Palladium(0)/Copper(I)-Cocatalyzed Cross-Coupling of the Zinc Reagent of Ethyl 3-Bromo-3,3-difluoropropionate with Aryl (Alkenyl) Halides: An Efficient Stereoselective Synthesis of *β*-Fluoro-α,*β*-unsaturated Esters

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Ethyl 3-bromo-3, 3-difluoropropionate (**1**) was prepared in an overall yield of 75% from the radical addition of dibromodifluoromethane to ethyl vinyl ether under $Na_2S_2O_4$ initiation, followed by oxidation of the acetal with Caro acid. The treatment of **1** with active zinc dust in anhydrous DMF at room temperature produced the zinc reagent $ZnBrCF_2CH_2CO_2C_2H_5$ (**2**). The cross coupling of the zinc reagent **2** with aryl (alkenyl) halides (R−X) in DMF using Pd(0)−Cu(I) as cocatalyst stereoselectively provided the *β*-fluoro-α,*β*-unsaturated esters ($RCF{=}CHCO_2C_2H_5$ **4**) directly and in moderate yields. An *E*/*Z* ratio ranging from 3:2 to 1:0 was observed. This is the first example that Cu(I) can improve the selectivity of the cross-coupling reaction. Mechanistic studies revealed that zinc reagent **2** underwent stereoselective elimination to produce (Z)-1-fluoro-2-(ethoxycarbonyl)-ethenylzinc reagent **6**, and then the cross-coupling of **6** with aryl(alkenyl) halides under palladium-(0) catalysis afforded the *β*-fluoro-α,*β*-unsaturated esters **4**.

Introduction

Monofluorine-containing organic molecules have been received considerable attention due to the high electron negativity and small atomic size that fluorine may confer to biologically active molecules, and great effort has been made to explore practical and effective methods for the synthesis of selective monofluorinated organic compounds.[1] Various fluorinating agents have been used to for the incorporation fluorine into a molecule;[2] however, most of these reagents are not only expensive and difficult to prepare, but there are also limitation to functional groups compatible with the reactive reagents. Another approach is to synthesize fluorine-containing intermediates and to use them as synthons. This is becoming the main trend for the construction of fluorinated compounds. Among these, monofluorinated acrylic esters, in particular, are interesting synthons due to their chemical versatility and potential for further elaboration into fluorinated analogues of natural products. Monofluoroacrylic esters of the type $CFH{=}CHCO_2R^3$ and $CH_2{=}CFCO_2R^4$ have been prepared by multistep sequences in which the α,*β*-unsaturated double bonds were introduced late in the synthesis by *β*-elimination reactions. α-Fluoro-α,*β*-unsaturated esters ($RCH{=}CFCO_2C_2H_5$), mainly prepared by the reaction of lithium triethylphosphonofluoroacetate with aldehydes,[5] have been used as building blocks for the preparation of the monofluorinated compounds of biological interest.[6] However, the synthetic application of *β*-fluoro-α,*β*-unsaturated esters ($RCF{=}CHCO_2C_2H_5$) is far less developed, because few reports have been published on the general and practical methods for the preparation of *β*-fluoro-α,*β*-unsaturated esters.[7] In this article, we document a novel,

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(1) (a) Welch, J. T.; Eswarakrishnan, S. *Fluorine Bioorganic Chemistry*; John Wiley & Sons: New York, 1991. (b) Filler, R., Kobayashi. Y., Yagupolski, L. M., Eds. *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*; Elsevier: Amsterdam, 1993. (c) Hudlicky, M., Pavlath, A. E., Eds. *Chemistry of Organic Fluorine Compounds II. A Critical Review*; American Chemical Society: Washington, D. C., 1995. (d) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123.

(2) (a) German, L., Zemskov, S., Eds. *New Fluorinating Agents in Organic Chemistry*; Springer-Verlag: Heidelberg, New York, 1989. (b) Lal, G. S.; Pez, G. P.; Syvret, R. G. *Chem. Rev.* **1996**, *96*, 1737. (c) Okonya, J. F.; Johnson, M. C.; Hoffman, R. V. *J. Org. Chem.* **1998**, *63*, 6409. (d) Lal, G. S.; Pez, G. P.; Pesaresi, R. J.; Prozonic, F. M. *Chem. Commun.* **1999**, 215.

(3) (a) Molines, H.; Wakselman, C. *J. Fluorine Chem.* **1984**, *25*, 447. (b) Molines, H.; Wakselman, C. *J. Fluorine Chem.* **1989**, *45*, 155. (c) Nguyen, T.; Leroy, J.; Wakselman, C. *J. Org. Chem.* **1993**, *58*, 3772. (d) Krishnan, G.; Sampson, P. *Tetrahedron Lett.* **1990**, *31*, 5609.

(4) (a) Tolman, V.; Spronglova, P. *Collect. Czech. Chem. Commun.* **1983**, *48*, 319. (b) Boguslavskaya, L. S.; Chuvatkin, N. N. *J. Fluorine Chem.* **1991**, *54*, 138. (c) Molines, H.; Nguyen, T.; Wakselman, C. *Synthesis* **1985**, 755. (d) Nguyen, T.; Molines, H.; Wakselman, C. *Synth. Commun.* **1985**, *15*, 925. (e) Gassen, K. R.; Bielefeldt, D.; Marhold, A.; Andres, P. *J. Fluorine Chem.* **1991**, *55*, 149. (f) Dapperheld, S.; Heumuller, R.; Ulmschneider, D. *J. Fluorine Chem.* **1991**, *54*, 74.

(5) (a) Pawson, B. A.; Chan, K. K.; Denoble, J.; Han, R. L.; Piermattie, V.; Specian, A. C.; Srisethnil, S. *J. Med. Chem.* **1979**, *22*, 1059. (b) Etemad-Moghadam, G.; Deyden-Penne, J. *Bull. Soc. Chim. Fr.* **1985**, 448. (c) Elkik, E.; Francesch, C. *Bull. Soc. Chim. Fr.* **1986**, 423.

(6) (a) Liu, R. S. H.; Matsumoto, H.; Asato, A. E.; Denny, M.; Schichida, Y.; Yoshizawa, T.; Dahlquist, F. W. *J. Am. Chem. Soc.* **1981**, *103*, 7195. (b) Camps, F.; Coll, J.; Fabrias, G.; Guerrero, A. *Tetrahedron* **1984**, *40*, 2871. (c) Patrick, T. B.; Lanahan, M. V.; Yang, C.; Walker, J. K.; Hutchinson, C. L.; Neal. B. E. *J. Org. Chem.* **1994**, *59*, 1210. (d) Patrick, T. B.; Neal, B. E. *Synlett.* **1996**, 1227. (e) Kim, B. T.; Min, Y. K.; Asami, T.; Park, N. K.; Kwon, O. Y.; Cho, K. Y.; Yoshida, S. *Tetrahedron Lett.* **1997**, *38*, 1797. (f) Robustell, B. J.; Abe, I.; Prestwich, G. D. *Tetrahedron Lett.* **1998**, *39*, 9385.

