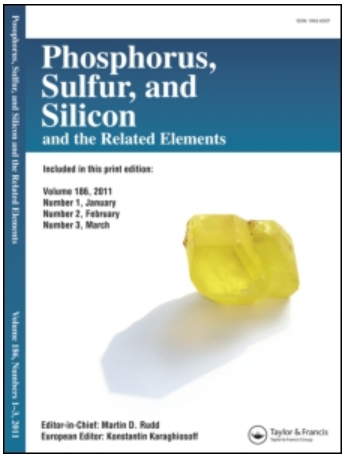

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STEREOSELECTIVE SYNTHESIS OF MONOFLUORO-OLEFINS FROM DIISOPROPYL(CARBOETHOXYFLUORO-METHYL)PHOSPHONATE

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Treatment of ethyl oxalyl chloride or methyl oxalyl chloride with lithium diisopropyl(carboethoxyfluoromethyl)phosphonate $[(i\text{-}PrO)_2P(O)CFCO_2Et]^-Li^+$ **2** followed by *in situ* nucleophilic addition with methylmagnesium iodide or vinyl magnesium bromide affords with exclusive E-stereoselectivity formation of diethyl-2-fluoro-3-methyl fumarate $(CH_3)(CO_2Et)C{=}CFCO_2Et$ **4** or 75% of the E-isomer of α-fluoro-β-vinyl-α,β-unsaturated diester (E,Z)-$(CH_2{=}CH)(CO_2C_2H_5)C{=}CFCO_2Et$ **5**, respectively. However, direct reaction of ethyl pyruvate with **2** gives the fluoro-olefin $(CH_3)(CO_2Et)C{=}CFCO_2Et$ **4** with 79% E-stereoselectivity. The E/Z ratio of $(CH_2{=}CH)(CO_2Et)C{=}CFCO_2Et$ **5** depends on the HMPT or DMPU cosolvents present in the reaction mixture.

Keywords: fluorophosphonate ylide; acylation; diene; E-stereoselectivity; cosolvent

INTRODUCTION

Fluorine, as a substituent, can significantly affect the properties of molecular systems due to its high electronegativity and small atomic volume. Vinyl fluorides such as α-fluoro-α,β-unsaturated diesters constitute a class of fluoro-organic molecules with interesting chemical and biological properties, because fluoro-olefins are potential mechanism-based enzyme inhibitors[1,2], and can be used as isosteric replacements for an amide bond in peptides.[3] There are only a few methods available to prepare α-fluoro-α,β-unsaturated diesters. Machleidt and Grell initially reported

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the reaction of diethyl(carboethoxyfluoromethyl)phosphonate anion with diethyloxalate to give diethyl 2-fluoro-3-ethoxyfumarate in 30% yield.[4] Wakselman has observed a 1:1 mixture of ethylenic triethylesters $(EtO_2CCFH)(CO_2Et)C{=}CHCO_2Et$ and the isomerization product $(EtO_2CCH_2)(CO_2Et)C{=}CFCO_2Et$ in the condensation of triphenylcarbethoxymethylene phosphorane with diethyloxalofluoroacetate in dimethylformamide.[5] We previously reported the synthesis of α-fluoro-α,β-unsaturated diester and substituted 2-fluoro-3-oxoesters from lithium diethyl fluorocarboethoxymethyl phosphonate $[(EtO)_2P(O)CFCO_2Et]^-Li^+$.[6] Herein, we describe a general, one pot synthesis of monofluoro-olefins from diisopropyl(carboethoxyfluoromethyl)phosphonate and show the different E and Z stereoselectivity of the diester prepared in the presence of metal ion (LiCl) or cosolvents such as HMPA or DMPU.

RESULTS AND DISCUSSION

Diisopropyl(carboethoxyfluoromethyl)phosphonate $(i\text{-}PrO)_2P(O)CFHCO_2Et$ **1**, prepared from triisopropyl phosphite with ethyl bromofluoroacetate,[7] reacts with n-butyllithium in THF to give the phosphonate carbanion $[(i\text{-}PrO)_2P(O)CFCO_2Et]^-Li^+$ **2**. The resultant **2** was a colorless, clear liquid and could be stored at room temperature for a longer period, at least for several days, without any change. Addition of a THF solution of anion $[(i\text{-}PrO)_2P(O)CFCO_2Et]^-Li^+$ **2** to a THF solution of ethyl oxalyl chloride or methyl oxalyl chloride forms the corresponding C-acylated phosphonates $(i\text{-}PrO)_2P(O)CF(COCO_2R')CO_2Et$ **3** ($R' = C_2H_5$, CH_3). The acylated phosphonate **3** ($R' = C_2H_5$), which was not isolated, exhibited a resonance at −176.2 ppm in the ^{19}F NMR spectrum (d, $J_{FCP} = 75$ Hz) and the proton decoupled ^{31}P NMR signals occurred as a doublet at 5.20 ppm (d, $J_{PCF} = 75$ Hz)

$$ClC(O)CO_2R' \xrightarrow[-78^\circ C \text{ to RT}]{[(i\text{-}PrO)_2P(O)CFCO_2Et]^-\,Li^+\ \mathbf{2}} \underset{\mathbf{3}}{(i\text{-}PrO)_2P(O)CF(COCO_2R')CO_2Et} + LiCl$$

