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Reactivity and regiochemical behavior in the solvolysis reactions of (2,2-difluorocyclopropyl)methyl tosylates

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Dedicated to Professor Tatlow on the occasion of his 80th birthday.

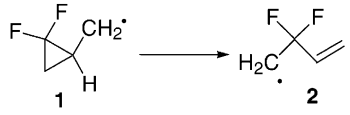
Abstract

The rate constants for acetolysis of (2,2-difluorocyclopropyl)methyl tosylate, and (2,2-difluoro-3-methylcyclopropyl)methyl tosylate at 92 °C and of 1-(2,2-difluorocyclopropyl)ethyl tosylate at 42 °C are reported and the reactivities and regiochemistries of ring opening of these systems are discussed and compared with expectations based on computational results. The results are discussed in terms of the use of (2,2-difluorocyclopropyl)methyl systems as mechanistic probes.

Keywords: (2,2-Difluorocyclopropyl)methyl radical and cation; Solvolysis; Kinetics; DFT calculations

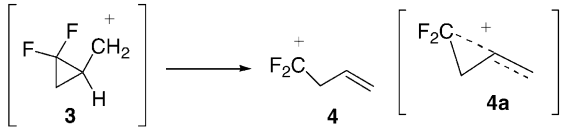
1. Introduction

The (2,2-difluorocyclopropyl)methyl radical, **1**, undergoes an extraordinarily fast, regiospecific unimolecular ring opening distal to the geminal fluorine substituents to form the 2,2-difluorobut-3-en-1-yl radical, **2** [1]. Its calculated activation barrier of 1.9 kcal/mol and estimated rate constant of 1.5×10^{11} s^{-1} at 25 °C qualifies this system as a "hypersensitive" probe of reactions involving radicals as intermediates [2]. As demonstrated by the extensive work of Newcomb and Chestney [3], a radical probe is made much more valuable if it can, by virtue of differences in regiochemistry, distinguish between a radical and a carbocation intermediate.



1 2

Because β-fluorine substituents destabilize carbocations [4], whereas α-fluorines are stabilizing [5], it appeared likely to us that reactions involving the (2,2-difluorocyclopropyl)-methyl cation, **3**, would undergo rearrangement via regiospecific cleavage of the *proximal* bond to form products ostensibly derived from the 1,1-difluorobut-3-en-1-yl cation, **4**. This intuitive prediction received support from preliminary DFT calculations that indicated a regiospecific conversion of **3** to a homoallylic, stabilized version of **4**, i.e. a highly unsymmetrical homoallylic cation (**4a**), with virtually no activation barrier [2].



3 4 4a

In a preliminary communication, we reported experimental, solvolytic results that confirmed this prediction for the parent (2,2-difluorocyclopropyl)methyl system [6], but the question remained regarding the degree to which alkyl substituents at the third position would modify the regioselective proximal cleavage in favor of distal cleavage. To the extent that distal cleavage prevailed, this would, of course, diminish the usefulness of the (2,2-difluorocyclopropyl)methyl system as a probe capable of distinguishing cationic from radical intermediates. A previous study of tosylate **5** by Schlosser and coworkers [7] demonstrated that the presence of two methyls at the third position induces virtually exclusive distal cleavage. In this paper, the kinetic and regiochemical impact of a single 3-methyl substituent

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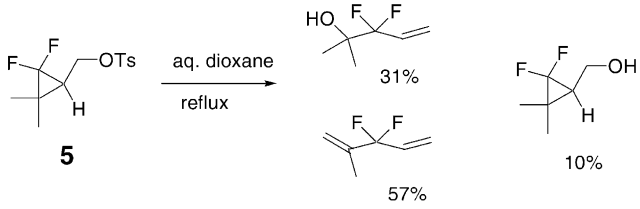
will be reported, along with additional pertinent experimental and computational results.

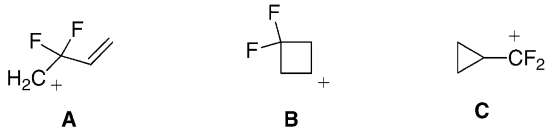


2. Results and discussion

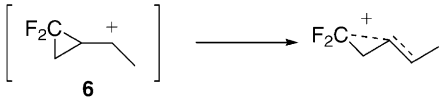
2.1. Computational results

Calculations were carried out attempting to locate the (2,2-difluorocyclopropyl)methyl cation on the potential energy surface at HF/6-31G(d), MP2/6-31G(d) and B3LYP/6-31G(d) levels of theory. However, in all the cases, the geometry optimizations starting from the (2,2-difluorocyclopropyl)methyl cation (**3**) structure all resulted in the optimized homoallylic, 1,1-difluorobut-3-en-1-yl cation (**4a**). The B3LYP/6-31G(d) optimized geometry of homoallylic cation (**4a**) is depicted in Fig. 1. The planar geometry of the CF_2^+ site of **4a**, and its unusually short C–F bonds (1.272 Å) are consistent with stabilization of the carbocation by its fluorine substituents. The 1.340 Å C–C bond indicated a fully characterized double bond. The Mulliken charge of the CF_2 group is +0.55, and that of the CH_2 at the original carbinyl position is +0.21.

The attempt to locate the 2,2-difluorobut-3-en-1-yl cation (**A**) also ended up as the 1,1-difluorobut-3-en-1-yl cation. These results indicate that on the potential energy surface, the (2,2-difluorocyclopropyl)methyl cation, at least in the gas phase, is not a minimum, and also that there are no saddle points connecting the (2,2-difluorocyclopropyl)-methyl to the 1,1-difluorobut-3-en-1-yl cation; thus there is no activation barrier for this transformation. Another possible cation, the 3,3-difluorocyclobutyl cation (**B**), was located, but it is 17.8 kcal/mol higher in energy than homoallylic cation **4a**. The most stable cation of the formula $C_4H_5F_2^+$ (**C**) that of (cyclopropyl)difluoromethyl cation was located and is 8.4 kcal/mol more stable than **4a**. However, because the bridged bicyclobutonium ion, which is the intermediate required for the scramble, was not located, it is unlikely that (**C**) would be formed from **4a**.



The secondary cation (**6**) with a methyl group at the α-position of the (2,2-difluorocyclopropyl)methyl system behaved identically to (**3**) at both the HF/6-31G(d) and B3LYP/6-32G(d) levels of theory. The structure of the ring-opened cation has been depicted in Fig. 3.



When the methyl substituent is at the third position on the ring (**7**), preliminary calculations indicated that the regiochemistry of the ring opening might well be altered. At HF/6-31G(d) level of theory, the geometry optimization starting from the ring closed primary cation ended up with the cation observed by the lengthening of C–C bond distal to the CF_2 group (Fig. 2). The distance of C_2–C_3 is 2.03 Å. This is not a

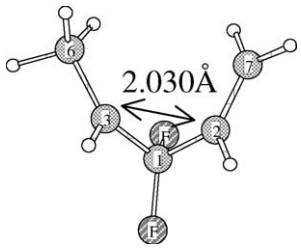


Fig. 2. Calculated structure of (2,2-difluoro-3-methylcyclopropyl)methyl cation (**7**) (HF/6-31G(d) level of theory).

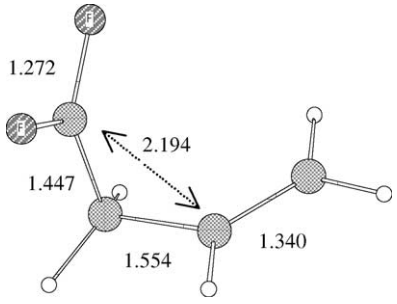


Fig. 1. B3LYP/6-31G(d) optimized structure of the homoallylic, 1,1-difluorobut-3-en-1-yl cation (**4a**). Distance is in Å.

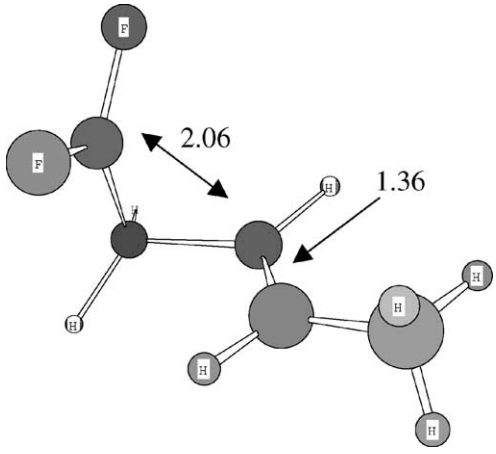
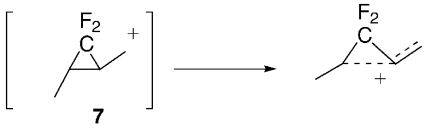


Fig. 3. Optimized structure for 1,1-difluoropent-3-en-1-yl cation (**6**) UB3LYP/6-311+G(2df, sp)//B3LYP/6-32G(d).

well-defined ring-opened cation, more likely being a delocalized cation.



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On the other hand, when this cation was optimized using the DFT method at the UB3LYP/6-311+G(2df, sp)//B3LYP/6-32G(d) level of theory, the carbocation optimized to give the CF_2-based, 1,1-difluoro-2-methylbut-3-en-1-yl cation (**8**) as depicted in Fig. 4. Without undertaking transition state calculations for this system, the results must be considered ambiguous regarding kinetic control, but would seem to predict that the CF_2-based cation is more stable for this system as well as the other two.

