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Journal of Fluorine Chemistry 125 (2004) 459–469
JOURNAL OF FLUORINE CHEMISTRY
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Trimethylsilyl fluorosulfonyldifluoroacetate (TFDA): a new, highly efficient difluorocarbene reagent

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Received 9 October 2003; received in revised form 2 December 2003; accepted 2 December 2003

Abstract

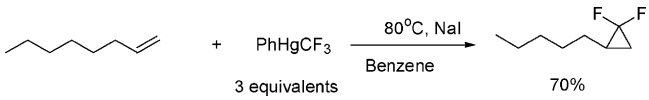
TFDA is readily prepared from the reaction of fluorosulfonyldifluoroacetic acid with trimethylsilyl chloride, and it is a very effective and efficient source of difluorocarbene for use in addition reactions to alkenes of a broad scope of reactivities. Acid-sensitive substrates may require an additional purification step involving treatment of the distilled TFDA with sufficient Et_3N to remove the acid impurity. Other trialkylsilyl fluorosulfonyldifluoroacetates can also be prepared, and they have been found to have reactivities similar to TFDA. The triethyl derivative, TEFDA is more convenient to prepare in a pure state and has similar reactivity to TFDA. Thus, it may prove to be a superior reagent.

Keywords: Trimethylsilyl fluorosulfonyldifluoroacetate; Difluorocarbene reagent; Addition reactions

1. Introduction

Fluorocyclopropanes first appeared on the chemical scene in 1952 with the inadvertent preparation of hexafluorocyclopropane by Atkinson [1], but since the advent of preparative difluorocarbene chemistry in 1960 [2], the methods for synthesis of *gem*-difluorocyclopropanes have generally involved the addition of difluorocarbene to alkenes [3–6]. Because of the interaction of the lone pairs of its two fluorine substituents with the carbene center, difluorocarbene is a relatively stabilized carbene, and it is, therefore, less reactive than other dihalocarbenes. Thus, although electron-rich alkenes react readily with $:CF_2$ under mild conditions, even modestly electron-deficient alkenes, such as 1-octene or cyclohexene, are reluctant substrates in reaction with $:CF_2$. In practice, there are only a few difluorocarbene reagents that have been found to react efficiently with such less-nucleophilic substrates.

Perhaps the best of the early $:CF_2$ reagents was Seyferth's phenyl-(trifluoromethyl)mercury reagent [7], which used in only modest excess, leads to good yields with a great variety of alkenes, including 1-octene, as in the example given below. Unfortunately, despite its excellent reactivity characteristics, Seyferth's reagent is only rarely used today, because of its toxicity and consequent lack of commercial availability. Its preparation is also both difficult and hazardous.



A second useful method for generating reactive difluorocarbene, and one that has been popular commercially, is the thermal decarboxylative elimination reaction of sodium chlorodifluoroacetate [2], which is optimally carried out at the high temperatures derived from refluxing solvents such as diglyme. The main practical problem associated with this difluorocyclopropanation procedure is the requirement that large excesses of Na^+-O_2CCF_2Cl must be used in order to obtain decent yields when using less-reactive substrates. (Note the 11 equivalents used in the example that is provided) [8].

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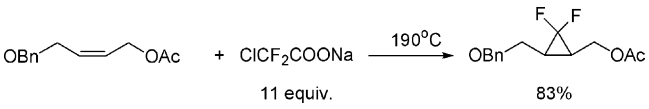
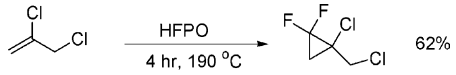
doi:10.1016/j.jfluchem.2003.12.002

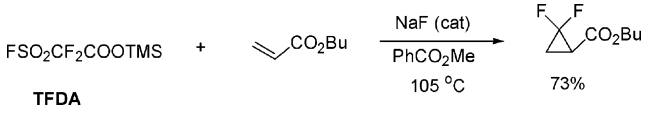


Hexafluoropropyleneoxide (HFPO) provides a third (gaseous) source of reactive :CF_2 when it is pyrolyzed in the presence of an alkene substrate at temperatures > 180 °C [9,10]. The use of this difluorocarbene precursor is, of course, limited by availability of the reagent and the fact that HFPO reactions must be carried out in an autoclave.

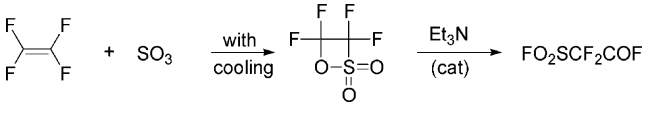


A number of other very nice difluorocarbene reagents have been developed over the years in the hope of discovering a convenient, generally useful, *room temperature* difluorocyclopropanation procedure [11–13]. However, as witnessed by the above examples of "reactive" sources of :CF_2, it has finally been recognized that *any* generally-useful difluorocarbene reagent must be capable of generating the :CF_2 at a sufficiently high temperature (>80 °C) to overcome the apparently substantial energy barrier for :CF_2 addition to all but the most reactive of alkenes.

Recently, we reported the discovery of a new difluorocarbene reagent, TFDA, that allows :CF_2 to be generated under conditions where it can add efficiently to even quite unreactive alkenes, such as acrylate esters [14,15].



TFDA, trimethylsilyl fluorosulfonyldifluoroacetate [16–18], can be conveniently prepared via the reaction of fluorosulfonyldifluoroacetic acid with trimethylsilylchloride [14,15]. The fluorosulfonyldifluoroacetic acid precursor remains expensive, but as shown below, deriving ultimately from the sultone formed by reaction of SO_3 with TFE [19], it can itself be prepared from the considerably less expensive fluorosulfonyldifluoroacetyl fluoride by treatment with water in a hydrocarbon solvent [19].



$$FO_2SCF_2COF + H_2O \xrightarrow[\text{ether}]{\text{pet}} FO_2SCF_2CO_2H$$

$$FO_2SCF_2CO_2H + Me_3SiCl \xrightarrow[\text{reflux}]{\text{neat}} \underset{\text{TFDA}}{FO_2SCF_2CO_2SiMe_3}$$

TFDA undergoes catalytic desilation with a fluoride source, followed by subsequent decarboxylation and loss of SO_2 to form :CF_2 plus F^-, which is quickly consumed via its desilative attack of another TFDA molecule. All of the products of this thermal, fluoride ion catalyzed decomposition of TFDA, other than the :CF_2 and the recycled fluoride, are lost as gases from the reaction mixture.

$$FSO_2CF_2CO_2TMS + F^- \rightarrow FSO_2CF_2CO_2^- + TMSF$$

$$FSO_2CF_2CO_2^- \rightarrow : CF_2 + CO_2 + SO_2 + F^-$$

When the reaction is carried out as prescribed, using alkene substrate neat or with a minimal amount of a sometimes specific diluent/solvent, at temperatures > 100 °C, and adding TFDA very slowly, difluorocyclopropanation can be very clean and efficient, with 2 equivalents of TFDA generally being sufficient to produce high yields with most alkenes. In this paper, we will present recent work directed at definition of the scope of use of TFDA to prepare 1,1-difluorocyclopropanes via addition of difluorocarbene to carbon–carbon double bonds [20,21].

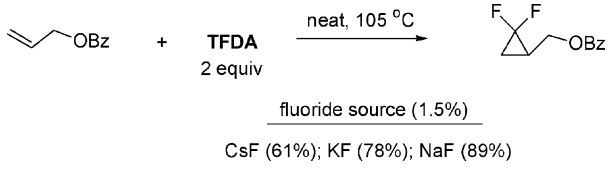
2. Results and discussion

Table 1 contains a representative list of alkenes to which this process has been successfully applied.

Experiments directed at optimization, some of which are included in Table 1, indicated that the choice of (a) diluent/solvent, (b) fluoride source, (c) temperature, and (d) rate of addition of the TFDA can strongly affect the yields of reactions with individual substrates. One thing that is apparent is that no single "recipe" can provide optimal results for all alkene substrates.

Data in Table 1 indicate clearly that choice of diluent/solvent can be of great importance in determining the outcome of TFDA reactions. For example toluene (T) diluent gives good results for the benzoate ester examples, but poor results for purely hydrocarbon substrates, whereas methyl benzoate (MB) enhances the reactivity of the hydrocarbon substrates. Although not usually being the optimal solvent, 3-pentanone (DEK), appears to be a generally useful solvent for TFDA reactions. Dilution is not generally an attribute, with minimal quantities of solvent usually proving optimal. One example to the contrary is the large scale reaction of TFDA with *n*-butyl acrylate (example: 17 equivalents) in which 200 ml of toluene (12 equivalents) is used with 20 g of substrate. The larger quantity of solvent in this case appeared to help minimize competitive polymerization of the acrylate ester.