$R' = C_2H_5, CH_3$

Treatment of the acylated phosphonate **3** with one equivalent of CH_3MgI or CH_2=CHMgBr gives α-fluoro-α,β-unsaturated diesters $(CH_3)(CO_2R')C$=$CFCO_2Et$ **4** and $(CH_2$=$CH)(CO_2R')C$=$CFCO_2Et$ **5** in 50–52% isolated yields.

$$(i\text{-}PrO)_2P(O)CF(COCO_2R')CO_2Et \xrightarrow[-78^{\circ}C \text{ to RT}]{RMgX} R(CO_2R')C{=}CFCO_2Et \quad (E, Z)$$

3

The results for the preparation of the α-fluoro-α,β-unsaturated diester $R(CO_2R')C$=$CFCO_2Et$ are summarized in Table I.

TABLE I Preparation of (E,Z)-$R(CO_2R')C$=$CFCO_2Et$ from $(i\text{-}PrO)_2P(O)CFHCO_2Et$

$$ClC(O)CO_2R' \xrightarrow[2)\ RMgX,\ -78^{\circ}C \text{ to RT}]{1)\ [(i\text{-}PrO)_2P(O)CFCO_2Et]^{-}Li^{+}\ \mathbf{2}} R(CO_2R')C{=}CFCO_2Et \quad (E, Z)$$

Entry	*R*	*R'*	*E/Z*[a]	*Yields (%)*[b]
1	CH_3	C_2H_5	100/0	52
2	CH_3	CH_3	100/0	50
3	CH_2=CH	C_2H_5	75/25	52
4	CH_2=CH	CH_3	72/28	51

a. E/Z ratio by ^{19}F NMR integration of the vinyl fluorine signals.
b. Isolated yields are based on $(i\text{-}PrO)_2P(O)CFHCO_2Et$.

The E-isomer is the exclusive product in the preparation of $(CH_3)(CO_2R')C$=$CFCO_2Et$ **4**. However, Z-stereoselectivity increases when R is a vinyl group (CH_2=CH-) in position 3 and 4. The repulsive interaction between the vinyl group and fluorine resulted in the formation of the E-isomer over the Z-isomer in the preparation of $(CH_2$=$CH)(CO_2Et)C$=$CFCO_2Et$ **5**.[6]

Different E/Z ratios were observed via varied methodology in the preparation of $(CH_3)(CO_2Et)C$=$CFCO_2Et$ **4**. The results are shown in Table II.

TABLE II Preparation of (E,Z)-$CH_3(CO_2Et)C{=}CFCO_2Et$ **4**

Entry	*Method*	*E/Z*[a]	*Isolated yields (%)*
1	A	100/0	52
2	B	45/55	65[b]
3	C	79/21	70

a. E/Z ratio by ^{19}F NMR integration of the vinyl fluorine signals.
b. See reference 6.

For example, acylation of the phosphonate carbanion $[(i\text{-PrO})_2P(O)CFCO_2Et]^-Li^+$ **2** with ethyl oxalyl chloride, followed by *in situ* reaction with CH_3MgI, provides a direct access to the E-isomer of $(CH_3)(CO_2Et)C{=}CFCO_2Et$ **4** (Method A).

$$ClC(O)CO_2Et \xrightarrow[2)\ CH_3MgI,\ -78^{\circ}C\ to\ RT]{1)\ [(i\text{-PrO})_2P(O)CFCO_2Et]^-Li^+} CH_3(CO_2Et)C{=}CFCO_2Et \quad \text{(Method A)}$$

4 (E / Z = 100 / 0)

Addition of ethyl pyruvate $CH_3C(O)CO_2Et$ to a THF solution of lithium diethyl(carboethoxyfluoromethyl)phosphonate anion $[(EtO)_2P(O)CFCO_2Et]^-Li^+$ gives an E/Z ratio of 45 to 55 of the compound (E,Z)-$CH_3(CO_2Et)C{=}CFCO_2Et$ (Method B)[6].

$$(EtO)_2P(O)CFHCO_2Et \xrightarrow[2)\ CH_3C(O)CO_2Et,\ -78^{\circ}C\ to\ RT]{1)\ n\text{-BuLi/THF}} CH_3(CO_2Et)C{=}CFCO_2Et \quad \text{(Method B)}$$

4 (E / Z = 45 / 55)

