Abstract

Title of Thesis: Synthesis of Highly-Strained Gem Difluoro
Compound by Reaction of Difluoromethylene
with Cycloalkenes

De-yi Yang, Master of Science in Chemistry, 1989

Thesis Directed by: Dr. A. Greenberg
Professor of Chemistry

trans-Cyclooctene is thought to be more reactive than cis-cyclooctene due to its trans-structure. When cis or trans-clooctene reacts with difluormethylene ($:CF_2$), trans-9,9-difluorobicyclo[6,1,0] nonane was generated in much higher yield than cis-9,9-difluorobicyclo[6,1,0]nonane. $[Ph_3P^+CF_2Br]Br^-$ was chosen to be the difluoromethylene precursor in this study. The reason was that the reaction condition for trans-cyclooctene and $:CF_2$ should be at low temperature. Only $[Ph_3P^+CF_2Br]Br^-$ could generate CF_2 at lower temperature (e.g. room temperature). We succeeded in the synthesis of trans-9,9-difluorobicyclo[6,1,0]nonane and its cis isomer and have demonstrated a principle of CF_2 reactivity.

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Synthesis of Highly-Strained Gem-Difluoro Compounds

by Reaction of Difluoromethylene and Cycloalkenes

By: Deyi Yang

Thesis submitted to the faculty of the Graduate School of the New Jersey Institute of Technology in partial fulfillment of the requirments for the degree of Master of Science in Chemistry.

1989

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Approval Sheet

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Compounds by Reaction of Difluoromethylene
with Cycloalkenes.

Name of Candidate: De-yi Yang
Master of Science in Chemistry
1989

Thesis and abstract approved:

_____   5/12/89

Dr. Arthur Greenberg   Date
Professor of Chemistry
Department of Chemical Engineering,
Chemistry & Environmental Science

_____   5/12/89

Dr. Barbara Kebbekus   Date
Professor of Chemistry
Department of Chemical Engineering,
Chemistry & Environmental Science

_____   5/12/89

Dr. Guanli Wu   Date
Visiting Professor of Chemistry
Department of Chemical Engineering,
Chemistry & Environmental Science

VITA

Name: De-yi Yang

Current Address:

Degree and data to be confered: M.S. in Chemistry.

Date of Birth:

Place of Birth:

College Attended	Date	Degree	Date of Degree
New Jersey Institute of Technology	9/87-10/89	M.S.	5/89
South China Institute of Technology	10/78-7/82	B.S	7/82

Major: Chemistry

Positions Held:

Position	Date	Address
Research Assistant	9/87-5/89	New Jersey Institute of Technology Newark, NJ 07102
Research Associate	9/82-12/86	South China Institute of Technology Guangzhou, China

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List of Figures

Chapter 1. Introduction

The history of fluorine[1] and its compounds is considerably younger than that of the other halogens. Hydrogen fluorine was first prepared by Scheele in 1771, and elementary fluorine was first prepared by Moissan in 1886. A systematic study of organic fluorine compounds did not start until about 1900 with Stewart's fluorine research in this field. A further important milestone in the chemistry of organic compounds of fluorine was the application of fluorinated derivatives of methane and ethane in refrigeration. This discovery initiated a new wave of research into the preparation and properties of these compounds. In about 1940 the importance of perfluoro derivatives was recognized, and several methods for their synthesis and manufacture were worked out, e.g. non-catalytic and catalytic fluorination with elementary fluorine, and fluorination by means of high-valency metal fluorides. At about the same time, polytetrafluoroethylene (Teflon) was discovered. Another important contribu-tion to fluorine chemistry was the development of electro-chemical fluorination by electrolysis of organic compounds in anhydrous hydrogen fluoride.

Numerous interesting reactions of fluorinated

derivatives being currently described bear witness to the increasing importance and development of organic fluorine compounds and showed that compounds and reactions of fundamental importance can still be discovered in this field.

The attractiveness and some peculiarities of the chemistry of organofluorine compounds originate in the physical and chemical properties of fluorinated compounds which differ considerably from those of other halogenated compounds, as well as from those of the corresponding hydrocarbons. A number of unusual chemical reactions are exhibited only by fluoro derivatives. Organic compounds of fluorine amount now to many thousands of derivatives (the 1974 Chemical Abstracts' estimate was 160,000), and publications in this field are now so numerous, that the literature dealing with fluorine compounds is rich and expanding extremely rapidly.

In recent years, considerable attention has been focused on the generation of difluoromethylene for the synthesis of gem-difluorocyclopropanes and other difluoromethylene derivatives. A variety of difluoromethylene precursors have been examined. Some

of the precursors are either inefficient or difficult to obtain in large quantities. Some of them require high temperature to release difluoromethylene. Some of them are convenient for generation of difluoromethylene from readily available commercial reagents. Different difluoromethylene precursors have been chosen for different synthetic applications for obtaining gem-difluorocyclopropane derivatives. For example, cis-cyclooctene can react with $PhHgCF_3$ and tri-n-butyltin bromide to give 9,9-difluorobicyclo[6,1,0]nonane in 56% yield[2] while reaction with Burton's reagent provides a much lower yield[3].

Methylene ($:CH_2$), the simplest carbene, is a very reactive reagent[4]. It can attack alkenes to form cyclopropanes. Methylene has two forms: singlet and triplet.
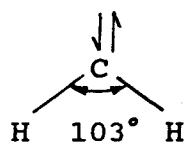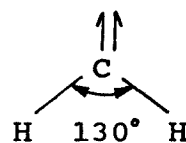
Singlet   Triplet

Singlet methylene has higher energy than triplet methylene. The difference in energy between these two forms is 11 kcal/mol. Since the carbon in carbenes has only six

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electrons, and is thus an electron-deficient carbon, carbenes have high reactivity.

Analogous to alkyl carbenes, dihalocarbenes, i.e. difluoromethylene ($:CF_2$); dichloromethylene ($:CCl_2$); dibromomethylene ($:CBr_2$) and diiodomethylene ($:CI_2$), have been used to prepare new bicyclic and tricyclic halogenated hydrocarbons and their derivatives.

Difluoromethylene is unusual because it is a ground-state singlet. Many methods are available for the generation of difluoromethylene: photolysis of difluorodiazirine (difluoroisodiazomethane)[5,6,7,8], treatment of chloro-difluoromethane with alkali alkoxides[9], treatment of dibromodifluoromethane with butyllithium[10], thermal decomposition of sodium chlorodifluoroacetate at 125-140°C [11,12,29], of perfluorocyclopropane, of perfluoropropane, of perfluoropropylene oxide[13,14,15], of tris(trifluoromethyl)-phosphine difluoride(perfluorotrimethylphosphorane)[16,17], of trimethyltrifluoromethylstannane alone or in the presence of sodium iodide[18,19,20,21,22,23], or of trifluoromethyl-phenylmercury [24,25,26].

Mitsch first reported that difluorodiazirine, CF_2N_2,

can be conveniently decomposed to difluoromethylene either thermally or by ultraviolet irradiation in 1964[27].

$$CF_2N_2 \xrightarrow{\text{hv}} [:CF_2] + N_2 \longrightarrow CF_2=CF_2 + N_2$$
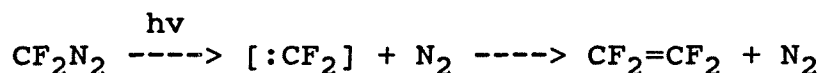
CF_2N_2 is stable in strong acids, storable without decomposition in glass and has been handled many times as a gas and neat liquid in the temperature range from $-196°C$ to $200°C$. Differential thermal analysis of CF_2N_2 indicates a gradual exothermic decomposition beginning at about $164°C$. The pyrolysis of difluorodiazirine (0.225g, 2.88×10^{-3} mole) was carried out by heating the sample at $165-180°C$ in a heavy-walled glass ampoule.

In the same year, Seyferth et al reported a new method of dihalomethylene generation based on trihalomethyl metal compounds[28]. This new procedure appeared to generate $:CF_2$ under the mildest conditions thus far and gave the best yields of gem-difluorocyclopropane:

$$(CH_3)_3SnCF_3 + NaI + >C=C< \longrightarrow (CH_3)_3SnI + >C\overset{\displaystyle\times}{\underset{F\ \ F}{\text{--}}}C< + NaF$$
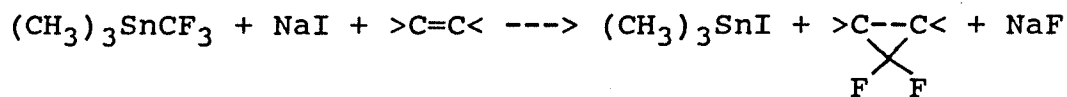
This reaction was carried out at $80°C$ for 12 hours in the presence of sodium iodide. When olefins are introduced into the reaction, gem-difluorocyclopropanes were produced

in yields ranging from moderate to excellent, depending on the nature of the olefins. This is one of the mildest procedures for the generation of difluoromethylene in solution. However, a drawback to the more general application of this reagent system in synthesis is the fact that trimethyl(trifluoromethyl)tin (Me_3SnCF_3) i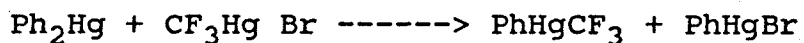s not a commercially available material. Furthermore, once prepared, Me_3SnCF_3 must be handled with suitable precautions, since it is unstable to atmospheric moisture. The CF_3 metal derivatives are even less practical. These considerations induced Seyferth and his co-workers to devote some attention to the possible application of trifluoromethylmercury compounds as CF_2 precursors.

In 1972, Seyferth et al provided another new method for difluoromethylene generation[29]. Their investigations showed phenyl(trifluoromethyl)mercury $(PhHgCF_3)$ to be an excellent difluoromethylene precursor. This procedure, however, suffers from the fact that neither of the organomercury starting materials is available commercially, and furthermore, phenylmercuric hydroxide first must be prepared in good purity for the phenylmercuric fluoride preparation. In order for phenyl(trifluoromethyl)mercury to be a really useful CF_2 reagent, a simpler and cheaper synthsis was

required. The improved preparative route to PhHgCF$_3$ is summarized by the following equations[30]:

$$HgO + 2CF_3CO_2H \longrightarrow Hg(O_2CCF_3)_2$$

$$Hg(O_2CCF_3)_2 \xrightarrow{300^{\circ}c} CF_3HgO_2CCF_3 + CO_2$$

$$CF_3HgO_2CCF_3 \xrightarrow{NaOH, H_2O} \xrightarrow{conc. HBr} CF_3HgBr$$

$$Ph_2Hg + CF_3Hg Br \longrightarrow PhHgCF_3 + PhHgBr$$
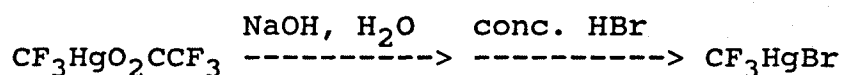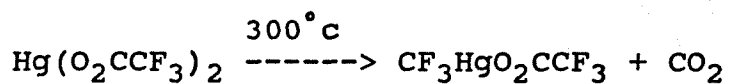
This route has the advantage that relatively cheap and readily available starting materials are used and that these reactions all are easily affected and can all be carried out on a fairly large scale. Phenyl(trifluoromethyl)mercury thus can be obtained in large amounts in good purity as a crystalline nonvolatile solid which is very stable thermally. It is not affected by light and atomospheric oxygen or moisture and thus can be stored indefinitely under ambient conditions.

PhHgCF$_3$ is very soluble in common organic solvents and serves as an excellent source of CF$_2$. The reaction PhHgCF$_3$ and 3 molar equiv of anhydrous sodium iodide in benzene in

the presence of olefins serves excellently in the synthesis of gem-difluorocyclopropanes. High product yields are obtained in reaction times of about 15 hours at 80-85°C.

