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Synthesis of γ-(Electron-withdrawing group)-Substituted α,α-Difluoro Ketones by UV-Initiated Addition of Iododifluoromethyl Ketones with Electron-Deficient Alkenes

Zai-Ming Qiu and Donald J. Burton*

Department of Chemistry, The University of Iowa, Iowa City, Iowa 52242

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Under UV irradiation (254 nm), iododifluoromethyl phenyl, alkyl, and chlorodifluoromethyl ketones [$RC(O)CF_2I$ (**1**), R: Ph (**a**); n-C_4H_9 (**b**), n-C_6H_{13} (**c**), $ClCF_2$ (**d**)] were reacted with a series of alkyl acrylates ($CH_2{=}CHCO_2R'$, R′: Et, n-Bu, t-Bu, and Me), *N,N*-dimethylacrylamide, acrylonitrile, and vinyl methyl ketone in the absence of solvent at ambient temperature. High yields of the corresponding 1:1 addition products [$RC(O)CF_2CH_2CHICO_2Et$ (**2**)] were obtained when **1** reacted with ethyl acrylates (50−79%). The reaction of **1a** with n-butyl acrylate gave a similar 1:1 adduct (51%). However, an addition−reduction product, $PhC(O)CF_2CH_2CH_2CO_2H$, was isolated in 44% yield when *tert*-butyl acrylate was reacted with **1a**. More interestingly, both 1:1 and 1:2 [$PhC(O)CF_2CH_2CH(CO_2Me)CH_2CHICO_2Me$] adducts were formed in a 1.3:1 ratio when **1a** was reacted with methyl acrylate under similar conditions, which indicated that the ester group exhibited an important effect on reaction selectivity. In the reaction with **1a**, ethyl and methyl acrylates also displayed significantly higher reactivity than that of n- or *tert*-butyl acrylates. **1** also reacted with *N,N*-dimethylacrylamide to afford high yields of the 1:1 adducts. However, telomeric products were obtained in the reaction of **1a** with acrylonitrile, and the 1:1 and pure 1:2 addition products were isolated in low yield. The reaction of acrylonitrile with alkyl-substituted iododifluoromethyl ketone, **1b**, gave only the reduced product, n-$C_4H_9C(O)CF_2H$, under similar conditions. With vinyl methyl ketone, the reaction of **1a** produced an addition−reduction product, $PhC(O)CF_2CH_2CH_2C(O)Me$, in 50% yield. The reactivity of $RC(O)CF_2I$ (**1**) varied with the substituted R groups in the reaction with ethyl acrylate and *N,N*-dimethylacrylamide: R, $ClCF_2 > Ph > n\text{-}C_4H_9 > n\text{-}C_6H_{13}$. Correspondingly, the reaction of **1a** with ethyl acrylate generated a polymer in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium. Treatment of the adducts with zinc in the presence of a catalytic amount of $NiCl_2{\cdot}6H_2O$ in moist THF afforded the corresponding γ-(electron-withdrawing group)-substituted α,α-difluoro ketones in high yields.

Introduction

Selective fluorinated organic compounds have many unique physical and chemical properties and have found wide application, especially in agrochemicals, pharmaceuticals, and as analytical probes and diagnostic tools in metabolic processes since the presence of fluorine in a molecule can significantly change physiological and biological activities.[1] This change is mainly attributed to the strong carbon−fluorine bond and increased lipid solubility. Also, the comparable size of fluorine with hydrogen (van der Waals radius) makes the fluorinated molecule indistinguishable from the nonfluorine-containing analogue. In addition, fluoroorganic compounds often show different chemical reactivities due to the high electronegativity of fluorine. Indeed, many dramatic enhancements of biological activity have been reported for selectively fluorinated, biologically important compounds.[2−4] Therefore, selective fluorination has been recognized as one of the most potentially important and efficient probes in finding and developing new biologically important compounds. Recently, many α,α-difluoro ketones have displayed powerful antitumor and anticancer properties and have been widely used as enzyme inhibitors because the more electrophilic α,α-difluorinated

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carbonyl group can easily form a stable tetrahedral intermediate with the weak nucleophilic serine residue of enzymes.[3]

The importance of these interesting biological properties prompted us to develop new, general, and efficient methodology for the preparation of α,α-difluoro ketones. Although the synthesis of carbonyl compounds containing an adjacent difluoromethylene group has attracted attention for many years, most work has focused on α,α-difluoro esters presumably because of the available Reformatsky reaction with halodifluoroacetates,[2,4] difluoroallyl halides,[5] and difluoropropargyl bromides.[6] Recently, the Reformatsky reaction has also been utilized for the synthesis of α,α-difluoro ketones using chlorodifluoromethyl ketones.[7] An alternative approach to α,α-difluoro esters is the Lewis acid-catalyzed reaction of difluoroketene silyl acetals with carbonyl substrates.[8] However, these reactions are limited to the generation of β-hydroxy-substituted α,α-difluorinated esters or ketones.

Direct fluorination with fluorinating agents, such as elemental fluorine, perchloryl fluoride, xenon difluoride, acetyl hypofluorite, and cesium fluoroxysulfate is another route to α-fluorinated ketones.[9] However, these routes have limited application due to the explosive, hazardous nature or expense of these reagents, the low yield or poor selectivity of the reactions, or the extremely severe reaction conditions. Recently, N−F compounds have also been successfully used as fluorinating agents for the synthesis of α-fluorinated ketones, and either mono- or difluorinated ketones can be obtained in good yields.[10] However, this reaction is only suitable for the fluorination of enolate anions or highly acidic methylene substrates, such as β-dicarbonyl derivatives, which limited their application with some functionalized substrates.

Other methods for α,α-difluoroallyl ketones include the reaction of the *gem*-difluoroallyl anion with esters,[11] which requires low reaction temperature, and many functionalities could not be tolerated under the reaction conditions. The Claisen rearrangement uses TFE in the preparation of the trifluorovinyl ether ($CF_2{=}CFOCH_2CH{=}CHR$) and initially produces the corresponding α,α-difluorinated acid fluoride $CH_2{=}CHCHRCF_2C(O)F$, which is converted to the α,α-difluoro ketone.[3c] With F−TEDA−BF_4, only 1-phenyl-substituted alkynes could be converted to α,α-difluoroketones.[12]

On the other hand, the addition of perfluoroalkyl iodides, R_fI, with carbon−carbon multiple bonds is one of the most important reactions for the introduction of R_f groups into organic molecules.[13,14] Recently, this reaction has been successfully extended to functionalized iododifluoromethyl derivatives [$FGCF_2I$, e.g., FG = ROC(O)−, $(RO)_2P(O)$−, $RS(O)_2$−, and $CF_2{=}CFCF_2$−].[15-18] However, because the fluoroalkyl radical is electrophilic, this reaction is mainly limited to addition with electron-rich olefins. Normally, with electron-deficient olefins, a low conversion to the 1:1 adduct and the formation of the undesired dimeric, telomeric, or polymeric products is observed.[19]

During our efforts to synthesize α,α-difluoro ketones, we have successfully developed a new, general and efficient method for the preparation of α,α-difluoro ketones *via* the addition of iododifluoromethyl ketones with alkenes in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium, followed by selective reduction of the iodine with Zn/$NiCl_2{\cdot}6H_2O$ under mild conditions.[20] An alternative route to α,α-difluoro-γ-iodo ketones is *via* UV-initiated reaction of iododifluoromethyl ketones with olefins.[21] In a preliminary report, we have extended this general addition reaction to electron-deficient alkenes.[22] The formed γ-(electron-deficient group)-substituted α,α-difluoro ketones have shown interesting reactivity and have been utilized as useful reagents for the synthesis of selectively fluorinated compounds, such as β-fluorinated pyrroles.[23] Herein, we wish to report our detailed experimental results on this alternative photochemical approach.

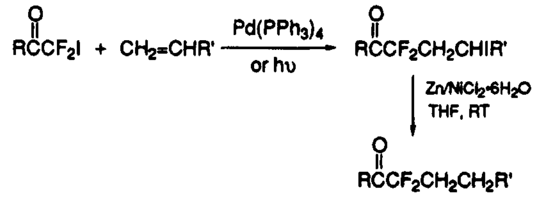

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Table 1. Reaction of 1 with 2 under UV Irradiation

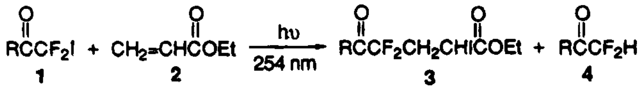
					yield[a] (%)	
entry	1	**1**:**2**	*t* (h)	conversn **1**[a] (%)	**3**	**4**
1	1a	1:3.4	4.5	88	84	6
2	1a	1:3.4	9	92	83 (62)	6
3	1a	1:3.4	24	94	93 (79)	6
4	1a	1:2	18	82	94	6
5	1b	1:3	3.5	17	89	10
6	1b	1:3	10	58	86	14
7	1b	1:3	20	81	89 (58)[a]	10
8	1c	1:3	24	62	82 (50)[b]	10
9	1c	1:2	48	50	85	6
10	1d	1:3	6	100	100 (78)	

[a] Determined by ^{19}F NMR analysis; NMR yield based on consumed **1**; isolated yield in parentheses based on **1**. [b] Small amounts of the addition–reduction (**5**) and 1:2 adduct (**6**) were observed in ^{19}F NMR and GC–MS spectra (3–10%).

