277.9942 (^{79}Br), 279.9922 (^{81}Br), found 277.9918 (^{79}Br), 279.9886 (^{81}Br). Anal. Calcd for $C_{13}H_{11}BrO_2$: C, 55.94; H, 3.97. Found: C, 55.32; H, 3.77.

E isomer: mp 70–72 °C; IR (KCl) 1760, 1640, 1220, 1200, 1100 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.37 (m, 5 H, Ph), 6.16–5.72 (m, 1 H, =CH), 5.44–5.20 (m, 2 H, =CH_2), 4.50 (dd, J = 7.6 Hz, J = 7.7 Hz, 1 H, OCH), 4.20 (d, J = 7.6 Hz, J = 2.6 Hz, 1 H, OCH), 3.96 (m, J = 7.6 Hz, 1 H, OCCH); MS *m/e* (%) 282 (1.10), 281 (M^+(^{81}Br) + 1, 11.44), 280 (M^+(^{81}Br), 53.35), 279 (M^+(^{79}Br) + 1, 17.88), 278 (M^+(^{79}Br), 53.35), 277 (M^+(^{79}Br) − 1, 7.88), 199 (M^+ − Br, 19.60), 155 (M^+ − Br − CO_2, 100.00), 141 (M^+ − Br − CO_2 − CH_2, 95.91), 129 (M^+ − Br − CO_2 − C_2H_2, 21.27), 128 (22.32), 127 (16.40), 115 (M^+ − Br − CO_2 − C_3H_4, 76.77). Anal. Calcd for $C_{13}H_{11}BrO_2$: C, 55.94; H, 3.97. Found: C, 55.52; H, 3.78.

α-(Chloromethylene)-β-(1′-propenyl)-γ-butyrolactone (2i): ot 120–122 °C (8 mmHg); IR (neat) 1760, 1620, 1090 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 6.55, 6.49 (d, J = 2.8 Hz, 1 H, =CHCl), 5.94–5.60 (m, 1 H, =CH), 5.34 (m, 1 H, =CH), 4.45 (t, J = 8.0 Hz, 1 H, OCH), 4.18, 3.80 (m, J = 8.0 Hz, J = 2.8 Hz, 1 H, OCCH), 3.95 (t, J = 8.0 Hz, 1 H, OCH), 1.75 (m, 3 H, CH_3); MS *m/e* (%) 176 (3.16), 175 (M^+(^{37}Cl) + 1, 27.39), 174 (M^+(^{37}Cl), 4.05), 173 (M^+(^{35}Cl) + 1, 73.79), 172 (M^+(^{35}Cl), 8.85), 157 (M^+(^{37}Cl) − OH, 3.56), 156 (1.19), 155 (M^+(^{35}Cl) − OH, 10.55), 145 (4.20), 144 (M^+(^{37}Cl) − OCH_2, 17.53), 143 (9.63), 142 (M^+(^{35}Cl) − OCH_2, 45.86), 137 (M^+ − Cl, 22.29), 131 (M^+(^{37}Cl) + 1 − CO_2, 1.36), 130 (M^+(^{37}Cl) − CO_2, 2.95), 129 (M^+(^{37}Cl) − 1 − CO_2, 5.87), 128 (M^+(^{35}Cl) − CO_2, 7.75), 127 (M^+(^{35}Cl) − 1 − CO_2, 14.72), 116 (M^+(^{37}Cl) − CO_2 − CH_2, 7.77), 115 (6.19), 114 (M^+(^{35}Cl) − CO_2 − CH_2, 20.86), 79 (100.00). Anal. Calcd for $C_5H_5ClO_2$: C, 55.67; H, 5.26. Found: C, 55.27; H, 5.40.

Cyclization of 4′-Chloro-2′(*E*)-butenyl 2-Propynoate (1b) in the Presence of Allyl Chloride. A mixture of **1b** (80 mg, 0.50 mmol), allyl chloride, and $PdCl_2(PhCN)_2$ (10 mg, 0.025 mmol) in acetic acid (2.5 mL) was stirred at room temperature. Workup as above afforded the products **2b** and **10** in pure form. Allyl chloride added, reaction time, and yields of **2b** and **10**, respectively, are as follows: 0.6 mmol, 3 h, 57%, 0%; 7 mmol, 21 h, 57%, 19%; 12 mmol, 24 h, 41%, 37% (22% of **1b** was recovered).

4′-Chloro-2′-butenyl 2-allyl-3-chloropropenoate (10): ot 95–97 °C (1.5 mmHg); IR (neat) 3080, 1710, 1620, 1600, 1200, 1110, 1100 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.42 (t, J = 1.4 Hz, 1 H), 5.82 (m, 3 H), 5.18 (m, 1 H), 5.10 (m, 1 H), 4.83 (d, J = 6.0 Hz, 2 H), 4.19 (d, J = 7.2 Hz, 2 H), 3.10 (m, J = 6.6 Hz, J = 1.4 Hz, 2 H); MS *m/e* (%) 235 (M^+(^{35}Cl) + 1, 0.06), 202 (M^+(^{37}Cl) + 1 − Cl, 2.59), 201 (M^+(^{37}Cl) − Cl, 21.92), 200 (M^+(^{35}Cl) − HCl, 10.33), 199 (M^+(^{35}Cl) − 2 − Cl, 79.32), 131 (M^+(^{37}Cl) − Cl − OC_4H_6, 28.84), 130 (7.99), 129 (M^+(^{35}Cl) − Cl − OC_4H_6, 95.26), 103 (M^+(^{37}Cl) − Cl − CO_2 − C_4H_6, 4.80), 102 (3.20), 101 (M^+(^{35}Cl) − Cl − CO_2 − C_4H_6, 10.27), 100 (3.96), 66 ($C_5H_6^+$, 27.23), 65 ($C_5H_5^+$, 100.00), 53 ($C_4H_5^+$, 85.20). Anal. Calcd for $C_{10}H_{12}Cl_2O_2$: C, 51.09; H, 5.14. Found: C, 51.67; H, 5.07.

Acknowledgment. We thank the National Natural Science Foundation of China and Academia Sinica for financial support.

Registry No. **1a**, 129178-04-7; **1b**, 129178-00-3; **1c**, 129178-03-6; **1d**, 129178-05-8; **1e**, 129178-07-0; **1f**, 129178-06-9; **1g**, 134078-80-1; **1h**, 134078-81-2; **1i**, 134078-82-3; (*Z*)-**2a**, 129178-02-5; (*E*)-**2b**, 134078-83-4; (*Z*)-**2b**, 129178-01-4; (*E*)-**2d**, 129178-10-5; (*Z*)-**2d**, 129178-08-1; (*E*)-**2f**, 129178-11-6; (*Z*)-**2f**, 129178-09-2; (*E*)-**2g**, 134078-85-6; (*Z*)-**2g**, 134078-84-5; (*E*)-**2h**, 134078-87-8; (*F*)-**2h**, 134078-86-7; (*Z,E*)-**2i**, 134078-88-9; (*Z,Z*)-**2i**, 134078-89-0; **3**, 129178-13-8; **10**, 134078-90-3; $PdBr_2(PhCN)_2$, 15003-43-7; $PdCl_2(PhCN)_2$, 14220-64-5; $PdCl_2$, 7647-10-1; $PdCl_2(PPh_3)_2$, 13965-03-2; $Pd(OAc)_2$, 3375-31-3; $PdI_2(PhCN)_2$, 36234-35-2; PdI_2, 7790-38-7; 2-propynoic acid, 471-25-0; 2-octynoic acid, 5663-96-7; 2-butynoic acid, 590-93-2; 3-phenyl-2-propynoic acid, 637-44-5; (*E*)-1,4-dibromo-2-butene, 821-06-7; (*Z*)-1,4-dichloro-2-butene, 1476-11-5; (*E*)-1,4-dichloro-2-butene, 110-57-6; (*E*)-1,4-dibromo-2,3-dimethyl-2-butene, 6044-73-1; bis(dibenzylideneacetone)-palladium, 32005-36-0; (*E*)-1,4-dichloro-2-pentene, 53920-96-0.

Supplementary Material Available: ^{1}H NMR spectra for compounds **1a,b,d,i**, **2d**, **2f** (*Z* isomer), **2g** (*Z* isomer), **2h** (*Z* isomer), **3**, and **10** (10 pages). Ordering information is given on any current masthead page.

A New Approach to α,α-Difluoro-Functionalized Esters

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The addition reaction of iododifluoroacetates to alkenes is initiated by copper powder (10–20 mol %) at 50–60 °C. Both terminal and internal alkenes give good yields of adducts. The reaction is also applicable to alkenes containing a variety of functional groups, such as epoxy, hydroxy, ketone, ester, and phosphonate moieties. This reaction can be carried out either neat or in solvents such as hexane, benzene, acetonitrile, DMF, DMSO, and HMPA and is suppressed by *p*-dinitrobenzene and di-*tert*-butyl nitroxide. A single electron transfer initiated radical mechanism is proposed. In the presence of nickel dichloride hexahydrate, reduction of the adducts with zinc in moist THF provides the corresponding α,α-difluoro esters in good yields.

Introduction

The introduction of fluorine into an organic molecule causes dramatic change in biological activities.[1] The change is mainly due to the high electronegativity of fluorine, the strong carbon–fluorine bond, and increased lipid solubility. In recent years, fluorinated ketones have been widely employed as enzyme inhibitors.[2] Therefore, the synthesis of compounds containing a difluoromethylene group adjacent to a carbonyl group has attracted much attention.

The most widely utilized method for the introduction of such types of functionality has been the Reformatsky reaction using halodifluoroacetates[3] and halodifluoromethyl ketones.[4] More recently, difluoroketene silyl

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acetates[5] have also been used for the synthesis of compounds bearing the carbalkoxydifluoromethyl group. However, these methods could not be applied for the direct preparation of α,α-difluoro esters.[6]

Although fluorination[7] of α-keto esters with sulfur tetrafluoride was used to synthesize α,α-difluoro esters, this reaction has limited application due to the volatility and high toxicity of sulfur tetrafluoride. In addition, the fluorination reaction has poor chemical selectivity; some functionalities could not be tolerated under the reaction conditions. Kobayashi[8] has developed a somewhat better methodology for the preparation of α,α-difluoro esters using (carbomethoxydifluoromethyl)copper from methyl iododifluoroacetate and copper in aprotic coordinating solvents. Although the reaction of this copper reagent with aryl, alkenyl, and allyl halides gave good yields of the coupled products, the reaction with butyl halide required elevated temperature in HMPA, and only a modest yield of α,α-difluorohexanoate was obtained.

More recently, the atom-transfer reaction of methyl iododifluoroacetate with alkenes has been reported by Kiseleva[9a] and Taguchi.[9b] However, the radical cyclization of allyl iododifluoroacetate using organotin reagents gave none of the desired product and only iododifluoroacetate was recovered.[10]

In a preliminary paper,[11] we briefly described the addition of iododifluoroacetates to alkenes in the presence of copper. This methodology provides a new approach to α,α-difluoro functionalized esters in good yields. We now wish to report detailed results.

