in the pseudodihedral angle. As shown in Table V, the TB3 flagpole interaction is clearly stronger in 5·HCl, and this is probably the ultimate cause responsible for the long-range effect of the 6-*gem*-dimethyl groups on the $C(sp^3)$–$C(sp^2)$ rotation barrier and, particularly, of the noteworthy differences in behavior between compounds 4·HCl and 5·HCl.

The *gem*-dimethyl group compresses the N–Me one (the C_6–N–Me bond angle is 114.1° in TB3). However, the buttressing of the *gem*-dimethyl is energetically less severe than the repulsion coming from the H_{ortho}–Me nonbonded interaction in the TB3* (the C_6–N–Me bond angle closes to 111.7°).

Conclusions

The barriers to rotation in two different 2-aryl-4-piperidone hydrochlorides have been determined by ^1H DNMR ($\Delta G^* = 46.0$ kJ mol^{-1} at −30 °C and 59.4 kJ mol^{-1} at 40 °C for 4·HCl and 5·HCl, respectively). Compound 5·HCl seems to exist in a single configuration with the N–Me group in equatorial position. Molecular mechanics calculations have proved to be useful in the determination of the global rotational process and also help in finding the interactions producing the barriers. Although the absolute values obtained in the MM2 calculations agree rather well with the experimental ones, they must be handled with care. Nevertheless, the theoretical calculations also perfectly reproduce the experimental trends with the proper relative order.[9]

The flagpole interactions existing in the cyclohexane moiety of the target compounds as well as the H–H unbonded interactions about the pivot bond are the main factors responsible for the barrier heights.

Registry No. 4, 73608-62-5; 4·HCl, 88091-29-6; 5, 75306-47-7; 5·HCl, 88091-33-2; 5·HCl (demethoxylated analogue), 125329-75-1; 6, 88091-30-9; 6·HCl, 88091-31-0.

Alkylation of (Fluorocarbethoxymethylene)tri-*n*-butylphosphorane: A Facile Entry to α-Fluoroalkanoates[1]

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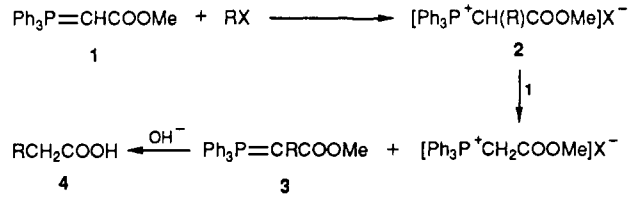
(Fluorocarbethoxymethyl)trialkylphosphonium bromides **6**, prepared from ethyl bromofluoroacetate and tertiary phosphines, react with *n*-butyllithium in THF to give the corresponding phosphoranes **7**. Reaction of the pregenerated (fluorocarbethoxymethylene)tri-*n*-butylphosphorane **7a** with primary alkyl iodides and activated alkyl bromides followed by in situ hydrolysis of the alkylated salts provides the fluoroalkanoates **9** in a one-pot reaction. In the case of secondary alkyl halides, no substitution was observed, the main reaction being decomposition of the phosphorane. However, the anion obtained from diisopropyl (fluorocarbethoxymethyl)phosphonate **10b** reacts with $CH_3CH(Ph)Br$ and $(CH_3)_2CHI$ to afford the corresponding alkylated phosphonates in good yields. Displacement of the phosphonate moiety either by base-induced hydrolysis or by reduction was unsuccessful.

Introduction

Elucidation of the mechanism of toxicity of fluoroacetate in living organisms led to a new wave of research into the preparation and properties of fluoro esters. 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] All of these applications are mainly due to the high electronegativity of fluorine, the increased bond strength of the carbon–fluorine bond, and the enhanced lipid solubility of fluorine substituted compounds.[3]

Although numerous literature methods exist to incorporate a fluorine atom adjacent to a carbonyl group, the limitations associated with them restrict their practicality. Extreme reaction conditions and special apparatus are required to effect a metathesis reaction between a halo ester and a metal fluoride or other fluoride ion source.[4]

Scheme I



The condensation reaction between fluoroacetates and alkylating agents under basic conditions employs toxic materials.[5] The explosion hazard associated with perchloryl fluoride limits its synthetic utility in the fluorination reactions.[6] Fluorination with hypofluorites limits the presence of functionalities that are susceptible to oxidation.[7] The strong Lewis acidity of specific fluorinating agents such as antimony fluorides, phosphorus fluorides, and fluorinated sulfuranes precludes their application toward a large number of bioactive molecules that are sensitive to acid, base, or both.[8]

(1) (a) Presented in part at the 21st Midwest Regional Meeting of the American Chemical Society, Kansas City, MO, November 1986, Abstract no. 709. Taken in part from the Ph.D. Thesis of A.T., University of Iowa, 1989. (b) A preliminary report of this work has appeared: Thenappan, A.; Burton, D. J. *Tetrahedron Lett.* **1989**, *30*, 3641.

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0022-3263/90/1955-2311$02.50/0

Table I. ^{19}F NMR and Isolated Yields of Ethyl α-Fluoroalkanoates

$$Bu_3P{=}CFCOOEt \xrightarrow[\text{2. } NaHCO_3(aq)]{\text{THF/-78 °C; 1. RX}} RCFHCOOEt$$

no.	R	% yield[a]	^{19}F NMR ppm[b]	^{19}F NMR J, Hz	bp, °C (mmHg)
9a	CH_3	59 (75)	-184.9 (dq)	23 and 49	50–51 (64)
9b	C_2H_5	42 (87)	-193.9 (dt)	24 and 49	60–61 (60)
9c	n-C_3H_7	42 (74)	-192.5 (dt)	24 and 48	94–95 (117)
9d	n-C_4H_9	34 (61)	-192.4 (dt)	24 and 49	93–94 (63)
9e	n-C_7H_{15}	52 (72)	-192.3 (dt)	25 and 49	93–94 (5)
9f	n-$C_{10}H_{21}$	44 (50)	-192.5 (dt)	25 and 49	115–116 (1)
9g	$PhCH_2$	59 (61)	-189.9 (dt)	24 and 48	69–70 (0.3)
9h	$CH_2{=}CHCH_2$	52 (73)	-192.1 (dt)	24 and 48	82–83 (28)
9i	$CH_3CH{=}CHCH_2$	38 (72)	-192.0 (dt) (*E*) -191.8 (dt) (*Z*)	26 and 51 26 and 48	84–85 (25)
9j	$PhCH{=}CHCH_2$	45 (76)	-191.5 (dt)	25 and 49	112–13 (0.5)
9k	$CH_3OCOCH{=}CHCH_2$	41 (45)	-191.6 (dt)	25 and 48	72–80 (0.6)

[a] Isolated yields are based on ethyl bromofluoroacetate, and the yields in parentheses are determined by ^{19}F NMR analysis of the reaction mixture using C_6F_6 as an internal standard. [b] ^{19}F NMR chemical shifts are referenced against internal $CFCl_3$.

Phosphoryl-stabilized carbanions and phosphonium ylids are powerful nucleophilic reagents in organic synthesis, and many of them are known to react with a variety of alkylating agents such as alkyl halides and trialkyloxonium salts to produce higher alkylated ylids.[9] Reaction of (carbomethoxymethylene)triphenylphosphorane (**1**) with alkyl, allylic, and benzylic halides to form the alkylated ylids **3**, and subsequent hydrolysis of **3** to produce a series of carboxylic acids **4**, has been reported[10] (Scheme I). Thus, alkylation followed by hydrolysis of **1** provides a convenient avenue to disubstituted methanes.

In contrast to the study made on the alkylation of **1**, there exist no reports on the alkylation of its fluorinated counterpart, viz. (fluorocarbalkoxymethylene)trialkylphosphorane **7**. In view of the enhancement of physiological activity caused by introduction of a fluorine atom adjacent to a carbonyl function,[11] we investigated the alkylation of (fluorocarbethoxymethylene)tri-*n*-butylphosphorane (**7a**) with primary alkyl iodides and activated alkyl bromides to form the corresponding phosphonium salts **8**. Subsequent hydrolysis of **8** under mild basic conditions provides ethyl α-fluoroalkanoates **9** in reasonable yields, and the results are summarized in Table I.

