Friedel—Crafts Reactions of 2,2-Difluorocyclopropanecarbonyl Chloride: Unexpected Ring-Opening Chemistry

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Supporting Information

ABSTRACT: The Friedel–Crafts reactions of 2,2-difluorocyclopropanecarbonyl chloride with various arenes did not lead to the straightforward formation of the expected aryl 2,2-difluorocyclopropyl ketones. Instead the reactions proceeded, to various degrees depending on the reactivity of the arene, via



an apparent rearrangement of the initially formed acylium ion to form novel aryl 3-chloro-3,3-difluoropropyl ketones. The ringopened product was formed exclusively, and therefore the reaction may be synthetically useful when relatively unreactive arene substrates such as benzene, toluene, and *p*-xylene are used. No conditions were found where ring-intact products could be formed exclusively when using substituted benzenes as substrates, with the very reactive substrate thiophene being most selective in that regard, favoring ring intact product 3 with a selectivity of 98:2. The regioselectivity of ring-opening was examined and compared with other related systems computationally.

INTRODUCTION

The chemistry of 2,2-difluorocyclopropyl ketones has become an area of recent interest to us as a consequence of our discovery of difluorocarbene reagent TFDA (trimethylsilyl 2-fluorosulfonyl-2,2-difluoroacetate), which facilitated their synthesis.¹ Two studies of reactions of 2,2-difluorocyclopropyl ketones that resulted in ring-opening were recently published. One was our study of the MgI₂-facilitated reactions of aryl 2,2-difluorocyclopropyl ketones with imines,² which led to products completely devoid of fluorine, and the second was of their ionic-liquid facilitated ring-opening by HBr. Examples of each of these reactions are given in Scheme 1.³

Unfortunately, use of TFDA for the synthesis of unsubstituted aryl difluorocyclopropyl ketones led only to moderate yields,³ probably due to competing polymerization of their α , β -unsaturated ketone precursors (Scheme 2). Therefore an alternative synthesis of the 2,2-difluorocyclopropyl ketones, which involving Friedel– Crafts acylation of activated aromatics using 2,2-difluorocyclopropanecarbonyl chloride, **1**, was considered. There were a number of published examples of successful use of the *nonfluorine*-containing cyclopropanecarbonyl chlorides in Friedel–Crafts acylations,⁴ including those shown in Scheme 3.⁵

Since the dichloro analogue 2,2-dichlorocyclopropanecarbonyl chloride had been used effectively under the usual acylation conditions,⁶ there was good reason to believe that use of 2,2-difluorocyclopropanecarbonyl chloride would lead to similar success.

RESULTS

2,2-Difluorocyclopropanecarbonyl chloride (1) was prepared from *n*-butyl 2,2-difluorocyclopropanecarboxylate via base-catalyzed hydrolysis followed by reaction of the carboxylic acid with thionyl chloride. When 1 was allowed to react with AlCl₃ in the









presence of 1 equiv of benzene in CH_2Cl_2 at 0 °C, surprisingly *none* of the expected aryl 2,2-difluorocyclopropyl ketone was obtained. Instead, only the ring-opened product **2a** was obtained,

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in 50% yield. Compounds of this structure, that is aryl 3-chloro-3, 3-difluorocyclopropyl ketones, have, to our knowledge, not been previously reported; so this reaction has potential synthetic importance.

When toluene, ethylbenzene, or *p*-xylene were used as the aromatic substrate, analogous ring-opened products (**2b**, **2c**, and **2d**) were again the only products observed, this time in 70%, 78%, and 78% yields, respectively (Scheme 4). Toluene and ethylbenzene gave only the para-products, no ortho-products being observed. That the ortho position was considerably less reactive than the para was demonstrated by a competition experiment between toluene and *p*-xylene. When the reaction was carried out with equal amounts of each substrate, the only product obtained (**2b**) derived from reaction with toluene.