The subsequent research of Seyferth et al[29] showed that CF_3HgI is a good CF_2 precursor (via the NaI procedure). However, CF_3HgI does not represent the ideal organomercury CF_2 reagent: it is volatile, hence organomercury toxicity can be a problem; it is decomposed by exposure to light (formation of red mercuric iodide) and in general has a poor shelf life. Thus, phenyl(trifluoromethyl)mercury definitely is a good reagent for generation of difluoromethylene, and is quite more reactive in CF_2 transfer chemistry than was the analogous Me_3SnCF_3 compounds[29].

In 1973, Burton and Naae[3] described a simple, facile and convenient one-step method of difluoromethylene generation from readily available commercial reagents. They found that when bromodifluoromethylphosphonium bromide, $[Ph_3P^+CF_2Br]Br^-$, was treated with sodium methoxide in the presence of tetramethylethylene, a 21% yield of the cyclopropane adduct was obtained.

Similarly, other olefins gave low yields of

cyclopropanes under similar conditions. This reaction

$$[Ph_3P^+CF_2Br]Br^- + NaOMe + \underset{Me}{\overset{Me}{>}}C=C\underset{Me}{\overset{Me}{<}} \quad ---\to \quad \underset{Me\quad Me}{\overset{Me\quad Me}{C-C}}_{F\quad F}$$
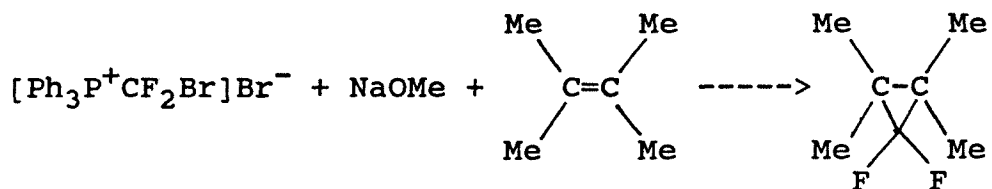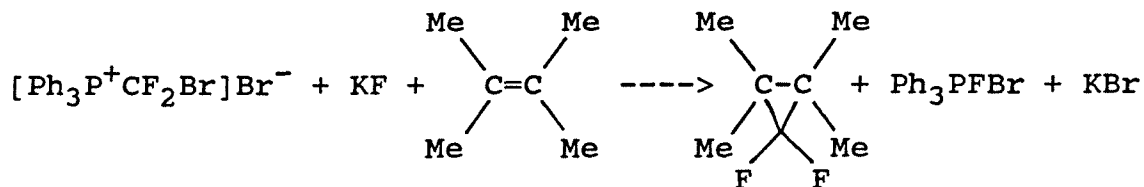
represents the first known example of carbene generation from a phosphonium salt. Burton and Naae indicated that a base was required to circumvent the competition of the nucleophile for the carbene. The base would form a strong bond to phosphorus and generate the carbene but would not compete for the carbene. The strength of the P-F bond (117 kcal/mole)[31] is comparable to the strength of the P-O bond (120 kcal/mole)[32]. Indeed, substitution of potassium fluoride or cesium fluoride in these reactions provides a smooth high-yield conversion of the phosphonium salt to the cyclopropane adduct.

$$[Ph_3P^+CF_2Br]Br^- + KF + \underset{Me}{\overset{Me}{>}}C=C\underset{Me}{\overset{Me}{<}} \quad --\to \quad \underset{Me\quad Me}{\overset{Me\quad Me}{C-C}}_{F\quad F} + Ph_3PFBr + KBr$$

In the subsequent investigation of this reactions, they found that prior preparation of $[Ph_3P^+CF_2Br]Br^-$ is unnecessary and that the phosphonium salt could be prepared

"in situ" from the appropriate phosphine and difluorodihalomethane in the presence of the fluoride salt and olefin. In 1975, Jefford and his co-workers used the same method as Burton's method to do the cheletropic reactions of fluoromethylene with norbornadienes[33].

$$R_3P + CF_2X_2 + MF + >C=C< \xrightarrow[\text{triglyme, 48 hr}]{\text{room temperature}} >C-C<$$
$$\underset{F \quad F}{\times}$$
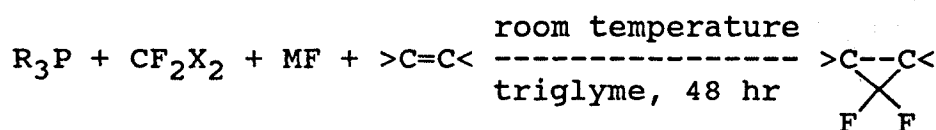
Other classical difluoromethylene precursors, such as tris(trifluoromethyl)difluorophosphorane[34], trifluoromethyl-iron tetracarbonyliodide[35], trifluoromethylgermanium tri-iodide[29], are less used now.

In the research reported in this dissertation, bromodifluoromethylphosphonium bromide was chosen as the difluoromethylene precursor. The synthetic goal of this study, trans-9,9-difluorobicyclo[6,1,0]nonane, the reaction product of trans-cyclooctene and difluoromethylene, might isomerize to its isomer, 9,9-difluoro-cis-bicyclo[6,1,0]nonane, under elevated temperature conditions. In addition, some difluoromethylene precursors (such as, PhHgCF$_3$) generate CF$_3{}^-$. When the CF$_3{}^-$ attacks trans-cyclooctene, isomerization might occur before reaction

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completion.   Thus, bromodifluoromethylphosphonium salt was chosen as the difluoromethylene precursor in the reaction of trans-cyclooctene and difluoromethylene since it is generated at mild temperatures and should add stereospecifically.

Chapter 2. Experimental Section

I. Materials and Apparatus

1. Starting Materials:

trans-Cyclooctene (made by the method of decomposition of N,N,N-trimethylcyclooctylammonium hydroxide[36])

cis-Cyclooctene [95% (GC), Fluka AG, No. 29650]

1-Methyl-1-cyclohexene [98%, Aldrich, No. 12980-1]

Potassium Fluoride [Purum p.a. Fluka, No. 60240]

Triethylene Glycol Dimethyl Ether (Triglyme) [>98% (GC), Fluka, No. 90420]

Triphenylphosphine (Ph$_3$P) [97% (HPLC), Fluka, No. 90420]

Dibromodifluoromethane (CBr$_2$F$_2$) [>98% (GC), Fluka, No. 34125]

2. Other Materials:

Ethanol, Anhydrous, [For UV, J.T. Baker, No. 9229-1]

Nitrogen [99.998%, Liquid Carbonic, UN-1066]

Helium [Zero Grade, Liquid Carbonic, UN-1046]

Hydrogen [Zero Grade, Liquid Carbonic, UN-1049]

3. Apparatus:

Varian 3300 Gas Chromatograph.

Varian 2700 Gas Chromatograph.

Varian EM 360L NMR Spectrometer.

Perkin-Elmer 1370 Infrared Spectrometer.

Capillary Melting Point Apparatus [Thomas Hoover]

II. Purification of Starting Materials

1. Commercial cis-cyclooctene and 1-methyl-1-cyclohexene were purified by distillation and dried by 5Å molecular sieves prior to use.

2. Commercial triphenylphosphine (m.p. 78-80 °c) was recrystallized from ethanol and converted to triphenyl-(bromodifluoromethyl)phosphonium bromide by reaction with commercial dibromodifluoromethane immediately before use. The melting point of the recrystallized triphenylphosphine is 80.5-81.5 °c.

3. Commercial potassium fluoride was dried by heating in a crucible over a free flame and allowing it to cool in a desiccator under slighly reduced pressure.
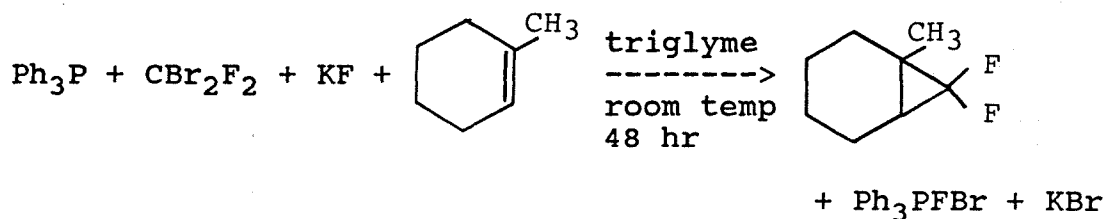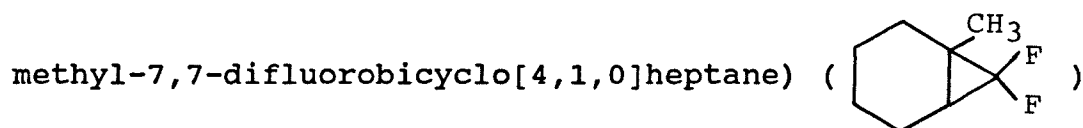

4. Triglyme was distilled and dried by 5Å molecular sieves prior to use[33].

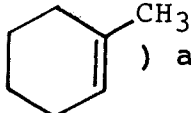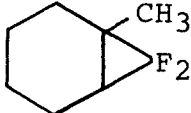III. Chromatographic and Spectroscopic Methods.

Analytical gas-liquid chromatography (GLC) separations were performed on Varian model 3300 and 2700 instruments. Identification of all new compounds were obtained by mass spectrometry (Rutgers, New Brunswick) and ^{1}H & ^{19}F NMR spectra (Rutgers, Newark). The relative product yields were obtained from the relative peak areas of GC.

IV. The Synthesis of 1-methyl-7,7-difluoronorcarane (or 1-methyl-7,7-difluorobicyclo[4,1,0]heptane) (

)

Ph_3P + CBr_2F_2 + KF +

triglyme
-------->
room temp
48 hr

+ Ph_3PFBr + KBr

To a solution of 26.23g (0.1 mole) of triphenylphosphine in 150 ml of triglyme was added 23.08 g (0.11 mole) of dibromodifluoromethane. The white salt triphenyl(bromo-difluoromethyl)phosphonium, was formed in 20 minutes after combining. The salt was stirred in solution under dry nitrogen for 30 minutes at room temperature. Next was added 9.62 g (0.1 mole) of 1-methyl-1-cyclohexene and 23.82 g (0.41 mole) of potassium fluoride. Stirring was

maintained at room temperature for 48 hours, whereupon a
dark-brown suspension resulted. The crude mixture was
distilled under vacuum (ca. 6 mm Hg) at room temperature.
The receiver was placed in a cool trap with a temperature of
-78 °C (dry ice-acetone). The crude mixture was starting
material ([structure: cyclohexene with CH_3 substituent]) and product ([structure: bicyclic norcarane with CH_3 and F_2 substituents]). The product was
isolated by GC (Varian 2700, TCD 50 °C) (Figure 1). Peak 2
was identified as the starting material and peak 3 as the
product. The yield of 1-methyl-7,7-difluoronorcarane is 22.1
%. The structure of the product (peak 3) was identified by
GC/MS (Figure 2), ^{19}F NMR (figure 3). In Figure 2, the peak
occuring at a mass of 146 corresponded to a fragment of the
product (MW=146). The other peak occured at a mass of 131
corresponded to M-CH_3. In Figure 3, the doublet peak at δ =
-81.6 appeared to be that of F_1 in the product, the another
doublet peak at δ = -72 appeared to be that of F_2. These two
fluorines were in different chemical surroundings. F_2 could
couple with the neighbor H atom. Thus, the doublet peak (δ =
-72) was split to two peaks on each peak. Therefore, the
data from the Figure 2 and 3 proved the existence of the
product.