Results and Discussion

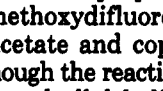
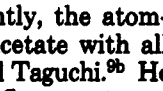
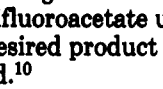
Iododifluoroacetates were easily prepared from the commercially available bromodifluoroacetates. When bromodifluoroacetates reacted with acid-washed zinc in the presence of a catalytic amount of mercury dichloride (5%) in triglyme at room temperature for 2–3 h,[12] ^{19}F NMR analysis of the reaction mixtures indicated the formation of the Reformatsky reagents in 70–90% yields. Upon treatment of the zinc reagents with iodine at 0 °C to room temperature, the corresponding iododifluoroacetates were isolated in 58–73% yields.

$$BrCF_2CO_2R + Zn \xrightarrow[TG]{HgCl_2} BrZnCF_2CO_2R \xrightarrow{I_2} ICF_2CO_2R$$

1a: R = CH_3, 58%
1b: R = C_2H_5, 64%
1c: R = $CH(CH_3)_2$, 73%

Table I. Copper-Initiated Reaction of 1 with Alkenes

$$ICF_2CO_2R + R^1CH{=}CHR^2 \xrightarrow[50\text{–}60\ ^\circ C]{Cu} R^2CHICHR^1CF_2CO_2R$$

no.	product	yield (%)
2	n-BuCHICH$_2$CF$_2$CO$_2$Me	75
3	n-C$_5$H$_{11}$CHICH$_2$CF$_2$CO$_2$Me	65
4	Me$_3$SiCHICH$_2$CF$_2$CO$_2$Me	83
5	n-BuCHICH$_2$CF$_2$CO$_2$Et	65
6	n-C$_5$H$_{11}$CHICH$_2$CF$_2$CO$_2$Et	76
7	n-C$_6$H$_{13}$CHICH$_2$CF$_2$CO$_2$Et	83
8	Me$_3$SiCHICH$_2$CF$_2$CO$_2$Et	70
9	n-C$_6$H$_{13}$CHICH$_2$CF$_2$CO$_2$^{i}Pr	76
10	Me$_3$SiCHICH$_2$CF$_2$CO$_2$^{i}Pr	72
11		80
12	HO(CH$_2$)$_8$CHICH$_2$CF$_2$CO$_2$Et	92
13	MeC(O)(CH$_2$)$_2$CHICH$_2$CF$_2$CO$_2$Et	67
14	EtO$_2$CCHMeCH$_2$CHICH$_2$CF$_2$CO$_2$Et	90
15	(EtO)$_2$P(O)CH$_2$CHICH$_2$CF$_2$CO$_2$Et	77
16	(EtO)$_2$P(O)CF$_2$CH$_2$CHICH$_2$CF$_2$CO$_2$Et	88
17		78
18		75
19	n-C$_3$H$_7$CHICH(n-C$_3$H$_7$)CF$_2$CO$_2$Et	72

The addition of 1 to terminal alkenes in the presence of copper gave the corresponding products at 50–60 °C. For example, in the case of the reaction of **1a** with 1-hexene and 15 mol % of copper powder in the absence of solvent at 55 °C, methyl 2,2-difluoro-4-iodooctanoate **2** was isolated in 75% yield.

$$ICF_2CO_2R + R'CH{=}CH_2 \xrightarrow[50\text{–}60\ ^\circ C]{Cu} R'CHICH_2CF_2CO_2R \quad 65\text{–}92\%$$

A variety of funtionalities on the alkenes can be tolerated under the reaction conditions. This method easily provided the precursors for the preparation of the α,α-difluoro functionalized esters. For example, upon treatment of **1b** with 9-decenol, neat, in the presence of 20 mol % of amount of copper at 55 °C for 3 h, the corresponding adduct was isolated in 92%. Similarly, other functional groups, including trimethylsilyl, epoxy, ester, ketone, and phosphonate on the alkenes did not interfere with the reaction. These results are summarized in Table I.

All the adducts exhibited a typical AB pattern signal in the ^{19}F NMR spectra. For example, ^{19}F NMR of **3** exhibited two doublets of multiplets at −102.4 ppm and at −107.4 ppm. The lower field signal is a doublet of doublet of doublets with J = 264, 17.1, and 14.7 Hz. The higher field signal is a doublet of triplets, with J = 264 and 17.1 Hz, respectively.

The addition reaction could also be successfully applied to internal alkenes. Upon reaction of **1b** with *trans*-3-octene and copper, adduct **19** was isolated in 75% yield as a mixture of diastereoisomers in a 1:1 ratio. The reaction with cyclohexene gave the corresponding trans and cis isomers in a 2:1 ratio. The structures of the isomers were assigned based on their ^{19}F NMR and ^{1}H NMR data.[13]

Previous reports by Coe[14] and Chen[15–17] documented that the addition of perfluoroalkyl iodides to alkenes can

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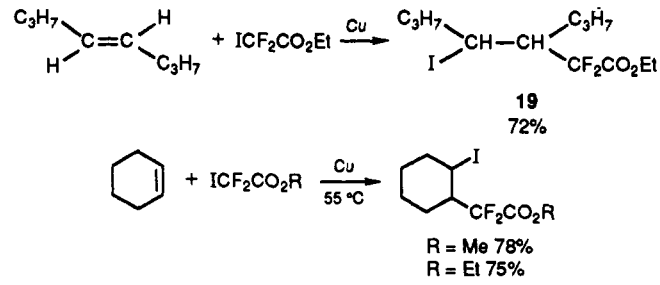
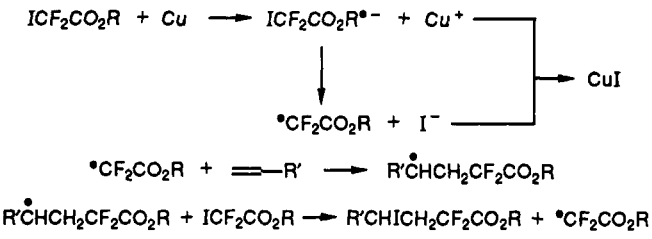
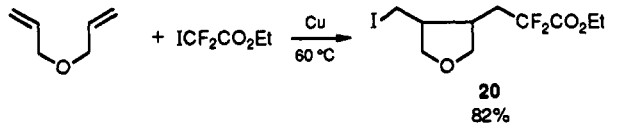


be initiated by copper. A single electron transfer mechanism has been proposed in the addition reactions.[14-16] Accordingly, we propose that reaction of 1 with alkenes may also involve a single electron transfer (SET) process.



The initiation step is likely to be an electron transfer from copper to 1 to produce a radical anion. The radical anion rapidly decomposes to the carbalkoxydifluoromethyl radical, which adds to the alkene, and then abstracts iodine from 1 to give the adduct and the carbalkoxydifluoromethyl radical, continuing the chain process. Evidence consistent with the proposed mechanism is that the reaction could be inhibited by both an electron scavenger and a radical inhibitor. For example, when **1b** was reacted with 1-octene and 20 mol % of copper in the presence of 20 mol % of *p*-dinitrobenzene at 55 °C for 4 h, no reaction was observed by ^{19}F NMR analysis; only **1b** was detected. Similarly, di-*tert*-butyl nitroxide completely suppressed the addition reaction under the same conditions.

Another recognized way to gain insight into the mechanism of the addition reaction is to conduct a ring closure reaction in the exo mode from the 5-hexenyl radical.[18] In order to test for the intermediacy of a radical, we reacted 1 with 1,6-heptadiene in the presence of copper. Upon reaction of **1b** with diallyl ether in the presence of copper at 60 °C, the tetrahydrofuran derivative **20** was formed. This result is similar to that obtained by Chen, who reported the reaction of perfluoroalkyl iodide with diallyl ether initiated by copper.[15]



Remarkable solvent effects on the reaction of perfluoroalkyl iodides with copper have been observed by Chen et al.[15,17] In coordinating solvents such as HMPA and DMSO, the (perfluoroalkyl)copper was proposed as the intermediate, which could be trapped by iodobenzene to give the (perfluoroalkyl)benzene. However, a perfluoroalkyl radical was suggested as a reactive intermediate for the reaction of perfluoroalkyl iodide with copper in poorly coordinating solvents, such as hexane and benzene. This radical reacted with alkenes to afford the corresponding adduct. Recently, Kobayashi[19] reported that when methyl iododifluoroacetate reacted with copper in either DMSO, DMF, or HMPA, (carbomethoxydifluoromethyl)copper was observed by ^{19}F NMR spectroscopy. It remained to be investigated whether or not similar solvent effects in the reaction of 1 with copper would take place.

We conducted the reaction of **1b** with alkenes and copper in a variety of solvents. As illustrated in Table II, the addition of **1b** to alkenes could be carried out in both poorly coordinating solvents and stronger coordinating solvents. For example, upon reaction of **1b** with copper and 1-octene in benzene, hexane, and acetonitrile at 55 °C, the corresponding adduct was obtained in 78, 81, and 92% of yields, respectively. When HMPA, DMSO, and DMF were employed as solvents, the reaction of **1b** with copper (Cu/**1b** = 2) and 1-octene at 55 °C gave good to excellent yields of adduct. No (carbalkoxydifluoromethyl)copper was observed in the ^{19}F NMR spectrum of the reaction mixture. In contrast, only (perfluoroalkyl)benzene was obtained in the reaction of perfluoroalkyl iodides with copper, 1-heptene, and iodobenzene in HMPA at 100 °C, which implies a (perfluoroalkyl)copper intermediate.[17] In DMSO, although some adduct was observed, the major product was still (perfluoroalkyl)benzene.[17] The difference in the reactivity between perfluoroalkyl iodides and 1 can be ascribed to the weak carbon–iodine bond of 1, due to the stabilization of the resulting carbalkoxydifluoromethyl radical by the adjacent carbonyl group. Thus, in the addition reaction of 1 with terminal alkenes, the initiation step or the efficiency of the chain propagation steps could be enhanced, resulting in a faster overall conversion of 1 to adducts instead of the formation of (carbalkoxydifluoromethyl)copper.

The competitive reaction between addition and formation of (perfluoroalkyl)copper depends on the reactivity of the alkene employed in the reaction of perfluoroalkyl iodide with alkene and copper.[17] When less active (relative to attack by radical) alkenes were used as substrates, the quantity of the copper reagent was increased.[17] One would anticipate that if a less active alkene reacted with 1 and copper in a stronger coordinating solvent, the addition reaction would become less favorable, and thereby (carbalkoxydifluoromethyl)copper would be generated. We used cyclohexene as a less active substrate. Upon reaction of cyclohexene with **1b** and excess copper in HMPA at 55 °C for 1 h, 65% of 18 and 4% of (carbethoxydifluoromethyl)copper (−44.5 ppm vs $C_6H_5CF_3$)[19] were observed by ^{19}F NMR analysis of the reaction mixture. This result suggests that a radical intermediate is also involved when the (carbethoxydifluoromethyl)copper is formed.