When the highly activated anisole was used as substrate, now the major product (75%) was **3e**, which retained the 2,2-difluorocyclopropane entity, along with 25% of ring-opened product **2e**

Scheme 3. Examples of Friedel–Crafts Acylation with Cyclopropanecarbonyl Chlorides



AICI₃ (1.2 equiv)

CH₂Cl₂, 0 °C

AICl₃ (1.2 equiv)

CH₂Cl₂, 0 °C

Scheme 4. Initial Friedel-Crafts Reactions of 1

(1 equiv)

(1 equiv)

(Scheme 5). The very electron-rich heterocycle thiophene was an excellent substrate, yielding 86% of a mixture of mostly (98:2) ring-intact product 3f.

When instead of 1 equiv of aromatic substrate 5 equiv were used in the reactions, some ring-intact product 3a (20%) was observed for benzene, and for toluene the ring-intact 3b was now the major product (90%). Xylene still yielded only ring-opened product 2d. Overall yields of the reactions were not much affected by the change from 1 to 5 equiv of aromatic substrate, nor could this change lead to *exclusive* formation of the desired ring-intact products 3 for any of the benzene derivatives. The results from all of these reactions are summarized in Table 1.

Methylene chloride was in retrospect fortuitously chosen as the solvent for these Friedel—Crafts reactions of acyl chloride **1** in our initial experiments. Other, perhaps equally traditional solvents for Friedel—Crafts reactions were later examined, and somewhat surprisingly, neither carbon disulfide nor nitrobenzene proved satisfactory as solvents. No acylation products were obtained when using either solvent. On the other hand, 1,2dichloroethane proved to be an excellent solvent for the reaction, providing higher overall yields, while giving considerably more unrearranged, ring-intact products (**3**) than the analogous reactions in methylene chloride (Scheme 6). It is not clear why this is so. Mixtures of AlCl₃ with both ethylene dichloride and CH_2Cl_2 (in the absence of **1**) slowly darken, with methylene chloride

 Table 1. Friedel—Crafts Reactions of Aromatics with 2,

 2-Difluorocyclopropanecarbonyl Chloride in Methylene

 Chloride^a

			ratio o	ratio of products		
substrate	equiv of substrate	overall yield (%)	2	3		
benzene	1	50	2a : 100	3a: 0		
benzene	5	55	2a : 80	3a : 20		
toluene	1	72	2b : 100	3b : 0		
toluene	5	70	2b : 10	3b : 90		
ethylbenzene	1	78	2c : 100	3c : 0		
<i>p</i> -xylene	1	78	2d: 100	3d : 0		
<i>p</i> -xylene	5	75	2d : 100	3d : 0		
anisole	1	52	2e : 25	3e : 75		
anisole	5	60	2e : 12	3e: 88		
thiophene	1	86	2 f: 2	3f: 98		
<i>a</i>						

 a Unless otherwise specified, all reactions were carried out with 6 mmol of 1, 7.2 mmol of AlCl₃ in 20 mL of CH₂Cl₂ at 0 °C for 2 h.



CF₂C

CF₂C

CH₃

2d (78%)

2 2a, X = H (50%) 2b, X = CH₃ (70%) 2c, X = CH₃CH₂ (78%)



 H_3C





Scheme 7. Relative Energies of Cyclopropyl Acylium Ions versus Their Respective Ring-Opened Ketene Carbocations (in kcal/mol), As Calculated by the ab Initio HF Method, in CH_2Cl_2 Environment

$X \xrightarrow{(O)}_{H}$ AICI ₃ $\xrightarrow{-AICI_4}_{H}$	x x 0 ⁺ H	rearrangement by contiguous C-C bond cleavage	x H x + C=0 5	or + X X C=0 6 H
	[0]	4 _F , X = F	+10.4	+40.9
	[0]	4 _{CI} , X = CI	+17.3	+44.8
	[0]	4_H, X = H	+40.9	+49.7

Table 2. Computed Ground States of Cyclopropane-Substituted Carbocations and Their Respective Ring-Opened Cations (ab initio HF and MP2/6-31G(d)) (kcal/mol)

