Structure, Synthesis, and Chemical Reactions of Fluorinated Cyclopropanes and Cyclopropenes

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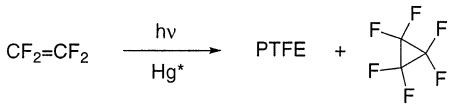
I. Introduction

1. Scope of the Review

Studies related to the synthesis and chemistry of fluorinated cyclopropanes and cyclopropenes go back to 1952, when Atkinson reported the isolation of hexafluorocyclopropane as a low-conversion product from the mercury-sensitized photolysis of tetrafluoroethylene.[1,2] Shortly thereafter, Tarrant and



Misani independently carried out the first designed syntheses of partially fluorinated cyclopropanes,[3,4] and the floodgates opened after 1960, when the first difluorocarbene reagents were discovered and found to be useful for the synthesis of an almost unlimited variety of fluorinated cyclopropanes.[5]

Since that time there has been a consistent and high level of interest in fluorinated cyclopropanes. The *chemistry* of fluorinated cyclopropanes and cyclopropenes will be emphasized in this review, although a brief, noncomprehensive summary of synthetic methods will also be presented, and the literature will be covered through the end of the year 2001. For the purpose of this review, "fluorinated cyclopropanes" will be defined as cyclopropane-containing compounds that bear at least one fluorine substituent *on the cyclopropane ring.* Therefore, cyclopropane compounds that otherwise contain fluorine but do not bear fluorine on the ring, such as trifluoromethylcyclopropanes, will not be discussed. The emphasis of this report is to provide a critical analysis of *the effect of fluorine substituents on cyclopropane and cyclopropene reactivity.*

2. The Nature of Fluorine as a Substituent

Fluorine substituents have a unique and often profound impact on the structure, energy, chemical reactivity, and physical properties of organic compounds. Although the various influences of fluorine have been discussed thoroughly in recent reviews of the subject,[6,7] it is worth mentioning briefly those key aspects that are relevant to this review.

The electronic influences of fluorine substituents on molecular properties can be attributed to the unique combination of fluorine's atomic properties, which include its high electronegativity and moderately small size, its three tightly bound, nonbonding electron pairs, and, being a second period element, the excellent match in size between fluorine's 2s and 2p orbitals with those of carbon.

There are a number of interrelated structural and thermochemical consequences that derive from these intrinsic properties of fluorine.[6] Its high electro-

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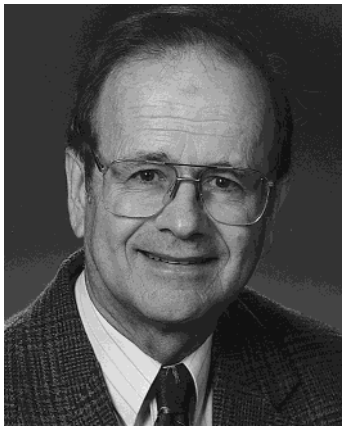
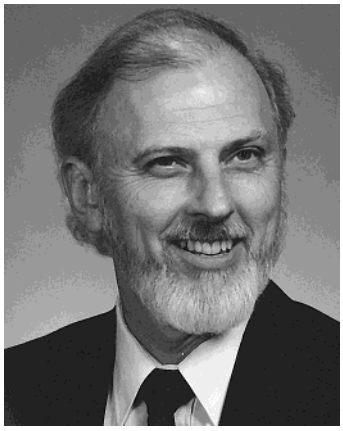


Bill Dolbier is Professor of Chemistry at the University of Florida. He received his B.S. in Chemistry from Stetson University in 1961 and obtained his Ph.D. in organic chemistry from Cornell University in 1965, working with Mel Goldstein. After one and a half years of postdoctoral work with Bill Doering at Yale, he joined the faculty at UF in 1966, where he has been ever since, serving as Chairman from 1983 to 1988. Bill's research interests continue to be physical organic in nature, and he maintains long-term interests in thermal homolytic reactions, pericyclic reactions, and free radical reactivity. Since 1975, his efforts have mainly focused on the study of molecules containing fluorine. In recent years, his efforts have increasingly been devoted to development of new synthetic methods in organofluorine chemistry. Bill received the ACS award for Creative Work in Fluorine Chemistry in 2000 and served as the Chairman of the Fluorine Division of the ACS in 1986. When not immersed in such activities, Bill's main interests continue to be his wife, Jing; son, Stephen; a couple of grandchildren; and a little handball.