(7) To our knowledge, only ethyl 3-phenyl-3-fluoro-2-propenoate was prepared by three different procedures, but the yield or the *E*/*Z* ratio of the product is not high. (a) Fluoriantion of alkenylstannanes with silver triflate and xenon difluoride: Tius, M. A.; Kawakami, J. K. *Synlett* **1993**, 207. (b) Monohydrofluorination of electrophilic alkynes with HF: Gorgues, A.; Stephan, D.; Cousseau, J. *J. Chem. Soc., Chem. Commun.* **1989**, 1493. (c) Carboxylation of 2,2-difluorovinyllithium: Gillet, J. P.; Sauvetre, R.; Normant, J. F. *Synthesis* **1982**, 297. (d) When our manuscript was examined, the stereoselective synthesis of (*E*)-*β*-fluoro-α,*β*-unsaturated esters by carbonylation of (*E*)-2-fluoro-1-iodo-1-alkenyliodonium salts had been reported: Hara, S.; Yamamoto, K.; Yoshida, M.; Fukuhara, T.; Yoneda, N. *Tetrahedron Lett.* **1999**, *40*, 7815.

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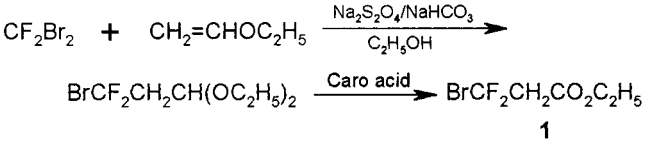
Scheme 1



general route to β-fluoro-α,β-unsaturated esters based on palladium(0)/copper(I)-cocatalyzed cross-coupling of the zinc reagent of ethyl 3-bromo-3,3-difluoropropionate with aryl (alkenyl) halides.

Results and Discussion

Synthesis of Ethyl 3-Bromo-3,3-difluoropropionate 1. Wakselman had reported[8] the preparation of ethyl 3-bromo-3,3-difluoropropionate **1** through the condensation of dibromodifluoromethane and ethyl vinyl ether under ultraviolet irradiation, subsequent treatment with ethanol, and then oxidation using Caro acid or *m*-chloroperoxybenzoic acid. However, the overall yield (three steps) is only 49%, and the first step is not convenient due to the difficulty in handling reactive and volatile substrates (the boiling points of dibromodifluoromethane and ethyl vinyl ether are 22 °C and 23 °C, respectively). We developed a convenient and practical synthesis of **1** in 75% overall yield (two steps) from the radical addition of dibromodifluoromethane to ethyl vinyl ether under $Na_2S_2O_4$ initiation[9] in ethanol, followed by oxidation of the acetal with Caro acid (Scheme 1). The radical addition is initiated by radical anion of sulfur dioxide ($SO_2^{\bullet-}$) produced by decomposition of $Na_2S_2O_4$. The transfer of a single electron to CF_2Br_2 from $SO_2^{\bullet-}$ gave $BrCF_2^{\bullet}$ and Br^-, and then $BrCF_2^{\bullet}$ added to ethyl vinyl ether to form intermediate $BrCF_2CH_2CH^{\bullet}OC_2H_5$, which abstracted a bromine from CF_2Br_2 to produce $BrCF_2CH_2CHBrOC_2H_5$. The reaction of $BrCF_2CH_2CHBrOC_2H_5$ with ethanol produced acetal.

Preparation of the Zinc Reagent of Ethyl 3-Bromo-3,3-difluoropropionate 2. Only one example of the synthetic application of **1** has been reported, in which the product of dehydrobromination of **1** acted as a dienophile in a Diels−Alder reaction to afford monofluorinated cyclohexadienol.[8] As a very useful fluorine-containing intermediate, further utilization of **1** would be a worthwhile undertaking. Since organozinc derivatives have been found to be increasingly useful reagents for carrying out organic transformations[10] and many fluorinated organozinc reagents provide a useful method for the introduction of fluorine to organic molecules,[11] we attempted to prepare the zinc reagent of **1**. Initially, the treatment of **1** with active zinc dust in anhydrous THF was performed. Though the exothermic reaction occurred at room temperature, ^{19}F NMR analysis of the reaction mixture revealed that the starting material **1** had disappeared; however, new peaks mainly included a small amount of zinc reagent **2** and much $HCF_2CH_2CO_2C_2H_5$ (Scheme 2). As such, it can be concluded first that zinc reagent **2** had formed, but it was not stable in THF, and

Scheme 2

that it would be necessary to find a solvent which can improve the stability of the zinc reagent **2**. Fortunately, when anhydrous DMF was used instead of THF as the solvent, an exothermic reaction occurred spontaneously at room temperature. ^{19}F NMR monitoring of the reaction mixture revealed that compound **1** had disappeared, and only a new triplet appeared at +16.5 ppm (J = 24.0 Hz)[12] corresponding to the zinc reagent **2**. Furthermore, the zinc reagent **2** in DMF is thermally stable in the range of room temperature to 80 °C, and in the absence of air or moisture showing no sign of decomposition.

Preparation of β-Fluoro-α,β-unsaturated esters 4. With the zinc reagent **2** in hand, we were interested in exploring the feasibility of using **2** in cross-coupling reactions. Although the palladium- or nickel-catalyzed cross-coupling between alkyl organozinc reagent and aryl halides is well-known,[13] the application of perfluorinated or fluorinated alkylzinc reagent as partner in cross-coupling reactions has rarely appeared.[14] When aryl (alkenyl) halides (1.0 equiv) were treated with zinc reagent **2** (1.5−2.0 equiv) in DMF under argon at 70 °C using $Pd(PPh_3)_4$ (5 mol %) and CuI (20 mol %) as cocatalyst, the cross-coupling reaction occurred smoothly, affording not the expected product **3**, but the β-fluoro-α,β-unsaturated esters **4** directly in moderate yields (Scheme 3 and Table 1). Compounds (*E*)-**4** and (*Z*)-**4** can be separated by flash chromatography. The configuration of double bond in **4** was assigned with the coupling constant of the vinyl proton and fluorine ((*E*)-**4** J_{H-F} = 16.0−25.0 Hz; (*Z*)-**4** J_{H-F} = 33.0−35.0 Hz).[15]