In experiments designed to determine the best fluoride initiator (catalyst), a series of reactions of TFDA with neat allyl benzoate demonstrated that NaF is superior to both CsF and KF as an initiator. This result may actually derive from NaF's poorer solubility characteristics.



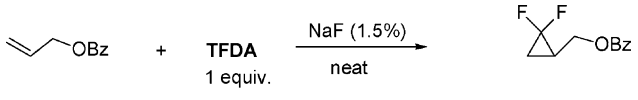
The temperature of the reaction greatly affected the efficiency of conversion of the substrate, as indicated by

Table 1
Reactions of TFDA with alkenes

Example	Alkene substrate	TFDA (equivalent)	T (°C)	Diluent[a]	Yield (%)	Refs.
1	1-Octene	2	110	0.5 MB	74	[14,22]
2		2	110	1.0 MB	63	
3		2	110	10 MB	24	
4		2	105	1.5 DEK	62	
5		2	110	Neat	0	
6	*trans*-1-Phenylpropene	2	115	1.0 T	0	[13]
7		2	120	1.0 MB	91	
8		2	120	1.0 BA	Equivalent quantity	
9		2	105	1.6 DEK	90	
10	Ethyl cinnamate	2	115	1.0 T	67	[a]
11		2	120	1.0 MB	63	
12		5	105	2.5 DEK	81	
13	Cinnamyl benzoate	2	120	1.0 T	87	[a]
14		2.5	120	1.0 MB	94	
15	Butyl acrylate	1.5	105	2.0 MB	73	[14]
16		2	105	1.75 DEK	52	[a]
17		2	110	12.0 T	55	[15]
18	Allyl benzoate	2	105	Neat	78	[14]
19	Allyl *p*-nitrobenzoate	2	97	Neat	49	[23]
20	3-Butenyl benzoate	1.5	105	Neat	89	[14,23]
21	4-Pentenyl benzoate	1.5	105	Neat	86	[14,23]
22	*trans*-2-Butenyl benzoate	2	120	Neat	76[bb]	[23]
23	3-Buten-2-yl benzoate	1.5	120	neat	66[c]	[23]
24	*trans*-Stilbene	2	105	2 DEK	36	[a]
25	1-Pentyl-1-hexenyl acetate	1.5	120	BA	92	[a]

[a] T: toluene; MB: methyl benzoate; DEK: 3-pentanone; BA: *n*-butyl acetate.
[b] Mixture of *cis:trans*: 1:9.
[c] 1:1 mixture of diastereomers.

the comparative data given below. Obviously, higher

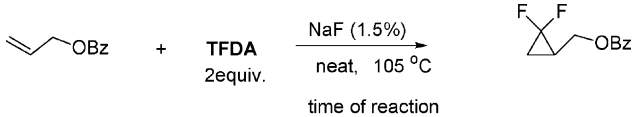


Temperature of reaction, °C

85 ° (27%); 105 ° (63%); 125 ° (75%); 145 ° (75%)

temperatures favor the addition of difluorocarbene to the relatively unreactive substrate, allyl benzoate, although there does not appear to be any advantage to using temperatures above 125 °C.

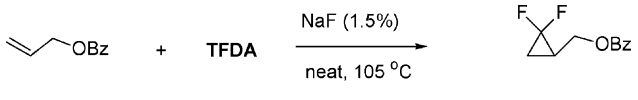
It was also shown that slow addition of the TFDA to the reaction mixture favors good cyclopropanation results.



time of reaction

1.5 h (58%); 2.6 h (83%); 4.5 h (86%)

For most substrates, 2 equivalents of TFDA were sufficient to provide optimal cyclopropanation yields, as indicated by the data below:

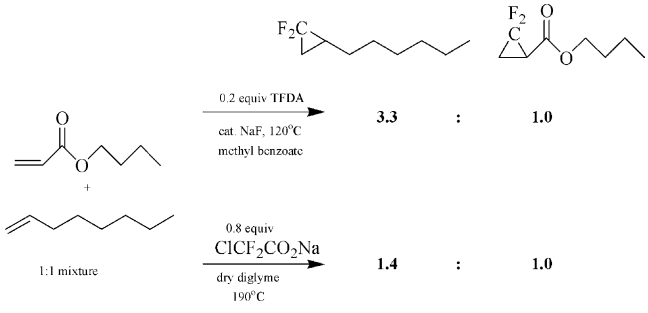


Equivalents of TFDA

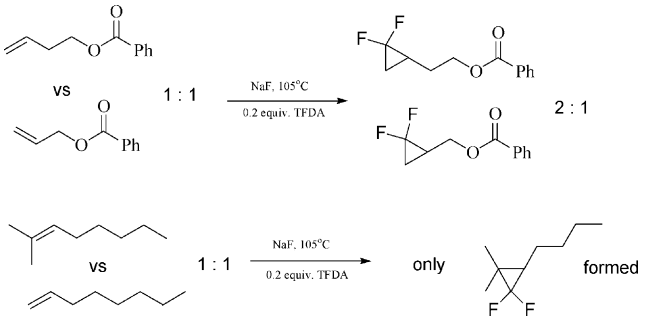
1 equiv. (63%); 1.5 equiv. (78%); 2 equiv (89%)

2.1. Comparative reactivity/selectivity of TFDA-derived difluorocarbene intermediate

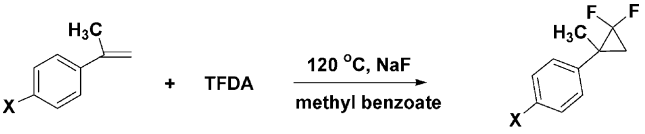
Examples of additions of difluorocarbene to substrates as electron deficient as α,β-unsaturated carbonyl compounds are few and far between [24,25]. Therefore, studies were carried out in order to obtain comparative reactivity data for this new difluorocarbene reagent. First, it was determined, in a direct competition study, that the :CF_2 generated from TFDA was not unique in adding to butyl acrylate; the :CF_2 generated from sodium chlorodifluoroacetate was also sufficiently reactive to accomplish this addition, and, considering the differences in temperature for the two experiments, the observed relative reactivities for acrylate versus 1-octene addition for the two reagents must be considered similar.



Likewise, the relative reactivities of allyl and 3-butenyl benzoate were consistent with expectations for an electrophilic carbene and exhibiting the kind of selectivities normally observed for addition of difluorocarbene [26].

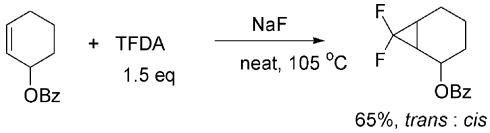


Lastly, a quantitative Hammett study of addition of $:CF_2$ generated from TFDA in its addition reactions to *p*-substituted α-methylstyrenes was carried out. As determined by a series of competition experiments, the relative reactivities of the different α-methylstyrenes were: *p*-CH_3, 1.3; H, 1.00; *p*-F, 0.84; *p*-Cl, 0.85; *p*-CF_3, 0.35. When these relative reactivities are plotted against the σ constants of the various substituents, the derived value of ρ (+0.58) can be compared favorably with that obtained (however, plotted against σ^+ values) by Moss and Mallon for the reaction of Seyferth's reagent with a series of substituted styrenes in benzene at 80 °C ($\rho = +0.57$) [27].



X = CF_3, Cl, F, H, CH_3, and OCH_3

Earlier there arose a mechanistic question as to whether the $:CF_2$ might in some manner be "delivered" by the carbonyl function in the benzoate ester substrates (presumably via a carbonyl ylide intermediate). In order to test this hypothesis, the reaction of TFDA with cyclohex-2-enyl benzoate was carried out, with the expectation that, if the $:CF_2$ were indeed delivered via the carbonyl ylide intermediate, a preference for the *cis*-product should be observed. However, no exceptional diastereoselectivity was observed in this reaction; hence there is no evidence for such exceptional mechanistic:



65%, *trans* : *cis* = 5:1

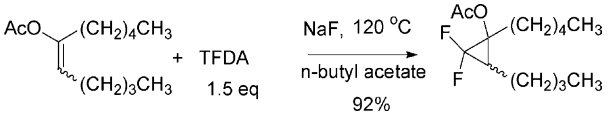
intervention in the TFDA difluorocarbene reactions. The observed 5:1 *trans*:*cis* ratio can be compared to that observed by Schlosser (9:1) using a different difluorocarbene method [28].