However, change from lithium diethyl(carboethoxyfluoromethyl) phosphonate $[(EtO)_2P(O)CFCO_2Et]^-Li^+$ to lithium diisopropyl(carboethoxyfluoromethyl)phosphonate $[(i\text{-PrO})_2P(O)CFCO_2Et]^-Li^+$ **2** leads to an increase in the E-isomer of the compound (E,Z)-$CH_3(CO_2Et)C{=}CFCO_2Et$ **4**. The E/Z ratio changes from 45/55 to 79/21 (Method C).

$$(i\text{-PrO})_2P(O)CFHCO_2Et \xrightarrow[2)\ CH_3C(O)CO_2Et,\ -78^{\circ}C\ to\ RT]{1)\ n\text{-BuLi/THF}} CH_3(CO_2Et)C{=}CFCO_2Et \quad \text{(Method C)}$$

4 (E / Z = 79 / 21)

The product **4**, prepared from Method A, exhibited a resonance at −125 ppm in the ^{19}F NMR spectrum (q, J = 4 Hz), and was assigned as the E-isomer. This assignment was confirmed by a Nuclear Overhauser Effect (NOE)[8] experiment. Figure I(a) is the normal ^{19}F NMR spectrum of compound $(CH_3)(CO_2Et)C{=}CFCO_2Et$ **4** at −125 ppm (q, J = 4.0 Hz) and Figure I(b) is the ^{19}F NMR spectrum of **4** in which the CH_3 group is irradiated. Subtraction of (a) from (b) gives a positive Nuclear Overhauser Effect, which indicates that the F and CH_3 are on the same side of the double bond. So, the only product **4** prepared in Method A was assigned as the E-isomer.

The E/Z ratios of **4** in Methods B and C were determined by integration of the vinyl fluorine signals in the ^{19}F NMR spectrum. The characteristic absorptions of the E and Z mixture of **4** were those of the vinyl fluorines whose signals appear at −115 and −125 ppm upfield from $CFCl_3$. The downfield chemical shift (-115 ppm) was assigned to the vinyl fluorine of the Z-isomer, whereas the upfield signal (-125 ppm) was assigned to the vinyl fluorine of the E isomer. For the compound (E,Z)-$(CH_3)(CO_2Et)C{=}CFCO_2Et$ **4**, the vinyl fluorine of the Z-isomer exhibits a downfield signal compared to the vinyl fluorine resonance of the E-isomer.

Methods B and C in the preparation of (E,Z)-$(CH_3)(CO_2Et)C{=}CFCO_2Et$ **4** follow the condensation of lithium diethy(carboethoxyfluoromethyl) phosphonate[6] $[(EtO)_2P(O)CFCO_2Et]^-Li^+$ or lithium diisopropyl(carboethoxyfluoromethyl)phosphonate $[(i\text{-}PrO)_2P(O)CFCO_2Et]^-Li^+$ **2** with ethyl pyruvate, respectively. Method A yields, exclusively, the E-isomer of $(CH_3)(CO_2Et)C{=}CFCO_2Et$, but methods B and C give an E/Z mixture of (E,Z)-$(CH_3)(CO_2Et)C{=}CFCO_2Et$. The Felkin-Anh model of asymmetric induction[6,9] predicts the exclusive formation of the diastereomer of (E)-$(CH_3)(CO_2Et)C{=}CFCO_2Et$ in method A. However, the formation of (E,Z)-$(CH_3)(CO_2Et)C{=}CFCO_2Et$ from methods B and C is analogous to that of the Wittig reaction and is well documented.[10,11] In the reaction between $[(i\text{-}PrO)_2P(O)CFCO_2Et]^-Li^+$ **2** and ethyl pyruvate, the presence of the isopropyl group probably results in the decomposition of betaine ion to (E)-isomer faster than its interconversion to **2** and ethyl pyruvate. This result leads to an increase of the E-isomer. [12] The stereochemical preference for method A is superior to the ethyl pyruvate condensations in methods B and C. In addition, method A avoid the preparation of the requisite α-ketoester.

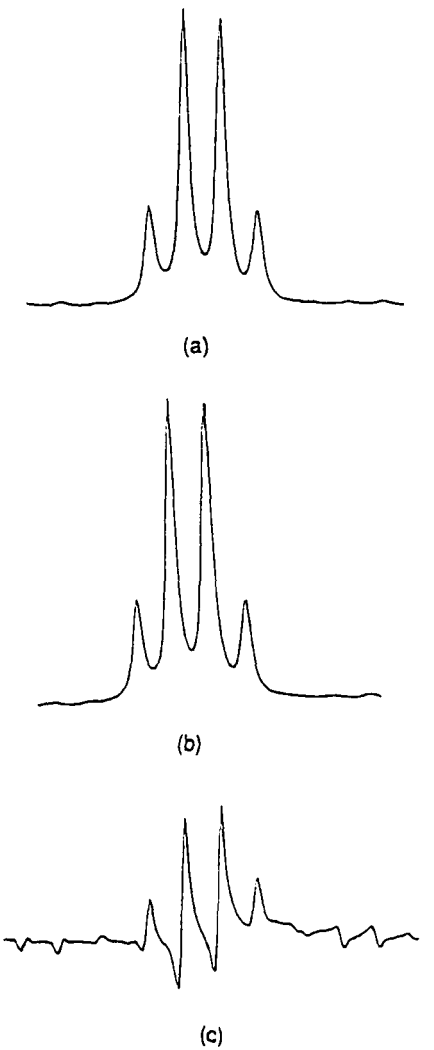
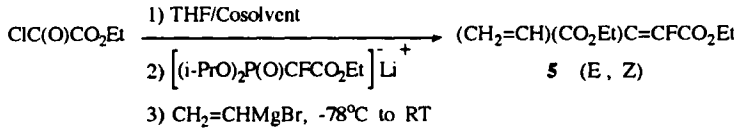


