SUPPORTING INFORMATION

Reactivity and Regiochemical Behavior of the 2,2-Difluorocyclopropylcarbinyl Cation. A New and Improved Mechanistic Probe to Distinguish Radical and Carbocation Intermediates

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Experimental Section

General remarks

Instruments: All ^{1}H NMR spectra were recorded at 300 MHz, ^{13}C spectra at 75 MHz and ^{19}F 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 parts per million (ppm) down field relative to tetramethylsilane (TMS) (δ=0.00) in $CDCl_3$. ^{13}C signals are expressed in ppm using the central peak of the $CDCl_3$ signal as internal standard (δ=77.00). ^{19}F NMR are reported in ppm using $CFCl_3$ as internal standard (δ=0.00). All kinetic studies were carried out using sealed NMR tubes submerged in an oil-bath with a Statim temperature controller.

Reagents: All reagents were obtained from Fisher except those mentioned. THF was dried through distillation from Na/Benzophenone. 2,2-difluorocyclopropylcarbinol was prepared through a new highly efficient *gem*-difluorocyclopropanation procedure. The experimental detail will be published soon.

2,2-difluorocyclopropylcarbinyl tosylate

A dry 5-ml round bottom flask was charged with 2,2-difluorocyclopropylcarbinol (115mg, 1.06 mmol, 1 eqv.) and pyridine (1.8ml). At 0 ^{0}C, tosyl chloride (408mg, 2.14 mmol, 2eqv.) was added and the reaction mixture maintained at –5 ^{0}C for 12 hrs. Then, 3 ml of ice water was added and the solution extracted with diethyl ether (2ml x 6). The combined ether layer was washed with 6 M HCl, water, brine, dried (Na_2SO_4 and Na_2CO_3). Removal of the solvent under reduced pressure afforded 146 mg of pure sulfonate (yellow oil, yield 53%). The tosylate was stored in diethyl ether solution over Na_2CO_3 (anhydrous); ^{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 145.096, 132.790, 129.939, 127.896, 112.300(t, $J_{t\,(F-C)}$ =283.0 Hz), 66.902 (d, J_d =5.5 Hz), 21.664, 20.933(dd, $J_{d\,(C-F)}$ =12.1 Hz, $J_{d\,(C-F)}$ =10.6 Hz), 15.294 (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 (1H, dddt, $J_{d\,(F-F)}$ =162.3 Hz, $J_{d\,(H-F)}$ = 13.3 Hz, $J_{d\,(H-F)}$ = 4.8 Hz, $J_{t\,(H-F)}$ = 1.7 Hz; HRMS (CI), $C_{11}H_{13}O_3F_2S$ $(M+1)^+$, calc. 262.0554 , found 263.0541(3.7), 91.0362(100).

2,2-difluorocyclopropylcarbinyl acetate

A dry 5-ml round bottom flask was charged with 2,2-difluorocyclopropylcarbinol (100mg, 0.93 mmol, 1 eqv.) and pyridine (1.2ml). At 0 ^{0}C, acetic anhydrous (300mg, 2.94 mmol, 3.2eqv.) was added and the reaction mixture maintained at –5 ^{0}C for 12 hours. Then, 3 ml of ice water was added and the solution extracted with diethyl ether (2ml x 6). The combined ether layer was washed with 6 M HCl, water, brine, dried

(Na_2SO_4 and Na_2CO_3). The removal of solvent by distillation afforded 82 mg of colorless liquid (yield 58%); ^{1}H NMR δ 4.19 (1H, dddd, $J_{d\,(H-H)}$ = 12.0 Hz, J_d = 7.5 Hz, J_d = 2.7 Hz, J_d = 1.2 Hz), 4.03 (1H, ddd, $J_{d\,(H-H)}$ = 12.0 Hz, J_d = 8.1 Hz, J_d = 1.8 Hz), 2.07(3H, s), 1.93 (1H, m), 1.50 (1H,m), 1.18 (1H, m); ^{13}C NMR δ 170.868, 112.941(t, $J_{t(C-F)}$ =283.0 Hz), 61.167 (d, J_d = 5.5 Hz), 20.989 (t, $J_{t(C-F)}$ =11.6 Hz), 20.836, 14.954 (t, $J_{t(C-F)}$ =11.0 Hz); ^{19}F NMR δ -129.77 (1F, dtdd, $J_{d\,(F-F)}$ =160.9 Hz, $J_{t(H-F)}$ =12.1 Hz, $J_{d(H-F)}$ =3.7 Hz, $J_{d(H-F)}$ =2.8 Hz), -143.996 (1F, dddt, $J_{d(F-F)}$ =160.9 Hz, $J_{d(H-F)}$ =13.3 Hz, $J_{d(H-F)}$ =4.8 Hz, $J_{t(H-F)}$ =1.5 Hz); HRMS (CI), $C_6H_9O_2F_2$ $(M+1)^+$, calc. 151.0571, found 151.0643(100).