2.2. Limitations and cautions

2.2.1. Residual acid

Limitations with respect to the utility of the TFDA reagent appear to derive almost entirely from the presence of trace amounts of residual acid (fluorosulfonyldifluoroacetic acid) in the reagent. This strong acid can lead to destruction of acid-sensitive alkene substrates, such as enol ethers. For example, the attempted reaction of TFDA (containing less than 3% acid), under the usual conditions, with the very acid sensitive enol ether, *t*-pentyl vinyl ether, led to no observable difluorocyclopropane product.

On the other hand, enol acetates were not so sensitive to the presence of small amounts of acid, and they proved to be satisfactory alkene substrates:



2.2.2. Shelf life

TFDA is very susceptible to hydrolysis, hydrolyzing virtually immediately when added to water, and therefore its "shelf-life" is not great. Indeed, it is always best to use freshly prepared (or at least freshly distilled) TFDA in reactions. If one needs to store TFDA, it is best stored in plastic bottles in a dry box. Refrigeration is unnecessary.

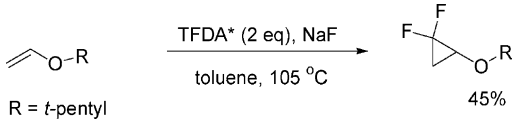
2.2.3. Skin sensitivity

Because of its ready hydrolysis back to its strong acid precursor, care should be taken to avoid all contact of TFDA with skin.

2.3. Improvement of TFDA reagent by removal of traces of acid

Although multiple redistillations of TFDA can virtually eliminate detectable amounts of acid, a more efficient and less tedious procedure for accomplishing this is to, first, determine the amount of residual acid by ^{19}F NMR, then add approximately 1 equivalent of triethylamine, filter the precipitated salt, and immediately carry on with the cyclopropanation procedure using the filtered TFDA.

Using such "acid-free" TFDA (TFDA*), the reaction with the acid-sensitive enol ethers was able to be carried out satisfactorily, as exemplified by the reaction with *t*-pentyl vinyl ether and as shown in Table 2.



R = *t*-pentyl

45%

Note the temperature sensitivity of the reaction with *n*-butyl vinyl ether. The observed higher yields at the lower temperatures may be due to the propensity of

Table 2
Cyclopropanations using TFDA* (acid free)

Vinyl enol ether CH_2–CHOR	T (°C)	Solvent	Yield (%)
R: t-pentyl	105	Toluene	45
R: n-C_4H_9	105	Toluene	Trace
	95	Toluene	36
	80	Benzene	44

difluorocyclopropyl ethers to undergo thermal decomposition, with ring opening, to form mixtures of products [3].

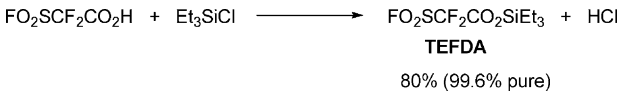
The scope and limitations of the use of acid-free TFDA* to difluorocyclopropanate acid-sensitive alkene substrates is currently being examined in detail.

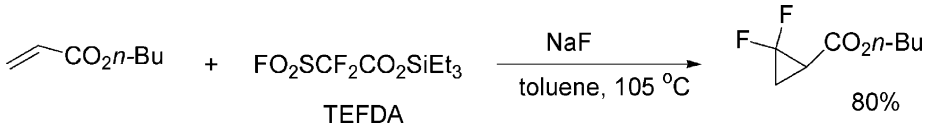
2.4. An alternative reagent, TEFDA

Hoping that use of a sterically larger trialkylsilyl group in place of trimethylsilyl might create a carbene source with improved shelf life and reactivity characteristics, a number of trialkylsilyl fluorosulfonyldifluoroacetates were prepared and tested as difluorocarbene reagents. As Tables 3 and 4 indicate, most could be prepared using procedures similar to that used for TFDA, and most of these trialkylsilyl esters proved to be satisfactory sources of :CF_2. However, none of them exhibited the superior shelf life or reactivity characteristics that had been hoped for, although the preparation of the triethyl derivative, triethylsilyl fluorosulfonyldifluoroacetate, TEFDA, proved somewhat easier than that of TFDA, and it could generally be obtained in a greater state of purity (less residual acid) after distillation. It also proved to be essentially equivalent to TFDA as a difluorocarbene source.

Table 3
Preparation of trialkylsilyl fluorosulfonyldifluoroacetates

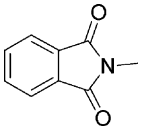
Silane used	Substrate/silane ratio	Time of reflux	Yield (%)	Acid impurity (%)
$ClSi(CH_3)_3$	1:4	12 h	80	2.0
$ClSi(CH_2CH_3)_3$	1:3	2 days	80	0.4
$ClSi(CH_3)_2CH_2CH_3$	1:2	7 days	64	3.0
$ClSi(CH_3)_2CH_2Cl$	1:2.5	4 days	69	3.3
$ClSi(CH_3)_2CH(CH_3)_2$	1:3	7 days	67	8.0
$ClSi(CH_3)_2C(CH_3)_3$	1:3	7 days	70	18.5
$ClSi(CH_3)_2Ph$	1:3	7 days	N/A	94





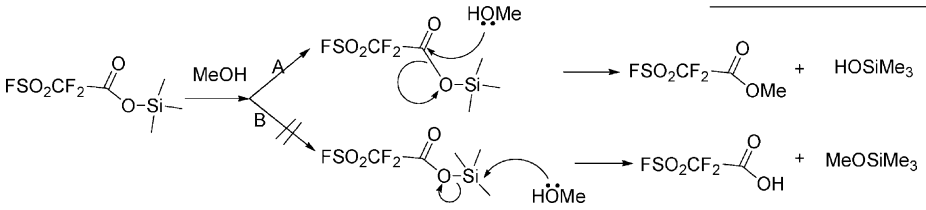
If base/moisture-induced decomposition of the trialkylsilyl esters had proceeded via attack at silicon, then one would have expected improved stability and shelf life as one placed bulkier alkyl substituents on the silicon. Since shelf life nor stability were so-enhanced, we concluded that the two α-fluorine substituents in TFDA, TEFDA, and the other trialkylsilyl esters must enhance carbonyl addition reactivity to such an extent that the mechanism of their reaction with oxynucleophiles involves C–O cleavage with attack at the carbonyl, rather than Si–O cleavage via attack at silicon.

Table 4
Syntheses of *gem*-difluorocyclopropanes using trialkylsilylfluorosulfonyldifluoroacetates

R_3Si	Alkene substituent	T (°C)	Solvent	Yield (%)
–$Si(CH_2CH_3)_3$	–$CO_2C_4H_9$	105	Toluene	80
–$Si(CH_2CH_3)_3$	–n-C_6H_{13}	105	Methylbenzoate	77[a]
–$Si(CH_3)_2CH_2CH_3$	–$CO_2C_4H_9$	105	Toluene	78
–$Si(CH_3)_2CH_2Cl$	–$CO_2C_4H_9$	105	Toluene	63
–$CH_2CH_2Si(CH_3)_3$	–$CO_2C_4H_9$	105	Toluene	64[a]
–$Si(CH_2CH_3)_3$[b]		105	Toluene	51

[a] ^{19}F NMR yield.
[b] Acid free.

This was borne out in an experiment where TEFDA was allowed to react with methanol. This reaction was shown to occur to preferentially form methyl fluorosulfonyldifluoroacetate, rather than



methoxytriethylsilane, which would have resulted from attack on silicon. Thus, it would appear that there is no advantage to the use of trialkylsilyl esters other than TFDA and TEFDA.

3. Summary

In summary, TFDA has been found to be a very effective and efficient source of difluorocarbene for use in addition reactions to alkenes of a broad scope of reactivities. For most applications, TFDA may be used without problem after purification by careful distillation, which will usually lead to the presence of up to 3–4% of residual acid impurity. In order to obtain satisfactory results, acid-sensitive substrates will usually require an additional purification step involving treatment of the distilled TFDA with sufficient Et_3N to remove the acid impurity. In spite of taking such measures to purify TFDA, there may still be substrates too sensitive to allow effective use. Further studies are ongoing to: (a) identify such substrate types, and (b) find ways to overcome the problems observed.Other trialkylsilyl fluorosulfonyldifluoroacetates can be prepared and have been found to have similar stabilities and reactivities as those of TFDA. The triethyl derivative, TEFDA is more convenient to prepare in a pure state and has similar reactivity to TFDA, and it may thus prove to be a superior reagent.

4. Experimental section

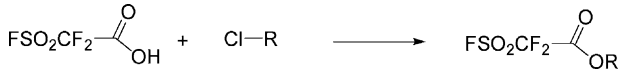
4.1. General experimental procedures

^1H, and ^{13}C NMR spectra were determined at 300 MHz (^1H), 75 MHz (^{13}C) using $CDCl_3$ as solvent, unless otherwise indicated, and tetramethylsilane as an internal standard; ^{19}F NMR spectra were measured at 282 MHz, referenced to external $CFCl_3$ in $CDCl_3$. Toluene was distilled under nitrogen immediately before use from sodium. Sodium fluoride (NaF) was dried in the oven. All other reagents and solvents were obtained from commercial sources and were used without additional purification.

