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Reactions of TFDA with Ketones. Synthesis of Difluoromethyl 2,2-Difluorocyclopropyl Ethers

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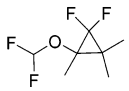
The sequential reaction of 2 equiv of difluorocarbene (generated from trimethylsilyl fluorosulfonyldifluoroacetate (TFDA) by treatment with catalytic fluoride ion) with a series of electron-rich aromatic ketones and α,β-unsaturated ketones leads to the formation of difluoromethyl 2,2-difluorocyclopropyl ethers in good yield.

Introduction

Difluoromethyl 2,2-difluorocyclopropyl ethers, **1**, have in the past attracted some interest in the agrochemical and pharmaceutical industries,[1−3] which is somewhat remarkable since there have been no straightforward, efficient procedures available for their synthesis. Fried,



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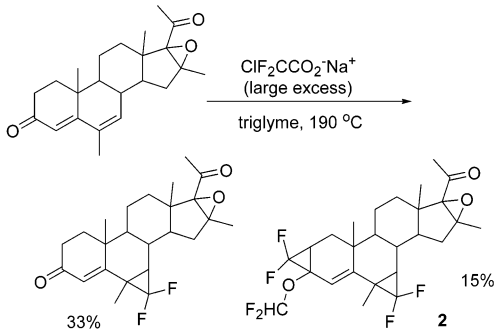
Popper, Crabbe, and their co-workers each reported the isolation of small quantities of compounds with this structure, as minor side products in their studies of the reaction of difluorocarbene (generated via the thermolysis of an excess of sodium chlorodifluoroacetate) with various steroidal enones, enol ethers, or esters.[4−7] For example, in the highest yield process reported, Popper observed the formation of 15% of a product (**2**) deriving from the reaction of 3 equiv of difluorocarbene with the given steroid precursor.[6]

Trimethylsilyl fluorosulfonyldifluoroacetate (TFDA) has recently been suggested to be a highly versatile source of difluorocarbene.[8] Unlike its precursor, fluorosulfonyldifluoroacetic acid, which has also been utilized as a difluorocarbene source for conversions of acids to their difluoromethyl esters[9] and alcohols and phenols to their difluoromethyl ethers,[10] TFDA releases difluorocarbene in a controlled, acid-free environment that appears to be essential for high yield additions of difluorocarbene to alkenes. Indeed, TFDA been shown to be useful for adding CF_2: to a wide variety of alkenes and alkynes, including very electron-deficient alkenes such as α,β-unsaturated esters.[8,11−13] However, in a very recent paper Chen and Xu report that TFDA is surprisingly not effective in the direct difluorocyclopropanation of α,β-unsaturated aromatic aldehydes and ketones.[14,15] Thus, they describe an indirect approach to accomplish this task, a process proceeding via the addition of difluorocarbene to the respective acetals or ketals.



We have also observed the lack of direct CF_2: addition to α,β-unsaturated aldehydes and ketones. However, in examining the progress of such reactions, it was noticed that the substrates disappear quickly upon addition of TFDA, and multiple new fluorine signals appear in ^{19}F NMR spectra of the crude reactions mixtures, including signals that can be attributed to difluorocyclopropanes. The aldehydes and the ketones undergo very different reactions, interestingly none of which involve the direct addition of CF_2: to the substrate double bond! In this

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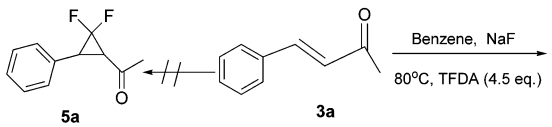
paper, we will discuss the chemistry that is going on with the α,β-unsaturated ketones and related electron-rich ketones, chemistry that leads to the formation of difluoromethyl 2,2-difluorocyclopropyl ethers in fair to good yield.

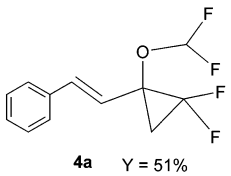
Results and Discussion

Trimethylsilyl fluorosulfonyldifluoroacetate (TFDA) can be readily prepared via the reaction of fluorosulfonyldifluoroacetic acid with trimethylsilyl chloride.[8,11,16] Through multiple redistillations of TFDA, one can eliminate most of the residual acid in the reagent, but such TFDA reagent will still contain small amounts (2−3%) of fluorosulfonyldifluoroacetic acid. Even traces of this strong acid can prove problematic in reactions of TFDA with some acid-sensitive alkene substrates. Therefore a procedure was developed to remove the last traces of residual acid from the TFDA.[13] This procedure involves treatment of the distilled TFDA with a quantity of triethylamine equivalent to the content of residual acid. After filtering the precipitated salt, the acid-free TFDA is generally used immediately.