1,1-difluoro-3-butenyl tosylate

A dry NMR tube with valve was charged with 2,2-difluorocyclopropylcarbinyl tosylate (0.2 g), trifluoroacetic acid (0.2 ml) and maintained at 53 ^{0}C for 12 hrs. Then, the reaction mixture was cooled to room temperature. After vacuum transfer, 1ml diethyl ether was added to the residue and the solution was treated with $MgSO_4$ and Na_2CO_3 at 0 ^{0}C. After filtration of the mixture and removal of the solvent, the residue was purified by flash column chromatography (hexanes: benzene=3:1) which provided **8** (R_f=0.12); ^{1}H NMR δ 7.593 (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 -68.300 (2F, t, $J_{t(H-F)}$ =12.7 Hz); ^{13}C NMR δ145.663, 134.035, 129.763, 128.054, 126.262, 123.789(t, $J_{t\,(C-F)}$ = 276.0 Hz), 121.993, 40.601(t, $J_{t\,(C-F)}$ = 27.4 Hz), 21.841; HRMS (FAB) $C_{11}H_{13}O_3F_2S$ $(M+1)^+$, calc. 263.0553, found 263.0553 (25), 173.0157(100), 91.0554(36).

1,1-difluoro-3-butenyl trifluoroacetate

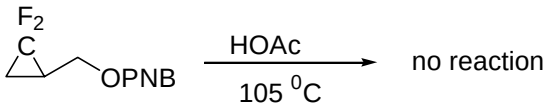
A dry NMR tube with valve was charged with 2,2-difluorocyclopropylcarbinyl tosylate (0.2 g), trifluoroacetic acid (0.2 ml) and maintained at 53 ^{0}C for 12 hrs. Then, the reaction mixture was cooled to room temperature. After vacuum transfer, 1 ml of $CDCl_3$ was added to the volatile reaction mixture and the solution treated with $MgSO_4$ and Na_2CO_3 at 0 ^{0}C which gave the $CDCl_3$ solution of 1,1-difluoro-3-butenyl trifluoroacetate; ^{1}H NMR δ 5.73 (1H, ddt, $J_{d\,(H-H)}$ = 17.1 Hz, $J_{d\,(H-H)}$ = 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 -71.647 (2F, t, $J_{t\,(F-H)}$ = 12.7 Hz), -75.958 (3F, s); HRMS (CI), $C_6H_6O_2F_5$ $(M+1)^+$, calc. 205.0288, found 205.0296(1.12), $C_4H_5F_2$ $(M+1-CF_3COOH)^+$, calc. 91.0359, found 91.0372(100)

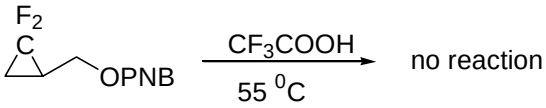
2,2-difluorocyclopropylcarbinyl trifluoroacetate

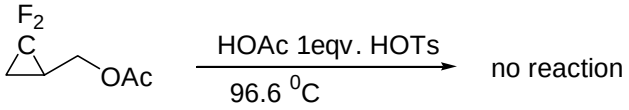
A dry 5 ml round bottom flask equipped with a magnetic stirring bar was charged 2,2-difluorocyclopropylcarbinol (200mg, 1.85 mmol) and 2,6-luctidine (218mg, 2 mmol, Acros). At 0 ^{0}C, under N_2, trifluoroacetic anhydrous (390 mg) was added dropwise and then the temperature raised to room temperature. Distillation (65~66 ^{0}C) of the reaction mixture afforded 280 mg colorless liquid (yield 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 157.356(q, $J_{q(C-F)}$ =42.8 Hz) , 114.370 (q, $J_{q(C-F)}$ =285.0 Hz), 112.200 (dd, $J_{d(C-F)}$ =282.0, $J_{d(C-F)}$ =284.0 Hz), 64.668 (d, J_d = 6.0 Hz), 20.225 (dd, $J_{d(C-F)}$ =12.6 Hz, $J_{d(C-F)}$ =11.1 Hz), 15.234 (t, $J_{t(C-F)}$ =11.6 Hz); ^{19}F NMR δ -75.436 (3F, s), -129.483 (1F, dt, $J_{d\,(F-F)}$ = 162.3 Hz, $J_{t\,(F-H)}$ = 10.5 Hz),