FIGURE 1 NOE experiment on (E)-$CH_3(CO_2Et)C{=}CFCO_2Et$ **4**. (a) Control ^{19}F NMR observed. (b) ^{19}F NMR spectrum with CH_3 protons irradiated. (c) Difference spectrum (x 16): Positive (6.2% increase) NOE

Similarly, the characteristic absorptions of the prepared E and Z mixture of $(CH_2{=}CH)(CO_2R')C{=}CFCO_2Et$ **5** (R′ = Et, Me) are those of the vinyl fluorines which appear as singlets at −128.1 and −117.6 ppm upfield from

$CFCl_3$. Change of the R′ group from Et to Me in $ClC(O)CO_2R'$ has little effect (from 75/25 to 72/28 on the stereochemistry of the product (E,Z)-$(CH_2{=}CH)(CO_2Et)C{=}CFCO_2Et$ **5**). Flash chromatography has been used to separate the two isomers of **5** to obtain isomerically pure compounds (E)-$(CH_2{=}CH)(CO_2Et)C{=}CFCO_2Et$ and (Z)-$(CH_2{=}CH)(CO_2Et)C{=}CFCO_2Et$. The E/Z assignment was also confirmed by Nuclear Overhauser Effect (NOE) experiments. The isomer which absorbs at −127.0 ppm in the ^{19}F NMR spectrum was assigned as the E-isomer. However, the isomer at −117.6 ppm was assigned as the Z-isomer. The stereochemistry of the α-fluoro-β-vinyl-α,β-unsaturated diester $(CH_2{=}CH)(CO_2Et)C{=}CFCO_2Et$ **5** prepared from $(i\text{-}PrO)_2P(O)CFHCO_2Et$ **1** was examined in the presence of metal ion or cosolvents such as HMPT or DMPU in the reaction mixture. This results are illustrated in Table III.

TABLE III Effect of metal ion or cosolvents on the stereochemistry of (E,Z)-$(CH_2{=}CH)(CO_2Et)C{=}CFCO_2Et$ **5** from $(i\text{-}PrO)_2P(O)CFHCO_2Et$



Entry	*Metal ion/Cosolvent*	*E/Z*	*Yields (%)*[a]
1	THF	75/25	64
2	THF/HMPT	88/12	63
3	THF/DMPU	89/11	60
4	THF/2LiCl	43/57	63

a. ^{19}F NMR yields, $C_6H_5CF_3$ as internal standard.

In the presence of HMPT or DMPU as cosolvents, the preparation of (E,Z)-$(CH_2{=}CH)(CO_2Et)C{=}CFCO_2Et$ **5** from $(i\text{-}PrO)_2P(O)CFHCO_2Et$ **1** was found to give 88–89% E-stereoselectivity. Approximately, the 14% of the E-isomer was increased. It was speculated that Li salts were influencing the stereochemistry. In order to probe this possibility, the reaction was carried out with addition of two equivalents of LiCl. It was observed that the Z-isomer of the product (E,Z)-$(CH_2{=}CH)(CO_2Et)C{=}CFCO_2Et$ **5** was increased from 25% to 57%. Different isomer ratios are possible for

(E,Z)(CH_2=CH)(CO_2R′)C=CFCO_2Et **5**when the betaine ion is associated with the lithium cation, or if the cation is coordinated by HMPT or DMPU and thus removed from the reaction site.

In summary, acylation of the phosphonate carbanion [(i-Pr$O)_2$P(O)$CFCO_2$Et]$^-Li^+$ **2** with methyl or ethyl oxalyl chloride, followed by *in situ* reaction of the acylated phosphonate with methylmagnesium iodide or vinyl magnesium bromide provide a direct entry to α-fluoro-α,β-unsaturated diesters. The different stereoselectivity of the diethyl-2-fluoro-3-methyl fumarate or α-fluoro-β-vinyl-α,β-unsaturated diester prepared was observed under different experimental methods and conditions.