Results and Discussion

Tertiary phosphines such as tri-*n*-butyl- and triphenylphosphines are known[12] to undergo a quaternization reaction with ethyl bromofluoroacetate (**5**) to give the corresponding phosphonium salts **6** in high yields (eq 1).

$$R_3P + \underset{\mathbf{5}}{CFHBrCOOEt} \rightarrow \underset{\mathbf{6a}:\ R = n\text{-Bu};\ \mathbf{b}:\ R = Ph}{[R_3P^+CFHCOOEt]Br^-} \quad (1)$$

The Wittig chemistry of the phosphoranes **7** derived from **6** has also been reported.[12] The reaction between equimolar quantities of tri-*n*-butylphosphine and ester **5** in THF at room temperature for 40 h produced the corresponding phosphonium salt **6a** as a homogeneous solution with 85–90% conversion. The THF solution of the salt, $[Bu_3P^+CFHC(O)OEt]Br^-$, was used for further reactions without any purification. Attempts to prepare the analogous triphenyl-substituted phosphonium salt **6b** from triphenylphosphine and ester **5** in THF did not yield the expected salt as a homogeneous solution. However, in dichloromethane the reaction between triphenylphosphine and the ester **5** was homogeneous, and the corresponding salt was formed in 70% isolated yield. The substitution with triphenylphosphine at room temperature was slow, and only 77% conversion was observed after 96 h. Neither the increase in concentration of the reactants nor the increase in reaction time improved the conversion.

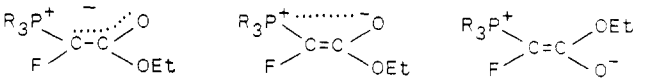


Figure 1.

Deprotonation of the phosphonium salts **6** with *n*-butyllithium in THF at -78 °C provided the corresponding phosphoranes **7** (eq 2) in almost quantitative yields. The

$$\underset{\mathbf{6}}{[R_3P^+CFHCOOEt]Br^-} + n\text{-BuLi} \xrightarrow[\text{THF}]{-78\ °C} \underset{\mathbf{7a}:\ R = n\text{-Bu};\ \mathbf{b}:\ R = Ph}{R_3P{=}CFCOOEt} \quad (2)$$

pregenerated phosphoranes were characterized by ^{19}F and $\{^1H\}^{31}P$ NMR spectroscopy. In the ^{19}F NMR spectrum, a THF solution of the tri-*n*-butyl-substituted phosphorane **7a** at room temperature exhibited two sets of doublets with a 1:1 ratio. They were observed at -239 (J_{PCF} = 40 Hz) and -240 ppm (J_{PCF} = 48 Hz), respectively. Similarly, the ^1H-decoupled ^{31}P NMR spectrum of **7a** exhibited signals at 21.2 (J_{PCF} = 40 Hz) and 20.8 ppm (J_{PCF} = 48 Hz), respectively. The analogous triphenyl-substituted phosphorane **7b**, derived from the corresponding phosphonium salt in THF, also exhibited two sets of doublets in the ^{19}F and $\{^1H\}^{31}P$ NMR spectra. The two signals in the ^{19}F NMR spectrum were observable at -239.2 (J_{FCP} = 55 Hz) and -239.6 ppm (J_{FCP} = 44 Hz), whereas the resonances in the ^{31}P NMR spectrum occurred at 13.9 (J_{PCF} = 53 Hz) and 13.4 ppm (J_{PCF} = 43 Hz), respectively.

The presence of two sets of signals in the ^{19}F and ^{31}P NMR spectra of **7** indicates that the ylids exist as a mixture of two geometrical isomers in THF. Delocalization of the negative charge through the ester carbonyl led to the formation of two isomers (Figure 1), and similar charge dispersion through the carbonyl group has been reported in stabilized phosphoranes such as phenacylidenetriphenylphosphorane, $Ph_3P{=}CHC(O)Ph$.[13] Although the

(9) Johnson, A. W. *Ylid Chemistry*; Organic Chemistry Monograph Vol. 7; Academic Press: New York, 1968.
(10) Bestmann, H. J.; Schulz, H. *Chem. Ber.* **1962**, *95*, 2921.
(11) Schlosser, M. *Tetrahedron* **1978**, *34*, 3. Welch, J. T. *Tetrahedron* **1987**, *43*, 3123.
(12) Gurusamy, N.; Burton, D. J. 188th ACS National Meeting, Philadelphia, PA, 1984, Abstract FLUO 12.

two isomers were not distinguishable from each other unequivocally, the isomer that exhibits a resonance at −239 ppm for **7a** is more reactive than the other toward primary alkyl iodides and activated alkyl bromides.

Deprotonation of the phosphonium salt **6** causes an upfield shift in the ^{19}F and ^{31}P NMR resonances with a simultaneous decrease in the $^2J_{PCF}$ value. These results, particularly the decrease in $^2J_{PCF}$ value, are attributed to the change in hybridization of the carbon attached to phosphorus and fluorine atoms. Furthermore, the isomer in which phosphorus and oxygen are cis to each other may be less reactive than the trans isomer as a result of strong interaction between the positively charged phosphorus moiety and the negatively charged oxygen.

The phosphorane **7a** reacts with primary alkyl iodides and activated alkyl bromides to form the corresponding C-alkylated phosphonium salts **8** in 45–87% yields as determined by ^{19}F NMR spectroscopy relative to hexafluorobenzene as an internal standard (eq 3). No alkylation was observed with primary alkyl bromides and activated alkyl chlorides such as allyl and benzyl chlorides.

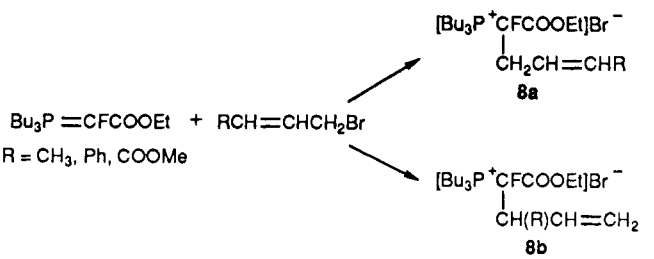
$$n\text{-}Bu_3P{=}CFCOOEt + RX \rightarrow \underset{\mathbf{8}}{[Bu_3P^+CF(R)COOEt]X^-} \quad (3)$$

Spectroscopic analysis of the reaction mixture at room temperature indicated that the substitution occurred only at carbon and not at oxygen. Alkylations of ester-stabilized phosphoranes such as **1** with alkyl halides are known to occur at carbon.[14] The substitutions at carbon and oxygen are distinguishable by virtue of their difference in the multiplicity of the fluorine signals in the ^{19}F NMR spectrum. When methyl iodide is employed as an alkylating agent, the signal in the ^{19}F NMR spectrum for the C-alkylated product is expected to exhibit a doublet of quartets, whereas alkylation at oxygen would be observable as a doublet. The doublet of quartets for the C-alkylated product arises as a result of coupling of the fluorine nucleus with phosphorus and the three methyl hydrogens at the α-carbon. In the case of the O-alkylated product, there is no coupling expected between the fluorine and the alkoxy hydrogens.

The nucleophilic substitution reaction of the phosphorane **7a** with allyl, crotyl, benzyl, cinnamyl, and 3-carbomethoxycrotyl bromides is rapid and completed in about 22 h. On the other hand, the alkylation with primary alkyl iodides is slow, and the reaction period varies from 8–166 h depending on the chain length of the iodides. For example, with methyl iodide the alkylation was completed in about 8 h, and with higher homologues such as ethyl, *n*-propyl, *n*-butyl, *n*-heptyl, and *n*-decyl the time required for completion of the reaction varies from 66–166 h. Increase of reaction temperature and increase in concentration of the iodides did not accelerate the substitution reaction. At elevated temperatures (>20 °C), the phosphorane begins to decompose to form ethyl fluoroacetate.

With crotyl, cinnamyl, and 3-carbomethoxycrotyl bromides, the alkylation occurred regiospecifically. Substitution was observed only at the carbon α to bromine and not at the γ-carbon. The two different regioisomers **8a** and **8b**, resulting from attack of the ylid at two different sites of the allylic halides, are distinguishable by virtue of the difference in the multiplicity of their fluorine signals in the ^{19}F NMR spectrum (Scheme II). The regioisomer **8a** is expected to exhibit a ddd pattern in the ^{19}F NMR spectrum, whereas the isomer **8b** is expected as a dd

Scheme II



pattern. The ^{19}F NMR signals of the alkylated salts derived from substituted allylic halides appear as ddd, indicating that the site of attack is at the α-position.

