Preparation of β-Fluoro-α-ketoesters from α-Ketoesters and Their Conversion to (*Z*)-β-Fluoro-α-aminoacrylate Derivatives

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Introduction

The presence of fluorine in biologically active compounds can impart a profound influence on their biological activity. This influence has led to the development of several potent agricultural and therapeutic agents.[1] As a consequence, organofluorine chemistry has seen a flurry of research activity recently. A continuing emphasis in this field has been placed on the development and evaluation of new fluorinating reagents,[2] enantioselective synthesis of α-fluorocarbonyl compounds,[2,3] and the synthesis of biologically active fluorinated compounds.[2,4] α-Fluorinated carbonyl compounds have previously been synthesized and studied as potential enzyme inhibitors.[1c,5] In this context, monofluorinated α-ketoesters have received a fair share of attention as peptidomimetic serine and cysteine protease inhibitors,[5c] as mechanistic probes for proteolysis,[1c] and as intermediates for the synthesis of β-fluoro α-amino esters.[1c]

Our interest in chemistry of 1,2,3-trifunctionalized compounds, which can efficiently be transformed into other 1,2,3-trifunctionalized products by independent, orthogonal functional group manipulation,[6] suggested that 3-fluoro-2-ketoesters could be very useful intermediates. For example, condensation reactions of 3-fluoro-2-ketoesters with carbamates and acetamide might provide β-fluorinated analogues of didehydroamino esters. Since didehydroamino acids possess interesting biological activities and are important constituents of antibiotic and phytotoxic peptides,[7] fluorinated analogues might display altered biological activities. β-Fluorinated didehydroamino acid derivatives are also interesting as precursors to the biologically important β-fluoro α-amino acids[1c,8] and as substrates for cross-coupling reactions.[7] We wish to report an improved synthesis of 3-fluoro-2-ketoesters from α-ketoesters and describe their condensation reactions with methyl carbamate and acetamide as a means of accessing β-fluorinated didehydroamino esters.

Results and Discussion

Several methods have been developed for the preparation of α -fluorinated carbonyl compounds.[1c,5a,b,9] Of these, several have previously been applied to the synthesis of 3-fluoro-2-ketoesters and acids. These include the ring opening of glycidic esters with HF−pyridine followed by Jones, Dess−Martin, or Swern oxidation;[5c,10] treatment of aminomalonates with chlorofluorocarbene followed by acid hydrolysis and decarboxylation to provide fluoropyruvic acid;[11] Claisen condensation of ethyl fluoroacetic acid and diethyl oxalate followed by hydrolysis and decarboxylation;[12] and fluorination of enolizable pyruvates with molecular fluorine.[13] With the advent of electrophilic NF fluorinating reagents, efficient and selective α-fluorination of carbonyl compounds can now be achieved.[2,3,9,14] One particular reagent, 1-(chloromethyl)-4-fluoro-1,4-diazabicyclo[2.2.2]octane bis(tetrafluoroborate) (**4**, also commonly referred to as Selectfluor) has proven to be extremely useful as a mild and site-selective electrophilic fluorinating agent.[4,14] Taking advantage of the convenience and mild reactivity of Selectfluor, we have developed an effective method for the synthesis of 3-fluoro-2-ketoesters **3** from α-ketoesters **1** (Scheme 1).

α-Ketoesters **1a**−**f** were transformed to the corresponding silyl enol ethers **2a**−**f** in quantitative yields by treatment with Et_3N and TMSCl in THF at room temperature.[6e,15] These were not purified but merely

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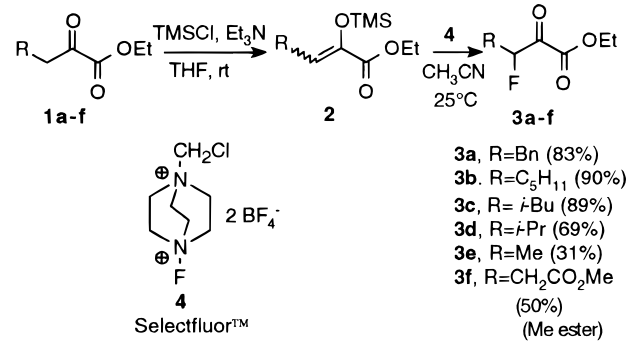
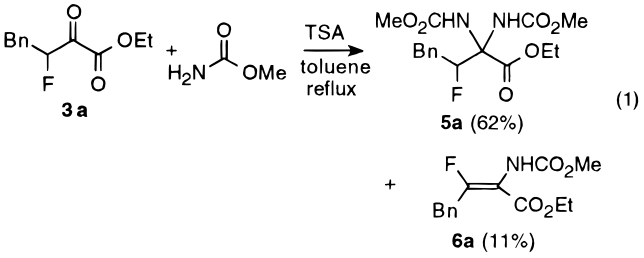
Scheme 1



isolated and then fluorinated with Selectfluor in CH_3CN at room temperature for a period of 3.5−6 h. The resulting 3-fluoro-2-ketoesters **3a**−**f** were obtained in generally high yields (Scheme 1). The isolated yields (after purification by column chromatography and bulb-to-bulb distillation) shown in Scheme 1 are a reflection of the high volatility of most of the fluorides **3**, particularly **3e**. The use of silyl enol ethers as fluorination substrates was necessary because the amount of enolization in α-ketoesters is insufficient for direct reaction with Selectfluor and because Selectfluor is ineffective at fluorinating highly reactive ketone enolates.[14a]