EXPERIMENTAL

^{31}P, ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-300WB spectrometer. ^{19}F NMR spectra were recorded on a Bruker MSL-300 multinuclear spectrometer. All chemical shifts are reported in parts per million downfield (positive) of the standard. ^{19}F NMR spectra are referenced against internal $CFCl_3$, ^1H and ^{13}C NMR spectra against internal $(CH_3)_4Si$, and ^{31}P NMR spectra against an external 85% H_3PO_4 capillary. The mass spectral analyses were performed on the instrument FININGAN MAT TSQ-46C. GLPC analyses were performed on a 5% OV-101 column with a thermal conductivity detector. Tetrahydrofuran was dried by distillation from sodium benzophenone ketyl. Trisopropyl phosphite was distilled from sodium metal under reduced pressure. Ethyl bromofluoroacetate was prepared similar to the reported preparation of ethyl chlorofluoroacetate.[13]Methyl oxalyl chloride, ethyl oxalyl chloride and hexamethylphosphoric triamide (HMPT) were distilled prior to use. Ethyl acetate, n-hexane and *N,N′*-dimethylpropyleneurea (DMPU) were used without further purification. The concentration of a 2.5 M n-hexane solution of n-butyllithium was determined by the method of Duhamel.[14] The normality of vinyl magnesium bromide CH_2=CHMgBr and of methyl magnesium iodide CH_3MgI were determined by the method of Bergbreiter.[15]

Preparation of diisopropyl(carboethoxyfluoromethyl) phosphonate (i-PrO)$_2$P(O)CFHCO$_2$Et 1

A 300 mL three-necked flask equipped with a Teflon-coated magnetic stir-bar, a thermometer, and an air condenser (15 cm) topped with a nitrogen tee tube leading to a source of nitrogen and a mineral oil bubbler was charged with 0.76 mol (158 g) of freshly distilled triisopropyl phosphite and 0.54 mol (100 g, 63 mL) of ethyl bromofluoroacetate. The contents of the flask were heated to 145°C for 12 hours. Distillation of the reaction mixture at 101–104°C and 0.5 mmHg gave 107 g (75%) of the above phosphonate; GLPC purity: 99%; ^{19}F NMR: −209.6 (d,d, J_{FCP} = 72.0, J_{FCH} = 48.0); ^{31}P NMR: 8.5 (J_{PCF} = 72.0); ^{1}H NMR: 5.40 (d, d, 1H, J_{HCF} = 44, J_{HCP} = 12, CFH), 4.80 (m, 2H, CH), 4.30 (q, 2H, J = 7.3, OCH_2), 1.4 – 1.3 (m, 15H, CH_3); ^{13}C NMR: 164.9 (d, J_{CCF} = 21.8, C=O), 84.6 (d,d, J_{CF}= 195, J_{CP} = 195, CFH), 62.3 (OCH_2), 24.1 (OCH), 14.1 (CH_3); MS m/z: 272 (M^++2, 8.0), 271 (M^++1, 77.0), 269 (M^+- 1, 2.0); FTIR (cm^{-1}): 2985 (m, C-H), 2933 (m), 1760 (s, C=O), 1279 (m, P=O), 1272 (s), 1221 (m, C-O-C), 1032 (m, P-O-C).

Preparation of (E)-(CH$_3$)(CO$_2$Et)C=CFCO$_2$Et from [(i-PrO)$_2$P(O)CFCO$_2$Et]$^-$Li$^+$, ClC(O)CO$_2$Et and CH$_3$MgI

A solution of 16.0 mmol (4.32 g) of (i-PrO)$_2$P(O)CFHCO$_2$Et and 30 mL of dry THF was cooled to −78°C in a dry ice/i-PrOH slush bath under N_2. To the cooled solution, 16.0 mmol (6.4 mL) of a 2.5 M n-hexane solution of n-butyllithium was added dropwise via a syringe. The resultant bright yellow solution was stirred at −78°C and maintained at that temperature. Into another 250 mL three-necked flask equipped as above was placed 20 mL of dry THF and 16.0 mmol (2.18 g, 1.9 mL) of ethyloxalyl chloride. The contents of the flask were stirred and cooled to −78°C via a dry ice/i-PrOH slush bath, and then the cold ylide generated in the first flask was added dropwise via syringe. The resulting mixture was stirred at −78°C for one hour and then allowed to warm to −10°C over 5 hours. ^{19}F NMR analysis of the reaction mixture revealed the complete consumption of the ylide and the presence of the product (i-PrO)$_2$P(O)CF(COCO$_2$Et)CO$_2$Et **3** at −176.2 ppm (d, J = 75.0 Hz). The reaction mixture was cooled again to −78°C via a dry ice/i-PrO slush bath and to the cooled solution, 16 mmols (5.4 mL) of a 3.0 M diethyl ether