Reactions of TFDA with α,β-Unsaturated Ketones. The reactions of TFDA with unsaturated ketones were investigated, initially using 4-phenylbut-3-ene-2-one **3a** as a model substrate for the purpose of optimization. Its reaction with acid-free TFDA (2.5 equiv) in benzene in the presence of 6 mol % anhydrous sodium fluoride at 80 °C for 7 h did not give simple adduct **5a** but, instead, gave compound **4a** in 20% yield after purification by column chromatography. Examination of the crude reaction mixture by ^{19}F NMR indicated that **4a** was the *only* cyclopropane-containing product that was formed in the reaction. It was characterized by peaks in the ^{1}H NMR at 1.90 ppm (m, 1H) and 2.07 ppm (m, 1H) for the cyclopropane hydrogens and a doublet of doublets at 6.35 ppm (J = 71.5 Hz, J = 75.4 Hz, 1H) due to the difluoromethoxy group. There were corresponding signals in its ^{19}FNMR spectrum at −80.8 ppm (m, 2F) for the difluoromethoxy group, and at −135.8 ppm (dm, $J_{(F-F)}$ = 161.7 Hz, 1F) and −139.6 ppm (dm, $J_{(F-F)}$ = 161.7 Hz, 1F) for the classic AB cyclopropyl CF_2 group. The molecular weight of the product was confirmed by HRMS. Use of a larger excess of TFDA (4.5 equiv) allowed the yield of compound **4a** to be improved to 51%, with additional TFDA not further increasing the yield.



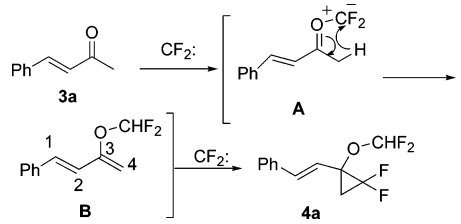
5a **3a**

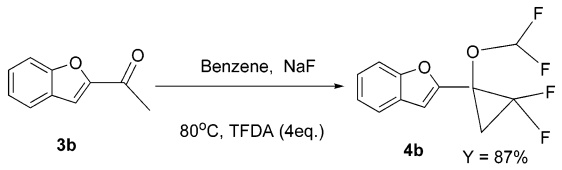


4a Y = 51%

The analogous reaction of benzofuran-2-yl methyl ketone with acid-free TFDA (4.0 equiv) in benzene in the presence of 6 mol % anhydrous sodium fluoride at 80 °C for 6 h gave compound **4b** in 87% yield, after recovering starting material via column chromatography.

SCHEME 1





3b **4b** Y = 87%

It was found that the rate of addition of the TFDA strongly affected the yields of these reactions. TFDA was usually added at the rate of 0.20−0.25 mL/h, using a syringe pump with a Teflon needle. Varying the temperature of the reactions indicated that 80 °C was optimal for the reactions of TFDA with these two ketone substrates. Various solvents (toluene, benzene, methyl benzoate, 3-pentanone) were tried, and toluene or benzene were found to be the best solvents for this reaction.

Mechanism. Although the reaction clearly involves the sequential reaction of 2 equiv of difluorocarbene with the substrates, the actual mechanism must still be considered uncertain. Nevertheless, we propose the mechanism depicted in Scheme 1, mainly because the overall results, including the relative reactivity of the various substrates, can be readily rationalized by it. This mechanism suggests initial formation of an oxonium ylide (intermediate **A**) formed from complexation of CF_2: with the carbonyl oxygen of **3a**, which then undergoes an intramolecular, orbital-symmetry-allowed, suprafacial hydrogen shift to give enol ether intermediate **B**. Addition of a second equivalent of difluorocarbene to **B** leads to the observed products. The presence of the aromatic substituent (which would of course stabilize the ylide) appears to be essential for the success of this overall reaction, since the compound where the phenyl has been replaced by one or two methyls does not undergo a useful reaction. In additional support of this mechanism, enol ethers related to **B** have been detected as minor components in a number of reactions of TFDA with ketones.

However, recognizing that TFDA is a potentially good TMS transfer agent and lacking direct evidence for the ylide intermediate, a mechanism involving trimethylsilyl enol ethers (**C**) as intermediates, such as that depicted in Scheme 2, must be considered a viable alternative.