Detector: TCD, 280°C
Injector: 250°C
Column: Initial 75°C
          Final   230°C
          Rate   20°C/min
Flow Rate: 28.0 ml/min

GC: Varian 2700

Triglyme

CH₃
F₂

CH₃

Start
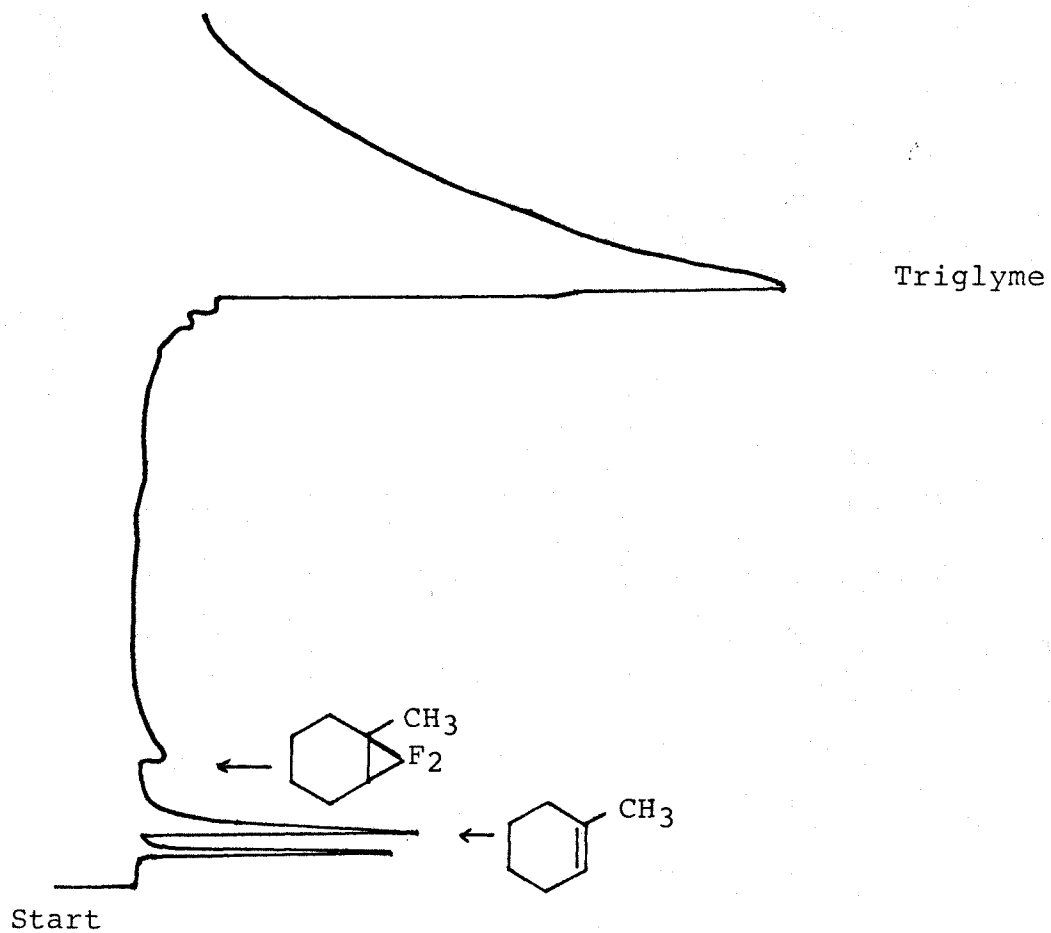
Figure 1. GC Chromatogram of the Mixture
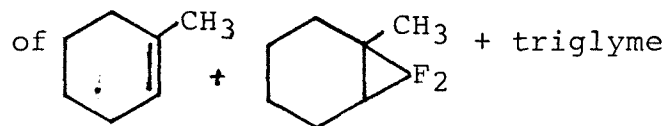
of [structure with CH₃] + [structure with CH₃ and F₂] + triglyme

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Figure 2. Mass Spectrum of 1-Methyl-7,7-difluorobicyclo[4,1,0]heptane
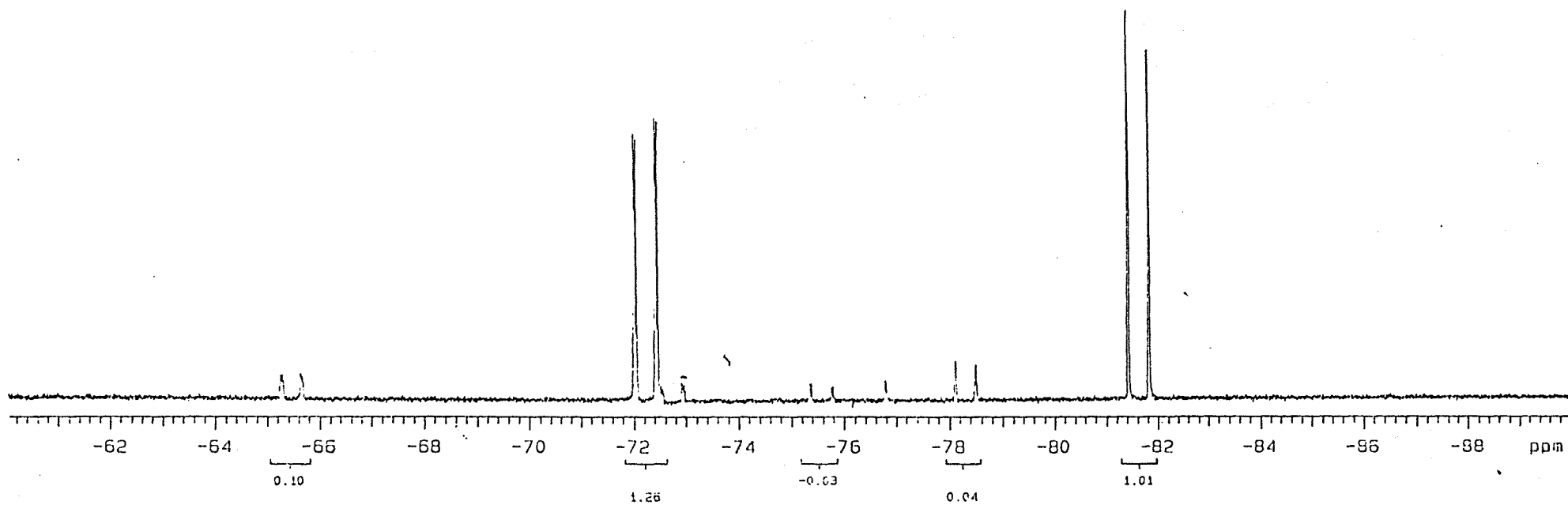
Figure 3. ^{19}F NMR of 1-Methyl-7,7-difluorobicyclo[4,1,0]heptane

(Chemical Shifts Relative To $C_6H_5-CF_3$ External Standard)

V. The Synthesis of cis-9,9-difluorobicyclo[6,1,0]nonane

Ph_3P + CBr_2F_2 + KF + [cyclooctene] $\xrightarrow[50°c, \ 48 \ hr]{triglyme}$ [product with F, F] + Ph_3PFBr + KBr

In a similar experiment, 23.2g (0.1 mole) of triphenylphosphine in 150 ml of triglyme was allowed to react at 50°C with 26 g (0.11 mole) of dibromodifluoro-methane, 11.0 g (0.1 mole) of cis-cyclooctene and 24 g of potassium fluoride. The crude mixture was distilled under about 6 mm Hg at room temperature and received by a very cold trap (-198°C, liquid nitrogen). The yield was calculated from the relative peak areas of GC (Figure 4) (Varian 3300 model, FID). The yield was 8.1 % (Figure 8,9). The structure elucidation was made from the GC/MS data (Figure 7,8). Referred to Figure 5 and 6, the peak (retention time = 3.923) in Figure 4 was the starting material (cis-cycloctene). There was a new peak occuring at a retention time of 5.0. This new peak should correspond to the product (cis-9,9-difluorobicyclo[6,1,0]nonane. In Figure

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Detector: FID, 250°C
Injector: 220°C
Column: Initial 75°C, Final 220°C,
Flow Rate: 28ml/min; Rate 20°C/min

GC: Varian 3300

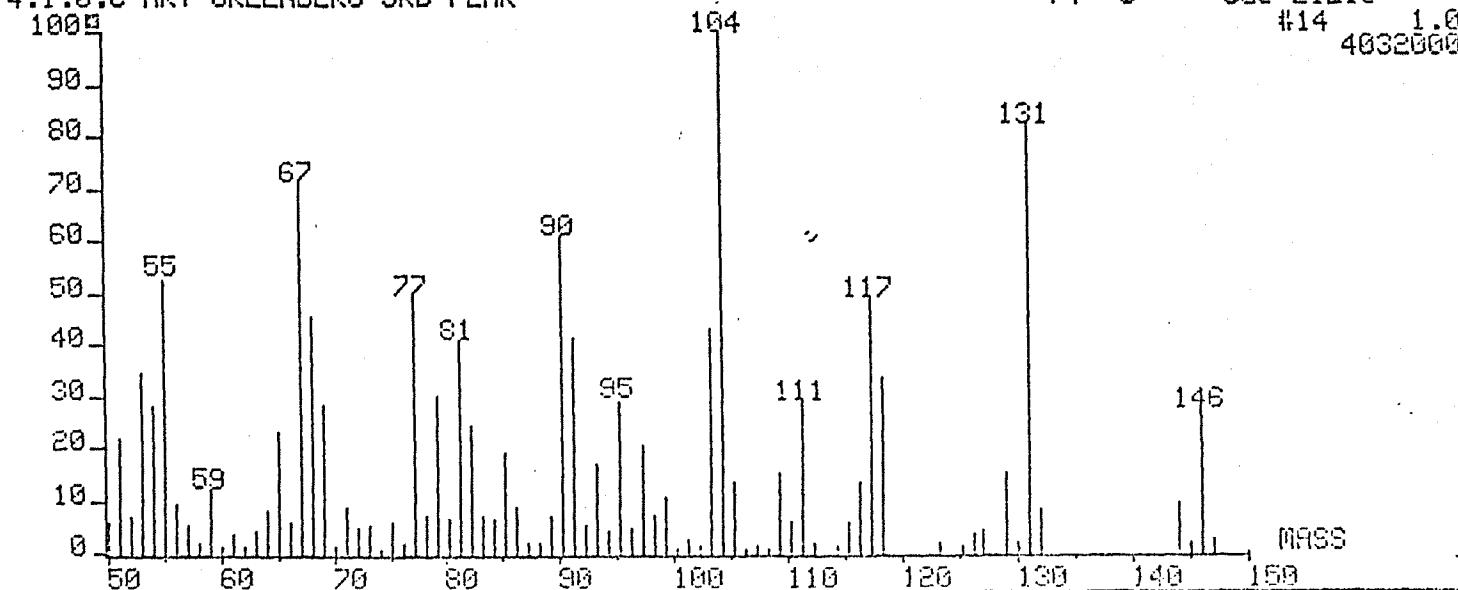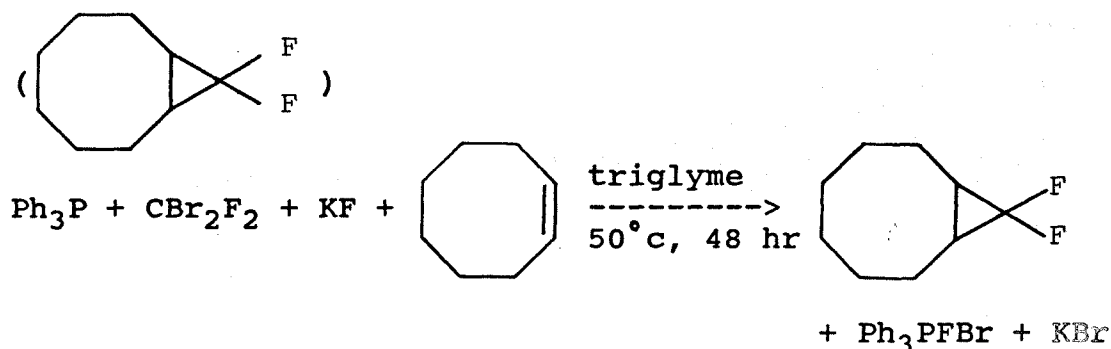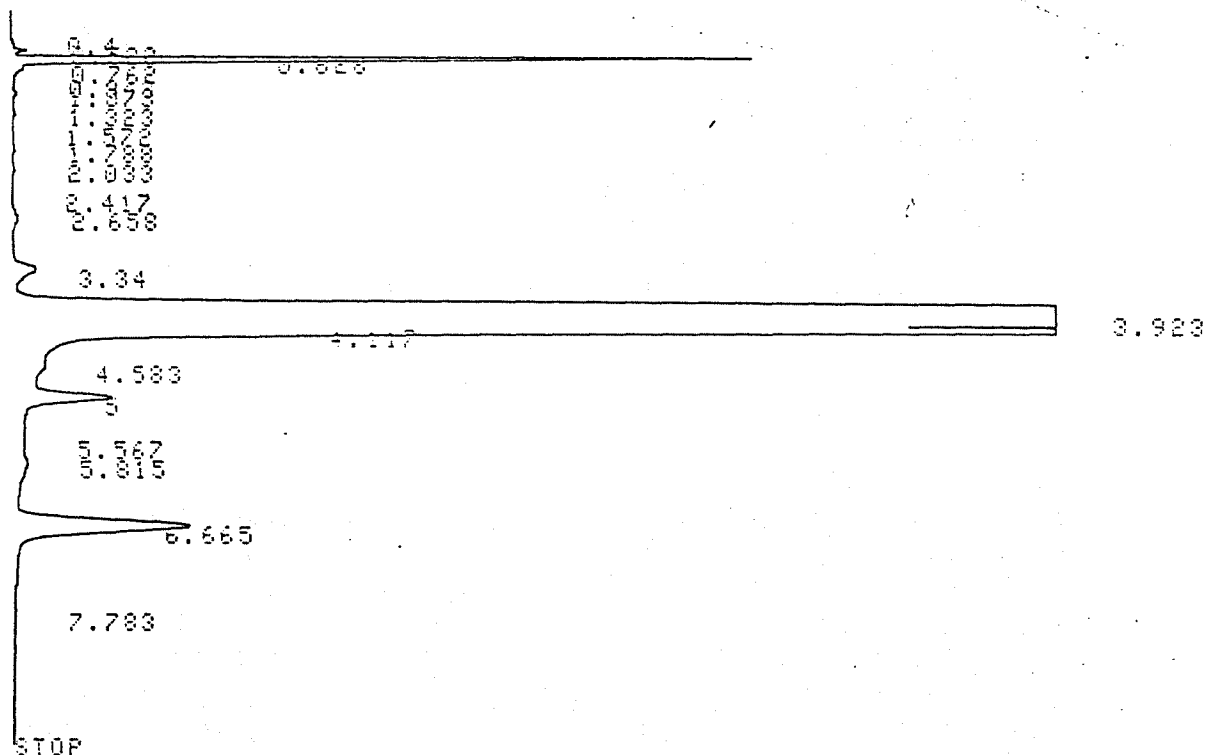CHROMATOPAC   C-R3A   FILE   0
SAMPLE NO   0   METHOD   41
REPORT NO   39