The following points derived from the cross-coupling reaction are noteworthy: (1) No appreciable reactions observed in the presence of CuI alone without $Pd(PPh_3)_4$. (2) Although the reaction could proceed using 5 mol % $Pd(PPh_3)_4$ alone as the catalyst, the *E*/*Z* selectivity is poor, only a 1:1 *E*/*Z* ratio was obtained. When 20 mol % CuI was added, the *E*/*Z* selectivity of product was greatly improved. For example, when iodobenzene was used as the reaction partner, the *E*/*Z* ratio of product **4** was changed from 1:1 (only 5 mol % $Pd(PPh_3)_4$ as catalyst) to 5:1 (5 mol % $Pd(PPh_3)_4$ and 20 mol % CuI as cocatalyst). For some halides, only *E* isomers were formed (entries 2, 4, 8, 12, 13, and 19). Use of 1.0 equiv of CuI offered no advantage over 20 mol % CuI. CuBr and CuCl both possessed similar effects on improving the *E*/*Z* selectivity of this reaction. Usually, addition of Cu(I) halide accelerates the rate of cross-coupling[16] but does not effect the *E*/*Z* selectivity. To the best of our knowledge, this is the first example that CuI can improve the selectivity of a

(8) Leroy, J.; Molines, H.; Wakselman, C. *J. Org. Chem.* **1987**, *52*, 290

(9) Huang, W. Y.; Lu, L.: Zhang, Y. F. *Chinese J. Chem.* **1990**, *3*, 281.

(10) Charette, A. B.; Beauchemin, A.; Marcoux, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 5114 and references therein.

(11) (a) Burton, D. J.; Yang, Z.-Y.; Morken, D. A. *Tetrahedron* **1994**, *50*, 2993. (b) Burton, D. J.; Yang, Z.-Y. *Tetrahedron* **1992**, *48*, 189.

(12) ^{19}F NMR spectra (56.4 Hz) were recorded on Varian EM-360L instrument using CF_3CO_2H as an external standard, upfield positive.

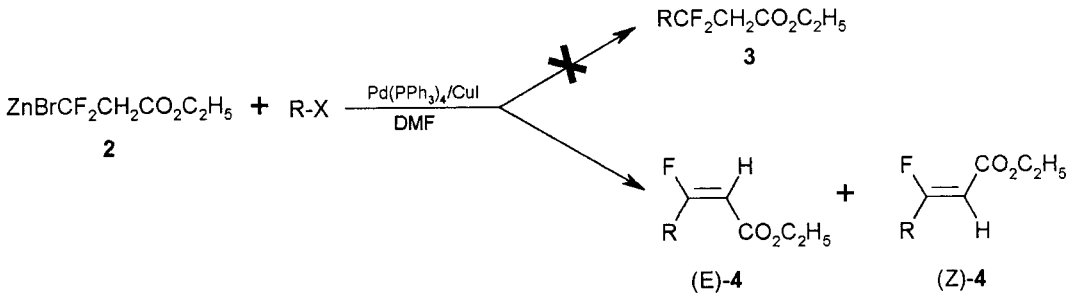
(13) (a) Giovannini, R.; Knochel, P. *J. Am. Chem. Soc.* **1998**, *120*, 11186. (b) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117. (c) Erdik, E. *Tetrahedron* **1992**, *48*, 9577.

(14) The cross-coupling of perfluoroalkylzinc iodides with alkenyl bromides: Kitazume, T.; Ishikawa, N. *J. Am. Chem. Soc.* **1985**, *107*, 5186.

(15) (a) Xiang, J.; Jiang, W. l.; Gong, J. C.; Fuchs, P. L. *J. Am. Chem. Soc.* **1997**, *119*, 4123. (b) Fields, R. *J. Fluorine Chem.* **1986**, *33*, 288.

(16) (a) Piers, E.; Romero, M. A. *J. Am. Chem. Soc.* **1996**, *118*, 1215. (b) Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748. (c) Han, X.; Stoltz, B. M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 7600 and references therein.

Scheme 3



cross-coupling reaction. (3) Both aryl bromides and aryl iodides can be effectively used for the coupling reaction; however, for aryl bromides, the reaction was somewhat sluggish and required a higher temperature and longer time. This difference of reactivity has made the chemoselective coupling possible with 4-bromoiodobenzene (entry 2). In addition, aryl triflates (entry 15) are also suitable substrates for the synthesis of β-fluoro-α,β-unsaturated esters. (4) The coupling reactions of vinyl halides (entries 16, 17) with zinc reagent **2** afforded the corresponding monofluorinated 1,3-dienes in good yields and high selectivities. Because conjugated dienes are important intermediates in organic synthesis due to a variety of aliphatic natural products containing the 1,3-diene unit,[17] these monofluorinated dienes should be very valuable in the synthesis of fluorinated analogues of natural products. (5) Because oligomers with 5-(3-aminopropyn-1-yl)-deoxyuridine were considered as potential antisense molecules,[18] and 5-(3-aminopropenyl)deoxyuridine triphosphate was suitable for the enzymatic synthesis of combinatorial DNA libraries,[19] 5-(2-(ethoxycarbonyl)-1-fluoro-1-ethenyl)deoxyuridine, prepared from the coupling reaction of iodo-nucleoside with zinc reagent (entry 19), should be useful in the preparation of fluorinated anticancer and antiviral agents.

Mechanism for the Formation of β-Fluoro-α,β-unsaturated Esters in the Presence of Pd(PPh$_3$)$_4$ without CuI. To explain the formation of unexpected compound **4** in the reaction of zinc reagent **2** with aryl (alkenyl) halides, the investigation of reaction mechanism was undertaken. A mixture of zinc reagent **2** (2.0 equiv, previously prepared clear solution in DMF), iodobenzene (1.0 equiv), and Pd(PPh$_3$)$_4$ (5 mol %) was heated at 70 °C in an NMR tube. ^{19}F NMR monitoring of the reaction mixture every 10 min revealed that the formation of **4** (*E*/*Z*: 1:1) was accompanied by the appearance of $HCF_2CH_2CO_2C_2H_5$; the amount of **4** and $HCF_2CH_2CO_2C_2H_5$ was equivalent, and ^{19}F NMR spectrum displayed a new triplet near the peak of zinc reagent corresponding possibly to $C_6H_5CF_2CH_2CO_2C_2H_5$. As the reaction time was prolonged, the new triplet disappeared quickly. Based upon these experimental results, the proposed mechanism for the formation of β-fluoro-α,β-unsaturated esters in the presence of Pd(PPh$_3$)$_4$ without CuI is outlined in Scheme 4. The cross-coupling of zinc reagent **2** with aryl (alkenyl) halides under palladium(0) catalysis formed compound $RCF_2CH_2CO_2C_2H_5$, which underwent elimination simultaneously to afford the β-fluoro-α,β-unsaturated esters **4**. Zinc reagent **2** acted as base and was converted to $HCF_2CH_2CO_2C_2H_5$ in the elimination reaction. Thus, zinc reagent **2** was used as both cross-coupling partner and base in the formation of β-fluoro-α,β-unsaturated esters **4**.