Merle A. Battiste has served as a member of the Chemistry Faculty at the University of Florida for over 41 years, as Professor of Chemistry since 1970, and as Chairman of the Organic Division (1974–1984). In this time he was an A. P. Sloan Fellow (1967–69), Fulbright Research Scholar (1974, Freiburg, Germany), and Erskine Fellow (1987, University of Cantebury, N. Z.). His sojourn as a southern chemist was perhaps presaged by his birth origin (Mobile, AL) and early chemical education at The Citadel (B.S., 1954), and at Louisiana State University (M.S., 1956, with Jim Traynham). Immigration to New York City for Ph.D. studies with Ron Breslow (Ph.D. Columbia, 1959) led to a year and a half postdoctoral studies with Saul Winstein at U.C.L.A., sandwiched between military duties as a 2nd Lt. in the U.S. Artillery School in Fort Sill, OK. Broadly defined, Merle's research interests have centered on the synthesis and study of novel molecular structures ranging in interest from the physical organic realm to bioorganic applications. Current interests include a continuing focus on cycloaddition constructs in organic synthesis and the application of organoaluminum and organofluorine reagents in the synthesis of novel and/or useful molecular targets. Outside of the lab, Merle's abiding interests are his wife, Jan, their respective children, and evolving grandchildren, two and counting.

negativity means that C−F bonds will always be very polar, with relatively high ionic character, and they will consequently be stronger than other C−X bonds. Second, in principle also because of its high electronegativity, fluorine prefers to bond to carbon orbitals that are high in p-character (i.e., less electronegative). This is reflected, for example, in the experimental 108.3° F−C−F bond angle and 113.7° H−C−H bond angle of CH_2F_2,[8] which indicate significantly greater degrees of p- and s-character in the carbon orbitals used for C−F and C−H bonding, respectively. Third, there are strong observed energetic preferences (a) for multiple fluorine substitution at carbon[9] and (b) for fluorine substituents to be attached to a carbon bearing other carbons rather than hydrogens.[10,11] The former effect has been attributed to "Coulombic interactions between the negatively charged fluorines and the increasingly more positively charged carbon." It is exemplified by isodesmic equations 1 and 2 below.[9] Such increased Coulombic

$$CF_4 + 3\,CH_4 \longrightarrow 4\,CH_3F \qquad (1)$$

ΔH = + 53 kcal/mol (exptl)

$$CH_2F_2 + CH_4 \longrightarrow 2\,CH_3F \qquad (2)$$

ΔH = +12.6 kcal/mol (calcd, MP3/6-311G*(6d))

interactions lead to the strengthening of all C−C bonds in the vicinity of the fluorine substituents, thus providing substance to the reputation of fluorinated hydrocarbons as having "enhanced thermal stability."

The latter effect can be described in terms of the effect of fluorine substituents on carbon hybridization. As the s-character of the carbon orbital forming the C−F bond *decreases*, it commensurately *increases* in the carbon orbitals used to bind to H or C. A methyl group can donate electron density to these more electronegative carbon orbitals via its σ-bond more effectively than can H, thus stabilizing the central carbon, as exemplified by isodesmic equation 3 below.[11]

$$CH_4 + CH_3CF_2CH_3 \longrightarrow CH_2F_2 + CH_3CH_2CH_3 \qquad (3)$$

ΔH (B3LYP) = -16.3 kcal/mol

Another factor that could also be involved in explaining this latter effect is the delocalization of the β-C−H bond electrons into the low-lying C−F σ^*-orbitals.[10] Although such effect of "negative hyperconjugation" is clearly important in the ability of β-fluorines to stabilize anions and in situations where an anomeric effect stabilizes molecules that have a fluorine and heteroatom attached to the same carbon,[12] the importance of delocalization of electrons into C−F σ^*-orbitals in neutral molecules remains a somewhat controversial subject.