Reactions of TFDA with Aryl Methyl Ketones. Considering the proposed reaction mechanism, it does not appear that the double bond in compound **3a** should be essential for the reaction. Indeed, when the reaction was carried out using aryl ketones in the place of unsaturated ketones, analogous reactions were observed to occur

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SCHEME 2

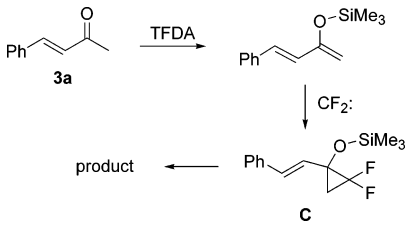
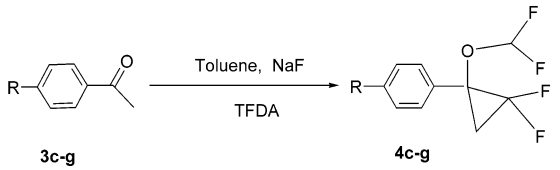


TABLE 1. Reaction of TFDA with Aryl Ketones

entry	ketone	R	temp (°C)[a]	TFDA (equiv)	yield of **4**
1	**3c**	H	120	4.0	27
2	**3d**	4-Me	115	4.5	68
3	**3e**	4-MeO	115	4.5	70
4	**3f**	4-NO_2	120	4.5	22
5	**3g**	3,4-diMeO	120	5.0	71

[a] Oil bath temperature.

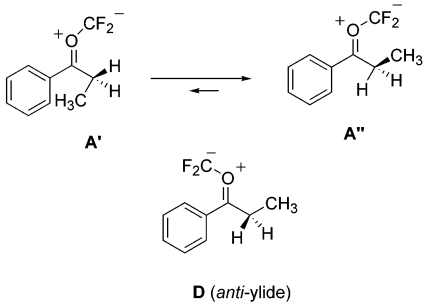
(Table 1). Use of different substituents on the aryl groups indicated that the reaction works best for electron-rich aryl methyl ketones. Higher temperatures also proved advantageous for the reactions with aryl methyl ketones. Thus, whereas treatment of acetophenone with TFDA (4.0 equiv) in benzene in the presence of 10 mol % anhydrous sodium fluoride at 80 °C for 5 h gave only a trace of desired compound **4c**, recovering mostly the acetophenone starting material, carrying the reaction out in refluxing toluene (at 110 °C) led to a 27% yield of product **4c** (Table 1, entry 1). A significant increase in yields of difluoromethyl 2,2-difluorocyclopropyl ethers **4d,e, f** (68−71%) was observed when electron-donating groups (4-Me, 4-MeO, 3,4-diMeO) were present in the starting aryl ketones. In contrast, the reaction of TFDA with an acetophenone bearing an electron-withdrawing substituent (R = 4-NO_2) led to a significantly lower yield (22%) of product **4f** under similar reaction conditions (Table 1, entry 4).



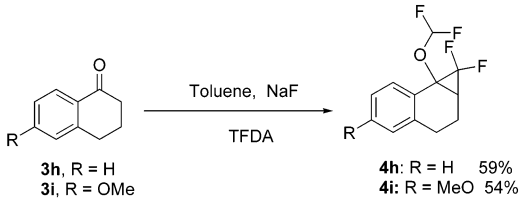
It should be mentioned that attempts to use simple *aliphatic* methyl ketones, such as 2-hexanone, as substrates in this reaction were unsuccessful.

Reactions of Aryl Alkyl Ketones. Somewhat surprisingly, no reaction was observed when propiophenone or isobutyrophenone were used as substrates in this reaction, despite numerous attempts at various temperatures with various solvents. This lack of reactivity was attributed to the unfavorable steric strain of required *syn*-oxonium ylide intermediate **A′** relative to both the alternative *syn*-ylide conformation **A″** and the *anti*-ylide isomer, **D**, which may be preferentially formed.

To test this steric hypothesis, reactions of TFDA with 1-tetralones were carried out, with the expectation that, because of the geometrical constraints of the system, tetralones should exhibit no reluctance to undergo the desired sequence of reactions. This expectation was realized when the reactions of TFDA with 1-tetralones

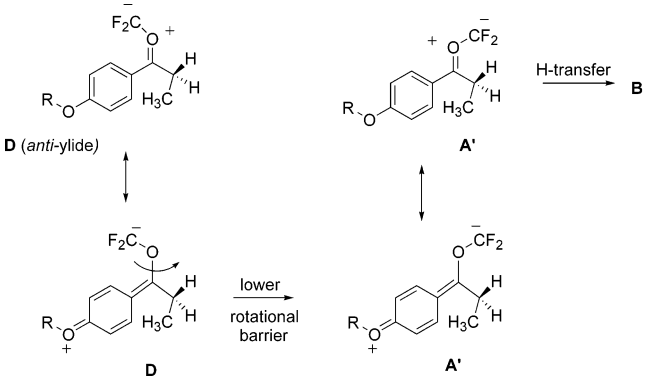


3h and **i** gave compounds **4h** and **4i** in good yields (54−59%).

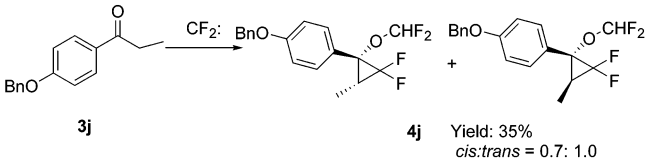


It was also found that placement of an electron-donating group, such as alkoxy, in the para position of propiophenone apparently provides sufficient stabilization of the oxonium ylide to allow conformation **A′** to become kinetically available for the H-transfer process, perhaps via facilitation of the interconversion of *syn* and *anti* oxonium ylides, **A** and **D**, as depicted in Scheme 3.