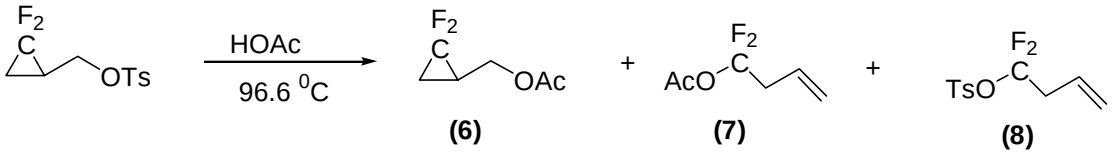
-143.291(1F, ddd, $J_{d(F-F)}$ = 162.0 Hz, $J_{d(F-H)}$ = 12.7 Hz, $J_{d(F-H)}$ =6.5 Hz) HRMS (CI), $C_6H_6O_2F_5$ $(M+1)^+$, calc. 205.0288, found 205.0283(0.62), 91.0369(100).

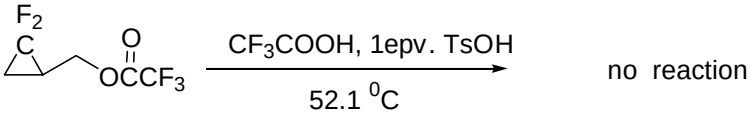
Solvolysis Studies

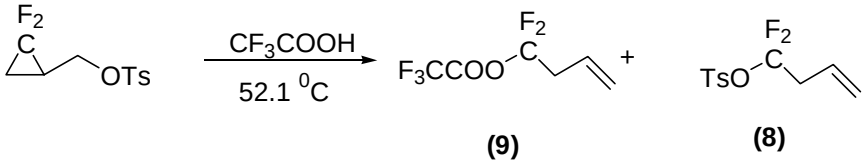












General procedure of kinetic studies

All of the kinetic studies followed this procedure except as described specifically. A capillary tube sealed with C_6D_6, 10mg of starting ester, 0.5mg of α,α,α-trifluorotoluene and 0.5ml solvent were sealed in a dry NMR tube. The tube was maintained at the given temperature in an oil bath and the progress of reaction was monitored by ^{19}F NMR.

Acetolysis of 2,2-difluorocyclopropylcarbinyl acetate

A 2ml vial was charged with TsOH .H_2O (6.3 mg, 0.03mmol), AcOH (50 µl), Ac_2O (6 mg), 2,2-difluorocyclopropylcarbinyl acetate (5-mg, 0.03 mmol) and internal standard α,α,α-trifluorotoluene (1.2mg). The solution was then sealed in capillary tube and maintained at 96.6 ^{0}C for 10 hrs. The ^{19}F NMR indicated no reaction.

Trifluoroacetolysis of 2,2-difluorocyclopropylcarbinyl trifluoroacetate

A 2ml vial was charged with TsOH.H_2O (9.3mg, 0.05mmol), CF_3COOH (50µl), $(CF_3CO)_2O$ (6mg), 2,2-difluorocyclopropylcarbinyl trifluoroacetate (10mg, 0.05 mmol) and internal standard α,α,α-trifluorotoluene (1.8mg). The solution was sealed in capillary tube and maintained at 52.1 ^{0}C for 4 hrs. The ^{19}F NMR indicated no reaction.

Trifluoroacetolysis of 2,2-difluorocyclopropylcarbinyl tosylate

A capillary tube (sealed) with 2,2-difluorocyclopropylcarbinyl tosylate (6mg), α,α,α-trifluorotoluene (0.3mg, internal standard) and trifluoroacetic acid (50µl) was maintained at 52.1± 0.2 ^{0}C. In the course of the reaction, two major products were

observed. The triplet peak at –69.326 ppm in ^{19}F NMR was assigned as 1,1-difluoro-3-butenyl tosylate (**8**); the other triplet peak at –73.651ppm was assigned as 1, 1-difluoro-3-butenyl trifluoroacetate (**9**). The ratio of 1,1-difluoro-3-butenyl trifluoroacetate: 1,1-difluoro-3-butenyl tosylate had been relatively stable (see Table 1). The disappearance of starting material followed first-order fashion (Table 1, Figure 1). The total mass balance of the reaction is 92.3%.