Results and Discussion

Pd(PPh$_3$)$_4$ could efficiently initiate the addition of iododifluoromethyl ketones,[20] R$_f$I,[24] and (iododifluoromethyl)phosphonate[16] with electron-rich olefins under mild conditions to give the corresponding 1:1 adducts. A single electron transfer mechanism is consistent with the Pd(PPh$_3$)$_4$ initiated addition reaction.[16,20,24] However, the reaction of iododifluoromethyl ketone, PhC(O)CF$_2$I, with ethyl acrylate under similar conditions was unsuccessful. A polymer was produced in minutes with low conversion (~15%) of the ketone to the 1:1 adduct.

Photolysis is one of the classic methods to initiate a radical reaction.[13a] The reaction of iododifluoromethyl ketones with electron-rich olefins under UV irradiation forms the corresponding addition products.[21] The UV-initiated addition of R$_f$I with electron-deficient olefins has also been explored, and high yields of R$_f$CH$_2$CHI*EWG* (*EWG*: electron-withdrawing-group) are obtained.[25] This successful result prompted us to further examine the photoreaction of iododifluoromethyl ketones with electron-deficient olefins. Under UV irradiation (254 nm), we found that iododifluoromethyl phenyl ketones (**1a**) smoothly reacted with ethyl acrylate (**2**) in the absence of solvent at ambient temperature. High yields of the corresponding 1:1 adduct, Ph(O)CF$_2$CH$_2$CHICO$_2$Et (**3a**, 83–93%), with a small amount of reduced byproduct, PhC(O)CF$_2$H (**4a**, ~6%), were formed as determined by ^{19}F NMR analysis of the reaction mixture. **3a** was isolated by distillation. Similarly, iododifluoromethyl alkyl (**1b**,**c**) and chlorodifluoromethyl (**d**) ketones were also reacted with **2** to give the corresponding 1:1 addition products in good yields. However, small amounts of the addition–reduction product (**5**) or 1:2 adducts (**6**) were sometimes observed in the reaction of **1b**,**c**. For example, irradiation of a mixture of **1b** and **2** (1:3) in a quartz tube for 20 h in a Rayonet photoreactor at ambient temperature resulted in 81% conversion of **1a**, in which 89% of **3b** and 10% of **4b** were formed as determined by ^{19}F NMR analysis. Distillation gave 58% of **3b**. The detailed results are summarized in Table 1.



$$\underset{\mathbf{1}}{\mathrm{RC(O)CF_2I}} + \underset{\mathbf{2}}{\mathrm{CH_2{=}CHC(O)OEt}} \xrightarrow[254\ \mathrm{nm}]{h\nu} \underset{\mathbf{3}}{\mathrm{RC(O)CF_2CH_2CHIC(O)OEt}} + \underset{\mathbf{4}}{\mathrm{RC(O)CF_2H}}$$

R: Ph (**a**), n-C$_4$H$_9$ (**b**), n-C$_6$H$_{13}$ (**c**), ClCF$_2$ (**d**)

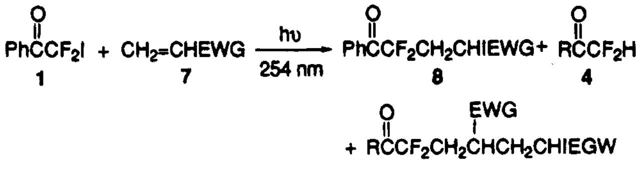
The conversion was dependent on the reaction time as illustrated in Table 1. Usually, some polymer was observed on the quartz tube wall above the liquid surface after reaction. Therefore, excess ethyl acrylate was used in the reaction to ensure a high conversion of **1**. The chlorodifluoromethyl-substituted ketone (**1d**) exhibited the highest reactivity, and the reaction with ethyl acrylate was completed in 6 h. The reaction of phenyl ketone (**1a**) resulted in 94% conversion after irradiation for 24 h. However, the conversion of **1b** was only 81% after irradiation for 20 h. The substitution of a longer alkyl group also decreased the reactivity, and 62% conversion was observed for the reaction of **1c** under similar reaction conditions (entry 8, Table 1).

Table 2. Reaction of 1a with 7 under UV Irradiation

			conversn	yield[a,b] (%)		
entry	**7** EWG	*t* (h)	**1a** (%)[a]	**8**	**9**	**4**
11	CO$_2$Me	7	90	53 (40)	40 (31)	5
12	CO$_2$Bu-*n*	24	59	94		6
13	CO$_2$Bu-*n*	72	77	89 (51)		7
14	CO$_2$Bu-*t*	72	60	90 (44)		10

[a] Determined by ^{19}F NMR analysis; the ratio of **1a**:**7** is 1:3. [b] NMR yield based on consumed **1**; isolated yield in parentheses based on **1**.

Similarly, methyl acrylate (**7e**, EWG = CO$_2$Me) was reacted with **1a**, and 90% conversion of **1a** was achieved after irradiation for 7 h. However, the reaction gave not only the 1:1 adduct **8e** but also the 1:2 addition product **9e** in a 1.3:1 ratio. **8e** (40%) was isolated by distillation of the reaction mixture, and chromatography of the distillation residue gave **9e** (31%). In order to further confirm the "ester group effect" on the selectivity, reactions with longer alkyl-substituted acrylate esters, e.g., *n*-butyl (**7f**) and *tert*-butyl (**7g**) acrylate, were conducted. In both cases, only 1:1 addition products were formed. However, in the reaction of the *tert*-butyl acrylate, the corresponding addition–reduction product, PhC(O)CF$_2$CH$_2$CH$_2$CO$_2$H (**8g**, 44%), was the only isolated product *via* chromatography. These results are summarized in Table 2.



$$\underset{\mathbf{1}}{\mathrm{PhC(O)CF_2I}} + \underset{\mathbf{7}}{\mathrm{CH_2{=}CHEWG}} \xrightarrow[254\ \mathrm{nm}]{h\nu} \underset{\mathbf{8}}{\mathrm{PhC(O)CF_2CH_2CHIEWG}} + \underset{\mathbf{4}}{\mathrm{RC(O)CF_2H}} + \mathrm{RC(O)CF_2CH_2CH(EWG)CH_2CHIEGW}$$

9 (EWG: CO$_2$Me, 31%)

EWG: CO$_2$Me (**8e**), CO$_2$Bu-n (**8f**), CO$_2$R' (R': CO$_2$Bu-t, **7g**; R': H, **8g**)

As shown in Table 2, methyl acrylate had similar reactivity with ethyl acrylate (Table 1) to **1a.** For example, 90% conversion of **1a** was achieved after irradiation for 7 h (entry 11). However, much lower reactivity was observed for the reaction of the *n*- and *tert*-butyl acrylates, in which only 60–77% conversion of **1a** was achieved even though the reaction mixture was irradiated for 72 h (entries 13 and 14, Table 2).

With *N*,*N*-dimethylacrylamide (**10**), the reaction of **1** also gave high yields of the corresponding 1:1 addition products **11** as summarized in Table 3. However, considerable amounts of the addition–reduction products (**12**) were also formed in the reaction of alkyl-substituted iododifluoromethyl ketones (**2b** and **2c**, entries18 and 19). Isolation by distillation resulted in partial decomposition due to the high boiling point of **11**; therefore, the addition

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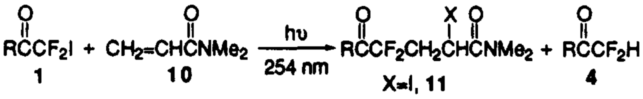
Table 3. Reaction of 1 with 10 under UV Irradiation

entry	1 (R)	1:10	t (h)	conversn[a] (%)	yield[a,b] (%) 11	12	4
15	Ph	1:4	4.5	88	95		5
16	Ph	1:4	15	94	95 (81)		4
17	Ph	1:3	24	93	93		6
18	n-C_4H_9	1:2	66	85	59	31[c]	10
19	n-C_6H_{13}	1:3	36	86	76 (60)	19	5

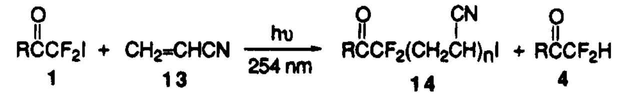
[a] Determined by ^{19}F NMR analysis. [b] NMR yield based on consumed **1**; isolated yield in parentheses based on **1**. [c] 56% of **12** was isolated by distillation because of the partial decomposition of **11** at high temperature.

products were isolated by chromatography on a silica gel column. Similar to the reaction with ethyl acrylate (Table 1), the phenyl-substituted iododifluoromethyl ketone (**1a**) exhibited higher reactivity than the alkyl-substituted ketones **1b**,**c**.



$$\underset{\mathbf{1}}{\mathrm{R\overset{O}{\overset{\|}{C}}CF_2I}} + \underset{\mathbf{10}}{\mathrm{CH_2{=}CH\overset{O}{\overset{\|}{C}}NMe_2}} \xrightarrow[254\ \mathrm{nm}]{h\nu} \underset{\mathrm{X{=}I},\ \mathbf{11};\ \mathrm{X{=}H},\ \mathbf{12}}{\mathrm{R\overset{O}{\overset{\|}{C}}CF_2CH_2\overset{X}{\overset{|}{C}}H\overset{O}{\overset{\|}{C}}NMe_2}} + \underset{\mathbf{4}}{\mathrm{R\overset{O}{\overset{\|}{C}}CF_2H}}$$