II. Fluorinated Cyclopropanes

Attempts by Hoffmann and Gunter in 1970 to explain early reports of enhanced reactivity of fluorinated cyclopropanes led to their predictions that fluorine could act as a π-donor on cyclopropane and lengthen (thus weaken) all of its bonds.[13−15] However, according to Schleyer,[16] the observed dramatic influence of fluorine substituents on the geometries, reactivity, and destabilization of fluorocyclopropanes

Table 1. Some Computed Cyclopropane Structures[21]

cyclopropane 	∠X−C−Y, deg	∠C_2–C_1–C_3, deg	r(C_1–C_2), Å	r(C_2–C_3), Å
X = Y = H	114.5	60	1.515	1.515
X = F, Y = H	111.8	61.4	1.496	1.527
X = Y = F	109.6	63.3	1.477	1.550

can be best explained on the basis of fluorine's electronegativity and consequent σ−acceptor nature, which leads to withdrawal of electron density from one of the two degenerate 1e″ molecular orbitals of cyclopropane, the one able to serve most effectively as a σ-donor, thus shortening the C1−C2 bonds and lengthening the C2−C3 bonds.[16]

As had been discussed earlier by Bent,[17] Bernett,[18] and Kollmar,[19] the structural and thermochemical consequences of fluorine substitution for cyclopropane can, also, perhaps simplistically, be understood in terms of the both singular and cumulative effect of fluorine on the *hybridization* of the carbon atom to which it is bound, as was the case for hydrocarbons in general (vide supra). Because of its high electronegativity, there is an energetic advantage for fluorine to form bonds to carbon using carbon orbitals of enhanced p-character. Since cyclopropane already uses significant excess p-character in forming its strained C−C bonds (note the essentially sp^2-character of the C-orbitals used to make the C−H bonds, as reflected by the H−C−H angle of 115°),[20] when an H or H's of cyclopropane are substituted by F, the F will "steal" p-character from the C−C bonds and, consequently, destabilize the C−C bonding of cyclopropane, leading to an increase in "strain" in the system. This reorganization of s- and p-character on the fluorine-bearing carbon also has a structural consequence, giving rise to an increase in the C2−C1−C3 bond angle and thus to a lengthening of the distal (C2−C3) bond in a manner consistent with the available calculated and experimental geometries of 1-fluoro- and 1,1-difluorocyclopropane.

1. Structure

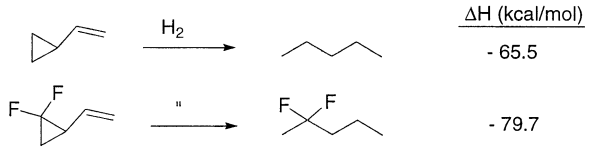
It has proved possible to quite accurately calculate the structures of virtually all of the possible fluorinated cyclopropanes,[11,16,21−23] and experimental structural data, where available,[8] correlate very well with the computational data. Table 1 presents some computational structural data of Boggs,[21] which is relevant to the discussions above and to follow.

Experimental structural data,[8] obtained by a combination of gas-phase electron diffraction and microwave techniques, are available for cyclopropane,[20] 1,1-difluoro-,[24] *cis*- and *trans*-1,2-difluoro-,[25,26] *cis*,*cis*- and *cis*,*trans*-1,2,3-trifluoro-,[27,28] 1,1,2,2-tetrafluoro-,[29] 1,1,2,3-tetrafluoro-,[30] and hexafluorocyclopropane.[31]

2. Strain Energies

Early kinetic studies indicating high thermal reactivity of fluorinated cyclopropanes led O'Neal and Benson to conclude that "strain energies per F atom substitution (for cyclopropane) seem to center around 5 kcal/mol/F."[32]

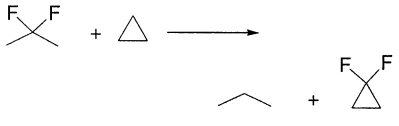
Scheme 1



Although there are no heats of combustion available for fluorinated cyclopropanes, the heats of hydrogenation of a few *gem*-difluorovinylcyclopropanes have been reported by Roth (i.e., Scheme 1),[33] and the incremental strains of 12−14 kcal/mol derived from these experiments, and presumably due to the geminal fluorines, are remarkably consistent with the earlier estimate of O'Neal and Benson.

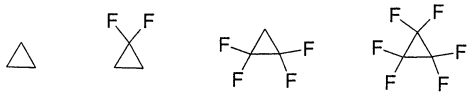
Enthalpy of combustion data reported by Ruchardt in 1997[34] have provided reliable strain-free fluorinated group equivalents that, in combination with Roth's heats of hydrogenation, allow an estimate of 41.8 kcal/mol for the strain of 1,1-difluorocyclopropane, with the incremental strain due to the geminal fluorines being 14.2 kcal/mol.