With an *E*/*Z* mixture of crotyl bromide and (*E*)-cinnamyl bromide, the stereochemistry of the double bond was retained.

The alkylated phosphonium salts **8** were hydrolyzed in situ by addition of 10% aqueous sodium bicarbonate solution (eq 4). Aqueous sodium carbonate and sodium

$$[Bu_3P^+CF(R)COOEt]X^- + NaHCO_3 \xrightarrow[4\ h]{rt} \underset{\mathbf{9}}{RCFHCOOEt} \quad (4)$$

hydroxide solutions were also effective in carrying out the hydrolysis. Spectroscopic analysis of the reaction mixture after hydrolysis revealed the presence of fluoroalkanoates **9**, indicating that saponification had not occurred.

In a similar reaction, secondary alkylating agents such as $CH_3CH(Ph)Br$, $(CH_3)_2CHI$, and $(CH_3)_2CHOTs$ react with **7a** to give very little (<10%) alkylation products at room temperature. Prolonged reaction time and increase of reaction temperature cause **7a** to decompose to form fluoroacetate. However, the anion derived from $(i\text{-}PrO)_2P(O)CFHC(O)OEt$ undergoes alkylation with secondary alkylating agents such as $CH_3CH(Ph)Br$ and $(CH_3)_2CHI$.

It has been clearly demonstrated that in olefin-forming reactions, the phosphonate carbanions, $[(RO)_2P(O)C^-HCOOEt]$ are more reactive than the corresponding phosphonium analogues $[R_3P{=}CHCOOEt]$.[15] The high reactivity is mainly due to decreased stabilization of the carbanion by valence-shell expansion of the phosphorus atom. A similar trend in reactivity is expected for the anion obtained from $(RO)_2P(O)CFHCOOEt$ toward electrophiles such as aldehydes, ketones, and alkyl halides.

The Michaelis–Arbusov reaction of trialkyl phosphites such as triethyl and triisopropyl phosphites with ethyl bromofluoroacetate to give the corresponding dialkyl (fluorocarbethoxymethyl)phosphonate **10** (eq 5) has been reported.[16]

$$(RO)_3P + CFHBrCOOEt \xrightarrow{140\text{–}150\ °C} \underset{\mathbf{10a}:\ R = Et;\ \mathbf{b}:\ R = i\text{-}Pr}{(RO)_2P(O)CFHCOOEt} + RBr \quad (5)$$

The anion derived from the phosphonate **10a** reacts with methyl iodide and allyl and benzyl bromides to afford the corresponding C-alkylated phosphonates **11** in 60–86% yields as determined by ^{19}F NMR spectroscopy relative to hexafluorobenzene as an internal standard (eq 6).

$$(EtO)_2P(O)CFHCOOEt \xrightarrow[2.\ RX]{1.\ n\text{-}BuLi} \underset{\mathbf{11}}{[(EtO)_2P(O)CF(R)COOEt]} + LiX \quad (6)$$

(13) Ramirez, F.; Dershowitz, S. *J. Org. Chem.* **1957**, *22*, 41.
(14) Bestmann, H. J.; Schulz, H. *Tetrahedron Lett.* **1960**, *4*, 5.
(15) Horner, L.; Klink, W.; Hoffmann, H. *Chem. Ber.* **1963**, *96*, 3133.
(16) Machleidt, H.; Wessendorf, R. *Justus Liebigs, Ann. Chem.* **1964**, *674*, 1.

However, attempts to remove the phosphonate moiety either by hydrolysis under basic reaction conditions or by reduction were not successful. The hydrolysis was attempted with aqueous bicarbonate, carbonate, and hydroxide solutions, while reduction of the phosphonates **11** with zinc and acetic acid also did not yield the desired fluoro esters.

Secondary alkyl halides such as $CH_3CH(Ph)Br$ and $(CH_3)_2CHI$ alkylate the phosphonate anion obtained from **10b** under reflux conditions to yield the corresponding C-alkylated phosphonates **12** in 60–72% isolated yields (eq 7). Treatment of the alkylated phosphonates **12** with

$$(i\text{-PrO})_2P(O)CFHCOOEt \xrightarrow[1.\ n\text{-BuLi}\ \ 2.\ RX]{THF/reflux} [(i\text{-PrO})_2P(O)CF(R)COOEt] + LiX \quad (7)$$

12a: R = $CH(CH_3)_2$
b: R = $CH(Ph)CH_3$

aqueous base under reflux conditions did not hydrolyze the phosphorus–carbon bond. However, treatment of **12a** with potassium fluoride in triglyme provides the desired α-fluoro ester, $(CH_3)_2CHCHFCOOEt$, along with $(i\text{-PrO})_2P(O)F$ in good yields. Due to the toxic nature of the byproduct,[17] the above reaction was not scaled up and the methodology was not extended to other alkylated phosphonates such as **11** and **12**.

Unlike alkylation, silylation of the anion **10a** with bromotrimethylsilane occurs at oxygen to yield the corresponding silyl ketene acetal **13** as a mixture of two geometrical isomers. The difference in regiochemistry may best be explained by the formation of a new silicon–oxygen bond in the product. When **13** was treated with water at room temperature, it hydrolyzed to form the starting phosphonate.

$$[(EtO)_2P(O)CFHCOOEt] \xrightarrow[2.\ Me_3SiBr]{1.\ n\text{-BuLi}} (EtO)_2P(O)\underset{F}{\diagdown}C{=}C\overset{OSiMe_3}{\diagup}\underset{OEt}{} \quad (8)$$

13

$\xrightarrow{H_2O}$

$[(EtO)_2P(O)CFHCOOEt]$

In conclusion, we have demonstrated that alkylation followed by in situ hydrolysis of (fluorocarbethoxymethylene)tri-*n*-butylphosphorane provides a viable synthesis of biologically important α-fluoroalkanoates. The mild reaction conditions employed in the synthesis permit the presence of sensitive functionalities, and, finally, our method offers the convenience of carrying out all the transformations in one pot from readily available materials.

Experimental Section

General. All the reactions were performed in an oven-dried apparatus that consisted of a two- or three-necked round-bottomed flask equipped with a septum port, a Teflon-coated magnetic stirbar, and a reflux condenser connected to a nitrogen source and mineral oil bubbler. The extra necks of the flask were fitted with glass stoppers. In this section, the size of the flask will be indicated for this standard assembly.

All boiling points were determined during fractional distillation using a partial immersion thermometer and are uncorrected. ^{19}F, ^{1}H, and ^{31}P NMR spectra were recorded on a JEOL FX90Q multinuclear spectrometer. ^{13}C NMR spectra were recorded on a Bruker WM360X spectrometer. All chemical shifts are reported in parts per million downfield (positive) of the standard. ^{19}F NMR spectra are referenced against internal $CFCl_3$, ^{1}H and ^{13}C NMR spectra against internal tetramethylsilane, and ^{31}P NMR spectra against an external 85% H_3PO_4 capillary. ^{13}C and ^{31}P NMR spectra were broadband decoupled from hydrogen nuclei. IR spectra were recorded as thin films on a Beckman Acculab spectrometer. Mass spectra were recorded on a Hewlett-Packard 5895 GC/MS system at 70 eV in the electron impact mode. GLPC analyses were performed on a Hewlett-Packard Model 5840A with a thermal conductivity detector. Cooling between 15 and 20 °C was effected using a Neslab Cryocool Immersion Cooler Model CC-100 II. High-resolution mass spectral analyses were performed by the University of Iowa High Resolution Mass Spectroscopy Facility using a VG ZAB-HF spectrometer operating at 70 eV in the electron impact mode. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN.

Materials. Ethyl bromofluoroacetate (**5**) was prepared by a method similar to the *Organic Syntheses*[18] preparation of ethyl chlorofluoroacetate. Tetrahydrofuran was obtained from Fisher and was purified by distillation from sodium benzophenone ketyl. Tri-*n*-butylphosphine was obtained from M&T and was purified by Blackburn's method.[19] Triphenylphosphine was obtained from M&T and was recrystallized from absolute ethanol. Triethyl phosphite was obtained from Aldrich Chemical Co. and was distilled from sodium metal at reduced pressure. *n*-Butyllithium (2.5 M *n*-hexane solution) was obtained from Aldrich Chemical Co., and its concentration was determined using Duhamel's procedure (method B).[20] Alkyl halides were obtained from Aldrich Chemical Co. and were distilled prior to use.