1a also reacted with acrylonitrile (**13**) under similar conditions (**1a**:**13** = 1:3). After irradiation for 25 h, 83% conversion of **1a** was achieved, in which 92% of adducts (**14**) with a small amount of **4a** (8%) were formed as determined by ^{19}F NMR analysis. However, **14** was a mixture of telomeric products, which exhibited complicated multiplets in the ^{19}F NMR spectrum (∼−98 ppm). GC−MS analysis showed a number of products; however, all of them failed to give molecular ion signals. Attempts to separate the products by distillation only gave unreacted **1a** and reduced **4a**. The 1:1 and pure 1:2 adducts were isolated by chromatography and further identified by ^1H and ^{13}C NMR and FTIR spectroscopy. However, other products with higher molecular weight were only observed by ^{19}F NMR spectroscopy without further identification because they were not stable and difficult to separate.



$$\underset{\mathbf{1}}{\mathrm{R\overset{O}{\overset{\|}{C}}CF_2I}} + \underset{\mathbf{13}}{\mathrm{CH_2{=}CHCN}} \xrightarrow[254\ \mathrm{nm}]{h\nu} \underset{\mathbf{14}\ \ n=1,2,3,\cdots}{\mathrm{R\overset{O}{\overset{\|}{C}}CF_2(CH_2\overset{CN}{\overset{|}{C}}H)_nI}} + \underset{\mathbf{4}}{\mathrm{R\overset{O}{\overset{\|}{C}}CF_2H}}$$

However, the alkyl, substituted iododifluoromethyl ketone, n-$C_4H_9C(O)CF_2I$ (**1b**), failed to react with acrylonitrile under similar conditions, <5% conversion of **1b**, and only the reduced byproduct, n-$C_4H_9C(O)CF_2H$, was observed in the ^{19}F NMR spectrum after the reaction mixture had been irradiated for 48 h.

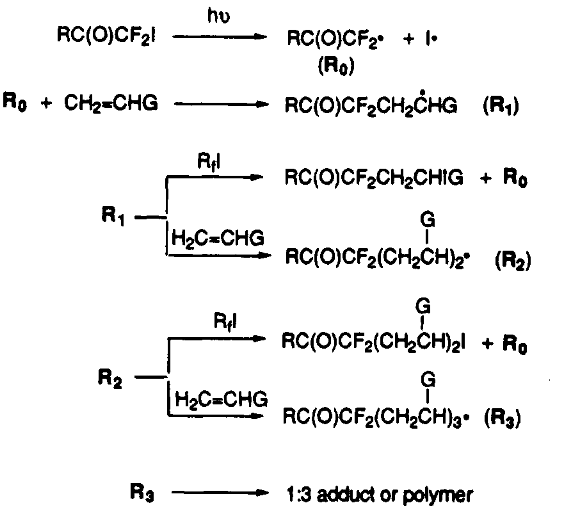
Usually, the phenyl-substituted α,α-difluoro-γ-iodo ketones display a simple triplet with a coupling constant of 17 Hz in the ^{19}F NMR spectrum, except *N*,*N*-dimethyl-4-benzoyl-4,4-difluoro-2-iodobutanamide (**11a**). All other α,α-difluoro-γ-iodo ketones and **11a** exhibit a typical AB pattern, indicating that the two fluorines in the adducts are not equivalent.[20] Each fluorine gave a doublet of doublet of doublets or doublet of triplets at -106 to −112 ppm with a fluorine−fluorine coupling of ∼280 Hz (only 259 Hz for **3d**). In ^1H NMR spectrum, the α-hydrogen ($-CH_2C\mathit{H}I-$) displays a typical doublet of doublets at 4.54−4.68 ppm by coupling with the two adjacent hydrogens (10 Hz and 3.2 Hz, respectively). A triplet is observed for CF_2 and its adjacent carbonyl carbon and CH_2 in the ^{13}C NMR spectrum ($-COCF_2CH_2-$). Also, a molecular ion (M^+) signal is observed for most of the products in the GC−MS spectrum. Some of them are further confirmed by high-resolution MS analysis.

Table 4. Reaction of 1 with 13 under UV Irradiation

entry	1 (R)	t (h)	conversn[a] (%)	yield[a] (%) 14	4
20	Ph	3.5	66	91	7
21	Ph	10	75	93	6
22	Ph	25	83	92[b]	8
23	n-C_4H_9	48	5		100

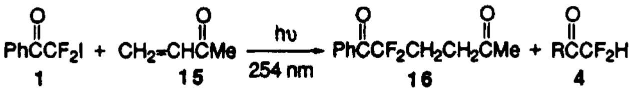
[a] Determined by ^{19}F NMR analysis; the ratio of **1**:**13** = 1:3. [b] **14** (n = 1, 12%; n = 2, 28%) was isolated based on **1**.

Scheme 1



(G: electron withdrawing group)

Also, vinyl methyl ketone (**15**) reacted with **1a** under similar conditions. In the presence of a large excess of **15** (**1a**:**15** = 1:5), a highly viscous liquid was produced after irradiation for 14 h due to polymerization of **15**. The reaction mixture was diluted with acetone and analyzed by ^{19}F NMR, which showed that **1a** had been completely consumed, and the addition−reduction product [$PhC(O)CF_2CH_2CH_2C(O)Me$ (**16**)] and the reduced byproduct [$PhC(O)CF_2H$, **4a**] were formed in 86% and 14% NMR yield, respectively, Table 4. **16** exhibits a typical triplet at −100.7 ppm ($^3J_{FH}$ = 17.4 Hz).[20]



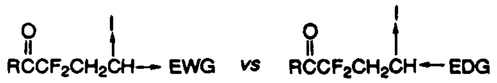
$$\underset{\mathbf{1}}{\mathrm{Ph\overset{O}{\overset{\|}{C}}CF_2I}} + \underset{\mathbf{15}}{\mathrm{CH_2{=}CH\overset{O}{\overset{\|}{C}}Me}} \xrightarrow[254\ \mathrm{nm}]{h\nu} \underset{\mathbf{16}}{\mathrm{Ph\overset{O}{\overset{\|}{C}}CF_2CH_2CH_2\overset{O}{\overset{\|}{C}}Me}} + \underset{\mathbf{4}}{\mathrm{R\overset{O}{\overset{\|}{C}}CF_2H}}$$

It has been demonstrated that the CF_2-I bond easily undergoes homolytic cleavage to generate the corresponding radical intermediate under photoreaction.[13,18a,b] Also, the radical reaction of iododifluoromethyl ketone with electron-rich alkenes either *via* SET or UV initiation has been confirmed.[20,21,25] Therefore, a similar mechanism for the addition of **1** with electron-deficient olefins is proposed (Scheme 1).

The different selectivity with methyl and ethyl acrylate has been observed in the reaction of short-chain perfluoroalkyl iodides ($C_nF_{2n+1}I$, n < 4) under similar conditions and accounted for by the corresponding steric effect of the ester groups.[25] This "ester effect" is not only observed in the reaction of iododifluoromethyl phenyl ketone with methyl and ethyl acrylates but is also further confirmed by the reaction with *n*-butyl and *tert*-butyl acrylates. The reaction of **1a** with hindered acrylate esters ($CH_2=CHCO_2R'$, R′ = *n*-Bu, *t*-Bu) affords predominantly the 1:1 addition products, whereas the reaction with methyl acrylate produces both 1:1 and 1:2 adducts. The formation of telomeric products in the reaction with acrylonitrile is another example controlled by this "ester effect": the smaller CN group (G) has less steric hindrance, which facilitates the radical intermediate (R_0, R_1, R_2, ...) to add to another molecule of the less hindered acrylonitrile (Scheme I). This "ester effect" is also a reasonable explanation for the different reactivity of the acrylates ($CH_2=CHCO_2R'$) to **1**: R′ = Me ~ Et ≫ *n*-Bu > *t*-Bu, as observed in Tables 1 and 2.

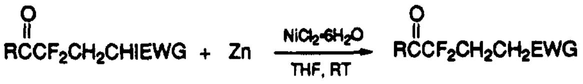
Another important phenomenon observed in the reactions was the distinct difference in reactivity between the iododifluoromethyl ketones: $ClCF_2C(O)CF_2I \gg PhC(O)CF_2I \gg n\text{-}C_4H_9C(O)CF_2I > n\text{-}C_6H_{13}C(O)CF_2I$, which has also been observed in the photoreaction of iododifluoromethyl ketones with electron-rich alkenes.[21] This order is coincident with the stability of the corresponding carboalkyldifluoromethyl radicals (R_0): $ClCF_2C(O)CF_2^\bullet \gg PhC(O)CF_2^\bullet \gg n\text{-}C_4H_9C(O)CF_2^\bullet > n\text{-}C_6H_{13}C(O)CF_2^\bullet$. The $ClCF_2$ group is a strong electron-withdrawing group which can stabilize the R_0 by an inductive effect, whereas $PhC(O)CF_2^\bullet$ can be stabilized by the conjugative effect of the phenyl group. In contrast, the substitution of an electron-donating alkyl group (n-C_6H_{13} and n-C_4H_9) on R_0 should destabilize the radical intermediate. Another possible explanation for this reactivity order could be accounted for by the length of the R group on R_0, n-C_6H_{13} > n-C_4H_9 > Ph > $ClCF_2$, because the longer R group can easily reach and shield the reactive center.

