Novel and practical preparation of α-fluoro-functionalized esters from fluoroiodoacetates

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The addition reaction of fluoroiodoacetates **2** to various electron-rich alkenes **3** initiated by iron powder in dry THF at 70–80 °C gave 1 : 1 adducts **4** in good yields. A variety of functionalities in the alkenes such as trimethylsilyl, alkoxy, acetoxy, hydroxy and ester could be tolerated under the reaction conditions. Reduction of the adducts **4** with Zn–AcOH in ethanol or Zn–$NiCl_2$·$6H_2O$ in moist THF was readily accomplished, and the overall procedure was amenable to a convenient one-flask procedure. Treatment of fluoroiodoacetates **2** with electron-deficient alkenes **7** in the presence of an Fe–$CrCl_3$·$6H_2O$–bpy bimetal redox system in ethanol at 70–80 °C resulted in the formation of iodine-free 1 : 1 adducts **8** in moderate to good yields. It is proposed that the addition reactions of fluoroiodoacetates **2** to electron-rich and electron-deficient alkenes proceeded through a single-electron-transfer mechanism.

Introduction

The introduction of fluorine into an organic molecule often causes significant changes in biological activity.[1] Elucidation of the mechanism of toxicity of fluoroacetate in living organisms led to increased interest in the preparation and properties of α-fluoro esters. Recently, the use of fluorine-substituted esters as analytical probes and diagnostic tools in metabolic processes has added to their stature as important compounds in biochemistry.[2] In addition, α-fluoroalkanoates have served as useful building blocks in the synthesis of more complex and biologically interesting molecules[3] such as 5-fluoro-6-oxo-PGE1 methyl ester,[3b] 24-fluoro-25-hydroxyvitamin D_3,[3c] F-ddA[3d] and F-ddC.[3e] More recently, optically active 2-fluorocarboxylic acids were used as building blocks in chiral dopants for ferroelectric liquid crystals[4,5] showing large values of spontaneous polarization.[6]

Previous approaches to the preparation of α-fluoro esters have included metathesis reactions,[7] alkylation of fluoroacetate ions,[8] reaction of α-hydroxy esters with (diethylamino)sulfur trifluoride (DAST) or hexafluoropropene-dialkylamine reagent (FAR)[9] or the use of α-siloxy esters with fluorophosphoranes,[10] reaction of diazonium intermediates (from α-amino acids) with pyridine (Py)–HF,[11] electrophilic fluorination of carbanions[12] or silyl enol esters,[13] Reformatsky reaction with bromofluoroacetates[14a–c] or chlorofluoroacetates,[14d] reduction of α-fluoro-α-alkenoic acids or esters[15] and alkylation or acylation–hydrolysis of α-fluoroalkoxycarbonyl phosphorus ylides.[16] However, all these methods exhibit little generality and utilize expensive, toxic, or unstable reagents, and do not tolerate a variety of functionalities or give low yields. Recently, Burton *et al.* reported[17] that reaction of fluoroiodoacetates with alkenes in the presence of zinc and nickel dichloride hexahydrate and pyridine in tetrahydrofuran (THF) afforded the corresponding α-fluoro esters in good yields. However, with electron-deficient alkenes or internal alkenes such as ethyl acrylate and cyclohexene under similar conditions, none of the desired adducts was formed and only fluoroacetate was observed. Thus the quest for efficient synthetic methods of α-fluoroalkanoates continues. In this paper we describe a novel, simple and practical method for the general preparation of this class of compounds.

Results and discussion

Fluoroiodoacetates were easily prepared by the exchange reaction of sodium iodide with chlorofluoroacetates, which are themselves prepared from chlorotrifluoroethene according to the literature procedure.[18] For example, ethyl chlorofluoroacetate **1b** reacted with an excess of anhydrous sodium iodide in dry acetone under reflux for 5 h to give ethyl fluoroiodoacetate **2b** in 91% yield (Scheme 1).

$$\underset{\textbf{1}}{ClCFHCO_2R^1} + NaI \xrightarrow[\text{reflux}]{\text{Dry acetone}} \underset{\textbf{2}}{ICFHCO_2R^1} + NaCl$$

a; R^1 = Me — **a** (78%)
b; R^1 = Et — **b** (91%)

Scheme 1

Fluoroiodoacetates add regioselectively, and in synthetically useful yields, to substituted alkenes, as shown in Table 1 (Scheme 2). In most of the cases observed, the reaction was complete within 12–16 h on heating a THF solution of fluoroiodoacetate **2** (1.0 mol equiv.) and alkene **3** (4.0 mol equiv.) at 70–80 °C (bath temp.) in the presence of acid-washed iron powder (20 mol%).

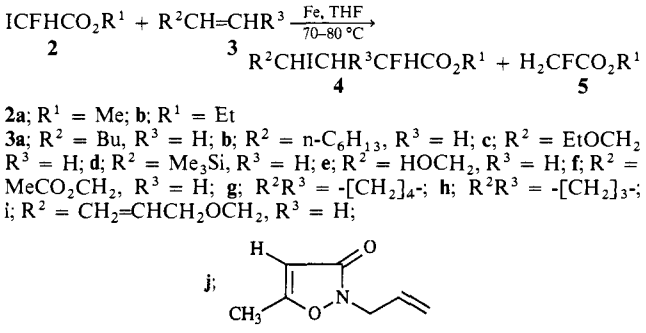
The reaction could be carried out in a variety of solvents. For example, upon reaction of ester **2b** with iron powder (20 mol%) and hex-1-ene **3a** in CH_3CN, dimethylformamide (DMF) or THF at 70–80 °C, the corresponding adduct **4a** was obtained in 82, 80, and 87% yield (Table 1, entries 3, 4, 7), respectively. Almost no product was observed when a similar reaction was attempted in hexane or in ethanol (entries 2, 5). Anhydrous THF seemed the most suitable solvent. In THF containing a little water, formation of compound **4a** was equally observed along with a significant amount (21%) of the toxic ethyl fluoroacetate **5b** (entry 6). The reaction also proceeded readily in the absence of solvent. For example, when neat hex-1-ene **3a** was treated with ester **2b** in the presence of iron powder (20 mol%) at 70–80 °C for 11 h, compound **4a** was isolated in 89% yield and no fluoroacetate **5b** was observed in the ^{19}F NMR spectrum of the reaction mixture (entry 1).

When a terminal alkene was used, the sole product, an α-fluoro-γ-iodo-functionalized ester **4**, was the isomer obtained from attack of the alkoxycarbonylfluoromethyl radical at the least substituted end of the alkene. In the presence of iron powder (20 mol%), for example, the addition of ethyl fluoroiodoacetate to oct-1-ene **3b** afforded ethyl 4-iodo-2-fluorodecanoate **4b** in 91% yield. Concerning functionalized olefins, allyl acetate **3f**, which has an acetoxy group, gave the adduct **4f** in 81% yield, and 5-methyl-2-(prop-2-enyl)isoxazol-3-(2*H*)-one **3j**, which has a 3-oxodihydroisoxazole moiety, gave

Table 1 Iron-initiated reaction of fluoroiodoacetates **2** with alkenes **3**[a] (see Schemes 2, 3 and 5)

