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Methyl 2,2-Difluoro-2-(fluorosulfonyl)acetate, a Difluorocarbene Reagent with Reactivity Comparable to That of Trimethylsilyl 2,2-Difluoro-2-(fluorosulfonyl)acetate (TFDA)

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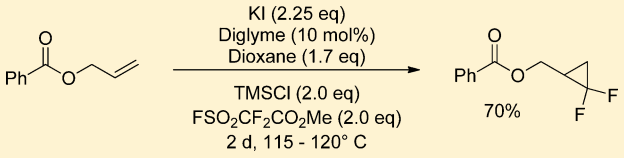
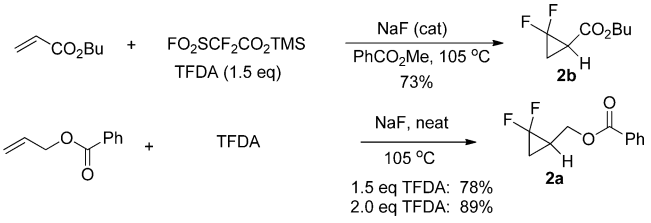
Supporting Information

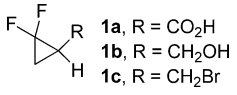
ABSTRACT: Under specific high concentration, high temperature conditions, methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (MDFA) has been found to act as a very efficient source of difluorocarbene, exhibiting carbene reactivity characteristics comparable to those exhibited by trimethylsilyl 2,2-difluoro-2-(fluorosulfonyl)acetate (TFDA). For example, in reaction with highly unreactive *n*-butyl acrylate and using only 2 equiv of MDFA, a yield of 76% of difluorocyclopropane product was obtained after 2 days.



Within the pharmaceutical and agrochemical community, *gem*-difluorocyclopropanes[1] are of considerable current interest, as witnessed by the number of patents filed over the past 7 years that include this structural feature. A SciFinder search for three major 2,2-difluorocyclopropyl building blocks (**1a**–**c**) provided 66 hits for patents or patent applications since our 2005 full paper appeared reporting the use of the difluorocarbene reagent trimethylsilyl 2,2-difluoro-2-(fluorosulfonyl)acetate (TFDA) to prepare such compounds.[2] There is little mention of these compounds in the journal or patent literature prior to the discovery of TFDA, and to this day TFDA remains the only difluorocarbene reagent that has sufficient reactivity to prepare the precursors of these building blocks in high yield. The reactions of TFDA to make the two precursors from which these three compounds can be readily prepared are given in Scheme 1.

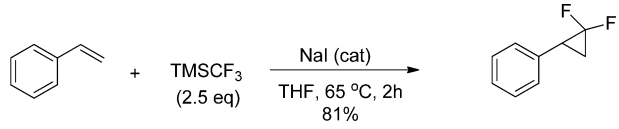
Scheme 1. Key Difluorocyclopropane Syntheses Using TFDA





Development and/or invention of new difluorocarbene reagents has remained an area of great interest and importance in the years following our report of TFDA, and a number of good, new reagents have been reported, both for use in preparing *gem*-difluorocyclopropanes[3−6] and for preparing difluoromethyl ethers or amines.[7−15] The most recent report involving the use of the Ruppert−Prakash reagent[6] was particularly useful, since it allowed reactions to be carried out at relatively low temperatures with relatively sensitive alkene substrates (Scheme 2).

Scheme 2. Recent Hu/Prakash Difluorocarbene Methodology



However, none of these new methods has been reported to react efficiently with the two relatively electron-deficient alkene substrates shown in Scheme 1 or with other relatively unreactive substrates, such as 1-alkenes. To accomplish that, one must use TFDA, which has remained a relatively expensive reagent that must be handled with great care. It is highly moisture-sensitive with a poor shelf life and is most effective when prepared immediately before use. Therefore we have sought an alternative reagent that might avoid these disadvantages but will still provide a highly reactive source of difluorocarbene. Somewhat surprisingly an "old friend" ended up providing the answer to our search.

Methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (MDFA) is arguably the very best precursor for *in situ* generation of trifluoromethylcopper in a process reported first by Chen in 1989 and finding great use ever since.[16−19] His original recipe remains sufficient for most substrates, but when necessary it can be enhanced by Pd^{II} catalysis.[20−22]

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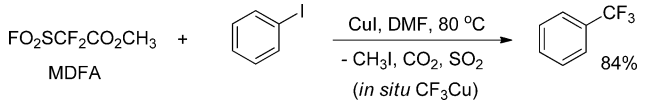
Mechanistically the formation of CF_3Cu proceeds via initial formation of difluorocarbene, which then combines with fluoride and Cu^+ to form the CF_3Cu (Scheme 3), and there

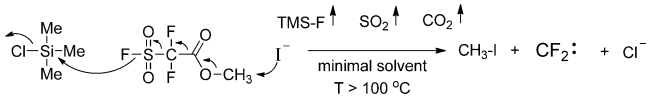
Scheme 3. Use of Methyl 2,2-Difluoro-2-(fluorosulfonyl)acetate To Prepare *in Situ* CF_3Cu



has been mention of difluorocarbene being able to be trapped by the classic, highly reactive carbene trap 2,3-dimethylbutene,[23] although to our knowledge until the present work no determined attempt has been made to actually use methyl 2,2-difluoro-2-(fluorosulfonyl)acetate as a reagent for the synthesis of *gem*-difluorocyclopropanes.

The crux of our plan was to initiate difluorocarbene formation from MDFA via its demethylation by iodide ion and then to limit the production of trifluoromethyl anion by removing the fluoride ion produced via trapping with trimethylsilyl chloride (TMSCl), as depicted in Scheme 4.

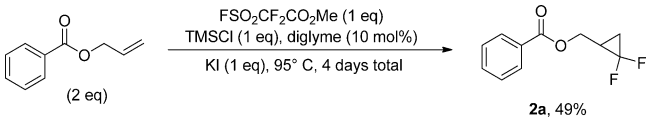
Scheme 4. Generation of Difluorocarbene from MDFA



In optimizing this process, two important factors remained relatively invariable on the basis of our experience with TFDA: high temperature and high concentration. Because of the relatively low reactivity of difluorocarbene, TFDA reactions were optimally carried out between 90 and 120 °C and neat or with minimal solvent present. In the case of our experiments with MDFA, it was found that, because of the use of KI as an at least stoichiometric reagent, small quantities of solvent were required, in order to allow the mixtures to be stirred. The choice of solvent turned out to be important. The relatively unreactive alkene allyl benzoate was chosen as the substrate with which to test the use of MDFA as a difluorocarbene source under various conditions.

Initial experiments at 95 °C, neat or with small amounts of diglyme added, led to promising results as exemplified in Scheme 5, but even after 4 days considerable MDFA remained,