It is worthwhile to mention that quite different thermal and photochemical stability has been observed between the γ-electron-withdrawing group (EWG) and γ-electron-donating group (EDG) substituted γ-iodo-α,α-difluoro ketones. The γ-EWG-substituted α,α-difluoro-γ-iodo ketones exhibit much higher thermal and photochemical stability and could be isolated by distillation. In contrast, the γ-EDG substituted α,α-difluoro-γ-iodo ketones are less stable, and a deep red color is always observed during the chromatographic isolation because of the formation of I_2. The higher stability of γ-EWG-substituted α,α-difluoro-γ-iodo ketone might be explained by the decreased polarity of the C−I bond due to the presence of the electron-withdrawing group, whereas the substitution of an electron-donating group increased the polarity which facilitated the cleavage of the C−I bond.



EWG: electron-withdrawing group;
EDG: electron-donating group.

Similarly, we tried to remove the iodine from the adduct *via* the reduction reaction with zinc and a catalytic amount of nickel chloride hexahydrate in moist THF.[15a,16,20] The corresponding α,α-difluorinated ketones were obtained in good yields, although a small amount of the HI-elimination product (<5%) was sometimes observed in the reaction. With a one-pot addition−reduction reaction, high yields of γ-EWG-substituted α,α-difluoro ketones were also obtained by the photoaddition of $RC(O)CF_2I$ with $CH_2=CHEWG$, followed by direct reduction with the $Zn/NiCl_2$ system.



$$RC(O)CF_2CH_2CHIEWG + Zn \xrightarrow[\text{THF, RT}]{NiCl_2\cdot 6H_2O} RC(O)CF_2CH_2CH_2EWG$$

R	EWG	Product
Ph	CO_2Et	**5a**, 81%
n-C_6H_{13}	CO_2Et	**5c**, 90%
n-C_4H_9	$CONMe_2$	**12b**, 71%

Conclusion

The reaction of iododifluoromethyl ketones with a series of electron-deficient alkenes under UV irradiation (254 nm) produced high yields of the corresponding 1:1 addition products, which provides a general and useful method for the synthesis of γ-(electron-deficient group)-substituted α,α-difluoro-γ-iodo ketones under mild conditions. The reactivity of the iododifluoromethyl ketones [$RC(O)CF_2I$] is effected by the substitutent groups (R), which exhibit the order: R = $ClCF_2$ ≫ Ph > n-C_4H_9 > n-C_6H_{13}. Also, the ester group (R′) on the acrylate ($CH_2=CHCO_2R'$) showed a distinct effect not only on selectivity for the formation of the 1:1 and 1:2 adducts, but also on reactivity. Higher reactivity of methyl and ethyl acrylates was observed compared with that of *n*-butyl and *tert*-butyl acrylates in the reaction with **1a**. A radical chain mechanism initiated by UV irradiation is proposed. The iodine in the adducts was readily reduced by zinc in the presence of a catalytic amount of nickel chloride hexahydrate in moist THF with high selectivity. The development of a one-pot addition−reduction reaction provided a more convenient, practical, and efficient method for the preparation of α,α-difluoro-functionalized ketones.

Experimental Section

General. All electron-deficient olefins,[26] Zn, and $NiCl_2\cdot 6H_2O$ were obtained from Aldrich Chemical Co. and used without further purification. Iododifluoromethyl ketones (**1**) were prepared as previously reported.[20] All reactions were performed in a quartz tube without removal of air and photolyzed in a Rayonet photochemical reactor equipped with 254 nm UV lamps. All boiling points were recorded during fractional distillation using a partial immersion thermometer and are uncorrected. Chromatography was conducted on a 60−200 mesh silica gel column (40 × 400 mm). The ^{19}F, ^1H, and ^{13}C NMR spectra were recorded in $CDCl_3$ solvent. All chemical shifts are reported in parts per million downfield (positive) of the standard. ^{19}F NMR spectra are referenced against internal $CFCl_3$ and ^1H and ^{13}C NMR spectra against internal tetramethylsilane (TMS). FTIR spectra were recorded in CCl_4 solution in a cell with 0.1 cm path length. GC−MS was performed at 70 eV, in the electron impact mode with a DB-1 column. GLPC analyses were performed on a 5% OV-101 column with a thermal conductivity detector. High-resolution mass spectra were measured by the University of Iowa High Resolution Mass Spectrometry Facility.

$Pd(PPh_3)_4$-Initiated Reaction of Iododifluoromethyl Phenyl Ketone (1a) with Ethyl Acrylate (2). A 50 mL two-neck flask was charged with 0.34 g (0.3 mmol) of $Pd(PPh_3)_4$ and 1.8 g (18 mmol) of ethyl acrylate under an atmosphere of N_2. Then, 1.69 g (6.0 mmol) of **1a** was added in one portion at rt with vigorous stirring. The reaction initiated in 10 s and produced a transparent highly viscous liquid in 5 min. The

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[26] All electron-deficient alkenes purchased from Aldrich Chemical Co. contained inhibitors and were used without further purification.

liquid was diluted with acetone and analyzed by ^{19}F NMR. Only 15% conversion of **1a** was observed.

Representative General Procedure for UV-Initiated Addition of $RC(O)CF_2I$ with Electron-Deficient Olefins. Ethyl 4,4-Difluoro-2-iodo-4-benzoylbutanoate (**3a**, **$PhC(O)CF_2CH_2CHICO_2Et$**). In a 50 mL quartz tube, 3.0 g (10.6 mmol) of iododifluoromethyl phenyl ketone (**1a**) and 3.7 g (37 mmol) of ethyl acrylate were added. After the tube was sealed, the reactants were mixed by shaking and then irradiated with 254 nm UV light in a Rayonet photochemical reactor at rt. After reaction for 24 h, ^{19}F NMR analysis of the reaction mixture showed that 94% of **1a** had been consumed, and 93% of **3a** and a small amount of 1:2 adduct (6%, **5a**) were formed. Distillation of the reaction mixture gave 3.2 g (yield: 79%; GLPC purity: 100%) of **3a**: bp 158−160 °C/4 mmHg; ^{19}F NMR δ -100.7 (t, J = 17.1 Hz); ^{1}H NMR δ 8.03 (d, J = 7.4 Hz, 2H), 7.63 (dt, J = 7.4 Hz, 1H), 7.48 (t, J = 7.7 Hz, 2H), 4.67 (dd, J = 10.6 Hz, 3.5 Hz, 1H), 4.22 (q, J = 7.1 Hz, 2H), 3.34 (ddt, J = 16.9 Hz, 15.6 Hz, 10.7 Hz, 1H), 2.88 (ddt, J = 17.6 Hz, 15.2 Hz, 3.5 Hz, 1H), 1.26 (t, J = 7.1 Hz, 3H); ^{13}C NMR δ 187.8 (t, J = 30.5 Hz), 170.7, 134.7, 131.3, 130.2, 128.8, 118.3 (t, J = 256.2 Hz), 62.1, 41.4 (t, J = 22.6 Hz), 13.6, 7.9; GC−MS (relative intensity, m/z) 382 (M$^+$, 0.12), 336 (M$^+$ − HOEt, 3.19), 309 (M$^+$ − CO_2Et, 2.52), 255 (M$^+$ − I, 36.08), 182 (3.90); HRMS found 382.9967, $C_{13}H_{14}O_3F_2I$ (M + 1) calcd 382.9956; FTIR 1741, 1704, 1599, 1450, 1325, 1282, 1254 cm^{-1}.

Ethyl 4,4-Difluoro-2-iodo-5-oxononanoate (**3b**, ***n*-$C_4H_9C(O)CF_2CH_2CHICO_2Et$**). Similarly, 2.5 g (9.5 mmol) of iododifluoromethyl *n*-butyl ketone (**1b**) and 2.86 g (28.6 mmol) ethyl acrylate were irradiated in a quartz tube for 20 h. The conversion of **1b** was 81% based on ^{19}F NMR analysis of the reaction mixture, in which 89% of **3b**, 10% of **4b**, and a small amount of 1:2 adduct (identified by GC−MS data) were formed. Distillation of the reaction mixture gave 2.0 g (58% isolated yield; GLPC purity: 95%) of **3b**: bp 102−104 °C/1.5 mmHg; ^{19}F NMR δ −106.9 (ddd, J = 282.6 Hz, 16.1 Hz, 14.1 Hz, 1F), −108.1 (ddd, J = 282.6 Hz, 18.4 Hz, 18.4 Hz, 1F); ^{1}H NMR δ 4.54 (dt, J = 10.5 Hz, 3.6 Hz, 1H), 4.22 (q, J = 7.1 Hz, 2H), 3.23−3.04 (m, 1H), 2.77−2.59 (m, 1H), 2.67 (t, J = 7.5 Hz, 2H), 1.60 (m, 4H), 1.28 (t, J = 7.1 Hz, 3H), 0.93 (t, J = 7.3 Hz, 3H); ^{13}C NMR δ 199.9 (t, J = 30.4 Hz), 170.8, 116.5 (t, J = 255.0 Hz), 62.3, 40.0 (t, J = 23.2 Hz), 35.8, 24.6, 22.1, 13.7, 7.7; GC−MS (relative intensity, m/z) 362 (M$^+$, 0.27), 342 (M$^+$ − HF, 0.18), 320 (M$^+$ − C_3H_6, 2.23), 317 (M$^+$ − OEt, 1.17), 289 (M$^+$ − CO_2Et, 1.28), 235 (M$^+$ − I, 23.50); FTIR 1743, 1718, 1465, 1374, 1359, 1217, 1209 cm^{-1}.