PKNO   TIME   AREA   MK IDNO   CONC   NAME

  1   0.628   75294   V   2.3653
  2   3.34   10884   V   0.3419
  3   3.923   2675605   V   84.0517
  4   4.117   324098 SV   10.1812
  5   5   20060 T   0.6302
  6   6.665   77343 SV   2.4297
                 ----------   ----------
         TOTAL   3183283   100

Figure 4. GC Chromatogram of the Mixture

    (cis-Cyclooctene and cis-9,9-Difluoro-
    bicyclo[6,1,0]nonane)

20

START

0.48

1.373

2.698

3.368

4.147   3.962

4.593
4.815

5.565

6.682

9.188

STOP 9.015

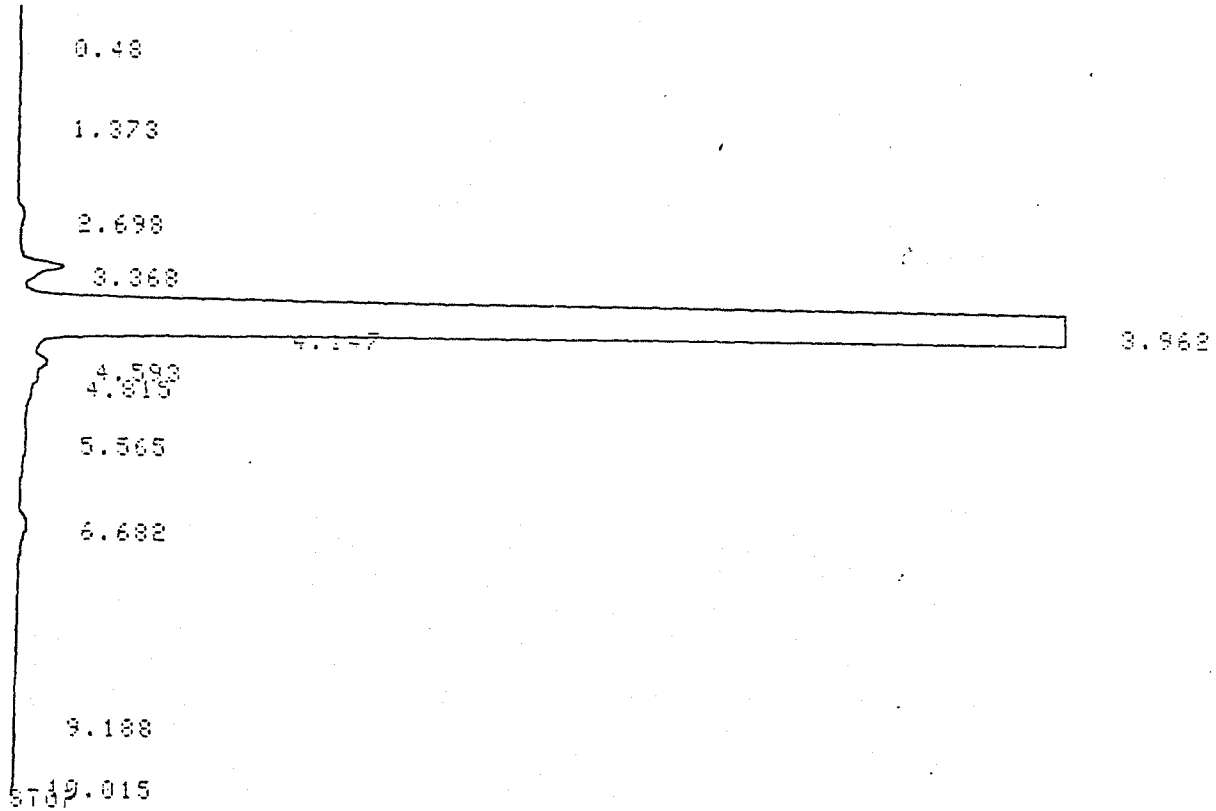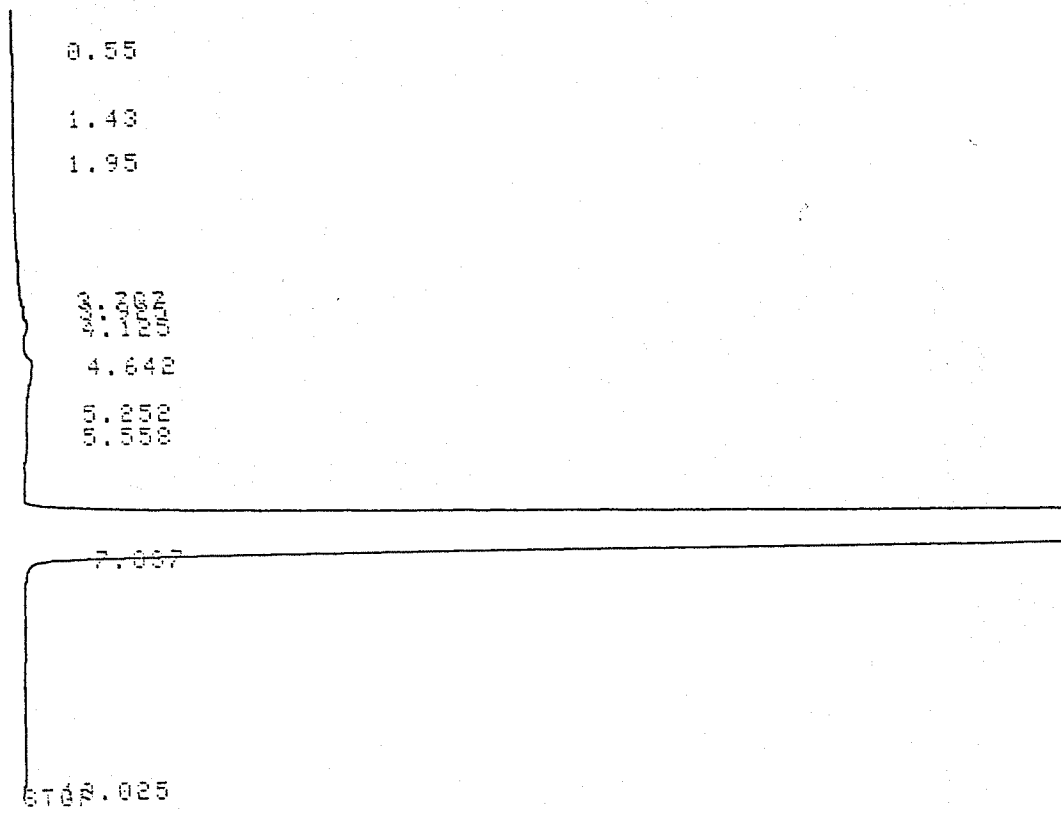CHROMATOPAC   C-R3A   FILE   0
SAMPLE NO   0   METHOD   41
REPORT NO   36

PKNO   TIME   AREA   MK   IDNO   CONC   NAME

  1   3.368   17679   V   0.5017
  2   3.962   3118594   V   88.495
  3   4.147   318123   V   9.0272
  4   4.593   14758   V   0.4188
  5   4.815   16286   V   0.4621
  6   5.565   15980   V   0.4535
  7   6.682   22614   V   0.6417
                   ----------   ----------
         TOTAL   3524033   100