With a simple and practical synthesis of monofluoro-α-ketoesters **3** in hand, their reactions could be examined easily. In an attempt to prepare *β*-fluorinated didehydroamino acids, a relatively unknown class of compounds,[8c,16] the condensation reaction of 3-fluoro-2-ketoesters **3** with methyl carbamate and acetamide was investigated. Treatment of 3-fluoro-2-ketoester **3a** with excess methyl carbamate (3 equiv) and catalytic *p*-TSA in refluxing toluene provided the bis-carbamate adduct **5a** as the major product in 62% isolated yield (eq 1). A small amount of the *β*-fluorinated didehydroamino ester **6a** (11% isolated yield) was produced as well.



(1)

The product distribution seen here contrasted with that seen in the condensation reaction of nonfluorinated analogues in which the bis-carbamate adduct and the didehydroamino ester were obtained in the ratio of 4:6, respectively.[17] The difference in the product distribution is a result of the enhanced electrophilicity of the central carbon in the fluorinated 1,2,3-trisubstituted intermediates.

Using 1.0−1.5 equiv of methyl carbamate, the condensation reaction provided only the *β*-fluorinated didehydroamino ester **6a** in 47% yield (eq 2). Fluoro ester **6a**

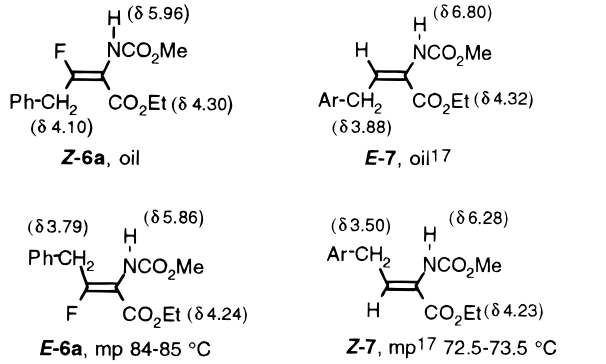
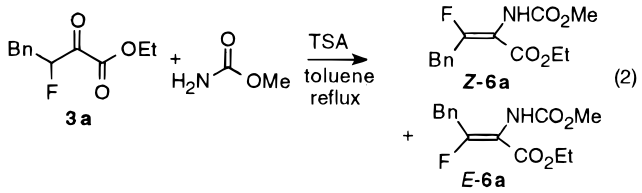


Figure 1. Chemical shifts for (*E*)- and (*Z*)-**6a** and their nonfluorinated analogs (*E*)- and (*Z*)-**7**.

was obtained as a mixture of *Z*- and *E*-diastereoisomers in the ratio of 5:2, respectively, as determined by ^{1}H NMR



(2)

of the crude product. The two diastereoisomers (*Z*)-**6a** and (*E*)-**6a** were separable by column chromatography (silica gel, EtOAc/hexanes, 1:4). The configuration of the isomers (*Z*)-**6a** and (*E*)-**6a** were assigned based on the following observations:

i. The same trends in melting points and chemical shifts were seen in fluorinated derivatives **6** as for the *Z*- and *E*-isomers of the nonfluorinated analogues **7** (Figure 1).[18] The benzylic protons, the urethane N−H proton, and the methylene protons of the ester ethoxy group in (*E*)-**7**, which is an oil, all lie at lower field than that of the corresponding protons in (*Z*)-**7** which is a solid with mp 72−73 °C. Of the isomers of **6a**, one is an oil with the chemical shifts of the benzylic protons, the urethane N−H proton, and the methylene group of the ester ethoxy group downfield from the corresponding protons in the other isomer, which is a solid with mp 83 °C. Thus the oil is assigned as (*Z*)-**6a**, and the solid is assigned as (*E*)-**6a**.

ii. This assignment is corroborated by the vicinal fluorine−carbon coupling constants between the ester carbonyl carbon and the vinylic fluorine atom. In the F-coupled ^{13}C NMR spectrum, isomer (*Z*)-**6a** had $^3J_{C,F} =$ 12.2 Hz while (*E*)-**6a** had $^3J_{C,F} \approx 0$ (slight broadening). In the corresponding nonfluorinated didehydroamino acid derivatives such as **7**, it has been shown that the vicinal coupling constant between the ester carbonyl carbon and the vinyl hydrogen is $^3J_{C,H} = 10$ Hz for the *E*-isomer and $^3J_{C,H} = 5.5$ Hz for the *Z*-isomer. Thus the same trend in coupling constants is seen for the fluorinated analogues as for the protio compounds.[18b]

(iii) Although the chemical shifts of the benzylic protons and the carbamate methoxy group protons are very close in the spectrum of the *E*-isomer making the use of NOE measurements to distinguish the two isomers problematic, the data support the assignment shown (Figure 2).