Scheme 5. Early MDFA Experiment

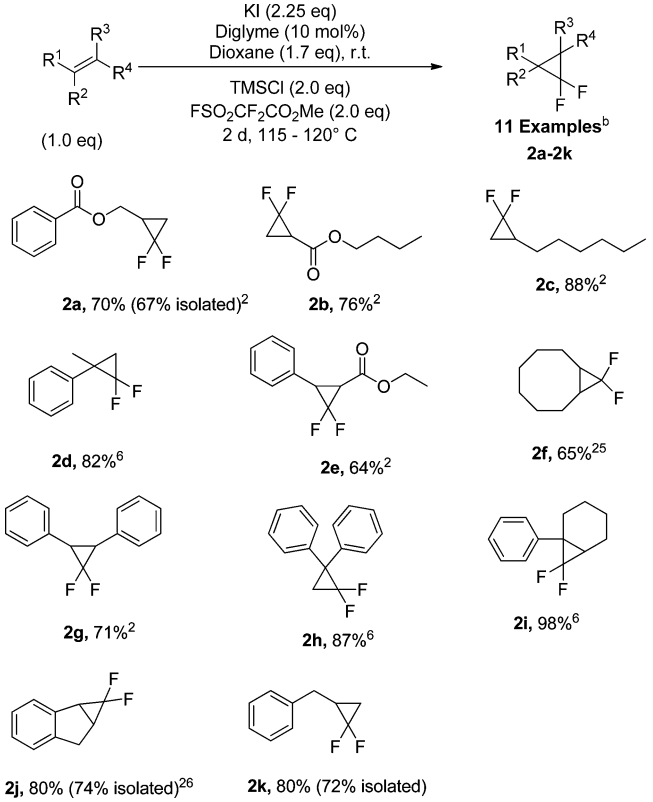


and yields of cyclopropane product were modest. KI proved superior to NaI as a source of iodide, whereas attempts to use the more soluble tetrabutylammonium bromide led to rapid, total destruction of the MDFA, with little or no cyclopropane product being formed. In such early experiments, the MDFA was added slowly, using a syringe pump, as was required when TFDA was used as the carbene precursor.

Optimization experiments determined that use of additional solvent led to more rapid consumption of MDFA, but lower yields of product. Use of too little solvent led to problems with stirring the reaction mixture as the reaction progressed. Diglyme proved better than either tetraglyme or dioxane, when used alone, but in the end a combination of diglyme and dioxane led to the most consistently advantageous results. The conditions that were eventually settled upon as optimal included using MDFA in 2-fold excess over substrate alkene, a reaction temperature of 110−120 °C, and a time of reaction of 2 days, which was required in order to ensure full conversion of the MDFA. Because of the slow rate of reaction, it was possible to simply mix all of the ingredients together prior to heating the reaction vessel to initiate the reaction. This is much more convenient than using a syringe pump, as was required for the TFDA reactions.

A broad selection of alkenes, of varying reactivity, was screened using the optimal conditions chosen for MDFA reaction, with the results being given in Table 1. The identities

Table 1. Synthesis of *gem*-Difluorocyclopropanes Using MDFA as Difluorocarbene Source[a]



[a]Yields reported are by NMR, with isolated yields also being obtained for **2a**, **2j**, and **2k**, . [b]All products are known,[2,6,24−26] except for **2k**

of known compounds **2a**−**2j** were initially determined on the basis of the characteristic AB system observed in their fluorine NMR spectra but were also confirmed by examination of their proton spectra. New compound **2k** was fully characterized on the basis of its ^1H, ^{13}C, and ^{19}F NMR spectra, its IR spectrum, and its exact mass as determined by HRMS.

On the basis of the results given in the Table, it can be seen that the level of reactivity attained by the use of MDFA as the source of difluorocarbene is very similar to that reported for TFDA. Although all of the examples given in the table were carried out at the 10.4 mmol scale (i.e., starting with 1.7 g of allyl benzoate), with NMR yields being reported, successful scale-up of the reaction was possible. When starting with 47.1

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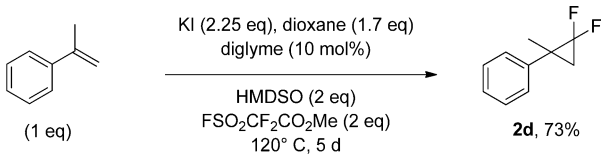
mmol (7.6 g) of allyl benzoate, the observed yield actually increased to 80%, with 79% of product **2a** (7.9 g) able to be isolated after 3 days.

It was also found that hexamethyldisiloxane (HMDSO) could be used as the fluoride trap in place of trimethylsilyl chloride. Unlike TMSCl, HMDSO is neither corrosive nor volatile. Unfortunately, in order to obtain similar conversions, much longer reaction times were required when using HMDSO (Scheme 6).

Scheme 6. MFDA Reaction Using HMDSO in Place of TMSCl



Although the time required for the difluorocarbene reactions of MDFA (2−3 days) is considerably longer than the 5 h generally required for the analogous difluorocarbene reactions of TFDA, the overall advantages of the MDFA reaction in terms of cost, safety, and ease of reaction should in most cases outweigh the time factor advantage of TFDA.

EXPERIMENTAL SECTION

General Considerations. The NMR spectra for ^{1}H, ^{13}C and ^{19}F were recorded in $CDCl_3$ at 300, 75.46, and 282 MHz, respectively, with chemical shifts being reported in ppm downfield from the respective internal standards (TMS for proton and carbon and $CFCl_3$ for fluorine spectra).