Figure 5. GC Chromatogram of Pure cis-Cyclooctene

START

0.55

1.43

1.95

3.292
4.125

4.642

5.252
5.558

7.037

STOP8.025

CHROMATOPAC   C-R3A   FILE   0
SAMPLE NO   0   METHOD   41
REPORT NO   37

PKNO   TIME   AREA   MK IDNO   CONC   NAME

   1   4.642   16551 V   0.6655
   2   5.558   13045 V   0.5245
   3   7.037   2457266 SV   98.8099
                   ---------   ------------
         TOTAL   2486863   100
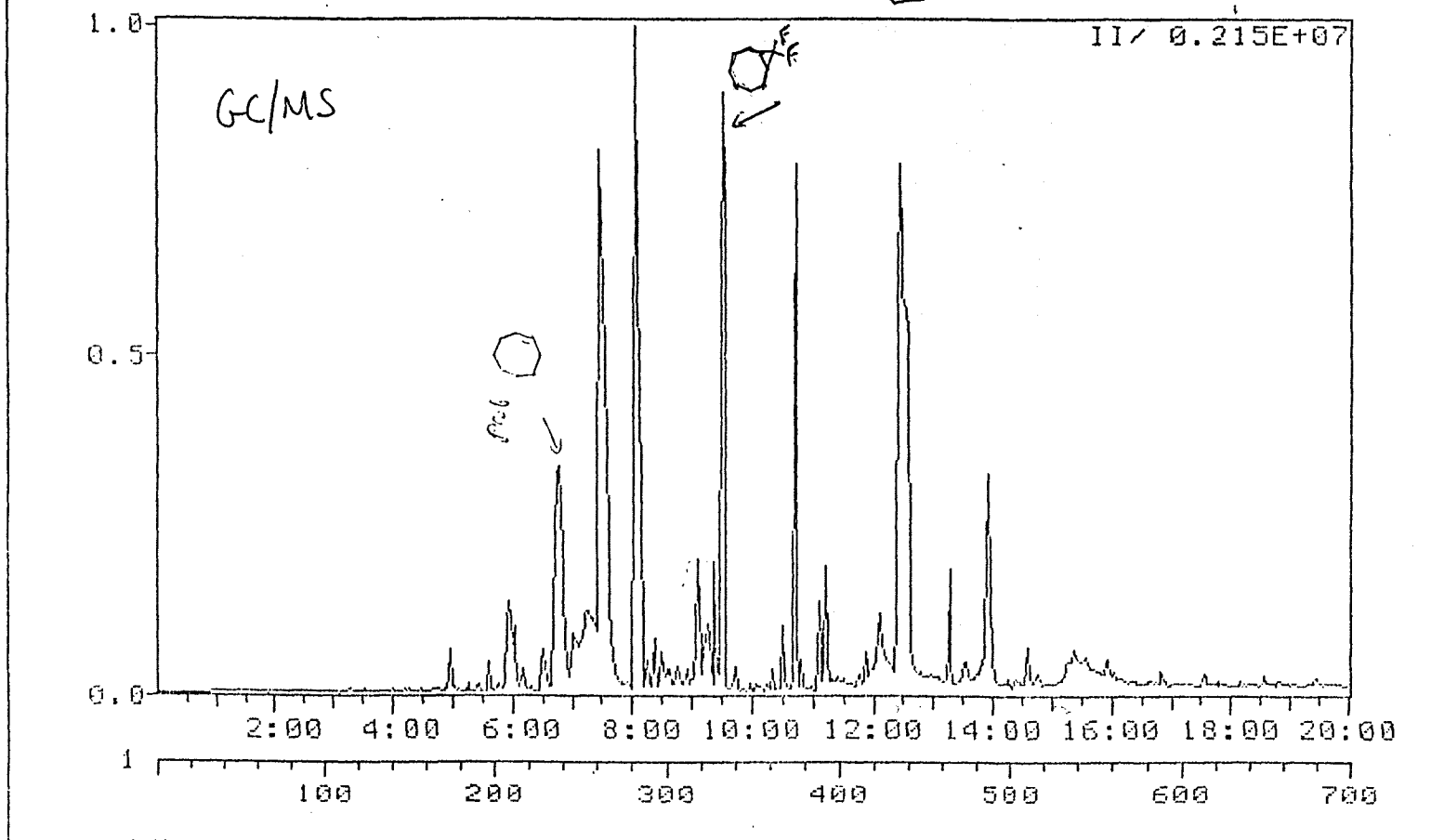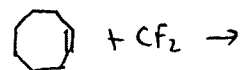
Figure 6. GC Chromatogram of Triglyme

22

Figure 7. GC/MS of Mixture for the Reaction:

cis-cyclooctene and CF_2
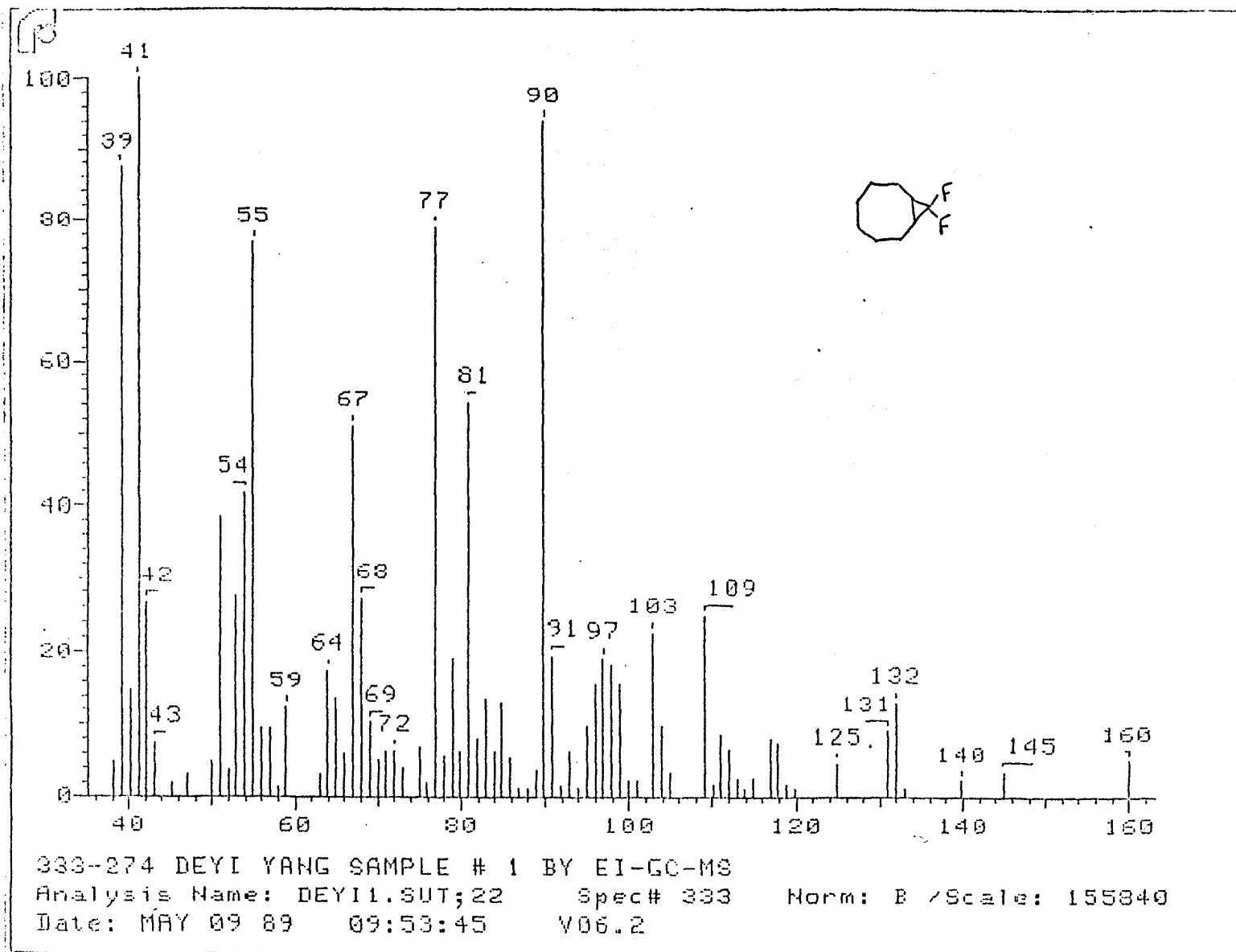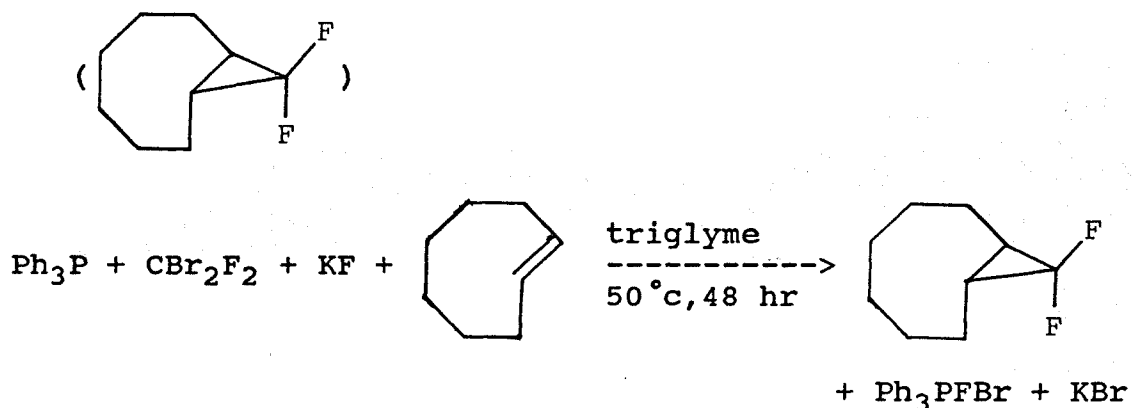
Figure 7. GC/MS of Mixture for the Reaction: cis-cyclooctene and CF_2

8, the peak occuring at a mass of 160 corresponded to a fragment of the product (call M_{cis}). The peak (mass=145) was for the fragment of M_{cis}-CH_3, and another peak (mass=109) for M_{cis}-CF_2-1. The peak at 90 is $C_4H_4F_2$. Figure 9.B is the ^{19}F NMR of the cis-9,9-difluorobicyclo[6,1,0]nonane.

VI. The Synthesis of trans-9,9-difluorobicyclo[6,1,0]nonane

$$Ph_3P + CBr_2F_2 + KF + \text{(trans-cyclooctene)} \xrightarrow[\text{50°c,48 hr}]{\text{triglyme}} \text{(product)} + Ph_3PFBr + KBr$$
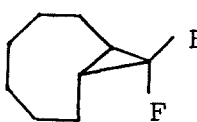
In a similar experiment, 2.32 g (10 mmole) of triphenylphosphine and 2.6 g (11 mmol) of dibromodifloromethane in 10 ml of triglyme was allowed to react at 50°C with 2.6 g (11 mmole) of trans-cyclooctene and 2.4 g (41 mmole) of potassium fluoride. The crude mixture was not distilled or purified by GC. The yield was 91.6 % from the GC chromatogram (Figure 10), and the data from ^{19}F NMR (Figure 9.A) and GC/MS spectra (Figure 12) and GC/MS spectra (Figure 11, 12) gave the structure information

for
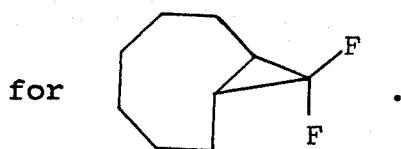
    In Figure 9, the big peak (retention time = 6.988) was
of the solvent, triglyme (refered to Figure 6). The small
peak with retention time of 3.898 was from the starting
material, trans-cyclooctene, with the same molecular weight
as cis-cyclooctene and whose retention time should be
approximate same as that of cis-cyclooctene (Figure 5).
Thus, the peak occured at retention time of 4.958
corresponded to the product (trans-9,9-
difluorobicyclo[6,1,0]nonane). Figure 10 is the ^{19}F NMR for
the product. The two fluorines in the trans-9,9-
difluorobicyclo[6,1,0]nonane are in equivalent chemical
surroundings. Thus, only one peak occured at chemical shift
of -75.20 ppm. Because the two fluorines coupled in a
complex manner and with the neighboring H atoms, the peak
was split to a complex multiplet. The GC/MS data from Figure
12 told us that the peak (mass = 160) was from the fragment

of (M_{trans}); the peak (mass = 145) was for the

($M_{trans}-CH_3$); and the peak (mass = 109) was for the
($M_{trans}-CF_2-1$).