Addition of silver ion to the condensation reaction of **3a** and methyl carbamate was used to test whether Ag^+

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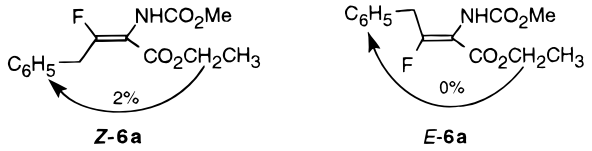
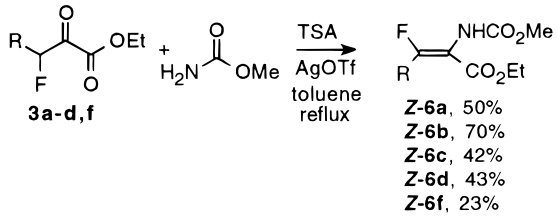


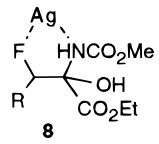
Figure 2. NOE measurements of (*Z*)- and (*E*)-**6a**.

could enhance the leaving ability of F and thereby produce the corresponding oxazolones as observed for the related β−nosyloxy-α-ketoesters.[6f] Interestingly, the condensation of **3a** and methyl carbamate in the presence of AgOTf provided only the *Z*-isomer of 3-fluoro-2-aminoacrylate derivative **6a** (as determined by ^{1}H NMR of the crude product).



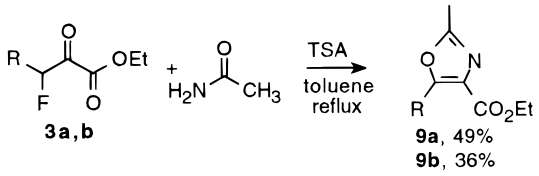
(3)

This stereocontrol was found to be general for a series 3-fluoro-2-ketoesters **3a**−**d,f** (eq 3) which gave only the *Z*-isomers of **6a**−**d,f** after refluxing with methyl carbamate in toluene in the presence of *p*-TSA and AgOTf for a period of 16−24 h. The 3-fluoro-2-aminoacrylate derivatives **6** were obtained in fair to good yields, in part, because the products were difficult to purify by column chromatography. The stereocontrol wrought by Ag(I) in this reaction was intriguing. Performing the reaction in two steps, i.e., initial reflux (24 h) of 3-fluoro-2-ketoester **3a**, methyl carbamate, and *p*-TSA in toluene followed by addition of AgOTf and refluxing of the reaction mixture for a further 24 h, provided the same 5:2 mixture of (*Z*)-**6a** and (*E*)-**6a** as was obtained in the complete absence of AgOTf. Clearly, AgOTf does not isomerize the *E*-isomer of **6a** to the *Z*-isomer. It is thus clear that the stereocontrol exerted by silver ion occurs before the dehydration of adduct **8** to the final product. One explanation for this stereocontrol is that chelation of silver ion with the fluorine atom and the carbamate nitrogen produces a conformational bias which favors the formation of the *Z*-isomer on dehydration.



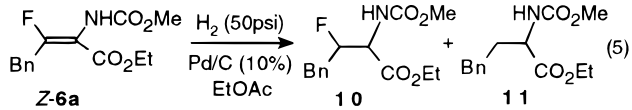
In contrast to the good results obtained with methyl carbamate, benzyl carbamate was found to be a poor partner for the condensation reaction with 3-fluoro-2-ketoester **3a**, giving the corresponding [(benzyloxycarbonyl)amino]acrylate in low yield (22%).

Acetamide showed different reactivity with 3-fluoro-2-ketoesters **3**. When 3-fluoro-2-ketoesters **3a,b**, acetamide, and *p*-TSA were refluxed in toluene for a period of 16−24 h, cyclocondensation to the oxazoles **9a,b** occurred, rather than formation of the expected 3-fluoro-2-(acetylamino)acrylate derivatives (eq 4). Apparently the nucleophilicity of an amide carbonyl group is sufficient to displace fluoride whereas the carbamate carbonyl group is not. Since the same compounds can be produced more efficiently from β-(nosyloxy)-α-ketoesters,[6f] this reaction was not pursued further.



(4)

Attempts to reduce 3-fluoro-2-aminoacrylate derivative **6a** using $NaCNBH_3$[16] or by catalytic hydrogenation with Et-DuPHOS−Rh(I) as catalyst in order to produce β-fluoro-α-amino esters have thus far been unsuccessful. Catalytic hydrogenation of **6a** over 10% Pd−C (catalyst: substrate ratio of 1:4 by mass), H_2 pressure of 50 psi, and reaction time of 24 h led to only 5% conversion to product. Under forcing conditions with a catalyst:substrate ratio of 3:1 by mass, hydrogenation of **6a** over 10% Pd−C at H_2 pressure of 50 psi and reaction time of 24 h provided a 1:1 mixture of what appeared to be the corresponding β-fluoro α-amino ester **10** and α-amino ester **11** (eq 5); however, these compounds were not separated nor pursued further.