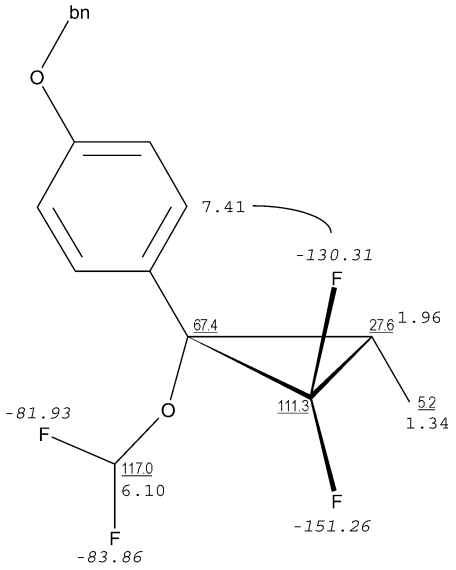
SCHEME 3



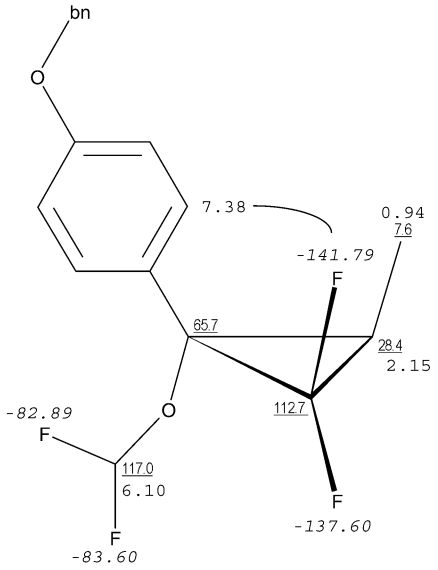
Thus, the reaction of 4-benzyloxypropiophenone with TFDA under the usual conditions gave compound **4j** as a mixture of isomers in a total yield of 35%. The *trans*/*cis* isomeric ratio was 1:0.7, with the structures of the *trans* and *cis* diastereomers being confirmed by NMR.



Representative ^1H, ^{13}C, and ^{19}F chemical shifts are given in Figure 1. Long range $^1H-^{13}C$ couplings seen in the GHMBC spectrum confirmed the structural identity of both compounds, e.g., for the case of *trans*-**4j**: 6.10−67.4, 1.34−67.4, 1.34−111.3.



trans-**4j**



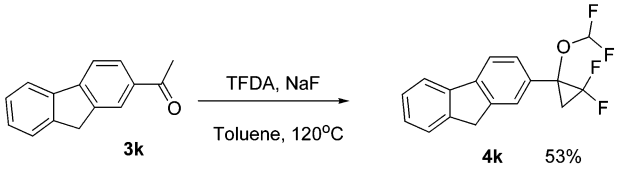
cis-**4j**

FIGURE 1. ^{1}H, ^{13}C, and ^{19}F NMR data for *trans*- and *cis*-**4j**.

A large coupling with the cyclopropyl proton (15.8 Hz in *trans*-**4j** and 17.5 Hz in *cis*-**4j**) identified the fluorine *cis* to it. The *trans* coupling was 3.5 Hz in *trans*-**4j** and 2.3 Hz in *cis*-**4j**. The methyl group displays 2.5 Hz couplings with both cyclopropyl fluorines in both compounds.

Only one of the cyclopropyl fluorines displayed an NOE with aromatic protons in the HOESY spectrum, namely, the one *trans* to the methyl in *trans*-**4j** and the one *cis* to the methyl in *cis*-**4j**; therefore the methyl and the aromatic substituent are *trans* in *trans*-**4j** and *cis* in *cis*-**4j**. The other cyclopropyl fluorine coupled with the fluorines in the difluoromethoxy group, $J_{-151.26,-83.86} = 5.9$ Hz and $J_{-151.26,-81.94} = 2.1$ Hz in *trans*-**4j** and $J_{-137.60,-82.89} = 7.2$ Hz and $J_{-137.60,-83.60} = 4.7$ Hz in *cis*-**4j**. These are through-space couplings that confirm the stereochemistry given in Figure 1.

X-ray crystal structure. We considered it of interest to obtain a crystalline difluoromethyl 2,2-difluorocyclopropyl ether for single-crystal X-ray analysis in order to ascertain the impact of the difluoromethoxy functionality on the difluorocyclopropane structure. To accomplish this, the reaction of TFDA (4.0 equiv) with 2-acetylfluorene, **3k**, was carried out to give **4k** in 53% isolated yield. Product **4k** was recrystallized from toluene, and its detailed structure was obtained by single-crystal X-ray analysis (Figure 2).