It is well-documented that the reaction temperature can influence the distribution of products in a competitive reaction. At room temperature (carbomethoxydifluoromethyl)copper[19] was readily prepared from the reaction of **1a** with copper in either HMPA or DMSO or DMF. When we reacted **1b** and 1-octene in the presence of excess copper in HMPA at 25 °C, 86% of 7 and 8% of (carbethoxydifluoromethyl)copper were formed. When the same reaction was carried out in DMSO at 25 °C for 45 min, 65% of 7 and 26% of the copper reagent were observed by ^{19}F NMR analysis of the reaction mixture. Addition of iodobenzene to this mixture gave ethyl 2-phenyl-2,2-difluoroacetate in quantitative yield. *p*-Dinitrobenzene failed to inhibit the reaction in DMSO under the same conditions. However, a radical inhibitor, di-*tert*-butyl nitroxide, completely suppressed the reaction,

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Table II. Reaction of 1 with 1-Octene and Copper in Solvents[a]

no.	R	solvent	t (min)	adduct[b] (%)	$CuCF_2CO_2R$[b] (%)
1	iPr	neat	200	76[c]	0
2	iPr	benzene	200	80[c]	0
3	iPr	hexane	300	73[c]	0
4	Et	CH_3CN	240	92	0
5	Et	DG	180	87	0
6	Et	DMF	150	92	0
7	Et	DMSO	30	94	0
8	Et	DMSO[d]	45	65	26
9	Et	HMPA	60	86	0
10	Et	HMPA[d]	180	86	8

[a] At 55 °C in all cases except entries 8 and 10. [b] Yields were determined by ^{19}F NMR vs $C_6H_5CF_3$. [c] Isolated yields. [d] Reaction at 25 °C.

and neither adduct nor copper reagent was observed by ^{19}F NMR spectroscopy. These results further imply that a radical intermediate may also be involved during the formation of (carbethoxydifluoromethyl)copper. In the presence of an alkene, the radical attacks the double bond faster than it couples with copper metal to form the copper reagent. Thus, adducts are major products in both poorly coordinating solvents and stronger coordinating solvents.

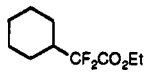
In order to prepare α,α-difluoro esters, we needed to remove iodine from the adducts. A number of methods for the reduction of carbon–halogen bonds employing transition-metal catalysts have been reviewed.[20] A mixture of metal hydrides with transition-metal salts such as $CoCl_2$,[21] $NiCl_2$,[22] CuCl,[23] $CeCl_3$,[24] $RhCl_3$,[25] and $TiCl_3$[26] are effective in removal of halogen from organic halides. However, these reagents serve effectively for a relatively constrained range of substrates, since they are also capable of reducing many other functionalities. Although radical dehalogenation with organotin hydrides[27] has proved particularly versatile, offering generally high yields and excellent selectivity in the presence of many other types of functionalities, they do suffer from some disadvantages. The tin reagents are relatively expensive, their use normally requires elevated temperatures, and the tin halide byproducts often require careful chromatographic separation from the desired products.

Colon[28] developed the reduction of organic halides with zinc in the presence of catalytic amounts of bis(triphenylphosphine)nickel chloride in DMF and at 50–70 °C. We found that the iodine atom of the adducts was reduced by zinc in presence of catalytic amounts of nickel chloride hexahydrate[29] in moist THF at room temperature. When

$$R'CHICHR''CF_2CO_2R + Zn \xrightarrow[THF,\ rt]{NiCl_2\cdot 6H_2O} R'CH_2CHR''CF_2CO_2R$$

Table III. Reduction of Adducts with Zinc and Nickel Chloride

$$R''CHICHR'CF_2CO_2R + Zn \xrightarrow[THF,\ rt]{NiCl_2\cdot 6H_2O} R''CH_2CHR'CF_2CO_2R$$

no.	product	yield (%)
5b	n-$BuCH_2CH_2CF_2CO_2Et$	87
6b	n-$C_5H_{11}CH_2CH_2CF_2CO_2Et$	85
7b	n-$C_6H_{13}CH_2CH_2CF_2CO_2Et$	81
9b	n-$C_6H_{13}CH_2CH_2CF_2CO_2{}^iPr$	79
10b	$Me_3SiCH_2CH_2CF_2CO_2{}^iPr$	72
12b	$HO(CH_2)_8CH_2CH_2CF_2CO_2Et$	71
13b	$MeC(O)(CH_2)_2CH_2CH_2CF_2CO_2Et$	74
14b	$EtO_2CCHMeCH_2CH_2CH_2CF_2CO_2Et$	88
15b	$(EtO)_2P(O)CH_2CH_2CH_2CF_2CO_2Et$	77
18b		85

the reaction was monitored by ^{19}F NMR, the typical AB pattern signal of the adducts changed to simple triplets after 45 min to a few hours. For example, after a mixture of zinc and 5 mol % of nickel dichloride hexahydrate and moist THF was stirred for 10 min, 7 was added and the mixture was stirred at 25 °C for 45 min. ^{19}F NMR analysis indicated that only **7b** (−106.4 ppm, t, $^3J_{F,H}$ = 17.2 Hz) was present and no 7 remained. As illustrated in Table III, a variety of functional groups, such as trimethylsilyl, hydroxy, ketone, ester, and phosphonate, could be tolerated under the reaction conditions. The isolated yields are good to excellent.

In conclusion, the reaction of 1 with a variety of alkenes gave the corresponding adducts in good yields in the presence of copper. The addition reactions can be conducted either neat or in a solvent and a SET-initiated radical mechanism is proposed. It is also suggested that the formation of (carbalkoxydifluoromethyl)copper may involve a radical intermediate in DMSO or in HMPA. Removal of iodine in the adducts was readily accomplished with zinc in the presence of nickel chloride in moist THF. The two step addition–reduction reaction provides a novel and practical synthesis of a variety of α,α-difluoro esters.

Experimental Section

General. All the reactions were performed in an oven-dried apparatus that consisted of a two- or three-necked flask equipped with an addition funnel, a Teflon-coated magnetic stir ring bar, and a reflux condenser connected to a nitrogen source and mineral oil bubbler. All boiling points were determined during fractional distillation using a partial immersion thermometer and are uncorrected. ^{19}F NMR, ^1H NMR, ^{13}C NMR, and ^{31}P NMR spectra were recorded on 90-MHz multinuclear and AC-300-MHz spectrometers. 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 NMR and ^{13}C NMR spectra against internal tetramethylsilane, and ^{31}P NMR against external H_3PO_4. FT-IR spectra were recorded as CCl_4 solutions using a solution cell with 0.1-cm path length. GC–MS spectra (m/e) were performed at 70 eV in the electron impact mode. GLPC analyses were performed on a 5% OV-101 column with a thermal conductivity detector.

Materials. Ethyl bromodifluoroacetate was obtained from PCR Co. Methyl bromodifluoroacetate and isopropyl bromodifluoroacetate were prepared by the literature procedure.[30] Nickel chloride hexahydrate, zinc, iodine, and all alkenes were obtained from Aldrich Chemical Co. except diethyl 1,1-difluoro-3-butenylphosphonate[31] and diethyl allylphosphonate and used without purification. Copper was prepared by the literature

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procedure.[32] THF, acetonitrile, benzene, hexane, diglyme, and dioxane were used without purification; DMF and DMSO were purified by distillation from calcium hydride.

General Procedure for the Preparation of Iododifluoroacetates: Ethyl Iododifluoroacetate (1b). A flask fitted with a stir ring bar and a N_2 inlet was charged with 19.5 g (0.3 mol) of Zn, 3.3 g (0.012 mmol) of $HgCl_2$, and 250 mL of triglyme. Then 50.8 g (0.25 mol) of ethyl bromodifluoroacetate was added slowly via syringe with stirring at 25 °C over 30 min. After the addition was completed, the reaction mixture was stirred for 3 h. A 101.6-g (0.4-mol) portion of I_2 was added and the solution stirred overnight. The reaction was flash distilled (<70 °C (0.1 mmHg)) to give a dark mixture of **1b** and solvent, which was poured into a beaker with Na_2SO_3 solution. The light yellow organic lower layer was separated, washed with water, dried over molecular sieves, and distilled to give 41.3 g (64%) of **1b**, GLPC purity 98%: ^{19}F NMR ($CDCl_3$) −57.9 (s); ^1H NMR ($CDCl_3$) 4.40 (q, $^3J_{H,H}$ = 7.0 Hz, 2 H), 1.38 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H); FT-IR (CCl_4) 2986 (m), 1774 (s), 1289 (s), 1162 (s), 1116 (s), 930 (s) cm^{-1}; MS 250 (M^+, 21.51), 177 (33.63), 127 (34.93), 123 (100), 51 (20.20).

Esters **1a** and **1b** were prepared similarly.

Methyl iododifluoroacetate (1a): yield 59%; ^{19}F NMR ($CDCl_3$) −57.7 (s); ^1H NMR ($CDCl_3$) 3.96 (s); FT-IR (CCl_4) 2959 (m), 1793 (s), 1778 (s), 1292 (s), 1163 (s), 1157 (s), 1106 (s) cm^{-1}; MS 236 (M^+, 42.51), 177 (43.71), 127 (43.71), 109 (100), 59 (62.28).

Isopropyl iododifluoroacetate (1c): yield 73%; ^{19}F NMR ($CDCl_3$) −58.1 (s); ^1H NMR ($CDCl_3$) 5.18 (hept, $^3J_{H,H}$ = 6.3 Hz, 1 H), 1.37 (d, $^3J_{H,H}$ = 6.3 Hz, 6 H); FT-IR (CCl_4) 2987 (m), 1771 (s), 1767 (s), 1378 (m), 1290 (s), 1165 (s), 1099 (s) cm^{-1}; MS 264 (M^+, 1.98), 177 (23.10), 127 (13.05), 43 (100), 41 (29.11).

Representative General Procedure for the Preparation of 2,2-Difluoro-4-iodo Esters: Methyl 2,2-Difluoro-4-iodooctanoate (2). A heterogeneous mixture of 0.2 g (3.2 mmol) of copper, 1.6 g (20 mmol) of 1-hexene, and 2.6 g (20 mmol) of **1a** was stirred at 55 °C under nitrogen for 6 h. The reaction mixture was distilled at reduced pressure to give 2.6 g (75%) of **2**, bp 95–96 °C (3.4 mmHg): ^{19}F NMR −101.9 (dt, $^2J_{F,F}$ = 264 Hz, $^3J_{F,H}$ = 14.6 Hz, 1 F), −107.7 (dt, $^2J_{F,F}$ = 264 Hz, $^3J_{F,H}$ = 17.1 Hz, 1 F); ^1H NMR 4.21 (m, 1 H), 3.89 (s, 3 H), 2.96–2.70 (m, 2 H), 1.16–1.38 (m, 6 H), 0.91 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H); ^{13}C NMR 163.93 (t, $^2J_{C,F}$ = 31.9 Hz), 115.28 (t, $^1J_{C,F}$ = 252.3 Hz), 53.54, 45.44 (t, $^3J_{C,F}$ = 23.3 Hz), 40.26, 31.57, 23.06 (t, $^3J_{C,F}$ = 3.8 Hz), 21.71, 13.89; FT-IR (CCl_4) 1045 (s), 1164 (s), 1213 (s), 1767 (s), 1774 (s), 2934 (s), 2960 (s) cm^{-1}; MS 193 (M^+ − I, 25.4), 131 (21.3), 127 (36.7), 93 (19.5), 77 (25.2), 59 (100), 41 (32.4).