(5)

Thus β-fluoro didehydroamino acids are remarkably resistant to hydrogenation. While dehydroamino esters and β-(silyloxy)-α,β-unsaturated esters are readily hydrogenated with a variety of chiral and achiral catalysts,[19] derivatives containing *both* an α-substituent and a β-substituent each with lone pairs of electrons are apparently poor substrates for catalytic hydrogenation.[7,20]

In summary, we have developed an efficient two-step synthesis of 3-fluoro-2-ketoesters **3** from α-ketoesters **1** using Selectfluor as fluorinating reagent. 3-Fluoro-2-ketoesters **3** were shown to condense with methyl carbamate in the presence of *p*-TSA, with or without AgOTf, to provide β-fluorinated didehydroamino esters **6**. The efficiency of this approach is somewhat better than results obtained by previously reported methods.[8a] Stereocontrol using AgOTf can direct the stereoselectivity of the condensation reaction leading to exclusive formation of the *Z*-isomer of 3-fluoro-2-aminoacrylate derivatives **6**. In contrast to carbamates, reaction of acetamides with β-fluoro α-ketoesters and *p*-TSA provided oxazoles **9** instead of fluorinated didehydroamino esters.

Experimental Section

Descriptions of instruments, general procedures, and chromatographic procedures have been described previously.[6e]

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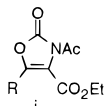
(20) Enamides with β-oxygen substituents such as i are also very resistant to hydrogenation.



General Procedure for the Preparation of Silyl Enol Ethers 2.[6e] A solution of the α-ketoester (**1**, 29.1 mmol) and chlorotrimethylsilane (3.73 g, 4.36 mL, 34.3 mmol) in anhydrous THF (30 mL) was stirred at room temperature as triethylamine (4.18 g, 5.76 mL, 41.3 mmol) was added dropwise. After 3.5 h at room temperature, the mixture was diluted with pentanes (≈50 mL) and filtered. The filtrate was washed with cold water (2 × 50 mL) and with cold brine (1 × 50 mL). The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure to provide the crude silyl enol ether **2** as a clear yellow liquid in quantitative yield. This material was used in the next step without further purification:

Ethyl 3-Fluoro-2-oxo-4-phenylbutanoate (3a). To a solution of 1-carbethoxy-1-(trimethylsilyloxy)-3-phenylpropene (**2a**, 2.78 g, 10.0 mmol) in 25 mL of anhydrous acetonitrile under N_2 was added 1-(chloromethyl)-4-fluoro-1,4-diazabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor, **4**, 3.54 g, 10.0 mmol). The mixture was stirred for 5 h at room temperature and monitored by TLC (EtOAc/hexanes, 1:4). After the starting material was gone, EtOAc (100 mL) was added to the reaction mixture, and the solution was washed with saturated brine (2 × 60 mL). The aqueous layer was extracted with EtOAc and the combined organic layers were dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography (hexanes: EtOAc, 4:1 to 2:1) to give the monofluorinated α-ketoester **3a** as a clear yellow oil (1.86 g, 83%). An analytical sample was prepared by vacuum distillation (Kugelrohr, 145 °C/0.06 mmHg): ^{1}H NMR δ 1.36 (t, J = 7.1 Hz, 3H), 3.12−3.37 (m, 2H), 4.33 (q, J = 7.1 Hz, 2H), 5.61 (ddd, $J_{H,F}$ = 48.3 Hz, J = 8.2 and 4.0 Hz, 1H), 7.23−7.24 (m, 5H); ^{13}C NMR δ 13.9, 37.7 (d, $J_{C,F}$ = 20.5 Hz), 62.9, 93.2 (d, $J_{C,F}$ = 185.8 Hz), 127.4, 128.6 (d, $J_{C,F}$ = 7.6 Hz), 129.3, 134.5 (d, $J_{C,F}$ = 1.5 Hz), 160.3, 190.2 (d, $J_{C,F}$ = 23.5 Hz); IR (neat) 1756, 1732, 1051 cm^{-1}. Anal. Calcd for $C_{12}H_{13}O_3F$: C, 64.28; H, 5.84. Found: C, 64.09; H, 5.81.

Ethyl 3-Fluoro-2-oxooctanoate (3b). By the same procedure 1-carbethoxy-1-(trimethylsilyloxy)-1-heptene (**2b**, 3.75 g, 14.5 mmol) was treated with Selectfluor (**4**, 5.14 g, 14.5 mmol). Monofluorinated α-ketoester **3b** was obtained as a clear yellow oil (2.77 g, 90%) following purification by vacuum distillation (Kugelrohr, 85 °C/0.06 mmHg); ^{1}H NMR δ 0.90 (t, J = 6.0 Hz, 3H), 1.30−1.50 (m, 7H), 1.52 (t, J = 7.0 Hz, 2H), 1.75−2.05 (m, 2H), 4.37 (q, J = 7.1 Hz, 2H), 5.41 (ddd, $J_{H,F}$ = 48.9 Hz, J = 8.1 and 4.0 Hz, 1H); ^{13}C NMR δ 13.74, 13.78, 22.2, 24.07, 24.09, 31.1 (d, $J_{C,F}$ = 20.5 Hz), 62.7, 93.1 (d, $J_{C,F}$ = 182.8 Hz), 160.6, 191.3 (d, $J_{C,F}$ = 23.5 Hz); IR (neat) 1756, 1732, 1057 cm^{-1}. Anal. Calcd for $C_{10}H_{17}O_3F\cdot{}^1/_2H_2O$: C, 56.32; H, 8.51. Found: C, 56.38; H, 8.56.