Acetolysis of 2,2-difluorocyclopropylcarbinyl tosylate

1. In pure HOAc

A capillary tube charged with 2,2-difluorocyclopropylcarbinyl tosylate (10mg), α,α,α-trifluorotoluene (0.5mg) and AcOH (50µl) was maintained at 96.3 ± 0.2 ^{0}C. In the course of the reaction, 3 major products were observed in ^{19}F NMR. The triplet peak at –67.851 ppm was assigned as 1,1-difluoro-3-butenyl tosylate (**8**); the triplet peak at –70.929 ppm was assigned as 1,1-difluoro-3-butenyl acetate (**7**); the AB pattern peaks at -129.5 ppm and –144.1 ppm was assigned as 2,2-difluorocyclopropylcarbinyl acetate (**6**). The disappearance of starting material followed first-order kinetics (Table 2, Figure 2). The ratio of ring closed product (**6**) to total ring opened products [(**7**) + (**8**)] was relatively stable at the early stage of the reaction (Table 2). Total mass balance was 92%.

2. In 0.200 M NaOAc/HOAc

A capillary tube charged with 2,2-difluorocyclopropylcarbinyl tosylate (10mg), α,α,α-trifluorotoluene (0.5mg) and 0.200M NaAc/AcOH (50µl) was maintained at 96.6 ± 0.2 ^{0}C. The same pattern of ^{19}F NMR spectrum as above was obtained and the data are

summarized in Table 3. The disappearance of starting material followed the first-order pattern (Figure 3). The total mass balance in the course of reaction was 90.3%.

3. In 0.400 M NaOAc/HOAc

A capillary tube charged with 2,2-difluorocyclopropylcarbinyl tosylate (10mg), α,α,α-trifluorotoluene (0.5mg) and 0.400M NaAc/AcOH (50µl) was maintained at 96.6 ± 0.2 ^{0}C. The same pattern of ^{19}F NMR spectrum as above was obtained and the data are summarized in Table 4. The disappearance of starting material followed the first-order pattern (Figure 4). The total mass balance in the course of reaction was 90.3%.

Kinetic Data

Table 1.

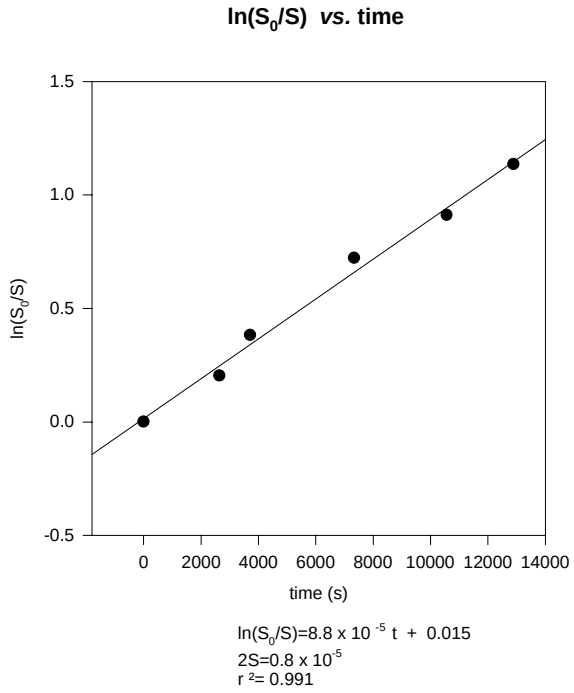
Trifluoroacetolysis of 2,2-difluorocyclopropylcarbinyl tosylate at (52.1± 0.1 ^{0}C)

	Time (sec.)	(5) [a]	$(5)_0/(5)$	$\ln[(5)_0/(5)]$	(9) : 8)
1	0	24.54	1.0000	0.0000	
2	2650	20.02	1.2258	0.2036	2.1
3	3721	16.68	1.4658	0.3824	2.1
4	7339	11.92	2.0587	0.7221	2.1
5	10562	9.87	2.4860	0.9108	2.0
6	12901	7.88	3.1142	1.1360	2.0

a. The relative amount of 2,2-difluorocyclopropylcarbinyl tosylate was represented by the integration of the peak at -145.6 in ^{19}F NMR.

Figure 1.

Trifluoroacetolysis of 2,2-difluorocyclopropylcarbinyl tosylate at (52.1± 0.1 ^{0}C)



$$k_t = k_\Delta = (8.8 \pm 0.8) \times 10^{-5}\ s^{-1}$$

Table 2.