General Procedure for the Synthesis of *gem*-Difluorocyclopropanes. A 100 mL three-necked, round-bottomed flask equipped with reflux condenser, rubber septum, and a magnetic stir bar was flame-dried under a nitrogen atmosphere. Then 3.88 g of oven-dried potassium iodide (23.4 mmol, 2.25 equiv) was added, and the flask allowed to cool to room temperature. A nitrogen atmosphere was maintained until the end of the reaction via a slow N_2 flow through a T-tube attached above the reflux condenser. Using a syringe, the alkene substrate (10.4 mmol, 1.0 equivalent), 1.5 mL of dioxane (17.6 mmol, 1.7 equiv), and 0.15 mL of diglyme (1.0 mmol, 0.1 equiv) were added in that order via injection through the rubber septum. The mixture was then heated by an oil bath maintained between 115 and 120 °C. At this temperature 2.26 g of trimethylsilyl chloride (20.8 mmol, 2.0 equiv) was added by syringe, followed by analogous addition of 4.0 g of MDFA (20.8 mmol, 2.0 equiv). The mixture was then stirred at 115−120 °C for 2 days. After the mixture cooled to approximately 40 °C, 30 mL of diethyl ether and 30 mL of distilled water were added, and the mixture was stirred for 30 min while cooling to room temperature. The two phases were then separated, and the aqueous layer was washed two times with 20 mL of diethyl ether. After drying the combined organic layers over anhydrous magnesium sulfate and filtering the mixture, the solvent was removed under reduced pressure to obtain a dark red residue. Yields were then determined directly by ^{19}F NMR of the residue in $CDCl_3$ using an appropriate amount of trifluoromethylbenzene as internal standard. When isolating a pure product from these small scale reactions it was most convenient to do so via column chromatography using silica gel and a 50:1 mixture of hexane and diethyl ether as eluent.

*2,2-Difluorocyclopropylmethyl Benzoate (**2a**).* When allyl benzoate was used as substrate according to the general procedure, the product was purified by column chromatography, and after removal of the solvent under vacuum the desired compound was obtained as a colorless liquid: NMR yield, 70%, (isolated yield, 1.48 g, 6.97 mmol, 67%); ^{1}H NMR δ 8.06 (m, 2H), 7.56 (m, 1H), 7.44 (m, 2H), 4.46 (m, 1H), 4.30 (m, 1H), 2.08 (m, 1H), 1.55 (m, 1H), 1.29 (m, 1H); ^{13}C NMR δ 166.4 (s), 133.2 (s), 129.9 (d, J_{FC} = 7.4 Hz), 129.8 (s), 128.5 (s), 113.1 (t, $^{1}J_{FC}$ = 283.0 Hz), 61.7 (d, $^{3}J_{FC}$ = 5.5 Hz), 21.2 (t, $^{2}J_{FC}$ = 11.2 Hz), 15.1 (t, $^{2}J_{FC}$ = 11.2 Hz); ^{19}F NMR δ −129.61 (dddm, $^{2}J_{FF}$ = 160 Hz, $^{3}J_{FH}$ = 13.0 and 11.6 Hz, 1F), −143.76 (ddm, $^{2}J_{FF}$ = 160 Hz, $^{3}J_{FH}$ = 13.3 Hz, 1F). The observed data are in accord with those reported in the literature.[2]