Such values are in good agreement with theoretical estimates of the heat of hydrogenation of 1,1-difluorocyclopropane to give 2,2-difluoropropane, which exceeds that of cyclopropane by 12.5 kcal/mol (RHF/6-31G*).[35] Alternatively, Wiberg used isodesmic equation 4 to obtain an estimate of the incremental strain energy derived from two geminal fluorine substituents on cyclopropane.[11]



(4)

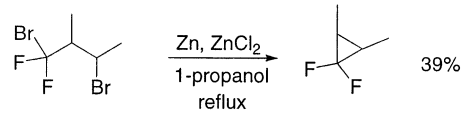
Although experimental heat of formation data are not available, the strain energies of more highly fluorinated cyclopropanes have been estimated computationally, with perfluorocyclopropane having more than double the strain of cyclopropane itself.[36−38]



Computational Strain Energy Data of Zeiger and Leibman (kcal/mol)[38]

3. Synthesis

It appears that the first purposeful preparation of a fluorine-substituted cyclopropane was carried out by Tarrant, Lovelace, and Lilyquist in 1955,[3] when they treated 1,3-dibromo-2,2-difluoro-2-methylbutane with Zn in 1-propanol and obtained a 39% yield of 1,1-difluoro-2,3-dimethylcyclopropane. With Doering



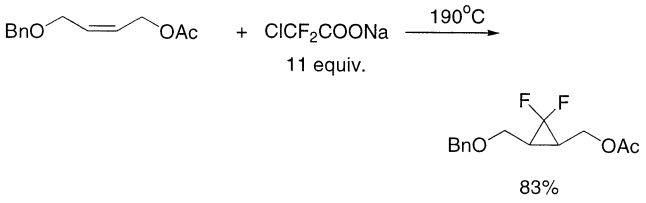
inventing "carbene chemistry" at about that same

time[39] and the advent of *fluoro*carbene chemistry a few years later, most synthetic strategies for fluorinated cyclopropanes since that time have revolved around the addition of either a fluorinated carbene to fluoro- or nonfluorinated alkenes or a hydrocarbon carbene to a fluoroalkene. There are excellent reviews available regarding the fluorocarbene-centered methodologies, so only a brief survey of the most useful of these methods will be presented here. Other methods for synthesizing fluorocyclopropanes will be presented in a little more detail.

3.1. Fluorocarbene Methods

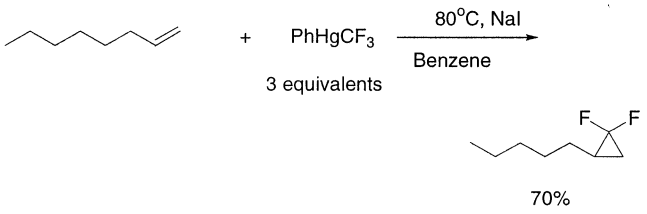
Difluorocarbene is by far the most important reagent in this category, and there are now many excellent methods for generating $:CF_2$ under conditions where it will add to a wide variety of alkenes, which almost always makes it the method of choice for the synthesis of *gem*-difluorocyclopropanes. In contrast, addition of fluorocarbene to alkenes is a reaction only rarely used to synthesize monofluorocyclopropanes. There are a number of good methods for generation of chlorofluorocarbene, and being more reactive than $:CF_2$ and more convenient than :CHF, its additions to alkenes, followed by a reductive step,[40] have probably provided the most common method for synthesis of monofluorocyclopropanes. There are good reviews on fluorocarbene chemistry,[41−43] and the reader is referred to them for more comprehensive coverage of this subject.