4.2. Synthesis of trialkylsilyl fluorosulfonyldifluoroacetates

4.2.1. The reaction of 2-fluorosulfonyl-2,2-difluoroacetic acid with chlorosilanes general reaction set-up

Unless otherwise indicated, reactions were carried out in 25 or 50 ml three-necked, round-bottomed flasks equipped with a magnetic stirrer, an addition funnel with nitrogen (N_2) inlet, and a water-cooled condenser with gas outlet. The gas outlet was connected by Tygon tubing to an empty 500 ml backup trap, and then to an inverted glass funnel outlet positioned just above a 500 ml beaker containing 15 g of sodium bicarbonate in 100 ml water.



4.2.2. Trimethylsilyl fluorosulfonyldifluoroacetate [14–16] (TFDA) (improved synthesis)

A 1 l, three-necked, round-bottomed flask, equipped with a magnetic stirrer, addition funnel with nitrogen (N_2) inlet, and a water-cooled condenser with gas outlet was set-up. The gas outlet was connected by Tygon tubing to an empty 500 ml backup trap, and then to an inverted glass funnel outlet positioned just above a 1 l beaker, which contained 60 g of $NaHCO_3$ in 300 ml of water. The flask was charged with 204.0 g (1.15 mol) of 2-fluorosulfonyl-2,2-difluoroacetic acid, and chlorotrimethylsilane (500 g, 4.6 mol, 4 equivalents) was added dropwise, with stirring and cooling with an ice bath over a 3 h period. Upon completion of addition, the mixture was allowed to warm to RT over a 3 h period, and then the mixture was refluxed overnight. Excess chlorotrimethylsilane was then recovered by simple distillation at atmospheric pressure, and the residue was finally distilled at reduced pressure to give 230 g of TFDA (80%) (bp: 73–74 at 35 mm) as a colorless liquid. Analysis by ^{19}F NMR indicated the presence of 2.0% residual acid in the distilled product.

4.2.3. Triethylsilyl fluorosulfonyldifluoroacetate (TEFDA)

Chlorotriethylsilane (27.0 g, 179 mmol, 3.0 equivalents) is added dropwise to 2-fluorosulfonyl-2,2-difluoroacetic acid (10.5 g, 59 mmol) during 1 h at 0 °C. The mixture is allowed to warm to RT for 2 h, and is heated at 100 °C for 48 h. Then the product mixture is distilled to give triethylsilyl fluorosulfonyldifluoroacetate (13.8 g, 80%)

(bp: 108–110 °C at 25 mm) as a colorless liquid: ^{1}H NMR δ 0.84–0.97 (m, 9H), 0.98–1.06 (m, 6H); ^{13}C NMR δ 4.1, 5.8, 112.2 (dt, $J = 31.5$, 300.3 Hz), 155.1 (t, $J = 28.6$ Hz); ^{19}F NMR δ 40.39 (s, 1F), −103.41 (s, 2F).

4.2.4. Ethyldimethylsilyl fluorosulfonyldifluoroacetate

Chloroethyldimethylsilane (5.0 g, 40.7 mmol, 2.0 equivalents) is added dropwise to 2-fluorosulfonyl-2,2-difluoroacetic acid (3.6 g, 20.2 mmol) during 1 h at 0 °C. The mixture is allowed to warm to RT for 2 h, and is heated at 100 °C for 7 days. The product mixture is then distilled to give ethyldimethylsilyl fluorosulfonyldifluoroacetate (3.4 g, 64%) (bp: 89–91 °C at 38 mm): ^{19}F NMR δ 40.55(s, 1F), −103.59 (s, 2F).

4.2.5. Chloromethyldimethylsilyl fluorosulfonyldifluoroacetate

Chloro(chloromethyl)dimethylsilane (32.7 g, 228.5 mmol, 2.5 equivalents) is added dropwise to 2-fluorosulfonyl-2,2-difluoroacetic acid (16.5 g, 91 mmol) during 1 h at 0 °C. The mixture is allowed to warm to RT for 2 h, and is heated at 100 °C for 7 days. The product mixture is distilled to give chloromethyldimethylsilyl fluorosulfonyldifluoroacetate (18.0 g, 69%) (bp: 111–112 °C at 43 mm) as a colorless liquid: ^{1}H NMR δ 0.22 (s, 6H), 2.74 (s, 2H); ^{13}C NMR δ −3.9, 27.0, 112.0 (dt, $J = 32.8$, 300.9 Hz), 155.1 (t, $J = 28.0$ Hz); ^{19}F NMR δ 40.99 (s, 1F), −103.73 (s, 2F).

4.2.6. Dimethylisopropylsilyl fluorosulfonyldifluoroacetate

Chlorodimethyl isopropyl silane (5.0 g, 36.6 mmol, 3.0 equivalents) is added dropwise to 2-fluorosulfonyl-2,2-difluoroacetic acid (2.17 g, 12.2 mmol) during 1 h at 0 °C. The mixture is allowed to warm to RT for 2 h, and is heated at 110 °C for 7 days. The product mixture is distilled to give dimethylisopropylsilyl fluorosulfonyldifluoroacetate (2.27 g, 67%) (bp: 88–91 °C at 52 mm) as a colorless liquid: ^{19}F NMR δ 40.61 (s, 1F), −103.51 (s, 2F).

4.2.7. tert-Butyldimethylsilyl fluorosulfonyldifluoroacetate

tert-Butyldimethylchlorosilane (5.1 g, 33.8 mmol, 3.0 equivalents) is added dropwise to 2-fluorosulfonyl-2,2-difluoroacetic acid (2.00 g, 11.3 mmol) during 1 h at 0 °C. The mixture is allowed to warm to RT for 2 h, and is refluxed for 7 days. The product mixture is distilled to give *tert*-butyldimethylsilyl fluorosulfonyldifluoroacetate (2.31 g, 70%) (bp: 94–98 °C at 41 mm) as a colorless liquid: ^{19}F NMR δ 40.64 (s, 1F), −103.55 (s, 2F).

4.2.8. Dimethylphenylsilyl fluorosulfonyldifluoroacetate

Chlorodimethylphenylsilane (10.0 g, 58.6 mmol, 3.0 equivalents) is added dropwise to 2-fluorosulfonyl-2,2-difluoroacetic acid (3.47 g, 19.5 mmol) during 1 h at 0 °C. The mixture is allowed to warm to RT for 2 h, and is refluxed for 7 days. The ^{19}F NMR spectrum indicated that the reaction mixture still contained 94% 2-fluorosulfonyl-2,2-difluoroacetic acid, so the mixture was not distilled.

4.3. Preparation of 2-(trimethylsilyl)ethyl fluorosulfonyldifluoroacetate

2-Fluorosulfonyl-2,2-difluoroacetic acid (17.8 g, 100 mmol) is added dropwise to phosphorus pentachloride (23.0 g, 110 mmol) at 0 °C and then is allowed to warm to RT for 30 min. After the mixture is heated to 60 °C for 2 h, 2-fluorosulfonyl-2,2-difluoroacetyl chloride is obtained (18.7 g, 95%) by fractionation as a colorless liquid: ^{13}C NMR δ 111.7 (dt, $J = 33.3$, 305.0 Hz), 160.2 (t, $J = 34.2$ Hz); ^{19}F NMR δ 40.44 (s, 1F), −100.08 (s, 2F).

2-(Trimethylsilyl)ethanol (5.92 g, 50 mmol) is added dropwise to 2-fluorosulfonyl-2,2-difluoroacetyl chloride (9.83 g, 50 mmol) during 30 min at 0 °C. The mixture is allowed to warm to RT for 1 h, and is heated at 80 °C for 2 h. The product mixture is distilled to give 2-(trimethylsilyl)ethyl fluorosulfonyldifluoroacetate (5.8 g, 42%) (bp: 78–80 °C at 46 mm) as a colorless liquid (3.3% residual 2-fluorosulfonyl-2,2-difluoroacetic acid was observed by ^{19}F NMR): ^{19}F NMR δ 40.59 (s, 1F), −103.71 (s, 2F).