The most notable aspect of the X-ray structure of **4k** is the impact of the difluoromethyl ether function on the cyclopropane bond lengths. As can be seen below Table 2, the C14−C16 bond (distal to the CF_2 group) and the C14−C15 bond (proximal to the CF_2 group) are substantially lengthened, and the C15−C16 bond is substantially shortened in comparison to the "normal" 1.553 and 1.464 Å observed for the distal and proximal C−C bonds, respectively, of unsubstituted or alkyl-substituted 1,1-difluorocyclopropanes.[17,18] The remaining proximal bond, in contrast, is significantly shortened.

TABLE 2. Cyclopropane Bond Lengths [Å] in Compound 4k

distal	C14−C16	1.614	C14−C16′	1.719
proximal	C14−C15	1.568	C14−C15′	1.731
proximal	C15−C16	1.259	C15′-C16′	1.413

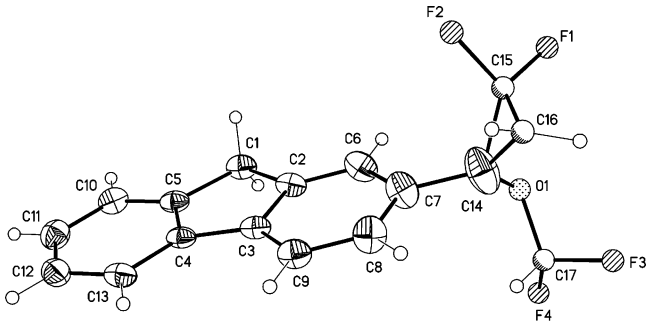


FIGURE 2. ORTEP drawing of compound **4k** (one of two observed conformations).

Conclusions

In summary we have developed a new and useful procedure for the preparation of difluoromethyl 2,2-difluorocyclopropyl ethers in fair to good yield from the sequential addition of 2 equiv of difluorocarbene to a

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variety of α,β-unsaturated ketones, aromatic ketones, and 1-tetralones using acid-free TFDA as the difluorocarbene precursor.

Experimental Section

Procedure for Removal of Trace Acid from TFDA. To a 5-mL, one-necked, round-bottomed flask equipped with a magnetic stirrer and a nitrogen (N_2) inlet was added 1.0 g of TFDA that, according to its ^{19}F NMR spectrum, contained 2.2% 2-fluorosulfonyl-2,2-difluoroacetic acid. Triethylamine (12.2 μL, 0.088 mmol) (1.0 equiv relative to residual acid) was added dropwise at room temperature using a syringe. The mixture was stirred for 5 min, and then the solid was filtered by a pipet with some cotton to obtain a colorless liquid. No residual 2-fluorosulfonyl-2,2-difluoroacetic acid could be observed by ^{19}F NMR after this treatment.

Procedure for Preparation of 2,2-Difluoro-1-difluoromethoxy-1-[(*E*)-2-phenylethenyl]cyclopropane, 4a. A 15-mL three-necked, round-bottomed flask was equipped with a magnetic stirrer, an addition funnel, and a water-cooled condenser bearing a nitrogen (N_2) inlet. Dry benzene (2.4 mL), sodium fluoride (5.1 mg, 0.12 mmol, 0.06 equiv) and 4-phenylbut-3-ene-2-one (292 mg, 2.0 mmol) (**3a**) were added to this flask. The solution was then heated to reflux, and slow N_2 bubbling was initiated for 1 h, after which TFDA (1.50 g, 6.0 mmol, 3.0 equiv) (free of acid according to ^{19}F NMR) was added slowly using a syringe pump via a Teflon needle at the rate of 0.25 mL/h. After 4 h, an additional amount of TFDA (1.0 g, 4.0 mmol, 2.0 equiv) was similarly added. When the addition was complete, the mixture refluxed for 3 h. After the solvent was removed under reduced pressure, the residue was purified by column chromatography on silica gel (hexanes/AcOEt: 20/1) to provide 110 mg (51%) of the yellow product, 2,2-difluoro-1-difluoromethoxy-1-[(*E*)-2-phenylethenyl]cyclopropane, **4a**: ^1H NMR($CDCl_3$) δ 1.87−1.94 (m, 1H), 2.02−2.12 (m, 1H), 6.13 (d, J = 16.1 Hz, 1H), 6.35 (dd, J = 71.5 and 75.4 Hz, 1H), 6.80 (d, J = 16.1 Hz, 1H), 7.28−7.44 (m, 5H); ^{13}C NMR δ 23.3, 63.0, 110.4 (dd, J = 291.1 and 198.1 Hz), 117.4 (dd, J = 256.3 and 259.3 Hz), 119.8, 126.7, 128.7, 128.8, 134.0, 135.2; ^{19}F NMR δ −80.8 (m, 2F), −135.8 (dm, $J_{(F-F)}$ = 161.7 Hz, 1F), −139.6 (dm, $J_{(F-F)}$ = 161.7 Hz, 1F); HRMS (EI) calcd for $C_{12}H_{10}F_4O$, M^+, 246.0668, found 246.0650.