*n-Butyl 2,2-Difluorocyclopropanecarboxylate (**2b**).* When *n*-butyl acrylate was used as substrate according to the general procedure, the product was purified by column chromatography to provide a colorless to yellow liquid: NMR yield, 76%; ^{1}H NMR δ 4.08 (t, J = 6.6 Hz, 2H), 2.36 (m, 1H), 1.98 (m, 1H), 1.66 (m, 1H), 1.57 (m, 2H), 1.33 (m, 2H), 0.87 (t, J = 7.3 Hz, 3H); ^{13}C NMR δ 166.8 (d, $^{3}J_{FC}$ = 1.7 Hz), 110.6 (dd, $^{1}J_{FC}$ = 283.0 and 288.1 Hz), 65.6 (s), 30.7 (s), 25.8 (t, $^{2}J_{FC}$ = 11.0 Hz), 19.2 (s), 16.6 (t, $^{2}J_{FC}$ = 11.1 Hz), 13.8 (s); ^{19}F NMR δ −126.54 (dtd, $^{2}J_{FF}$ = 153.6 Hz, $^{3}J_{FH}$ = 12.4 and 6.2 Hz, 1F), −141.33 (ddd, $^{2}J_{FF}$ = 153.6 Hz, $^{3}J_{FH}$ = 12.2 and 4.8 Hz, 1F). The observed data are in accord with those reported in the literature.[2]

*1,1-Difluoro-2-hexylcyclopropane (**2c**).* From reaction with 1-octene the product yield was determined by NMR: 88%; ^{19}F NMR δ −128.46 (dm, $^{2}J_{FF}$ = 155.5 Hz), 1F), −145.22 (ddd, $^{2}J_{FF}$ = 155.5 Hz, $^{3}J_{FH}$ = 12.8 and 3.6 Hz, 1F). The observed data are in accord with those reported the literature.[2,27]

*(2,2-Difluoro-1-methylcyclopropyl)benzene (**2d**).* From reaction with α-methyl styrene, a colorless liquid was obtained: NMR yield, 82%; ^{1}H NMR δ 7.28 (m, 5H), 1.64 (m, 1H), 1.49 (s, 3H), 1.34 (m, 1H); ^{13}C NMR δ 139.3 (t, J_{FC} = 2.1 Hz), 128.7 (s), 128.5 (d, J_{FC} = 2.1 Hz), 127.3 (s), 114.7 (dd, $^{1}J_{FC}$ = 289.5 and 287.2 Hz), 31.4 (dd, $^{2}J_{FC}$ = 10.9 and 9.9 Hz), 22.6 (t, J = 9.9 Hz), 21.5 (dd, $^{3}J_{FC}$ = 6.5, 1.9 Hz); ^{19}F NMR δ −132.92 (dd, $^{2}J_{FF}$ = 149.9, $^{3}J_{FH}$ = 13.4 Hz, 1F), −137.96 (dd, $^{2}J_{FF}$ = 149.9, $^{3}J_{FH}$ = 12.4 Hz, 1F). The observed data were in accord with those reported in the literature.[6]

*Ethyl 2,2-Difluoro-3-phenylcyclopropanecarboxylate (**2e**).* When ethyl cinnamate was used as substrate in the above general procedure, the crude product was purified by column chromatography to obtain a yellow liquid: NMR yield, 64%; ^{19}F NMR δ −133.5 (dd, $^{2}J_{FF}$ = 152 Hz, $^{3}J_{FH}$ = 13.2 Hz, 1F), −134.70 (ddd, $^{2}J_{FF}$ = 152 Hz, $^{3}J_{FH}$ = 12.9 and 3.3 Hz, 1F). The observed data were in accord with those reported in the literature.[2]

*9,9-Difluorobicyclo[6.1.0]nonane (**2f**).* When *cis*-cyclooctene was used in the above general procedure, the crude product was purified by column chromatography, with the product being isolated as a colorless liquid: NMR yield, 65%; ^{1}H NMR δ 1.82 (d, J = 11.4 Hz, 2H), 1.52 (m, 4H), 1.29 (m, 8H); ^{19}F NMR δ −125.3 (dt, $^{2}J_{FF}$ = 157.2 Hz, $^{3}J_{FH}$ = 13.8 Hz, 1F), −153.4 (d, $^{2}J_{FF}$ = 157.0 Hz, 1F). The spectral data were in accord with those in the literature.[25]

*trans-3,3-Difluoro-1,2-diphenylcyclopropane (**2g**).* When *trans*-stilbene was used as substrate according to the general procedure, the crude product was purified by column chromatography, with the product being isolated as a white solid: NMR yield, 71%; ^{1}H NMR δ 7.23 (m, 10H), 2.95 (t, $^{3}J_{FH}$ = 7.6 Hz, 2H); ^{19}F NMR δ −134.6 (t, $^{3}J_{FH}$ = 7.6 Hz, 2F). The spectral data were in accord with those in the literature.[2]