4.4. Synthesis of gem-difluorocyclopropanes

4.4.1. 3-(2,2-Difluorocyclopropyl)propyl benzoate [14]

A 25 ml dry two-neck round bottom flask, equipped with a magnetic stirring bar, was charged with 2.3 mg of initiator NaF and 0.900 g (4.8 mmol) of 4-pentenyl benzoate. Under N_2 and at 105 °C, 1.8 g (7.2 mmol, 1.5 equivalents) of TFDA was added slowly using a syringe pump via a Teflon® needle over a period of 5 h. (When 1.3 equivalents of TFDA was added, the conversion is 97% and after 1.5 equivalents of carbene precursor was added, no starting material remained in the reaction mixture.) Upon the completion of the addition, the reaction mixture was stirred for 20 min and cooled to room temperature and diluted with 30 ml of diethyl ether. The solution was washed with water, 5% sodium bicarbonate, water and brine and dried over sodium sulfate. The solvent was removed under reduced pressure. Purification of the products on flash column chromatography (10% diethyl ether/hexanes) provided 0.98 g of colorless liquid (yield, 86%): ^{1}H NMR δ 8.02 (2H, d, $J_d = 7.8$ Hz), 7.53 (1H, t, $J_t = 7.3$ Hz), 7.41 (2H, t, $J_t = 7.6$ Hz), 4.33 (2H, t, $J_t = 6.4$ Hz), 1.88 (2H, p, $J_p = 6.8$ Hz), 1.60 (2H, m), 1.52 (1H, m), 1.36 (1H, tdd, $J_t = 11.1$ Hz, $J_d = 7.5$ Hz, $J_d = 4.0$ Hz), 0.90 (1H, dtd, $J_d = 13.2$ Hz, $J_t = 7.1$ Hz, $J_d = 3.5$ Hz); ^{13}CNMR δ 166.4, 132.85, 130.1, 129.4, 128.3, 114.3 (t, $J_{t(F-C)} = 283.5$ Hz), 64.0, 27.9 (d, $J_{d(F-C)} = 1.5$ Hz), 23.5 (d, $J_{d(F-C)} = 3.5$ Hz, 21.9 (t, $J_{t(F-C)} = 10.6$ Hz), 16.0 (t, $J_{t(F-C)} = 10.6$ Hz); ^{19}F NMR δ −128.6 (1F, dt, $J_{d(F-F)} = 155.8$ Hz, $J_{t(F-H)} = 12.7$ Hz), −145.2 (1F, dd, $J_{d(F-F)} = 155.8$ Hz, $J_{d(F-H)} = 12.7$ Hz); HRMS (CI) calculated: $C_{13}H_{15}O_2F_2$, $(M + 1)^+$, 241.1040, found: 241.1000.

4.4.2. 2,2-Difluorocyclopropylmethyl benzoate [14]

As described above, a neat reaction with allyl benzoate, followed by purification by column chromatography (10%

diethyl ether/hexanes): Colorless liquid; ^{1}H NMR δ 8.04 (2H, m), 7.56 (1H, tt, $J_t = 7.5$ Hz, $J_t = 1.5$ Hz), 7.44 (2H, m), 4.45 (1H, dddd, $J_{d(H-H)} = 12.0$ Hz, $J_{d(H-H)} = 7.5$ Hz, $J_{d(F-H)} = 2.7$ Hz, $J_d = 1.5$ Hz), 4.29 (1H, ddd, $J_{d(H-H)} = 12.0$ Hz, $J_{d(H-H)} = 8.1$ Hz, $J_d = 1.8$ Hz), 2.08 (1H, dddt, $J_d = 13.2$ Hz, $J_d = 11.4$ Hz, $J_d = 7.8$ Hz, $J_t = 7.8$ Hz), 1.56 (1H, tdd, $J_t = 11.4$ Hz, $J_d = 7.8$ Hz, $J_d = 4.5$ Hz), 1.29 (1H, dtd, $J_d = 13.2$ Hz, $J_t = 7.8$ Hz, $J_d = 3.9$ Hz); ^{13}C NMR δ 166.4, 133.2, 129.8, 129.7, 128.4, 113.0 (t, $J_{t(C-F)} = 282.5$ Hz), 61.6 (d, $J_{d(C-F)} = 5.5$ Hz), 21.2 (t, $J_{t(C-F)} = 11.6$ Hz), 15.0 (t, $J_{t(C-F)}$ $J_{t(C-F)}$ $J_{t(C-F)} = 11.1$ Hz); ^{19}F NMR δ 129.6 (1F, ddddd, $J_{d(F-F)} = 160.0$ Hz, $J_{d(F-H)} = 13.0$ Hz, $J_{d(F-H)} = 11.6$ Hz, $J_{d(F-H)} = 4.0$ Hz, $J_{d(F-H)} = 2.5$ Hz, $J_{d(F-H)} = 0.6$ Hz), 143.8 (1F, ddddd, $J_{d(F-F)} = 160.0$ Hz, $J_{d(F-H)} = 13.3$ Hz, $J_{d(F-H)} = 4.8$ Hz, $J_{d(F-H)} = 2.0$ Hz, $J_{d(F-H)} = 0.6$ Hz); HRMS (CI) $C_{11}H_{11}O_2F_2$ $(M + 1)^+$, calculated: 213.0727, found: 213.0752.

4.4.3. 2-(2,2-Difluorocyclopropyl)ethyl benzoate [14]

As described above, a neat reaction with 3-butenyl benzoate, followed by column chromatography purification. (10% diethyl ether/hexanes). Colorless liquid. ^{1}H NMR δ 8.04 (2H, m), 7.55 (1H, m), 7.43 (2H, m), 4.39 (2H, m), 1.96 (1H, m), 1.88 (1H, m), 1.65 (1H, ddq, $J_d = 13.8$ Hz, $J_d = 11.1$ Hz, $J_q = 7.2$ Hz), 1.44 (1H, tdd, $J_t = 11.7$ Hz, $J_d = 7.8$ Hz, $J_d = 4.2$ Hz), 1.00 (1H, dtd, $J_d = 12.9$ Hz, $J_t = 7.5$ Hz, $J_d = 2.4$ Hz); ^{13}C NMR δ 166.5, 133.0, 130.1, 129.6, 128.4,113.9 (t, $J_{t(F-C)} = 283.5$ Hz), 63.7 (d, $J_{d(F-C)} = 2.0$ Hz), 26.4 (d, $J_d = 4.1$ Hz), 19.7 (t, $J_{t(F-C)} = 11.1$ Hz), 15.9 (t, $J_{t(F-C)} = 10.6$ Hz); ^{19}F NMR δ −129.4 (1F, dddtd, $J_{d(F-F)} = 155.8$ Hz, $J_{d(F-H)} = 13.8$ Hz, $J_{d(F-H)} = 12.7$ Hz, $J_{t(F-H)} = 3.7$ Hz, $J_{d(F-H)} = 1.1$ Hz), −144.3 (1F, dddt, $J_{d(F-F)} = 155.8$ Hz, $J_{d(F-H)} = 12.7$ Hz, $J_{d(F-H)} = 4.2$ Hz, $J_{t(F-H)} = 1.4$ Hz); HRMS (CI), $C_{12}H_{13}O_2F_2$ $(M + 1)^+$, calculated: 227.0884, found: 227.0889.

4.4.4. syn- and anti-7,7-difluoro-2-bicyclo[4.1.0]heptyl benzoate [28]

As described above, a neat reaction with cyclohexen-3-yl benzoate, followed by purification by column chromatography (10% diethyl ether/hexanes) resulted in a 5:1 ratio of *anti* to *syn* product (total yield, 65%): *syn* isomer, a colorless liquid; ^{1}H NMR δ 8.07 (2H, d, $J_d = 7.5$ Hz), 7.57 (1H, t, $J_t = 7.5$ Hz), 7.45 (2H, t, $J_t = 7.5$ Hz), 5.44 (1H, dtd, $J_d = 10.2$ Hz, $J_t = 6.6$ Hz, $J_d = 3.0$ Hz), 2.10 ∼ 1.86 (3H, m), 1.76 ∼ 1.18 (5H, m); ^{13}C NMR δ 166.3, 133.0, 130.3, 129.7, 128.3, 115.0 (t, $J_t = 285.1$ Hz), 67.8 (t, $J_{t(F-C)} = 2.0$ Hz), 26.7 (dd, $J_{d(F-C)} = 3.5$ Hz, $J_{d(F-C)} = 1.1$ Hz), 22.1 (t, $J_{t(F-C)} = 11.1$ Hz), 21.6 (d, $J_{d(F-C)} = 3.5$ Hz), 20.9 (dd, $J_{d(F-C)} = 12.1$ Hz, $J_{d(F-C)} = 9.1$ Hz), 15.7 (d, $J_{d(F-C)} = 2.5$ Hz); ^{19}F NMR δ −123.5 (1F, dt, $J_{d(F-F)} = 160.0$ Hz, $J_{d(F-H)} = 12.7$ Hz), −148.2 (1F, d, $J_{d(F-F)} = 160.0$ Hz); HRMS (CI), calculated: $C_{14}H_{15}O_2F_2$, $(M + 1)^+$, 253.1040, found: 253.1008.