solution of methylmagnesium iodide was added dropwise via a syringe. The resultant mixture was allowed to warm to room temperature over 6 hours and stirred at that temperature overnight. The reaction mixture was poured into water (60 mL), the organic layer separated, and the water layer extracted with ether (3 × 50 mL). The ether extracts were combined with the organic layer and the combined fractions were washed with dilute hydrochloric acid until the washings were neutral to litmus paper. The resulting solution was washed successively with saturated brine solution (30 mL) and water (30 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated on a rotary evaporator. The residue was loaded onto a flash chromatography column (120 g silica gel, 200–425 mesh) and eluted with an n-hexane/ethyl acetate (24/1) mixture to give 1.69 g (52%) of the compound (E)-$CH_3(CO_2Et)C{=}CFCO_2Et$. ^{19}F NMR: −125.0, (q, $J_{FCCCH(cis)} = 3.84$); ^1H NMR: 4.29 (q, J = 7.2, CH_2), 4.27 (q, 2H, J = 7.2, CH_2), 2.05 (d, 3H, $J_{HCCCF} = 3.87$, $C{=}CCH_3$), 1.33 (t, 3H, J = 7.2, OCH_2CH_3), 1.32 (t, 3H, J = 7.2, OCH_2CH_3); ^{13}C NMR: 169.9 (d, $J_{CCCF} = 13$, C=O), 159.7 (d, $J_{CCF} = 35$, C=O), 147.9 (d, $J_{CF} = 266$, C-F), 121.7 (d, $J_{CCF} = 18$, C=CF), 62.1 (s, OCH_2), 61.8 (s, OCH_2), 14.0 (s, CH_3), 13.9 (d, $J_{CCCF} = 5$, $CH_3C{=}CF$), 13.8 (s, CH_3); MS m/z: 204 (M^+, 0.37), 189 (M^+-Me, 4.91), 159 (M^+-OEt, 11.0), 131 (M^+-CO_2Et, 100), 103 (M^+-CO_2Et-$CH_2{=}CH_2$, 7.5); FTIR (cm^{-1}): 2984 (m, C-H), 1767 (m), 1739 (vs, C=O), 1675 (m, C=C), 1287 (s, C-F), 1111 (m, C-O-C). High resolution MS: calculated: 204.0798; observed: 204.0813.

Preparation of (E)-$(CH_3)(CO_2Me)C{=}CFCO_2Et$ from $[(i\text{-}PrO)_2P(O)CFCO_2Et]^-Li^+$, $ClC(O)CO_2Me$ and CH_3MgI

Yield: 50%. ^{19}F NMR: −125.1 (q, $^4J_{F,H} = 3.87$); ^1H NMR: 2.03 (d, 3H, $^4J_{H,F(cis)} = 3.91$, CH_3), 4.30 (q, 2H, $^3J_{H,H}$= 7.33, OCH_2), 3.83 (s, 3H, OCH_3), 2.03 (d, 3H, $^4J_{H,F(cis)} = 3.91$, CH_3), 1.35 (t, 3H, J = 7.2, OCH_2CH_3); ^{13}C NMR: 167.5 (d, $J_{CCCF} = 13$, C=O), 159.7 (d, $J_{CCF} = 35$, C=O), 148.0 (d, $J_{CF} = 266$, C-F), 121.5 (d, $J_{CCF} = 18$, C=CF), 62.2 (s, OCH_2), 52.6 (s, OCH_3), 14.0 (s, CH_3), 12.9 (d, $J_{CCCF} = 5$, $CH_3C{=}CF$); MS m/z: 190 (M^+, 1.2), 159 (M^+-OCH_3, 13.9), 145 (M^+-OCH_2CH_3, 48.9), 131 (M^+-CO_2CH_3, 100), 117 (M^+-$CO_2CH_2CH_3$, 20.9). FTIR (cm^{-1}): 2985 (m, C-H), 1746 (s), 1743 (s, C=O), 1736 (s C=C), 1305 (s), 1298 (s, C-F).

Preparation of (E,Z)-$(CH_3)(CO_2Et)C{=}CFCO_2Et$ from $[(i\text{-}PrO)_2P(O)CFCO_2Et]^-Li^+$ and $CH_3C(O)CO_2Et$ (Method C)

A solution of 5.0 mmol (1.35 g) of $(i\text{-}PrO)_2P(O)CFHCO_2Et$ and 12 mL of dry THF was cooled to −78°C in a dry ice/i-PrOH slush bath under N_2. To the cooled solution, 5.0 mmol (2.0 mL) of a 2.5 M n-hexane solution of n-butyllithium was added dropwise via a syringe. The resultant bright yellow solution was stirred at −78°C for 20 minutes and then 5.0 mmol (0.58 g) of ethyl pyruvate was added dropwise via a syringe. The resultant mixture was stirred at −78°C for one hour and then allowed to warm to room temperature over 5 hours and stirred at that temperature overnight. The reaction mixture was poured into water (40 mL) and extracted with ether (3 × 30 mL). The combined extracts were washed with dilute hydrochloric acid and water (20 mL), dried with anhydrous $MgSO_4$, filtered, and concentrated on a rotary evaporator. The residue was loaded onto a flash chromatography column (60 g silica gel, 200–425 mesh) and eluted with an n-hexane/ethyl acetate (24/1) mixture to obtain 0.72 g (70%) of (E)- and (Z)-$CH_3(CO_2Et)C{=}CFCO_2Et$. The E/Z ratio of $CH_3(CO_2Et)C{=}CFCO_2Et$, determined by the integration of the vinyl fluorine signals in the ^{19}F NMR spectrum, is 79 to 21. The vinyl fluoride region of the (E)-isomer gives a signal at −125 ppm and the (Z)-isomer at −115 ppm.