Methyl 2,2-Difluoro-4-iodononanoate (3). Similarly, **3** was prepared from 2.0 g (20 mmol) of 1-heptene, 2.4 g (10 mmol) of **1a**, and 0.1 g (1.6 mmol) of copper. Distillation of the reaction mixture gave 2.62 g (65%) of **3**, bp 102–103 °C (3.2 mmHg): ^{19}F NMR ($CDCl_3$) −102.4 (ddd, $^2J_{F,F}$ = 264 Hz, $^3J_{F,H}$ = 14.7 Hz, $^3J_{F,H}$ = 17.1 Hz, 1 F), −107.4 (dt, $^2J_{F,F}$ = 264 Hz, $^3J_{F,H}$ = 16.0 Hz, 1 F); ^1H NMR ($CDCl_3$) 4.26–4.18 (m, 1 H), 3.90 (s, 3 H), 2.95–2.69 (m, 2 H), 1.83–1.68 (m, 2 H), 1.53–1.32 (m, 6 H), 0.90 (t, $^3J_{H,H}$ = 6.4 Hz, 3 H); FT-IR (CCl_4) 1079 (s), 1163 (s), 1200 (s), 1769 (s), 1778 (s), 2933 (s), 2958 (s) cm^{-1}; MS 207 (M^+ − I, 12.6), 175 (14.2), 145 (17.9), 127 (27.3), 77 (30.1), 59 (100), 55 (27.3), 43 (22.70), 41 (42.9).

Methyl 2,2-Difluoro-4-iodo-4-(trimethylsilyl)butanoate (4). Similarly, **4** was prepared from 1.0 g (10 mmol) of trimethylvinylsilane, 1.2 g (5 mmol) of **1a**, and 0.05 g (0.8 mmol) of copper. Distillation of the reaction mixture gave 1.4 g (83%) of **4**, bp 88–91 °C (3.1 mmHg): ^{19}F NMR ($CDCl_3$) −102.4 (dt, $^2J_{F,F}$ = 260 Hz, $^3J_{F,H}$ = 12.4 Hz, 1 F), −108.7 (ddd, $^2J_{F,H}$ = 260 Hz, $^3J_{F,H}$ = 15.1 Hz, $^3J_{F,H}$ = 17.9 Hz, 1 F); ^1H NMR ($CDCl_3$) 3.91 (s, 3 H), 3.12–3.08 (m, 1 H), 2.68–2.89 (m, 2 H), 0.19 (s, 9 H); ^{13}C NMR ($CDCl_3$) 163.97 (t, $^2J_{F,C}$ = 25.0 Hz), 115.67 (t, $^1J_{F,C}$ = 252.8 Hz), 53.40, 39.09 (t, $^2J_{F,C}$ = 22.4 Hz), 4.37, −2.56; FT-IR (CCl_4) 1023 (m), 1094 (s), 1202 (s), 1254 (s), 1769 (s), 1778 (s), 2957 (s) cm^{-1}; MS 336 (M^+, 1.8), 189 (33.4), 185 (87.8), 117 (100), 98 (70.3), 89 (86.4), 77 (69.4), 73 (78.4), 59 (73.6), 43 (23.5).

Ethyl 2,2-Difluoro-4-iodooctanoate (5). Similarly, **5** was prepared from 0.82 g (10 mmol) of 1-hexene, 1.25 g (5 mmol) of **1b**, and 0.1 g (1.5 mmol) of copper. Distillation of the reaction mixture gave 1.1 g (65%) of **5**, bp 102–104 °C (3.4 mmHg): ^{19}F NMR ($CDCl_3$) −102.2 (ddd, $^2J_{F,F}$ = 264 Hz, $^3J_{F,H}$ = 17.1 Hz, $^3J_{F,H}$ = 14.7 Hz, 1 F), −107.6 (dt, $^2J_{F,F}$ = 264 Hz, $^3J_{F,H}$ = 17.1 Hz, 1 F); ^1H NMR ($CDCl_3$) 4.34 (q, $^3J_{H,H}$ = 7.1 Hz, 2 H), 4.22 (m, 1 H), 2.96–2.69 (m, 2 H), 1.84–1.70 (m, 2 H), 1.55–1.27 (m, 4 H), 1.37 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H), 0.93 (t, $^3J_{H,H}$ = 6.9 Hz, 3 H); ^{13}C NMR 163.43 (t, $^2J_{C,F}$ = 32.0 Hz), 115.24 (t, $^1J_{C,F}$ = 251.6 Hz), 63.18, 45.43 (t, $^2J_{C,F}$ = 23.2 Hz), 40.21, 31.63, 23.22 (t, $^3J_{C,F}$ = 4.1 Hz), 22.27, 21.71, 13.88; FT-IR (CCl_4) 1079 (s), 1191 (s), 1288 (s), 1301 (s), 1764 (s), 1774 (s), 2963 (s) cm^{-1}; MS 289 (M^+ − OEt, 1.3), 207 (75.4), 113 (45.3), 77 (57.3), 69 (80.7), 55 (56.1), 43 (86.8), 29 (100).

Ethyl 2,2-Difluoro-4-iodononanoate (6). Similarly, **6** was prepared from 1.0 g (10.1 mmol) of 1-heptene, 1.25 g (5 mmol) of **1b**, and 0.08 g (1.3 mmol) of copper. Distillation of the reaction mixture gave 1.3 g (76%) of **6**, bp 112–114 °C (3.4 mmHg): ^{19}F NMR ($CDCl_3$) −102.1 (ddd, $^2J_{F,F}$ = 264 Hz, $^3J_{F,H}$ = 17.2 Hz, $^3J_{F,H}$ = 14.7 Hz, 1 F), −107.6 (dt, $^2J_{F,F}$ = 264 Hz, $^3J_{F,H}$ = 17.2 Hz, 1 F); ^1H NMR ($CDCl_3$) 4.35 (q, $^3J_{H,H}$ = 7.1 Hz, 2 H), 4.22 (m, 1 H), 2.96–2.70 (m, 2 H), 1.85–1.72 (m, 2 H), 1.54–1.24 (m, 6 H), 1.38 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H), 0.90 (t, $^3J_{H,H}$ = 6.7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) 163.90 (t, $^2J_{F,C}$ = 32.7 Hz), 115.28 (t, $^1J_{F,C}$ = 252.0 Hz), 53.55, 45.40 (t, $^2J_{F,H}$ = 23.1 Hz), 40.50, 30.74, 29.12, 23.18, 22.46, 14.00; FT-IR (CCl_4) 1080 (s), 1114 (s), 1203 (s), 1763 (s), 1774 (s), 2960 (s) cm^{-1}; MS 303 (M^+ − OEt, 1.4), 221 (100), 175 (97.8), 131 (77.3), 83 (80.3), 77 (85.0), 43 (39.7), 41 (55.2).

Ethyl 2,2-Difluoro-4-iododecanoate (7). Similarly, **7** was prepared from 2.85 g (25 mmol) of 1-octene, 5.0 g (20 mmol) of **1b**, and 0.2 g (3.1 mmol) of copper. Distillation of the reaction mixture gave 6.1 g (85%) of **7**, bp 96–98 °C (0.4 mmHg): ^{19}F NMR ($CDCl_3$) −102.1 (dt, $^2J_{F,F}$ = 266.1 Hz, $^3J_{F,H}$ = 17.1 Hz, 1 F), −107.6 (dt, $^2J_{F,F}$ = 266.1 Hz, $^3J_{F,H}$ = 17.1 Hz, 1 F); ^1H NMR ($CDCl_3$) 4.34 (q, $^3J_{H,H}$ = 7.2 Hz, 2 H), 4.21 (m, 1 H), 3.01–2.65 (m, 2 H), 1.75 (m, 2 H), 1.51 (m, 1 H), 1.37 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H), 1.30 (m, 6 H), 0.89 (t, $^3J_{H,H}$ = 6.7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) 163.41 (t, $^2J_{F,C}$ = 32.9 Hz), 115.24 (t, $^1J_{F,C}$ = 251.5 Hz), 63.17, 45.43 (t, $^2J_{F,C}$ = 23.2 Hz), 40.51, 31.63, 29.48, 28.25, 23.31, 22.59, 14.04, 13.90; FT-IR (CCl_4) 2959 (s), 1773 (s), 1762 (s), 1375 (s), 1291 (s), 1188 (s), 1079 (s) cm^{-1}; MS 363 (M^+ + 1, 0.02), 235 (17.96), 189 (30.83), 151 (53.88), 99 (31.55), 69 (39.81), 57 (100), 43 (87.86).

Ethyl 2,2-Difluoro-4-iodo-4-(trimethylsilyl)butanoate (8). Similarly, **8** was prepared from 1.0 g (10 mmol) of vinyltrimethylsilane, 1.25 g (5 mmol) of **1b**, and 0.08 g (1.25 mmol) of copper. Distillation of the reaction mixture gave 1.2 g (70%) of **8**, bp 97–99 °C (1.8 mmHg): ^{19}F NMR ($CDCl_3$) −102.3 (ddd, $^2J_{F,H}$ = 261 Hz, $^3J_{F,H}$ = 14.6 Hz, $^3J_{F,H}$ = 12.2 Hz, 1 F), −108.6 (dt, $^2J_{F,H}$ = 73 = 17.1 Hz, 1 F); ^1H NMR ($CDCl_3$) 4.36 (q, $^3J_{H,H}$ = 7.1 Hz, 2 H), 3.11 (t, $^3J_{H,H}$ = 6.6 Hz, 1 H), 2.64 (m, 2 H), 1.38 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H), 0.18 (s, 9 H); ^{13}C NMR ($CDCl_3$) 163.77 (t, $^2J_{F,C}$ = 31.9 Hz), 115.74 (t, $^1J_{F,C}$ = 252.6 Hz), 63.19, 39.16 (t, $^2J_{F,C}$ = 24.2 Hz), 13.94, 4.41 (t, $^3J_{F,C}$ = 4.2 Hz), −2.42; FT-IR (CCl_4) 1095 (s), 1191 (s), 1254 (s), 1761 (s), 1774 (s), 2960 (m) cm^{-1}; MS 350 (M^+, 2.3), 185 (54.5), 103 (100), 84 (25.7), 77 (53.7), 73 (78.0).