General Procedure: Preparation of $[Bu_3P^+CFHC(O)OEt]Br^-$ (6a). A 200-mL, two-necked, round-bottomed flask equipped with a septum port, a magnetic stirbar, and a reflux condenser connected to a nitrogen source was charged sequentially with 25 mL of THF, 5.1 g of tri-*n*-butylphosphine (25 mmol), and 4.6 g of ethyl bromofluoroacetate (25 mmol). The resulting homogeneous solution was stirred at room temperature for 40 h, and ^{19}F NMR analysis of the reaction mixture indicated that 90% of the ester had been converted into the corresponding phosphonium salt **6a**, which was utilized for further reactions without any additional purification. ^{19}F and ^{31}P NMR spectra of **6a** exhibited the following signals: ^{19}F NMR −209.4 (dd), J_{FCP} = 55 Hz, J_{FCH} = 40 Hz; ^{31}P NMR 38.7 (d), J_{PCF} = 54 Hz.

General Procedure: Preparation of $Bu_3P{=}CFC(O)OEt$ (7a). The phosphonium salt, **6a**, prepared by the general procedure from 22 mmol of tri-*n*-butylphosphine and 25 mmol of ethyl bromofluoroacetate in 25 mL of THF in a 200-mL, two-necked flask equipped with a standard assembly, was cooled to −78 °C via a dry ice/isopropyl alcohol bath. To the cooled solution was added 9.5 mL of *n*-butyllithium (23.8 mmol) dropwise via syringe. The resulting bright yellow solution was stirred at −78 °C for 20 min and maintained at that temperature for further transformations. ^{19}F and ^{31}P NMR analyses of the yellow solution at room temperature exhibited the following signals: ^{19}F NMR −239.0 (d), J_{FCP} = 40 Hz, and −240.0 (d), J_{FCP} = 48 Hz; ^{31}P NMR 21.2 (d), J_{PCF} = 40 Hz, and 20.8 (d), J_{PCF} = 48 Hz.

Preparation of $[Ph_3P^+CFHC(O)OEt]Br^-$ (6b). A 500-mL, two-necked, round-bottomed flask equipped with a septum port, a magnetic stirbar, and a reflux condenser connected to a nitrogen source was charged sequentially with 150 mL of dry CH_2Cl_2 and 52.4 g (200 mmol) of triphenylphosphine. The resultant homogeneous solution was stirred, and then 37.0 g (200 mmol) of ethyl bromofluoroacetate was added in one portion via syringe. After 72 h of stirring at room temperature, ^{19}F NMR analysis of the reaction mixture indicated that 77% of ester had been converted into the corresponding phosphonium salt **6b**. Additional stirring did not improve the conversion. Concentration of the reaction mixture to one-third of its original volume on a rotary evaporator yielded a viscous residue. The residue was diluted with 300 mL of diethyl ether, and the resultant mixture was stirred vigorously at room temperature for 48 h to give a yellow solid, which was

(17) Saunders, B. C. *Some Aspects of the Chemistry and Toxic Action of Organic Compounds Containing Phosphorus and Fluorine*; Cambridge University Press: Cambridge, 1957.

(18) Englund, B. *Organic Syntheses*; John Wiley and Sons: New York, 1963; Collect. Vol. IV, p 423.

(19) Blackburn, G. M.; Parratt, M. J. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1417.

(20) Duhamel, L.; Plaquevent, J. C. *J. Org. Chem.* **1979**, *44*, 3404.

suction filtered and dried at 0.5 mmHg overnight to give 62 g (70% yield) of the titled compound. The ^{19}F and ^{31}P NMR spectra of **6b** exhibited the following signals: ^{19}F NMR −202.5 (dd), J_{FCP} = 68 Hz, J_{FCH} = 42 Hz; ^{31}P NMR 25.2 (d), J_{PCF} = 69 Hz.

General Procedure for the Preparation of RCFHCOOEt 9 as Described by the Preparation of $CH_3CFHCOOEt$ (9a). To a cooled (−78 °C) solution of the ylid **7a**, generated from 35 mmol of tri-*n*-butylphosphine, 35 mmol of ethyl bromofluoroacetate, and 33 mmol of *n*-butyllithium in 50 mL of THF in a 300-mL two-necked flask equipped with the standard assembly, was added 5 g of methyl iodide (35 mmol) via syringe in one portion. The resulting mixture was stirred at −78 °C for 1 h, allowed to warm to room temperature over 8 h, and then hydrolyzed by addition of 30 mL of a 10% aqueous $NaHCO_3$ solution. After the resulting mixture was stirred at room temperature for 6 h, the organic layer was separated, and the aqueous layer was extracted with diethyl ether (2 × 30 mL). The combined organic materials were washed successively with brine (2 × 25 mL) and water (2 × 25 mL), dried over anhydrous $MgSO_4$, and concentrated via atmospheric distillation to give a brownish residue. Redistillation of the residue through a 6-in. Vigreux column at 50–51 °C (64 mmHg) (lit.[21] 34 °C (15 mm)) gave 2.5 g (59% yield) of $CH_3CFHCOOEt$, 99.8% pure by GLPC analysis. ^{19}F NMR data is reported in Table I. ^1H NMR: 1.6 (dd, $^3J_{H,F}$ = 24 Hz, $^3J_{H,H}$ = 7 Hz), 5.0 (dq, $^2J_{H,F_{gem}}$ = 49 Hz), 4.3 (q, $^3J_{H,H}$ = 7 Hz), and 1.3 (t). ^{13}C NMR: 18.3 (d, $^2J_{C,F}$ = 22 Hz), 85.7 (d, $^1J_{C,F}$ = 181 Hz), 170.5 (d, $^2J_{C,F}$ = 23 Hz), 61.5 (s), and 14.2 (s). IR: 2980 (s), 2950 (s), 1750 (s), 1455 (s), 1370 (s), 1290 (s), 1215 (s), 1065 (w), 1030 (w), 940 (m), 870 (m). Mass spectrum: *m/e* 121 (0.2), 120 (1.7, M^+), 92 (9.6), 77 (7.6), 75 (9.7), 61 (8.3), 47 (100), 46 (35.2), 45 (30.5), 43 (7.5), 31 (14.5), 29 (78), 28 (13.8), and 27 (24.3). Anal. Calcd for $C_5H_9O_2F$: C, 49.99; H, 7.55; F, 15.82. Found: C, 49.50; H, 7.48; F, 15.57.

Preparation of $CH_3CH_2CFHCOOEt$ (9b). Similarly, **9b** was prepared by the general procedure from 25 mmol (5.1 g) of tri-*n*-butylphosphine, 25 mmol (4.6 g) of ethyl bromofluoroacetate, 23 mmol (9.2 mL) of *n*-butyllithium, and 28.1 mmol (4.4 g) of ethyl iodide in 25 mL of THF. The reaction mixture was stirred at −78 °C for 1 h, allowed to warm to 15 °C over 6 h, and maintained at that temperature for 60 h using a cryocool immersion cooler. The reaction mixture was purified as described above to give a brownish residue, and distillation of the residue through a 6-in. Vigreux column at 60–61 °C (60 mmHg) gave 1.4 g (42% yield) of $CH_3CH_2CFHCOOEt$, 95% pure by GLPC analysis. ^{19}F NMR data is reported in Table I. ^1H NMR: 1.0 (t, $^3J_{H,H}$ = 7 Hz), 1.9 (m, $^3J_{F,H}$ = 24 Hz), 4.9 (ddd, $^2J_{F,H_{gem}}$ = 49 Hz, $^3J_{H,H}$ = 7 and 5 Hz), 4.3 (q, $^3J_{H,H}$ = 7 Hz), and 1.3 (t). ^{13}C NMR: 8.6 (d, $^3J_{C,F}$ = 4 Hz), 25.9 (d, $^2J_{C,F}$ = 21 Hz), 90.0 ($^1J_{C,F}$ = 184 Hz), 169.9 (d, $^2J_{C,F}$ = 24 Hz), 61.3 (s), and 14.2 (s). IR: 2980 (m), 2960 (sh, w), 2880 (sh, w), 1765 (s), 1740 (s), 1470 (w), 1380 (w), 1300 (m), 1215 (s), 1130 (m), 1035 (m), and 990 (w). Mass spectrum: *m/e* 134 (1.7, M^+), 106 (56), 89 (8.5), 78 (19.4), 61 (100), 60 (50), 59 (23.7), 49 (10.3), 45 (28.9), 43 (18.2), 41 (76.5), 39 (18.8), 29 (79.2), 28 (12.8), and 27 (19.2). Anal. Calcd for $C_6H_{11}O_2F$: C, 53.72; H, 8.26; F, 14.16. Found: C, 53.24; H, 8.22; F, 14.37.