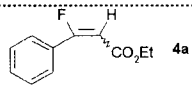
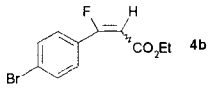
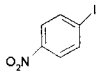
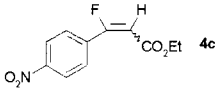
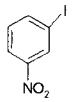
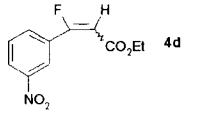
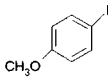
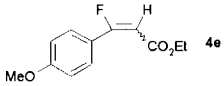
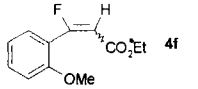
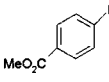
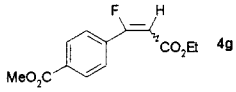
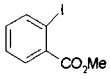
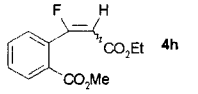
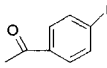
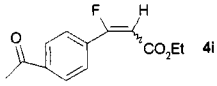
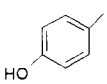
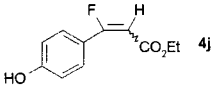
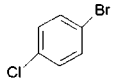
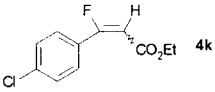
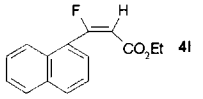
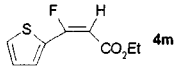
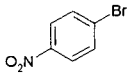
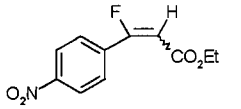
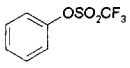
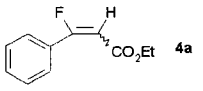
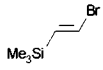
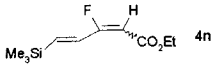
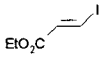
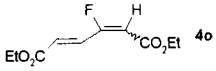
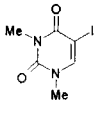
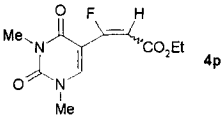
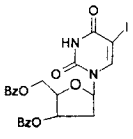
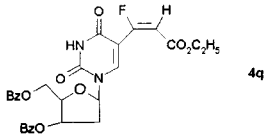
Mechanism for the Selective Formation of (*E*)-β-Fluoro-α,β-unsaturated Esters in the Presence of Both Pd(PPh$_3$)$_4$ and CuI. Pd(PPh$_3$)$_4$ was necessary for the formation of β-fluoro-α,β-unsaturated esters, and addition of CuI to the reaction mixture improved the *E*/*Z* selectivity. Initially experiments were performed to determine if CuI was operative in the double bond isomerization of β-fluoro-α,β-unsaturated esters. In fact, when CuI was added to the solution of the mixture of 1:1 *E*/*Z* β-fluoro-α,β-unsaturated esters in DMF and stirred at 80 °C for 4 h, the *E*/*Z* ratio did not change anymore. This result implied that CuI with Pd(PPh$_3$)$_4$ together took part in the selective formation of β-fluoro-α,β-unsaturated esters; a number of reactions were done to explain how this affects the selectivity. A mixture of zinc reagent **2** (1.5 equiv, previously prepared clear solution in DMF), iodobenzene (1.0 equiv), Pd(PPh$_3$)$_4$ (5 mol %), and CuI (20 mol %) was heated at 70 °C in NMR tube. ^{19}F NMR monitoring of the reaction mixture every 10 min revealed that the zinc reagent **2** disappeared in 1 h and **4** (*E*/*Z*: 5:1) was formed. Furthermore, the ^{19}F NMR spectrum displayed a new doublet of doublets at +36.3 ppm (J = 80.0, 16.0 Hz) corresponding to compound **5**. The appearance of **5** prompted the study of the mechanism of selective formation of (*E*)-β-fluoro-α,β-unsaturated esters. Thus, the following experiments were performed to probe the path of the formation of **5** and to assign the structure of compound **5**. Treatment of zinc reagent **2** with either 5 mol % of Pd(PPh$_3$)$_4$ or 1.0 equiv of iodobenzene at 70 °C for 2 h did not produce compound **5**, and zinc reagent **2** was unchanged as determined by ^{19}F NMR. However, when a mixture of zinc reagent **2** and 20 mol % of CuI was stirred at 70 °C for only 10 min, the ^{19}F NMR spectrum showed that zinc reagent **2** was totally converted to compound **5**. Then the reaction mixture was analyzed by GC−MS and GC−IR. The infrared spectra of compound **5** showed carbonyl stretching at 1750 cm^{-1} and strong absorption at 1666 cm^{-1}, characteristic of a double bond. The MS of compound **5** showed the molecular ion peak at *m*/*z* 118. Based on these data and the chemical shift and coupling constants in the ^{19}F NMR spectrum (+36.3 ppm, dd, J = 80.0, 16.0 Hz), the structure of compound **5** was assigned to ethyl (*E*)-3-fluoro-2-propenoate. This structure was further proven by comparison with the chemical shift and coupling

(17) (a) Trost, B. M.; Lautens, M.; Peterson, B. *Tetrahedron Lett.* **1983**, *24*, 4525. (b) Sakai, T.; Seko, T.; Tsuji, A.; Vtaka, M.; Takeda, A. *J. Org. Chem.* **1982**, *47*, 1101. (c) Cha, J. K.; Oh, T. *Curr. Org. Chem.* **1998**, *2*, 217. (d) Smith, A. B., III.; Ott, G. R. *J. Am. Chem. Soc.* **1998**, *120*, 3935.

(18) Heystek, L. E.; Zhou, H. Q.; Dande, P.; Gold, B. *J. Am. Chem. Soc.* **1998**, *120*, 12165.

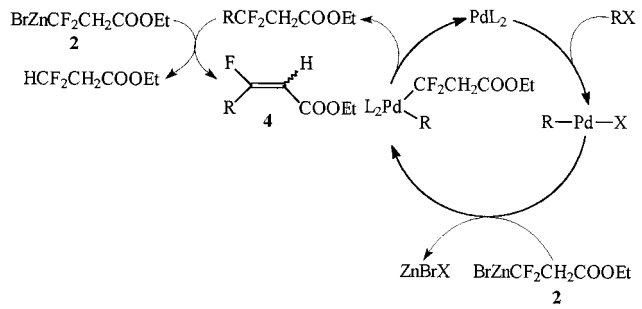
(19) Sakthivel, K.; Barbas, C. F., III. *Angew. Chem., Int. Ed.* **1998**, *37*, 2872.