Isopropyl 2,2-Difluoro-4-iododecanoate (9). Similarly, **9** was prepared from 2.3 g (20 mmol) of 1-octene, 2.6 g (10 mmol) of **1c**, and 0.2 g (3.1 mmol) of copper. Distillation of the reaction mixture gave 3.0 g (79%) of **9**, bp 135–137 °C (1.4 mmHg): ^{19}F NMR ($CDCl_3$) −102.4 (ddd, $^2J_{F,F}$ = 261 Hz, $^3J_{F,H}$ = 12.2 Hz, $^3J_{F,H}$ = 15.5 Hz, 1 F), −108.3 (ddd, $^2J_{F,F}$ = 261 Hz, $^3J_{F,H}$ = 17.1 Hz, $^3J_{F,H}$ = 14.7 Hz, 1 H); ^1H NMR ($CDCl_3$) 5.15 (hept, $^3J_{H,H}$ = 5.8 Hz, 1 H), 4.23 (pent, $^3J_{H,H}$ = 5.9 Hz, 1 H), 3.08–2.56 (m, 2 H), 1.74 (m, 2 H), 1.38–1.31 (m, 14 H), 0.88 (m, 3 H); FT-IR (CCl_4) 1080 (s), 1129 (s), 1212 (s), 1377 (s), 1758 (s), 1769 (s), 2830 (m), 2959 (s) cm^{-1}; MS 317 (1.04), 207 (24.29), 189 (15.07), 77 (9.04), 57 (55.32), 43 (100).

Isopropyl 2,2-Difluoro-4-iodo-4-(trimethylsilyl)butanoate (10). Similarly, **10** was prepared from 1.5 g (15 mmol) of trimethylvinylsilane, 2.1 g (8 mmol) of **1c**, and 0.1 g (1.5 mmol). Distillation of the reaction mixture gave 2.1 g (72%) of **10**, bp 98–100 °C (3.5 mmHg): ^{19}F NMR ($CDCl_3$) −102.9 (dt, $^2J_{F,F}$ = 261 Hz, $^3J_{F,H}$ = 14.6 Hz, 1 H), −107.9 (dt, $^2J_{F,H}$ = 261 Hz, $^3J_{F,H}$ = 16.6 Hz, 1 H); ^1H NMR ($CDCl_3$) 5.16 (hept, $^3J_{H,H}$ = 6.2 Hz, 1 H), 3.10 (t, $^3J_{H,H}$ = 6.8 Hz, 1 H), 2.61 (td, $^3J_{H,F}$ = 16.4 Hz, $^3J_{H,H}$ = 6.8 Hz, 2 H), 1.35 (d, $^3J_{H,H}$ = 6.2 Hz, 6 H), 0.16 (s, 9 H); FT-IR (CCl_4) 1087 (s), 1185 (s), 1208 (s), 1253 (s), 1755 (s), 1770 (s), 2970 (m), 2984 (s); MS 364 (M^+, 0.5), 230 (30.6), 195 (100), 185 (57.4), 103 (55.9), 77 (45.6), 73 (77.7), 43 (51.6).

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Ethyl 2,2-Difluoro-4-iodo-7,8-epoxyoctanoate (11). Similarly, **11** was prepared from 1.0 g (10 mmol) of 5,6-epoxy-1-hexene, 1.3 g (5 mmol) of **1b**, and 0.6 g (1 mmol) of copper. Distillation of the reaction mixture gave 1.4 g (80%) of **11**, bp 100–101 °C (0.05 mmHg): ^{1}H NMR ($CDCl_3$) 4.35 (q, $^3J_{H,H}$ = 7.1 Hz, 2 H), 4.27 (m, 1 H), 2.96–2.90 (m, 2 H), 2.78–2.74 (m, 2 H), 2.54–2.48 MS 1 H), 2.16–1.78 (m, 4 H), 1.37 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H); ^{19}F NMR ($CDCl_3$) –101.8 (dm, $^2J_{F,F}$ = 264 Hz, 1 F), –107.7 (dt, $^2J_{F,F}$ = 264 Hz, $^3J_{F,H}$ = 17 Hz, 1 F); ^{13}C NMR ($CDCl_3$) 163.24 (t, $^2J_{F,C}$ = 32.0 Hz), 115.12 (t, $^1J_{F,C}$ = 252.1 Hz), 63.27, 51.35, 50.39, 46.81, 46.66, 45.28 (t, $^3J_{F,C}$ = 23.2 Hz), 45.19 (t,$^3J_{F,C}$ = 23.2 Hz), 37.02, 36.53, 32.61, 32.12, 22.14, 21.95 (t, $^4J_{F,C}$ = 4.0 Hz), 13.87; FT-IR (CCl_4) 2985 (m), 1773 (s), 1763 (s), 1445 (m), 1375 (m), 1210 (s), 1190 (s), 1075 (s) cm^{-1}; MS 349 (M^+ + 1, 0.01), 221 (25.74), 155 (37.50), 103 (44.49), 79 (44.12), 55 (100), 41 (48.90).

Ethyl 2,2-Difluoro-4-iodo-12-hydroxydodecanoate (12). A mixture of 0.8 g (5 mmol) of 9-decenol, 1.3 g (5 mmol) of **1b**, and 0.06 g (1 mmol) of copper was stirred at 60 °C for 2 h. Column chromatography of the reaction mixture on silica gel (hexane:ethyl acetate = 2:3) gave 1.9 g (92%) of **12**: ^{1}H NMR ($CDCl_3$) 4.35 (q, $^3J_{H,H}$ = 7.2 Hz, 2 H), 4.17 (m, 1), 3.64 (t, $^3J_{H,H}$ = 6.4 Hz, 2 H), 2.90–2.65 (m, 2 H), 2.05 (s, 1 H), 1.46–1.18 (m, 19 H); ^{19}F NMR ($CDCl_3$) –102.1 (dt, $^2J_{F,F}$ = 259 Hz, $^3J_{F,H}$ = 12 Hz, 1 F), –107.7 (dt, $^2J_{F,F}$ = 264 Hz, $^3J_{F,H}$ = 12 Hz, 1 H); ^{13}C NMR ($CDCl_3$) 163.44 (t, $^2J_{F,C}$ = 32.0 Hz), 115.20 (t, $^1J_{F,F}$ = 253.7 Hz), 63.24, 62.67, 45.31 (t, $^2J_{F,C}$ = 23.3 Hz), 40.40, 32.68, 29.43, 29.32, 28.45, 25.72, 23.30 (t, $^3J_{F,C}$ = 4.1 Hz), 20.98, 13.88; FT-IR (CCl_4) 3638 (w), 2933 (s), 1772 (s), 1762 (s), 1239 (s), 1185 (s), 1075 (s) cm^{-1}; MS 407 (M^+ + 1, 0.03), 215 (14.05), 97 (14.05), 83 (46.28), 69 (81.82), 55 (100), 41 (55.37).

Ethyl 2,2-Difluoro-4-iodo-7-oxooctanoate (13). Similarly, **13** was prepared from 0.5 g (5 mmol) of 5-hexen-2-one, 1.3 g (5 mmol) of **1b**, and 0.06 g (1 mmol) of copper. Column chromatography of the reaction mixture on silica gel (hexane:ethyl acetate = 2:3) gave 1.2 g (62%) of **13**: ^{1}H NMR ($CDCl_3$) 4.35 (t, $^3J_{H,H}$ = 7.1 Hz, 2 H), 4.25 (m, 1 H), 3.01–2.61 (m, 5 H), 2.18 (s, 3 H), 2.15–1.92 (m, 1 H), 1.37 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H); ^{19}F NMR ($CDCl_3$) –102.1 (dt, $^2J_{F,F}$ = 264.0 Hz, $^3J_{F,H}$ = 17 Hz, 1 F); –107.3 (dt, $^2J_{F,H}$ = 264.0 Hz, $^3J_{F,H}$ = 17.1 Hz, 1 F); ^{13}C NMR ($CDCl_3$) 206.92, 163.24 (t, $^2J_{F,C}$ = 32.3 Hz), 115.06 (t, $^1J_{F,C}$ = 254.0 Hz), 63.34, 45.30 (t, $^2J_{F,C}$ = 23.2 Hz), 43.41, 34.12, 30.05, 22.26 (t, $^3J_{F,C}$ = 4.5 Hz), 13.87; FT-IR ($CDCl_3$) 2985 (m), 1773 (s), 1762 (s), 1722 (s), 1186 (s), 1093 (s) cm^{-1}; MS 350 (M^+, 0.01), 221 (52.74), 129 (2.19), 99 (5.17), 58 (15.81), 43 (100).

Diethyl 2,2-Difluoro-4-iodo-6-methylheptane-1,7-dioate (14). Similarly, **14** was prepared from 0.7 g (5 mmol) of ethyl 2-methyl-4-pentenoate, 1.3 g (5 mmol) of **1b**, and 0.06 g (1 mmol) of copper. Column chromatography of the reaction mixture on silica gel (hexane:ethyl acetate = 4:1–3:2) gave 1.8 g (90%) of **14**: ^{1}H NMR ($CDCl_3$) 4.34 (q, $^3J_{H,H}$ = 7.2 Hz, 2 H), 4.25–4.07 (m, 3 H), 2.90–2.64 (m, 3 H), 2.28–2.04 (m, 1 H), 1.85–1.65 (m, 1 H), 1.36 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H), 1.26 (m, 3 H), 1.21 (d, $^3J_{H,H}$ = 7.0 Hz, 3 H), 1.13 (d, $^3J_{H,H}$ = 7.0 Hz, 3 H); ^{19}F NMR ($CDCl_3$) –101.8 (dm, $^2J_{F,F}$ = 254.0 Hz), –108.2 ((dm, $^2J_{F,F}$ = 254.0 Hz); FT-IR (CCl_4) 2983 (m), 1775 (s), 1760 (s), 1741 (s), 1374 (s), 1185 (s), 1095 (s) cm^{-1}; MS 393 (M^+ + 1, 0.15), 265 (83.23), 191 (100), 171 (86.23), 143 (43.71), 115 (20.1), 99 (36.4), 55 (35.93).