Cycle meth	opropyl- yl cation	x	< СН2 ⁺	x x	\sim	X	\sim
			` _H 11		10	12	
Х	Solvent?	HF	MP2	HF	MP2	HF	MP2
X = H	no	[0]	[0]	+21.6	+30.6	+21.6	+30.6
	yes	[0]	[0]	+17.2	+24.5	+17.2	+24.5
X = F	no	[0]	[0]	+1.2	+3.6	+40.6	+53.1
	yes	[0]	[0]	- 12.4	+0.5	+25.8	+49.5
Cycle	opropyl-	, x	,0	, × ⊦	Į.	X	(_م
acyl	ium ion	^+			EC=0	+	F ^C
			~ _н 4	^ ·	5	6	Ή
X = H	no	[0]	[0]	+45.1	+55.0	+45.1	+55.0
	yes	[0]	[0]	+40.9	+52.6	+40.9	+52.6
X = CI	no	[0]	[0]	+16.2	+19.9	+38.0	+39.2
	yes	[0]	[0]	+17.3	+20.9	+44.8	+47.7
X = F	no	[0]	[0]	+12.4	+19.8	+52.0	+61.8
	yes	[0]	[0]	+10.4	+18.2	+49.7	+59.4
Prot	onated		+0~H	X			0 ^{-H}
cyclopropyl ketone		X	Ĭ	x*/	≫ ^О `н	^ ∠^	۲,
		x 🛧	✓ `Ph	15	Ph	+ 40	🄨 `Ph
		··· v	14			16	
X = H	no	[0]	[0]	+43.2	+54.6	+43.2	+54.6
	yes	[0]	[0]	+38.0	+48.8	+38.0	+48.8
X = F	no	[0]	[0]	+20.9	+24.0	+55.0	+61.2
	yes	[0]	[0]	+15.6	+17.9	+48.8	+56.2

appearing to be less stable. Thus the exact nature of the catalyst may vary somewhat for the two solvents. Neither reaction is totally homogeneous.

DISCUSSION

As indicated above, these results were unexpected because precedent of Friedel-Crafts reactions with both the

Scheme 8. Isodesmic Equations Describing the Effect of Geminal Fluorine and Chlorine Substituents on Cyclopropane Ring Strain (kcal/mol)





Figure 1. Hybrid structure for difluoro acylium ion 4.

unsubstituted and the 2,2-dichlorocyclopropanecarbonyl chlorides gave no evidence of rearrangement to analogous ringopened products.^{4–6} Why should the 2,2-difluorocyclopropyl system behave differently? Most likely the results reflect the difference in the thermodynamics of the hypothetical rearrangements of the respective acylium ion intermediates (4). Insight into this issue was gained through computation.

The ground states of a series of cyclopropane-substituted carbocations and their respective ring-opened cations were calculated in the gas phase at HF and MP2/6-31G(d) levels of theory using the Gaussian 03 Revision E01 package.⁷ The stability provided by the solvent (dichloromethane) was also considered and calculated by using the Onsager model for both HF and MP2 methods. The results of these calculations are given in Table 2.





Scheme 10. Attempted AlCl₃-Catalyzed Rearrangement of 2,2-Difluorocyclopropyl Ketone



Scheme 7 summarizes the HF computational data for the solvated 2,2-difluoro-, 2,2-dichloro-, and unsubstituted-cyclopropyl acylium ions $(4_{\rm F}, 4_{\rm Cb} \text{ and } 4_{\rm H})$ and their respective possible rearranged carbocations (5 and 6). The calculations indicate that in each case, the acylium ions 4 were more stable than either of the ketene carbocations 5 and 6 that could have been obtained from rearrangement. In both the fluorine- and the chlorine-substituted systems, cations $\mathbf{6}_{\mathrm{F}}$ and $\mathbf{6}_{\mathrm{Cl}}$ were substantially less stable than $\mathbf{5}_{\mathrm{F}}$ and 5_{Cb} respectively, because of the detrimental inductive effects of the β -halogen substituents. Fluorinated carbocation **5**_F is more stable than chlorinated analogue 5_{Cl} for two reasons. First, α fluorines stabilize carbocations whereas α -chlorines do not, and second because there is a larger release of cyclopropane strain in the fluorinated case. The substantial (\sim 12–13 kcal/mol) impact of geminal fluorines on the strain of cyclopropanes has long been recognized and its magnitude confirmed experimentally⁸ and computationally.9 However, to our knowledge, there is no comparable information available on the thermodynamic effect of geminal chlorines. Thus we provide the appropriate isodesmic equation for chlorine in Scheme 8, the value calculated by using the same method used by Wiberg in his computational study of fluorinated cyclopropanes.9 Our corroborative calculation for the fluorine system is also included. These calculations confirm that geminal chlorines do in fact increase the strain of cyclopropane, but much less so than geminal fluorine substituents.

