (31), 149 (130). Anal. Calcd for $C_{12}H_{16}F_2O_6$: C, 48.98; H, 5.48. Found: C, 48.84; H, 5.68.

β-Fluoro-α-oxobenzenepropanoic Acid (10). A solution of the coupling product **7a** (2.3g, 10 mmol) and Me_3SiI (30 mmol) in chloroform (20 mL) was refluxed under nitrogen for 16 h. The reaction mixture was then concentrated *in vacuo*, and the residue was taken up in methanol (20 mL). After being allowed to stand at room temperature for 3 h, the methanolic solution was concentrated and the solid thus obtained was washed with cold chloroform to afford 1.73 g (95%) of acid **10** which was found to be sensitive to oxygen and exist in solution in the enol form: mp 131–133 °C (from Et_2O–hexane); ^1H NMR (CD_3COCD_3) δ 7.90 (m, 2H), 7.45 (m, 3H); ^{19}F NMR (CD_3COCD_3) δ 63.5 (s); MS (EI, *m/z*) 182 (M^+, 1) 122 (42), 105 (100) 77 (67). Anal. Calcd for $C_9H_7FO_3$: C, 59.35; H, 3.87. Found: C, 59.36, H, 3.78.

(*Z*)-3-Fluoro-2-methoxy-3-phenylpropenoic Acid (9). A solution of the coupling product **7a** (2.3g, 10 mmol) and sodium hydroxide (0.80 g, 20 mmol) in 80% aqueous ethanol (20 mL) was stirred at room temperature for 8 h. The reaction mixture was then diluted with water (80 mL) and washed with diethyl ether (2 × 20 mL). After acidification with 1 N HCl solution, the aqueous phase was extracted with diethyl ether (3 × 20 mL). The combined ether extracts were washed with brine and dried over Na_2SO_4. Removal of the solvent gave 1.8 g (90%) of pure **9**: mp 129–131 °C (from Et_2O–hexane); ^1H NMR ($CDCl_3$) δ 9.0 (br.s, 1H), 7.45 (m, 5H), 3.86 (s, 3H); ^{19}F NMR ($CDCl_3$) δ 12.0 (s); MS (EI, *m/z*) 196 (M^+, 100), 181 (7), 165 (7), 125 (37), 105 (52). Anal. Calcd for $C_{10}H_9FO_3$: C, 61.23 H,.4.62. Found: C, 61.32; H, 4.56. A single crystal of **9** for X-ray analysis was obtained by recrystallization from a mixture of diethyl ether and hexane.

***erythro*-β-Fluorophenylalanine (11).** The acid **10** (0.90 g, 5.0 mmol) was dissolved in 25% aqueous ammonia (10 mL), and the solution was mantained at 40 °C for 3 h. The resultant brown solution was cooled to 10 °C, and $NaBH_4$ (0.51 g, 15 mmol) was added. The reaction mixture was then evacuated with a water pump for 20 min while a stream of nitrogen was bubbled in. After an additional 2 h at 30 °C, the reaction was worked up as described in the literature[4a] to give 0.36 g (40%) of compound **11** as white solid: mp 161–162 dec (lit.[4a] mp 168–169 C dec). The spectral data of compound **11** are in accord with those reported in the literature.

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