Preparation of (E,Z)-$(CH_2{=}CH)(CO_2Et)C{=}CFCO_2Et$ from $(i\text{-}PrO)_2P(O)CFHCO_2Et$, $ClC(O)CO_2Et$ and $CH_2{=}CHMgBr$

Yield: 52%. (E)-isomer: ^{19}F NMR: −128.1 (m, J_{FCCCH}= 0.99); ^1H NMR: 6.73 (m, 1H, =CH), 5.56 (d,d, 1H, J_{HCCH}(cis) = 10.57, J_{HCH} = 1.93, $=CH_2$), 5.51 (d, 1H, $J_{HCCH(trans)}$ = 17.1, $=CH_2$), 4.40 (q, 2H, J_{HCCH} = 7.16, OCH_2), 4.28 (q, 2H, J_{HCCH} = 7.10, OCH_2), 1.38 (t, 3H, J = 7.2, OCH_2CH_3), 1.31 (t, 3H, J = 7.2, OCH_2CH_3); ^{13}C NMR: 164.5 (d, J_{CCCF}= 11, C=O), 159.7 (d, J_{CCF} = 53, C=O), 144.9 (d, J_{CF} = 276, C-F), 125.8 (d, J_{CCF} = 5, C=CF), 125.6 (s, $=CH_2$), 123.0 (d, J_{CCCF} = 5, CH-C=CF), 62.3 (s, OCH_2), 62.1 (s, OCH_2), 14.0 (s, CH_3), 13.9 (s, CH_3); MS m/z: 216 (M^+, 43.2), 189 ($M^+ - CH_2{=}CH$, 3.3), 188 ($M^+ - CH_2{=}CH_2$, 34.3), 171 (M^+- OCH_2CH_3, 23.9), 160 ($M^+ - CH_2CH_3 - CH_2{=}CH$, 58.2), 143 ($M^+$- $CO_2CH_2CH_3$, 49.3), 142 (M^+-$OCH_2CH_3 - CH_2{=}CH$, 100), 115 ($M^+ - COCH_2CH_3 - CH_2{=}CH_2$, 6.23); FTIR ($cm^{-1}$): 2984 (w, C-H), 1742

(s), 1734 (m, C=O), 1652 (m, C=C), 1635 (m), 1324 (s), 1286 (s, C-F). (Z)-isomer: ^{19}F NMR: −119.3 (s); ^{1}H NMR: 7.34 (d,d,d, 1H, J_{HCCCF} = 1.26, =CH), 5.52 (d,d, 1H, $J_{HCCH(cis)}$ = 10.91, J_{HCH} = 1.74, $=CH_2$), 5.50 (d, 1H, $J_{HCCH(trans)}$ = 17.7, $=CH_2$), 4.37 (q, 2H, J_{HCCH} = 7.15, OCH_2), 4.34 (q, 2H, J_{HCCH} = 7.13, OCH_2), 1.36 (t, 3H, J = 7.2, OCH_2CH_3), 1.35 (t, 3H, J = 7.2, OCH_2CH_3); ^{13}C NMR: 164.5 (d, J_{CCCF} 4, C=O), 160.0 (d, J_{CCF} = 34, C=O), 144.8 (d, J_{CF} = 268, C-F), 127.2 (d, J_{CCF} = 19, C=CF), 126.9 (s, $=CH_2$), 123.0 (d, J_{CCCF} = 11, CH-C=CF), 62.2 (s, OCH_2), 62.0 (s, OCH_2), 14.2 (s, CH_3), 14.1 (s, CH_3); MS m/z: 217 (M^+ + 1, 1.37), 216 (M^+, 13.6), 189 (M^+ − CH_2=CH, 1.5), 171 (M^+- OCH_2CH_3, 24.7), 160 (M^+ - CH_2CH_3 − CH_2=CH, 47.1), 143 (M^+- $CO_2CH_2CH_3$, 13.7), 142 (M^+ − OCH_2CH_3 − CH_2=CH, 100); FTIR (cm^{-1}): 2962 (m), 2935 (m, C-H), 1761 (m, C=O), 1740 (s, C=C), 1371 (m), 1334 (s), 1302 (s), 1261 (s, C-F). High resolution MS: calculated: 216.0798; observed: 216.0803.