anti isomer: ^{1}H NMR δ 8.073 (2H, dm, $J_d = 7.5$ Hz), 7.575 (1H, tt, $J_t = 7.5$ Hz), 7.451 (2H, tm, $J_t = 7.5$ Hz), 5.362 (1H, t, $J_t = 4.2$ Hz), 1.932 (1H, m), 1.84 ∼ 1.50 (6H, m), 1.401 (1H, m); ^{13}C NMR δ 165.780, 133.042, 130.297, 129.576, 128.368, 113.331 (t, $J_{t(F-C)} = 284.5$ Hz), 64.921, 26.981 (t, $J_{t(F-C)} = 2.5$ Hz), 22.474 (t, $J_{t(F-C)} = 10.9$ Hz), 18.094(t, $J_{t(F-C)} = 10.6$ Hz), 16.478, 15.917; ^{19}F NMR δ 125.994 (1F, dt, $J_{d(F-F)} = 162.3$ Hz, $J_{t(F-H)} = 15.0$ Hz), 149.677 (1F, d, $J_{d(F-F)} = 162.3$ Hz); HRMS (CI), calculated: $C_{14}H_{15}O_2F_2$, $(M + 1)^+$, 253.1040, found: 253.1039.

4.4.5. Ethyl trans-3-phenyl-2,2-difluorocyclopropylcarboxylate

As described above, reaction of ethyl cinnamate in 2.5 equivalents 3-pentanone solvent, using 2 equivalents of TFDA with the reaction temperature being 105 °C (yield, 81%): ^{1}H NMR δ 1.33 (t, $J = 7.4$ Hz, 3H), 2.75 (m, 1H), 3.50 (m, 1H), 4.3 (q, $J = 7.4$ Hz, 2H), 7.30 (m, 5H); ^{19}F NMR, δ −133.5 (dd, $J = 151.4$ and 14.9 Hz), −134.6 (dd, $J = 151.4$ and 12.7 Hz). HRMS (M^+): calculated for $C_{12}H_{12}O_2F_2$: 226.0805; found: 226.0816.

4.4.6. trans-1,1-Difluoro-2-methyl-3-phenylcyclopropane

As described above, reaction of *trans*-1-phenylpropene in 2.5 equivalents 3-pentanone solvent, using 2 equivalents of TFDA with the reaction temperature being 105 °C (yield, 90%): ^{1}H NMR, δ 1.40 (m, 3H), 1.90 (m, 1H), 2.35 (m, 1H), 7.5 (m, 5H); ^{19}F NMR, δ −137.7 (dd, $J = 153.4$ and 12.8 Hz), −138.7 (dd, $J = 153.4$ and 12.8 Hz) (Table 5).

4.4.7. trans-2,2-Difluoro-3-phenylcyclopropylmethyl benzoate

As described above, reaction of *trans*-cinnamyl benzoate in 1 equivalent methyl benzoate solvent, using 2 equivalents of TFDA with the reaction temperature being 120 °C (yield, 94%): ^{1}H NMR, δ 2.43 (m, 1H), 2.80 (m, 1H), 4.60 (m, 2H), 7.5 (m, 10H); ^{19}F NMR, δ −135.6 (dd, $J = 157.9$ and 13.8 Hz), −137.4 (dd, $J = 157.9$ and 13.8 Hz); HRMS (M^+): calculated for $C_{17}H_{14}O_2F_2$: 288.0962; found: 288.0971.

4.4.8. trans-1,1-Difluoro-2-bromomethyl-3-phenylcyclopropane

As described above, reaction of *trans*-cinnamyl benzoate in 1 equivalent methyl benzoate solvent, using 2 equivalents of TFDA with the reaction temperature being 120 °C (yield, 32%): ^{1}H NMR, δ 7.25 (m, 5H), 3.68 (m, 1H), 3.54 (m, 1H), 2.63 (m, 1H), 2.34 (m, 1H); ^{13}C NMR, δ 132.6, 128.9, 128.5, 127.9, 35.4 (t, $J = 11$ Hz), 32.2 (t, $J = 11$ Hz), 28.26; ^{19}F NMR, δ −134.5 (dd, $J = 158$ and 12 Hz), −136.8 (dd, $J = 158$ and 12 Hz); HRMS (M^+): calculated for $C_{10}H_{10}BrF_2$: 246.9934, found: 246.9937.

4.4.9. trans-1,1-Difluoro-2,3-diphenylcyclopropane

As described above, reaction of *trans*-stilbene in 2.5 equivalents 3-pentanone solvent, using 2 equivalents of TFDA with the reaction temperature being 105 °C (yield,

Table 5
Summary of ^{19}F NMR data for 1,1-difluorocyclopropane products

R_1	R_2	R_3	R_4	δ (ppm)	J_{AB} (Hz)	Ref.
H	H	H	*n*-C_6H_{13}	−128.4, −145.0	155	[22]
CH_3	H	H	Ph	−137.8, −138.7	152.3	[13]
Ph	H	H	CO_2Et	−133.4, −134.6	151.4	[a]
H	H	H	$CO_2{}^nBu$	−126.5, −141.7	154	[15]
Ph	H	H	CH_2O_2CPh	−135.6, −137.4	157.9	[a]
Ph	H	H	CH_2Br	−134.5, −136.8	158	[a]
H	H	H	CH_2O_2CPh	−129.6, −143.8	160.0	[a]
H	H	H	CH_2O_2CPh-*p*-NO_2	−129.8, −143.7	161.1	[23]
H	H	H	$(CH_2)_2O_2CPh$	−129.4, −144.3	155.8	[23]
H	H	H	$(CH_2)_3O_2CPh$	−128.6, −145.2	155.8	[23]
CH_3	H	H	CH_2O_2CPh	*cis*: −126.0, −153.7	160.2	[23]
				trans: −140.3, −141.5	160.0	[23]
H	H	H	$CH(CH_3)O_2CPh$	(a) −127.7, −142.4	162	[23]
				(b) −129.0, −144.3	162	[23]
H	H	H	O-*n*-Bu	−131.8, −149.5	164.5	[a]
H	H	H	O-*t*-pentyl	−131.8, −146.3	163.3	[a]
H	H	H	Phthalimidyl	−134.0, −142.7	163.3	[a]
Ph	H	H	Ph	*trans*: 134.5	–	[a]

[a] This work.

36%): ^1H NMR, δ 3.05 (t, 2H), 7.35 (m, 10H); ^{19}F NMR, δ −134.5 (t, $J = 8.5$ Hz).

4.5. General procedure for preparation of 1,1-difluoro-2-methyl-2-p-X-phenylcyclopropanes (for Hammett study)

The reactions were carried out as described above, except that 1 equivalent of methyl benzoate was added as solvent, 2 equivalents of TFDA were used, and the reaction was carried out at 120 °C. The yields reported are NMR yields, using trifluoromethylbenzene as an internal standard.

- $X = Cl$: 89% yield; ^{19}F NMR δ −136.4 (dd, $^2J_{F,F}$= 149.5 Hz, $^3J_{H,F}$= 12.1 Hz, 1F), −138.1 (dd, $^2J_{F,F}$= 149.5 Hz, $^3J_{H,F}$ = 12.1 Hz, 1F).
- $X = CH_3$: 60% yield; ^{19}F NMR δ −136.9 (dd, $^2J_{F,F}$ = 149.5 Hz, $^3J_{H,F}$ = 12.1 Hz, 1F), −138.0 (dd, $^2J_{F,F}$ = 149.5 Hz, $^3J_{H,F}$ = 12.1 Hz, 1F).
- $X = CF_3$: 34% yield; ^{19}F NMR δ −62.8 (s, 3F), −132.2 (dd, $^2J_{F,F}$ = 149.2 Hz, $^3J_{H,F}$ = 12.7 Hz, 1F), −136.0 (dd, $^2J_{F,F}$ = 149.2 Hz, $^3J_{H,F}$ = 12.7 Hz, 1F).
- $X = F$: 55% yield; ^{19}F NMR δ −132.7 (dd, $^2J_{F,F}$ = 151.2 Hz, $^3J_{H,F}$ = 13.8 Hz, 1F), −137.9 (dd, $^2J_{F,F}$ = 151.2 Hz, $^3J_{H,F}$ = 12.1 Hz, 1F).
- $X = H$: 85% yield; ^{19}F NMR δ −132.8 (dd, $^2J_{F,F}$ = 149.5 Hz, $^3J_{H,F}$ = 15.2 Hz, 1F), −137.8 (dd, $^2J_{F,F}$ = 149.5 Hz, $^3J_{H,F}$ = 12.1 Hz, 1F).