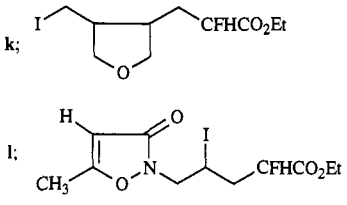
Entry	2	3	Solvent	t (h)	Adduct 4	Conv. (%)[b]	4 (%)[c]	5 (%)[b]
1	**2b**	**3a**	Neat	11	**4a**	100	89	0
2	**2b**	**3a**	Hexane	12	**4a**	< 5		
3	**2b**	**3a**	CH_3CN	12	**4a**	100	82	6
4	**2b**	**3a**	DMF	12	**4a**	100	80	15
5	**2b**	**3a**	EtOH	12	**4a**	10		
6	**2b**	**3a**	THF[d]	12	**4a**	100	79[b]	21
7	**2b**	**3a**	THF	12	**4a**	100	87	4
8[e]	**2b**	**3a**	THF	12	**4a**	0		
9[f]	**2b**	**3a**	THF	12	**4a**	75		
10[g]	**2b**	**3a**	THF	12	**4a**	72		
11	**2b**	**3b**	THF	12	**4b**	100	91	0
12	**2b**	**3c**	THF	12	**4c**	100	84	7
13	**2b**	**3d**	THF	10	**4d**	100	88	0
14	**2b**	**3e**	THF	24	**4e**	100	47	37
15	**2b**	**3f**	THF	16	**4f**	100	81	8
16	**2b**	**3g**	THF	12	**4g**	100	73[h]	17
17	**2b**	**3h**	THF	20	**4h**	60	79[i]	8
18	**2a**	**3a**	THF	12	**4l**	100	86	< 5
19	**2a**	**3c**	THF	12	**4j**	100	82	9
20	**2b**	**3i**	THF	13	**4k**	100	81	11
21[j]	**2b**	**3j**	THF	16	**4l**		71	

[a] All reactions were carried out at 70–80 °C (bath temp), **2**:**3**: Fe = 1:4:0.2 unless otherwise noted. [b] Determined by ^{19}F NMR spectroscopy. [c] Isolated yields based on substrate **2**. [d] Containing a little water. [e] *p*-DNB (10 mol%) was added. [f] HQ (30 mol%) was added. [g] The reaction was carried out in air. [h] *cis*:*trans* = 1:1. [i] Isolated yield based on consumed **2b**, *cis*:*trans* = 53:47. [j] **2**:**3**: Fe = 1.3:1:0.2. Isolated yield based on consumed **3j**.



2a; R^1 = Me; **b**; R^1 = Et
3a; R^2 = Bu, R^3 = H; **b**; R^2 = n-C_6H_{13}, R^3 = H; **c**; R^2 = $EtOCH_2$ R^3 = H; **d**; R^2 = Me_3Si, R^3 = H; **e**; R^2 = $HOCH_2$, R^3 = H; **f**; R^2 = $MeCO_2CH_2$, R^3 = H; **g**; R^2R^3 = -$[CH_2]_4$-; **h**; R^2R^3 = -$[CH_2]_3$-; **i**; R^2 = CH_2=$CHCH_2OCH_2$, R^3 = H;

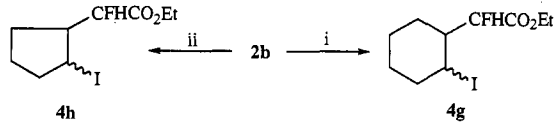
4a; R^1 = Et, R^2 = Bu, R^3 = H; **b**; R^1 = Et, R^2 = n-C_6H_{13}, R^3 = H; **c**; R^1 = Et, R^2 = $EtOCH_2$; R^3 = H; **d**; R^1 = Et, R^2 = Me_3Si, R^3 = H; **e**; R^1 = Et, R^2 = $HOCH_2$, R^3 = H; **f**; R^1 = Et, R^2 = $MeCO_2CH_2$, R^3 = H; **g**; R^1 = Et, R^2R^3 = -$[CH_2]_4$-; **h**; R^1 = Et, R^2R^3 = -$[CH_2]_3$-; **i**; R^1 = Me, R^2 = Bu, R^3 = H; **j**; R^1 = Me, R^2 = $EtOCH_2$, R^3 = H;



Scheme 2

the adduct **41** in 71% yield. Similarly, alkenes containing other functional groups, such as trimethylsilyl, alkoxy, hydroxy and ester, were tolerated under the reaction conditions and also gave the corresponding adducts in good yield. Thus, this method easily provided the precursors for the preparation of the α-fluoro-functionalized esters. Furthermore, the versatility of the retained iodo and other functionalities, such as ester, in the product makes this method very useful in organic synthesis.

The reaction was successful even with internal alkenes, although the reaction time was longer and the yield was lower (Scheme 3). Examination of the ^{19}F NMR spectrum of the crude reaction mixture in the case of addition of ester **2b** to cyclohexene **3g** revealed a 1:1 ratio of *cis* and *trans* addition products (entry 16). The reaction of compound **2b** with cyclopentene **3h** gave the corresponding *trans* and *cis* isomers in

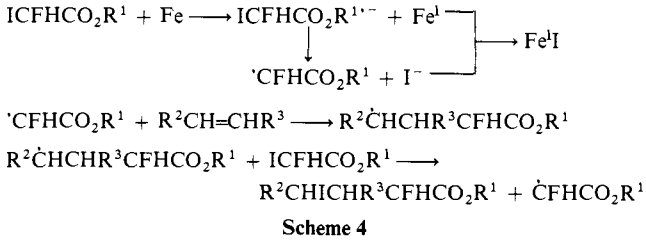


Scheme 3 *Reagents and conditions:* i, **3g**, Fe, THF, 70–80 °C; ii, **3h**, Fe, THF, 70–80 °C

a 47:53 ratio (entry 17). The structures of the isomers were assigned based on their ^{19}F NMR and ^1H NMR data.[19] These results are summarized in Table 1.

According to the widely accepted single-electron-transfer (SET) mechanism for the reaction of perfluoroalkyl iodides with alkenes initiated by metal,[20] we propose that the addition reaction of substrate **2** with alkenes **3** may also involve a single-electron-transfer process.

The reaction is initiated by electron transfer from iron to ester **2** to produce a radical anion. The radical anion rapidly decomposes to the alkoxycarbonylfluoromethyl radical, which adds to the alkene, and then abstracts iodine from a second molecule of ester **2** to give the adduct **4** and the alkoxycarbonylfluoromethyl radical, continuing the chain process (Scheme 4).



Scheme 4

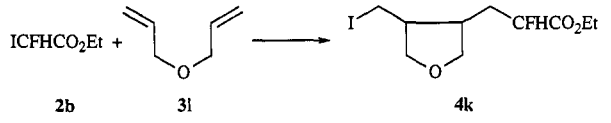
Both complete inhibition of the reaction by an electron scavenger and partial suppression by a radical inhibitor are consistent with the proposed mechanism. For example, when compound **2b** was reacted with hex-1-ene **3a** and iron (20 mol%) catalyst in the presence of *p*-dinitrobenzene (*p*-DNB; 10 mol%) at 70–80 °C for 12 h, compound **2b** remained and no 1:1 adduct **4a** was observed in the ^{19}F NMR spectrum of the reaction mixture (entry 8). A similar reaction in the presence of hydroquinone (HQ; 30 mol%) resulted in only 75% conversion

Table 2 Results of reduction of adducts **4**[a] (see Scheme 6)

Entry	4	Method	t (h)	6	Yield (%)[b]
1	**4a**	B	4	**6a**	84
2	**4a**	A	1	**6a**	88
3	**4b**	A	3	**6b**	86
4	**4c**	B	4	**6c**	82
5	**4c**	A	7	**6c**	79
6	**4d**	B	4	**6d**	79
7	**4d**	A	12	**6d**	82
8	**4g**	B	4	**6g**	73
9	**4g**	A	9	**6g**	81
10[c]	**4i**	B	4	**6i**	81
11	**4i**	A	3	**6i**	84
12	**4k**	A	10	**6k**	83

[a] Method A: **4** (1.5 mmol), Zn (3 mmol), $NiCl_2 \cdot 6H_2O$ (0.15 mmol) in moist THF (4 cm^3) under N_2 at room temperature. Method B: **4** (1 mmol), Zn (1.5 mmol), HOAc (0.5 cm^3) in ethanol (3 cm^3) under N_2 at 80 °C. [b] Isolated yields based on substrate **4**. [c] Using MeOH as solvent.