Ethyl 3-Fluoro-5-methyl-2-oxohexanoate (3c). By the same procedure 1-carbethoxy-4-methyl-1-(trimethylsilyloxy)-1-pentene (**2c**, 2.44 g, 10.0 mmol) was treated with Selectfluor (**4**, 3.54 g, 10.0 mmol). Monofluorinated α-ketoester **3c** was obtained as a clear yellow oil (1.70 g, 89%) following purification by vacuum distillation (Kugelrohr, 75 °C/0.06 mmHg); ^{1}H NMR δ 0.99 (d, J = 7.3 Hz, 3H), 1.19 (d, J = 7.1 Hz, 3H), 1.40 (t, J = 7.1 Hz, 3H), 1.60−1.90 (m, 3H), 4.36 (q, J = 7.1 Hz, 2H), 5.45 (ddd, $J_{H,F}$ = 49.7 Hz, J = 9.2 and 2.5 Hz, 1H); ^{13}C NMR δ 13.9, 21.4, 23.0, 24.7, 39.7 (d, $J_{C,F}$ = 20.5 Hz), 62.8, 92.1 (d, $J_{C,F}$ = 182.1 Hz), 160.6, 191.4 (d, $J_{C,F}$ = 23.5 Hz); IR (neat) 1756, 1732, 1057 cm^{-1}. Anal. Calcd for $C_9H_{15}O_3F$: C, 56.83; H, 7.95. Found: C, 56.64; H, 8.16.

Ethyl 3-Fluoro-4-methyl-2-oxopentanoate (3d). By the same procedure 1-carbethoxy-3-methyl-1-(trimethylsilyloxy)-1-butene (**2d**, 1.70 g, 7.40 mmol) was treated with Selectfluor (**4**, 2.62 g, 7.40 mmol). Monofluorinated α-ketoester **3d** was obtained as a clear yellow oil (0.900 g, 69%) following purification by vacuum distillation (Kugelrohr, 45 °C/0.06 mmHg); ^{1}H NMR δ 0.97 (d, J = 7.0 Hz, 3H), 1.11 (d, J = 7.0 Hz, 3H), 1.38 (t, J = 7.1 Hz, 3H), 2.20−2.45 (m, 1H), 4.36 (q, J = 7.1 Hz, 2H), 5.21 (dd, $J_{H,F}$ = 48.5 Hz, J = 3.8 Hz, 1H); ^{13}C NMR δ 13.9, 15.8, 30.3 (d, $J_{C,F}$ = 20.5 Hz), 62.7, 96.8 (d, $J_{C,F}$ = 185.8 Hz), 161.0, 191.6 (d, $J_{C,F}$ = 24.3 Hz); IR (neat) 1756, 1732, 1060 cm^{-1}. Anal. Calcd for $C_9H_{15}O_3F$: C, 54.54; H, 7.44. Found: C, 54.77; H, 7.30.

Ethyl 3-Fluoro-2-oxobutanoate (3e). By the same procedure 1-carbethoxy-1-(trimethylsilyloxy)propene (**2e**, 90% purity, 2.02 g, 10.0 mmol) was treated with Selectfluor (**4**, 3.54 g, 10.0 mmol). Monofluorinated α-ketoester **3e** was obtained as a volatile clear yellow oil (0.66 g, 90% purity, 31% yield) following purification by vacuum distillation (Kugelrohr, rt−40 °C/0.06 mmHg); ^{1}H NMR δ 1.39 (t, J = 7.3 Hz, 3H), 1.65 (dd, $J_{H,F}$ = 23.6 Hz, J = 7.1 Hz, 3H), 4.37 (q, J = 7.2 Hz, 2H), 5.45 (dq, $J_{H,F}$ = 48.3 Hz, J = 7.0 Hz, 1H); ^{13}C NMR δ 13.9, 17.1 (d, $J_{C,F}$ = 21.3 Hz), 62.9, 89.7 (d, $J_{C,F}$ = 180.5 Hz), 160.6, 191.3 (d, $J_{C,F}$ = 23.0 Hz); IR (neat, including hydrate) 3484, 1735 br, 1054 cm^{-1}.