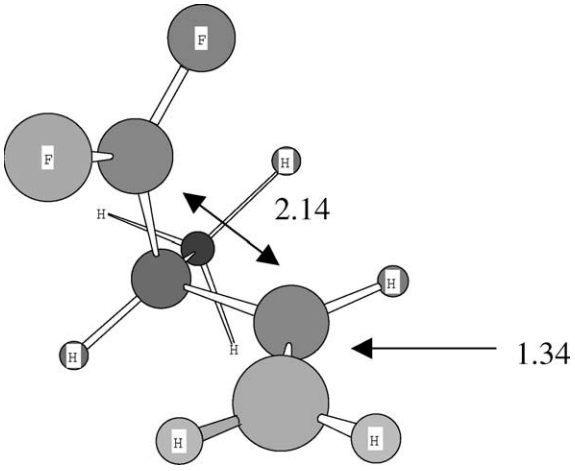
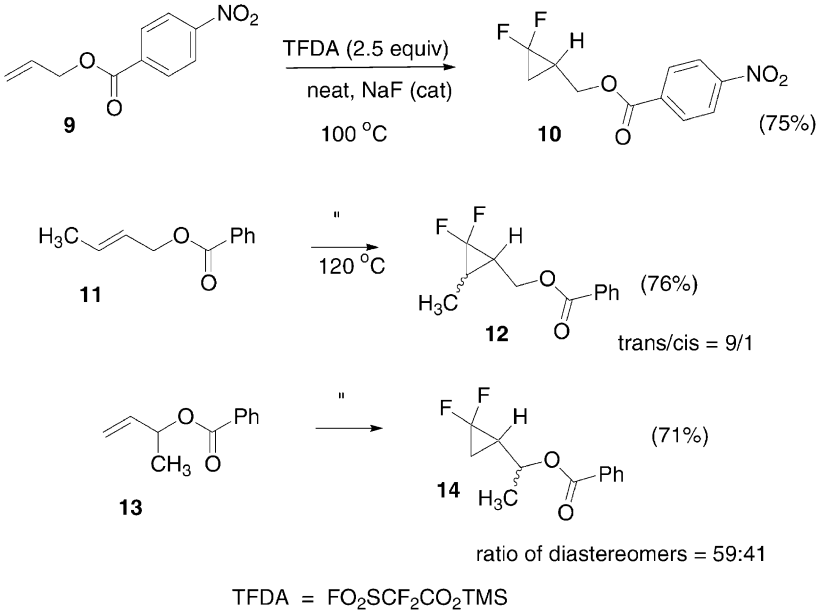


Fig. 4. Optimized structure for 1,1-difluoro-2-methylbut-3-en-1-yl cation (**8**) UB3LYP/6-311+G(2df, sp)//B3LYP/6-32G(d).

2.2. Syntheses of the solvolysis substrates

Difluorocarbene was added to allyl benzoates, **9**, **11**, and **13** to prepare (2,2-difluorocyclopropyl)methyl derivatives **10**, **12**, and **14** in high yield, using the new difluorocarbene reagent, trimethylsilyl 2,2-difluoro-2-(fluorosulfonyl)acetate (TFDA). Initially, it was planned to use directly the *p*-nitrobenzoate, **10**, as the solvolysis substrate, but it proved too unreactive both in HOAc and in CF_3CO_2H. Thus, the tosylate derivative, **15**, was prepared in a straightforward manner from **10**, as described in Section 3.

Although starting from pure *trans*-**11**, the product, **12**, obtained from the TFDA reaction had a significant *cis*-component (*trans*/*cis* = 9:1). We have generally observed that the conditions of difluorocarbene–alkene addition reactions using TFDA as the source of CF_2: can give rise to *cis*–*trans* isomerization of alkene substrate double bonds. Such results compromise the ability to use this reagent in a stereospecific difluorocarbene addition process. We have no definitive rationale for these competing isomerizations, although one possibility is that the SO_2 co-product is inducing the isomerization. In this case, the mixture of geometrical isomers was used in the solvolysis study.

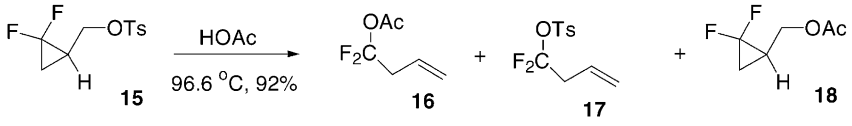


Likewise, product **14**, obtained by CF_2: addition to alkene substrate **13**, is a near equivalent mixture of diastereoisomers. This mixture of diastereomers was used in the subsequent solvolysis study.

2.3. Solvolysis of (2,2-difluorocyclopropyl)methyl tosylate, *15*

Solvolysis of (2,2-difluorocyclopropyl)methyl tosylate, **15**, in glacial acetic acid at 96.6 °C led to the formation

of both ring-opened (**16** and **17**) and non-ring-opened products (**18**), with **16** and **17** reflecting exclusively the regiochemistry of ring opening (proximal) that had been predicted computationally [2].



16 : **17** : **18** = 39 : 4.4 : 56.5

The assignment of structures to non-ring-opened product (**18**) and ring-opened products **16** and **17** was straightforward, based upon their characteristic ^{19}F NMR spectra: the AB system of **18** at δ − 129.8 ($J_{F,F}$ = 161 Hz, $J_{H,F}$ = 12 Hz) and −144.0 ($J_{F,F}$ = 161 Hz, $J_{H,H}$ = 13 Hz), and the triplets at δ −67.9 ($J_{F,F}$ = 13 Hz) and −71.0 ($J_{F,F}$ = 12 Hz) derived from **17** and **16**, respectively (Fig. 5).

Assuming that the ring-opened and ring-closed products derived from competing S_N1 and S_N2 processes, respectively, the partial rate factors for the two processes were calculated. Thus, the S_N1 process, in which tosylate **15** undergoes heterolytic cleavage to (presumably) form ring-opened cation **4**, which then is trapped by either HOAc or TsO^- to give products **16** and **17**, was assigned a first-order rate constant (k_Δ) of 4.4 (±0.1) × 10^{-6} s^{-1}, and the process involving solvent participation, which led to ring-closed product **18**, was assigned a pseudo first-order rate constant (k_S) of 5.8 (±0.1) × 10^{-6} s^{-1}.

In order to confirm that competitive unimolecular and bimolecular reactions were involved, and that all three products are not derived from the common intermediate carbocation **4a**, additional acetolysis experiments were carried out in 0.200 and 0.400 M NaOAc/HOAc solutions. The results are given in Table 1.

Correcting k_S by subtracting the background k_S (HOAc) (which is the k_S in pure HOAc), one can obtain the pseudo first-order rate constants k_S ($^-$OAc) that reflect the rates of nucleophilic attack by acetate ion. The values for k_S ($^-$OAc), 1.8 (±0.1) × 10^{-5} and 3.6 (±0.4) × 10^{-5} s^{-1} for 0.200 and 0.400 M [$^-$OAc], respectively, clearly demonstrate the dependence on [$^-$OAc], hence the S_N2 nature of the process that leads to non-ring-opened product **18**. On the other hand, the values of k_Δ for the three reactions increase only slightly, consistent with the influence of a small salt effect on the ionization process.

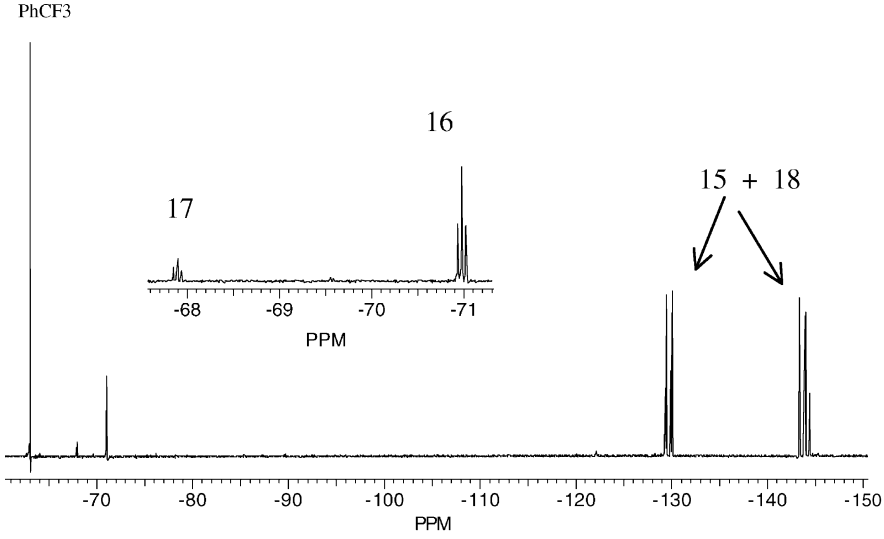
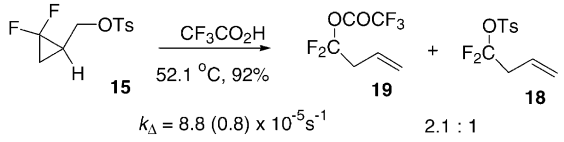


Fig. 5. ^{19}F Spectrum of tosylate **15** HOAc solvolysis product mixture.

Table 1
Kinetic results for solvolyses of (2,2-difluorocyclopropyl)methyl tosylate (**15**) in NaOAc/HOAc solutions at 96.6 °C

Conditions	k_{obs} (×10^{-5} s^{-1})	Mass balance (%)	Ratio **18**:(**16** + **17**)	k_S (×10^{-6} s^{-1})	k_Δ (×10^{-6} s^{-1})
Pure HOAc	1.0 ± 0.1	92	57:43	5.8	4.4
0.200 M NaOAc	2.87 ± 0.07	92	84:16	24	4.6
0.400 M NaOAc	4.7 ± 0.3	90	90:10	42	4.7

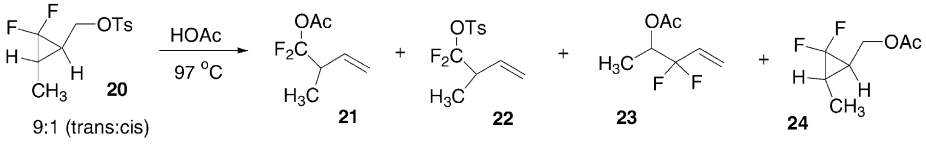
These results do not completely rule out the possibility that some of **18** might be formed via the S_N1 process. However, when the solvolysis was carried out in trifluoroacetic acid, a solvent of high ionizing power but poor nucleophilicity, only ring-opened products, **18** and **19**, were formed, under conditions where the potential ring-closed product, (2,2-difluorocyclopropyl)methyl trifluoroacetate, was demonstrated to be stable to the solvolytic conditions.