Thus ketene carbocation S_F , with fluorines at the cationic carbon, is considerably more stable (relative to the acylium ion) than either the chlorine-substituted or the unsubstituted, ring-opened carbocations, S_{CI} or S_H . Therefore it would not be unreasonable to consider the actual "intermediate" in the difluoro case to be best represented as a resonance hybrid (4') of

structures 4 and 5, as depicted in Figure 1, with the CF_2 carbon bearing significant + charge (much more so than the CH_2 group). The situation therefore might well behave much like a "bromonium" ion does, and undergo direct displacement at that carbon, which has the weaker C-C bond, that is at the CF_2 carbon.

With this in mind, the trend shown in Table 1 for rearranged versus rearranged products for the various arene substrates can nicely be explained by a mechanism in which attack of *hybrid* acylium ion 4' by chloride ion competes with its direct acylation reaction with arene, the former process leading to rearranged products (2) and the latter to unrearranged products (3). This mechanism is depicted in Scheme 9. Consistent with this mechanism is the fact that the most reactive arene substrates, that is, anisole and thiophene, are the ones whose direct reactions with acylium ion 4' compete effectively with chloride attack of 4'. Strongly indicative are the experiments with five times the amount of benzene and toluene, which now yielded nonrearranged, ring-intact products. Both of these observations are consistent with the competitive mechanism proposed in Scheme 9.

Of course, there is also the possibility that the unrearranged products 3 might have rearranged to 2 under the reaction conditions. However, this possibility was ruled out by two experiments. First, allowing the reactions to run for twice as long did not lead to increased amount of rearranged products. Second, an experiment in which 2,2-difluorocyclopropyl ketone 3b was stirred in CH_2Cl_2 at 0 °C with AlCl₃ for 2 h, led to no conversion to 2b; indeed no reaction at all was observed (Scheme 10).

The regiochemistry of the nucleophile-induced ring-opening of acylium ion 4' is consistent with that which was observed in our recent study of the solvolysis of 2,2-difluorocyclopropylmethyl tosylate (9) (Scheme 11),¹⁰ which also resulted *only* in formation of products derived from the hypothetical ring-opened difluoromethyl carbocation **10**. A computational examination of this cyclopropylmethyl cation system, with and without fluorines, indicates that, in this case, difluoro ring-opened cation **10**, in a solvated environment, is actually more stable, by 12 kcal, than its respective ring-closed cation **11** (Scheme 12).

In stark contrast, the regiochemistry of the above two reactions is different from that observed by us in our study of the mechanistically similar HBr-induced ring-opening of aryl 2,2difluorocyclopropyl ketones (shown above in Scheme 1).³ In a Scheme 11. Solvolysis of 2,2-Difluorocyclopropylmethyl Tosylate



Scheme 12. Relative Energies of Cyclopropylmethyl Cations versus Their Respective Ring-Opened Allylcarbinyl Carbocations (in kcal/mol), As Calculated by the ab Initio HF Method, in CH₂Cl₂ Environment

	X CH ₂ + =	$x \rightarrow x^{+}$	or + X X
	11	10	12
X = H	[0]	+17.2	+17.2
X = F	[0]	- 12.4	+25.8