Acetolysis of 2,2-difluorocyclopropylcarbinyl tosylate in pure HOAc at (96.3 ± 0.2) ^{0}C

	Time (sec.)	(5)[a]	$(5)_0/(5)$	$\ln[(5)_0/(5)]$	(6)[b] : (7) + (8)[c]	(7) : (8)
1	0	48.10	1.0000	0.0000		
2	7203	44.21	1.0882	0.0845	1.3	8.8
3	14505	40.52	1.1871	0.1715	1.2	7.8
4	21600	38.61	1.2358	0.2117	1.3	6.9
5	28274	35.71	1.3470	0.2979	2.6	3.2

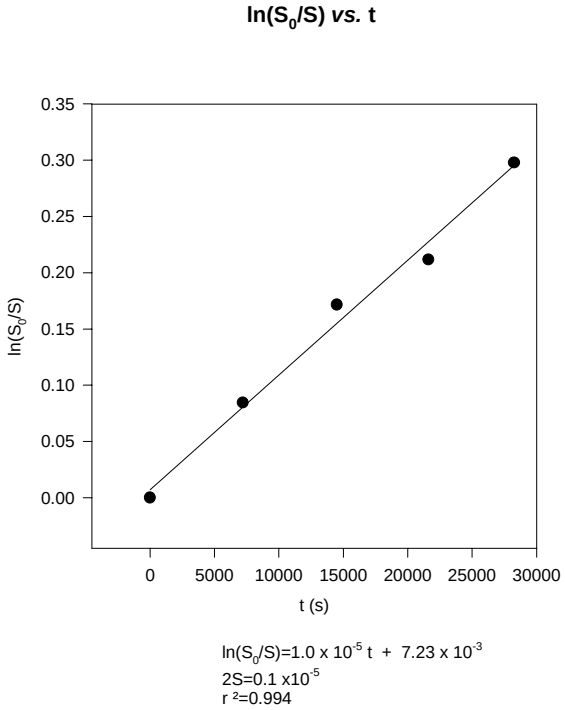
a. The relative amount of 2,2-difluorocyclopropylcarbinyl tosylate was represented by the integration of the peak at -145.6 in ^{19}F NMR.

b. Because of overlap of the peaks of (6) with starting material, few assumptions were employed to obtain (6)'s total integration. (i). The integration values of the two sets of peaks of AB peak are equal. (ii). The ratio of the integration values of the set of peaks around –144 ppm is 1.15. For example, (-143.3) : (-143.7) = 1.15.

c. Because there were no other significant amount of products were observed, we assumed that only the formations of (6), (7) and (8) contribute to the total rate.

Figure 2.

Acetolysis of 2,2-difluorocyclopropylcarbinyl tosylate in pure HOAc at (96.3 ± 0.2) ^{0}C



$$k_t = (1.0 \pm 0.1)\ x10^{-5}\ s^{-1}$$

$$k_\Delta = k_t/2.3 = 4.3\ x\ 10^{-6}\ s^{-1}$$

$$k_s = 1.3\ k_t/2.3 = 5.7\ x\ 10^{-6}\ s^{-1}$$

Table 3. Acetolysis of 2,2-difluorocyclopropylcarbinyl tosylate in 0.200 M NaOAc/HOAc at (96.6 ± 0.2) ^{0}C

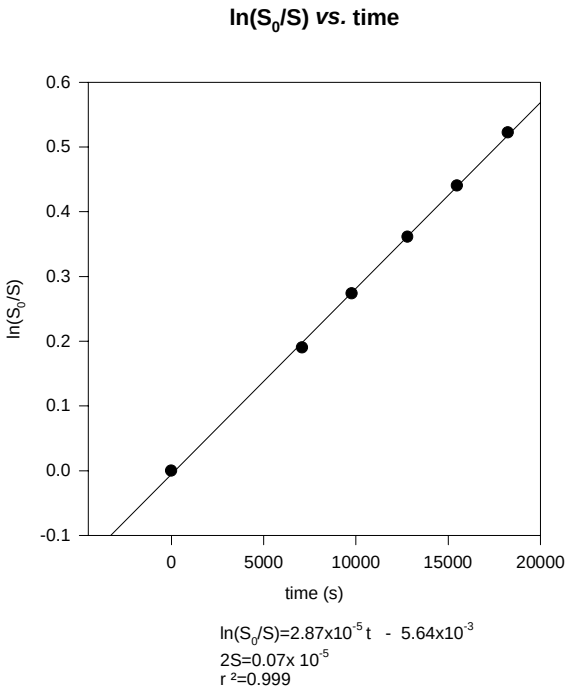
	Time (sec.)	(5)[a]	$(5)_0/(5)$	$\ln[(5)_0/(5)]$	(6)[b] : [(6) + (7) + (8)]
1	0	93.62	1.0000	0.0000	
2	7093	77.40	1.2096	0.1903	84.0%
3	9793	71.20	1.3149	0.2738	85.7%
4	12793	65.26	1.4346	0.3609	86.5%
5	15493	60.30	1.5525	0.4399	86.9%
6	18253	55.53	1.6859	0.5223	87.5%