The above solvolytic results are completely consistent with the ionization of **15** proceeding directly and regiospecifically to the homoallylic carbocation **4a**, as had been predicted computationally [2].

2.4. Solvolysis of (3-methyl-2,2-difluorocyclopropyl)methyl tosylate, *20*

Solvolysis of tosylate **20** in glacial acetic acid at 96.3 °C resulted in the formation of three, ring-opened products, **21**–**23**, as well as the non-ring-opened product **24**.



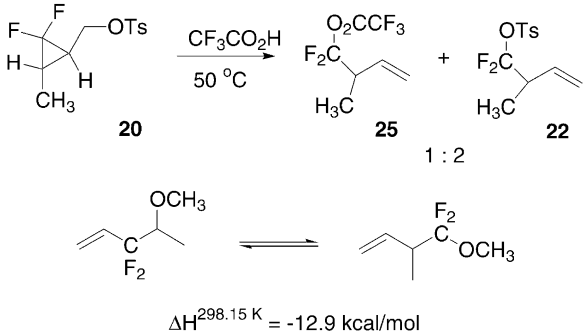
Conversion	21	22	23	24	Mass balance
20%	28.1%	6.9%	8.1%	56.8%	100% (assume)
89%	15.7	1.0	38.6	44.6	53%

Ring-opened products **21** and **22** reflect proximal ring cleavage, whereas the formation of **23** reflects distal ring cleavage. Thus, it appears that there is kinetic competition between proximal and distal ring cleavage in this solvolysis reaction. Of course, the presence of **24** indicates that direct displacement by solvent participation competes with the S_N1, ionization process that leads to the other three products. Acetate product **21** is unstable under the acidic solvolysis conditions, probably converting to the alcohol which ends up as the acid fluoride.

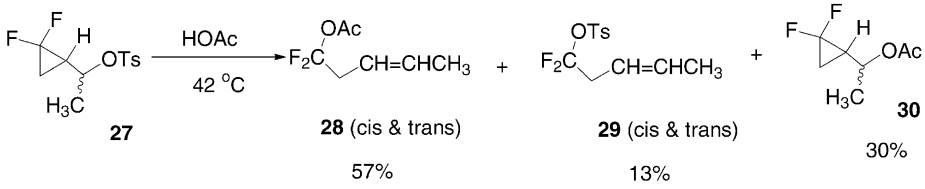
As was the case in the solvolysis of tosylate **15**, differentiating between ring-opened and non-ring-opened products was, on the basis of their ^{19}F NMR spectra, a simple task in analyzing products from the acetolysis of **20**. The presence of any product retaining the *gem*-difluorocyclopropyl entity (such as **24**) would be unambiguously recognized from its characteristic AB system, usually between −130 and −150 ppm and with characteristic $J_{F,F}$ coupling constants of ∼160 Hz. Any ring-opened product (such as **21** and **22**) containing the RCF_2OAc or RCF_2OTs functionalities, respectively, appear between −75 and −85 ppm, and finally, product **23**, with its CF_2 group not bound to oxygen, appears as an AB system centered at ∼110 ppm. Thus, *trans*-**24** was characterized by its AB spectrum (d, d) at δ −139.7 ($J_{F,F} = 158$ Hz, $J_{F,H} = 14.5$ Hz) and −141 ($J_{F,F} = 159$ Hz, $J_{F,H} = 12.2$ Hz); **21** by its AB spectrum (d, d) at δ 78.7 ($J_{F,F} = 148$ Hz, $J_{F,H} = 10$ Hz) and 80.4 ($J_{F,F} = 147$ Hz, $J_{F,H} = 14$ Hz); **22** by its doublet at δ −74.9 ($J_{F,H} = 10$ Hz) (with detectable AB sidebands indicating a $J_{F,F}$ of 137 Hz); and product **23** by its AB spectrum (d, t) at δ 108.4 ($J_{F,F} = 250.2$ Hz, $J_{F,H} = 10$ Hz) and 113.8 ($J_{F,F} = 250.2$ Hz, $J_{F,H} = 12$ Hz). All the four products were isolated and characterized, with **22**–**24** being synthesized independently to confirm structures. Products **21** and **22** were too unstable to isolate in a pure state.

The disappearance of **20** was observed to follow first-order kinetics with a rate constant of 1.49 (±0.02) × 10^{-4} s^{-1} at 96.6 (±0.1) °C. Assuming competing k_Δ and k_S processes, one can assign values of 6.40 (±0.02) × 10^{-5} s^{-1} and 8.50 (±0.02) × 10^{-5} to the first-order rate constant, k_Δ, and the pseudo first-order rate constant k_S, respectively.

In order to assess more fully the S_N1 pathway for the solvolysis of **20**, its reaction in CF_3CO_2H was examined. Only two significant products were observed, both deriving from proximal bond cleavage. This must reflect thermodynamic control of the CF_3CO_2H reaction to the extent that any product resulting from distal bond cleavage must be *reversibly formed* and end up as **22** or **25**. Indeed, calculations (UBLYP/6-311+g(2df, 2p)//UB3LYP/6-31g(d)) of the hypothetical reaction (Eq. (1)) indicate a significantly greater thermodynamic stability for structural type **22** (α-alkoxy) in comparison to type **23** (β-alkoxy).



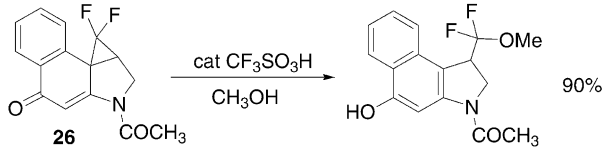
Thus, although, kinetically, nucleophilic attack on the intermediate cation or cations leads competitively to products derived from distal and proximal cleavage, the products derived from proximal cleavage must be more stable than those obtained from distal cleavage.



(early, kinetically-controlled ratios of products)

From these results it can be concluded that the presence of a 'single methyl substituent' at the third position of the (2,2-difluorocyclopropyl)methyl system is sufficient to induce competitive solvolytic proximal and distal cleavage under condition of kinetic control. The methyl substituent of **20** gives rise to approximately a 10-fold increase in the rate constant k_Δ as would be expected on the basis of its carbocation-stabilizing ability.

In the only previous literature report that is relevant to this result [8], Boger found that even with alkyl substitution at the third position, the acid catalyzed ring opening of spirocyclohexadienone, **26**, led only to its proximal ring cleavage.



2.5. Solvolysis of 1-(2,2-difluorocyclopropyl)ethyl tosylate, 27

Modification of the (2,2-difluorocyclopropyl)methyl system into a secondary tosylate, such as **27**, was expected to affect the reactivity of the system, but not the regiochemistry of the ring opening process. Indeed, when tosylate **27** was heated, in a preliminary experiment, in HOAc at 97 °C for 30 min (a length of time when little of the primary tosylate **15** would have reacted), all starting material disappeared, and four ring-opened products derived from proximal ring cleavage were observed to be formed. That these products were ring opened was readily discerned from the ^{19}F NMR spectrum of the crude product mixture, which revealed two pairs of triplets due to the *cis*- and *trans*-isomers of **28** and **29**, in the range −74 to −82 ppm.

When the solvolysis was carried out at a lower temperature (42 °C), results similar to those observed for **15**, including formation of a significant amount of non-ring opened product (**30**), were obtained. The ratio of ring-opened to non-ring-opened products was ∼2.3, and the rate constant for disappearance of **27** at 42.1 °C was found to be 1.64 $(\pm 0.02) \times 10^{-5}$ s^{-1}. After 36 h of reaction, all starting material was gone, and the ratios of products had modified only slightly to 50:17:33, thus indicating that the products were moderately stable to the reaction conditions and that kinetic control of products had been obtained.

The failure to observe acetate **30** at the higher temperature (97 °C) is presumably due to an acid catalyzed rearrangement of this more reactive secondary acetate to ring-opened acetates **28**. The observed ring-opened versus non-ring-opened product distribution from tosylate **27** at the lower temperature (42 °C), compared to those of primary tosylates **15** and **20** at 96.6 °C, suggests that k_S was less competitive with k_Δ for the secondary substrate than for the primary substrates.

2.6. Relative reactivity of (2,2-difluorocyclopropyl)methyl cation systems

With tosylates **15**, **20** and **27** undergoing ultra-fast ring opening upon solvolysis, with well understood regiochemistries different from those exhibited by analogous radicals, the (2,2-difluorocyclopropyl)methyl system certainly qualifies as a hypersensitive probe capable of distinguishing between cation and radical mechanisms.

In evaluating the potential efficacy of a new mechanistic probe, in addition to its ability to differentiate between the intermediacy of a radical and a carbocation, it should ideally play simply the role of an "observer" of the reaction. That is, it should not exert a significant mechanistic influence upon the reaction system it is testing. If the diagnostic probe itself has a steric or electronic bias so as to favor or disfavor one of the possible mechanistic pathways, then the interpretation of the results from use of such a probe may be ambiguous. This is certainly one of the potential flaws of any cyclopropylcarbinyl system that purports to distinguish carbocation from radical intermediates, because although the cyclopropyl group should exert little if any kinetic influence upon a radical-forming process, it is well recognized to enhance greatly formation of carbocations. Cyclopropylmethyl tosylate, for example, undergoes acetolysis with a rate constant more than 100,000 times that of the model primary system, isobutyl tosylate (Table 2).