Ethyl 2,2-Difluoro-4-iodo-5-(diethoxyphosphinyl)pentanoate (15). Similarly, **15** was prepared from 0.9 g (5 mmol) of diethyl allylphosphonate, 1.3 g (5 mmol) of **1b**, and 0.06 g (1 mmol) of copper. Column chromatography of the reaction mixture on silica gel (hexane:ethyl acetate = 2:3) gave 1.65 g (77%) of **15**: ^{1}H NMR ($CDCl_3$) 4.24 (m, 3 H), 4.03 (m, 4 H), 2.98 (m, 1 H), 2.75 (m, 1 H), 2.52 (ddd, $^2J_{H,P}$ = 19.6 Hz, $^3J_{H,H}$ = 7.2 Hz, $^4J_{H,H}$ = 1.9 Hz, 2 H), 1.26 (m, 9 H); ^{19}F NMR ($CDCl_3$) –102.7 (dt, $^2J_{F,F}$ = 266 Hz, $^3J_{F,H}$ = 17.0 Hz, 1 F), –107.9 (dt, $^2J_{F,F}$ = 266 Hz, $^3J_{F,H}$ = 17.0 Hz, 1 F); ^{31}P NMR ($CDCl_3$) 24.8 (s); ^{13}C NMR ($CDCl_3$) 163.22 (t, $^2J_{F,C}$ = 32.0 Hz), 114.94 (t, $^1J_{F,C}$ = 254 Hz), 63.30, 62.32 (d, $^2J_{P,C}$ = 7.2 Hz), 44.85 (dt, $^2J_{P,C}$ = 40.2 Hz, $^2J_{F,C}$ = 17.2 Hz), 38.94 (d, $^1J_{P,C}$ = 136 Hz), 16.39 (d, $^3J_{P,C}$ = 5.9 Hz), 13.88, 7.75; FT-IR (CCl_4) 2985 (m), 1770 (s), 1763 (s), 1302 (m), 1254 (s), 1183 (s), 1074 (s) cm^{-1}; MS 301 (M^+ – I, 4.67), 227 (93.94), 199 (52.02), 171 (100), 149 (54.55), 81 (51.52), 65 (34.60).

Ethyl 2,2,6,6-Tetrafluoro-4-iodo-6-(diethoxyphosphinyl)-hexanoate (16). Similarly, **16** was prepared from 1.1 g (5 mmol) of diethyl (1,1-difluoro-3-butenyl)phosphonate, 1.3 g (5 mmol) of **1b**, and 0.06 g (1 mmol) of copper. Column chromatography of the reaction mixture on silica gel (hexane:ethyl acetate = 3:2) gave 2.1 g (88%) of **16**: ^{1}H NMR ($CDCl_3$) 4.49 (pent, $^3J_{H,H}$ = 6.7 Hz, 1 H), 4.36 (q, $^3J_{H,H}$ = 7.2 Hz, 2 H), 4.29 (m, 4 H), 3.03–2.84 (m, 4 H), 1.40 (t, $^3J_{H,H}$ = 7.1 Hz, 6 H), 1.38 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H); ^{19}F NMR ($CDCl_3$) –102.5 (dt, $^2J_{F,F}$ = 266.1 Hz, $^3J_{F,H}$ = 14.7 Hz, 1 F), –107.6 (dt, $^2J_{F,F}$ = 266.1 Hz, $^3J_{F,H}$ = 14.7 Hz, 1 F), –112.3 (ddd, $^2J_{F,P}$ = 105.0 Hz, $^3J_{F,H}$ = 41.5 Hz, $^3J_{F,H}$ = 19.5 Hz, 2 F); ^{31}P NMR ($CDCl_3$) 5.52 (t, $^2J_{F,P}$ = 105.0 Hz); ^{13}C NMR ($CDCl_3$) 163.16 (t, $^2J_{F,C}$ = 33.0 Hz), 121.52 (td, $^1J_{F,C}$ = 262.4 Hz, $^1J_{P,C}$ = 215.0 Hz), 115.84 (d, $^1J_{P,C}$ = 210 Hz), 64.90 (d, $^2J_{P,C}$ = 7.0 Hz), 63.35, 44.97 (t, $^2J_{F,C}$ = 23.2 Hz), 44.72 (t, $^2J_{F,C}$ = 19.6 Hz), 16.39, 13.83, 5.26; FT-IR (CCl_4) 2986 (m), 1774 (s), 1762 (s), 1276 (s), 1179 (s), 1097 (s), 981 (s) cm^{-1}; MS 479 (M^+ + 1, 3.08), 351 (85.57), 267 (100), 163 (44.3), 109 (51.80), 81 (59.02), 65 (55.15).

Methyl 2,2-Difluoro-2-(2-iodocyclohexyl)acetate (17). Similarly, **17** was prepared from 0.8 g (10 mmol) of cyclohexane, 1.2 g (5 mmol) of **1a**, and 0.1 g (1.5 mmol) of copper. Distillation of the reaction mixture gave 1.25 g (78%) of **17**, which is a mixture of trans and cis isomers, bp 105–108 °C (3 mmHg): ^{19}F NMR (DMSO) trans –105.7 (dd, $^2J_{F,F}$ = 263.7 Hz, $^3J_{F,H}$ = 12.2 Hz, 0.7 F), –112.7 (dd, $^2J_{F,F}$ = 263.7 Hz, $^3J_{F,H}$ = 17.1 Hz, 0.7 F); cis –110.6 (d, $^3J_{F,H}$ = 12.2 Hz, 0.3 F), –110.8 (d, $^3J_{F,H}$ = 17.1 Hz, 0.3 F); ^{1}H NMR ($CDCl_3$) trans[13] 4.32 (ddd, $^3J_{H,H}$ = 15.5 Hz, $^3J_{H,H}$ = 8.4 Hz, $^3J_{H,H}$ = 4.0 Hz, C*H*I, 0.7 H); **cis**[13] 4.66 (br, C*H*I, 0.3 H), 3.89 (s, 3 H), 2.72 (m, 0.7 H), 2.38–1.32 (m, 8 H); ^{13}C NMR ($CDCl_3$) 164.19 (t, $^2J_{F,C}$ = 32.9 Hz), 163.98 (t, $^2J_{F,C}$ = 33.0 Hz), 116.48 (t, $^1J_{F,C}$ = 257.6 Hz), 115.45 (t, $^1J_{F,C}$ = 255.3 Hz), 53.48, 48.26 (t, $^2J_{F,C}$ = 21.1 Hz), 47.00 (t, $^2J_{F,C}$ = 22.8 Hz), 39.50, 37.30, 28.94, 26.72, 25.93, 25.25 (t, $^3J_{F,C}$ = 3.5 Hz), 25.09, 24.69, 24.61, 23.49, 22.29, 22.17; FT-IR (CCl_4) 1086 (s), 1170 (s), 1201 (s), 1247 (s), 1764 (s), 1769 (s), 1774 (s), 1780 (s), 2940 (s), 2950 (s) cm^{-1}; GC–MS trans 318 (M^+, 2.6), 191 (51.0), 171 (98.9), 127 (49.8), 91 (48.2), 81 (25.9), 77 (59.5), 59 (100), 39 (43.2); **cis** 259 (M^+ – CO_2Me, 1.3), 191 (57.1), 171 (100), 127 (36.0), 91 (43.8), 81 (26.9), 77 (50.1), 59 (80.3), 39 (32.6).

Ethyl 2,2-Difluoro-2-(2-iodocyclohexyl)acetate (18). Similarly, **18** was prepared from 1.24 g (15 mmol) of cyclohexene, 2.5 g (10 mmol) of **1b**, and 0.1 g (1.5 mmol) of copper. Distillation of the reaction mixture gave 2.5 g (75%) of **18**, which is a mixture of cis and trans isomers, bp 110 °C (1.4 mmHg): ^{19}F NMR (DMSO) trans –106.0 (dd, $^2J_{F,F}$ = 263.7 Hz, $^3J_{F,H}$ = 12.2 Hz, 1 F), –112.3 (dd, $^2J_{F,F}$ = 263.7 Hz, $^3J_{F,H}$ = 12.2 Hz, 1 F); cis –110.9 (d, $^3J_{F,H}$ = 17.0 Hz, 1 F), –111.3 (d, $^3J_{F,H}$ = 12.2 Hz, 1 F); ^{1}H NMR ($CDCl_3$) 4.66–4.29 (m, 3 H), 2.75–2.65 (m, 1 H), 2.35–1.47 (m, 8 H), 1.38 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H); FT-IR (CCl_4) 2942 (s), 1774 (s), 1760 (s), 1288 (m), 1176 (s), 1083 (s) cm^{-1}; GC–MS trans 332 (M^+, 0.02), 205 (58.63), 185 (36.14), 157 (100), 131 (45.78), 81 (50.20); cis 332 (M^+, 0.26), 205 (49.59), 185 (35.12), 157 (100), 131 (42.51), 81 (39.67).

Ethyl 2,2-Difluoro-4-iodo-3-propylheptanoate (19). Similarly, **19** was prepared from 1.2 g (10 mmol) of 3-octene, 1.3 g (5 mmol) of **1b**, and 0.08 g (1.25 mmol) of copper. Distillation of the reaction mixture gave 1.3 g (72%) of **19**, which is a diastereoisomeric mixture, bp 114–116 °C (3.4 mmHg): ^{19}F NMR ($CDCl_3$) –113.8 (d, $^3J_{F,H}$ = 17.1 Hz), –114 (d, $^3J_{F,H}$ = 12.2 Hz); ^{1}H NMR ($CDCl_3$) 4.49–4.26 (m, 3 H), 2.71 (m, 1 H), 2.06 (m, 1 H), 1.78–1.24 (m, 10 H), 0.94 (m, 6 H); ^{13}C NMR ($CDCl_3$) 163.89 (t, $^2J_{F,C}$ = 32.9 Hz), 116.61 (t, $^1J_{F,C}$ = 257.0 Hz), 63.12, 50.77 (t, $^2J_{F,C}$ = 20.4 Hz), 48.05 (t, $^2J_{F,C}$ = 21.8 Hz), 41.78, 37.55, 33.39, 33.34, 32.26 (t, $^3J_{F,C}$ = 4.6 Hz), 32.20, 31.97, 31.90, 28.14, 28.06, 23.90, 23.06, 21.65, 21.56, 14.25, 14.09, 14.01, 13.94, 12.97, 12.93; FT-IR (CCl_4) 2964 (s), 1770 (s), 1764 (s), 1294 (s), 1189 (s), 1097 (s), 1053 (s) cm^{-1}; GC–MS (a) 289 (M^+ – CO_2Et, 1.1), 235 (100), 187 (23.0), 121 (25.5), 77 (40.3), 29 (36.3); (b) 289 (M^+ – CO_2Et, 0.8), 235 (100), 187 (19.4), 121 (19.7), 77 (43.2), 29 (40.1).

Reaction of 1b with Diallyl Ether and Copper. Similarly, a mixture of 1.0 g (10 mmol) of diallyl ether, 1.25 g (5 mmol) of **1b**, and 0.08 g (1.25 mmol) of copper was stirred at 55 °C for 3 h. Distillation of the reaction mixture gave 1.43 g (82%) of **20**, which is a 1:3 mixture of geometrical isomers, bp 115–119 °C (1.5 mmHg): ^{19}F NMR ($CDCl_3$) –101.5 to –109.0 (m); ^{1}H NMR ($CDCl_3$) 4.32 (q, $^3J_{H,H}$ = 7.1 Hz, 2 H), 4.05–3.15 (m, 6 H), 2.73–2.07 (m, 4 H); IR (CCl_4) 2985 (s), 1775 (s), 1773 (s), 1769 (s), 1761 (s), 1308 (s), 1192 (s), 1097 (s), 1073 (s) cm^{-1}; MS (a) 348 (M^+, 1.06), 221 (76.60), 191 (86.17), 143 (65.43), 97 (78.72), 77 (100), 55 (68.09);

(b) 348 (M^+, 0.24), 221 (25.37), 191 (26.49), 97 (58.96), 77 (89.55), 55 (97.01), 41 (100).