Figure 9.A. ^{19}F NMR of trans-9,9-Difluorobicyclo[6,1,0]nonane

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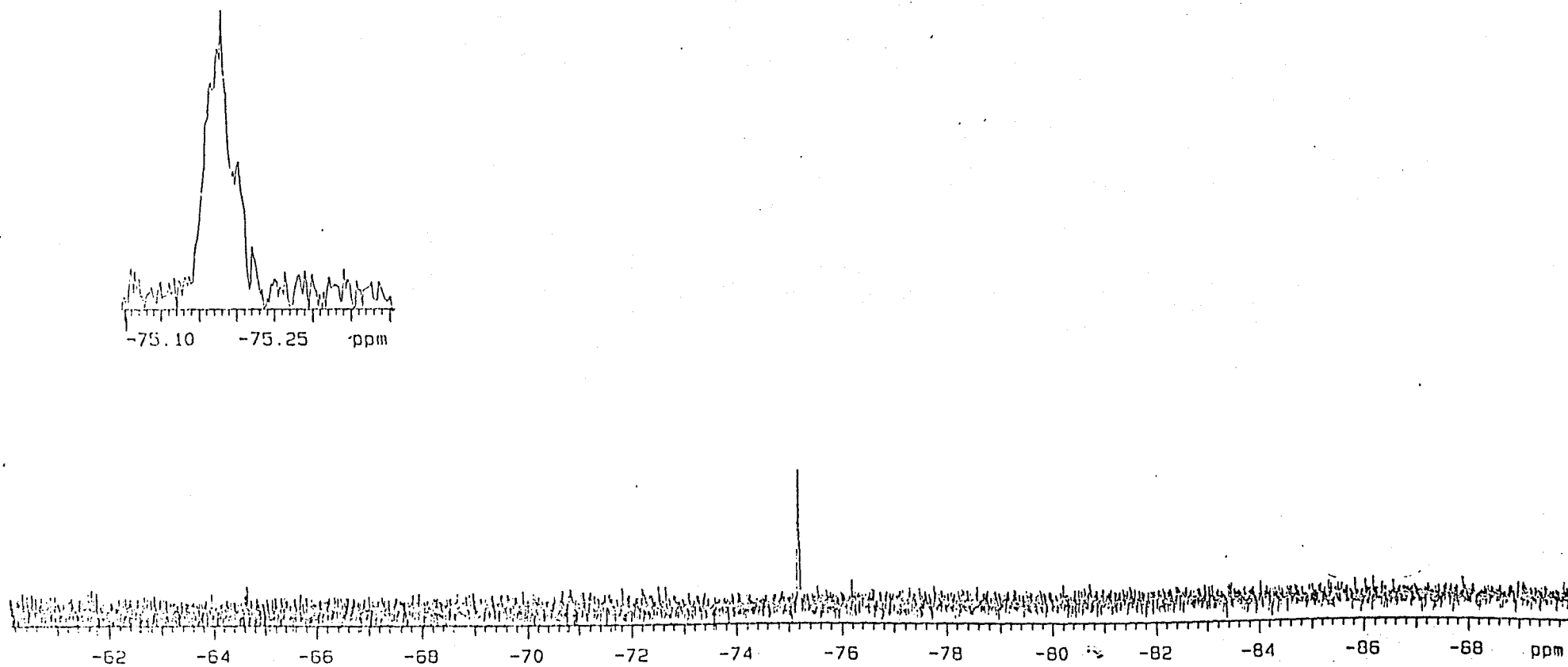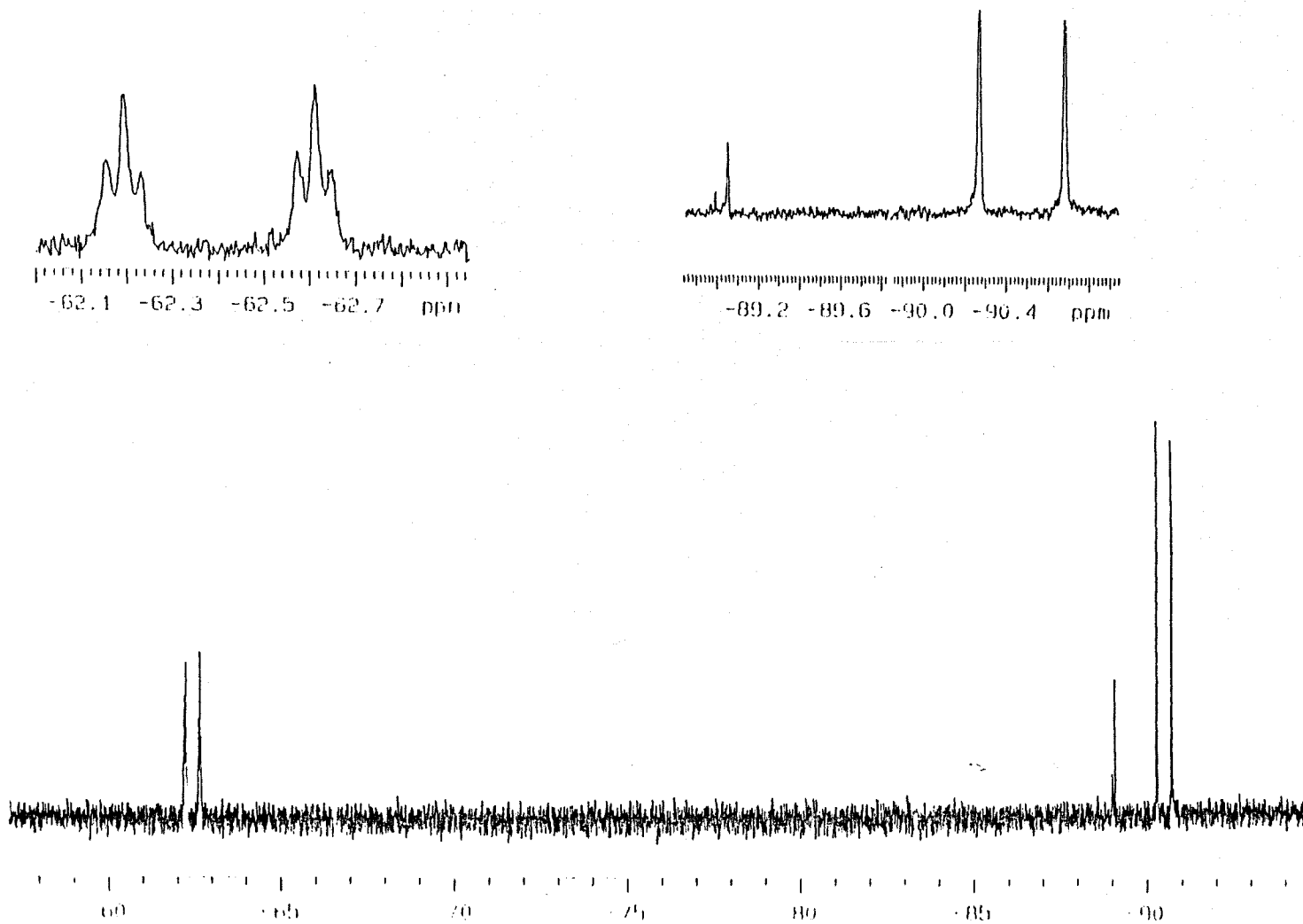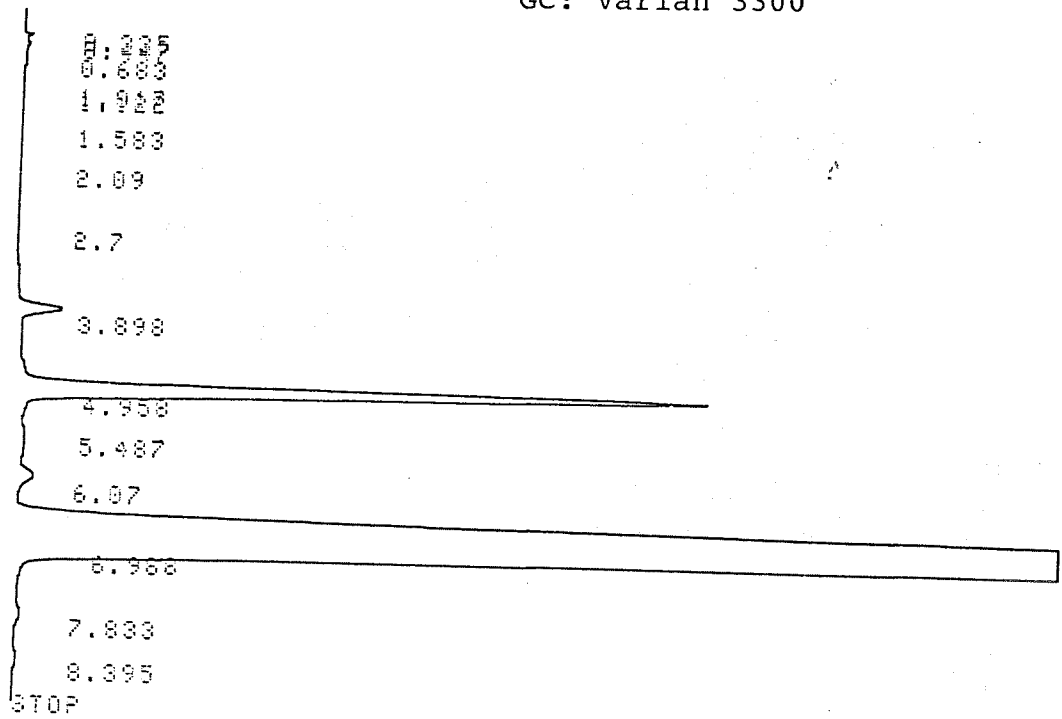Figure 9.B. ^{19}F NMR of cis-9,9-difluorobicyclo[6,1,0]nonane
(CF$_3$C$_6$H$_5$ is used as external standard)

Detector: FID, 250°C
Injector: 220°C
Column: Initial 75°C
        Final 220°C
        Rate 20°C/min
Rate: 30.0 ml/min

GC: Varian 3300

START

0.295
0.683
1.922
1.583
2.09

2.7

3.898

4.958
5.487
6.07

6.988

7.833
8.395
STOP

CHROMATOPAC   C-R3A   FILE   0
SAMPLE NO   0   METHOD   41
REPORT NO   42

PKNO   TIME   AREA   MK IDNO   CONC   NAME

1.   3.898   14723   V   0.6286
2   4.958   172496   V   7.3645
3   6.988   2155030   V   92.0068
                  ---------   ------------
        TOTAL   2342250   100

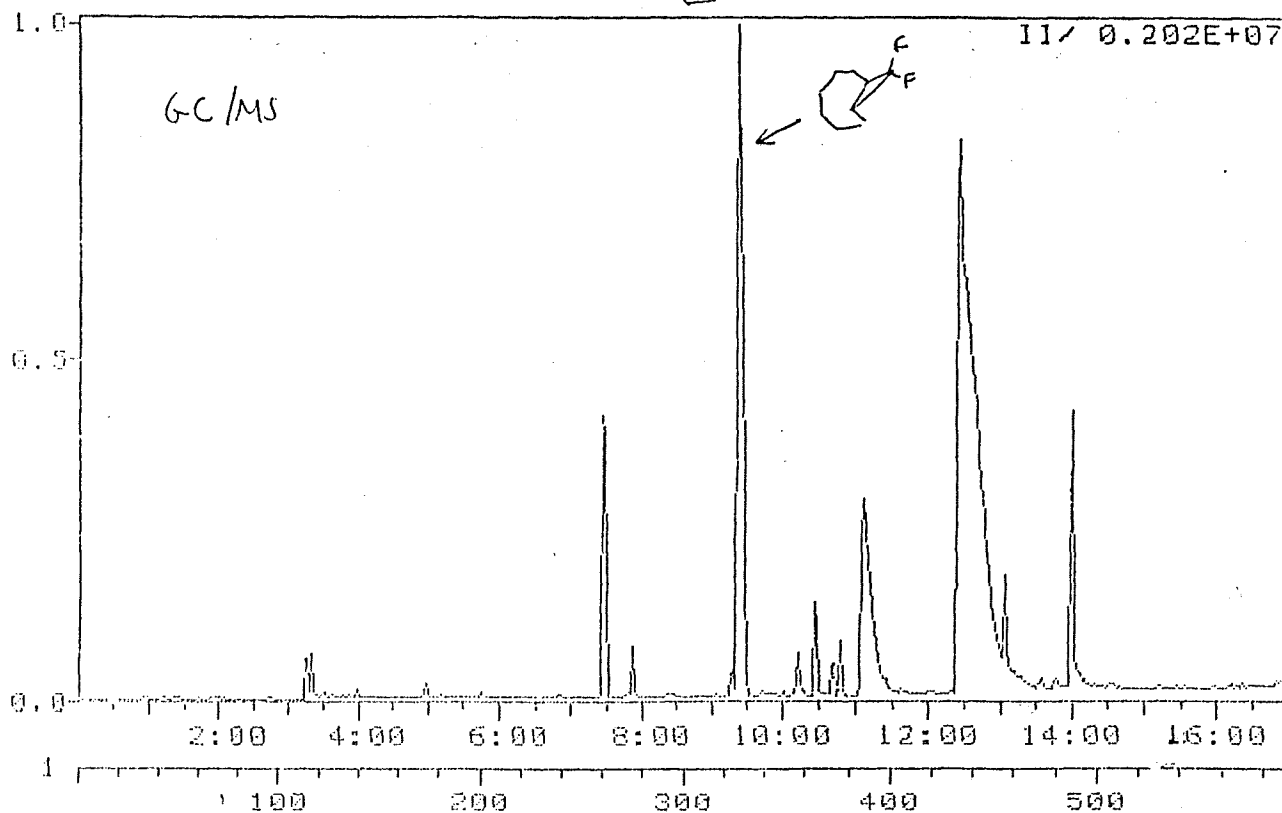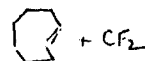Figure 10.GC Chromatogram of the Mixture of