Table 1. Palladium/Copper-Cocatalyzed Cross-Coupling of 2 with Halides

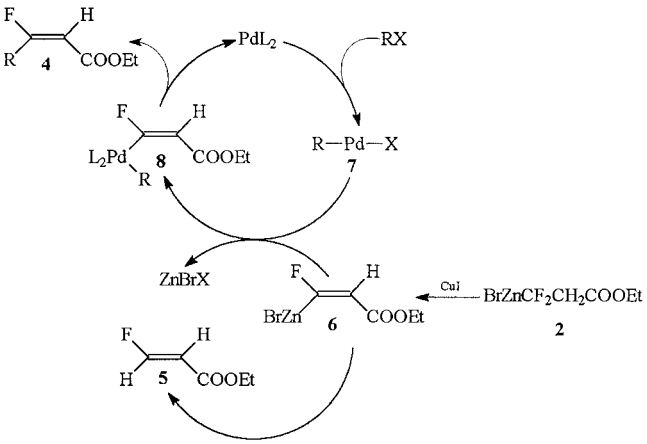
Entry	R-X	Temp(°C)/ Time (h)	Product	Yield (%)[a]	E/Z[b]
1		70/2	 4a	50	5:1
2		70/8	 4b	48	only E
3		70/1.5	 4c	77	8:1
4		70/8	 4d	65	only E
5		70/4	 4e	76	3:2
6		70/7	 4f	72	8:1
7		70/6	 4g	75	8:1
8		70/8	 4h	73	only E
9		70/8	 4i	78	4:1
10		70/3	 4j	69	4:1
11		80/12	 4k	56	8:1
12		70/18	 4l	47	only E
13		70/5	 4m	78	only E
14		75/8	 4c	73	8:1
15		75/3	 4a	47	3:1
16		70/5	 4n	78	6:1
17		70/3	 4o	76	8:1
18		70/12	 4p	65	4:1
19		70/18	 4q	41	only E

[a] Total yield of two isolated isomers based on organic halides. [b] Determined by ^{19}F NMR.

Scheme 4



Scheme 5



constants of isopropyl (*E*)-3-fluoro-2-propenoate in the ^{19}F NMR spectrum (+35.0 ppm, dd, $J = 80.0$, 15.0 Hz).[3] The formation of compound **5** indicated zinc reagent **2** was dehydrofluorinated stereoselectively to produce (*Z*)-1-fluoro-2-(ethoxycarbonyl)ethenylzinc reagent **6** in the presence of CuI, though **6** was not detected by ^{19}F NMR monitoring. There remains the question of what is the hydrogen source that converts **6** to **5**? When zinc reagent **2** in d_7-DMF (d_7-DMF was used instead of DMF as the solvent for the preparation of **2**) was treated with 20 mol % of CuI at 70 °C for 10 min, zinc reagent **2** was also totally converted to compound **5**. This suggests that **6** reacted with HF rather than abstracting a hydrogen from the solvent to form **5**. From the above experimental results, the proposed mechanism for the selective formation of (E)-*β*-fluoro-α,*β*-unsaturated esters in the presence of both $Pd(PPh_3)_4$ and CuI is outlined in Scheme 5. Oxidative addition of the $Pd(0)L_2$ complex to the aryl (alkenyl) halide afforded **7**. Substitution of the halide with **6** afforded **8**. Reductive elimination of **8** gave (*E*)-*β*-fluoro-α,*β*-unsaturated ester **4** with regeneration of the active catalyst. The formation of **6** plays role in the stereoselective synthesis of (*E*)-*β*-fluoro-α,*β*-unsaturated ester.

The following points derived from the reaction mechanism for the cross-coupling reaction in the presence of both $Pd(PPh_3)_4$ and CuI are noteworthy: (1) some aryl (alkenyl) halides proceed by both pathways shown in Scheme 5 and Scheme 4, which afforded the mixture of *E*/*Z* (*E*/*Z*: from 3:2 to 8:1) compound **4**. The others underwent the sole pathway outlined in Scheme 5, which produced compound (*E*)-**4** exclusively. (2) At present, the mechanistic pathway of totally selective conversion of **2** using 20 mol % of CuI to the vinyl zinc reagent **6** remains obscure. (3) As outlined in Scheme 5, CuI was used as base for the dehydrofluorination of **2** to give **6**; thus, we reasoned that the Lewis base should produce similar effects in this coupling reaction. Indeed, treatment of zinc reagent **2** (2.0 equiv, previously prepared clear solution in DMF) with iodobenzene (1.0 equiv), $Pd(PPh_3)_4$ (5 mol %), and triethylamine (20 mol %) at 70 °C for 8 h produced the (*E*)-**4** exclusively. However, triethylamine was used instead of CuI as a base for other aryl halides (*p*-HOC_6H_5I and p-$MeCOC_6H_5I$ were tested), and for these, the coupling reaction was unsuccessful.

Summary

In conclusion, this paper describes an efficient general route to ethyl 3-bromo-3, 3-difluoropropionate (**1**). We have demonstrated that the palladium(0)/copper(I)-co-catalyzed cross-coupling of the zinc reagent of ethyl 3-bromo-3,3-difluoropropionate with aryl(alkenyl) halides allows preparation of *β*-fluoro-α,*β*-unsaturated esters (**4**). Studies on synthetic applications to produce mono-fluorinated compounds of biological interest is currently underway.

Experimental Section

The preparation of *β*-fluoro-α,*β*-unsaturated esters was performed under an argon atmosphere in flame-dried glassware. DMF was freshly distilled from CaH_2. CuI was purified by a literature procedure.[20] Commercial zinc powder was activated by a standard method.[21]

Preparation of Ethyl 3-Bromo-3,3-difluoropropionate (1). A 250 mL, three-necked, round-bottomed flask was equipped with an efficient magnetic stirring bar, a thermometer, and a dry ice−acetone condenser. To this flask were added dibromodifluoromethane (31.5 g, 150 mmol), ethyl vinyl ether (7.2 g, 100 mmol), $Na_2S_2O_4$ (26.1 g, 150 mmol), $NaHCO_3$ (25.2 g, 300 mmol), and ethanol (40 mL). After the mixture was stirred at 60 °C for 2 h, the reaction mixture was poured into water (30 mL) and extracted with diethyl ether (3 × 20 mL). After evaporation of the solvent, the residue was distilled under reduced pressure gave 20 g of acetal (81% yield) as a colorless liquid (bp 64 °C/4 mmHg). The caro acid, prepared from 85% sulfuric acid (144 g) and ammonium persulfate (114 g), was added at 5−10 °C for 30 min to a vigorously stirred solution of the above prepared acetal (24.7 g, 100 mmol) in ethanol (200 mL). The reaction mixture was stirred for 24 h at room temperature. The reaction mixture was poured into ice water (600 mL), and extracted with diethyl ether (3 × 250 mL). After evaporation of the solvent, the residue was distilled under reduced pressure gave 20 g of **1** (91% yield) as a colorless liquid (bp 58−60 °C/20 mmHg). ^1H NMR ($CDCl_3$) δ 4.20(2H, q, $J = 7.0$ Hz), 3.42 (2H, t, $J = 16.0$ Hz), 1.28 (3H, t, $J = 7.0$ Hz); ^{19}F NMR ($CDCl_3$) δ −34 (s); IR (cm^{-1}) 1750, 1220.