Reaction of 1b with 1-Octene and Copper in Presence of Inhibitor. A mixture of 0.032 g (0.5 mmol) of copper, 0.084 g (0.5 mmol) of *p*-dinitrobenzene, 0.45 g (4 mmol) of 1-octene, and 0.75 g (3 mmol) of **1b** in 5 mL of hexane was stirred at 60 °C for 4 h. ^{19}F NMR indicated that no reaction occurred; only **1b** was detected.

Similarly, after a mixture of 0.75 g (3 mmol) of **1b** with 0.45 g (4 mmol) of 1-octene, 0.032 g (0.5 mmol) of copper, and 0.07 g (0.5 mmol) of di-*tert*-butyl nitroxide was stirred at 60 °C for 4 h, ^{19}F NMR indicated no reaction.

Reaction of 1b with 1-Octene and Copper in Solvent. A mixture of 0.45 g (4 mmol) of 1-octene, 0.5 g (2 mmol) of **1b**, and 0.26 g (4 mmol) of copper in 4 mL of solvent was stirred at 25–55 °C for 30 min to 5 h. The yields of **7** and (carbethoxydifluoromethyl)copper[19] were determined by ^{19}F NMR (vs $C_6H_5CF_3$). All results are summarized in Table II.

Reaction of 1b with Cyclohexene and Copper in Solvent. A mixture of 0.33 g (4 mmol) of cyclohexene, 0.5 g (2 mmol) of **1b**, and 0.26 g (4 mmol) of copper in 4 mL of HMPA was stirred at 55 °C for 1 h. ^{19}F NMR analysis indicated 65% of **18**, 9% of ethyl difluoroacetate, and 4% of (carbethoxydifluoromethyl)copper[19] (−44.5 ppm vs $C_6H_5CF_3$).

Representative General Procedure for the Reduction of the Adducts: Ethyl 2,2-Difluorodecanoate (7b). A flask fitted with a stir ring bar and a condenser topped with a N_2 inlet was charged with 0.65 g (10 mmol) of Zn, 0.12 g (0.5 mmol) of $NiCl_2{\cdot}6H_2O$, 1 drop of water, and 10 mL of THF. The resultant mixture was stirred at 25 °C for 15 min, and then 1.8 g (5 mmol) of **7** was added and stirred for 45 min. The reaction mixture was then poured into NH_4Cl solution and extracted with ether (2 × 50 mL). The combined ether layers were washed with water and dried over $MgSO_4$. After evaporation of the ether, the residue was distilled to give 0.95 g (81%) of **7b**, bp 96–97 °C (1.8 mmHg): ^{19}F NMR ($CDCl_3$) −106.4 (t, $^3J_{F,H}$ = 17.2 Hz); ^1H NMR ($CDCl_3$) 4.31 (q, $^3J_{H,H}$ = 7.2 Hz, 2 H), 2.15–1.96 (m, 2 H), 1.46 (m, 2 H), 1.34 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H), 1.28 (m, 9 H), 0.88 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) 163.41 (t, $^2J_{F,C}$ = 33.0 Hz), 115.23 (t, $^1J_{F,C}$ = 249.0 Hz), 63.46, 45.41 (t, $^2J_{F,C}$ = 23.2 Hz), 40.49, 31.60, 29.47, 28.23, 23.30 (t, $^3J_{F,C}$ = 3.8 Hz), 22.58, 14.00, 13.85; FT-IR (CCl_4) 2957 (s), 1772 (s), 1761 (s), 1304 (s), 1229 (s), 1184 (s), 1085 (s) cm^{-1}; MS 236 (M^+, 0.42), 193 (32.91), 179 (46.33), 157 (32.91), 129 (32.63), 101 (35.59), 57 (100), 43 (94.79).

Ethyl 2,2-Difluorooctanoate (5b). Similarly, **5b** was isolated in 87% yield: ^{19}F NMR ($CDCl_3$) −106.4 (t, $^3J_{F,H}$ = 17.0 Hz); ^1H NMR ($CDCl_3$) 4.32 (q, $^3J_{H,H}$ = 7.2 Hz, 2 H), 2.10–1.96 (m, 2 H), 1.49–1.41 (m, 2 H), 1.34 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H), 1.38–1.31 (m, 6 H), 0.89 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) 164.53 (t, $^2J_{F,C}$ = 33.22 Hz), 116.49 (t, $^1J_{F,C}$ = 251.2 Hz), 62.71, 34.58 (t, $^2J_{F,C}$ = 23.3 Hz), 31.67, 28.98, 22.64, 21.53, 14.06, 13.99; FT-IR (CCl_4) 2933 (s), 1773 (s), 1763 (s), 1305 (m), 1190 (s), 1072 (s) cm^{-1}; MS 207 (M^+ − 1, 1.62), 141 (25.88), 139 (58.77), 111 (29.39), 69 (28.51), 43 (100).

Ethyl 2,2-Difluorononanoate (6b). Similarly, **6b** was isolated in 85% yield: ^1H NMR ($CDCl_3$) 4.32 (q, $^3J_{H,H}$ = 7.1 Hz, 2 H), 2.08 (m, 2 H), 1.35 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H), 1.58–1.28 (m, 8 H), 0.89 (t, $^3J_{H,H}$ = 6.9 Hz, 3 H); ^{19}F NMR ($CDCl_3$): −106.4 (t, $^3J_{F,H}$ = 17.1 Hz); ^{13}C NMR ($CDCl_3$) 164.53 (t, $^2J_{F,C}$ = 35.0 Hz), 116.49 (t, $^1J_{F,C}$ = 249.2 Hz), 62.71, 34.59 (t, $^2J_{F,C}$ = 23.1 Hz), 31.67, 29.11, 28.98, 22.65, 21.53, 14.06, 14.00; FT-IR (CCl_4) 2983 (m), 1774 (s), 1764 (s), 1305 (s), 1206 (s), 1188 (s), 1079 (s) cm^{-1}; MS 194 (M^+ − C_2H_4, 0.37), 193 (M^+ − Et, 2.77), 115 (12.66), 101 (12.03), 57 (43.67), 43 (100), 41 (58.23).

Isopropyl 2,2-Difluorodecanoate (9b). Similarly, **9b** was isolated in 79% yield, bp 96–98 °C (1.4 mmHg): ^{19}F NMR ($CDCl_3$) −106.5 (t, $^3J_{F,H}$ = 17.1 Hz); ^1H NMR ($CDCl_3$) 5.14 (hept, $^3J_{H,H}$ = 6.2 Hz, 1 H), 2.10–1.96 (m, 2 H), 1.45–1.38 (m, 2 H), 1.32–1.01 (m, 16 H), 0.88 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) 163.98 (t, $^2J_{F,C}$ = 33.1 Hz), 116.41 (t, $^1J_{F,C}$ = 250.0 Hz), 70.87, 34.55 (t, $^2J_{F,C}$ = 23.2 Hz), 31.84, 29.26, 29.12, 22.69, 21.54, 14.09; FT-IR (CCl_4) 2984 (s), 2924 (s), 1769 (s), 1759 (s), 1377 (s), 1182 (s), 1082 (s) cm^{-1}; MS 207 (M^+ − C_3H_7, 0.62), 119 (1.33), 69 (8.46), 57 (43.75), 43 (100), 41 (36.40).

Isopropyl 2,2-Difluoro-4-(trimethylsilyl)butanoate (10b). Similarly, **10b** was isolated in 72% yield, bp 60 °C (1.5 mmHg): ^1H NMR ($CDCl_3$) 5.15 (hept, $^3J_{H,H}$ = 6.3 Hz, 1 H), 2.00 (m, 2 H), 1.32 (d, $^3J_{H,H}$ = 6.3 Hz, 6 H), 0.59 (m, 2 H), 0.02 (s, 9 H); ^{19}F NMR ($CDCl_3$) −108.0 (t, $^3J_{F,H}$ = 17.1 Hz); ^{13}C NMR ($CDCl_3$) 163.94 (t, $^2J_{F,C}$ = 33.34 Hz), 116.91 (t, $^1J_{F,C}$ = 250 Hz), 70.73, 29.41 (t, $^2J_{F,C}$ = 24.5 Hz), 21.55, 7.77 (t, $^3J_{F,C}$ = 2.6 Hz), −2.09; FT-IR (CCl_4) 2985 (m), 1769 (s), 1758 (s), 1376 (s), 1302, 1207, 1074 cm^{-1}; MS 181 (2.21), 104 (17.66), 77 (37.77), 73 (100), 59 (31.52), 43 (86.96).

Ethyl 2,2-Difluoro-12-hydroxydodecanoate (12b). Similarly, **12b** was prepared from 0.8 g (2 mmol) of **12**, 0.3 g (4.6 mmol) of zinc, 0.07 g (0.3 mmol) of $NiCl_2{\cdot}6H_2O$, and 1 drop of water in 3 mL of THF. Usual workup gave a residue, which was purified by column chromatography on silica gel (hexane:ethyl acetate = 7:3) to give 0.4 g (71%) of **12b**: ^{19}F NMR ($CDCl_3$); −106.4 (t, $^3J_{F,H}$ = 17.1 Hz); ^1H NMR ($CDCl_3$) 4.23 (q, $^3J_{H,H}$ = 7.1 Hz, 2 H), 3.63 (t, $^3J_{H,H}$ = 6.8 Hz, 2 H), 2.48 (s, 1 H), 2.03–1.29 (m, 20 H); FT-IR (CCl_4) 3639 (m), 2930 (s), 1772 (s), 1457 (m), 1304 (s), 1192 (s) cm^{-1}; MS 279 (M^+ − 1, 0.10), 193 (31.25), 101 (27.70), 83 (27.36), 69 (54.05), 55 (100), 41 (70.95).

Ethyl 2,2-Difluoro-7-oxooctanoate (13b). Similarly, **13b** was isolated in 74% yield, bp 68–70 °C (0.05 mmHg): ^{19}F NMR ($CDCl_3$) −106.4 (t, $^3J_{F,H}$ = 17.1 Hz); ^1H NMR ($CDCl_3$) 4.32 (q, $^3J_{H,H}$ = 7.1 Hz, 2 H), 2.47 (t, $^3J_{H,H}$ = 7.1 Hz, 2 H), 2.14 (s, 3 H), 2.19–2.00 (m, 2 H), 1.63 (pent, $^3J_{H,H}$ = 7.5 Hz, 2 H), 1.47 (m, 2 H), 1.35 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) 208.06, 164.22 (t, $^2J_{F,C}$ = 33.1 Hz), 116.22 (t, $^1J_{F,C}$ = 149.5 Hz), 62.83, 43.06, 34.36 (t, $^2J_{F,C}$ = 23.3 Hz), 29.88, 23.11, 21.12 (t, $^3J_{F,C}$ = 4.2 Hz), 13.97; FT-IR (CCl_4) 2984 (m), 1771 (s), 1762 (s), 1722 (s), 1185 (s), 1099 (s) cm^{-1}; MS 222 (M^+, 0.19), 137 (4.33), 81 (11.30), 71 (16.42), 58 (56.02), 43 (100).