Scheme 13. S_N 2-like Mechanism for HBr-Induced Ring-Opening of Ketone 3a



typical reaction of this type, when phenyl 2,2-difluorocyclopropyl ketone, **3a**, was allowed to react with HBr in an ionic liquid based reaction medium, the reaction resulted in the exclusive formation of 4-bromo-3,3-difluoro-1-phenylbutan-1-one, **13**, not the 4-bromo-4,4-difluoro product analogous to **2a** (Scheme 13). In this paper, the regiochemical outcome was rationalized on the basis of an S_N 2-like mechanism, where bromide ion preferentially attacked at the more reactive CH₂ carbon of the cyclopropane ring, a mechanism that is remarkably similar to that proposed in Scheme 7 for the chloride-induced ring-opening of acylium ion 4', but which results in an *entirely different* regiochemical outcome! How can one rationalize the observed difference in regiochemical outcome for these two very similar reactions?

Again, one turns to theory for a possible answer. Calculating the relative energies of the protonated ketone intermediates, 14a, fluorinated and nonfluorinated, and the two respective ringopened enol carbocations, 15a and 16a, led to predicted more endothermic energetics for the hypothetical ring-opening of protonated ketone 14a than for the acylium cation 4 (Scheme 14). This would be consistent with a more S_N 2-like process for 14a Scheme 14. Relative Energies of Protonated Phenyl and *n*-Butyl Cyclopropyl Ketones versus Their Respective Ring-Opened Enol Carbocations (in kcal/mol), As Calculated by the ab Initio HF Method, in CH₂Cl₂ Environment

×	X II R	X X X V H	or $x x 0^{-H}$
	14a , R = Ph	15 ^Ŕ	16
	14b , R = <i>n</i> -Bu		
R = Ph, X = H	[0]	+38.0	+38.0
R = Ph, X = F	[0]	+15.6	+48.8
R = <i>n-</i> Bu, X = H	[0]	+36.6	+36.6
R = <i>n-</i> Bu, X = F	[0]	+12.4	+45.5

than for the acylium ion 4, which is consistent with the results, although admittedly, it is difficult to argue that the difference between +15.6 and +10.4 kcal/mol (15_F compared to 5_F) would be sufficient in and of itself to explain a complete switch in regiochemistry for the two reactions.

Another factor can also be contributing significantly to the different regiochemical outcomes. Bromide ion is a much better nucleophile than chloride ion, and therefore bromide would be a more "aggressive" nucleophile in an $S_N 2$ reaction than would chloride ion. Thus, all other things being equal, bromide ion would be more likely than chloride ion to take advantage of the greater $S_N 2$ reactivity of the CH₂ group of protonated ketone 14a. The observed regiochemical dichotomy can be compared with the notoriously variable regiochemical behavior of unsymmetrical epoxides in their ring-opening reactions with nucleophiles depending on choice of nucleophile and/or choice of Lewis or protic acid.

CONCLUSIONS

In conclusion, the Friedel—Crafts reactions of 2,2-difluorocyclopropanecarbonyl chloride (1) with various arenes did not lead to the straightforward formation of the expected aryl 2,2-difluorocyclopropyl ketones (3). Instead the reactions proceeded, to various degrees depending on the reactivity of the arene, via an apparent rearrangement of the initially formed acylium ion to form novel aryl 3-chloro-3,3-difluoropropyl ketones (2). The formation of the ringopened product 2 was exclusive, and therefore could be synthetically useful, when relatively unreactive arene substrates such as benzene, toluene, and *p*-xylene are used, and when the reactions are run under dilute conditions with only 1 equiv of arene being used. No conditions were found where ring-intact products could be formed exclusively when using substituted benzenes as substrates, with the very reactive substrate thiophene being most selective in that regard, favoring ring intact product 3 with a selectivity of 98:2.