Procedure for Preparation of 1-(Benzofuran-2-yl)-2,2-difluoro-1-difluoromethoxycyclopropane, 4b. Precisely as described above, dry benzene (1.2 mL), sodium fluoride (2.6 mg, 0.06 mmol, 0.06 equiv), and benzofuran-2-yl-methyl ketone (160 mg, 1.0 mmol) (**3b**) were allowed to react with two batches of acid-free TFDA (0.51 g, 2.0 mmol, 2.0 equiv) and then 0.51 g (2.0 mmol, 2.0 equiv). After analogous purification by column chromatography 96 mg (87%) of the yellow oil product, 1-(benzofuran-2-yl)-2,2-difluoro-1-difluoromethoxycyclopropane, **4b**, was obtained: ^1H NMR ($CDCl_3$) δ 2.21−2.36 (m, 2H), 6.42 (dd, J = 71.7 and 74.6 Hz, 1H), 6.94 (s, 1H), 7.24−7.32 (m, 1H), 7.33−7.40 (m, 1H), 7.50−7.54 (m, 1H), 7.58−7.63 (m, 1H); ^{13}C NMR δ 22.8, 58.0, 108.4, 109.0 (dd, $J_{(F-C)}$= 292.0 and 293.6 Hz), 111.6, 117.1 (dd, J = 259.9 and 263.9 Hz), 121.7, 123.4, 125.7, 127.3, 147.3, 155.2; ^{19}F NMR δ −82.6 (m, 2F), −134.7 (dm, $J_{(F-F)}$ = 158.7 Hz, 1F), −140.1 (dm, $J_{(F-F)}$ = 158.7 Hz, 1F); HRMS (EI) calcd for $C_{12}H_8F_4O_2$, M^+, 260.0460, found 260.0457.

General Procedure for Preparation of Difluoromethyl 2,2-Difluoro-1-substituted Cyclopropyl Ethers. A 15-mL three-necked, round-bottomed flask was equipped with a magnetic stirrer, an addition funnel, and a water-cooled condenser bearing a nitrogen (N_2) inlet. The flask was charged with solvents, sodium fluoride (0.06 equiv) and appropriate ketones **3c**−**k**. The solution was heated to reflux, and slow N_2 bubbling was initiated for 1 h. Acid-free TFDA (0.6 g, 2 mmol, 2.0 equiv) was added slowly using a syringe pump via a Teflon needle at the rate of 0.25 mL/h. After 3 h, an additional amount of TFDA was added. The reaction mixture was heated at the same temperature for 4 h. After removing the solvent under reduced pressure, the residue was purified by column chromatography on silica gel (hexanes/AcOEt, 20/1) to give the desired products, **4c**−**k**.

2,2-Difluoro-1-difluoromethoxy-1-phenylcyclopropane, 4c: yellow oil, yield 27%; ^1H NMR ($CDCl_3$) δ 2.02−2.21 (m, 2H), 6.16 (dd, J = 72.0 and 76.1 Hz, 1H) 7.41−7.51 (m, 5H); ^{13}C NMR δ 21.9 (t, J = 10.1 Hz), 98.2, 109.5 (t, $J_{(F-C)}$ = 291.8 Hz), 116.8 (t, $J_{(F-C)}$ = 258.6 Hz), 128.8, 129.0, 129.8, 131.1; ^{19}F NMR δ −83.1 (m, 2F), −134.9 (dm, $J_{(F-F)}$ = 158.7 Hz, 1F), −140.8 (dm, $J_{(F-F)}$ = 158.7 Hz, 1F); HRMS (EI) calcd for $C_{10}H_8F_4O$, M^+, 220.0511, found 220.0513.

2,2-Difluoro-1-difluoromethoxy-1-(4′-methylphenyl)cyclopropane, 4d: yellow oil, yield 68%; ^1H NMR ($CDCl_3$) δ 1.98−2.18 (m, 2H), 2.39 (s, 3H), 6.16 (dd, J = 72.0 and 76.4 Hz, 1H) 7.25 (d, J = 8.1 Hz, 1H), 7.37 (d, J = 8.1 Hz, 1H); ^{13}C NMR δ 21.2, 21.9 (t, J = 10.6 Hz), 63.6, 98.2, 109.7 (dd, $J_{(F-C)}$ = 289.1 and 294.6 Hz), 116.8 (dd, $J_{(F-C)}$ = 259.8, and 256.4 Hz), 128.0, 128.8, 129.7, 140.0; ^{19}F NMR δ −83.2 (m, 2F), −134.8 (dm, $J_{(F-F)}$ = 158.7 Hz, 1F), −141.0 (dm, $J_{(F-F)}$ = 158.7 Hz, 1F); HRMS (EI) calcd for $C_{11}H_{10}F_4O$, M^+, 234.0668, found 234.0671.