In evaluating the efficacy of this probe, the acetolysis rate of the tosylate **15** which reflects the ease of cation formation, was compared with those of isobutyl tosylate and cyclopropylmethyl tosylate (which we extrapolated from their respective activation parameters) (Tables 2 and 3) [9,10].

Table 2
Relative rate (k_Δ) of acetolysis of primary tosylates at 96.6 °C

Substrates	Relative rate	Reference
Cyclopropylmethyl tosylate	8.4×10^4	[9]
(2,2-Difluorocyclopropyl)methyl tosylate (**15**)	1	This work
(3-Methyl-2,2-difluorocyclopropyl)methyl tosylate (**20**)	10	This work
Isobutyl tosylate	0.56	[10]

Table 3
Data for solvolysis kinetic run of **27**

Time (s)	C_0/C_t	$\ln(C_0/C_t)$	Time (s)	C_0/C_t	$\ln(C_0/C_t)$
0	1	0	17,072	1.32169	0.27891
2,134	1.03299	0.03246	19,206	1.37785	0.32052
4,268	1.07075	0.06836	21,340	1.41654	0.34821
6,402	1.11002	0.10438	23,474	1.46452	0.38152
8,536	1.15228	0.14175	25,608	1.52605	0.42268
10,670	1.18538	0.17006	27,742	1.56822	0.44994
12,802	1.22372	0.2019	29,876	1.63016	0.48868
14,938	1.26287	0.2338	32,010	1.6846	0.52153

At 96.6 °C, the 8.4×10^4 times decrease of acetolysis rate of (2,2-difluorocyclopropyl)methyl tosylate (**15**) relative to that of cyclopropylmethyl tosylate, reveals a substantial inductive destabilizing influence on the ionization transition state of **15** due to the fluorine substituents on its ring.

Since the rate constant (k_Δ) of **15** is only 1.8 times greater than that of isobutyl tosylate at 96.6 °C, the net result of the fluorine substituents is to essentially eliminate the rate enhancing effect of the cyclopropylmethyl moiety (in **15**) relative to a typical primary substrate, such as isobutyl tosylate. Thus, the (2,2-difluorocyclopropyl)methyl system should exhibit *no* kinetic bias towards either the radical or the carbocation mechanism. It is also not expected that (2,2-difluorocyclopropyl)methyl systems, **15**, **20** and **27** should have any specific steric problems or stereoelectronic influences. Therefore, since they have been demonstrated to be effectively electronically benign, we would conclude on the basis of our kinetic, regiochemical and computational studies, that the (2,2-difluorocyclopropyl)methyl system should be capable of acting as an effective, hypersensitive probe of radical and/or carbocation mechanisms.

3. Experimental

All ^{1}H NMR spectra were recorded at 300 MHz, ^{13}C NMR spectra at 75 MHz and ^{19}F NMR spectra at 282 MHz on Varian VXR-300, Mercury-300 and Gemini-300 NMR spectrometers. The chemical shifts of ^{1}H signals are reported in ppm down field relative to tetramethylsilane (TMS) ($\delta = 0.00$) in $CDCl_3$. ^{13}C signals are expressed in ppm using the central peak of the $CDCl_3$ signal as internal standard ($\delta = 77.00$). ^{19}F NMR are reported in ppm using $CFCl_3$ as internal standard ($\delta = 0.00$). All kinetic studies were carried out using sealed NMR tubes submerged in an oil bath with a Statim temperature controller.

All the reagents were obtained from Fisher except those mentioned. THF was dried through distillation from Na/benzophenone. 2,2-Difluoro-2-(fluorosulfonyl)acetic acid was provided by Professor Qing-Yun Chen, from Shanghai Institute of Organic Chemistry.

3.1. Computational methodology

Density functional theory calculations were performed using the Gaussian 98 program package [11]. Structures and transition structures were optimized using restricted Becke's hybrid three parameter functional (B3LYP) [12] and the 6-31G(d) basis set [13]. Using the same level of theory, vibrational frequency calculations were performed on all stationary points to determine thermal energies. Thermal energies, the sum of zero-point, vibrational, rotational, and translational energies at 285.15 K, were obtained using unscaled frequencies. Single-point energies were calculated using UB3LYP level of theory using the 6-311+G(2df, 2p) basis set [14].

3.2. Preparative procedures

3.2.1. Trimethylsilyl 2,2-difluoro-2-(fluorosulfonyl)acetate

A dry 1 l three neck round bottom flask, equipped with magnetic stirrer and an additional funnel, was charged with 150 g (0.85 mol) 2,2-difluoro-2-(fluorosulfonyl)acetic acid. Under N_2, at 0 °C, 329 g (3.05 mol, 3.6 eq.) of trimethylsilyl chloride was added dropwise. The generated gas was passed through 10% NaOH aqueous solution to remove HCl. Then, the reaction mixture was stirred at room temperature over night. Distillation at 27 mmHg, 62–63 °C gave 166 g (0.66 mol, 78%). ^{1}H NMR δ: 0.40 (s); ^{13}C NMR δ: 155.1 (t, $J_{(C-F)} = 27.0$ Hz), 112.2 (dt, $J_{d(C-F)} = 31.5$ Hz, $J_{t(C-F)} = 299.0$ Hz), −1.1; ^{19}F NMR δ: 40.6 (1F, s), −103.7 (2F, s); HRMS (CI) $C_5H_{10}O_4S_1Si_1F_3$ $(M+1)^+$. Calcd.: 251.0212, Found: 251.0015.

3.2.2. Allyl p-nitrobenzoate (**9**)

A 250 ml dry three necked round bottom flask, equipped with a magnetic stirrer, a condenser and an additional flask, was charged with 80 ml dry THF and 8.7 g (150 mmol, 1 eq., Aldrich) allyl alcohol and 11.9 g (150 mmol) pyridine. At 0 °C, 100 ml dry THF solution of 32.4 g of *p*-nitrobenzoyl chloride (180 mmol, Acros) was added dropwise. After stirring at room temperature for 8 h, the reaction mixture was filtered, and solvent removed under reduced pressure. Ethyl acetate (400 ml) was added, and the solution washed with water, 5% $NaHCO_3$, water and brine. After drying (Na_2SO_4), solvent was removed under reduced pressure to give 15.3 g of **9** (yellow liquid, 49%). ^{1}H NMR δ: 8.23 (4H, aromatic AA′XX′), 6.02 (1H, ddt, $J_{d(H-H)} = 17.1$, 10.5 Hz,

$J_{t(H-H)} = 5.9$ Hz), 5.41 (1H, d and pseudo-q, $J_{d(H-H)} = 17.1$ Hz, $J_{q(H-H)} = 1.4$ Hz), 5.31 (1H, d and pseudo-q, $J_{d(H-H)} = 10.5$ Hz, $J_{q(H-H)} = 1.4$ Hz), 4.84 (2H, dt, $J_{d(H-H)} = 5.9$ Hz, $J_{t(H-H)} = 1.4$ Hz); ^{13}C NMR δ: 164.278, 150.490, 135.454, 130.701, 123.490, 119.090, 66.391; HRMS (CI) $C_{10}H_{10}O_4N$ $(M+1)^+$. Calcd.: 208.0610, Found: 208.0604.

3.2.3. (2,2-Difluorocyclopropyl)methyl p-nitrobenzoate (**10**)

A 100 ml dry three necked round bottom flask, equipped with a magnetic stirrer, was charged with 12.25 g (59.2 mmol) of **9**, and a small amount of CsF. At 97 °C, with stirring, 32.4 g (130 mmol) of TFDA was slowly added using a syringe pump, at a rate of 1.67 ml/h. The reaction was then cooled to room temperature and 0.125 g of product was separated by flash column chromatography (silica gel, 10% diethyl ether/hexanes) ($R_f = 0.28$, 20% diethyl ether/hexanes), from 0.28 g of the reaction mixture (total 16.7 g). This gave **10** in an isolated yield of 49% (74%, ^{1}H NMR yield). ^{1}H NMR δ: 8.24 (4H, aromatic AA′XX′), 4.52 (1H, dddd, $J_{d(H-H)} = 12.0$ Hz, $J_d = 7.5$, 2.7, 1.2 Hz), 4.32 (^{1}H, ddd, $J_d = 12.0$, 8.1, 1.8 Hz), 2.10 (1H, m), 1.60 (1H, m), 1.31 (1H, m); ^{13}C NMR δ: 164.5, 150.6, 135.1, 130.8, 123.6, 112.8 (t, $J_{t(F-C)} = 283.1$ Hz), 62.6 (d, $J_d = 5.5$ Hz), 20.9 (t, $J_{t(F-C)} = 11.1$ Hz), 15.1 (t, $J_{t(F-C)} = 11.6$ Hz); ^{19}F NMR δ: −129.8 (1F, dtt, $J_{d(F-F)} = 161.1$ Hz, $J_{t(F-H)} = 12.1$, 3.7 Hz), −143.7 (1F, ddd, $J_{d(F-F)} = 161.1$ Hz, $J_{d(F-H)} = 13.3$ Hz, $J_{d(F-H)} = 4.5$ Hz); HRMS (CI) $C_{11}H_{10}O_4F_2N_1$ $(M+1)^+$. Calcd.: 258.0578, Found: 258.0585.