Difluorocarbene. Because of its relatively unreactive nature, the use of difluorocarbene to prepare *gem*-difluorocyclopropanes presented a considerable synthetic challenge in the years since its discovery in 1960, until it was realized that the key to a successful method required that the generation of $:CF_2$ be at sufficiently high temperature (>80 °C) to overcome the substantial energy barrier for addition to all but the most reactive of alkenes. Indeed, the first published method for adding difluorocarbene to alkenes, pyrolysis of sodium chlorodifluoroacetate in refluxing diglyme (∼190 °C),[5] to this day remains one of the most favored and reliable ways of making difluorocyclopropanes. Although a large (10−15-fold)

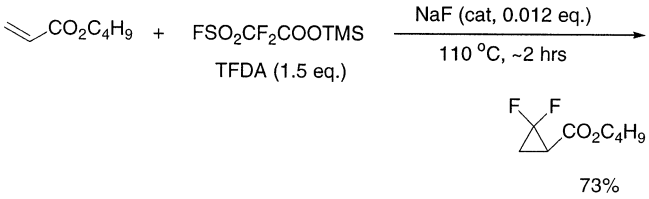


excess of reagent is often required, good conversions of alkenes, even quite unreactive ones,[44] can generally be obtained. Another method that also gives good results with alkenes over a broad reactivity range is Seyferth's reagent, $PhHgCF_3$,[45] which decomposes in the presence of NaI in refluxing benzene to form a reactive $:CF_2$ species. Unfortunately, despite its excellent reactivity characteristics, Seyferth's reagent is only rarely used today because of its toxicity and consequent lack of commercial availability.

Another effective source of difluorocarbene is the recently reported trimethylsilyl fluorosulfonyldi-

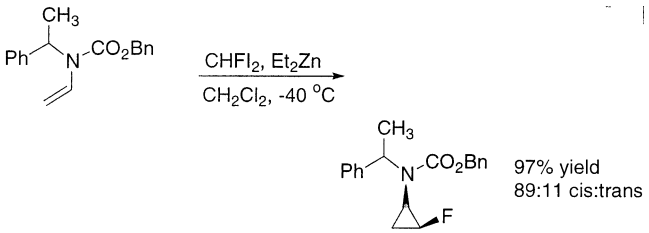


fluoroacetate (TFDA), which also generates $:CF_2$ under conditions where it adds efficiently to even quite unreactive alkenes, such as acrylate esters.[46,47]



For additions of $:CF_2$ to electron-rich alkenes, that is alkenes bearing at least *three* alkyl substituents or more strongly donating groups such as alkoxy or phenyl, there are a number of convenient, room-temperature methods available, perhaps the best two being those utilizing the precursors introduced by Burton (Ph_3P/CF_2Br_2) and Dolbier (Zn/CF_2Br_2).[48−50]

Fluorocarbene. Although there are various methods for generation of the less stable, more reactive *mono*fluorocarbene,[51,52] none are as convenient, efficient, or generally useful as those discussed above for difluorocarbene. Essentially all of the methods for preparation of :CHF involve dehalogenation of $CHFBr_2$ or preferentially of $CHFI_2$, which upon treatment with Et_2Zn forms a fluorocarbene reagent that appears to add quite efficiently to alkenes.[53,54] Similar

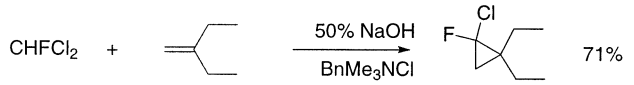


results are obtained using copper powder as the reductant, but much longer times of reaction are required.[55] However, perhaps because of the relative inaccessibility of the precursor, these reactions with $CHFI_2$ have not yet been fully assessed or widely used to make fluorocyclopropanes.

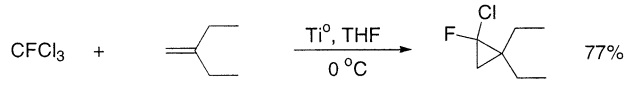
To synthesize cyclopropanes containing a CHF group, it has been most usual to proceed via the relatively convenient and often high-yield addition of either chlorofluorocarbene or bromofluorocarbene to an alkene, followed by replacement of the chlorine or bromine atoms with hydrogen.[41]

Chlorofluorocarbene. Although there are three good general methods for generation of chlorofluorocarbene, the excellent Seyferth method (using $PhHgCFCl_2$ in refluxing benzene)[56] is no longer recommended because of the toxic hazards of its synthesis and use. Dehydrochlorination of $CHFCl_2$ to generate :CFCl has been effectively accomplished by a number

of techniques,[41,42] but the most useful appear to utilize phase-transfer conditions.[57−59]

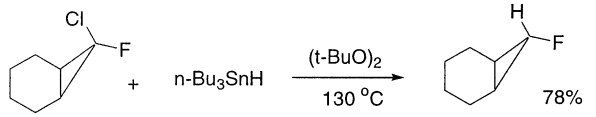


The final approach involves a relatively convenient dechlorination of $CFCl_3$ by reduced titanium, which is produced from the in situ reduction of $TiCl_4$ by $LiAlH_4$.[60] Using a 3-fold excess of $CFCl_3$ and Ti



reagent relative to the alkene substrate, good to excellent yields can be obtained from a wide variety of alkenes.