Diethyl 4-(2,2-difluoro-3-heptanonyl)-2-iodo-1,5-pentanedioate (6b, *n*-$C_4H_9C(O)CF_2CH_2CH(CO_2Et)CH_2CHICO_2Et$): GC−MS (relative intensity, m/z) 463 (M$^+$ + 1, 0.14), 418 (M$^+$ − EtOH, 2.56), 336 (M$^+$ − I + H, 12.50), 257 (5.97), 211 (3.92), 183 (5.81), 137 (4.59), 101 ($^+CH_2CH_2CO_2Et$, 4.87), 85 ($C_4H_9CO^+$, 100), 57 ($C_4H_9^+$, 59.43), 55 (23.05).

Ethyl 4,4-Difluoro-2-iodo-5-oxoundecanoate (**3c**, ***n*-$C_6H_{13}C(O)CF_2CH_2CHICO_2Et$**). Similarly, 2.3 g (7.9 mmol) of iododifluoromethyl *n*-hexyl ketone (**1c**) and 2.38 g (23.8 mmol) of ethyl acrylate were irradiated in a quartz tube for 24 h. ^{19}F NMR analysis showed that 62% of **1c** had been consumed, and 82% of **3c**, 10% of **4c**, and a small amount of 1:2 adduct were formed. Distillation of the reaction mixture gave a mixture of **3c**, the addition−reduction and addition−elimination products. This reaction was repeated, and **3c** (1.55 g, isolated yield: 50%) and the 1:2 adduct (0.1 g; 2.5%) were isolated by chromatography on silica gel (hexane−CH_2Cl_2 eluant). **3c**: ^{19}F NMR δ −106.9 (ddd, J = 282.9 Hz, 17.3 Hz, 16.1 Hz, 1F), 108.1 (ddd, J = 282.9 Hz, 17.6 Hz, 15.2 Hz, 1F); ^{1}H NMR δ 4.54 (dd, J = 10.5 Hz, 3.8 Hz, 1H), 4.22 (q, J = 7.1 Hz, 2H), 3.23˜3.04 (m, 1H), 2.77−2.59 (m, 1H), 2.67 (t, J = 7.1 Hz, 2H), 1.61 (m, 2H), 1.31−1.26 (m, 6H), 1.28 (t, J = 7.1 Hz, 3H), 0.89 (t, J = 6.0 Hz, 3H); ^{13}C NMR δ 199.9 (t, J = 30.5 Hz), 170.7, 116.5 (t, J = 254.7 Hz), 62.2, 40.0 (t, J = 23.2 Hz), 36.1, 31.5, 28.6, 22.6, 22.5, 14.0, 13.7, 7.7 (t, J = 4.4 Hz); GC−MS (relative intensity, m/z) 390 (M$^+$, 0.37), 391 (0.26), 371 (M$^+$ − F, 0.35), 344 (M$^+$ − HOEt, 0.99), 320 (6.15), 263 (M$^+$ − I, 4.29), 113 ($C_4H_9CO^+$, 100), 57 ($C_6H_{13}^+$, 100); FTIR 1744, 1717, 1375, 1360, 1216, 1210 cm^{-1}.

Diethyl 2-iodo-4-(2,2-difluoro-3-nonanonyl)-1,5-pentanedioate (6c, *n*-$C_6H_{13}C(O)CF_2CH_2CH(CO_2Et)CH_2CHICO_2Et$): ^{19}F NMR δ −105.5−106.7 (m); ^{1}H NMR δ 4.35−4.28 (m,1H), 4.25−4.13 (m, 4H), 2.82−2.01 (m, 7H), 1.61 (t, J = 6.2 Hz, 2H), 1.37−1.25 (m, 12H), 0.89 (t, J = 6.7 Hz, 3H); ^{13}C NMR δ 200.4 (t, J = 31.2 Hz), 173.2, 170.7, 117.1 (t, J = 253.4 Hz), 61.3, 62.0, 39.4, 38.4, 36.0, 31.5, 34.4 (t, 22.8 Hz), 34.3 (t, J = 23.1 Hz), 28.6, 22.6, 22.5, 18.0, 15.3, 14.1, 14.0, 13.7; GC−MS (relative intensity, m/z) 490 (M$^+$, 0.50), 491 (0.09), 445 (M$^+$ − OEt, 3.34), 363 (M$^+$ − I, 17.67), 127 (2.65), 113 ($C_6H_{13}CO^+$, 100), 101 (5.38), 95 (5.81), 85 ($C_6H_{13}^+$, 42.33); FTIR 1738, 1719, 1457, 1372, 1360, 1219 cm^{-1}.

Ethyl 6-Chloro-2-iodo-4,4,6,6-tetrafluoro-5-oxoheptanoate (**3d**, **$ClCF_2C(O)CF_2CH_2CHICO_2Et$**). Similarly, **3d** (3.25 g, 78% isolated yield; GLPC purity: 98%) was prepared from 3.1 g (10.6 mmol) of **1d** and 3.2 g (32.0 mmol) ethyl acrylate and isolated by distillation from the reaction mixture: bp 83−84 °C/2.4 mmHg; ^{19}F NMR δ −65.7 (dt, J = 165.5 Hz, 12.7 Hz, 1F), −66.3 (dt, J = 165.4 Hz, 12.7 Hz, 1F), −110.0 (dtt, J = 259.5 Hz, 25.1 Hz, 12.3 Hz, 1F), −112.4 (dtt, J = 259.4 Hz, 24.7 Hz, 12.3 Hz, 1F); ^{1}H NMR δ 4.66 (dt, J = 11.1 Hz, 3.2 Hz, 1H), 4.23 (q, J = 7.1 Hz, 2H), 3.83 (m, 1H), 2.82 (m, 1H), 1.29 (t, J = 7.1 Hz, 3H); ^{13}C NMR δ 199.9 (t, J = 30.4 Hz), 172.0, 127.6 (t, J = 304.1 Hz), 120.3 (t, J = 253.6 Hz), 62.7, 39.6 (t, J = 22.5 Hz), 13.7, 7.7; GC−MS (relative intensity, m/z) 390 (M$^+$, 1.42), 345/347 (M$^+$ − OEt, 16.36/5.41), 327 (M$^+$ − Cl, 42.68), 317/319 (M$^+$ − CO_2Et, 9.15/1.13), 297/295 (M$^+$ − CO_2Et-HF, 15.24/6.50), 263 (M$^+$ − I, 3.91), 207/209 [$ClCF_2C(OH)CF_2$-$CH{=}CH_2^+$, 100, 36.99], 127 (I$^+$, 20.33); HRMS found 389.9159, $C_8H_8O_3F_4ClI$ calcd 389.0143; FTIR 1741, 1717, 1360, 1161 cm^{-1}.

Hydrate of Ethyl 6-Chloro-2-iodo-4,4,6,6-tetrafluoro-5-oxoheptanoate (3d (H_2O), $ClCF_2C(OH)_2CF_2CH_2CHICO_2Et$). Hydration of ethyl 2-iodo-4,4-difluoro-4-(chlorodifluoroacetyl)butyrate was observed in the ^{19}F NMR spectrum during the analysis: ^{19}F NMR δ −65.7 (dt, J = 174.1, 9.6 Hz, 1F), −66.4 (dt, J = 174.1, 9.4 Hz, 1F), −103.0 (d of multiplet, J = 287.5 Hz, 1F), −105.8 (d of multiplet, J = 287.5 Hz, 1F); ^{1}H NMR δ 4.59 (dd, J = 10.6, 3.8 Hz, 1H), 4.0−4.36 (broad, s, 2H); ^{13}C NMR δ 93.6 (t, J = 28.3 Hz); FTIR 3600−3100 (broad, OH) cm^{-1}.

UV-Initiated Addition of $PhC(O)CF_2I$ with Methyl Acrylate. Similarly, in a 50 mL quartz tube, 2.82 g (10.0 mmol) of iododifluoromethyl phenyl ketone (**1a**) and 2.58 g (30 mmol) of methyl acrylate (**7e**) were added. After the tube was sealed, the reactants were mixed by shaking and then irradiated with 254 nm UV light in a Rayonet photochemical reactor at rt. After reaction for 7 h, 90% of **1a** had been consumed and gave the 1:1 (**8e**) and 1:2 (**9e**) adducts and reduced **4a** in 53%, 40%, and 5% NMR yields, respectively, as determined by ^{19}F NMR, GLPC, and GC−MS analysis. Distillation of the reaction mixture gave 1.47 g of **8e** (yield: 50%, NMR purity: 99%). Chromatography of the distillation residue through a silica gel column produced 1.4 g of **9e** (yield: 31%; NMR purity: 97%).