of the starting substrate **2b** as determined by ^{19}F NMR analysis (entry 9). Furthermore, stirring of compound **2b** and diallyl ether (DAE) **3i** in the presence of iron (20 mol%) at 70–80 °C, the THF derivative **4k** was obtained in 81% yield (entry 20; Scheme 5). This result shows strong evidence for a radical mechanism.[20,21]



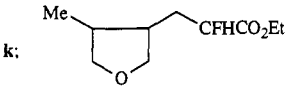
2b **3i** **4k**

Scheme 5 *Reagents and conditions:* Fe, THF, 70–80 °C

Adducts **4** could be easily reduced by treatment with Zn–$NiCl_2 \cdot 6H_2O$ in moist THF at room temperature (method A)[22] or with zinc in HOAc and ethanol at 80 °C (method B).[23] For example, when compound **4a** was added to a mixture of zinc in the presence of nickel chloride hexahydrate in moist THF and the resultant mixture was stirred at room temperature for 1 h, ^{19}F NMR analysis indicated that only α-fluoroalkanoate **6a** (88% yield) was formed. Reduction of compound **4a** by zinc in HOAc and ethanol at 80 °C for 4 h gave compound **6a** in 84% yield. As illustrated in Table 2, compounds **4b**, **4c**, **4d**, **4g**, **4i** and **4k** could also be readily converted to the corresponding iodine-free α-fluoro esters **6** by method A or B in good yields, respectively (Table 2; Scheme 6).

$$\underset{\mathbf{4}}{R^2CHICHR^3CFHCO_2R^1} + Zn \xrightarrow[\text{or HOAc–EtOH, 80 °C}]{NiCl_2 \cdot 6H_2O\text{–THF–room temp.}} \underset{\mathbf{6}}{R^2CH_2CHR^3CFHCO_2R^1}$$

6a; R^1 = Et, R^2 = Bu, R^3 = H; **b**; R^1 = Et, R^2 = n-C_6H_{13}, R^3 = H; **c**; R^1 = Et, R^2 = $EtOCH_2$, R^3 = H; **d**; R^1 = Et, R^2 = Me_3Si, R^3 = H; **g**; R^1 = Et, R^2R^3 = -$[CH_2]_4$-; **i**; R^1 = Me, R^2 = Bu, R^3 = H;



Scheme 6

The addition–reduction two-step sequence for the preparation of α-fluoro esters could be simplified without purification of the adducts **4**. After the iron-catalysed addition reaction was complete, zinc and HOAc in ethanol were added. The corresponding α-fluoro esters were obtained upon stirring of the resultant mixture at 80 °C for 4 h (Scheme 7). The results are presented in Table 3.

Although iron powder is a highly efficient initiator for the

Table 3 One-flask preparation of α-fluoroalkanoates **6** (see Scheme 7)

Entry	2	3	t (h)	6	Yield (%)[a]
1	**2b**	**3a**	17	**6a**	81
2	**2a**	**3a**	17	**6i**	76
3	**2b**	**3b**	17	**6b**	79
4	**2b**	**3c**	19	**6c**	71
5	**2b**	**3d**	16	**6d**	75
6	**2b**	**3g**	17	**6g**	67

[a] Isolated yields based on substrate **2**.

$$\underset{\mathbf{2}}{ICFHCO_2R^1} + \underset{\mathbf{3}}{R^2CH{=}CHR^3} \xrightarrow[70\text{–}80\ °C]{Fe,\ THF} [\mathbf{4}] \xrightarrow[EtOH,\ 80\ °C]{Zn,\ HOAc} \mathbf{6}$$

Scheme 7

reaction of fluoroiodoacetates with electron-rich alkenes, it does not satisfactorily initiate the reaction of fluoroiodoacetates with electron-deficient alkenes such as ethyl acrylate. Only a 30% conversion of substrate **2b** was observed in its attempted addition to ethyl acrylate **7b** *via* reaction with iron power (20 mol%), and the predominant reactions were polymerization of the acrylate and reduction of substrate **2b** to ethyl fluoroacetate **5b**. The fact that electron-deficient alkenes such as ethyl acrylate could not be used as substrates has limited the scope of the iron-initiated addition reaction.

Previous reports[24] indicated that the addition of per(poly)-fluoroalkyl iodides or bromides to electron-deficient alkenes could be efficiently initiated by a bimetal redox system. We found that the reaction of compounds **2** with electron-deficient alkenes could also be readily initiated by a bimetal redox system.

In a preliminary series of experiments, the electron sources YCl_3–Zn,[24b] $CrCl_3 \cdot 6H_2O$–Zn, bromo(pyridine)cobaloxime(III)–Zn,[24c,d] $CrCl_3 \cdot 6H_2O$–Fe[24e] and $C_2H_5CO_2H$–Zn,[25] as catalysts in the reaction of ethyl fluoroiodoacetate **2b** with ethyl acrylate **7b**, were examined. As a result, $CrCl_3 \cdot 6H_2O$–Zn, $C_2H_5CO_2H$–Zn, bromo(pyridine)cobaloxime(III)–Zn and YCl_3–Zn were found not to initiate the above reaction to give the desired 1:1 adducts, and only ethyl fluoroacetate **5b** was obtained, in 100% yield as estimated by ^{19}F NMR spectroscopy. Although the adducts were obtained in the case of the reaction of substrate **2b** with alkene **7b** catalysed by $CrCl_3 \cdot 6H_2O$–Fe redox system in ethanol, a significant amount (48%) of the toxic ester **5b** was observed by ^{19}F NMR analysis in the reaction mixture.

A careful search for more favourable reaction conditions resulted in the observation of a beneficial effect due to the introduction of pyridine (py) in the reaction medium. On addition of pyridine (4 mol equiv. relative to $CrCl_3 \cdot 6H_2O$), the ratio of α-fluoro ester **8b** to ethyl fluoroacetate **5b** increased from 52:48 to 71:29 (Table 4, entries 1, 2). The reaction conditions could be further optimized by the replacement of pyridine by 2,2'-bipyridine (bpy), as a putative ligand of a presumably active low-valent chromium species, in ethanol solution. As shown in Table 4, the ratio of **8b**:**5b** was raised to 81:19 (entry 3). Solvents showed a significant effect on this reaction. For example, upon reaction of compound **2b** with electron-deficient alkenes **7b** initiated by $CrCl_3 \cdot 6H_2O$–Fe redox system in the presence of bpy in ethanol solution, a 81% yield (estimated by ^{19}F NMR spectroscopy) was obtained whereas in THF or in DMF solution a decreased yield was obtained (entries 3–5). Thus, the best reaction conditions were the following: A mixture of a catalytic amount of $CrCl_3 \cdot 6H_2O$ (0.2 mol. equiv.) and an excess of iron powder (1.5 mol equiv.) in ethanol was stirred under nitrogen for 5 min, then added bpy (0.4 mol equiv.) was added. After 15 min, a solution of fluoroiodoacetate **2** (1.0 mol equiv.) and electron-deficient alkene **7** (1.5 mol equiv.) in ethanol was added dropwise to the

Table 4 The addition of fluoroiodoacetates **2** to electron-deficient alkenes **7**[a] (see Scheme 8)

Entry	2	7	t (h)	8	Conv. (%)[b]	8 (%)[c]	5 (%)[b]
1[d]	b	b	8	$EtO_2CCH_2CH_2CFHCO_2Et$ **8b**	92	52[b]	48
2[e]	b	b	10	**8b**	100	71[b]	29
3	b	b	10	**8b**	100	81[b] (69)	19
4[f]	b	b	10	**8b**	100	57[b]	24
5[g]	b	b	10	**8b**	100	54[b]	22
6[h]	b	b	12		0		
7[i]	b	b	12	**8b**	72		
8[j]	a	a	11	$MeO_2CCH_2CH_2CFHCO_2Me$ **8a**	100	71	17
9[j]	a	c	10	$MeO_2CCFHCH_2CH_2CN$ **8c**	100	74	14
10	b	c	10	$EtO_2CCFHCH_2CH_2CN$ **8d**	100	78	10
11	b	d	12	$CH_3COCH_2CH_2CFHCO_2Et$ **8e**	100	75	12
12	b	a	12	$MeO_2CCH_2CH_2CFHCO_2Et$ **8f**	100	67	21