Diethyl 2,2-Difluoro-6-methylheptane-1,7-dioate (14b). Similarly, **14b** was isolated in 88% yield: ^{19}F NMR ($CDCl_3$) −106.5 (t, $^3J_{F,H}$ = 17.1 Hz); ^1H NMR ($CDCl_3$) 4.32 (q, $^3J_{H,H}$ = 7.1 Hz, 2 H), 4.23 (q, $^3J_{H,H}$ = 7.1 Hz, 2 H), 2.44 (m, 1 H), 2.18–1.98 (m, 2 H), 1.74–1.21 (m, 4 H), 1.35 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H), 1.26 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H), 1.16 (d, $^3J_{H,H}$ = 7.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$) 176.23, 164.31 (t, $^2J_{F,C}$ = 32.7 Hz), 116.24 ($^1J_{F,C}$ = 250.2 Hz), 62.81, 60.35, 39.33, 34.46 (t, $^2J_{F,C}$ = 23.8 Hz), 33.17, 19.42, 17.09, 14.28, 14.00; FT-IR (CCl_4) 2982 (s), 1769 (s), 1762 (s), 1760 (s), 1736 (s), 1375 (s), 1189 (s), 1097 (s) cm^{-1}; MS 267 (M^+ + 1, 0.16), 193 (25.81), 115 (28.63), 102 (100), 69 (25.81), 55 (29.44).

Ethyl 2,2-Difluoro-5-(diethoxyphosphinyl)pentanoate (15b). Similarly, **15b** was isolated in 77% yield: ^{19}F NMR ($CDCl_3$) −106.6 (t, $^3J_{F,H}$ = 17.1 Hz); ^1H NMR ($CDCl_3$) 4.33 (q, $^3J_{H,H}$ = 7.1 Hz, 2 H), 4.10 (m, 4 H), 2.20 (m, 2 H), 1.83 (m, 4 H), 1.35 (m, 9 H); ^{31}P NMR ($CDCl_3$) 30.5; ^{13}C NMR ($CDCl_3$) 164.06 (t, $^2J_{F,C}$ = 33.0 Hz), 115.98 (t, $^1J_{F,C}$ = 252.7 Hz), 62.96, 61.76 (d, $^2J_{P,C}$ = 7.4 Hz), 34.90 (td, $^2J_{F,C}$ = 23.6 Hz, $^2J_{P,C}$ = 14.6 Hz), 25.28 (d, $^1J_{P,C}$ = 142.8 Hz), 16.51, 16.44 (d, $^3J_{P,C}$ = 5.1 Hz), 13.97; FT-IR (CCl_4) 2985 (s), 1770 (s), 1763 (s), 1299 (s), 1249 (s), 1179 (s), 1094 (s), 1062 (s) cm^{-1}; MS 303 (M^+ + 1, 1.54), 229 (38.37), 179 (81.40), 138 (100), 125 (77.71), 111 (43.02), 81 (31.67).

Ethyl 2,2-Difluoro-2-cyclohexylacetate (18b). Similarly, **18b** was isolated in 85% yield, bp 71–72 °C (1.6 mmHg): ^{19}F NMR ($CDCl_3$) −114.2 (d, $^3J_{F,H}$ = 15.0 Hz); ^1H NMR ($CDCl_3$) 4.32 (q, $^3J_{H,H}$ = 7.0 Hz, 2 H), 2.17–2.02 (m, 1), 1.83–1.56 (m, 6 H), 1.35 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H), 1.25–1.13 (m, 4 H); ^{13}C NMR ($CDCl_3$) 163.89 (t, $^2J_{F,C}$ = 30.3 Hz), 117.28 (t, $^1J_{F,C}$ = 254.9 Hz), 62.35, 42.18 (t, $^2J_{F,C}$ = 22.0 Hz), 25.71, 25.21, 24.65 (t, $^3J_{F,C}$ = 3.9 Hz), 14.00; FT-IR (CCl_4) 2942 (s), 1772 (s), 1764 (s), 1299 (s), 1194 (s), 1116 (s), 1062 (s) cm^{-1}; MS 207 (M^+ + 1, 4.23), 124 (96.97), 113 (69.70), 83 (82.83), 81 (98.99), 55 (84.85), 41 (100).

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Registry No. **1a**, 109872-87-9; **1b**, 7048-30-8; **1c**, 127224-05-9; **2**, 120695-81-0; **3**, 127224-06-0; **4**, 127224-07-1; **5**, 127224-09-3; **5b**, 111934-95-3; **6**, 127224-10-6; **6b**, 134682-37-4; **7**, 134682-24-9; **7b**, 134682-38-5; **8**, 127224-11-7; **9**, 127224-15-1; **9b**, 134682-39-6; **10**, 127224-14-0; **10b**, 134682-40-9; **11**, 134682-25-0; **12**, 134682-26-1; **12b**, 134682-41-0; **13**, 134682-27-2; **13b**, 134682-42-1; **14**, 134682-28-3; **14b**, 134682-43-2; **15**, 134682-29-4; **15b**, 134704-98-6; **16**, 134704-97-5; *cis*-**17**, 129377-88-4; *trans*-**17**, 129377-92-0; *cis*-**18**, 134682-30-7; *trans*-**18**, 134682-32-9; **18b**, 134682-44-3; **19** (isomer 1), 134682-31-8; **19** (isomer 2), 134682-33-0; *cis*-**20**, 134682-35-2; *trans*-**20**, 134682-36-3; ethyl bromodifluoroacetate, 667-27-6;

methyl bromodifluoroacetate, 683-98-7; isopropyl bromodifluoroacetate, 134682-34-1; copper, 7440-50-8; 1-hexene, 592-41-6; 1-heptene, 592-76-7; trimethylvinylsilane, 754-05-2; 1-octene, 111-66-0; 5,6-epoxy-1-heptene, 10353-53-4; 9-decanol, 13019-22-2; 5-hexen-2-one, 109-49-9; ethyl 2-methyl-4-pentanoate, 53399-81-8; diethylallylphosphonate, 1067-87-4; diethyl (1,1-difluoro-3-butenyl)phosphonate, 80077-71-0; cyclohexene, 110-83-8; 3-octene, 592-98-3; diallyl ether, 557-40-4.

Supplementary Material Available: ^{1}H, ^{19}F, and ^{13}C NMR spectra for all relevant compounds (32 pages). Ordering information is given on any current masthead page.

Cyclization of 9-Substituted Decanoic Acid Derivatives to 9-Decanolide and 9-Decanelactam

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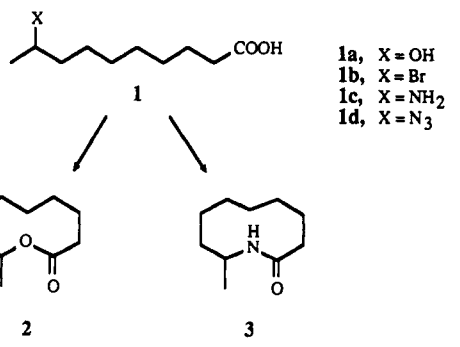
Several standard and some novel cyclization reactions have been applied to 9-substituted decanoic acids to establish which are the optimum procedures for lactonization and lactamization at 80 °C under identical high-dilution conditions. The methods of Galli-Mandolini and Kellogg (cyclization of 9-bromodecanoate ion), Gerlach (cyclization of *S*-2-pyridyl 9-hydroxydecanethioate in the presence of $AgClO_4$), and Yamaguchi (activation of the carboxyl group as a mixed anhydride) in the presence of an excess of DMAP appear to be the most useful for the preparation of the 10-membered lactone, phoracantolide I, under these conditions. Analogously, treatment of *S*-2-pyridyl 9-azidodecanethioate with $Sn(SePh)_3^-$ afforded the best yield of the 10-membered lactam. The mixed anhydrides RCOOCOAr (Ar = 2,4,6-trichlorophenyl) are more reactive than thioesters RCOSPy (Py = 2-pyridyl) with benzyl alcohol or benzylamine; it is confirmed that the addition of DMAP activates the reaction of alcohols with mixed anhydrides much more than with pyridyl thioesters, while the addition of Ag^+ strongly activates RCOSPy in relation to either RCOOCOAr or $RCOOSO_2Mes$.

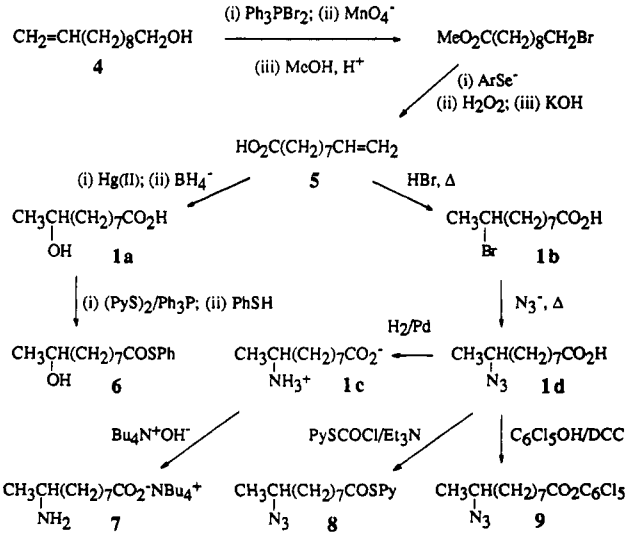
In connection with a research project aimed at preparing modified macrolides of potential therapeutic interest, we focused our attention on relevant lactonization and lactamization procedures[1] developed in the past two decades to perform the crucial step in the synthesis of these and related natural products. Rather than checking randomly some of these methods on our modified secoerythronolides,[2] we considered that a comparison under similar conditions on a much more readily available substrate would be more useful. Thus, we chose a set of 9-substituted decanoic acids 1, which could afford (±)-phoracantolide I (9-decanolide, 2)[3] or its analogue 2-aza-3-methylcyclodecanone (9-decanelactam, 3), because of their simplicity, but also because their cyclization was a challenge since, as it is well-known, the formation of medium-sized rings is much more difficult than that of smaller and larger cyclic compounds (Scheme I).

We report here our results—percentages of monomers 2 and 3 and the corresponding cyclic dimers—at 80 °C in all cases under identical high-dilution conditions. Thus, we have compared the relative cyclization rates of substrates 1, usually after conversion of their COOH groups into different, more reactive carboxyl derivatives.

Scheme I



Scheme II



Several routes to 9-hydroxy-, 9-bromo-, 9-amino-, and 9-azidodecanoic acid (1a–d) can be envisaged starting from available substances such as 10-undecenoic acid or 10-

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