+ triglyme

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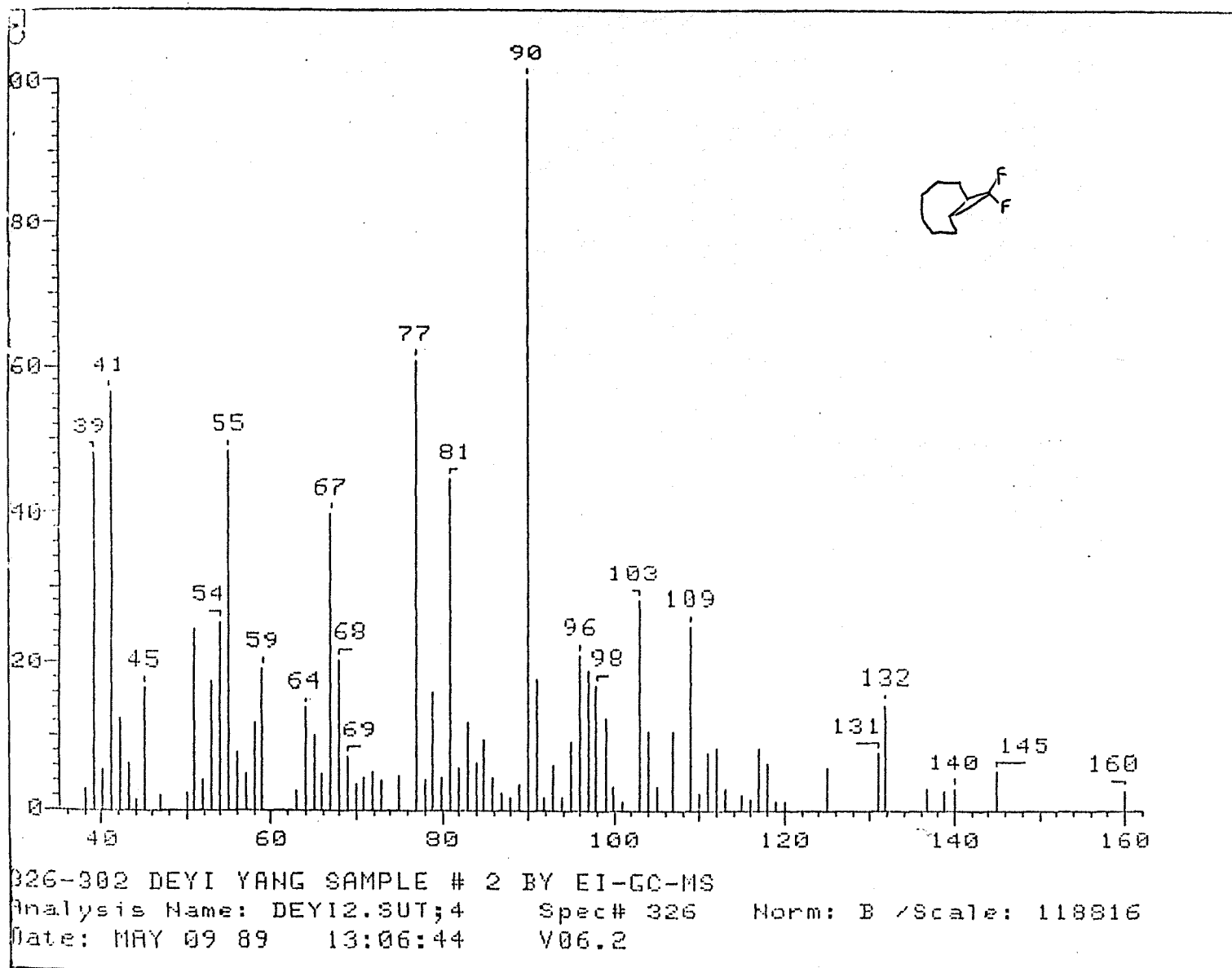Figure 11. GC/MS of the Reaction Mixture of
trans-Cyclooctene and CF_2

Figure 12. GC/MS of the trans-9,9-difluorobicyclo[6,1,0]nonane

Chaper 3. Results and Discussion

According to the experimental results described in Chapter 2, we can synthesize trans-9,9-difluorobicyclo-[6,1,0]nonane very conveniently from trans-cyclooctene using bromodifluoromethylphosphonium bromide as the source of difluoromethylene at 50°C. Compared with reactions of 1-methyl-1-cyclohexene or cis-cyclooctene with difluoromethylene, trans-cyclooctene is more reactive with difluoromethylene and provides much higher yields under the similar conditions. During the experiments, we found that the syntheses were difficult and the yields were very low if the commercial starting materials (cis-cyclooctene, 1-methyl-cyclohexene, triphenylphosphine, potassium fluoride, and triglyme) were not purified of thoroughly dried before reaction.

1. 1,1-difluoropropane is one of the derivatives of cyclopropane. Cyclopropane is the conventionally simplest and unavoidably strained molecule[37]. In cyclopropane, it is found that the C-C bonds are shorter and have higher vibrational stretching frequencies than the corresponding quantities for propane[37]. It is also noted[38] that larger cyclopropare has a ^{13}C-H nmr coupling constant than either

the primary or secondary C-H bonds in propane.

Figure 13.   C-C and C-H bonding in cyclopropane

Experimental measurements of the corresponding C-C homolysis (e.g. heating cyclopropane to form acyclic trimethylene) show that in cyclopropane the C-C bond is considerably weaker, i.e., of lower bond strength, than in propane.   In cyclopropane, the orbital overlap outside the ring or nuclear perimeter (Figure 14) and as the maximum overlap is not along the internuclear line, the resultant bonds have been referred to as "bent"[39].
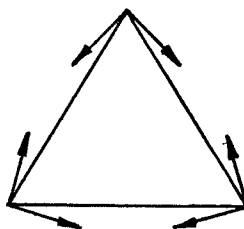

Figure 14. Arrows denote directions of hybrid orbitals at the carbon atoms of cyclopropane

Calculations and nmr spectral data indicate that the C-C bonding orbitals in cyclopropane are sp^5-hybridized and

the C-H bonds are sp^2-hybridized with H-C-H bond angles of 118[37].

$$\text{(a)} \qquad \text{(b)} \qquad \text{(c)}$$
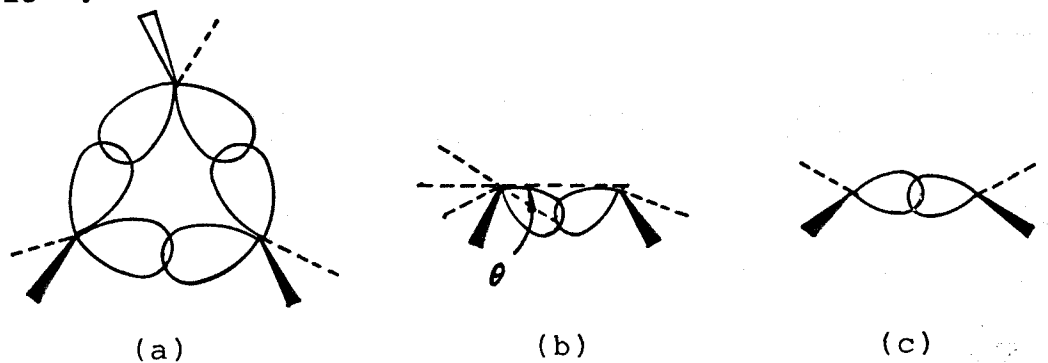
Figure 15. (a) A bent-bond picture of cyclopropane.
(b) Bent bond connecting two CH_2 fragments in which   is the angle of bending.
(c) A normal bond.

Table 1. Some C-H Bond Properties[38]

C-H Property	$H-C_{sp}^2$	H-C	$H-C_{sp}^3$
Angle $C\diagdown_H^H$	116°	118°	109.5°
IR $V_{CH-freq.}$	3034	3009	2853 cm^{-1}
C-H length	1.086	1.093	1.102 Å
C-H force constant	5.1	5.05	4.79×10^5 dynes/cm
$J(^{13}C-H)$	156-170	157-166.5	125 Hz
% s character	33	33	25

From Table 1, one can be seen that cyclopropane has a

large pi-electron density in the plane of the cyclopropane ring.

1,1-Difluorocyclopropane is a gas at room temperature. It is relatively stable and shows no appreciable decomposition during the period in which it was used for spectroscopy (approximately eight months). In 1,1-difluorocyclopropane, the fluorine withdraws electrons from the cyclopropane ring and affects the stabilization of the cyclopropane. The effect of the fluorine as a substituent is of particular interest because of its small size and hence its unique intrinsic character. The unusual properties of fluorine as a substituent derive largely from three factors. Thes factor are fluorine's high electronegativity, its three nonbonded electron pairs, and the fact that, as a second period element, its orbital dimensions are such that excellent overlap is possible, both in forming σ bonds and in π -conjugative interactions with contiguous carbon π systems. The high electonegativeity and effective orbital σ overlap combine to give rise to a very polar, very short C-F σ bond (1.317 $\overset{\circ}{A}$ relative to 1.766 $\overset{\circ}{A}$ for a C-Cl bond). Moreover, the bond strength of the C-F bond seems strongly dependent upon carbon's hybridization such that there is a significant thermodynamic advantage for fluorine to be bound

to carbon orbitals with high p character (i.e., sp^3 orbitals). Fluorine is apparently able to donate electrons to a conjugated π system[40].

A particulartly interesting consequence of fluorine's unique character as a substituent is its effect on a cyclopropane system. O'Neal and Benson were the first to comment on the unusual kinetic and thermodynamic consequences of fluorine substitution on cyclopropane[41]. From examination of the available data, O'Neal and Benson estimated that there is an increase of strain of 4.5-5 kcal/mol per fluorine substituent on a cyclopropane ring. They reasoned that the greater thermal reactivity of these compounds was a ground-state effect since they found no evidence of radical stabilization by fluorine substituents. Indeed, they also obtained results which indicate that fluorine substituents provide no stabilization to a carbon radical[42].

Hoffmann discussed the general effect of electron donor (and acceptor) substituents on the bond strengths of cyclopropane and concluded that a potent donor such as fluorine should weaken the bond opposite to the carbon bearing the substituent(s) (the C_2-c_3 bond). while the

adjacent bonds should be strengthened[43]. Gunter predicted a general weakening of bonds in the cyclopropane system with fluorine substitution[44].

A structure determination of 1,1-difluorocyclopropane and recent theoretical calculations are consistent with Hoffmann's conclusion inasmuch as the C_1-C_2 bond is seen to be shortened (1.464 Å) and the C_2-C_3 bond lengthened (1.553 Å) relative to cyclopropane itself (1.514 Å) (Figure 16)[40].