2,2-Difluoro-1-difluoromethoxy-1′-(4′-methoxyphenyl)-cyclopropane, 4e: yellow oil, yield 70%; ^1H NMR ($CDCl_3$) δ 1.94−2.18 (m, 2H), 3.83 (s, 3H), 6.15 (dd, J = 72.5 and 76.6 Hz, 1H) 6.95 (dm, J = 8.7 Hz, 1H), 7.41 (dm, J = 8.7 Hz, 1H); ^{13}C NMR δ 22.1 (t, J = 10.1 Hz), 55.3, 63.3, 109.7 (dd, J = 288.8 and 294.1 Hz), 114.3, 116.8 (t, $J_{(F-C)}$ = 258.4 Hz), 122.9, 130.6, 160.6; ^{19}F NMR δ −83.4(m, 2F), −134.4 (dm, $J_{(F-F)}$ = 158.7 Hz, 1F), −141.1 (dm, $J_{(F-F)}$ = 158.7 Hz, 1F); HRMS (EI) calcd for $C_{11}H_{10}F_4O_2$, M^+, 250.0617, found 250.0621.

2,2-Difluoro-1-difluoromethoxy-1-(4′-nitrophenyl)cyclopropane, 4f: yellow oil, yield 22%; ^1H NMR ($CDCl_3$) δ 2.15−2.38 (m, 2H), 6.25 (t, J = 72.7 Hz, 1H) 7.65 (d, J = 8.7 Hz, 1H), 8.29 (d, J = 8.7 Hz, 1H); ^{13}C NMR δ 22.5, 62.1, 116.8 (t, $J_{(F-C)}$ = 259.8 Hz), 119.5 (t, $J_{(F-C)}$ = 336.4 Hz), 124.0, 129.1, 139.0, 148.3; ^{19}F NMR δ −82.1 (dd, J = 9.1 and 73.2 Hz, 2F), −135.5 (dm, $J_{(F-F)}$ = 161.8 Hz, 1F), −139.8 (dm, $J_{(F-F)}$ = 161.8 Hz, 1F); LRMS $C_{10}H_7F_4NO_3$, 265 (M^+), 215 (M − CF_2).

2,2-Difluoro-1-difluoromethoxy-1-(3′,4′-dimethoxyphenyl)cyclopropane, 4g: yellow oil, yield 71%; ^1H NMR ($CDCl_3$) δ 1.96−2.16 (m, 2H), 3.90 (s, 3H), 3.91 (s, 3H), 6.15 (dd, J = 72.3 and 76.6 Hz, 1H) 6.88 (d, J = 8.2 Hz, 1H), 6.97−7.02 (m, 2H); ^{13}C NMR δ 22.1, 55.9, 56.0, 109.6 (d, J = 6.0 Hz), 110.8, 111.8, 116.7 (dd, J = 212.0 and 236.2 Hz), 117.7 (dd, J = 182.8 and 204.5 Hz), 121.7, 123.1, 149.3, 150.2; ^{19}F NMR δ −83.6 (m, 2F), −134.6 (dm, $J_{(F-F)}$ = 158.7 Hz, 1F), −140.9 (dm, $J_{(F-F)}$ = 158.7 Hz, 1F); HRMS (EI) calcd for $C_{12}H_{12}F_4O_3$, M^+, 280.0723, found 280.0729.

1,1-Difluoro-7b-difluoromethoxy-1a,2,3,7b-tetrahydro-1*H*-cyclopropa[*a*]naphthalene, 4h: yellow oil, yield 59%. ^1H NMR ($CDCl_3$) δ 1.86−2.01 (m, 1H), 2.16−2.27 (m, 1H), 2.48−2.72 (m, 2H), 2.77−2.89 (m, 1H), 6.24 (dd, J_1 = 70.8 Hz, J_2 = 77.2 Hz, 1H), 7.19 (d, J = 6.7 Hz, 1H), 7.25−7.38 (m, 2H), 7.62−7.68 (m, 1H); ^{13}CNMR δ 15.2, 26.1, 28.8 (t, J = 11.6 Hz), 60.8, 111.0 (dd, J = 298.6, 299.1 Hz), 117.2 (t, J = 258.6 Hz), 126.5, 126.9, 127.4, 128.3, 128.9, 135.7; ^{19}F NMR δ −81.6 (m, 2F), −130.9 (dd, $J_{d(F-F)}$ = 158.7 Hz, $J_{d(F-H)}$ = 12.2 Hz, 1F), −143.9 (d, $J_{d(F-F)}$ = 158.7 Hz, 1F); HRMS (EI) calcd for $C_{12}H_{10}F_4O$, M^+, 246.0668, found 246.0667.