*2,2-Difluoro-1,1-diphenylcyclopropane (**2h**).* When 1,1-diphenylethylene was used as substrate according to the general procedure, the crude product was purified by column chromatography, with the product being isolated as a white solid: NMR yield, 87%, ^{1}H NMR δ 7.32 (m, 4H), 7.23 (m, 4H), 7.15 (m, 2H), 1.99 (m, 2H); ^{19}F NMR δ −130.4 (t, $^{3}J_{FH}$ = 8.6 Hz, 2F). The spectral data were in accord with those in the literature.[6]

*7,7-Difluoro-1-phenylbicyclo[4.1.0]heptanes (**2i**).* When 1-phenylcyclohexene was used according to the general procedure, the crude product was purified by column chromatography, with the product being isolated as a colorless liquid: NMR yield, 98%; ^{1}H NMR δ 7.20 (m, 5H), 2.09 (m, 1H), 1.91 (m, 1H), 1.72 (m, 3H), 1.30 (m, 4H); ^{13}C NMR δ 142.0 (d, J_{FC} = 2.1 Hz), 128.6 (s), 128.4 (d, J_{FC} = 2.1 Hz), 127.0 (s), 115.8 (t, $^{1}J_{FC}$ = 290.7 Hz), 31.2 (t, $^{2}J_{FC}$ = 10.2 Hz), 27.5 (t, J_{FC} = 2.7 Hz), 23.5 (dd, $^{2}J_{FC}$ = 10.6 and 9.4 Hz), 21.3 (dd, J_{FC} = 2.6 and 1.7 Hz), 20.9 (dd, J_{FC} = 2.0, 1.1 Hz), 17.1 (d, J_{FC} = 1.0 Hz); ^{19}F NMR δ −128.3 (dd, $^{2}J_{FF}$ = 149.7 Hz, $^{3}J_{FH}$ = 14.7 Hz, 1F), −143.5 (d,

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$^2J_{FF}$ = 149.7 Hz, 1F). The spectral data were in accord with those in the literature.,[6]

*1,1-Difluoro-1,1a,6,6a-tetrahydrocyclopropa[a]indene (**2j**).* When indene was used as substrate according to the general procedure, the crude product was purified by column chromatography, with the product being isolated as a pale yellow liquid: NMR yield, 80% (isolated yield, 1.279 g, 74%); ^{1}H NMR δ 7.22 (m, 1H), 7.10 (m, 3H), 3.14 (m, 3H), 2.38 (m, 1H); ^{13}C NMR δ 143.3 (dd, $^3J_{FC}$ = 5.1, 2.8 Hz), 137.2 (s), 127.1 (s), 126.8 (s), 125.1 (s), 124.6 (d, J_{FC} = 1.4 Hz), 113.1 (dd, $^1J_{FC}$ = 295.5, 280.7 Hz), 35.5 (t, $^2J_{FC}$ = 12.9 Hz), 32.0 (d, $^3J_{FC}$ = 2.1 Hz), 27.3 (dd, $^2J_{FC}$ = 14.0, 10.2 Hz); ^{19}F NMR δ −127.9 (dt, $^2J_{FF}$ = 151.3, $^3J_{FH}$ = 12.9 Hz, 1F), −153.7 (d, $^2J_{FF}$ = 151.4 Hz, 1F); GC−MS (exact mass, DART-TOF-MS): calcd $C_{10}H_8F_2$ $(M)^+$ 166.0594, found 166.0617; calcd $C_{10}H_9F_2$ $(M + H)^+$, 167.0672, found 167.0672. The spectral data wee in accord with those in the literature.[26]