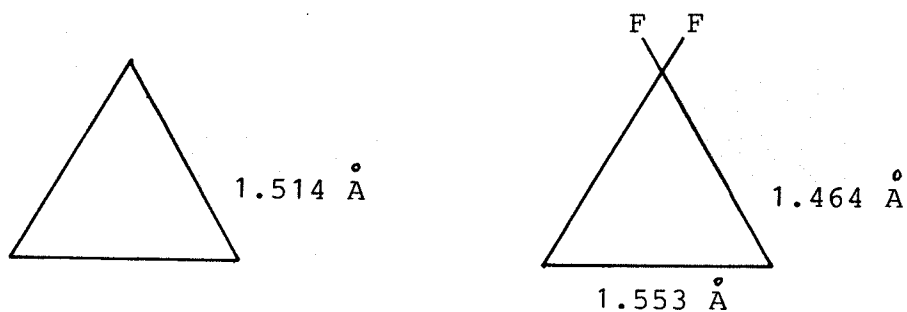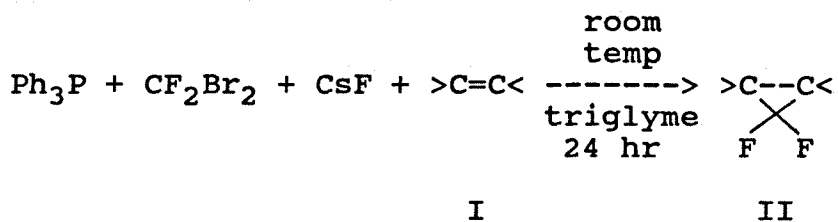Figure 16. Cyclopropane and 1,1-Difluorocyclopropane

2. Burton's investigation[3] showed that higher yields of formation of 1,1-difluorocyclopropanes were obtained if the substituents on the >C=C< were more than two when bromodifluoromethylphosphonium bromide was chosen as the difluoromethylene precursor.

If (I) was tetramethylethylene [$(CH_3)_2C=C(CH_3)_2$], the yield of (II) was 79%. But if (I) was isobutylene

37

$$\text{Ph}_3\text{P} + \text{CF}_2\text{Br}_2 + \text{CsF} + \text{>C=C<} \xrightarrow[\substack{\text{triglyme} \\ \text{24 hr}}]{\substack{\text{room} \\ \text{temp}}} \text{>C--C<}$$

I   II

[$(CH_3)_2C=CH_2$], the yield of (II) was 66%. Since 1,1-difluorocyclopropane has a large pi-electron density in the plane of the cyclopropane ring, and the fluorine atoms destabilize the cyclopropane ring, the alkyl substituents can stabilize the cyclopropane ring by hyperconjugation. The more the number of alkyl substituents, the more stable the cyclopropane. We got the same result that the formation yield (22.1%) of 1,1-difluorocyclopropane from 1-methyl-1-cyclohexene was higher than yield (8.1%) from cis-cyclooctene in our experiment.

3. trans-cyclooctene is a highly strained dissymmetric olefin whose optical stability is dependent upon the rigidity of the hexamethylene chain that comprises the ring. Its thermodynamic and kinetic parameters are: $\Delta H°$(trans-cis) = + 9.2 kcal/mole[45]; ΔG^*_{rac} = 36 kcal/mole[46]; strain energy = + 16.7 kcal/mole. Its strain energy largely arises from its twisted olefin linkage. The conformation and precise structure of trans-cyclooctene have been studied. X-Ray

studies of a platinum complex of trans-cyclooctene indicated
thet the ring was in the "twist" (or "crown") conformation
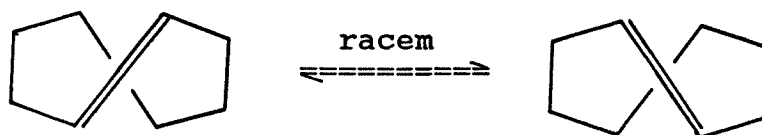(Figure 17)[47]:

Figure 17. Conformation of trans-cyclooctene

Other structure studies of trans-cyclooctene have been
made by scientists. According to the twist structure of
trans-cyclooctene, it can be predicted that trans-
cyclooctene is higher in activity than cis-cyclooctene. The
experiment reported in this dissertation proved this
prediction. The formation yield (91.6%) of the 1,1-difluoro-
cyclopropane from trans-cyclooctene was much higher than the
yield (8.1%) from cis-cyclooctene.

4. According to the Hoffmann discussion mentioned
above, the fluorine should weaken the bond opposite to the
carbon bearing the substituent(s) (the C_2-C_3 bond) in the
1,1-difluorocyclopropane. Dolbier reported that there was a
rapid thermal interconversion of exo and endo isomers 1 and
2 at 60°c (eq.1) and 3 and 4 at 320°c (eq.2)[40]:

For 3 $\rightleftharpoons$ 4, the $\Delta H^\circ = -0.72 \pm 0.05$ kcal/mol, which was

1   2

eq. 1

3   4

eq. 2
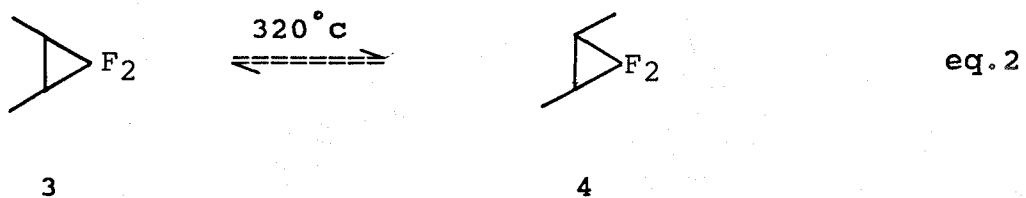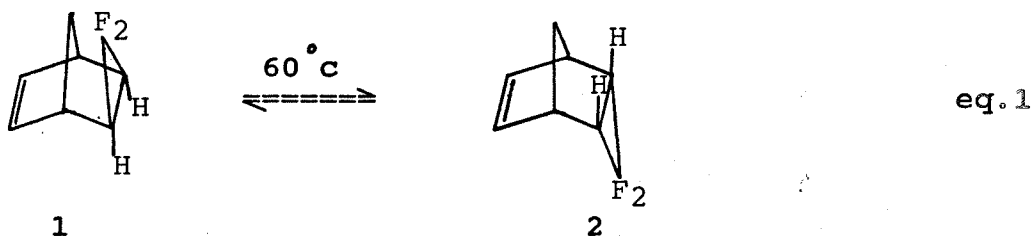
not inconsistent with the observed -1.1 kcal/mol for the hydrocarbon system. This result was consistent with O'Neal and Benson's approximation of the increase in strain which would be expected for two fluorine substituents.
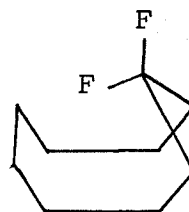
Compared to the cis-9,9-difluorobicyclo[6,1,0]nonane, trans-9,9-difluorobicyclo[6,1,0]nonane is probably higher in strained energy due to the trans-fusion.

If 4 is less stable than 5, thermodynamically, 4 would isomerize to 5 under certain conditions (e.g. higher temperature). Thus, in choosing difluoromethylene precursors, the conditions of difluoromethylene generation

40

trans-9,9-difluorobicyclo-
[6,1,0]nonane

cis-9,9-difluorobicyclo-
[6,1,0]nonane

4

5

Figure 18. The structure of trans-9,9-difluorobicyclo-
[6,1,0]nonane and cis-9,9-difluorobicyclo[6,1,0]nonane

from its precursor must be carefully considered. Phenyl(trifluoromethyl)mercury (PhHgCF$_3$) is a very useful CF$_2$ reagent. It can react with many olefins to give excellent yields in the presence of anhydrous sodium iodide in benzene medium. However, PhHgCF$_3$ needs to be heated to release CF$_2$ (e.g. 80-85 c)[2]. Considering the stability of 4, PhHgCF$_3$ was not chosen as the CF$_2$ precursor in the research. Another reason we did not use PhHgCF$_3$ is that PhHgCF$_3$ would give CF$_3^-$ during the reaction. This CF$_3^-$ might first attack the double bond of the trans-cyclooctene, then, the addition intermediate (6) may change the structure to its isomer (7) before the reaction finish (eq.3-5).

$$PhHgCF_3 \text{ --------> } PhHg^+ + CF_3^-$$ eq.3

41

eq.4

eq.4

eq.5
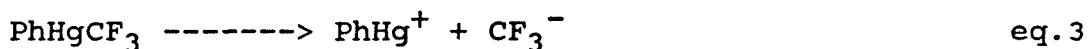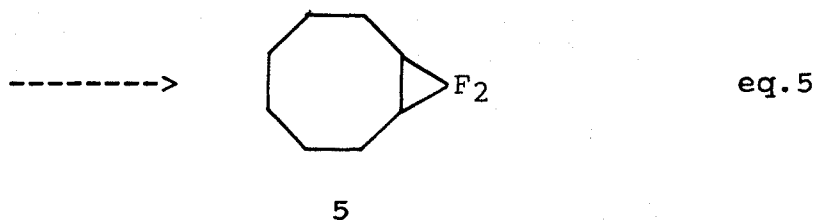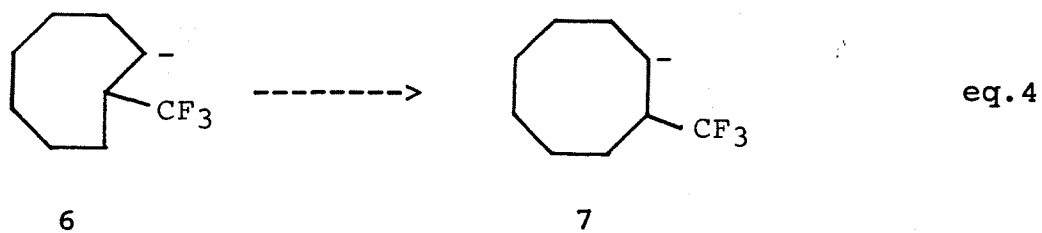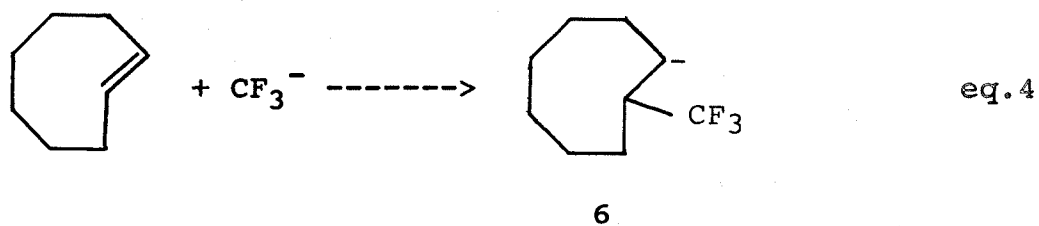
Me$_3$SnCF$_3$ is an earlier CF$_2$ precursor. In the presence of sodium iodide, it releases CF$_2$ in 1,2-dimethoxyethane (DME) at 80-85°c as shown in the following equations:

Me$_3$SnCF$_3$ + Na$^+$I$^-$ ----> Me$_3$SnI + Na$^+$CF$_3^-$

Na$^+$CF$_3^-$ ----> NaF + CF$_2$
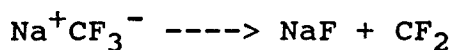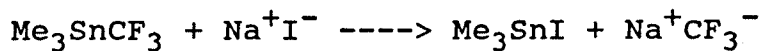
However, it may be possible that Na$^+$CF$_3^-$ ionizes to give CF$_3^-$ before releasing CF$_2$. In addition, most thermal studies of fluorine-substituted cyclopropanes show that CF$_2$

42

extrusion from polyfluorocyclopropanes is a well-known reaction in higher temperature. To avoid the high temperature in the reaction of trans-cyclooctene and $:CF_2$, $[Ph_3P^+CF_2Br]Br^-$ was chosen as the $:CF_2$ precursor because this salt is able to give $:CF_2$ at low temperature.

Chapter 4. Conclusion

This investigation has shown $[Ph_3P^+CF_2Br]Br^-$ to be a good CF_2 precursor. It could be conveniently prepared "in situ" from the appropriate phosphine and difluorodibromomethane in the presence of the fluoride salt. It releases CF_2 under lower temperature to give on reaction with trans-cyclooctene, 9,9-difluorobicyclo[6,1,0]nonane in high yield. It is clear that twisting of the double bond in trans-cyclooctene lowers its adiabatic ionization potential (8.53 eV) to a value comparable to that for a more highly-substituted olefin such as 1-methylcyclohexene (8.67 eV)[48]. In contrast, cis-cyclooctene's adiabatic ionization potential is high (8.82 eV) [49] and this makes it resistent to CF_2 attack.

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