4.5.1. Procedure for the Hammett Study

The binary mixture of two different *p*-substituted α-methylstyrenes (equimolar, 1.1 mmol) in methyl benzoate (2 equivalents, 300 mg, 2.2 mmol) with 3 mg of NaF was stirred under N_2 and heated to 100 °C. Then 0.2 equivalent of TFDA was added slowly to the mixture at 100 °C and the mixture maintained at 100 °C for one additional hour. After the mixture was cooled to RT, trifluoromethylbenzene was added as an internal standard, and the ratio of products determined by ^{19}F NMR. On the basis of the ratios that were obtained, the following relative reactivities were obtained: CH_3 (1.3), H (1), F (0.84), Cl (0.85), CF_3 (0.35). A plot of the log of these relative reactivities versus σ_p resulted in Fig. 1.

4.6. General procedure for preparation of n-butyl 2,2-difluorocyclopropanecarboxylate [14,15]

A 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 toluene, sodium fluoride (0.06 equivalent) and *n*-butyl acrylate. The solution was heated to reflux and slow N_2 bubbling was initiated for 1 h. The appropriate trialkylsilyl fluorosulfonyldifluoroacetate (1.5–1.6 equivalents) was added dropwise, and the mixture was heated

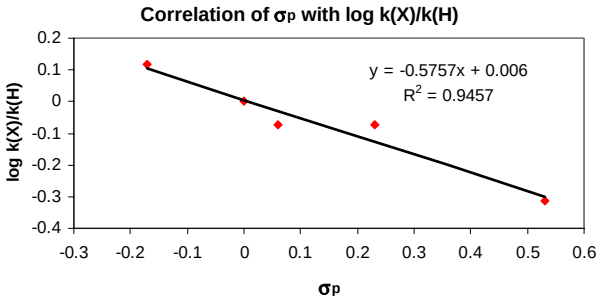


Fig. 1. Hammett plot for difluorocyclopropanation of *p*-substituted α-methylstyrenes.

overnight. Toluene was removed by simple distillation at atmospheric pressure, and the residue distilled at reduced pressure to obtain *n*-butyl 2,2-difluorcyclopropanecarboxylate: bp 93–95 °C at 50 mm; a colorless liquid; ^{1}H NMR δ 0.88 (t, $J = 7.4$ Hz, 1H), 1.26–1.42 (m, 1H), 1.50–1.69 (m, 3H), 1.89–2.02 (m, 1H), 2.27–2.43 (m, 1H), 4.08 (t, $J = 6.6$ Hz, 1H); ^{13}C NMR δ 13.4, 16.2 (t, $J = 11.1$ Hz), 18.9, 25.5 (t, $J = 11.1$ Hz), 30.4, 65.2, 110.6 (dd, $J = 283.0$, 288.1 Hz), 166.5; ^{19}F NMR δ −126.6 (dm, $J = 152.6$ Hz, 1F), −141.3 (dm, $J = 152.6$ Hz, 1F).

4.6.1. Using ethyldimethylsilyl fluorosulfonyldifluoroacetate

The flask was charged with dry toluene (6.4 ml), NaF (12.6 mg, 0.06 equivalent) and *n*-butyl acrylate (0.64 g, 5.0 mmol). Ethyldimethylsilyl fluorosulfonyldifluoroacetate (2.0 g, 7.5 mmol) was added, and the above procedure followed to give 0.69 g of *n*-butyl 2,2-difluorocyclopropanecarboxylate (78%).

4.6.2. Using chloromethyldimethylsilyl fluorosulfonyldifluoroacetate

The flask was charged with dry toluene (12.8 ml), NaF (25.2 mg, 0.06 equivalent), *n*-butyl acrylate (1.28 g, 10.0 mmol), and chloromethyldimethylsilyl fluorosulfonyldifluoroacetate (4.55 g, 16.0 mmol, 1.6 equivalents) added, and the above procedure followed to give 1.12 g of *n*-butyl 2,2-difluorocyclopropanecarboxylate (63%).

4.6.3. Using triethylsilyl fluorosulfonyldifluoroacetate (TEFDA)

The flask was charged with dry toluene (6.4 ml), NaF (12.6 mg, 0.06 equivalent) and *n*-butyl acrylate (0.64 g, 5.0 mmol). Triethylsilyl fluorosulfonyldifluoroacetate (TEFDA) (2.2 g, 7.5 mmol, 1.5 equivalents) was added. *n*-Butyl 2,2-difluorcyclopropanecarboxylate was obtained (0.70 g, 80%).

4.6.4. Using 2-(trimethylsilyl)ethyl fluorosulfonyldifluoroacetate

A two-neck round bottom was charged dry toluene (1.2 ml), NaF (2.5 mg, 0.06 equivalent) and *n*-butyl acrylate (0.13 g, 1.0 mmol). Then 2-(trimethylsilyl)ethyl fluorosulfonyldifluoroacetate (0.56 g, 2.0 mmol, 2.0 equivalents) in a plastic syringe was added dropwise via a Teflon needle at the rate of 0.4 ml/h (controlled by syringe pump). The reaction mixture was heated at 105 °C overnight and then cooled to RT. An amount of 35.0 mg of trifluorotoluene was added as a internal standard. ^{19}F NMR indicated that 64% of *n*-butyl 2,2-difluorocyclopropanecarboxylate was obtained.

4.6.5. 1,1-Difluoro-2-hexylcyclopropane

A two-neck round bottomed flask was charged with methyl benzoate (0.06 ml, 0.5 equivalent), sodium fluoride (2.5 mg, 0.06 equivalent) and 1-octene (0.16 ml, 1.0 mmol). Then triethylsilyl fluorosulfonyldifluoroacetate (0.44 g, 1.5 mmol, 1.5 equivalents) in a plastic syringe was added dropwise via a Teflon needle at the rate of 0.25 ml/h (controlled by syringe pump). The reaction mixture was heated at 105 °C overnight and then cooled to RT. An amount of 36.0 mg of trifluorotoluene was added as a internal standard. ^{19}F NMR indicated that 1,1-difluoro-2-hexylcyclopropane was obtained (77%): ^{19}F NMR δ −128.5 (dm, J = 155.6 Hz, 1F), −142.5 (dm, $J = 155.6$ Hz, 1F).

4.6.6. N-(2,2-Difluorocyclopropyl)phthalimide

A three-neck round bottomed flask bearing a reflux condenser with N_2 inlet was charged with dry toluene (1.2 ml), sodium fluoride (2.6 mg, 0.06 equivalent) and *N*-vinylphthalimide (0.17 g, 1.0 mmol). The mixture was heated in a 105 °C oil bath for 1 h. Fresh TEFDA (0.6 g, 2 mmol, 2.0 equivalents) (free of acid according to ^{19}F NMR) was added slowly using a syringe with a Teflon needle at the rate of 0.30 ml/h. After 3 h, an additional amount of fresh TEFDA (0.3 g, 1 mmol) was added to achieve complete conversion. The reaction mixture was heated at 105 °C overnight. After the solvent was removed under reduced pressure, the residue was purified by column chromatography on silica gel (hexanes/AcOEt: 10/1) to give *N*-(2,2-difluorocyclopropyl)phthalimide (0.115 g, 51%) as white solid: mp 150–152 °C; ^{1}H NMR δ 2.02–2.24 (m, 2H), 3.22–3.32 (m, 1H), 7.72–7.79 (m, 2H), 7.84–7.92 (m, 2H); ^{13}C NMR δ 16.6 (t, $J = 11.2$ Hz), 28.4 (m), 109.3 (dd, $J = 283.4$, 286.4 Hz), 123.6, 131.6, 134.4, 167.6; ^{19}F NMR δ −134.0 (dm, $J = 163.3$ Hz, 1F), −142.7 (dm, $J = 163.3$ Hz, 1F); analytically calculated for $C_{11}H_7F_2NO_2$: C, 59.20; H, 3.16; N, 6.28; Found: C, 59.04; H, 3.03; N, 6.08.

4.7. Procedure for removal of traces of acid from trialkylsilyl fluorosulfonyldifluoroacetates

A 10 ml, one-necked, round-bottomed flask equipped with a magnetic stirrer and a nitrogen (N_2) inlet was used. The flask was charged with 3.0 g of TFDA that contained 3.6% 2-fluorosulfonyl-2,2-difluoroacetic acid according to its ^{19}F NMR spectrum. Triethylamine (60.0 μl, 0.43 mmol) (1.0 equivalent 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 pipette with some cotton to obtain a colorless liquid. No residual 2-fluorosulfonyl-2,2-difluoroacetic acid could be observed by ^{19}FNMR after this treatment.