[a] All reactions were carried out in ethanol at 70–80 °C unless otherwise noted; **2**:**7**:Fe:$CrCl_3$·$6H_2O$: Bpy = 1:1.5:1.5:0.2:0.4. [b] Determined by ^{19}F NMR spectroscopy. [c] Isolated yields based on substrate **2**. [d] In the absence of bpy. [e] Replacement of Bpy by Py. [f] Using THF as solvent. [g] Using DMF as solvent. [h] *p*-DNB (10 mol%) was added. [i] HQ (30 mol%) was added. [j] Using MeOH as solvent.

mixture at 70–80 °C. The reaction mixture was stirred until disappearance of the starting material. Usual work-up gave 1:1 iodine-free hydro adducts **8** (Scheme 8). The results obtained are summarized in Table 4.

$$\underset{\mathbf{2}}{ICFHCO_2R^1} + \underset{\mathbf{7}}{CH_2{=}CHEWG} \xrightarrow[\text{Bpy, EtOH}]{\text{Fe, } CrCl_3{\cdot}6H_2O} R^1O_2CCFHCH_2CH_2EWG + \underset{\mathbf{8}}{\mathbf{5}}$$

7a; EWG = CO_2Me; **b**; EWG = CO_2Et; **c**; EWG = CN; **d**; EWG = COMe

Scheme 8 Compounds **8** are enumerated in Table 4.

Such an addition proceeded smoothly with various alkenes. No polymerized or telomerized product was founded. Ethyl acrylate **7b** gave the corresponding adduct **8b** in 69% yield. When methanol was used as solvent, methyl acrylate **7a** gave the corresponding methyl ester **8a** in 71% yield. In addition, this reaction also worked well with acrylonitrile **7c**, and α,β-unsaturated ketones such as methyl vinyl ketone **7d**.

The reaction is also believed to proceed through a single-electron-transfer mechanism (Scheme 9). Evidence consistent

$$\underset{\mathbf{2}}{ICFHCO_2R^1} + Cr(bpy)_2^{2+} \longrightarrow ICFHCO_2R^{1\cdot -} + Cr(bpy)_2^{3+} \longrightarrow Cr(bpy)_2I$$

(i. Fe; ii. Bpy)

$$Cr^{3+} \cdot CFHCO_2R^1 + I^-$$

$$\cdot CFHCO_2R^1 + CH_2{=}CHEWG \longrightarrow \underset{\mathbf{8'}}{R^1O_2CCFHCH_2\dot{C}HEWG}$$

$$R^1O_2CCFHCH_2\dot{C}HEWG \longrightarrow R^1O_2CCFHCH_2CH_2EWG$$

Scheme 9

with the proposed mechanism is that the reaction could be completely inhibited by *p*-dinitrobenzene (entry 6) and partially suppressed by hydroquinone (entry 7).

The initial step of the reaction might involve an electron transfer from the *in situ* generated low-valent chromium species to fluoroiodoacetate **2**. The radical formed after cleavage of the halide added to the alkenes **7** to form radical **8'**, which gave adduct product **8** by abstraction of a hydrogen atom or further reduction of the intermediate radical adduct.

In conclusion, the strategy outlined here for preparation of α-fluoro esters avoids the utilization of toxic and hazardous materials and extreme reaction conditions. The ready availability of suitable catalysts and precursors, the simplicity of the experimental procedure, and the good yields obtained make this approach a simple and practical route for the synthesis of a variety of biologically important α-fluoro-functionalized esters.

Experimental

All boiling points were uncorrected. IR spectra were obtained with a Shimadzu IR-440 instrument. Proton magnetic resonance spectra were recorded with a JEOL FX-90Q (90 MHz) or Bruker AM-300 (300 MHz) spectrometer and are reported in ppm downfield of internal tetramethylsilane (δ-units); ^{19}F magnetic resonance spectra were measured with external CF_3CO_2H (TFA) standard by a Varian EM-360 (56.4 MHz) spectrometer (upfield positive). *J*-Values are given in Hz. Mass spectral data were taken on a Hewlett–Packard HP-5989A spectrometer and HRMS data were obtained on a Finnigan MAT-8430 spectrometer.

Methyl chlorofluoroacetate **1a** and ethyl chlorofluoroacetate **1b** were prepared by the literature procedure.[18] 5-Methyl-2-(prop-2-enyl)isoxazol-3(2*H*)-one **3j** was prepared according to the literature procedure.[26] $NiCl_2$·$6H_2O$, $CrCl_3$·$6H_2O$, NaI, zinc, py, bpy and all alkenes were used without purification. Iron powder as commercial reagent was simply treated with 10% hydrochloric acid, washed successively, with water, acetone, and diethyl ether, and subsequently dried under reduced pressure. THF, acetone, acetonitrile, hexane, and DMF were dried and distilled before use by the usual procedures. AcOH, anhydrous MeOH and EtOH as commercial reagents were used without purification.

General procedure for the preparation of fluoroiodoacetates 2

A solution of chlorofluoroacetate **1** (0.2 mol) in dry acetone (40 cm^3) was added, during 1 h, to a stirred solution of anhydrous sodium iodide (0.5 mol) in dry acetone (160 cm^3) at room temperature. When the addition was complete the reaction mixture was stirred under reflux for 5 h. The solution was condensed under reduced pressure to 100 cm^3 and then treated with water (200 cm^3) and extracted with diethyl ether (3 × 100 cm^3). The combined ethereal layers were washed (saturated aq. $NaHSO_3$ and water successively), then dried over $MgSO_4$. After removal of the diethyl ether, the residual liquid was distilled under reduced pressure to give fluoroiodoacetate **2**.

Methyl fluoroiodoacetate **2a** (78%). Oil, bp 53–55 °C/12 mmHg; δ_F(60 MHz; CCl_4) 82.0 (1 F, d, *J* 51.0, CFH); δ_H(90 MHz; CCl_4) 3.77 (3 H, s, Me) and 6.91 (1 H, d, *J* 51.0, CFH).

Ethyl fluoroiodoacetate **2b** (91%). Oil, bp 63–64 °C/11 mmHg (lit.,[27] 68–72 °C/14 mmHg); δ_F(60 MHz; CCl_4) 82.0 (1 F, d, *J* 51.0, CFH); δ_H(90 MHz; CCl_4) 1.30 (3 H, t, *J* 7.0, Me), 4.26 (2 H, q, *J* 7.0, CH_2) and 6.92 (1 H, d, *J* 51.0, CFH).

General procedure for the preparation of 2-fluoro-4-iodo esters 4

A heterogeneous mixture of acid-washed iron powder (1 mmol), electron-rich alkene **3** (20 mmol), fluoroiodoacetate **2** (5 mmol) and THF (10 cm^3) was stirred at 70–80 °C (bath temp.)

under nitrogen for 11–24 h. The mixture was then poured into water and extracted with diethyl ether (3 × 20 cm^3). The combined ethereal layers were washed (saturated aq. $NaHSO_3$ and brine, successively), then dried over $MgSO_4$. The solvent was removed, and the product was chromatographed on silica gel with ethyl acetate–light petroleum (distillation range 60–90 °C) as eluent, to give the corresponding compound **4**.