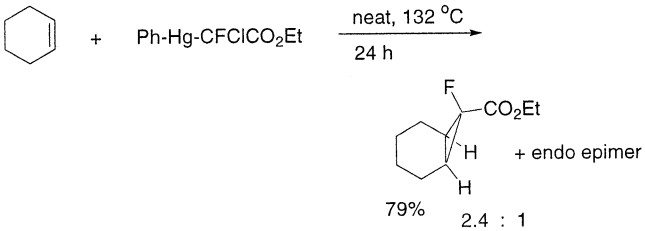
The chlorine substituents of these 1-chloro-1-fluorocyclopropanes can be readily replaced by hydrogen, generally homolytically using *n*-Bu_3SnH, to form fluorocyclopropanes, reactions which are reported to be highly stereoselective.[40,61]



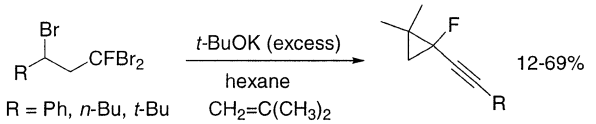
They can also be induced to undergo productive ionic reactions, generally accompanied by ring opening to form 2-fluoroallylic cations, as will be discussed later (section 4.1.1).

Bromofluorocarbene. Perhaps because of the relative inaccessibility of its precursors, :CFBr, although quite effective in its addition reaction with alkenes (and subsequent reductions to fluorocyclopropanes),[41−43] has relatively infrequently been used to synthesize the respective halofluorocyclopropane compounds.

Fluorocarbethoxycarbene. Seyferth developed organometallic mercury precursors of fluorocarbethoxycarbene that were very effective in adding to alkenes to form 1-fluorocyclopropane carboxylic esters.[62]



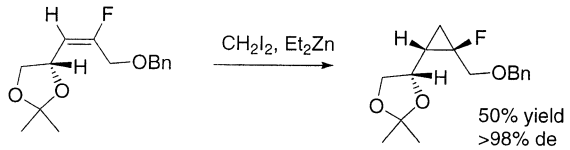
Fluoroalkynylcarbenes. Consecutive eliminations from 3-substituted 1-fluoro-1,1,3-tribromopropanes lead to the formation of fluoroalkynylcarbenes, which can be trapped by alkenes to form 1-fluoro-1-alkynylcyclopropanes.[63]



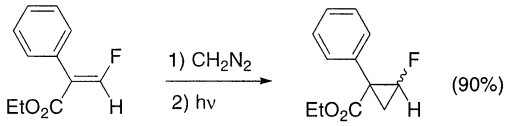
3.2. Carbene Additions to Fluoroalkenes

Not so commonly utilized, but nevertheless quite effective to their purpose, are reactions of carbenes, carbenoids, or diazo compounds with fluoroalkenes to form fluorocyclopropanes. Haszeldine's addition of dichlorocarbene to vinyl fluoride was the first reported example of such a reaction,[64] and shortly thereafter, Walborsky made 1-fluorocyclopropanecarboxylic esters by a then-novel addition of a diphenyldiazomethane to ethyl α-fluoroacrylate.[65]

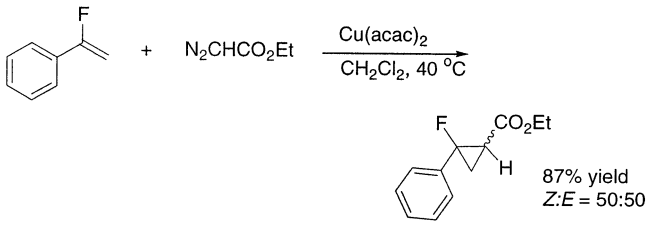
In recent years, such additions have become more common. Taguchi has carried out chiral Simmon−Smith-type chemistry on functionalized fluoroalkenes,[66,67] Kirk has used diazomethane for a similar