4.7.1. 2,2-Difluorocyclopropyl tert-pentyl ether

A three-neck round bottomed flask bearing a reflux condenser and N_2 inlet was charged with dry toluene (6.0 ml), sodium fluoride (12.6 mg, 0.06 equivalent) and *tert*-pentyl vinyl ether (0.73 ml, 5.0 mmol). The mixture was heated in a 105 °C oil bath. TFDA (2.5 g, 10 mmol, 2.0 equivalents) (treated as described above by Et_3N) was added slowly using a syringe with a Teflon needle at the rate of 0.4 ml/h. After

the addition was complete, the reaction mixture was heated at 105 °C for 3 h. The residue was then distilled at reduced pressure to obtain 2,2-difluorocyclopropyl *tert*-pentyl ether (containing toluene) (bp, 65–70 °C; 230 mm) (purity, 19.3% in toluene; yield, 45%) as a colorless liquid: ^{1}H NMR δ 1.29 (t, $J = 7.4$ Hz, 3H), 1.59 (s, 3H), 1.60 (s, 3H), 1.62–1.76 (m, 1H), 1.78–2.20 (m, 3H), 3.81–3.91 (m, 1H); ^{13}C NMR δ 8.3, 18.1 (t, $J = 11.1$ Hz), 24.7 (d, $J = 1.1$ Hz), 24.9, 33.3, 50.9(m), 111.2 (dd, $J = 289.1$, 292.2 Hz); ^{19}F NMR δ −131.81 (dm, $J = 163.3$ Hz, 1F), −146.34 (dm, $J = 163.3$ Hz, 1F).

4.7.2. N-Butyl-2,2-difluorocyclopropyl ether

A three-necked, round bottomed flask bearing a reflux condenser and N_2 inlet was charged with dry toluene (6.4 ml), sodium fluoride (12.6 mg, 0.06 equivalent) and *n*-butyl vinyl ether (distilled) (0.65 ml, 5.0 mmol). The mixture was heated in a 95 °C oil bath. TFDA (2.5 g, 10 mmol, 2.0 equivalents) (treated as described above by Et_3N) was added slowly using a syringe with a Teflon needle at the rate of 0.4 ml/h. The reaction mixture was heated at 95 °C for 4 h, and the residue then distilled at atmospheric pressure to obtain *n*-butyl-2,2-difluorcyclopropyl ether in toluene (yield, 36%) as a colorless liquid: ^{1}H NMR δ 1.14 (t, $J = 7.3$ Hz, 3H), 1.50–1.68 (m, 4H), 1.72–1.84 (m, 2H), 3.66–3.79 (m, 3H); ^{13}C NMR δ 13.7, 17.9 (t, $J = 10.6$ Hz), 19.1, 31.4, 56.8 (m), 71.4 (d, $J = 2.0$ Hz) 111.4 (dd, $J = 289.1$, 290.6 Hz); ^{19}F NMR δ −131.81 (dm, $J = 164.8$ Hz, 1F), −149.52 (dm, $J = 164.8$ Hz, 1F).

If the reaction mixture was heated at 105 °C, only a trace of product was observed by ^{19}F NMR.

When the reaction was carried out identically as above, but in refluxing dry benzene (6.4 ml), 0.47 g of 9 h was obtained (purity, 70%; yield, 44%).

4.8. The reaction of TFDA with methanol

A three-necked, round-bottomed flask was equipped with a magnetic stirrer, addition funnel, and water-cooled condenser with a nitrogen (N_2) inlet. The flask was charged with TFDA (12.5 g, 50 mmol), and the solution stirred at 0 °C. Methanol (1.6 g, 50 mmol) was added dropwise, the mixture allowed to warm to room temperature for 2 h, and then refluxed overnight. The product mixture was distilled at atmospheric pressure to give 4.5 g, (100%) hydroxytrimethylsilane (bp: 99–101 °C; literature, 100 °C): ^{1}H NMR (acetone-d_6) δ 0.09 (s); ^{13}C NMR (acetone-d_6) δ 2.1. The residue was distilled at reduced pressure to methyl fluorosulfonyldifluoroacetate (3.6 g, 80%) (bp: 76–80 °C at 200 mm) as a colorless liquid. ^{1}H NMR (acetone-d_6) δ 4.16 (s, 3H); ^{13}C NMR (acetone-d_6) δ 56.9, 113.4 (td, $J = 298.7$, 33.2 Hz), 157.7 (t, $J = 24.8$ Hz); ^{19}F NMR (acetone-d_6) δ 40.58 (t, $J = 6.1$ Hz, 1F), −103.41 (d, $J = 6.1$ Hz, 1F).

Acknowledgements

The support of this work in part by the National Science Foundation (CHE-9982587 and CHE-0239884) and by an NSF-REU grant to the University of Florida is gratefully acknowledged.

References

[1] B. Atkinson, D. McKeagan, Chem. Commun. (1966) 189–190.
[2] J.M. Birchall, G.E. Cross, R.N. Haszeldine, Proc. Chem. Soc. (1960) 81–81.
[3] W.R. Dolbier Jr., M.A. Battiste, Chem. Rev. 103 (2003) 1071–1098.
[4] D.J. Burton, J.L. Hahnfeld, in: P. Tarrant (Ed.), Fluorine Chemistry Reviews, Marcel Dekker, Inc., New York, 1977, pp. 119–188.
[5] D.L.S. Brahms, W.P. Dailey, Chem. Rev. 96 (1996) 1585–1632.
[6] M.H. Rock, in: Houben-Weyl, Methods of Organic Chemistry Thieme, Stuttgart, Verlag, 1999, pp. 498–505.
[7] D. Seyferth, S.P. Hopper, J. Org. Chem. 37 (1972) 4070–4075.
[8] R. Csuk, L. Eversmann, Tetrahedron 54 (1998) 6445–6456.
[9] P.B. Sargeant, J. Org. Chem. 35 (1970) 678.
[10] W.R. Dolbier Jr., S.F. Sellers, B.H. Al-Sader, T.H. Fielder, S. Elsheimer, B.E. Smart, Israel J. Chem. 21 (1981) 176–184.
[11] D.J. Burton, D.G. Naae, J. Am. Chem. Soc. 95 (1973) 8467–8468.
[12] Y. Bessard, U. Muller, M. Schlosser, Tetrahedron 46 (1990) 5213–5221.
[13] W.R. Dolbier Jr., H. Wojtowicz, C.R. Burkholder, J. Org. Chem. 55 (1990) 5420–5422.
[14] F. Tian, V. Kruger, O. Bautista, J.-X. Duan, A.-R. Li, W.R. Dolbier Jr., Q.-Y. Chen, Org. Lett. 2 (2000) 563–564.
[15] W.R. Dolbier Jr., J.-X. Duan, F. Tian, Q.-Y. Chen, Org. Synth. 80 (2003) 172–176.
[16] Originally reported by: R.J. Terjeson, J. Mohtasham, D.H. Peyton, G.L. Gard, J. Fluorine Chem. 42 (1989) 187–200.
[17] W. Xu, Q.-Y. Chen, J. Org. Chem. 67 (2002) 9421–9427.
[18] W. Xu, Q.-Y. Chen, Org. Biomol. Chem. 1 (2003) 1151–1156.
[19] D.C. England, M.A. Dietrich, R.V. Lindsey, J. Am. Chem. Soc. 82 (1960) 6181–6188.
[20] Feng Tian, Taken in part from the Ph.D. Dissertation, University of Florida, Florida, 1999.
[21] J. Marshall Baker, Taken in part from the Ph.D. Dissertation, University of Florida, Florida, 2002.
[22] B. Erni, H.G. Khorana, J. Am. Chem. Soc. 102 (1980) 3888–3896.
[23] M.A. Battiste, F. Tian, J.M. Baker, O. Battista, J. Villalobos, W.R. Dolbier Jr., J. Fluorine Chem. 119 (2003) 39–51.
[24] C. Beard, N.H. Dyson, J.H. Fried, Tetrahedron Lett. 28 (1966) 3281–3286.
[25] D.C. England, L. Solomon, C.G. Krespan, J. Fluorine Chem. 3 (1973) 63–89.
[26] R.A. Moss, in: M. Jones Jr., R.A. Moss (Eds.), Carbenes, John Wiley & Sons, New York, 1973, pp. 153–304.
[27] R.A. Moss, C.B. Mallon, J. Am. Chem. Soc. 97 (1975) 344–347.
[28] M. Schlosser, Y. Bessard, Tetrahedron 46 (1990) 5222–5229.