Methyl 4,4-difluoro-2-iodo-4-benzoylbutanoate (8e, $PhC(O)CF_2CH_2CHICO_2Me$): bp 110−115 °C/0.025 mmHg; ^{19}F NMR δ −100.7 (t, J = 17.0 Hz); ^{1}H NMR δ 8.06 (dd, J = 7.5 Hz, 1.5 Hz, 2H), 7.63 (dt, J = 7.5, 1.5 Hz, 1H), 7.47 (t, J = 7.5 Hz, 2H), 4.68 (dd, J = 10.5, 3.0 Hz, 1H), 3.74 (s, 3H), 3.40 (ddt, J = 18.0, 15.3, 10.3 Hz, 1H), 2.89 (ddt, J = 17.7, 15.3, 3.6 Hz, 1H); ^{13}C NMR δ 187.7 (t, J = 30.6 Hz), 171.2, 134.7, 131.2, 130.2, 128.8, 118.2 (t, J = 254.4 Hz), 53.1, 41.1 (t, J = 22.7 Hz), 7.2; GC−MS (relative intensity, m/z) 336 (M$^+$ − HOMe, 0.81), 337 (0.61), 309 (M$^+$ − CO_2Me, 0.98), 241 (M$^+$ − I, 12.11), 127 (I$^+$, 1.99), 105 ($PhCO^+$, 100); FTIR 1744, 1704, 1269, 1256, 1204, 1177 cm^{-1}.

Dimethyl 4-(2,2-difluoro-2-benzoyl)ethyl-2-iodo-1,5-pentanedioate (9e, $PhC(O)CF_2CH_2CH(CO_2Me)CH_2CHICO_2Me$): mp 98.5−99.5 °C; ^{19}F NMR δ −99.5 (m); ^{1}H NMR δ 8.09 (d, J = 6.0 Hz, 2H), 7.63 (t, J = 7.5 Hz, 1H), 7.49 (t, J = 9.0 Hz, 2H), 4.36 (dd, J = 12.0, 6.0 Hz,1H), 3.75 (s, 3H), 3.71 (s, 3H), 2.91−2.66 (m, 2H), 2.54−2.23 (m, 3H); ^{13}C NMR δ 188.3 (t, J = 31.3 Hz), 173.7, 173.5, 171.2, 134.4, 131.6, 130.3, 128.8, 118.7 (t, J = 255.1 Hz)/118.6 (t, J = 255.0 Hz), 53.0, 52.3, 35.5 (t, J = 22.6 Hz), 39.5, 38.9, 14.6; GC−MS (relative intensity, *m/z*) 423 ($M^+ - MeO$, 0.28), 396 ($M^+ - CO_2Me + 1$, 0.29), 328 ($M^+ - I + H$, 5.39), 127 (1.54), 105 ($PhCO^+$, 100); FTIR 1744, 1705, 1653, 1636, 1559, 1541 cm^{-1}.

UV-Initiated Addition of 1a with n-Butyl Acrylate (7f). *n*-Butyl 4,4-Difluoro-2-iodo-4-benzoylbutanoate (8f, Ph$COCF_2CH_2CHICO_2$Bu-*n*). Similarly, 2.82 g (10.0 mmol) of iododifluoromethyl phenyl ketone (**1a**) and 3.84 g (30.0 mmol) of *n*-butyl acrylate (**7f**) were irradiated in a quartz tube for 72 h. ^{19}F NMR analysis showed that 77% of **1a** had been consumed, and 86% of the 1:1 adduct (**8f**) and 7% of **4a** were formed. Chromatography gave 2.46 g (60% isolated yield; GLPC purity: 96%) of **8f:** ^{19}F NMR δ −100.8 (t, $J = 16.9$ Hz); ^1H NMR δ 8.08 (dt, $J = 8.49$, 1.15 Hz, 1H), 7.64 (tt, $J = 7.43$, 2.51 Hz, 1H), 7.49 (tm, $J = 7.92$ Hz), 4.68 (dd, $J = 10.62$, 3.48 Hz, 1H), 4.17 (t, $J = 6.6$ Hz, 2H), 3.40 (ddt, $J = 17.0$, 15.5, 10.6 Hz, 1H), 2.97−2.85 (m, 1H), 1.69−1.60 (m,2H), 1.47−1.35 (m, 2H), 0.94 (t, $J = 7.3$ Hz); ^{13}C NMR δ 187.9 (t, $J = 30.5$ Hz), 170.9 (s), 134.7 (s), 131.4 (s), 130.3 (s), 128.8 (s), 118.3 (t, $J = 256.3$ Hz), 66.0 (s), 41.2 (t, $J = 22.7$ Hz), 30.2 (s), 19.0 (s), 13.6 (s), 7.9 (t, $J = 4.1$ Hz); GC−MS (relative intensity, *m/z*) 410 (M^+, 0.07), 337 ($M^+ - OC_4H_9$, 0.58), 283 ($M\text{-}I^+$, 12.33), 105 ($PhCO^+$, 100), 77 (34.88); HRMS found 410.0185, $C_{15}H_{17}O_3F_2I$ calcd 410.0191; FTIR 1741, 1704, 1451, 1282, 1254, 1197, 1188, 1175 cm^{-1}.

UV-Initiated Addition of 1a with *tert*-Butyl Acrylate (7g). 4,4-Difluoro-4-benzoylbutyric Acid (8g, $PhCOCF_2CH_2CH_2CO_2H$). Similarly, 2.82 g (10.0 mmol) of iododifluoromethyl phenyl ketone (**1a**) and 3.84 g (30.0 mmol) of *tert*-butyl acrylate were irradiated in a quartz tube for 72 h. ^{19}F NMR analysis showed that 65% of **1a** had reacted, and 90% of the 1:1 addition−reduction product, **8g**, and 10% of **4a** were formed. Chromatography through a silica gel column gave 1.0 g of **8g** (44% isolated yield; NMR purity: 100%): ^{19}F NMR δ −101.1 (t, $J = 16.9$ Hz); ^1H NMR δ 10.84 (s, broad, 1H), 8.11 (d, $J = 7.4$ Hz, 2H), 7.64 (tt, $J = 7.4$, 5.6 Hz, 1H), 7.5 (t, $J = 7.9$ Hz, 2H), 2.73−2.77 (m,2H), 2.64−2.49 (m, 2H); ^{13}C NMR δ 188.6 (t, $J = 31.6$ Hz), 178.2 (s), 134.5 (s), 131.7 (s), 130.3 (t, $J = 5.3$ Hz), 128.8 (s), 119.0 (t, $J = 253.9$), 28.9 (t, $J = 23.7$ Hz), 26.7 (t, $J = 5.2$ Hz); DIP-MS (relative intensity, *m/z*) 228 (M^+, 0.05), 227 (0.05), 211 ($M\text{-}OH^+$, 3.50), 183 ($M\text{-}CO_2H^+$, 5.39), 105 (100), 77 (100), 51 (62.35); FTIR 3350 (broad), 1718, 1706, 1600, 1450, 1279 cm^{-1}.

UV-Initiated Addition of 1 with *N,N*-dimethylacrylamide. *N,N*-Dimethyl-4-benzoyl-4,4-difluoro-2-iodobutanamide (11a, $Ph(O)CF_2CH_2CHIC(O)NMe_2$). Similarly, 3.2 g (11.3 mmol) of iododifluoromethyl phenyl ketone (**1a**) and 4.50 g (45.4 mmol) of *N,N*-dimethylacrylamide (**10**) were charged in a quartz tube and irradiated for 15 h. ^{19}F NMR analysis showed that 94% of **1a** had been converted and gave 95% of the 1:1 adduct product, **11a**, and 5% of 4a. Distillation resulted in partial decomposition of **11a** at 143−146 °C/0.01 mmHg. The reaction was repeated, and **11a** was isolated by chromatography through a silica gel column (3.48 g, 81% isolated yield; NMR purity: 98%): mp 85−85.5 °C; ^{19}F NMR δ -100.0 (ddd, $J = 280.7$, 21.5, 12.9 Hz, 1F), −102.1 (ddd, $J = 280.7$, 20.4, 11.7 Hz, 1F); ^1H NMR δ 8.07 (d, $J = 7.9$ Hz, 2H), 7.64 (t, $J = 7.3$ Hz, 1H), 7.49 (t, $J = 7.7$ Hz, 2H), 4.87 (dd, $J = 9.8$, 3.2 Hz, 1H), 3.74−3.46 (m, 1H), 3.06−2.7 (m,1H), 3.06 (s, 3H), 2.96 (s, 3H); ^{13}C NMR δ 188.4 (t, $J = 29.4$ Hz), 169.5, 134.5, 131.6, 130.2, 128.8, 118.3 (t, $J = 255.3$ Hz), 41.7 (t, $J = 22.6$ Hz), 37.7, 36.7, 7.4; GC−MS (relative intensity, *m/z*) 381 (M^+, 0.50), 337 ($M^+ - NMe_2$, 27.89), 318 ($M^+ - HF\text{-}NMe_2$′ 3.93), 310 ($PhCOCF_2CH_2CH_2I^+$, 5.48), 255 ($M^+ - I + 1$, 33.07), 105 ($PhCO^+$, 100); HRMS found 382.0102, $C_{13}H_{15}O_2NF_2I$ ($M^+ + 1$) calcd 382.0117; found 254.0981, $C_{13}H_{14}O_2NF_2$ ($M^+ - I$) calcd 254.0992; FTIR 1705, 1702, 1663, 1559, 1541, 1507, 1450 cm^{-1}.