EXPERIMENTAL SECTION

Materials and Methods. Unless otherwise specified, proton, fluorine, and carbon NMR spectra were obtained in CDCl₃ at 300, 282, and 75.46 MHz, respectively, and chemical shifts are reported in ppm upfield relative to TMS for proton and carbon, and upfield of fluorotrichloromethane for fluorine. All aryl 2,2-difluorocyclopropyl ketones obtained and discussed in this work have been previously reported and characterized.³

Experimental Procedures

Preparation of 2,2-difluorocyclopropanecarbonyl Chloride $(1)^{11}$

2,2-Difluorocyclopropanecarboxylic acid:¹² Potassium hydroxide (18.4 g, 3 equiv) was dissolved in 93 mL of water. *n*-Butyl 2, 2-difluorocyclopropanecarboxylate (19.5 g, 1 equiv)¹³ was added to the solution and the mixture heated to reflux and stirred for 10 h. The solution was cooled to room temperature, after which the volatiles were removed by rotary evaporation. Water was added to the crude solid dropwise until it dissolved. Concentrated hydrochloric acid was added dropwise until the solution reached a pH of 2. The acidic solution then was extracted with diethyl ether, after which the diethyl ether layer was then dried with anhydrous MgSO₄ and filtered, and the ether solvent was removed via rotary evaporation to provide 2,2-difluorocyclopropanecarboxylic acid as a pale yellow solid (9.4 g, 70%).¹² The acid was used without further purification in the next step.

2,2-Difluorocyclopropanecarbonyl chloride (1):¹¹ 2,2-Difluorocyclopropanecarboxylic acid (9.0 g) was dissolved in 75 mL of thionyl chloride under nitrogen. The solution was then heated to 60 °C and stirred for 6 h, after which the crude reaction mixture was distilled at atmospheric pressure to provide 2,2-difluorocyclopropanecarbonyl chloride 1 as a transparent, colorless liquid (9.3 g, 90%): bp 106–107 °C;¹¹ ¹¹ NMR δ 1.98 (m, 1H), 2.27 (m, 1H), 3.02 (m, 1H); ¹⁹F NMR δ –124.6 (dm, *J* = 149 Hz, 1F), –138.3 (dm, *J* = 149 Hz, 1F).

Typical Procedure for Friedel–Crafts Reactions of 2, 2-Difluorocyclopropanecarbonyl Chloride (1). Under nitrogen, appropriate (1 or 5) equivalents of the aromatic compound were added via syringe to 20 mL of anhydrous CH_2Cl_2 at 0 °C.2,2-Difluorocyclopropanecarbonyl chloride (1) (0.5 mL, 0.84 g, 1 equiv) was added to the solution at 0 °C followed by slow addition of 0.956 g (1.2 equiv) of AlCl₃. The mixture was then stirred under N₂ for 2 h at 0 °C. Then, water was slowly added to the mixture until two distinct layers formed and bubbling ceased. The entire solution was added to NaHCO₃ solution and the products were extracted with CH_2Cl_2 . The CH_2Cl_2 layer was then dried with anhydrous MgSO₄, filtered, and then removed via rotary evaporation under reduced pressure, leaving behind a liquid crude mixture of aromatic compound plus product. Relative amounts of products 2 and 3 were determined by ¹⁹F NMR analysis of the crude product mixture. Isolation of pure products was accomplished by column chromatography, using silica gel with hexane as eluent.

4-Chloro-1-phenyl-4,4-difluorobutan-1-one (2a): solid, 54%, mp 37–38 °C; ¹H NMR δ 2.79 (m, 2H), 3.30 (t, *J* = 7.2 Hz, 2H), 7.47 (m, 2H), 7.59 (m, 1H), 7.97 (d, *J* = 8.1 Hz, 2H); ¹⁹F NMR δ –51.4 (t, *J* = 12.4 Hz, 2F); ¹³C NMR δ 32.7 (t, *J*_{FC} = 2.6 Hz), 36.5 (*J*_{FC} = 25.2 Hz), 128.3, 129.0, 130.0 (*J*_{FC} = 291 Hz), 133.8, 136.4, 196.5; HRMS (EI) calcd for C₁₀H₉OF₂Cl [M + H]⁺ 218.0304, found 218.0305. Anal. Calcd for C₁₀H₉OF₂Cl: *C*, 54.94; H, 4.15. Found: *C*, 55.01; H, 4.08.