Ethyl 2-fluoro-4-iodooctanoate **4a** (87%). Oil, bp 101–102 °C/0.2 mmHg (Found: C, 37.5; H, 5.6; F, 5.6. Calc. for $C_{10}H_{18}FIO_2$: C, 37.99; H, 5.74; F, 6.01%); ν_{max}(neat)/cm^{-1} 2910, 1765, 1740, 1280, 1200, 1080 and 1030; δ_F(60 MHz; $CDCl_3$) 112.4 (0.43 F, dt, *J* 48.8 and 24.4, CFH) and 116.8 (0.57 F, m, CFH); δ_H(300 MHz; $CDCl_3$) 0.92 (3 H, t, *J* 6.9, Me), 1.21–2.71 (11 H, m), 4.27 (3 H, m, CH_2O and CHI), 5.07 (0.43 H, ddd, *J* 48.8, 7.5 and 5.2, CFH) and 5.16 (0.57 H, ddd, *J* 49.5, 10.8 and 2.2, CFH); *m*/*z* 271 (M^+ − EtO, 1.45%), 189 (M^+ − I, 40.48), 169 (44.23), 143 (26.67), 123 (28.60), 115 (5.60) and 95 (M^+ − HI − HF − CO_2Et, 100).

Ethyl 2-fluoro-4-iododecanoate **4b** (91%). Oil (Found: C, 41.7; H, 6.3. Calc. for $C_{12}H_{22}FIO_2$: C, 41.87; H, 6.44%); ν_{max}(neat)/cm^{-1} 2900, 1765, 1740, 1200, 1080 and 1020; δ_F(60 MHz; $CDCl_3$) 112.5 (0.41 F, dt, *J* 48.8 and 24.4, CFH) and 116.9 (0.59 F, m, CFH); δ_H(300 MHz; $CDCl_3$) 0.89 (3 H, t, *J* 6.85, Me), 1.22–2.56 (15 H, m), 4.20–4.31 (3 H, m, CHI and CH_2O), 5.08 (0.41 H, ddd, *J* 48.8, 7.5 and 5.2, CFH) and 5.17 (0.59 H, ddd, *J* 49.5, 10.8 and 2.2, CFH); *m*/*z* 345 (M^+ + 1, 8.56%), 299 (1.72), 217 (M^+ − I, 33.86), 197 (27.83), 171 (15.91), 151 (26.16) and 123 (M^+ − CO_2Et − HF − HI, 100).

Ethyl 5-ethoxy-2-fluoro-4-iodopentanoate **4c** (84%). Oil, bp 79–80 °C/0.08 mmHg (Found: C, 34.0; H, 5.0. Calc. for $C_9H_{16}FIO_3$: C, 33.98; H, 5.07%); ν_{max}(neat)/cm^{-1} 2900, 1760, 1735, 1200 and 1085; δ_F(60 MHz; $CDCl_3$) 112.5 (0.44 F, dt, *J* 49.0 and 24.5, CFH) and 116.5 (0.56 F, m, CFH); δ_H(300 MHz; $CDCl_3$) 1.28 (6 H, m), 2.43 (2 H, m, CH_2CFH), 3.47–3.80 (4 H, m, CH_2OCH_2), 4.27 (2 H, q, *J* 7.1, CO_2CH_2), 4.32 (1 H, m, CHI), 5.06–5.11 (0.5 H, m, CFH) and 5.23–5.27 (0.5 H, m, CFH); *m*/*z* 319 (M^+ + 1, 7.61%), 273 (M^+ − EtO, 100), 253 (9.53), 225 (7.01), 191 (M^+ − I, 50.75), 145 (4.60) and 117 (M^+ − HI − CO_2Et, 59.00).

Ethyl 2-fluoro-4-iodo-4-(trimethylsilyl)butanoate **4d** (88%). Oil (Found: M^+, 332.0119. $C_9H_{18}FIO_2Si$ requires M, 332.0105); ν_{max}(neat)/cm^{-1} 2920, 1760, 1735, 1242, 1065 and 1030; δ_F(60 MHz; CCl_4) 109.2 (0.42 F, dt, *J* 48.0 and 24.0, CFH) and 117.5 (0.58 F, m, CFH); δ_H(300 MHz; $CDCl_3$) 0.17 (9 H, s, 3 × Me), 1.31 (3 H, t, *J* 7.1, $CO_2CH_2CH_3$), 2.36–1.97 (2 H, m, CH_2Si), 3.25 (1 H, m, CHI), 4.27 (2 H, q, *J* 7.1, CH_2O), 5.08 (0.42 H, ddd, *J* 48.0, 6.8 and 5.6, CFH) and 5.16 (0.58 H, m, CFH); *m*/*z* 333 (M^+ + 1, 3.26%), 317 (M^+ − CH_3, 7.75), 205 (M^+ − I, 19.24), 195 (M^+ − I − HF, 33.41), 167 (M^+ − $SiMe_3$ − HF − CO_2Et, 54.09) and 73 (Me_3Si, 100).

Ethyl 2-fluoro-5-hydroxy-4-iodopentanoate **4e** (47%). Oil [Found: M^+ − EtO, 244.9463. $C_5H_7FIO_2$ ($C_7H_{12}FIO_3$ − EtO) requires *m*/*z*, 244.9474]; ν_{max}(neat)/cm^{-1} 3370 (OH), 2910, 1750, 1200 and 1080; δ_F(60 MHz; $CDCl_3$) 113 (0.46 F, dt, *J* 49.0 and 24.5, CFH) and 116.7 (0.54 F, m, CFH); δ_H(300 MHz; $CDCl_3$) 1.32 (3 H, t, *J* 7.0, Me), 2.38 (2 H, m, CH_2CFH), 2.51 (1 H, br, OH), 3.9–4.5 (5 H, m) and 5.01–5.34 (1 H, m, CFH); *m*/*z* 273 (M^+ − OH, 45.29%), 253 (9.02), 245 (M^+ − EtO, 17.35), 225 (M^+ − EtO − HF, 17.35), 199 (M^+ − H_2O − CO_2Et, 3.59), 163 (M^+ − I, 32.14), 117 (M^+ − HI − EtO, 100) and 89 (94.30).

Ethyl 5-acetoxy-2-fluoro-4-iodopentanoate **4f** (81%). Oil (Found: C, 32.15; H, 4.1. Calc. for $C_9H_{14}FIO_4$: C, 32.55; H, 4.25%); ν_{max}(neat)/cm^{-1} 2930, 1750, 1740, 1220, 1085 and 1020; δ_F(60 MHz; $CDCl_3$) 112.4 (0.42 F, dt, *J* 49.4 and 24.7, CFH) and 116.3 (0.58 F, m, CFH); δ_H(300 MHz; $CDCl_3$) 1.33 (3 H, t, *J* 7.1, Me), 2.10 (3 H, s, CH_3CO_2), 2.40 (2 H, m, CH_2CFH), 4.24–4.45 (5 H, m, 2 × CH_2O and CHI), 4.98–5.08 (0.5 H, m, CFH) and 5.15–5.24 (0.5 H, m, CFH); *m*/*z* 273 (M^+ − CH_3CO_2, 23.60%), 245 (7.24), 225 (5.21), 205 (M^+ − I, 35.70), 163 (20.27) and 43 (100).

Ethyl 2-fluoro-2-(2-iodocyclohexyl)acetate **4g** (73%). Oil (Found: M^+, 314.0141. $C_{10}H_{16}FIO_2$ requires M, 314.0179); ν_{max}(neat)/cm^{-1} 2900, 1760, 1730, 1200 and 1085; δ_F(60 MHz; $CDCl_3$) 116.0 (0.5 F, dd, *J* 48.6 and 20.4, *trans*-CFH) and 130.1 (0.5 F, dd, *J* 46.5 and 30.0, *cis*-CFH); δ_H(300 MHz; $CDCl_3$) 1.2–2.32 (11 H, m), 2.60 (1 H, m, C*H*CFH), 4.28 (3 H, m, CH_2O and CHI), 5.20 (0.5 H, dd, *J* 46.5 and 3.3, *cis*-CFH) and 5.33 (0.5 H, dd, *J* 48.6 and 1.9, *trans*-CFH); *m*/*z* 315 (M^+ + 1, 16.95%), 269 (6.04), 221 (M^+ − HF − CO_2Et, 4.66), 187 (M^+ − I, 31.78), 167 (M^+ − I − HF, 97.55) and 139 (M^+ − I − HF − CH_2=CH_2, 100).