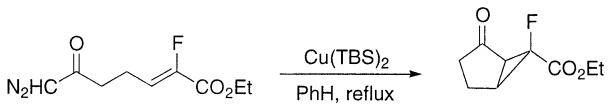
cyclopropanation of a *β*-fluoro-α,*β*-unsaturated ester,[68] and Haufe has used transition metal catalysis



to add diazo esters to α-fluorostyrene, with the reaction exhibiting good diastereo- and enantioselectivity when chiral ligands were used with copper(I) triflate.[69,70] Last, Nakazato's group carried out an



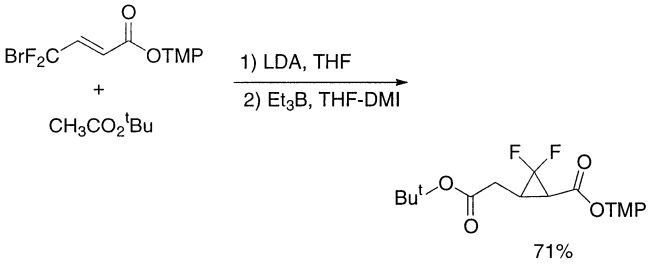
intramolecular cyclization of a diazo ketone onto a fluoroalkene.[71]



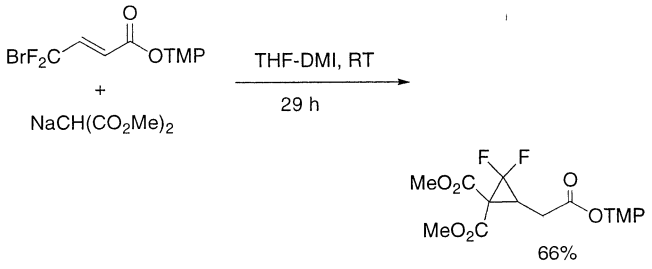
3.3. Non-Carbene Methods

Although carbene methodologies are dominant when it comes to making fluorinated cyclopropanes, much as they are for making cyclopropanes in general, in the past decade a number of novel, non-carbene approaches to the synthesis of fluorinated cyclopropanes have been developed. Taguchi's group has been very active in this area, being responsible for two of these inventive methods.[67]

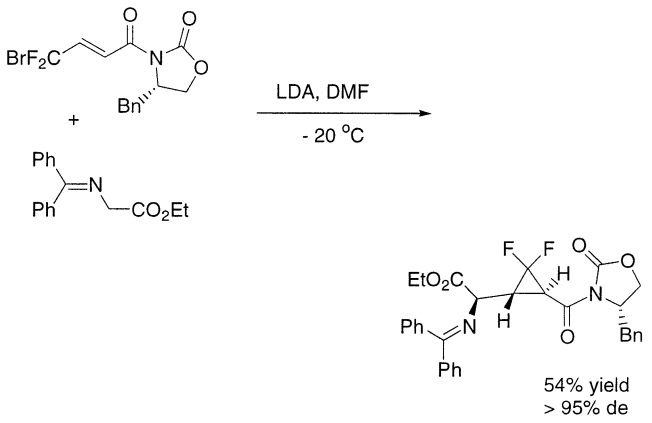
The Use of 4-Bromo-4,4-difluorocrotonate. Taguchi first discovered a remarkable tandem Michael/cyclization process that occurred when the reaction of 4-bromo-4,4-difluorocrotonate with ester or amide enolates was followed by addition of Et_3B.[72]



When malonate anion is the Michael donor, the cyclization step occurs at the malonate carbon, and no Et_3B is required.[67] Likewise, when a croton*amide*

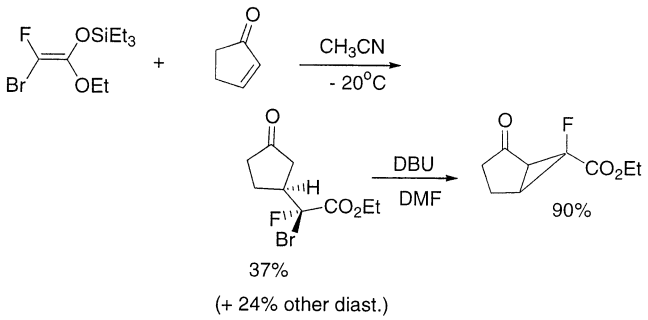


is used instead of the TMP ester, cyclopropane is formed, but again no Et_3B is needed.[73]