(2,2-Difluorocyclopropyl)(phenyl)methanone (3a):³ liquid, obtained in 11% yield when using 5 equiv of benzene; ¹H NMR δ 1.80 (m, 1H), 2.42 (m, 1H), 3,38 (m, 1H), 7.46 (m, 2H), 7.60 (m, 1H), 8.02 (m, 2H); ¹⁹F NMR δ –124.72 (m, 1F), –140.58 (m, 1F).

4-Chloro-1-(4-methylphenyl)-4,4-difluorobutan-1-one (2b): solid, mp, 61–63.5 °C, 72% and 7% yield, respectively, when using 1 or 5 equiv of toluene; ¹H NMR δ 2.43 (s, 3H), 2.79 (m, 2H), 3.29 (m, 2H), 7.28 (m, 2H), 7.88 (m, 2H); ¹⁹F NMR δ –51.4 (t, *J* = 12.4 Hz, 2F); ¹³C NMR δ 21.91, 32.6 (t, *J*_{FC} = 3.0 Hz), 36.6 (t, *J*_{FC} = 24.7 Hz), 129.4, 129.7, 129.97 (t, *J*_{FC} = 291 Hz), 133.9, 144.7, 196.2; HRMS (EI) calcd for C₁₁H₁₁OF₂Cl [M + H]⁺ 233.0539, found 233.0387. Anal. Calcd for C₁₁H₁₁OF₂Cl: C, 56.79; H, 4.77. Found: C, 56.88; H, 4.68.

(2,2-Difluorocyclopropyl)(4-methylphenyl)methanone (3b):³ solid, mp 37–38 °C, 63% yield when using 5 equiv of toluene; ¹H NMR δ 1.75 (m, 1H), 2.39 (m, 1H), 2.40 (s, 3H), 3.35 (m, 1H), 7.49 (m, 2H), 7.66 (m, 2H); ¹⁹F NMR δ –124.70 (m, 1F), –140.70 (m, 1F).

4-Chloro-1-(4-ethylphenyl)-4,4-difluorobutan-1-one (2c): liquid, 78%, bp 132 °C/10 mmHg; ¹H NMR δ 1.27 (t, *J* = 7.8 Hz, 3H),

2.68–2.86 (m, 4H), 3.29 (t, J = 7.8 Hz, 2H), 7.30 (d, J = 8.1 Hz, 2H), 7.90 (d, J = 8.1 Hz, 1H); ¹⁹F NMR δ –51.45 (t, J = 12.4 Hz, 2F); ¹³C NMR δ 15.3, 29.1, 32.6, 36.5 (t, J = 25.0 Hz), 128.4, 129.9 (t, J = 291 Hz), 133.8, 134.1, 150.8, 196.2; HRMS (EI) calcd for C₁₂H₁₃OF₂Cl [M]⁺ 246.0623, found 246.0604. Anal. Calcd for C₁₂H₁₃OF₂Cl: C, 58.43; H, 5.31. Found: C, 58.08; H, 5.28.

4-Chloro-1-(2,5-dimethylphenyl)-4,4-difluorobutan-1-one (**2d**): liquid, bp 91 °C/10 mmHg, 78% and 75%, respectively, when using 1 or 5 equiv of *p*-xylene; ¹H NMR δ 2.38 (s, 3H), 2.46 (s, 3H), 2.77 (m, 2H), 3.23 (t, *J* = 7.5 Hz, 2H), 7.20 (m, 2H), 7.48 (br s, 1H); ¹⁹F NMR δ –51.43 (t, *J* = 12.4 Hz, 2F); ¹³C NMR δ 21.0, 21.1, 35.1 (t, *J* = 2.5 Hz), 36.6 (t, *J* = 25.4 Hz), 129.4, 129.9 (t, *J* = 292 Hz), 132.3, 132.8, 135.6, 135.7, 136.7, 200.0; HRMS (EI) calcd for C₁₂H₁₃OF₂Cl [M + H]⁺ 246.0623, found 246.0616. Anal. Calcd for C₁₂H₁₃OF₂Cl: C, 58.43; H, 5.31. Found: C, 58.16; H, 5.32.