General Procedure for the Preparation of *β*-Fluoro-α,*β*-unsaturated Esters 4. Freshly activated zinc powder (104 mg, 1.6 mmol) was added to the stirred solution of **1** (325 mg, 1.5 mmol) in DMF (10 mL) at room temperature. After the heat evolution had ceased, iodobenzene (200 mg, 1.0 mmol), $Pd(PPh_3)_4$ (58 mg, 0.05 mmol), and purified CuI (22 mg, 0.2 mmol) were added to the zinc reagent solution. The reaction mixture was heated to 70 °C and stirred for 2 h, and then ethyl acetate (10 mL) was added to the reaction mixture. The mixture was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel, eluting with a solution of hexanes−ethyl acetate (100:1) to give the separated *E*/*Z* isomers of ethyl 3-phenyl-3-fluoro-2-propenoate (97 mg, 50% yield). The *E*-isomer was less polar.

(20) Kauffman, G. B.; Fang, L. Y. *Inorg. Synth.* **1983**, *22*, 101.
(21) Tsuda, K.; Ohki, E.; Nozoe, S. *J. Org. Chem.* **1963**, *28*, 783.

Ethyl 3-Phenyl-3-fluoro-2-propenoate (4a). (*E*)-Isomer: ^{1}H NMR (CD_3COCD_3) **δ** 7.78−7.49 (5H, m), 5.93 (1H, d, J = 20.8 Hz), 4.12 (2H, q, J = 7.0 Hz), 1.18 (3H, t, J = 7.0 Hz); ^{19}F NMR (CCl_4) **δ** 0.3 (d, J = 20.8 Hz); MS (m/z) 194 (M^+, 18.21), 149 (100.00); IR (cm^{-1}) 1726, 1659. Anal. Calcd for $C_{11}H_{11}FO_2$: C, 68.04; H, 5.67; F, 9.79. Found: C, 68.33; H, 5.83; F, 9.80. **(*Z*)-Isomer**: ^{1}H NMR (CD_3COCD_3) **δ** 7.81−7.78 (2H, m), 7.58−7.53 (3H, m), 6.12 (1H, d, J = 34.4 Hz), 4.21 (2H, q, J = 7.0 Hz), 1.29 (3H, t, J = 7.0 Hz); ^{19}F NMR (CCl_4) **δ** 17.6 (d, J = 34.4 Hz); MS (m/z) 194 (M^+, 20.24), 149 (100.00).

(*E*)-Ethyl 3-(4-bromophenyl)-3-fluoro-2-propenoate (4b): ^{1}H NMR (CD_3COCD_3) δ 7.70 (4H, s), 5.99 (1H, d, J = 20.8 Hz), 4.11 (2H, q, J = 7.0 Hz), 1.18 (3H, t, J = 7.0 Hz); ^{19}F NMR (CCl_4) δ 1.3 (d, J = 20.8 Hz); MS (m/z) 273 (M^+, 4.86), 227 (100.00); IR (cm^{-1}) 1728, 1656; HRMS calcd for $C_{11}H_{10}Br^{79}FO_2$: 271.9849, found: 271.9847.

Ethyl 3-(4-Nitrophenyl)-3-fluoro-2-propenoate (4c). (*E*)-Isomer: ^{1}H NMR (CD_3COCD_3) δ 8.34 (2H, d, J = 8.3 Hz), 8.00 (2H, d, J = 8.4 Hz), 6.12 (1H, d, J = 20.2 Hz), 4.12 (2H, q, J = 7.0 Hz), 1.17 (3H, t, J = 7.0 Hz); ^{19}F NMR (CCl_4) δ 1.6 (d, J = 20.2 Hz); MS (m/z) 240 (M^++1, 0.68), 239 (M^+, 2.92), 194 (100.00); IR (cm^{-1}) 1724, 1664. Anal. Calcd for $C_{11}H_{10}FNO_4$: C, 55.23; H, 4.18; N, 5.86. Found: C, 55.44; H, 4.24; N, 5.80. **(*Z*)-Isomer:** ^{1}H NMR (CCl_4) δ 8.27 (2H, d, J = 8.0 Hz), 7.84 (2H, d, J = 8.0 Hz), 5.93 (1H, d, J = 33.0 Hz), 4.23 (2H, q, J = 7.0 Hz), 1.37 (3H, t, J = 7.0 Hz); ^{19}F NMR (CCl_4) δ 19.0 (d, J = 33.0 Hz); MS (m/z) 240 (M^+ + 1, 7.03), 239 (M^+, 36.10), 194 (100.00).

(*E*)-Ethyl 3-(3-nitrophenyl)-3-fluoro-2-propenoate (4d): ^{1}H NMR (CD_3COCD_3) **δ** 8.62 (1H, s), 8.43−8.40 (1H, m), 8.17−8.14 (1H, m), 7.83 (1H, t, J = 8.4 Hz), 6.11 (1H, d, J = 20.3 Hz), 4.13 (2H, q, J = 7.0 Hz), 1.18 (3H, t, J = 7.0 Hz); ^{19}F NMR (CCl_4) **δ** 2.3 (d, J = 20.3 Hz); MS (m/z) 239 (M^+, 2.85), 194 (100.00); IR (cm^{-1}) 1724, 1662. Anal. Calcd for $C_{11}H_{10}FNO_4$: C, 55.23; H, 4.18; N, 5.86. Found: C, 55.02; H, 4.21; N, 5.84.

Ethyl 3-(4-Methoxyphenyl)-3-fluoro-2-propenoate (4e). (*E*)-Isomer: ^{1}H NMR (CCl_4) δ 7.80 (2H, d, J = 9.0 Hz), 6.90 (2H, d, J = 9.0 Hz), 5.73 (1H, d, J = 21.0 Hz), 4.13 (2H, q, J = 7.0 Hz), 3.86 (3H, s), 1.30 (3H, t, J = 7.0 Hz); ^{19}F NMR (CCl_4) δ 0.7 (d, J = 21.0 Hz); MS (m/z) 224 (M^+, 62.01), 179 (100.00); IR (cm^{-1}) 1723, 1630. Anal. Calcd for $C_{12}H_{13}FO_3$: C, 64.29; H, 5.80. Found: C, 64.40; H, 5.79. **(*Z*)-Isomer:** ^{1}H NMR (CCl_4) δ 7.5 (2H, d, J = 9.0 Hz), 6.8 (2H, d, J = 9.0 Hz), 5.62 (1H, d, J = 33.0 Hz), 4.1 (2H, q, J = 7.0 Hz), 3.8 (3H, s), 1.3 (3H, t, J = 7.0 Hz); ^{19}F NMR (CCl_4) δ 17.6 (d, J = 33.0 Hz).