3.2.4. (2,2-Difluorocyclopropyl)methanol

A 80 ml 10% of NaOH/H_2O solution was added to the reaction mixture mentioned above. At 80 °C, this mixture was stirred for 2 h, and then cooled to room temperature. Water (200 ml) was added, and the mixture was extracted with diethyl ether (five times, 100 ml). The combined ether layer was washed with 5% $NaHCO_3/H_2O$, H_2O, and brine, and then dried over Na_2SO_4. Ether was removed under reduced pressure. Distillation of the residue gave 3.7 g (34.3 mmol, two-step yield 58%) product (60 mmHg, 76–80 °C). ^{1}H NMR δ: 3.75 (1H, dddd, $J_{d(H-H)} = 12.0$ Hz, $J_d = 6.6$, 3.0, 1.2 Hz), 3.64 (1H, ddm, $J_{d(H-H)} = 12.0$ Hz, $J_d = 8.1$ Hz), 1.87 (1H, m), 1.75 (1H broad), 1.44 (1H, m), 1.14 (1H, m); ^{13}C NMR δ: 113.7 (t, $J_{t(F-C)} = 282.0$ Hz), 60.0 (d, $J_d = 5.6$ Hz), 24.2 (t, $J_{t(F-C)} = 11.1$ Hz), 14.5 (t, $J_{t(F-C)} = 11.0$ Hz); ^{19}F NMR δ: −129.1 (1F, dt, $J_{d(F-F)} = 160.3$ Hz, $J_{d(F-H)} = 12.7$ Hz), −144.7 (1F, dd, $J_{d(F-F)} = 160.3$ Hz, $J_{d(F-H)} = 12.7$ Hz); HRMS (CI) $C_4H_7O_1F_2$ $(M+1)^+$. Calcd.: 109.0465, Found: 109.0531 (0.23), 91.0363 (100).

3.2.5. (2,2-Difluorocyclopropyl)methyl tosylate (**15**)

A dry 5 ml round bottom flask was charged with 115 mg (1.06 mmol) (2,2-difluorocyclopropyl)methanol, 1.8 ml pyridine. At 0 °C, 408 mg (2.14 mmol) of tosyl chloride was added. The reaction mixture was maintained at −5 °C for 12 h, whereupon 3 ml of ice water was added, and the solution was extracted with diethyl ether (2 ml × 6). The combined ether layers were washed with 6 M HCl/H_2O, water, and brine, then dried over Na_2SO_4 and Na_2CO_3. After the solvent was removed under reduced pressure, 146 mg (0.56 mmol, 53%) of pure product **15** (yellow oil) was obtained. Tosylate **15** was kept in diethyl ether solution in the presence of anhydrous Na_2CO_3. ^{1}H NMR δ: 7.56 (4H, aromatic AA′XX′), 4.06 (2H, d, $J_{d(H-H)} = 7.8$ Hz), 2.42 (3H, s), 1.91 (1H, m), 1.52 (1H, m), 1.18 (1H, m); ^{13}C NMR δ: 145.1, 132.8, 129.9, 127.9, 112.3 (t, $J_{t(F-C)} = 283.0$ Hz), 66.9 (d, $J_d = 5.5$ Hz), 21.7, 20.9 (dd, $J_{d(C-F)} = 12.1$ Hz, $J_{d(C-F)} = 10.6$ Hz), 15.3 (t, $J_{t(C-F)} = 11.6$ Hz); ^{19}F NMR δ: −129.7 (1F, dtdm, $J_{d(F-F)} = 162.3$ Hz, $J_{t(F-H)} = 13.0$ Hz, $J_{d(F-H)} = 4.0$ Hz), −143.2 (^{1}H, dddt, $J_{d(F-F)} = 162.3$ Hz, $J_{d(H-F)} = 13.3$, 4.8 Hz, $J_{t(H-F)} = 1.7$ Hz; HRMS (CI) $C_{11}H_{13}O_3F_2S$ $(M+1)^+$. Calcd.: 262.0554, Found; 263.0541 (3.7), 91.0362 (100).

3.2.6. (2,2-Difluorocyclopropyl)methyl acetate (**18**)

A dry 5 ml round bottom flask was charged with 100 mg (0.93 mmol) (2,2-difluorocyclopropyl)methanol, 1.2 ml pyridine. At 0 °C, 300 mg (2.94 mmol) of acetic anhydride was added. The reaction mixture was maintained at −5 °C for 12 h. Then, 3 ml of ice water was added, and the solution was extracted with diethyl ether (2 ml × 6). The combined ether layer was washed with 6 M HCl/H_2O, water, and brine, and then dried over Na_2SO_4 and Na_2CO_3. After the solvent was removed by distillation, 82 mg (0.54 mmol, 58%) of pure product **18** was obtained. ^{1}H NMR δ: 4.19 (1H, dddd, $J_{d(H-H)} = 12.0$ Hz, $J_d = 7.5$, 2.7, 1.2 Hz), 4.03 (1H, ddd, $J_{d(H-H)} = 12.0$ Hz, $J_d = 8.1$, 1.8 Hz), 2.07 (3H, s), 1.93 (1H, m), 1.50 (1H, m), 1.18 (1H, m); ^{13}C NMR δ: 170.9, 112.9 (t, $J_{t(C-F)} = 283.0$ Hz), 61.2 (d, $J_d = 5.5$ Hz), 21.0 (t, $J_{t(C-F)} = 11.6$ Hz), 20.8, 15.0 (t, $J_{t(C-F)} = 11.0$ Hz); ^{19}F NMR δ: −129.8 (1F, dtdd, $J_{d(F-F)} = 160.9$ Hz, $J_{t(H-F)} = 12.1$ Hz, $J_{d(H-F)} = 3.7$, 2.8 Hz), −144.0 (1F, dddt, $J_{d(F-F)} = 160.9$ Hz, $J_{d(H-F)} = 13.3$, 4.8 Hz, $J_{t(H-F)} = 1.5$ Hz); HRMS (CI) $C_6H_9O_2F_2$ $(M+1)^+$. Calcd.: 151.0571, Found: 151.0643 (100).

3.2.7. 1,1-Difluorobut-3-en-1-yl tosylate (**17**)

A dry NMR tube with valve charged with 0.2 g (2,2-sdifluorocyclopropyl)methyl tosylate, 0.2 ml trifluoroacetic acid, was maintained at 53 °C for 12 h. Then, the reaction mixture was cooled to room temperature. After vacuum transfer, 1 ml diethyl ether was added into the residue. The solution was treated with $MgSO_4$and Na_2CO_3 at 0 °C. Filtration of the mixture, followed by vacuum removal of the solvent, gave a mixture. Flash column chromatography (hexanes/benzene = 3:1) provided pure product **17** ($R_f = 0.12$). ^{1}H NMR δ: 7.59 (4H, aromatic AA′XX′), 5.65 (1H, m), 5.24 (2H, m), 2.83 (2H, tdt, $J_{t(F-H)} = 12.3$ Hz, $J_{d(H-H)} = 6.9$ Hz, $J_{t(H-H)} = 1.2$ Hz), 2.45 (3H, s); ^{19}F NMR δ: −68.3 (2F, t, $J_{t(H-F)} = 12.7$ Hz); ^{13}C

NMR δ: 145.7, 134.0, 129.8, 128.1, 126.3, 123.8 (t, $J_{t(C-F)} = 276.0$ Hz), 122.0, 40.6 (t, $J_{t(C-F)} = 27.4$ Hz), 21.8; HRMS (FAB) $C_{11}H_{13}O_3F_2S$ $(M+1)^+$. Calcd.: 263.0553, Found: 263.0553 (25), 173.0157 (100), 91.0554 (36).

3.2.8. 1,1-Difluorobut-3-en-1-yl trifluoroacetate (**19**)

A dry NMR tube with valve charged with 0.2 g (2,2-difluorocyclopropyl)methyl tosylate, 0.2 ml trifluoroacetic acid, was maintained at 53 °C for 12 h. Then the reaction mixture was cooled to room temperature. After vacuum transfer, 1 ml $CDCl_3$ was added into the volatile reaction mixture. The solution was treated with $MgSO_4$ and Na_2CO_3 at 0 °C. This gave a $CDCl_3$ solution of **19**. ^{1}H NMR δ: 5.73 (1H, ddt, $J_{d(H-H)} = 17.1$, 10.2 Hz, $J_{t(H-H)} = 6.9$ Hz), 5.33 (1H, dm, $J_{d(H-H)} = 10.2$ Hz), 5.30 (1H, dm, $J_{d(H-H)} = 17.1$ Hz), 3.04 (2H, dt, $J_{d(H-H)} = 6.9$ Hz, $J_{t(F-H)} = 12.6$ Hz); ^{19}F NMR δ: −71.6 (2F, t, $J_{t(F-H)} = 12.7$ Hz), −76.0 (3F, s); HRMS (CI) $C_6H_6O_2F_5$ $(M+1)^+$. Calcd.: 205.0288, Found 205.0296 (1.12); $C_4H_5F_2$ $(M+1-CF_3COOH)^+$. Calcd.: 91.0359, Found: 91.0372 (100).