a. The relative amount of 2,2-difluorocyclopropylcarbinyl tosylate was represented by the integration of the peak at -145.6 in ^{19}F NMR.

b. Because there were no other significant amount of products were observed, we assumed that only the formations of (6), (7) and (8) contribute to the total rate.

Figure 3.

Acetolysis of 2,2-difluorocyclopropylcarbinyl tosylate in 0.200 M NaOAc/HOAc at (96.6 ± 0.2) ^{0}C



$$k_t = (2.87 \pm 0.07)\ x10^{-5}\ s^{-1}$$

$$k_s = k_t\ x\ 84.0\% = 2.41\ x\ 10^{-5}\ s^{-1}$$

$$k_\Delta = k_t - k_s = 4.6\ x10^{-6}\ s^{-1}$$

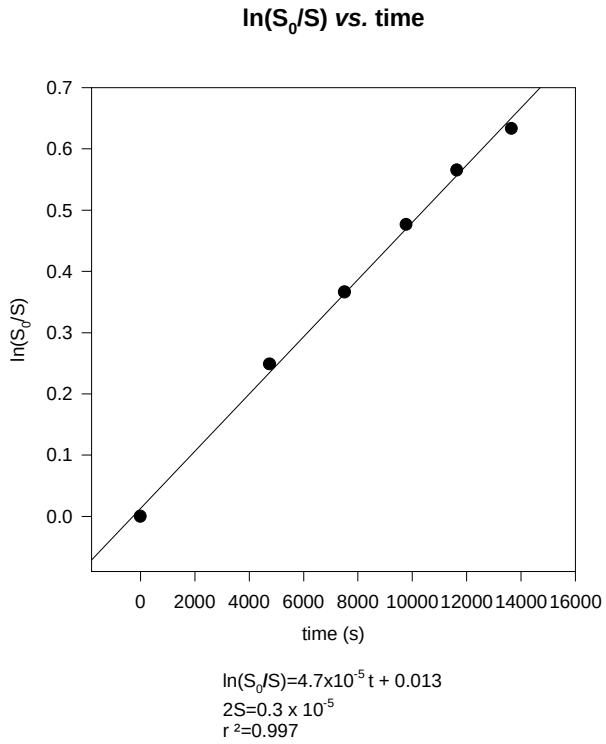
Table 4. Acetolysis of 2,2-difluorocyclopropylcarbinyl tosylate in 0.400 M NaOAc/HOAc at (96.3 ± 0.2) ^{0}C

	Time (sec.)	(5)[a]	$(5)_0/(5)$	$\ln[(5)_0/(5)]$	(6)[b] : [(6) + (7) +(8)]
1	0	95.30	1.0000	0.0000	
2	4753	74.33	1.2821	0.2485	90.0%
3	7503	66.08	1.4422	0.3662	91.9%
4	9783	59.19	1.6100	0.4762	92.6%
5	11643	54.15	1.7600	0.5653	93.4%
6	13653	50.60	1.8834	0.6331	93.7%

a. The relative amount of 2,2-difluorocyclopropylcarbinyl tosylate was represented by the integration of the peak at -145.6 in ^{19}F NMR.

b. Because there were no other significant amount of products were observed, we assumed that only the formations of (6), (7) and (8) contribute to the total rate.

Figure 4. Acetolysis of 2,2-difluorocyclopropylcarbinyl tosylate in 0.400 M NaOAc/HOAc at (96.6 ± 0.2) ^{0}C



$$k_t = (4.7 \pm 0.3)\ x10^{-5}\ s^{-1}$$

$$k_s = k_t\ x\ 90.0\% = 4.2\ x\ 10^{-5}\ s^{-1}$$

$$k_\Delta = k_t - k_s = 4.7\ x10^{-6}\ s^{-1}$$