(*E*)-Ethyl 3-(2-methoxyphenyl)-3-fluoro-2-propenoate (4f): ^{1}H NMR (CD_3COCD_3) **δ** 7.51−7.45 (1H, m), 7.38−7.34 (1H, m), 7.10 (1H, d, J = 8.5 Hz), 7.04−6.98 (1H, m), 5.90 (1H, d, J = 17.0 Hz), 4.00 (2H, q, J = 7.1 Hz), 3.85 (3H, s), 1.07 (3H, t, J = 7.1 Hz); ^{19}F NMR (CCl_4) **δ** −3.7 (d, J = 17.0 Hz); MS (m/z) 224 (M^+, 24.61), 193 (100.00); IR (cm^{-1}) 1729, 1670. Anal. Calcd for $C_{12}H_{13}FO_3$: C, 64.29; H, 5.80. Found: C, 63.90; H, 5.90.

Methyl 4-(2-(Ethoxycarbonyl)-1-fluoro-1-ethenyl)benzoate (4g). (*E*)-Isomer: ^{1}H NMR (CD_3COCD_3) δ 8.09 (2H, d, J = 8.3 Hz), 7.84 (2H, d, J = 8.3 Hz), 6.03 (1H, d, J = 20.6 Hz), 4.12 (2H, q, J = 7.1 Hz), 3.91 (3H, s), 1.17 (3H, t, J = 7.1 Hz); ^{19}F NMR (CCl_4) δ 0.6 (d, J = 20.6 Hz); MS (m/z) 252 (M^+, 24.44), 207 (100); IR (cm^{-1}) 1728, 1649. Anal. Calcd for $C_{13}H_{13}FO_4$: C, 61.90; H, 5.16. Found: C, 61.76; H, 5.28. **(*Z*)-Isomer:** ^{1}H NMR (CCl_4) δ 7.90 (2H, d, J = 9.0 Hz), 7.60 (2H, d, J = 9.0 Hz), 5.80 (1H, d, J = 33.0 Hz), 4.16 (2H, q, J = 7.0 Hz), 3.86 (3H, S), 1.26 (3H, t, J = 7.0 Hz); ^{19}F NMR (CCl_4) δ 18.3 (d, J = 33.0 Hz); MS (m/z) 252 (M^+, 21.27), 207 (100.00).

(*E*)-Methyl 2-(2-(ethoxycarbonyl)-1-fluoro-1-ethenyl)-benzoate (4h): ^{1}H NMR (CD_3COCD_3) δ 8.05−8.03 (1H, m), 771−7.65 (2H, m), 7.57−7.54 (1H, m), 5.91 (1H, d, J = 17.2 Hz), 3.95 (2H, q, J = 7.1 Hz), 3.85 (3H, s), 1.03 (3H, t, J = 7.2 Hz); ^{19}F NMR (CCl_4) δ −10.0 (d, J = 17.2 Hz); MS (m/z) 252 (M^+, 1.13), 179 (100.00); IR (cm^{-1}) 1730, 1674. Anal. Calcd for $C_{13}H_{13}FO_4$: C, 61.90; H, 5.16. Found: C, 61.69; H, 5.28.

Ethyl 3-(4-Acetylphenyl)-3-fluoro-2-propenoate (4i). (*E*)-Isomer: ^{1}H NMR (CD_3COCD_3) δ 8.06 (2H, d, J = 8.4 Hz), 7.83 (2H, d, J = 8.4 Hz), 6.02 (1H, d, J = 20.4 Hz), 4.14 (2H, q, J = 7.1 Hz), 2.63 (3H, s), 1.17 (3H, t, J = 7.1 Hz); ^{19}F NMR (CCl_4) δ 3.6 (d, J = 20.4 Hz); MS (m/z) 236 (M^+, 34.97), 221 (100.00); IR (cm^{-1}) 1725, 1690, 1661. Anal. Calcd for $C_{13}H_{13}FO_3$: C, 66.10; H, 5.51. Found: C, 65.95; H, 5.70. **(*Z*)-Isomer:** ^{1}H NMR (CD_3COCD_3) δ 8.09 (2H, d, J = 8.4 Hz), 7.92 (2H, d, J = 8.4 Hz), 6.26 (1H, d, J = 34.3 Hz), 4.20 (2H, q, J = 7.1 Hz), 2.63 (3H, S), 1.27 (3H, t, J = 7.2 Hz); ^{19}F NMR (CCl_4) δ 21.6 (d, J = 34.3 Hz); MS (m/z) 236 (M^+, 28.78), 221 (100.00).

Ethyl 3-(4-Hydroxyphenyl)-3-fluoro-2-propenoate (4j). (*E*)-Isomer: ^{1}H NMR (CD_3COCD_3) δ 7.65 (2H, d, J = 9.5 Hz), 6.90 (2H, d, J = 9.5 Hz), 5.73 (1H, d, J = 22.1 Hz), 4.10 (2H, q, J = 7.1 Hz), 1.19 (3H, t, J = 7.1 Hz); ^{19}F NMR (CCl_4) δ 3.0 (d, J = 22.1 Hz); MS (m/z) 211 (M^+ + 1, 24.15), 210 ((M^+, 43.48), 165 (100.00); IR (cm^{-1}) 3388, 1699, 1652. Anal. Calcd for $C_{11}H_{11}FO_3$: C, 62.86; H, 5.24; F, 9.05. Found: C, 62.77; H, 5.49; F, 8.86. **(*Z*)-Isomer:** ^{1}H NMR (CD_3COCD_3) δ 7.63 (2H, d, J = 8.8 Hz), 6.98 (2H, d, J = 8.8 Hz), 5.89 (1H, d, J = 34.8 Hz), 4.15 (2H, q, J = 7.1 Hz), 1.24 (3H, t, J = 7.1 Hz); ^{19}F NMR (CCl_4) δ 17.0 (d, J = 34.8 Hz); MS (m/z) 210 ((M^+, 40.89), 165 (100.00).