3.2.9. (2,2-Difluorocyclopropyl)methyl trifluoroacetate

A dry 5 ml round bottom flask equipped with magnetic stir bar was charged with 200 mg (1.85 mmol) of (2,2-difluorocyclopropyl)methanol, and 218 mg of 2,6-lutidine (2 mmol). The system was cooled to 0 °C. With stirring, under the protection of N_2, 390 mg of trifluoroacetic anhydride was added, the temperature raised to room temperature, and 30 min later, the reaction mixture was distilled to give 280 mg colorless liquid at 65 °C (1.37 mmol, 74%). ^{1}H NMR δ: 4.40 (2H, AB pattern), 2.04 (1H, m), 1.62 (1H, m), 1.30 (1H, m); ^{13}C NMR δ: 157.4 (q, $J_{q(C-F)} = 42.8$ Hz), 114.4 (q, $J_{q(C-F)} = 285.0$ Hz), 112.2 (dd, $J_{d(C-F)} = 282.0$, 284.0 Hz), 64.7 (d, $J_d = 6.0$ Hz), 20.2 (dd, $J_{d(C-F)} = 12.6$, 11.1 Hz), 15.2 (t, $J_{t(C-F)} = 11.6$ Hz); ^{19}F NMR δ: −75.4 (3F, s), −129.5 (1F, dt, $J_{d(F-F)} = 162.3$ Hz, $J_{t(F-H)} = 10.5$ Hz), −143.3 (1F, ddd, $J_{d(F-F)} = 162.0$ Hz, $J_{d(F-H)} = 12.7$ Hz, $J_{d(F-H)} = 6.5$ Hz); HRMS (CI) $C_6H_6O_2F_5$ $(M+1)^+$. Calcd.: 205.0288, Found: 205.0283 (0.62), 91.0369 (100).

3.2.10. 2-Buten-1-yl benzoate (**11**)

A dry 250 ml three necked round bottom flask was charged with dry diethyl ether (80 ml), crotyl alcohol (5.00 g, 69.34 mmol), and triethylamine (14.16 g, 138.96 mmol). Under nitrogen and at 0 °C, benzoyl chloride (9.94 g, 70.7 mmol) was added slowly via an addition funnel overnight. The reaction mixture was diluted with 10 ml of diethyl ether. The ether layer was washed with water, 0.5N HCl, 5% $NaHCO_3$, brine, and dried over $MgSO_4$. After filtering and removing the solvent under reduced pressure, 10.33 g of pure ester **11** (yellow oil, yield 84%) were obtained. ^{1}H NMR δ: 8.15 (2H, d), 7.65 (^{1}H, m), 7.53 (2H, m), 5.79 (2H, m), 4.55 (2H, m), 1.55 (3H, m); ^{13}C NMR δ: 166.5, 132.9, 131.4, 130.6, 130.4, 129.7, 128.9, 128.9, 125.2, 65.7, 17.9; HR-MS (FAB), $C_{11}H_2O_2$ $(M+1)$. Calcd.: 177.0917, Found: 177.0917.

3.2.11. (2,2-Difluoro-3-methylcyclopropy)methyl benzoate (**12**)

A dry 25 ml two necked round bottom flask was charged with 2-buten-1-yl benzoate **11** (7.3800 g, 41.88 mmol) and sodium fluoride (0.100 g, catalyst). To this mixture TFDA (16.00 ml, 83.76 mmol) was added via a glass syringe at a rate of 0.35 ml/h while the mixture was heated to 120 °C with reflux under nitrogen. The resulting material was diluted with diethyl ether, washed with water and brine, and dried over $MgSO_4$. The ether was removed giving impure **12**, which was then purified via column chromatography ($R_f = 0.3$, 5% ethyl ether/hexanes) resulting in a 7.36 g mixture of both isomers (*cis*/*trans* = 1:9, 76%). ^{1}H NMR δ: 8.06 (2H, m), 7.58 (1H, dt), 7.45 (2H, m), 4.39 (2H, m), 1.62 (2H, m), 1.22 (3H, m); ^{13}C NMR δ: 166.7, 133.4, 130.1, 129.9, 128.6, 115.5 (t, $^1J_{C-F} = 287.3$ Hz), 61.9, 27.8 (t, $^2J_{C-F} = 10.8$ Hz), 22.1 (t, $^2J_{C-F} = 10.3$ Hz), 11.1; ^{19}F NMR *cis* isomer δ: −126.0 (1F, dt, $^2J_{F-F} = 160.2$ Hz, $^3J_{H-F} = 13.7$ Hz), −153.7 (1F, d, $^2J_{F-F} = 160.2$ Hz); *trans* isomer δ: −140.3 (2F, dd, $^2J_{F-F} = 160.0$ Hz, $^3J_{H-F} = 14.9$ Hz); HR-MS (FAB) $C_{12}H_{12}O_2F_2$ $(M+1)$. Calcd.: 227.0884, Found: 227.0884.

3.2.12. (2,2-Difluoro-3-methylcyclopropyl)methanol

In a dry 150 ml one necked round bottom flask equipped with a condenser, 25 ml of 3 M NaOH and (2,2-difluoro-3-methylcyclopropyl)methyl benzoate **12** (3.27 g, 14.5 mmol) were combined and heated to 110 °C. After the reaction ran overnight, the product was extracted with ether, brine and dried over $MgSO_4$. After filtration and removal of ether, 1.62 g of product was obtained (92%). ^{1}H NMR δ: 3.65 (2H, m), 2.32 (1H, s), 1.38 (1H, m), 1.60 (3H, m); ^{13}C NMR δ: 115.9 (t, $^1J_{C-F} = 287.1$ Hz), 59.9, 31.0 (t, $^2J_{C-F} = 10.1$ Hz), 21.5 (t, $^2J_{C-F} = 10.6$ Hz), 11.1; ^{19}F NMR *cis* isomer δ: −126.0 (1F, dt, $^2J_{F-F} = 158.7$ Hz, $^3J_{H-F} = 13.7$ Hz), −154.5 (1F, d, $^2J_{F-F} = 158.7$ Hz); *trans* isomer δ: −140.5 (2F, m); LR-MS (EI) $C_5H_7OF_2$: 105 (46), 91 (38), 77 (54), 51 (100), 43 (64).

3.2.13. (2,2-Difluoro-3-methylcyclopropyl)methyl tosylate (**20**)

A mixture of (2,2-difluoro-3-methylcyclopropyl)methanol (0.56 g, 4.62 mmol) and pyridine (1.85 g, 9.64 mmol) was placed in a reaction vial. At 0 °C, tosyl chloride (1.35 g, 4.62 mmol) was added and the reaction mixture was maintained at −5 °C for 12 h. The resulting material was diluted with diethyl ether and washed with water, 1 M HCl, and brine and then dried over $MgSO_4$ and Na_2CO_3. Filtration and removal of ether resulted in a 0.63 g mixture of both isomers (yellow oil, *cis*/*trans* = 1:13, 46%). Tosylate **20** was stored in diethyl ether solution over Na_2CO_3 (anhydrous). ^{1}H NMR δ: 7.80 (2H, d), 7.36 (2H, d), 4.08 (2H, m), 2.45 (3H, s), 1.46 (2H, m), 1.15 (3H, m); ^{13}C NMR δ: 145.4, 133.0, 130.5,

130.2, 128.0, 127.2, 114.6 (t, $^1J_{C-F} = 286.0$ Hz), 67.4, 27.4 (t, $^2J_{C-F} = 11.0$ Hz), 22.4 (t, $^2J_{C-F} = 10.0$ Hz), 21.7, 10.8; ^{19}F NMR *cis* isomer δ: −125.6 (1F, dt, $^2J_{F-F} = 162.2$ Hz, $^3J_{H-F} = 12.8$ Hz), −153.4 (1F, d, $^2J_{F-F} = 160.1$ Hz); *trans* isomer δ: −143.2 (2F, dd, $^2J_{F-F} = 162.3$ Hz, $^3J_{H-F} = 13.3$ Hz); HR-MS (FAB) $C_{12}H_{14}O_3F_2S$ ($M + 1$). Calcd.: 277.0711, Found: 277.0749.

3.2.14. 1,1-Difluoro-2-methylbut-3-en-1-yl tosylate (22)

A dry reaction vessel was charged with (2,2-difluoro-3-methylcyclopropyl)methyl tosylate (**20**) (0.2 g), trifluoroacetic acid (0.2 ml) and maintained at 50 °C for 4 h. Then the reaction mixture was cooled to room temperature. After filtration of the mixture and removal of the solvent, the residue was purified by flash column chromatography ($R_f = 0.38$, 10% ethyl acetate/hexanes) which provided **22** (yellow oil, 20%). ^{1}H NMR δ: 7.84 (2H, d), 7.35 (2H, d), 5.66 (1H, ddd, $^3J_{trans\,H-H} = 17.33$ Hz, $^3J_{H-H} = 10.01$, 10.25 Hz), 5.18 (2H, m), 2.30 (1H, m), 2.45 (3H, s), 1.12 (3H, d); ^{13}C NMR δ: 145.9, 134.4, 133.1 (t, $^3J_{C-F} = 2.0$ Hz), 130.5, 128.6, 128.6, 128.3, 127.2 (t, $^1J_{C-F} = 134.4$ Hz), 119.5, 44.3 (t, $^2J_{C-F} = 15.7$ Hz), 21.9, 13.2 (t, $^3J_{C-F} = 13.0$ Hz); ^{19}F NMR δ: −74.6 (2F, d, $^2J_{F-F} = 9.6$ Hz); LRMS (EI) $C_{12}H_{14}O_3F_2S$: 155 (8), 104 (18), 91 (100), 77 (8), 65 (39).