*(2,2-Difluorocyclopropylmethyl)benzene (**2k**).* When allylbenzene was used according to the general procedure, the crude product was purified by column chromatography, with the product being isolated as a colorless liquid: NMR yield, 80% (isolated yield, 1.26 g,72%); ^{1}H NMR δ 7.30 (m, 5H), 2.87 (dd, $^2J_{HH}$ = 15.3 Hz, $^3J_{HH}$ = 8.1 Hz, 1H), 2.76 (ddd, $^2J_{HH}$ = 15.0 Hz, $^3J_{HH}$ = 6.8 Hz, J = 3.0 Hz, 1H), 1.71 (m, 1H), 1.39 (m, 1H), 0.99 (m, 1H); ^{13}C NMR, δ 139.9 (d, $^4J_{FC}$ = 1.5 Hz, Ar), 128.9 (s, Ar), 128.5 (d, $^5J_{FC}$ = 1.1 Hz, Ar), 126.7 (s, Ar), 114.6 (t, $^1J_{FC}$ = 289 Hz, CF_2), 33.1 (dd, $^3J_{FC}$ = 4.2 and 1.2 Hz, CH_2), 23.6 (dd, $^2J_{FC}$ = 11.2 and 9.7 Hz, cyclopropyl CH), 16.6 (t, $^2J_{FC}$ = 10.5 Hz, cyclopropyl CH_2); ^{19}F NMR δ −128.7 (dtt, $^2J_{FF}$ = 155 Hz, $^3J_{HF}$ = 13.2, J_{HF} = 3.6 Hz, 1F), −143.5 (ddd, $^2J_{FF}$ = 155 Hz, $^3J_{HF}$ = 13.0 Hz, J_{HF} = 3.9 Hz, 1F); IR (FT-IR, thin film), 3030.7, 2921.2, 1604.9, 1474.3, 1286.7, 1236.7, 1190.2, 1020.9, 966.5, 903.0, and 741.9 cm^{-1}; GC−MS (exact mass, DART-TOF-MS): calcd $C_{10}H_{11}F_2$, $(M + H)^+$ 169.0829, found 169.0824; calcd $C_{10}H_{10}F_2$ $(M)^+$ 168.0751, found 168.0753.

Large Scale Synthesis of 2,2-Difluorocyclopropylmethyl Benzoate (2a). A 250 mL three-necked, round-bottomed flask, equipped as described earlier with reflux condenser, rubber septum, and a large magnetic stir bar, was flame-dried under a nitrogen atmosphere. Then 17.6 g of oven-dried potassium iodide (106 mmol, 2.25 equiv) was added, and the flask allowed to cool to room temperature. A nitrogen atmosphere was maintained until the end of the reaction via a slow N_2 flow through a T-tube attached above the reflux condenser. Using a syringe, 7.64 g of allyl benzoate (47.1 mmol, 1.0 equiv), 7.0 mL of dioxane (79.7 mmol, 1.7 equiv), and 0.63 g of diglyme (4.7 mmol, 0.1 equiv) were added in that order via injection through the septum. The mixture was heated up to 115 °C (oil bath temperature). At this temperature 20.2 g of trimethylsilyl chloride (94.2 mmol, 2.0 equiv) was added, followed by addition of 18.1 g of MDFA (94.2 mmol, 2.0 equiv). For 3 days the mixture was stirred at 120 °C. After the mixture cooled to approximately 40 °C, 90 mL of diethyl ether and 90 mL of distilled water were added, and the mixture was stirred for 30 min as the reaction cooled to room temperature. The two phases were separated, and the aqueous layer was washed two times with 50 mL of diethyl ether. After drying the combined organic layers over anhydrous magnesium sulfate and filtering the mixture, the solvent was removed under reduced pressure to obtain a dark red residue. The product was isolated by column chromatography (hexanes/Et_2O, 50:1) to provide a pale yellow liquid: NMR yield, 80% (isolated yield, 7.90 g, 37.2 mmol, 79%).

■ ASSOCIATED CONTENT

Supporting Information

^{1}H, ^{13}C, and ^{19}F NMR spectra and IR spectrum of new compound **2k**; ^{1}H spectra of **2a**, **2b**, **2d**, **2f**, **2g**, **2h**, **2i**, and **2j**, and ^{19}F NMR spectra of **2c** and **2e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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