Preparation of $CH_3CH_2CH_2CFHCOOEt$ (9c). Similarly, **9c** was prepared by the general procedure from 50 mmol (10.1 g) of tri-*n*-butylphosphine, 50 mmol (9.3 g) of ethyl bromofluoroacetate, 48 mmol (19.2 mL) of *n*-butyllithium, and 59.4 mmol (10.1 g) of *n*-propyl iodide in 50 mL of THF. The reaction mixture was stirred at −78 °C for 1 h, allowed to warm to 15 °C over 6 h, and maintained at that temperature for 160 h using a cryocool immersion cooler. The reaction mixture was purified as described above to give a viscous residue, and distillation of the residue through a 6-in. Vigreux column at 94–95 °C (117 mmHg) gave 3.1 g (42% yield) of $CH_3CH_2CH_2CFHCOOEt$, 95% pure by GLPC analysis. ^{19}F NMR data is reported in Table I. ^1H NMR: 0.97 (t, $^3J_{H,H}$ = 7 Hz), 1.5 (sextet), 1.9 (m, $^3J_{H,F}$ = 24 Hz), 4.9 (dt, $^2J_{F,H_{gem}}$ = 49 Hz, $^3J_{H,H}$ = 6 Hz), 4.3 (q, $^3J_{H,H}$ = 7 Hz), and 1.3 (t). ^{13}C NMR: 13.6 (s), 17.9 (d, $^3J_{C,F}$ = 3 Hz), 34.5 (d, $^2J_{C,F}$ = 21 Hz), 88.9 (d, $^1J_{C,F}$ = 184 Hz), 170.1 (d, $^2J_{C,F}$ = 24 Hz), 61.4 (s), and 14.2 (s). IR: 2980 (s), 2930 (s), 1800 (s), 1780 (s), 1500 (m), 1420 (m), 1325 (m), 1240 (m), 1180 (m), 1070 (m), 1030 (w), and 900 (w). Mass spectrum: *m/e* 121 (2.1), 106 (78.4), 78 (47.7), 75 (28.2), 74 (13.3), 60 (10.2), 59 (19.2), 56 (11.7), 55 (100), 47 (44.6), 46 (16.6), 45 (20.1), 43 (18.4), 41 (14.5), 39 (11.4), 29 (80.1), 28 (10.8), and 27 (20.9).

Preparation of $CH_3(CH_2)_2CH_2CFHCOOEt$ (9d). Similarly, **9d** was prepared by the general procedure from 50 mmol (10.1 g) of tri-*n*-butylphosphine, 50 mmol (9.3 g) of ethyl bromofluoroacetate, 48 mmol (19.2 mL) of *n*-butyllithium, and 60.0 mmol (11.0 g) of *n*-butyl iodide in 50 mL of THF. The reaction mixture was stirred at −78 °C for 1 h, allowed to warm to 15 °C over 6 h, and maintained at that temperature for 132 h using a cryocool immersion cooler. The reaction mixture was purified as described above to give a viscous residue, and distillation of the residue through a 6-in. Vigreux column at 93–94 °C (63 mmHg) gave 2.8 g (34% yield) of $CH_3(CH_2)_2CH_2CFHCOOEt$, 99% pure by GLPC analysis. ^{19}F NMR data is reported in Table I. ^1H NMR: 0.88 (t, $^3J_{H,H}$ = 7 Hz), 1.46 (m), 1.87 (m, $^3J_{H,F}$ = 24 Hz), 4.86 (dt, $^2J_{H,F_{gem}}$ = 49 Hz, $^3J_{H,H}$ = 6 Hz), 4.2 (q, $^3J_{H,H}$ = 7 Hz), and 1.3 (t). ^{13}C NMR: 13.8 (s), 22.3 (s), 26.6 (d, $^3J_{C,F}$ = 3 Hz), 32.2 (d, $^2J_{C,F}$ = 21 Hz), 89.1 (d, $^1J_{C,F}$ = 184 Hz), 170.1 (d, $^2J_{C,F}$ = 24 Hz), 61.4 (s), and 14.2 (s). IR: 2980 (s), 2900 (m), 1780 (s), 1760 (s), 1485 (w), 1400 (m), 1310 (m), 1230 (s) 1165 (w), and 1060 (m). Mass spectrum: *m/e* 163 (0.5), 161 (0.1), 106 (100), 78 (37.9), 69 (33.6), 59 (10.3), 43 (20), 41 (26.2), and 29 (20.2). Anal. Calcd for $C_8H_{15}O_2F$: C, 59.23; H, 9.32; F, 11.71. Found: C, 59.72; H, 9.63; F, 11.26.

Preparation of $CH_3(CH_2)_5CH_2CFHCOOEt$ (9e). Similarly, **9e** was prepared by the general procedure from 50 mmol (10.1 g) of tri-*n*-butylphosphine, 50 mmol (9.3 g) of ethyl bromofluoroacetate, 48 mmol (19.2 mL) of *n*-butyllithium, and 60.0 mmol (13.2 g) of *n*-heptyl iodide in 50 mL of THF. The reaction mixture was stirred at −78 °C for 1 h, allowed to warm to 15 °C over 6 h, and maintained at that temperature for 72 h using a cryocool immersion cooler. The reaction mixture was purified as described above to give a viscous residue, and distillation of the residue through a 6-in. Vigreux column at 93–94 °C (5 mmHg) gave 5.3 g (52% yield) of $CH_3(CH_2)_5CH_2CFHCOOEt$, 97% pure by GLPC analysis. ^{19}F NMR data is reported in Table I. ^1H NMR: 0.92 (t, $^3J_{H,H}$ = 7 Hz), 1.37 (m), 1.30 (pentet), 1.88 (m, $^3J_{F,H}$ = 25 Hz), 4.9 (dt, $^2J_{F,H_{gem}}$ = 49 Hz, $^3J_{H,H}$ = 6 Hz), 4.3 (q), and 1.3 (t). ^{13}C NMR: 14.1 (s), 22.7 (s), 29.2–31.9 (s), 24.5 (d, $^3J_{C,F}$ = 3 Hz), 32.6 (d, $^2J_{C,F}$ = 22 Hz), 89.1 (d, $^1J_{C,F}$ = 185 Hz), 170.0 (d, $^2J_{C,F}$ = 23 Hz), 61.3 (s), and 14.2 (s). IR: 2955 (s), 2900 (s), 1775 (s), 1495 (m), 1405 (m), 1310 (m), 1235 (s), 1165 (m), 1135 (m), 1065 (m), and 895 (w). Mass spectrum: *m/e* 175 (5.3), 161 (9.5), 143 (11), 106 (100), 78 (46.4), 73 (11.2), 69 (27.3), 59 (18), 57 (21.4), 56 (10), and 55 (29.1). Anal. Calcd for $C_{11}H_{21}O_2F$: C, 64.68; H, 10.36; F, 9.29. Found: C, 64.06; H, 10.48; F, 9.27.