Ethyl 2-fluoro-2-(2-iodocyclopentyl)acetate **4h** (79%). Oil (Found: M^+, 300.0010. $C_9H_{14}FIO_2$ requires M, 300.0023); ν_{max}(neat)/cm^{-1} 2910, 1758, 1200 and 1060; δ_F(60 MHz; $CDCl_3$) 119.7 (0.47 F, dd, *J* 49.4 and 30.0, *trans*-CFH) and 126.3 (0.53 F, dd, *J* 48.2 and 30.0, *cis*-CFH); δ_H(300 MHz; $CDCl_3$) 1.23–2.4 (9 H, m), 2.78 (1 H, m, CFHC*H*), 4.30 (3 H, m, CHI and CH_2O), 4.88 (0.53 H, dd, *J* 48.2 and 3.6, *cis*-CFH) and 5.13 (0.47 H, dd, *J* 49.4 and 2.5, *trans*-CFH); *m*/*z* 301 (M^+ + 1, 1.54%), 173 (M^+ − I, 80.00), 153 (M^+ − I − HF, 51.70) and 125 (M^+ − I − HF − CH_2=CH_2, 100).

Methyl 2-fluoro-4-iodooctanoate **4i** (86%). Oil [Found: M^+ − EtO, 271.0003. $C_8H_{13}FIO$ ($C_9H_{16}FIO_2$ − MeO) requires *m*/*z*, 270.9994]; ν_{max}(neat)/cm^{-1} 2920, 1762, 1738, 1278, 1200 and 1075; δ_F(60 MHz; $CDCl_3$) 112.4 (0.43 F, dt, *J* 48.5 and 24.2, CFH) and 116.4 (0.57 F, m, CFH); δ_H(300 MHz; $CDCl_3$) 0.93 (3 H, t, *J* 7.1, Me), 1.28–2.56 (8 H, m), 3.82 (3 H, s, OMe), 4.24 (1 H, m, CHI), 5.12 (0.43 H, ddd, *J* 48.5, 7.3 and 5.2, CFH) and 5.21 (0.57 H, ddd, *J* 49.5, 10.8 and 2.1, CFH); *m*/*z* 303 (M^+ + 1, 7.01%), 271 (M^+ − MeO, 1.99), 175 (M^+ − I, 37.98), 155 (M^+ − I − HF, 53.91), 143 (20.97), 123 (29.25) and 95 (M^+ − HF − HI − CO_2Me, 100).

Methyl 5-ethoxy-2-fluoro-4-iodopentanoate **4j** (82%). Oil (Found: C, 31.5; H, 4.5. Calc. for $C_8H_{14}FIO_3$: C, 31.60; H, 4.64%); ν_{max}(neat)/cm^{-1} 2910, 2820, 1762, 1738, 1280, 1200 and 1085; δ_F(60 MHz; $CDCl_3$) 112.0 (0.48 F, dt, *J* 50.0 and 25.0, CFH) and 115.7 (0.52 F, m, CFH); δ_H(300 MHz; $CDCl_3$) 1.21 (3 H, t, *J* 7.0, Me), 2.19–2.64 (2 H, m, CFHCH_2), 3.50–3.81 (4 H, m, 2 × CH_2O), 3.82 (3 H, s, CO_2Me), 4.32 (1 H, m, CHI), 5.08–5.13 (0.5 H, m, CFH) and 5.25–5.29 (0.5 H, m, CFH); *m*/*z* 305 (M^+ + 1, 7.96%), 273 (M^+ − MeO, 5.31), 259 (M^+ − EtO, 100), 239 (17.76), 177 (M^+ − I, 75.41), 131 (6.82) and 117 (77.60).

Ethyl 2-fluoro-3-[4-(iodomethyl)tetrahydrofuran-3-yl]propionate **4k** (81%). Oil, bp 126–128 °C/0.1 mmHg (Found: C, 36.7; H, 5.0. Calc. for $C_{10}H_{16}FIO_3$: C, 36.38; H, 4.89%); ν_{max}(neat)/cm^{-1} 2929, 2860, 1760, 1440, 1380, 1280, 1200 and 1075; δ_F(60 MHz; $CDCl_3$) 112.4–116.0 (1 F, m, CFH); δ_H(300 MHz; $CDCl_3$) 1.33 (3 H, t, *J* 7.1, Me), 1.8–2.32 (3 H, m), 2.4–3.75 (5 H, m), 3.98 (2 H, m, CH_2I), 4.28 (2 H, q, *J* 7.1, CO_2CH_2), 4.85–4.89 (0.5 H, m, CFH) and 5.02–5.05 (0.5 H, m, CFH); *m*/*z* 331 (M^+ + 1, 100.00%), 330 (M^+, 4.87), 285 (15.80), 257 (M^+ − CO_2Et, 8.25), 203 (M^+ − I, 52.68), 173 (M^+ − I − HF, 37.33), 157 (38.72), 109 (25.16) and 81 (59.24).

Ethyl 2-fluoro-4-iodo-5-(5-methyl-3-oxo-2,3-dihydroisoxazol-2-yl)pentanoate **4l** (71%). Oil (Found: C, 35.6; H, 4.0; N, 3.7. Calc. for $C_{11}H_{15}FINO_4$: C, 35.60; H, 4.07; N, 3.77%); ν_{max}(neat)/cm^{-1} 2995, 1760, 1685, 1635, 1200, 1090 and 1020; δ_F(60 MHz; $CDCl_3$) 114.0 (0.45 F, dt, *J* 49.0 and 24.5, CFH) and 118.2 (0.55 F, m, CFH); δ_H(300 MHz; $CDCl_3$) 1.28 (3 H, m, $CO_2CH_2CH_3$), 2.21 [3 H, s, C(5)Me], 2.37 (2 H, m, CFHCH_2), 4.09–4.48 (5 H, m, CH_2O, CHI and CH_2N), 4.99–5.05 (0.5 H, m, CFH), 5.15–5.21 (0.5 H, m, CFH) and 5.46 [1 H, s, C(4)H]; *m*/*z* 372 (M^+ + 1, 8.23%), 326 (M^+ − EtO, 12.91), 298 (M^+ − CO_2Et, 3.43), 199 (M^+ − I − EtO, 13.84), 112 (100) and 98 (23.23).

Reaction of ester 2b with hex-1-ene 3a and iron powder in the presence of inhibitor

A mixture of acid-washed iron powder (1 mmol), electron-rich alkene **3** (20 mmol), ethyl fluoroiodoacetate **2b** (5 mmol), *p*-dinitrobenzene (0.5 mmol) and THF (10 cm^3) was stirred at 70–80 °C under nitrogen for 12 h. ^{19}F NMR spectroscopy indicated that no reaction had occurred, and only substrate **2b** was detected.

Similarly, after a mixture of acid-washed iron powder (1 mmol), electron-rich alkene **3** (20 mmol), ethyl fluoroiodoacetate **2b** (5 mmol), hydroquinone (1.5 mmol) and THF (10 cm^3) was stirred at 70–80 °C under nitrogen for 12 h, ^{19}F NMR analysis indicated that the conversion of substrate **2b** was 75%.

Reduction of adducts 4 with zinc in the presence of nickel dichloride hexahydrate (method A)

Typical procedure. A mixture of zinc (3 mmol), $NiCl_2{\cdot}6H_2O$ (0.15 mmol), a drop of water, and THF (4 cm^3) was stirred at room temperature for 10 min; adduct **4** (1.5 mmol) was added, and the resultant mixture was stirred at room temp. for 1–12 h and then poured into a beaker containing aq. NH_4Cl (10 cm^3) and diethyl ether (20 cm^3). Solids were removed by filtration, and the organic layer was separated. The aqueous layer was extracted with diethyl ether (3 × 10 cm^3) and the combined ethereal layers were washed with brine, then dried over $MgSO_4$. The solvent was removed, and the residue was purified by chromatography on silica gel with ethyl acetate–light petroleum (60–90 °C) as eluent, to give compound **6**.