Methyl 4-Carbomethoxy-3-fluoro-2-oxobutanoate (3f). By the same procedure 1,3-dicarbomethoxy-1-(trimethylsilyloxy)-propene (**2f**, 3.70 g, 15.0 mmol) was treated with Selectfluor (**4**, 5.32 g, 15.0 mmol). Monofluorinated α-ketoester **3f** was obtained as a clear yellow oil (1.45 g, 50%) following purification by bulb-to-bulb distillation (150 °C, 0.10 mmHg). An analytical sample of **3f** was obtained upon further purification by flash chromatography (EtOAc/CH_2Cl_2, 1:9): ^{1}H NMR (0.4 ketoester and 0.6 hydrate) δ 2.84−3.27 (m, 2H, CH_2-ketoester and hydrate), 3.74 (s, 1.2H, OCH_3-ketoester), 3.75 (s, 1.8H, OCH_3-hydrate), 3.90 (s, 1.8H, OCH_3-hydrate), 3.94 (s, 1.2H, OCH_3-ketoester), 4.60 (br s, 1H, OH-hydrate), 4.72 (br s, 1H, OH-hydrate), 5.17 (ddd, $J_{H,F}$ = 45.7 Hz, J = 7.5 and 5.0 Hz, 0.6H, CHF-hydrate), 5.70 (ddd, $J_{H,F}$ = 46.3 Hz, J = 6.0 and 4.4 Hz, 0.4H, CHF-ketoester); ^{13}C NMR (0.4 ketoester and 0.6 hydrate) δ 34.0 (d, $J_{C,F}$ = 23.5 Hz, hydrate), 36.8 (d, $J_{C,F}$ = 22.8 Hz, ketoester), 52.3, 52.6, 53.3, 53.8, 89.0 (d, $J_{C,F}$ = 185.9 Hz, hydrate), 89.5 (d, $J_{C,F}$ = 176.7 Hz, ketoester), 92.7 (d, $J_{C,F}$ = 26.6 Hz), 160.4 (d, $J_{C,F}$ = 1.6 Hz, ketoester), 169.3, 170.7, 171.3 (d, $J_{C,F}$ = 6.1 Hz, hydrate), 188.1 (d, $J_{C,F}$ = 22.0 Hz, ketoester); IR (neat, ketoester + hydrate) 3467, 2960, 1746 (br) cm^{-1}. Anal. Calcd for $C_{12}H_{13}O_3F\cdot 0.6H_2O$: C, 41.43; H, 5.07. Found: C, 41.37; H, 4.84.

Ethyl 2,2-Bis[(methoxycarbonyl)amino]-3-fluoro-4-phenylbutanoate (5a). A mixture of ethyl 3-fluoro-2-oxo-4-phenylbutanoate (**3a**, 0.670 g, 3.00 mmol), methyl carbamate (1.13 g, 15.0 mmol), and *p*-toluenesulfonic acid monohydrate (0.060 g, 0.30 mmol) in 60 mL of toluene was refluxed overnight. The reaction mixture was cooled to room temperature, EtOAc (60 mL) was added, and the mixture was washed with water (2 × 60 mL) and brine (60 mL), dried ($MgSO_4$), and concentrated in vacuo to provide a yellow solid. The crude product was chromatographed on a silica gel column eluting with CH_2Cl_2/EtOAc (9:1) to provide the bis-carbamate adduct **5a** as a white crystalline solid upon recrystallization from EtOAc/hexanes (0.667 g, 62%): mp 142−145 °C; ^{1}H NMR δ 1.34 (t, J = 7.1 Hz, 3H), 2.72−3.50 (m, 2H), 3.64 (s, 3H), 3.66 (s, 3H), 4.35 (q, J = 7.1 Hz, 2H), 5.44 (ddd, $J_{H,F}$ = 47.3 Hz, $J_{H,H}$ = 9.4 and 2.7 Hz, 1H), 6.40 (br s, 1H), 6.49 (br s, 1H), 7.25 (m, 5H); ^{13}C NMR δ 14.0, 36.2 (d, $J_{C,F}$ = 21.2 Hz), 52.3, 52.4, 63.4, 71.8 (d, $J_{C,F}$ = 22.7 Hz), 92.4 (d, $J_{C,F}$ = 188.9 Hz), 126.9, 128.6, 129.2, 136.2, 154.9, 155.3, 167.1; IR (KBr) 3415, 3317, 3100−2900, 1756, 1734, 1692 cm^{-1}; MS (ES+) 378.9 (M + Na)$^+$. Fluoroaminoacrylate **6a** was also isolated as a yellow oil (0.090 g, 11%): Spectral characterization identical with that given below.