Preparation of $CH_3(CH_2)_8CH_2CFHCOOEt$ (9f). Similarly, **9f** was prepared by the general procedure from 50 mmol (10.1 g) of tri-*n*-butylphosphine, 50 mmol (9.3 g) of ethyl bromofluoroacetate, 48 mmol (19.2 mL) of *n*-butyllithium, and 52.5 mmol (13.2 g) of *n*-decyl iodide in 50 mL of THF. The reaction mixture was stirred at −78 °C for 1 h, allowed to warm to 15 °C over 6 h, and maintained at that temperature for 72 h using a cryocool immersion cooler. The reaction mixture was purified as described above to give a viscous residue, and distillation of the residue through a 6-in. Vigreux column at 115–116 °C (1 mmHg) gave 5.4 g (44% yield) of $CH_3(CH_2)_8CH_2CFHCOOEt$, 98% pure by GLPC analysis. ^{19}F NMR data is reported in Table I. ^1H NMR: 0.88 (t, $^3J_{H,H}$ = 7 Hz), 1.45 (sext), 1.27 (m), 1.88 (m, $^3J_{H,F}$ = 25 Hz), 4.87 (dt, $^2J_{F,H_{gem}}$ = 49 Hz, $^3J_{H,H}$ = 6 Hz), 4.3 (q), and 1.3 (t). ^{13}C NMR: 14.1 (s), 22.8 (s), 29.2–29.7 (s), 32.0 (s), 24.5 (d, $^3J_{C,F}$ = 3 Hz), 32.6 (d, $^2J_{C,F}$ = 22 Hz), 89.1 (d, $^1J_{C,F}$ = 184 Hz), 170.0 (d, $^2J_{C,F}$ = 23 Hz), 61.3 (s), and 14.2 (s). IR: 2950 (s), 2865 (m), 1770 (s), 1480 (m), 1385 (w), 1290 (w), 1215 (m), 1105 (w), and 1040 (w). Mass spectrum: *m/e* 199 (3.7), 185 (13.2), 175 (12.4), 161 (15), 106 (100), 91 (11.2), 78 (31.5), 73 (16.1), 71 (13.8), 69 (18.3), 67 (10.4), 59 (14.2), 57 (32.9), 56 (13.4), 55 (47.4), and 53 (10.2). Anal. Calcd for $C_{14}H_{27}O_2F$: C, 68.25; H, 11.05; F, 7.71. Found: C, 67.76; H, 11.38; F, 7.31.

Preparation of $PhCH_2CFHCOOEt$ (9g). Similarly, **9g** was prepared by the general procedure from 25 mmol (5.1 g) of tri-*n*-butylphosphine, 25 mmol) (4.6 g) of ethyl bromofluoroacetate, 24 mmol (9.6 mL) of *n*-butyllithium, and 36 mmol (6.1 g) of benzyl bromide in 25 mL of THF. The reaction mixture was stirred at −78 °C for 1 h, allowed to warm to 20 °C over 5 h, and maintained at that temperature for 16 h using a cold water bath. The reaction

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mixture was purified as described above to give a viscous residue, and distillation of the residue through a 6-in. Vigreux column at 69–70 °C (0.3 mmHg) (lit.[5] 136–138 °C (20 mmHg) gave 2.9 g (59% yield) of $PhCH_2CFHCOOEt$, 99.9% pure by GLPC analysis. ^{19}F NMR data is reported in Table I. ^1H NMR: 7.21–7.31 (m), 3.16 (m, $^3J_{H,H}$ = 4 Hz), 5.05 (ddd, $^2J_{F,H_{gem}}$ = 49 Hz, and $^3J_{H,H}$ = 8 Hz), 4.18 (q, $^3J_{H,H}$ = 7 Hz), and 1.21 (t). ^{13}C NMR: 127.1 (s), 128.5 (s), 129.4 (s), 135.2 (s), 38.7 (d, $^2J_{C,F}$ = 21 Hz), 89.2 (d, $^1J_{C,F}$ = 187 Hz), 169.1 (d, $^2J_{C,F}$ = 24 Hz), 61.5 (s), and 14.1 (s). IR: 3040 (w), 3010 (w), 2970 (w), 1745 (s), 1275 (w), 1185 (m), 1080 (m), 1020 (m), 740 (w), and 690 (w). Mass spectrum: *m/e* 196 (1.2, M^+), 176 (63.1), 148 (31.5), 147 (28.9), 132 (12.7), 131 (100), 123 (31.3), 122 (16.5), 104 (22.1), 103 (60.4), 91 (93.2), 78 (10.5), 77 (34.3), and 51 (14.4). Anal. Calcd for $C_{11}H_{13}O_2F$: C, 67.33; H, 6.68; F, 9.68. Found: C, 67.12, H, 6.69; F, 9.66.

Preparation of CH_2=$CHCH_2CFHCOOEt$ (9h). Similarly, **9h** was prepared by the general procedure from 25 mmol (5.1 g) of tri-*n*-butylphosphine, 25 mmol (4.6 g) of ethyl bromofluoroacetate, 24 mmol (9.6 mL) of *n*-butyllithium, and 36.4 mmol (4.4 g) of allyl bromide in 25 mL of THF. The reaction mixture was stirred at −78 °C for 1 h, allowed to warm to 20 °C over 5 h, and maintained at that temperature for 15 h using a cold water bath. The reaction mixture was purified as described above to give a viscous residue, and distillation of the residue through a 6-in. Vigreux column at 82–83 °C (28 mmHg) (lit.[5] 75–76 °C (35 mmHg)) gave 1.9 g (52% yield) of CH_2=$CHCH_2CFHCOOEt$, 96% pure by GLPC analysis. ^{19}F NMR data is reported in Table I. ^1H NMR: 5.22 (dd, $^2J_{H,H_{gem}}$ = 1 Hz, $^3J_{H,H_{cis}}$ = 4 Hz), 5.17 (dd, $^3J_{H,H_{trans}}$ = 11 Hz), 5.82 (dtd = m, $^3J_{H,H_{vic}}$ = 7 Hz), 2.65 (m, $^3J_{H,H_{vic}}$ = 5 Hz), 4.94 (ddd, $^2J_{H,F_{gem}}$ = 49 Hz), 4.26 (q, $^3J_{H,H_{vic}}$ = 7 Hz), and 1.3 (t). ^{13}C NMR: 119.2 (s), 131.0 (d, $^3J_{C,F}$ = 3 Hz), 36.8 (d, $^2J_{C,F}$ = 21 Hz), 88.2 (d, $^1J_{C,F}$ = 184 Hz), 169.3 (d, $^2J_{C,F}$ = 24 Hz), 61.5 (s), and 14.2 (s). IR: 3100 (w), 3000 (s), 1760 (s), 1645 (m), 1380 (m), 1290 (m), 1220 (s), 1085 (m), 1030 (m), 990 (w), 925 (m), and 860 (w). Mass spectrum: *m/e* 98 (44.5), 97 (22.5), 81 (22.5), 73 (71.7), 72 (32.9), 70 (27.7), 67 (11), 60 (12.7), 59 (16.2), 55 (16.2), 54 (13.3), 53 (100), 51 (20.9), 47 (31.2), 46 (32.9), 45 (25.4), 43 (16.8), 42 (31.2), 41 (35.3), and 40 (13.3). Anal. Calcd for $C_7H_{11}O_2F$: C, 57.52; H, 7.59; F, 13.00. Found: C, 57.23; H, 7.70; F, 12.86.