Ethyl 2-fluorooctanoate **6a**[17] (88%). Oil; δ_F(60 MHz; $CDCl_3$) 114.1 (1 F, dt, *J* 49.0 and 24.5, CFH); δ_H(300 MHz; $CDCl_3$) 0.89 (3 H, t, *J* 7.0, Me), 1.25–1.51 (11 H, m), 1.8–1.95 (2 H, m, CH_2CF), 4.25 (2 H, q, *J* 7.1, CH_2) and 4.86 (1 H, dt, *J* 49.0 and 6.0, CFH); *m/z* 191 (M^+ + 1, 4.95%), 190 (M^+, 2.70), 161 (15.03), 129 (21.45), 106 ($M^+ - CH_2{=}CH[CH_2]_3CH_3$, 100), 101 (15.32), 78 (39.49), 69 (18.77), 55 (53.09) and 43 (34.26).

Ethyl 2-fluorodecanoate **6b**[17] (86%). Oil; ν_{max}(neat)/cm^{-1} 2900, 1761, 1738, 1195 and 1080; δ_F(60 MHz; $CDCl_3$) 114.2 (1 F, dt, *J* 49.0 and 24.5, CFH); δ_H(300 MHz; $CDCl_3$) 0.89 (3 H, t, *J* 7.0, Me), 1.18–1.52 (15 H, m), 1.85 (2 H, m, $CFCH_2$), 4.26 (2 H, q, *J* 7.1, CO_2CH_2) and 4.86 (1 H, dt, *J* 49.0 and 6.0, CFH); *m/z* 219 (M^+ + 1, 14.02%), 173 (0.51), 106 ($M^+ - CH_2{=}CH[CH_2]_5CH_3$, 100), 78 (35.22), 69 (17.46), 57 (22.06) and 43 (31.12).

Ethyl 5-ethoxy-2-fluoropentanoate **6c** (79%). Oil (Found: M^+, 192.1165. $C_9H_{17}FO_3$ requires M, 192.1162); ν_{max}(neat)/cm^{-1} 2910, 2800, 1758, 1735, 1190 and 1100; δ_F(60 MHz; $CDCl_3$) 115.0 (1 F, dt, *J* 50.0 and 25.0, CFH); δ_H(300 MHz; $CDCl_3$) 1.20 (3 H, t, *J* 7.1, Me), 1.31 (3 H, t, *J* 7.1, Me), 1.75 (2 H, m, CH_2), 1.85–2.10 (2 H, m, $CFCH_2$), 3.47 (4 H, m, 2 × CH_2O), 4.26 (2 H, q, *J* 7.1, CO_2CH_2) and 4.94 (1 H, ddd, *J* 50.0, 7.6 and 4.3, CFH); *m/z* 193 (M^+ + 1, 31.94%), 192 (M^+, 2.29), 163 (28.26), 147 (M^+ – EtO, 83.46), 119 ($M^+ - CO_2Et$, 48.57) and 59 (100).

Ethyl 2-fluoro-4-(trimethylsilyl)butanoate **6d**[17] (82%). Oil; ν_{max}(neat)/cm^{-1} 2910, 1762, 1738, 1240, 1200, 1075 and 1020; δ_F(60 MHz; $CDCl_3$) 114.2 (1 F, dt, *J* 49.3 and 24.7, CFH); δ_H(300 MHz; $CDCl_3$) 0.0 (9 H, s, 3 × Me), 0.6 (2 H, m, $SiCH_2$), 1.29 (3 H, t, *J* 7.1, $CO_2CH_2CH_3$), 1.87 (2 H, m, $CFCH_2$), 4.25 (2 H, q, *J* 7.1, CO_2CH_2) and 4.80 (1 H, ddd, *J* 49.3, 6.3 and 5.1, CFH); *m/z* 191 ($M^+ - CH_3$, 17.21%), 161 (M^+ – EtO, 2.30), 133 ($M^+ - SiMe_3$, 4.49) and 73 (Me_3Si, 100).

Ethyl 2-cyclohexyl-2-fluoroacetate **6g** (81%). Oil (Found: M^+, 188.1204. $C_{10}H_{17}FO_2$ requires M, 188.1212); ν_{max}(neat)/cm^{-1} 2900, 1760, 1734, 1254, 1100 and 1020; δ_F(60 MHz; $CDCl_3$) 121.0 (1 F, dd, *J* 49.3 and 22.0, CFH); δ_H(300 MHz; $CDCl_3$) 1.12–2.0 (14 H, m), 4.26 (2 H, q, *J* 7.1, CO_2CH_2) and 4.67 (1 H, dd, *J* 49.3 and 4.3, CFH); *m/z* 189 (M^+ + 1, 14.03%) and 106 ($M^+ - C_6H_{10}$, 100.00).

Methyl 2-fluorooctanoate **6i** (84%). Oil [Found: M^+ – C_2H_5, 147.0859. $C_7H_{12}FO_2$ ($C_9H_{17}FO_2 - C_2H_5$) requires *m/z* 147.0821]; ν_{max}(neat)/cm^{-1} 2910, 1765, 1740, 1210 and 1080; δ_F(60 MHz; $CDCl_3$) 114.7 (1 F, dt, *J* 49.1 and 24.6, CFH); δ_H(300 MHz; $CDCl_3$) 0.87 (3 H, t, *J* 7.0, Me), 1.21–1.52 (8 H, m), 1.88 (2 H, m, CH_2CF), 3.77 (3 H, s, CO_2Me) and 4.88 (1 H, dt, *J* 49.1 and 6.0, CFH); *m/z* 177 (M^+ + 1, 71.37%), 147 (15.66), 127 (6.11), 115 (20.40) and 92 ($M^+ - CH_2{=}CH[CH_2]_3CH_3$, 100).

Ethyl 2-fluoro-3-(4-methyltetrahydrofuran-3-yl)propionate **6k**[17] (83%). Oil; ν_{max}(neat)/cm^{-1} 2980, 1770, 1745, 1210, 1090 and 1030; δ_F(60 MHz; $CDCl_3$) 114.2 (1 F, dt, *J* 49.2 and 24.6, CFH); δ_H(300 MHz; $CDCl_3$) 0.97 (2.1 H, dd, *J* 6.6 and 1.0, *trans*-CH_3), 1.06 (0.9 H, dd, *J* 10.2 and 6.2, *cis*-CH_3), 1.33 (3 H, t, *J* 7.1, Me), 1.75–2.25 (2 H, m, CHCH), 2.39 (2 H, m, $CFCH_2$), 3.44–4.02 (4 H, m, CH_2OCH_2), 4.27 (2 H, q, *J* 7.1, CO_2CH_2), 4.80–4.85 (0.5 H, m, CFH) and 4.96–5.02 (0.5 H, m, CFH); *m/z* 204 (M^+, 3.53%), 159 (M^+ – EtO, 5.96), 139 (10.44), 111 ($M^+ - HF - CO_2Et$, 17.84), 84 (100), 69 (68.98), 55 (27.22) and 43 (13.36).

Reduction of adducts 4 with zinc and acetic acid in ethanol (method B)

Typical procedure. A mixture of an adduct **4** (1 mmol) and zinc (1.5 mmol) in a mixture of acetic acid (0.5 cm^3) and ethanol (3 cm^3) was stirred at 80 °C for 4 h and allowed to cool. Water (10 cm^3) was added, and the aqueous layer was extracted with diethyl ether (3 × 10 cm^3). The combined ethereal layers were washed (10% aq. $NaHCO_3$ and brine, successively), then dried over $MgSO_4$. The solvent was removed, and the residue was purified by chromatography on silica gel with ethyl acetate–light petroleum (60–90 °C) as eluent, to give the corresponding compound **6**. Products **6a**, **6c**, **6d**, **6g** and **6i** were obtained in 84, 82, 79, 73 and 81% yield, respectively.