3.2.15. (2,2-Difluoro-3-methylcyclopropyl)methyl acetate (24)

A dry reaction vessel was charged with (2,2-difluoro-3-methylcyclopropyl)methanol (0.12 g, 0.98 mmol, pyridine (0.13 ml, 1.97 mmol), and 0.95 ml of dry diethyl ether. After cooling the mixture to 0 °C under nitrogen, acetic anhydride (0.10 ml, 0.98) was added slowly via a syringe and the reaction was allowed to run overnight. The resulting mixture was diluted with ether and the product was extracted with 0.6 M HCl, 5% $NaHCO_3$, and brine and dried over $MgSO_4$. Filtration and removal of ether resulted in a 0.13 g mixture of both isomers of **24** (yellow oil, *cis*/*trans* = 1:10, 98%). ^{1}H NMR δ: 4.21 (1H, m), 4.01 (1H, m), 2.07 (3H, s), 1.46 (1H, m), 1.19 (3H, m); ^{13}C NMR δ: 171.1, 115.2 (t, $^1J_{C-F} = 287.6$ Hz), 61.4, 27.6 (t, $^2J_{C-F} = 10.6$ Hz), 22.0 (t, $^2J_{C-F} = 10.1$ Hz), 21.1, 11.1; ^{19}F NMR *cis* isomer δ: −126.4 (1F, dt, $^2J_{F-F} = 160.2$ Hz, $^3J_{H-F} = 13.7$ Hz), −153.8 (1F, d, $^2J_{F-F} = 158.7$ Hz); *trans* isomer δ: −140.5 (2F, dd, $^2J_{F-F} = 174.0$ Hz, $^3J_{H-F} = 15.3$ Hz); LRMS (EI) $C_7H_{10}O_2F_2$: 105 (100), 43 (100).

3.2.16. 3,3-Difluoropent-4-en-2-ol

Acid washed zinc (0.40 g, 6.1 mmol) and acetaldehyde (0.20 g, 4.5 mmol) in 3.0 ml of dry THF were combined in a dry reaction vessel under nitrogen. After the mixture was cooled to 0 °C, a mixture of 1-bromo-1,1-difluoroprop-2-ene (0.48 g, 3.1 mmol) (obtained from Oakwood Products), in 1.5 ml of dry THF was added slowly to the zinc/aldehyde mixture via a syringe. The reaction was cooled to room temperature and stirred overnight. To the reaction mixture 5% HCl was added and the mixture was stirred for 5 min. Excess zinc was filtered off and the organic layer was separated. The aqueous layer was extracted with ether. The organic layer washed with saturated $NaHCO_3$ and dried over $MgSO_4$. Filtration and removal of ether resulted in a 0.39 g of 3,3-difluoropent-4-en-2-ol (yellow oil, 53%). ^{1}H NMR δ: 5.98 (1H, m), 5.72 (1H, m), 5.56 (1H, d, $^3J_{cis\,H-H} = 10.99$ Hz), 3.96 (1H, m), 2.14 (1H, s), 1.26 (3H, d); ^{13}C NMR δ: 129.8 (t, $^2J_{C-F} = 25.5$ Hz), 121.5 (t, $^3J_{C-F} = 9.5$ Hz), 120.6 (t, $^1J_{C-F} = 240.9$ Hz), 69.7 (t, $^2J_{C-F} = 29.5$ Hz), 16.3 (t, $^3J_{C-F} = 2.3$ Hz); ^{19}F NMR δ: −112.2 (2F, dt, $^2J_{F-F} = 247.2$ Hz, $^3J_{H-F} = 10.7$ Hz); LR-MS (EI) $C_5H_7OF_2$: 105 (13), 103 (19), 83 (14), 77 (30), 59 (11), 51 (20), 43 (53), 45 (100).

3.2.17. 3,3-Difluoropent-4-en-2-yl acetate (23)

In a dry reaction vessel, 0.950 ml of dry diethyl ether, triethyl amine (0.31 ml, 1.64 mmol), and 3,3-difluoropent-4-en-2-ol (0.12 g, 0.98 mmol) were combined and cooled to 0 °C. Acetyl chloride (0.058 ml, 0.82 mmol) was added slowly via a syringe and the reaction ran overnight. The reaction mixture was diluted with ether and the product was extracted with 0.6 M HCl, water, brine and dried over $MgSO_4$. Filtration and removal of ether resulted in a 0.080 g of **23** (yellow oil, yield 60%). ^{1}H NMR δ: 5.86 (1H, m), 5.66 (1H, m), 5.67 (1H, m), 5.09 (1H, m), 2.20 (3H, s), 1.23 (3H, m); ^{19}F NMR δ: −111.1 (2F, dt, $^2J_{F-F} = 250.2$ Hz, $^3J_{H-F} = 9.2$ Hz); LR-MS (EI) $C_7H_9O_2F_2$: 165 (7), 145 (10), 77 (5), 51 (7), 43 (100).

3.2.18. 1,1-Difluoro-2-methylbut-en-1-yl trifluoroacetate (25)

A dry reaction vessel was charged with (2,2-difluoro-3-methylcyclopropyl)methyl tosylate (**20**) (0.2 g), trifluoroacetic acid (0.2 ml) and maintained at 50 °C for 4 h. Then, the reaction mixture was cooled to room temperature. After vacuum transfer, 1 ml of $CDCl_3$ was added to the volatile reaction mixture and the solution was treated with $MgSO_4$ and Na_2CO_3 at 0 °C which gave the $CDCl_3$ solution of 1,1-difluoro-2-methylbut-3-en-1-yl trifluoroacetate (**25**). ^{1}H NMR δ: 5.76 (1H, ddd, $^3J_{trans\,H-H} = 17.58$ Hz, $^3J_{H-H} = 9.52$, 10.01 Hz), 5.28 (2H, m), 3.13 (^{1}H, m), 1.26 (3H, d); ^{19}F NMR δ: −79.5 (2F, dt, $^2J_{F-F} = 148.0$ Hz, $^3J_{H-F} = 10.7$ Hz), 76.0 (3F, s); LRMS (EI) $C_7H_7O_2F_5$: 83 (12), 55 (100).

3.2.19. Buten-3-yl benzoate, 13

To a mixture of 3-hydroxybutene (25.6 g, 0.355 mol), triethylamine (48 g, 0.474 mol), and dry ethyl ether (100 ml), a 32.0 g (0.228 mol) portion of benzoyl chloride was added, dropwise. The reaction mixture was heated to reflux and allowed to react overnight. A 150 ml portion of ethyl acetate was added to the reaction mixture, which was then washed with 0.5 M HCl and brine and dried over $MgSO_4$. The solvent was removed, and the crude product was distilled (95 °C at 1 mmHg) giving 22.4 g of buten-3-yl

benzoate, **13** (57%). ^{1}H NMR δ: 8.07 (d, 2H), 7.5 (m, 3H), 5.95 (m, 1H), 5.60 (m, 1H), 5.38 (d, ^3J = 17.2 Hz, 1H), 5.25 (d, ^3J = 10.5 Hz, 1H), 1.43 (d, 3H); ^{13}C NMR δ: 166.0, 137.9, 133.1, 130.8, 129.8, 128.6, 116.1, 71.8, 20.3; HR-EI $C_{11}H_{12}O_2$. Calcd.: 176.0837, Found: 176.0873.

*3.2.20. 1-(2,2-Difluorocyclopropyl)ethyl benzoate, **14***

To 8.65 g (49.1 mmol) of the **13** and 13 mg (0.3 mmol) of NaF at 120 °C, 2.7 equivalents of TFDA were added via a pyrex syringe equipped with a Teflon® needle using a syringe pump at a rate of 0.49 ml/h resulting in an equal mixture of diastereomers of **14** (66%). ^{1}H NMR δ: 8.06 (m, 2H), 7.56 (m, 1H), 7.45 (m, 2H), 5.04 (m, 1/2H), 4.98 (m, 1/2H), 1.82–1.21 (m, 6H); ^{13}C NMR δ: 166.2, 165.7, 133.3, 133.3, 130.5, 130.4, 129.9, 128.6, 128.6, 113.2 (t, $^1J_{C-F}$ = 284 Hz), 113.0 (t, $^1J_{C-F}$ = 283 Hz), 69.7, 69.4, 27.7 (t, $^2J_{C-F}$ = 10 Hz), 27.1 (t, $^2J_{C-F}$ = 11 Hz), 21.1, 19.6, 16.5 (t, $^2J_{C-F}$ = 10 Hz), 14.7 (t, $^2J_{C-F}$ = 12 Hz); ^{19}F NMR δ: −127.7 (dt, $^2J_{F-F}$ = 162 Hz, $^3J_{H-F}$ = 15 Hz, 1/2F), −129.0 (dt, $^2J_{F-F}$ = 162 Hz, $^3J_{H-F}$ = 13 Hz, 1/2F), −142.4 (dd, $^2J_{F-F}$ = 162 Hz, $^3J_{H-F}$ = 13 Hz, 1/2F). −144.3 (dd, $^2J_{F-F}$ = 162 Hz, $^3J_{H-F}$ = 13 Hz, 1/2F); HRMS-EI ($C_{12}H_{12}F_2O_2$). Calcd.: 226.0805, Found: 226.0715.

3.2.21. 1-(2,2-Difluorocyclopropyl)ethanol

1-(2,2-Difluorocyclopropyl)ethyl benzoate (**14**) (2.10 g, 9.3 mmol) in 20 ml 3 M aqueous NaOH was heated to reflux overnight. Extraction with ethyl ether, washing with brine, drying with anhydrous $MgSO_4$, and removal of ethyl ether resulted in 0.72 g of the alcohol (63% yield). ^{1}H NMR δ: 3.65 (m, 1/2H), 3.60 (m, 1/2H), 1.70 (bs, ^{1}H), 1.65–1.08 (m, 6H); ^{13}C NMR δ: 114.1 (t, $^1J_{C-F}$ = 282 Hz), 113.5 (t, $^1J_{C-F}$ = 282 Hz), 67.1, 66.4, 29.9 (t, $^2J_{C-F}$ = 10 Hz), 29.7 (t, $^2J_{C-F}$ = 9.6 Hz), 23.7, 22.0, 15.3 (t, $^2J_{C-F}$ = 10 Hz), 14.6 (t, $^2J_{C-F}$ = 9.6 Hz); ^{19}F NMR δ: −127.6 (dtd, $^2J_{F-F}$ = 162.8 Hz, $^3J_{H-F}$ = 12.8, 4.3 Hz, 1/2F), −128.6 (dtd, $^2J_{F-F}$ = 162.8 Hz, $^3J_{H-F}$ = 12.8, 4.3 Hz, 1/2F), −143.3 (dd, $^2J_{F-F}$ = 162.3 Hz, $^3J_{H-F}$ = 12.8 Hz, 1/2F), −145.3 (dd, $^2J_{F-F}$ = 162.3 Hz, $^3J_{H-F}$ = 12.8 Hz, 1/2F); MS-EI *m/z* (relative intensity): 105 ($M - H_2O$, 100).