Ethyl 3-(4-Chorophenyl)-3-fluoro-2-propenoate (4k): ^{1}H NMR (CD_3COCD_3) δ 7.78 (2H, d, J = 8.5 Hz), 7.54 (2H, d, J = 8.7 Hz), 5.97 (1H, d, J = 20.7 Hz), 4.12 (2H, q, J = 7.1 Hz), 1.19 (3H, t, J = 7.1 Hz); ^{19}F NMR (CCl_4) δ 3.67 (d, J = 20.7 Hz); MS (m/z) 228 (M^+, 36.43), 183 (100.00); IR (cm^{-1}) 1726, 1659; HRMS calcd for $C_{11}H_{10}FCl^{35}O_2$: 228.0354, found: 228.0336.

(*E*)-Ethyl 3-(2-naphthyl)-3-fluoro-2-propenoate (4l): ^{1}H NMR (CD_3COCD_3) δ 8.11−7.92 (3H, m,), 7.69−7.56 (4H, m), 6.22 (1H, d, J = 17.1 Hz), 3.90 (2H, q, J = 7.1 Hz), 0.92 (3H, t, J = 7.1 Hz); ^{19}F NMR (CCl_4) δ −7.7 (d, J = 17.1 Hz); MS (m/z) 244 (M^+, 55.81), 171 (100.00); IR (cm^{-1}) 1728, 1667. Anal. Calcd for $C_{15}H_{13}FO_2$: C, 73.77; H, 5.33. Found: C, 73.78; H, 5.43.

(*E*)-Ethyl 3-(2-thiophene-yl)-3-fluoro-2-propenoate (4m): ^{1}H NMR (CD_3COCD_3) δ 8.09 (1H, d, J = 3.8 Hz), 7.90−7.88 (1H, m), 7.25−7.21 (1H, m), 5.83 (1H, d, J = 24.2 Hz), 4.20 (2H, q, J = 7.1 Hz), 1.26 (3H, t, J = 7.2 Hz); ^{19}F NMR (CCl_4) δ 3.3 (d, J = 24.2 Hz); MS (m/z) 201 (M^+, 9.19), 200 (M^+-1, 55.33), 155 (100.00); IR (cm^{-1}) 1716, 1634. Anal. Calcd for $C_9H_{10}FSO_2$: C, 53.73; H, 4.98. Found: C, 54.00; H, 4.62.

Ethyl 3-Fluoro-5-(trimethylsilyl)penta-2,4-dienoate (4n). (2*E*)-Isomer: ^{1}H NMR (CD_3COCD_3) δ 7.57 (1H, d−d, J = 27.2, 19.2 Hz), 6.77 (1H, d, J = 18.7 Hz), 5.63 (1H, d, J = 19.2 Hz), 4.17 (2H, q, J = 7.1 Hz), 1.25 (3H, t, J = 7.1 Hz), 0.0 (9H,s); ^{19}F NMR (CCl_4) δ 23.0 (d−d, J = 27.2, 18.7 Hz); MS (m/z) 217 (M^+ + 1, 20.30), 77 (100.00); IR (cm^{-1}) 1720, 1645. Anal. Calcd for $C_{10}H_{17}FO_5Si$: C, 55.56; H, 7.87. Found: C, 55.55; H, 8.06. **(2*Z*)-Isomer:** ^{1}H NMR (CD_3COCD_3) δ 6.72 (1H, d, J = 18.9 Hz), 6.53 (1H, d−d, J = 22.4, 18.9 Hz), 5.58 (1H, d, J = 32.8 Hz), 4.14 (2H, q, J = 7.1 Hz), 1.27 (3H, t, J = 7.1 Hz), 0.0 (9H, s); ^{19}F NMR (CCl_4) δ 24.0 (ddd, J = 32.8, 22.4, 3.5 Hz); MS (m/z) 217 (M^+ + 1, 10.68), 77 (100.00).

(2*E*)-Diethyl 3-fluorohexa-2,4-dienedioate (4o): ^{1}H NMR (CD_3COCD_3) δ 8.18 (1H, dd, J = 29.1, 15.9 Hz), 6.47 (1H, d−d, J = 15.9, 0.5 Hz), 5.97 (1H, d−d, J = 18.0, 0.4 Hz), 4.26 (2H, q, J = 6.8 Hz), 4.19 (2H, q, J = 7.1 Hz), 1.30 (3H, t, J = 7.2 Hz), 1.27 (3H, t, J = 6.8 Hz); ^{19}F NMR (CCl_4) δ 25.6 (d−d, J = 29.0, 18.0 Hz); MS (m/z) 217 (M^++1, 10.40), 143 (100.00); IR (cm^{-1}) 1724, 1657. Anal. Calcd for $C_{10}H_{13}FO_4$: C, 55.56; H, 6.02. Found: C, 55.80; H, 6.22.

(*E*)-Ethyl 3-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-3-fluoro-2-propenoate (4p): ^{1}H NMR (CD_3COCD_3) δ 8.07 (1H, s), 5.86 (1H, d, J = 16.4 Hz), 4.09 (2H, q, J = 7.1 Hz), 3.50 (3H, s), 3.27 (3H, s), 1.19 (3H, t, J = 7.1 Hz); ^{19}F NMR (CCl_4) δ 2.0 (d, J = 16.4 Hz); MS (m/z) 256 (M^+, 15.92), 184 (100.00); IR (cm^{-1}) 1716, 1674; HRMS calcd for $C_{11}H_{13}FN_2O_4$: 256.0860, found: 256.0848.

(*E*)-3,5-Di-*O*-benzoyl-5-[1-fluoro-2-(ethoxycarbonyl)-ethenyl]-2-deoxyuridine (4q): α^{20}_D −69.3° (c = 0.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.08−7.97 (5H, m), 7.66−7.42 (6H, m),

6.48−6.37(1H, m), 5.67−5.64 (2H, m), 4.77−4.65 (2H, m), 4.62−4.60 (1H, m), 4.08 (2H, g, J = 7.1 Hz), 2.88−2.77 (1H, m), 2.46−2.35 (1H, m), 1.23 (3H, t, J = 7.1 Hz); ^{19}F NMR (CCl_4) δ 3.3 (d, J = 17.0 Hz); MS (FAB, m/z) 553 ($M^+ + 1$, 29.00), 154 (100.0); IR (cm^{-1}) 3199, 1721, 1601; HRMS (FAB) calcd for $C_{28}H_{26}FN_2O_9$: 553.1622, found: 553.1593.

(*E*)-Ethyl 3-Fluoro-2-propenoate (5). A mixture of zinc reagent **2** and 20 mmol % of CuI was stirred at 70 °C for 10 min. Then the reaction was analyzed by ^{19}F NMR, GC−IR and GC−MS. ^{19}F NMR (DMF) δ 33.6 (dd, J = 80.0, 16.0 Hz). MS (m/z) 119 ($M^+ + 1$, 8.0), 118 (M^+, 10.5), 43 (100.0). IR (cm^{-1}) 1750, 1666.

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