Preparation of an *E* and *Z* Mixture of CH_3CH=$CHCH_2CFHCOOEt$ (9i). Similarly, **9i** was prepared by the general procedure from 25 mmol (5.1 g) of tri-*n*-butylphosphine, 25 mmol (4.6 g) of ethyl bromofluoroacetate, 24 mmol (9.6 mL) of *n*-butyllithium, and 36.0 mmol (4.8 g) of an *E* and *Z* mixture of crotyl bromide (*E*/*Z* = 85/15) in 25 mL of THF. The reaction mixture was stirred at −78 °C for 1 h, allowed to warm to 20 °C over 5 h, and maintained at that temperature overnight using a cold water bath. The reaction mixture was purified as described above to give a viscous residue, and distillation of the residue through a 6-in. Vigreux column at 84–85 °C (25 mmHg) gave 1.5 g (38% yield) of an *E* and *Z* mixture of CH_3CH=$CHCH_2CFHCOOEt$, 99.7% pure by GLPC analysis. The *E*/*Z* ratio of the distilled product as determined by GLPC was 86/14. ^{19}F NMR data is reported in Table I. ^1H NMR (for *E* isomer): 1.69 (dd, $^3J_{H,H}$ = 6 Hz, $^4J_{H,H_{cis}}$ = 1 Hz), 5.58 (m, $^3J_{H,H_{trans}}$ = 14 Hz), 5.45 (m, $^3J_{H,H}$ = 7 Hz), 2.58 (m, $^3J_{H,H}$ = 5 Hz), 4.88 (ddd, $^2J_{H,F_{gem}}$ = 49 Hz, $^3J_{H,H}$ = 7 Hz), 4.3 (q, $^3J_{H,H}$ = 7 Hz), and 1.3 (t). For Z isomer: 1.64 (dd, $^3J_{H,H}$ = 7 Hz, $^4J_{H,H_{trans}}$ = 1 Hz), 5.58 (m, $^3J_{H,H_{cis}}$ = 7 Hz), 5.45 (m), 2.58 (m, $^3J_{H,H}$ = 6 Hz), 4.92 (dt, $^2J_{H,F_{gem}}$ = 49 Hz), 4.30 (q, $^3J_{H,H}$ = 7 Hz), and 1.30 (t). ^{13}C NMR (for E isomer): 17.9 (s), 130.0 (s), 123.5 (d, $^3J_{C,F}$ = 4 Hz), 35.8 (d, $^2J_{C,F}$ = 22 Hz), 88.7 (d, $^1J_{C,F}$ = 186 Hz), 169.4 (d, $^2J_{C,F}$ = 24 Hz), 61.4 (s), and 14.2 (s). For Z isomer: 17.9 (s), 128.4 (s), 122.4 (s), 30.2 (d, $^2J_{C,F}$ = 22 Hz) 88.5 (d, $^1J_{C,F}$ = 185 Hz), 169.4 (d, $^2J_{C,F}$ = 24 Hz), 61.5 (s), and 14.2 (s). IR: 3040 (w), 2980 (m), 2940 (m), 1750 (s), 1455 (w), 1385 (m), 1285 (m), 1220 (s), 1135 (w), 1100 (m), 1070 (m), 1040 (m), 980 (m), and 870 (w). Mass spectrum: *m/e* 141 (2.8), 140 (26.6), 125 (52.5), 112 (10), 111 (10.4), 97 (100), 95 (17), 87 (25.6), 86 (17.5), 85 (19), 84 (11.4), 78 (22.3), 67 (69), 66 (21.3), 65 (13.9), 60 (10), 59 (56), 57 (12), 55 (57), 51 (10), 49 (11.1), 43 (15.8), 41 (38.9), 39 (47.7), 29 (46.5), 28 (16.9), and 27 (18.9). Anal. Calcd for $C_8H_{13}O_2F$: C, 60.02; H, 8.19; F, 11.86. Found: C, 60.21; H, 8.42; F, 11.89.

Preparation of (*E*)-$PhCH$=$CHCH_2CFHCOOEt$ (9j). Similarly, **9j** was prepared by the general procedure from 25 mmol (5.1 g) of tri-*n*-butylphosphine, 25 mmol (4.6 g) of ethyl bromofluoroacetate, 23 mmol (9.2 mL) of *n*-butyllithium, and 28.1 mmol (5.5 g) of (*E*)-cinnamyl bromide in 25 mL of THF. The reaction mixture was stirred at −78 °C for 1 h, allowed to warm to 20 °C over 6 h, and maintained at that temperature for 16 h using a cold water bath. The reaction mixture was purified as described above to give a viscous residue, and distillation of the residue through a 6-in. Vigreux column at 112–113 °C (0.5 mmHg) gave 2.5 g (45% yield) of (*E*)-$PhCH$=$CHCH_2CFHCOOEt$, 97% pure by GLPC analysis. ^{19}F NMR data is reported in Table I. ^1H NMR: 7.26 (s, broad), 6.41 (dt, $^3J_{H,H_{trans}}$ = 17 Hz), 6.23 (dt, $^3J_{H,H}$ = 6 Hz), 2.80 (dt, $^3J_{H,F}$ = 25 Hz, $^3J_{H,H}$ = 6 Hz), 4.96 (dt, $^2J_{H,F_{gem}}$ = 49 Hz), 4.2 (q, $^3J_{H,H}$ = 7 Hz), and 1.2 (t). ^{13}C NMR: 126.2 (s), 127.5 (s), 128.5 (s), 134.2 (s), 122.3 (s), 136.8 (s), 36.1 (d, $^2J_{C,F}$ = 21 Hz), 88.3 (d, $^1J_{C,F}$ = 186 Hz), 169.1 (d, $^2J_{C,F}$ = 23 Hz), 61.4 (s), and 14.2 (s). IR: 3000 (s), 2930 (sh, m), 1785 (s), 1480 (w), 1405 (w), 1315 (m), 1235 (s), 1120 (m), 1060 (m), 1000 (m), 775 (w), and 735 (w). Mass spectrum: *m/e* 222 (1.8, M^+), 202 (13.7), 130 (13.5), 129 (100), 128 (35.3), 127 (13.9), 117 (35.3), 115 (33.9), 97 (12.6), 95 (10.4), 91 (17), 86 (30.2), 84 (52.2), 83 (14.6), 81 (12.6), 77 (19.9), 73 (24.7), 71 (13.5), 69 (17.7), 67 (10.3), 57 (21.3), 55 (22.5), and 51 (34.6).

Preparation of (*E*)-CH_3OCOCH=$CHCH_2CFHCOOEt$ (9k). Similarly, **9k** was prepared by the general procedure from 30 mmol (6.1 g) of tri-*n*-butylphosphine, 30 mmol (5.6 g) of ethyl bromofluoroacetate, 29 mmol (11.6 mL) of *n*-butyllithium, and 30.0 mmol (5.4 g) of (*E*)-methyl 4-bromocrotonate in 50 mL of THF. The reaction mixture was stirred at −78 °C for 1 h, allowed to warm to 20 °C over 5 h, and maintained at that temperature for 14 h using a cold water bath. The reaction mixture was purified as described above to give a dark brown residue, which was loaded onto a 16.8 cm o.d. × 54 cm flash chromatography column that contained 12 cm of silica gel (230–400 mesh/Aldrich). A mixture of *n*-hexane/ethyl acetate (81/19) was used as the eluent, and 20-mL fractions were collected. The progress of the separation was monitored by TLC, and all the active fractions were combined and rotary evaporated to give 3.5 g of pale yellow residue. Distillation of the residue through a short-path distillation apparatus at 72–80 °C (0.6 mmHg) gave 2.5 g (41% yield) of (*E*)-CH_3OCOCH=$CHCH_2CFHCOOEt$, 93% pure by GLPC analysis. ^{19}F NMR data is reported in Table I. ^1H NMR: 3.73 (dd), 6.0 (dq, $^3J_{H,H_{trans}}$ = 16 Hz), 6.9 (dtq, $^3J_{H,H}$ = 7 Hz) 2.8 (m, $^3J_{H,H}$ = 5 Hz), 5.0 (dt, $^2J_{H,F_{gem}}$ = 49 Hz), 4.3 (q, $^3J_{H,H}$ = 7 Hz), and 1.3 (t). ^{13}C NMR: 51.6 (s), 166.0 (s), 142.0 (s), 125.0 (s), 35.3 (d, $^2J_{C,F}$ = 22 Hz), 87.1 (d, $^1J_{C,F}$ = 188 Hz), 168.6 (d, $^2J_{C,F}$ = 23 Hz), 61.8 (s), and 14.2 (s). IR: 2985 (w), 2952 (w), 1769 (s), 1732 (s), 1664 (w), 1662 (w), 1436 (m), 1320 (m), 1303 (m), 1274 (m), 1212 (m), 1198 (m), 1183 (m), 1171 (m), 1100 (w), 1039 (w), and 976 (w). Mass spectrum: *m/e* 205 (0.2), 204 (0.2, M^+), 173 (13.4), 172 (55.3), 153 (31.5), 144 (21.7), 131 (89), 130 (26.9), 125 (67), 117 (10.7), 116 (25.7), 115 (13.7), 112 (10.7), 11 (96.5), 103 (10.8), 100 (21), 99 (100), 97 (98.4), 89 (14.9), 83 (10.2), 82 (18.9), 81 (31), 73 (13.1), 72 (34.2), 71 (51.2), 69 (27.9), 68 (17.1), 59 (62.1), 55 (18.7), 53 (27.6), 51 (15.1), and 1 (63.3).