*3.2.22. 1-(2,2-Difluorocyclopropyl)ethyl tosylate, **27***

Under nitrogen, a 1.56 g (8.2 mmol) portion of tosyl chloride was added to a mixture of 1-(2,2-difluorocyclopropyl)ethanol (4.1 mmol) in pyridine (7.5 ml) at 0 °C for 5 h. A 20 ml portion of ether was added to the reaction mixture and washed with cold water and then 5% $NaHCO_3$ followed by 0.5 M HCl. The resulting organic mixture was dried over sodium sulfate. The resulting tosylate **27** was obtained by the removal of ether. ^{1}H NMR δ: 7.80 (d, 2H), 7.41 (d, 2H), 3.50 (m, 1H), 2.50 (s, 3H), 1.5–1.1 (m, 6H); ^{19}F NMR δ: −127.5 (dt, $^2J_{F-F}$ = 162.8 Hz, $^3J_{H-F}$ = 12.8 Hz, 0.6F), −129.7 (dt, $^2J_{F-F}$ = 162.8 Hz, $^3J_{H-F}$ = 12.8 Hz, 0.4F), −141.9 (dd, $^2J_{F-F}$ = 162.3 Hz, $^3J_{H-F}$ = 12.8 Hz, 0.6H), −143.8 (dd, $^2J_{F-F}$ = 162.3 Hz, $^3J_{H-F}$ = 12.8 Hz, 0.4H).

3.3. Solvolysis procedures and kinetics

*3.3.1. Acetolysis of (2,2-difluoro-3-methylcyclopropyl)methyl tosylate (**20**)*

A capillary tube charged with (2,2-difluoro-3-methylcyclopropyl)methyl tosylate (**20**) (5.4 mg), HOAc (40 μl), and Ac_2O (7.9 μl) was maintained at 96.3 (±0.2) °C in a Varian VXR-500 NMR. The progression of the reaction was monitored by ^{19}F NMR at 282 MHz by placing the sealed capillary tube in a dry NMR tube, adding $CDCl_3$, and obtaining a spectrum every 15 min with 1.2 s of acquisition time. During the course of the reaction, four major products were observed. The doublet at −75.8 ppm was assigned as 1,1-difluoro-2-methylbut-3-en-1-yl tosylate (**22**); the AB patterns centered at −80.3, −110.1, and −140.5 ppm were assigned as 1,1-difluoro-2-methylbut-3-en-1-yl acetate (**21**), 3,3-difluoropent-4-en-2-yl acetate (**23**), (2,2-difluoro-3-methylcyclopropyl)methyl acetate (**24**), respectively. The disappearance of starting material followed first-order kinetics (Figs. 6 and 7).

*3.3.2. Trifluoroacetolysis of (2,2-difluoro-3-methylcyclopropyl)methyl tosylate (**20**)*

A capillary tube (sealed) with (2,2-difluoro-3-methylcyclopropyl)methyl tosylate (6.2 mg) and trifluoroacetic acid (50 μl) was maintained at 50.7 (±0.2) °C in an oil bath. The progression of the reaction was monitored by ^{19}F NMR by placing the sealed capillary tube in a dry NMR tube and solvating with $CDCl_3$. During the course of the reaction, two major products were observed. The doublet of doublet signal at −75.4 ppm in the ^{19}F NMR was assigned to 1,1-difluoro-2-methylbut-3-en-1-yl tosylate (**22**) and the doublet of doublet signal at −81.0 ppm was assigned to 1,1-difluoro-2-methylbut-3-en-1-yl trifluoroacetate (**25**). The ratio of **25**:**22** was found to be 1:2.

*3.3.3. Solvolysis of 1-(2,2-difluorocyclopropyl)ethyl tosylate, **27***

In a 1.1–1.2 mm i.d. × 10 mm pyrex capillary tube, 5.7 mg (0.021 mmol) of tosylate **27** was added to 5.9 mg of acetic anhydride, 0.5 mg of α,α,α-trifluorotoluene, and 40 μl glacial acetic acid. The reaction tube was sealed using a flame and placed in an NMR tube along with $CDCl_3$. In a Varian VXR 300 MHz NMR spectrometer, the sample was heated to 40.0 °C where a ^{19}F NMR spectrum was recorded every 30 min to measure the disappearance of starting material and the appearance of product. Four major ring-opened products were observed in the ^{19}F NMR. Based upon the parent system, the triplets (J = 13 Hz) at −67.9 and −68.3 ppm were assigned as *cis*- and *trans*-1,1-difluoropent-3-en-1-yl tosylate, **29**, respectively. The triplets (J = 13 Hz) at −71.1 and −71.6 ppm were assigned as *cis*- and *trans*-1,1-difluoropent-3-en-1-yl acetate, **28**, respectively.

$$\ln\left(\frac{C_0}{C_t}\right) = (1.64E-05 \pm 2.3E-07)t - (2.08E-03 \pm 4.3E-03) \quad (1)$$

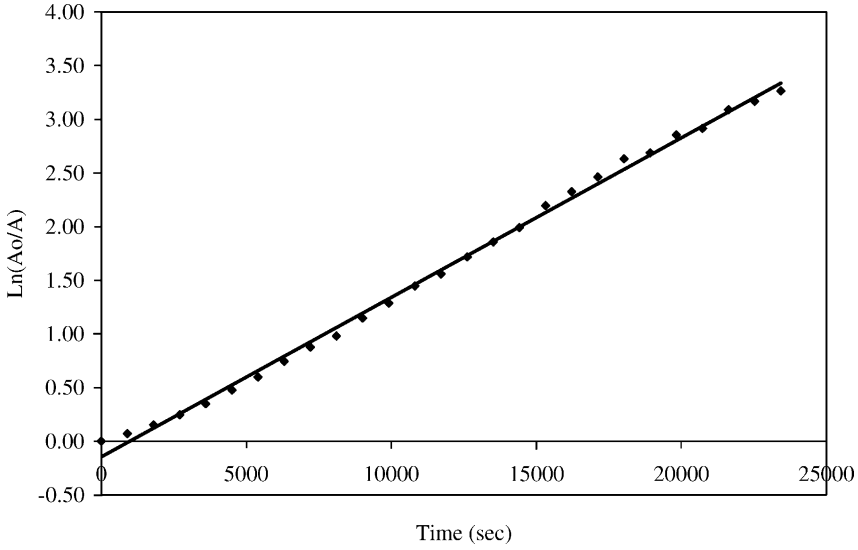


Fig. 6. Acetolysis of (2,2-difluoro-3-methylcyclopropyl)methyl tosylate at (96.3 (±0.1) °C).

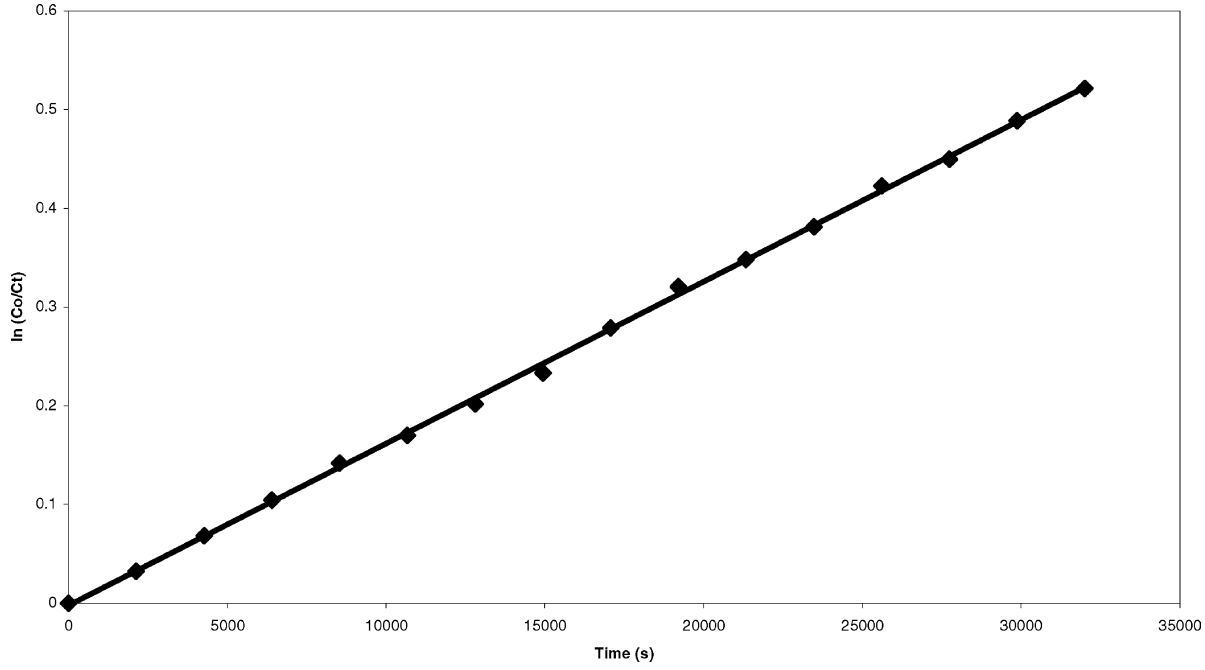


Fig. 7. Plot of kinetic data for solvolysis of **27**.

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