***N,N*-Dimethyl-4,4-difluoro-5-oxononanamide (12b, *n*-$C_4H_9C(O)CF_2CH_2CH_2C(O)NMe_2$).** Similarly, 2.62 g (10.0 mmol) of iododifluoromethyl *n*-butyl ketone (**1b**) and 2.0 g (20.2 mmol) of *N,N*-dimethylacrylamide were charged into a quartz tube and irradiated with 254 nm UV light for 66 h. ^{19}F NMR analysis showed that the conversion of **1a** was 85%, and 59% of the 1:1 adduct product, **11b**, 31% of the addition−reduction product (**12b**), and 10% of **4b** were formed. Distillation of the reaction mixture gave 1.31 g of **12b** (part of **11b** decomposed to form **12b** during the distillation; yield: 56%; GLPC purity: 92%): bp 135−137 °C/3−4 mmHg; ^{19}F NMR δ −108.1 (t, $J = 16.9$ Hz, 1F); ^1H NMR δ 2.69 (t, $J = 7.5$ Hz, 2H), 2.37 (t, $J = 7.5$ Hz, 2H), 2.41−2.24 (m, 2H), 1.63−1.55 (m, 2H), 3.07 (s, 3H), 2.97 (s, 3H); ^{13}C NMR δ 200.8 (t, $J = 30.2$ Hz), 171.1, 118.0 (t, $J = 251.8$ Hz), 37.4, 36.0, 35.8, 28.6 (t, $J = 25.4$), 24.8, 23.3, 22.2, 13.2; GC−MS (relative intensity, *m/z*) 235 (M^+, 0.80), 236 (0.13), 215 ($M - HF^+$, 0.34), 193 (8.55), 178 ($M^+ - C_4H_9$, 0.88), 87 ($HCF{=}CHCH_2CO^+$, 100); HRMS found 235.1370, $C_{11}H_{19}O_2NF_2$ calcd 235.1383; FTIR 1744, 1659, 1506, 1497, 1466, 1412, 1364, 1152 cm^{-1}.

***N,N*-Dimethyl-2-iodo-4,4-difluoro-5-oxoundecanamide (11c, *n*-$C_6H_{13}C(O)CF_2CH_2CHIC(O)NMe_2$).** Similarly, 2.90 g (10.0 mmol) of iododifluoromethyl *n*-heptyl ketone (**1c**) and 3.0 g (30.3 mmol) of *N,N*-dimethylacrylamide were charged into a quartz tube and irradiated with 254 nm UV light for 36 h. ^{19}F NMR and GC−MS analyses of the mixture showed that the conversion of **1c** was 86%, and 76% of the 1:1 adduct product (**11c**), 19% of the addition−reduction product (**12c**), 5% of **4b**, and a small amount of addition−elimination (−HI) product were formed. **11c** (2.33 g, yield: 60%; GLPC purity: 98%) was isolated by chromatography on a silica gel column with hexane−CH_3CO_2Et eluant (8:2). **12c** and the addition−elimination (−HI) product were identified by GC−MS spectra only from the reaction mixture. **11c**: ^{19}F NMR δ −104.9 (dt, $J = 267.0$ Hz, 13.9 Hz, 1F), −108.8 (dt, $J = 267.0$, 18.0 Hz, 1F); ^1H NMR δ 4.73 (dd, $J = 10.19$ Hz, 3.27 Hz, 1H), 3.44−3.24 (m, 1H), 3.04 (s, 3H), 2.92 (s, 3H), 2.75−2.58 (m, 3H), 1.62−1.52 (m, 2H), 1.30 (m, 6H), 0.89 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR δ 199.8 (t, $J = 29.2$ Hz), 168.9, 116.1 (t, $J = 254.4$ Hz), 40.6 (t, $J = 24.0$ Hz), 37.1, 36.0, 31.1, 28.1, 22.0, 13.5, 7.2; GC−MS (relative intensity, *m/z*) 389 (M^+, 1.68), 347 ($M^+ - C_3H_6$), 319 ($M^+ - C_5H_{10}$, 2.13), 277 ($M^+ - C_6H_{12}CO$, 86.75), 262 ($M^+ - I$, 10.99), 242 ($M^+ - I - HF$, 12.05), 213 ($CHF{=}CHCHICO^+$, 16.57), 100 (90.39); HRMS found 389.0656, $C_{12}H_{22}O_2NF_2I$, calcd 389.0656; FTIR 1742, 1659, 1467, 1414, 1403, 1346, 1161 cm^{-1}.

***N,N*-Dimethyl-4,4-difluoro-5-oxoundecanamide (12c, *n*-$C_6H_{13}C(O)CF_2CH_2CH_2C(O)NMe_2$):** GC−MS (relative intensity, *m/z*) 263 (M^+, 0.58), 243 ($M^+ - HF$, 0.39), 206 ($M^+ - C_4H_9$, 1.38), 193 ($M^+ - C_5H_{10}$, 8.05), 151 ($M^+ - C_6H_{12}CO$, 26.06), 150 ($M^+ - C_6H_{13}CO$, 11.02), 113 ($C_6H_{13}CO^+$, 6.41), 100 ($^+CH_2CH_2CONMe_2$, 8.58), 85 ($C_6H_{13}CO^+$, *100*), 72 (Me_2NCO^+, 15.04).

***N,N*-Dimethyl-4,4-difluoro-5-oxo-2-undecenamide (*n*-$C_6H_{13}C(O)CF_2CH{=}CHC(O)NMe_2$):** GC−MS (relative intensity, *m/z*) 261 (M^+, 0.97), 241 ($M^+ - HF$, 1.60), 221 ($M^+ - 2HF$, 2.63), 204 ($M^+ - C_4H_9$, 9.98), 189 ($M^+ - Me_2NCO$, 4.08), 176 ($M^+ - C_6H_{13}$, 4.71), 169 ($M^+ - Me_2NCO - HF$, 5.11), 149 ($M^+ - C_6H_{12}CO$, 5.26), 133 ($M^+ - C_6H_{13}CO - Me$, 3.49), 100 ($^+CH_2CH_2CONMe_2$, 22.56), 72 (Me_2NCO^+, 100), 55 (29.57), 44 (Me_2N^+, 14.33), 41 (11.89).

UV-Initiated Addition of 1 with Acrylonitrile (13). 2.82 g (10.0 mmol) of **1a** and 1.6 g (30.0 mmol) of acrylonitrile were charged into a quartz tube and irradiated with 254 nm UV light. The reaction was monitored by ^{19}F NMR analysis as detailed in Table 4. After reaction for 25 h, 83% of **1a** was consumed, and telomeric products (**14**), which showed complicated multiplets around −98 ppm (^{19}F NMR), and the reduction byproduct (**4a**) were formed in 92% and 8% yield, respectively. GC−MS analysis of the mixture displayed multiple peaks; all of them only gave small fragment signals with $PhCO^+$ as the base peak. Distillation of the reaction *mixture gave only unreacted* **1a** *and* **4a** even *though the* oil bath was heated to 200 °C at full vacuum. Chromatography of the residue through a silica gel column gave the 1:1 (**14**, $n = 1$, yield: 12%) and 1:2 adducts (**14**, $n = 2$, yield: 28%) with hexane−CH_3CO_2Et (9:1) eluant, which were identified by ^1H and ^{13}C NMR and FTIR spectroscopy. A mixture of other telomeric products was collected by chromatography after the 1:2 adduct, which exhibited multiplets at approximately −98 ppm, the typical chemical shift for $-C(O)CF_2CH_2-$, in the ^{19}F NMR spectrum.

2-Iodo-4,4-difluoro-4-benzoylbutanenitrile (14, $n = 1$, $Ph(O)CF_2CH_2CHICN$): ^{19}F NMR δ −98.6 (ddd, $J = 300.8$, 20.0 Hz, 10.2 Hz, 1F), −101.0 (ddd, $J = 300.8$, 19.7, 13.5 Hz, 1F); ^{1}H NMR δ 8.09 (dd, J = 8.4, 1.2 Hz, 2H), 7.67 (tm, J = 7.5 Hz, 1H), 7.51 (tm, J = 7.9 Hz, 2H), 4.70 (dd, J = 10.2, 4.7 Hz, 1H), 3.23–3.02 (m, 2H); FTIR 1702, 1684, 1546 cm^{-1}.

4-(2,2-Difluoro-2-benzoylethyl)-2-iodo-1,5-pentanedinitrile (14, *n* = 2, $Ph(O)CF_2CH_2CH(CN)CH_2CHICN$: ^{19}F NMR δ −98.0 (ddd, J = 303.7, 20.0, 11.6 Hz, 1F), −99.6 (ddd, J = 303.6, 19.4, 14.4 Hz, 1F); ^{1}H NMR δ 8.14 (d, 9.0 Hz, 2H), 7.69 (tt, J = 9.0 Hz, 1H), 7.53 (t, J = 7.5 Hz, 2H), 4.45 (dd, J = 9.0, 6.0 Hz, 1H), 3.36–3.26 (m, 2H), 2.89–2.50 (m, 2H), 2.39 (t, J = 7.7 Hz, 2H); ^{13}C NMR δ 187.4 (t, J = 31.0 Hz), 135.1, 130.4, 130.7, 129.0, 117.8 (t, J = 253.2 Hz), 118.8/115.9, 41.0/39.3, 35.0 (t, J = 23.6 Hz), 26.0, −8.0/−12.0; FTIR 2944, 1701, 1636, 1221 cm^{-1}.