General Procedure: Preparation of (i-PrO)$_2$P(O)CFHC(O)OEt (10b). A 300-mL, three-necked, round-bottomed flask equipped with a magnetic stirbar, a glass stopper, a thermometer, and an air condenser connected to a nitrogen source was charged with 187 g of triisopropyl phosphite (0.9 mol) and 120 g of ethyl bromofluoroacetate (0.65 mol). The resulting mixture was stirred and heated to 145 °C for 6 h, and then ^{19}F NMR analysis of the reaction mixture indicated that 80% of fluoroacetate had been converted to the corresponding phosphonate **10b**. Distillation of the crude reaction mixture through a 6-in. Vigreux column at 98–100 °C (0.4 mmHg) gave 130 g of (74% yield) (i-PrO)$_2$P(O)-CFHC(O)OEt, 99.8% pure by GLPC analysis. ^{19}F and ^{31}P NMR spectra of **10b** exhibited the following signals. ^{19}F NMR: −210.6 (dd), J_{FCP} = 72 Hz, J_{FCH} = 48 Hz. ^{31}P NMR: 8.3 (d), J_{PCF} = 72 Hz.

Preparation of (i-PrO)$_2$P(O)CF[CH(Ph)CH$_3$]COOEt (12a). A 100-mL two-necked flask equipped with a septum port, a magnetic stirbar, and a reflux condenser connected to a source of nitrogen was charged sequentially with 50 mL of THF and 9.4 g of **10b** (34.8 mmol). The resulting solution was stirred and cooled to −78 °C (dry ice/isopropyl alcohol bath), and then 14 mL of *n*-butyllithium (35 mmol) was added dropwise via syringe. Stirring at −78 °C was continued for 20 min, and then 6.8 g of CH_3CH-

(Ph)Br (36.5 mmol) was added via syringe in one portion. The resultant mixture was stirred and warmed to room temperature over 4 h and then refluxed for 24 h. The reaction mixture was cooled to room temperature and then quenched with 100 mL of water. The two layers were separated, and the aqueous layer was extracted with diethyl ether (3 × 25 mL). The organic materials were combined and dried over anhydrous $MgSO_4$, filtered, and concentrated on a rotary evaporator to give a dark brown residue. Distillation of the residue through a short path distillation apparatus at 134–135 °C (<0.005 mmHg) via a diffusion pump afforded 7.8 g (60% yield) of **12a**. ^{19}F NMR ($CDCl_3$): −188.9 (dd), J_{FCP} = 84 Hz, J_{FCCH} = 34 Hz, and −191.4 (dd), J_{FCP} = 88 Hz, J_{FCH} = 34 Hz. ^{31}P NMR: 10.0 (d), J_{PCF} = 85 Hz, and 10.9 (d), J_{PCF} = 89 Hz. IR: 3080 (sh, w), 3040 (sh, w), 2990 (s), 2940 (s), 1760 (s), 1735 (s), 1600 (w), 1500 (w), 1460 (m), 1380 (m), 1270 (s), 1115 (s), 1000 (s), 775 (m), and 700 (w). Anal. Calcd for $C_{18}H_{28}O_5FP$: C, 57.75; H, 7.54; F, 5.07; P, 8.27. Found: C, 58.40; H, 7.82; F, 5.29; P, 7.59.

Preparation of $(i\text{-PrO})_2P(O)CF[CH(CH_3)_2]COOEt$ (12b). A 100-mL two-necked flask equipped with a septum port, a magnetic stirbar, and a reflux condenser connected to a source of nitrogen was charged sequentially with 50 mL of THF and 6.5 g of **10b** (24 mmol). The resulting solution was stirred and cooled to −78 °C (dry ice/isopropyl alcohol bath), and then 9.6 mL of *n*-butyllithium (24 mmol) was added dropwise via syringe. Stirring at −78 °C was continued for 20 min, and then 4.3 g of $(CH_3)_2CHI$ (25 mmol) was added via syringe in one portion. The resultant mixture was stirred and warmed to room temperature over 4 h and refluxed for 24 h. The reaction mixture was cooled to room temperature and then quenched with 100 mL of water. The two layers were separated, and the aqueous layer was extracted with diethyl ether (3 × 25 mL). The organic materials were combined and dried over anhydrous $MgSO_4$, filtered, and concentrated on a rotary evaporator to give a dark brown residue. Distillation of the residue through a short-path distillation apparatus at 77–83 °C (<0.005 mmHg) via a diffusion pump afforded 5.4 g (72% yield) of **12b**. ^{19}F NMR ($CDCl_3$): −193.7 (dd), J_{FCP} = 89 Hz, J_{FCCH} = 31 Hz. ^{31}P NMR: 11.4 (d), J_{PCF} = 89 Hz. IR: 2970 (s), 2940 (s), 1755 (s), 1740 (s), 1465 (s), 1380 (m), 1265 (s), 1180 (m), 1140 (s), 1110 (s), 1020 (s), 895 (m), 870 (w), and 750 (m). High-resolution mass spectrum (DIP, EI): mass obtained for $C_{13}H_{27}O_5FP$, $(M + 1)^+$ = 313.158 015 930 0; calculated for $(M + 1)^+$ = 313.155 670 2.

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Comparison of the Tautomerization and Hydrolysis of Some Secondary and Tertiary Enamines

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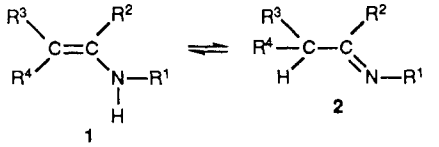
N-Phenylcyclohex-1-en-1-amine, *N*-(*p*-chlorophenyl)cyclohex-1-en-1-amine, the *N*-aryl-2-methylprop-1-en-1-amines, Me_2C = $CHNLC_6H_4X$, L = H,D, X = H, *p*-Cl, *p*-Me, *p*-MeO, *m*-NO_2, the *N*-alkyl-2-methylprop-1-en-1-amines, Me_2C = CHNDR, R = Me, Et, and the (*E*)-*N*-alkylprop-1-en-1-amines, MeHC = CHNDR, R = Me, *t*-Bu, were generated in solution from their *N*-trimethylsilyl derivatives and characterized by NMR spectroscopy. *N*-(*p*-Nitrophenyl)-2-methylprop-1-en-1-amine was isolated from the reaction of isobutyraldehyde and *p*-nitroaniline, and appreciable amounts (>10%) of the *N*-arylcyclohex-1-en-1-amines and *N*-aryl-2-methylcyclohex-1-en-1-amines were found to be present at equilibrium in DMSO-d_6 solution when the aryl group was phenyl, *p*-chlorophenyl, *m*-nitrophenyl, or *p*-nitrophenyl. The kinetics of hydrolysis of all the *N*-aryl secondary enamines obtained in the above ways were measured in aqueous solution and compared with those of the corresponding *N*-methyl tertiary enamines. With all enamines there was a region of pH in which k_{obsd} was proportional to 10^{-pH}, and under such conditions it was considered that the rate-determining step was C-protonation. This was supported by the isotope effect k_{H^+}/k_{D^+} = ca. 3, the observation of general acid catalysis, the much faster rate of hydrolysis of the corresponding imines, and the negative ρ^- values. It was found that in the cyclohexenyl series the secondary and tertiary enamines were hydrolyzed at similar rates when the substituents in the aryl group were the same, but in the 2-methylcyclohexenyl and 2-methylpropenyl series the secondary enamines were hydrolyzed much faster than the corresponding tertiary enamines. This was attributed to the tertiary enamines being hindered from attaining the most favorable conformation for p-π conjugation.

Introduction

The mechanism of hydrolysis of tertiary enamines has been studied by several groups of workers.[1-5] In general at high pHs the rate-limiting step is protonation of the double bond, and when the acidity is increased this changes to being breakdown of the intermediate carbinolamine.

Some secondary enamines are sufficiently stable to exist in detectable amounts in equilibrium with the corresponding imines. Thus, the enamine–imine equilibria (**1** ⇌ **2**) have been studied by Clark and Parker[6] and by Ahlbrecht and his co-workers[7] who showed, as expected, that the enamine is stabilized when R^3 or R^4 is methyl or aryl. It has also been possible to generate less stable



secondary enamines quantitatively or at concentrations greater than those present at equilibrium by methanolysis

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