(*Z*)-Ethyl 2-[(Methoxycarbonyl)amino]-3-fluoro-4-phenyl-2-butenoate (6a). To ethyl 3-fluoro-2-oxo-4-phenylbutanoate (**3a**, 0.66 g, 3.0 mmol) in toluene (60 mL) were added methyl carbamate (0.22 g, 3.0 mmol), AgOTf (0.78 g, 3.0 mmol), and *p*-toluenesulfonic acid monohydrate (0.06 g, 0.30 mmol). The mixture was refluxed overnight then cooled to room temperature, EtOAc (60 mL) was added, and the mixture was washed with water (2 × 60 mL) and brine (60 mL), dried ($MgSO_4$), and concentrated in vacuo to provide a yellow solid. The crude product was chromatographed on a silica gel column eluting with CH_2Cl_2/EtOAc (97:3) to provide fluoroaminoacrylate (*Z*)-**6a** as a yellow oil (0.41 g, 50%): ^{1}H NMR δ 1.32 (t, J = 7.1 Hz, 3H), 3.72 (s, 3H), 4.10 (d, $J_{H,F}$ = 26.8 Hz, 2H), 4.30 (q, J = 7.1 Hz, 2H), 5.96 (br s, 1H), 7.31 (m, 5H); ^{13}C NMR δ 14.1, 35.7 (d, $J_{C,F}$ = 22.0 Hz), 52.8, 61.7, 111.9 (d, $J_{C,F}$ = 15.9 Hz), 127.1, 128.7, 128.8, 134.9, 154.5, 163.9 (d, $J_{C,F}$ = 12.2 Hz), 164.0 (d, $J_{C,F}$ = 270.8 Hz); IR (neat) 3322, 3100−2850, 1723 (br), 1650 cm^{-1}. Anal. Calcd for $C_{14}H_{16}NO_4F$: C, 59.78; H, 5.73; N, 4.98. Found: C, 59.68; H, 5.58; N, 4.83.

Performing this reaction in the absence of AgOTf provided a mixture of the *E*- and *Z*-isomers of **3a** in the ratio of 5:2, respectively, with a combined yield of 47%. The two isomers were separated by column chromatography (EtOAc/hexanes, 1:4) to give (*Z*)-**6a** as a yellow oil and (*E*)-**6a**: White needle-shaped crystals, mp 84−85 °C; ^{1}H NMR δ 1.28 (t, J = 7.1 Hz, 3H), 3.73 (s, 3H), 3.79 (d, $J_{H,F}$ = 18.3 Hz, 2H), 4.24 (q, J = 7.1 Hz, 2H), 5.86 (d, J = 3.4 Hz, 1H), 7.28 (m, 5H); ^{13}C NMR δ 14.1, 36.3 (d,

$J_{C,F}$ = 23.5 Hz), 52.9, 61.5, 111.0 (d, $J_{C,F}$ = 29.6 Hz), 127.3, 128.7, 128.9, 134.0, 156.0, 163.3 (br, $J_{C,F}$ = 0 Hz), 168.4 (d, $J_{C,F}$ = 280.7 Hz)

Ethyl 2-[(Methoxycarbonyl)amino]-3-fluoro-2-octenoate (6b). By the same procedure ethyl 3-fluoro-2-oxooctanoate (**3b**, 0.31 g, 1.5 mmol) in toluene (30 mL) was condensed with methyl carbamate (0.11 g, 1.5 mmol) in the presence of AgOTf (0.39 g, 1.5 mmol) and *p*-toluenesulfonic acid monohydrate (0.030 g, 0.15 mmol). The crude product was chromatographed on a silica gel column eluting with CH_2Cl_2/EtOAc (97:3) to provide fluoroaminoacrylate **6b** as a yellow oil (0.30 g, 70%): ^{1}H NMR δ 0.90 (t, J = 7.0 Hz, 3H), 1.30 (t, J = 7.1 Hz, 3H), 1.33 (m, 4H), 1.65 (m, 2H), 2.75 (dt, $J_{H,F}$ = 26.4 Hz, $J_{H,H}$ = 7.5 Hz, 2H), 3.73 (s, 3H), 4.26 (q, J = 7.1 Hz, 2H), 5.90 (br s, 1H); ^{13}C NMR δ 13.9, 14.1, 22.3, 25.9, 29.7 (d, $J_{C,F}$ = 22.0 Hz), 31.1, 52.7, 61.4, 111.1 (d, $J_{C,F}$ = 16.7 Hz), 154.6, 164.1 (d, $J_{C,F}$ = 12.2 Hz), 167.5 (d, $J_{C,F}$ = 272.4 Hz); IR (neat) 3336, 3100−2850, 1723 (br), 1650 cm^{-1}. Anal. Calcd for $C_{12}H_{20}NO_4F$: C, 55.16; H, 7.72; N, 5.36. Found: C, 55.39; H, 7.46; N, 5.45.

Ethyl 2-[(Methoxycarbonyl)amino]-3-fluoro-5-methyl-2-hexenoate (6c). By the same procedure ethyl 3-fluoro-5-methyl-2-oxohexanoate (**3c**, 1.14 g, 6.00 mmol) in toluene (120 mL) was condensed with methyl carbamate (0.440 g, 6.00 mmol) in the presence of AgOTf (1.56 g, 6.00 mmol) and *p*-toluenesulfonic acid monohydrate (0.120 g, 0.600 mmol). The crude product was chromatographed on a silica gel column eluting with CH_2Cl_2/EtOAc (97:3) to provide fluoroaminoacrylate **6c** as a yellow oil (0.62 g, 42%): ^{1}H NMR δ 0.99 (d, J = 6.6 Hz, 6H), 1.31 (t, J = 7.2 Hz, 3H), 2.04 (m, 1H), 2.66 (dd, $J_{H,F}$ = 27.2 Hz, $J_{H,H}$ = 7.2 Hz, 2H), 3.73 (s, 3H), 4.25 (q, J = 7.2 Hz, 2H), 5.87 (br s, 1H); ^{13}C NMR δ 14.1, 22.2, 26.7, 38.3 (d, $J_{C,F}$ = 21.2 Hz), 52.7, 61.3, 111.8 (d, $J_{C,F}$ = 15.9 Hz), 154.6, 164.1 (d, $J_{C,F}$ = 12.2 Hz), 166.8 (d, $J_{C,F}$ = 272.3 Hz); IR (neat) 3330, 2961−2850, 1724 (br), 1650 cm^{-1}. Anal. Calcd for $C_{11}H_{18}NO_4F$: C, 53.43; H, 7.34; N, 5.66. Found: C, 53.60; H, 7.37; N, 5.41.