Preparation of (E,Z)-$(CH_2$=CH)(CO_2Me)C=CFCO_2Et from $(i\text{-}PrO)_2$P(O)CFHCO_2Et, ClC(O)CO_2Me and CH_2=CH$MgBr$

Yield: 51%. (E)-isomer: ^{19}F NMR: −127.0 (m); ^{1}H NMR: 6.72 (m, 1H, =CH), 5.55 (d,d, 1H, $J_{HCCH(cis)}$ = 10.85, J_{HCCH}= 1.94, $=CH_2$), 5.49 (d, 1H, $J_{HCCH(trans)}$ = 17.7, $=CH_2$), 4.31 (q, 2H, J_{HCCH} = 7.11, OCH_2), 3.86 (s, 3H, OCH_3), 1.34 (t, 3H, OCH_2CH_3); ^{13}C NMR: 165.0 (d, J_{CCCF} = 11, C=O), 159.8 (d, J_{CCF}= 33, C=O), 145.1 (d, J_{CF} = 276, C-F), 125.7 (d, J_{CCF} = 5, C=CF), 123.1 (d, J_{CCCF} = 5, CH-C=CF), 125.5 (s, $=CH_2$), 62.4 (s, OCH_2), 52.8 (s, OCH_3), 14.0 (s, CH_3); MS m/z: 202 (M^+, 39.7), 174 (M^+ − CH_2=CH, 100), 157 (M^+- OCH_2CH_3, 32.2), 143 (M^+- CO_2CH_3, 58.2), 129 (M^+- $CO_2CH_2CH_3$, 63.4); FTIR (cm^{-1}): 2951 (m, C-H), 1739 (s, C=O), 1721 (s, C=C), 1300 (s), 1297 (s, C-F). (Z)-isomer: ^{19}F NMR: −117.6 (s); ^{1}H NMR: 7.34 (m, 1H, J_{HCCCF} = 1.28, =CH), 5.52 (d,d,d, 1H, $J_{HCCH(cis)}$= 10.99, J_{HCH} = 0.88, J_{HCCF} = 0.44, $=CH_2$), 5.47 (d, 1H, $J_{HCCH(trans)}$ = 17.6, $=CH_2$), 4.34 (q, 2H, J_{HCCH} = 7.12, OCH_2), 3.89 (s, 3H, OCH_3), 1.36 (t, 3H, OCH_2CH_3); ^{13}C NMR: 164.4 (d, J_{CCCF} 4, C=O), 159.9 (d, J_{CCF} 34, C=O), 144.9 (d, J_{CF} = 268, C-F), 126.8 (s, $=CH_2$), 125.5 (d, J_{CCCF} = 11, CH-C=CF), 123.5 (d, J_{CCF} = 14, C=CF), 62.2 (s, OCH_2), 52.7 (s, OCH_3), 14.1 (s, CH_3); MS m/z: 202 (M^+, 2.5), 129 (M^+- $CO_2CH_2CH_3$, 4.5); FTIR (cm^{-1}): 2924 (m, C-H), 1743 (s), 1740 (s, C=O), 1650 (w, C=C), 1371 (s), 1269 (s, C-F).

General Procedure to Establish Dependence of the Stereochemistry on Cosolvent and Metal Ion of (E,Z)-$(CH_2{=}CH)(CO_2Et)C{=}CFCO_2Et$ 5 As Deduced from the Reaction of $(i\text{-}PrO)_2P(O)CFHCO_2Et$ with $ClC(O)CO_2Et$ in THF/HMPT and $CH_2{=}CHMgBr$

A solution of 4.1 mmol (1.1 g) of $(i\text{-}PrO)_2P(O)CFHCO_2Et$ and 8 mL of dry THF was cooled to −78°C in a dry ice/i-PrOH slush bath under N_2. To the cooled solution, 4.1 mmol (1.7 mL) of a 2.5 M n-hexane solution of n-butyllithium was added dropwise via a syringe. The resultant bright yellow solution was allowed to warm to 5°C and maintained at that temperature. Into another 100 mL three-necked flask was placed 8 mL of dry THF, 4 mmol (0.6 mL) of hexamethylphosphoric triamide (HMPT), and 4.1 mmol (0.55 g) of ethyloxalyl chloride. The contents of the flask were stirred and cooled to −78°C in a dry ice/i-PrOH slush bath, and then the cold ylide generated in the first flask was added dropwise via a syringe. The resulting mixture was stirred at −78°C for one hour and then allowed to warm to −10°C over 5 hours. The reaction mixture was cooled again to −78°C via a dry ice/i-PrOH slush bath and to the cooled solution, 4.0 mmol (4.0 mL) of a 1.0 M THF solution of vinylmagnesium bromide was added dropwise via a syringe. The resultant mixture was allowed to warm to room temperature over 6 hours and stirred at that temperature overnight. The reaction mixture was poured into water (45 mL), the organic layer was separated, washed with water (20 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated on a rotary evaporator to give 63% ^{19}F NMR yield of (E,Z)-$(CH_2{=}CH)(CO_2Et)C{=}CFCO_2Et$ **5**. The E/Z ratio of the unsaturated diester determined by the integration of the vinyl fluorine signals in the ^{19}F NMR spectrum is 88 to 12.

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