4-Chloro-1-(4-methoxyphenyl)-4,4-difluorobutan-1-one (2e): solid, mp, 40.5–43 °C, 13% and 9% yield, respectively, when using 1 or 5 equiv of anisole; ¹H NMR δ 2.77 (m, 2H), 3.25 (t, *J* = 7.5 Hz, 2H), 3.88 (s, 3H), 6.95 (dm, *J* = 9 Hz, 2H), 7.96 (dm, *J* = 9 Hz, 2H); ¹⁹F NMR δ –51.4 (t, *J* = 12.4 Hz, 2F); ¹³C NMR δ 32.3, 36.6 (t, *J* = 18.5 Hz), 55.7, 114.1, 129.4, 130.0 (t, *J* = 291 Hz), 130.5, 164.1, 195.1; HRMS (EI) calcd for C₁₁H₁₁O₂F₂Cl [M + H]⁺ 249.0494, found 249.0473. Anal. Calcd for C₁₁H₁₁O₂F₂Cl: C, 53.13; H, 4.46. Found: C, 53.50; H, 4.33.

(2,2-Difluorocyclopropyl)(4-methoxyphenyl)methanone (3e):³ liquid, 39% and 51% yields, respectively, when using 1 or 5 equiv of anisole; ¹H NMR δ 1.68 (m, 1H), 2.30 (m, 1H), 3.36 (m, 1H), 3.72 (s, 3H), 6.96 (m, 2H), 7.54 (m, 2H); ¹⁹F NMR δ –124.74 (m, 1F), –140.8 (m, 1F).

4-Chloro-4,4-difluoro-1-(thiophen-2-yl)butan-1-one (2f): liquid, 2% yield; ¹H NMR δ 2.79 (m, 2H), 3.30 (m, 2H), 7.00 (t, *J* = 4.5 Hz, 1H), 7.16 (dd, *J* = 5.7 and 1.2 Hz, 1H), 7.21 (dd, *J* = 3.8 and 1.0 Hz, 1H); ¹⁹F NMR δ –51.5 (t, *J* = 12.4 Hz).

(2,2-Difluorocyclopropyl)(thiophen-2-yl)methanone (3f): solid, mp 47–49 °C, 84% yield; ¹H NMR δ 1.83 (m, 1H), 2.39 (m, 1H), 3.29 (m, 1H), 7.19 (t, *J* = 4.5 Hz, 1H), 7.72 (dd, *J* = 5.7 and 1.2 Hz, 1H), 7.82 (dd, *J* = 3.8 and 1.0 Hz, 1H); ¹³C NMR δ 16.2 (t, 9 Hz), 30.2 (t, *J* = 11 Hz), 111.7 (t, *J* = 289 Hz), 128.7, 133.2, 135.0, 144.4, 183.2; ¹⁹F NMR, δ - 124.6 (dtd *J* = 149,12.4 and 6.2 Hz, 1F), -140.9 (ddd, *J* = 148, 21, and 4.2 Hz, 1F); HRMS (EI) calcd for C₈H₆OF₂S: [M + H]⁺ 189.0180, found 189.0190. Anal. Calcd for C₈H₆OF₂S: C, 51.06; H, 3.21. Found: C, 50.94; H, 3.11.

ASSOCIATED CONTENT

Supporting Information. ¹H, ¹³C, and ¹⁹F NMR spectra of compounds **2a**-**e** and **3f** and ¹H and ¹⁹F NMR spectra of compounds **1**, **2f**, **3a**, **3b**, and **3e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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NOTE ADDED AFTER ASAP PUBLICATION

Scheme 7 and related text have been corrected as has an in-text reference to Scheme 9. The correct version reposted on April 14, 2011.