However, similar reaction of **1b** with acrylonitrile gave only low conversion (>5% NMR yield) and mainly **4b** with minor addition products observed in ^{19}F NMR spectrum after irradiation for 48 h.

UV-Initiated Addition of 1a with Vinyl Methyl Ketone (15), 2,2-Difluoro-1-phenyl-1,5-heptanedione ($PhC(O)CF_2(CH_2)_2C(O)CH_3$, 16). A 2.82 g (10.0 mmol) sample of **1a** and 3.5 g (50.0 mmol) of vinyl methyl ketone were charged into a quartz tube and irradiated for 14 h. A highly viscous liquid was obtained due to the polymerization of **15**. Acetone (5 mL) was added, and ^{19}F NMR analysis of the reaction mixture showed that **1a** had been completely consumed to give 86% of **16** and 14% of the reduction byproduct **4a**. **16** showed a simple triplet in the ^{19}F NMR which indicated the formation of the addition–reduction product. Distillation of the reaction mixture gave 1.13 g (50%) of 2,2-difluoro-1-phenyl-1,5-heptanedione (GLPC purity: 99%): bp 92–94 °C/0.05 mmHg; ^{19}F NMR δ −100.8 (t, J = 17.4 Hz, 1F); ^{1}H NMR δ 8.10 (d, J = 7.4 Hz, 2H), 7.65 (tt, J = 7.4 Hz, 1H), 7.50 (t, J = 7.7 Hz, 2H), 2.79 (t, J = 7.5 Hz, 2H), 2.51 (m, 2H), 1.63–1.55 (m, 2H), 2.24 (s, 3H); ^{13}C NMR δ 207.3 (d, J = 13.1 Hz), 189.0 (t, J = 30.9 Hz), 134.6, 131.7, 130.2 (t, J = 6.0 Hz), 128.8, 119.3 (t, J = 253.3 Hz), 35.8 (t, J = 4.1 Hz), 30.1, 28.1 (t, J = 23.7 Hz); GC–MS (relative intensity, m/z) 226 (M^+, 0.08), 206 ($M - HF^+$, 1.69), 186 ($M - 2HF^+$, 1.17), 183 ($M - CH_3CO^+$, 2.09), 105 ($PhCO^+$, 100), 77 (Ph^+, 86.78), 51 (16.19); FTIR 2876, 1784, 1745, 1720, 1437, 1423 cm^{-1}.

Representative Procedure for the Reduction of γ-(Electron-withdrawing group)-Substituted α,α-Difluoro-γ-iodo Ketones. Ethyl 4,4-Difluoro-4-benzoylbutanoate (5a, $Ph(O)CF_2CH_2CH_2CO_2Et$). A 25 mL two-neck flask fitted with a magnetic stirring bar and a condenser topped with a N_2 inlet was charged with 0.41 g (6.3 mmol) of zinc dust, 0.16 g (0.78 mmol) of $NiCl_2 \cdot 6H_2O$, one drop of water, and 10 mL of THF. The mixture was stirred at rt for 10 min. The green color of the $NiCl_2 \cdot 6H_2O$ faded and the mixture turned black. Then, 2.0 g (5.2 mmol) of **3a** was added, and the reaction mixture was stirred at rt overnight. ^{19}F NMR analysis of the mixture showed that the typical AB pattern signal of **3a** had disappeared to give a new triplet (90%). The reaction mixture was poured into 20 mL of aqueous NH_4Cl solution and extracted with diethyl ether (3 × 20 mL). The combined ether extracts were washed with water (2 × 10 mL) and dried over $MgSO_4$. After rotary evaporation to remove the solvent, the residue gave 1.08 g (81% yield; GLPC purity: 94%) of **5a** by chromatography through a silica gel column (hexane:CH_3CO_2Et = 9:1). **5a**: ^{19}F NMR δ -101.1 (t, J = 16.6 Hz); ^{1}H NMR δ 8.09 (d, J = 9.0 Hz, 2H), 7.61 (t, J = 7.5 Hz, 1H), 7.47 (t, J = 7.5 Hz, 2H), 4.15 (q, J = 7.0 Hz, 2H), 2.61–2.53 (m, 4H), 1.24 (t, J = 7.1 Hz, 3H); ^{13}C NMR δ 188.8 (t, J = 31.0 Hz), 171.9, 134.5, 131.8, 130.2, 128.8, 119.2 (t, J = 254.0 Hz), 60.9, 29.4 (t, J = 23.8 Hz), 26.8 (t, J = 4.9 Hz), 14.2; GC–MS (relative intensity, m/z) 257 ($M^+ + 1$, 0.02), 236 ($M^+ - HF$, 11.57), 211 ($M^+ - EtO$, 47.84), 183 ($M^+ - CO_2Et$, 52.94), 105 ($PhCO^+$, 100), 77 (Ph^+, 100); HRMS found 256.0889, $C_{13}H_{21}O_3F_2$ calcd 256.0910; FTIR 1741, 1705, 1600, 1450, 1323, 1266 cm^{-1}.

Ethyl 4,4-Difluoro-5-oxoundecanoate (5c, *n*-$C_6H_{13}(O)CF_2CH_2CH_2CO_2Et$). Similarly, **5c** (1.34 g, yield: 90%; GLPC purity: 98%) was prepared from 2.2 g (5.6 mmol) of **3c**, 0.74 g (11.3 mmol) of zinc, and 0.16 g (0.67 mmol) of $NiCl_2 \cdot 6H_2O$ in THF and isolated by column chromatography through a silica gel column (hexane:CH_3CO_2Et = 9:1). A small amount of HI-elimination product (<5%) was also observed by ^{19}F NMR and GC–MS spectroscopy. **5c**: ^{19}F NMR δ −108.4 (t, J = 16.9 Hz); ^{1}H NMR δ 4.14 (q, J = 7.1 Hz, 2H), 2.68 (t, J = 7.1 Hz, 2H), 2.50 (t, J = 7.7 Hz, 2H), 2.33 (ddt, J = 8.15, 8.19, 17.1 Hz, 2H), 1.62 (m, 2H), 1.31 (m, 6H), 1.25 (t, J = 7.3 Hz, 3H), 0.89 (t, J = 6.3 Hz, 3H); ^{13}C NMR δ 200.6 (t, J = 31.1 Hz), 171.8, 121.0 (t, J = 252.1 Hz), 60.9, 36.3, 31.7, 28.8, 28.2 (t, J = 23.7 Hz), 26.7 (t, J = 4.8 Hz), 22.8, 22.6, 14.2, 14.1; GC–MS (relative intensity, m/z) 244 ($M^+ - HF$, 0.32), 219 ($M^+ - EtO$, 0.26), 194 ($M^+ - C_5H_{10}$, 6.18), 179 ($M^+ - C_6H_{13}$, 2.29), 161 ($M^+ - C_6H_{12} - HF$, 2.41), 113 ($C_6H_{13}CO^+$, 100); HRMS found 244.1450 ($M^+ - HF$), $C_{13}H_{21}O_3F$ calcd 244.1474; found 194.0764 ($M^+ - C_5H_{10}$), $C_8H_{12}O_3F_2$ calcd 194.0754; FTIR 1743, 1466, 1457, 1308, 1261, 1185 cm^{-1}.

Ethyl 4,4-difluoro-5-oxo-2-undecenoate (*n*-$C_6H_{13}(O)CF_2CH{=}CHCO_2Et$): ^{19}F NMR δ −107.8 (d, J = 11.7 Hz); GC–MS (relative intensity, m/z) 262 (M^+, 2.69), 263 (0.39), 205 ($M^+ - C_4H_9$, 6.18), 189 ($M^+ - CO_2Et$, 10.34), 177 ($M^+ - C_6H_{13}$, 11.84), 149 ($M^+ - C_6H_{13}$, 24.44), 129 ($M^+ - C_6H_{13}CO - HF$, 14.29), 113 ($C_6H_{13}CO^+$, 73.68), 85 ($C_6H_{13}^+$, 37.59), 43 ($C_3H_7^+$, 100).

Synthesis of γ-(Electron-withdrawing group)-Substituted α,α-Difluoro Ketones by One-Pot Addition–Reduction Reaction. *N,N*-Dimethyl 4,4-Difluoro-5-oxononanamide (12b, *n*-$C_4H_9C(O)CF_2CH_2CH_2C(O)NMe_2$). Similarly, 2.62 g (10.0 mmol) of iododifluoromethyl *n*-butyl ketone (**1b**) and 3.0 g (20.3 mmol) *N,N*-dimethylacrylamide were charged into a quartz tube and irradiated with 254 nm UV light for 72 h. ^{19}F NMR analysis showed that 88% of **1b** had been consumed to give 52% of the 1:1 adduct product, **11b**, 28% of the addition–reduction product (**12b**), and 11% of **4b**. The reaction mixture was transferred to another flask charged with 0.75 g (11.5 mmol) of zinc and 0.18 g (0.75 mmol) of $NiCl_2 \cdot 6H_2O$ in 10 mL of moist THF. The reaction mixture was stirred for 30 min at rt and then poured into a beaker containing 50 mL of saturated aqueous NH_4Cl solution and 40 mL of ether. The solids were removed by filtration and washed with ether. The combined organic layer was washed with water and then dried over $MgSO_4$. After evaporation of the ether, 1.67 g (71% yield; GLPC purity: 96%) of **12c** was isolated by distillation of the residue.

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Supporting Information Available: Copies of NMR spectra (16 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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