General procedure for the one-flask preparation of 2-fluoro esters 6

Preparation of 2-fluoro esters **6** was carried out as previously described using acid-washed iron powder (1 mmol), electron-rich alkene **3** (20 mmol), fluoroiodoacetate **2** (5 mmol) and THF (10 cm^3). After the mixture had been stirred at 70–80 °C (bath temp.) under nitrogen for 12 h, zinc (10 mmol), acetic acid (2 cm^3) and EtOH (5 cm^3) were added to the reaction mixture. The resultant mixture was stirred at 80 °C for an additional 4–6 h and then cooled to room temperature. Water (30 cm^3) was added, and the aqueous layer was extracted with diethyl ether (3 × 20 cm^3). The combined ethereal layers were washed (10% aq. $NaHCO_3$ and brine successively), then dried over $MgSO_4$. The solvent was removed, and the residue was purified by chromatography on silica gel with ethyl acetate–light petroleum (60–90 °C) as eluent, to give the corresponding compound **6**. Products **6a–d**, **6g** and **6i** were obtained in 81, 79, 71, 75, 67, and 76% yield, respectively.

General procedure for the addition reaction of fluoroiodoacetates 2 to electron-deficient alkenes 7 initiated by the $CrCl_3{\cdot}6H_2O$–Fe–bpy redox system

A mixture of iron powder (7.5 mmol) and $CrCl_3{\cdot}6H_2O$ (1 mmol) in ethanol (10 cm^3) was stirred under nitrogen for 5 min, then bpy (2 mmol) was added. After 15 min, a solution of fluoroiodoacetate **2** (5 mmol) and electron-deficient alkene **7** (7.5 mmol) in ethanol (5 cm^3) was added dropwise to the mixture at 70–80 °C. The reaction mixture was stirred until disappearance of the starting material. The mixture was then poured into 10% aq. hydrochloric acid (30 cm^3) and extracted with diethyl ether (3 × 20 cm^3). The combined ethereal layers were washed (10% aq. $NaHCO_3$ and brine, successively), then dried over $MgSO_4$. The solvent was removed, and the residue was purified by chromatography on silica gel with ethyl acetate–light petroleum (60–90 °C) as eluent, to give the corresponding compound **8**.

Dimethyl 2-fluoropentanedioate **8a** (71%). Oil [Found: M^+ − MeO, 147.0422. $C_6H_8FO_3$ ($C_7H_{11}FO_4$ − MeO) requires *m/z*, 147.0457]; ν_{max}(neat)/cm^{-1} 2900, 1760, 1738, 1435, 1200 and 1078; δ_F(60 MHz; $CDCl_3$) 116.0 (1 F, dt, *J* 48.8 and 24.4, CFH); δ_H(300 MHz; $CDCl_3$) 2.1–2.4 (2 H, m, $CFCH_2$), 2.51 (2 H, m, CH_2CO_2), 3.7 (3 H, s, Me), 3.81 (3 H, s, Me) and 5.0 (1 H, ddd, *J* 48.8, 7.9 and 4.3, CFH); *m/z* 179 (M^+ + 1, 9.33%), 147 (M^+ − MeO, 74.28), 119 (M^+ − CO_2Me, 97.73), 71 (63.17) and 59 (100).

Diethyl 2-fluoropentanedioate **8b**[12b] (69%). Oil; ν_{max}(neat)/cm^{-1} 1758, 1735, 1190 and 1080; δ_F(60 MHz; $CDCl_3$) 116.2 (1 F, dt, *J* 49.0 and 24.4, CFH); δ_H(300 MHz; $CDCl_3$) 1.27 (3 H, t, Me), 1.32 (3 H, t, *J* 7.0, Me), 2.20 (2 H, m, $CFCH_2$), 2.50 (2 H, m, CH_2CO_2), 4.16 (2 H, q, *J* 7.0, $CH_2CO_2CH_2$), 4.27 (2 H, q, *J* 7.0, $CFHCO_2CH_2$) and 4.90 (1 H, ddd, *J* 49.0, 7.7 and 4.3, CFH); *m/z* 161 (M^+ − EtO, 73.95%), 133 (31.45) and 105 (100).

Methyl 4-cyano-2-fluorobutanoate **8c** (74%). Oil (Found: M^+, 145.0550. $C_6H_8FNO_2$ requires M, 145.0539); ν_{max}(neat)/cm^{-1} 2900, 1755, 1745, 1440, 1220 and 1080; δ_F(60 MHz; $CDCl_3$) 116.7 (1 F, dt, *J* 48.3 and 24.2, CFH); δ_H(300 MHz; $CDCl_3$) 2.21 (2 H, m, $CFCH_2$), 2.58 (2 H, m, CH_2CN), 3.84 (3 H, s, Me) and 5.04 (1 H, ddd, *J* 48.3, 7.7 and 4.1, CFH); *m/z* 146 (M^+ + 1, 90.53%), 114 (12.19), 86 (M^+ − CO_2Me, 13.96) and 55 (100).

Ethyl 4-cyano-2-fluorobutanoate **8d** (78%). Oil (Found: M^+, 159.0698. $C_7H_{10}FNO_2$ requires M, 159.0696); ν_{max}(neat)/cm^{-1} 2980, 1762, 1220, 1200 and 1090; δ_F(60 MHz; $CDCl_3$) 117.0 (1 F, dt, *J* 48.4 and 24.2, CFH); δ_H(300 MHz; $CDCl_3$) 1.33 (3 H, t, *J* 7.1, Me), 2.27 (2 H, m, $CFCH_2$), 2.58 (2 H, m, CH_2CN), 4.29 (2 H, q, *J* 7.1, CH_2O) and 5.01 (1 H, ddd, *J* 48.4, 7.9 and 4.0, CFH); *m/z* 160 (M^+ + 1, 100%), 158 (M^+ − 1, 1.64), 132 (M^+ − HCN, 95.49), 114 (M − EtO, 35.19), 86 (M^+ − CO_2Et, 51.76) and 69 (31.42).

Ethyl 2-fluoro-5-oxohexanoate **8e**[12b] (75%). Oil; ν_{max}(neat)/cm^{-1} 2930, 1758, 1712, 1200 and 1080; δ_F(60 MHz; $CDCl_3$) 116.1 (1 F, dt, *J* 49.0 and 24.5, CFH); δ_H(300 MHz; $CDCl_3$) 1.30 (3 H, t, *J* 7.1, Me), 2.16 (3 H, s, COMe), 1.93–2.34 (2 H, m), 2.62 (2 H, m), 4.24 (2 H, q, *J* 7.1, CO_2CH_2) and 4.92 (1 H, ddd, *J* 49.0, 7.6 and 4.5, CFH); *m/z* 177 (M^+ + 1, 100%), 176 (M^+, 7.53), 161 (M^+ − CH_3, 2.45), 131 (M^+ − EtO, 61.08), 103 (25.30) and 43 (61.36).

1-Ethyl 5-methyl 2-fluoropentanedioate **8f** (67%). Oil (Found: M^+, 192.0812. $C_8H_{13}FO_4$ requires M, 192.0798); ν_{max}(neat)/cm^{-1} 1760 and 1740; δ_F(60 MHz; CCl_4) 115.7 (1 F, dt, *J* 48.8 and 24.4, CFH); δ_H(300 MHz; $CDCl_3$) 1.32 (3 H, t, *J* 7.1, Me), 2.20 (2 H, m), 2.50 (2 H, m), 3.70 (3 H, s, CO_2Me), 4.27 (2 H, q, *J* 7.1, CO_2CH_2) and 4.98 (1 H, ddd, *J* 49.0, 7.1 and 4.3, CFH); *m/z* 193 (M^+ + 1, 14.61%), 161 (M^+ − MeO, 100), 147 (M^+ − EtO, 17.22), 133 (M^+ − CO_2Me, 18.22) and 119 (M^+ − CO_2Et, 29.70).

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