Ethyl 2-[(Methoxycarbonyl)amino]-3-fluoro-4-methyl-2-pentenoate (6d). By the same procedure ethyl 3-fluoro-4-methyl-2-oxopentanoate (**3d**, 0.820 g, 4.65 mmol) in toluene (95 mL) was condensed with methyl carbamate (0.380 g, 4.65 mmol) in the presence of AgOTf (1.19 g, 4.65 mmol) and *p*-toluenesulfonic acid monohydrate (0.0900 g, 0.465 mmol). The crude product was chromatographed on a silica gel column eluting with CH_2Cl_2/EtOAc (97:3) to provide fluoroaminoacrylate **6d** as a yellow oil (0.470 g, 43%): ^{1}H NMR δ 1.18 (d, J = 7.0 Hz, 6H), 1.31 (t, J = 7.2 Hz, 3H), 3.58 (dm, $J_{H,F}$ = 27.5 Hz, $J_{H,H}$ = 7.0 Hz, 1H), 3.72 (s, 3H), 4.26 (q, J = 7.2 Hz, 2H), 5.86 (br s, 1H); ^{13}C NMR δ 14.0, 18.7, 28.4 (d, $J_{C,F}$ = 21.3 Hz), 52.6, 61.3, 109.8 (d, $J_{C,F}$ = 17.5 Hz), 154.6, 164.0 (d, $J_{C,F}$ = 12.2 Hz), 169.9 (d, $J_{C,F}$ = 275.3 Hz); IR (neat) 3320, 2978−2850, 1723 (br), 1650 cm^{-1}. Anal. Calcd for $C_{10}H_{16}NO_4F$: C, 51.50; H, 6.9, N, 6.01. Found: C, 51.49; H, 6.81; N, 6.07.

2-Methyl-4-carbethoxy-5-benzyloxazole (9a). By the same procedure ethyl 3-fluoro-2-oxo-4-phenylbutanoate (**3a**, 0.33 g, 1.5 mmol) in toluene (30 mL) was condensed with acetamide (0.09 g, 1.5 mmol) in the presence of *p*-toluenesulfonic acid monohydrate (0.030 g, 0.15 mmol). The crude product was chromatographed on a silica gel column eluting with CH_2Cl_2/EtOAc (9:1) to provide oxazole **9a** as a clear yellow oil (0.18 g, 49%): ^{1}H NMR δ 1.40 (t, J = 7.2 Hz, 3H), 2.42 (s, 3H), 4.34 (s, 2H), 4.40 (q, J = 7.2 Hz, 2H), 7.29 (m, 5H); ^{13}C NMR δ 13.7, 14.3, 31.9, 60.9, 126.9, 128.6, 128.7, 136.3, 157.4, 160.1, 162.2; IR (neat) 3100−2850, 1750, 1708, 1616 cm^{-1}. Anal. Calcd for $C_{14}H_{15}NO_3 \cdot 0.4H_2O$: C, 66.6; H, 6.31; N, 5.55. Found: C, 66.85; H, 6.10; N, 5.72.

2-Methyl-4-carbethoxy-5-pentyloxazole (9b). By the same procedure ethyl 3-fluoro-2-oxo-octanoate (**3b**, 0.62 g, 3.0 mmol) in toluene (60 mL) was condensed with acetamide (0.18 g, 3.0 mmol) in the presence of *p*-toluenesulfonic acid monohydrate (0.060 g, 0.30 mmol). The crude product was chromatographed on a silica gel column eluting with CH_2Cl_2/EtOAc (9:1) to provide oxazole **9b** as a clear yellow oil (0.24 g, 36%): ^{1}H NMR δ 0.90 (t, J = 6.6 Hz, 3H), 1.35 (m, 4H), 1.39 (t, J = 7.1 Hz, 3H), 1.67 (m, 2H), 2.45 (s, 3H), 2.99 (t, J = 7.6 Hz, 2H), 4.37 (q, J = 7.1 Hz, 2H); ^{13}C NMR δ 13.7, 13.8, 14.3, 22.2, 25.8, 27.4, 31.2, 60.7, 126.9, 159.3, 160.0, 162.3; IR (neat) 2960, 2933, 2872, 1750, 1713, 1615 cm^{-1}. Anal. Calcd for $C_{12}H_{19}NO_3$: C, 63.98; H, 8.5; N, 6.22. Found: C, 64.17; H, 8.62; N, 6.01.

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Supporting Information Available: ^{13}C spectra of **5a** and (*E*)-**6a** (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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