1,1-Difluoro-7b-difluoromethoxy-5-methoxy-1a,2,3,7b-tetrahydro-1*H*-cyclopropa[*a*]naphthalene, 4i: yellow oil, yield 54%; ^1H NMR ($CDCl_3$) δ 1.91−2.07 (m, 1H), 2.09−2.20 (m, 1H), 2.40−2.67 (m, 2H), 2.73−2.84 (m, 1H), 3.81 (s, 3H), 6.21 (dd, J = 70.8 and 77.7 Hz, 1H), 6.71 (s, 1H), 6.88 (dd, J = 8.4 and 2.3 Hz, 1H), 7.53 (d, J = 8.7 Hz, 1H); ^{13}C NMR δ 16.0, 26.5, 28.2 (t, J = 11.1 Hz), 55.2, 60.5, 110.9 (dd, J = 299.6 and 297.2 Hz), 112.8, 113.9, 117.1 (t, J = 258.7 Hz), 119.1, 128.2, 137.8, 159.6; ^{19}F NMR δ −81.8 (m, 2F), −132.2 (dd, J = 158.7 and 18.3 Hz, 1F), −144.5 (d, $J_{(F-F)}$ = 158.7 Hz, 1F); HRMS (EI) calcd for $C_{13}H_{12}F_4O_2$, M^+, 276.0773, found 276.0778.

2,2-Difluoro-1-difluoromethoxy-(4′-benzyloxyphenyl)-cyclopropane, 4j: white solid, mp: 59−62 °C, yield 35% (*trans*/*cis* = 1:0.7); HRMS (EI) calcd for $C_{18}H_{16}F_4O_2$, M^+, 340.1086, found 340.1087. *trans*-Isomer: ^{1}H NMR ($CDCl_3$) δ 1.34 (d, J = 6.5 Hz, 3H), 1.96 (dqd, J = 16.3, 6.6 and 3.5 Hz, 1H), 5.06 (s, 2H), 6.10 (dd, J = 75.9 and 73.5 Hz, 1H), 7.00−7.06 (m, 2H), 7.34−7.46 (m, 7H); ^{19}F NMR δ −81.93 (dd, J = 168.1 and 75.9 Hz, 1F), −83.86 (dd, J = 168.1 and 73.5 Hz, 1F), −130.31 (ddq, J = 160.9, 15.8 and 2.6 Hz, 1F), −151.26 (dcv, J = 160.9 and 3.1 Hz, 1F). *cis*-Isomer: ^{1}H NMR ($CDCl_3$) δ 0.94 (ddt, J = 6.9, 2.2 and 1.1 Hz, 3H), 2.15 (dqd, J = 17.5, 6.7 and 2.3 Hz, 1H), 5.06 (s, 2H), 6.10 (t, J = 74.3 Hz, 1H), 7.01 (d, J = 8.8 Hz, 2H), 7.34−7.46 (m, 7H); ^{19}F NMR δ −82.89 (ddd, J = 168.9, 74.5 and 7.2 Hz, 1F), −82.89 (ddd, J = 168.9, 74.2 and 4.7 Hz, 1F), −137.60 (ddddq, J = 161.4, 17.0, 7.6, 4.7 and 2.3 Hz, 1F), −141.79 (d, J = 161.4 Hz, 1F).

2,2-Difluoro-1-difluoromethoxy-1-(9*H*-fluoren-2-yl)cyclopropane, 4k: yellow needles, mp 88−90 °C, yield 53%; ^{1}H NMR ($CDCl_3$) δ 2.07−2.23 (m, 1H), 3.94 (s, 3H), 6.21 (dd, J_1 = 72.3 and 76.4 Hz, 1H), 7.32−7.44 (m, 2H), 7.49 (d, J = 7.9 Hz, 1H), 7.57 (d, J = 7.2 Hz, 1H), 7.66 (s, 1H), 7.82 (t, J = 6.8 Hz, 2H); ^{13}C NMR δ 22.1 (t, J = 10.5 Hz), 36.2, 63.9, 109.7 (dd, J = 289.0 and 296.2 Hz), 116.3 (t, J = 257.3 Hz), 120.2, 120.3, 125.1, 125.7, 127.0, 127.5, 127.8, 129.1, 140.6, 143.4, 143.6, 143.9; ^{19}F NMR δ −81.3 (m, 2F), −134.4 (dm, $J_{(F-F)}$ = 158.7 Hz, 1F), −140.8 (dm, $J_{(F-F)}$ = 158.7 Hz, 1F); HRMS (EI) calcd for $C_{17}H_{12}F_4O$, M^+, 308.0824, found 308.0827.

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Supporting Information Available: X-ray experimental details, drawings, and tables; general experimental methods; and ^{1}H, ^{19}F, and ^{13}C NMR spectra of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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