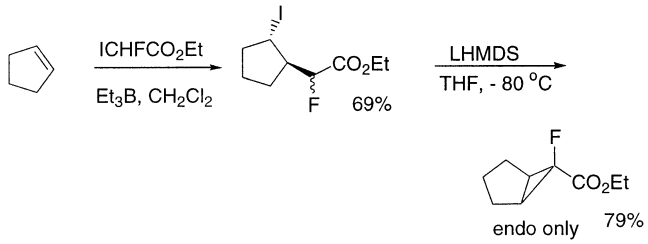


Hopefully, we will see more of this interesting type of chemistry in the future.

Anionic Three-Membered Ring Formation. Taguchi has also developed two methods involving nucleophilic cyclizations of enolate anions to form fluorinated cyclopropanes. The first one is closely related to the above reactions of the bromodifluorocrotonates. It involves Michael addition of a bromofluoroacetate enolate to acyclic enone, followed by enolate driven intramolecular cyclopropane formation by displacement of Br^-.[74] No SET chemistry needs to be invoked in this reaction—simply S_N2 chemistry.

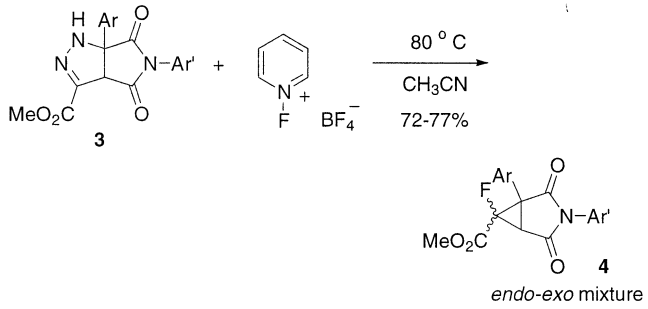


The second one involves an iodine transfer/radical addition process, followed by intramolecular displacement of iodide by the enolate of the resultant α-fluoro ester.[74]

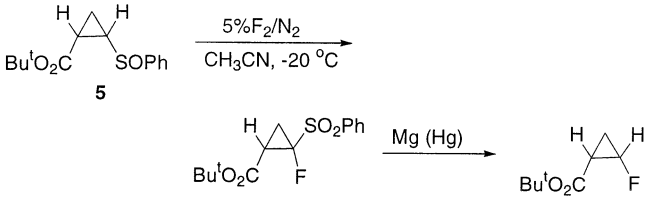


As in the immediately preceding example, this cyclopropane-forming reaction is almost certainly simple S_N2 chemistry.

Oxidative Fluorination. Recently, Kostikov's group reported a novel method for synthesizing 1-fluoro-cyclopropanecarboxylates, which upon further refinement might find some general utility. It was found that the oxidative fluorination of 2-pyrazoline substrate, **3**, led to nonstereoselective formation of a mixture of the endo and exo epimeric products **4** in good yields, based on conversion of substrate.[75]



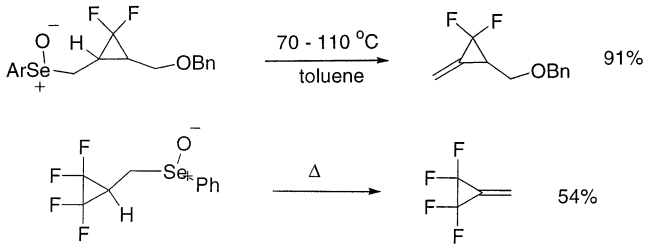
Direct Fluorination. Toyota's group has observed a Pummerer-like replacement of the α-hydrogen of phenylsulfinylcyclopropane, **5**, by fluorine using elemental fluorine.[76]



3.4. Synthesis of Fluorinated Methylenecyclopropanes

Fluorinated methylenecyclopropanes have been synthesized in order to study their thermal isomer-

izations, and they have also been prepared for use as synthetic intermediates. Although their first preparation was by simple addition of HFPO-derived difluorocarbene to allene,[77] since that time their syntheses have been accomplished via the mild and selective method of selenoxide elimination,[78−80] as indicated by the examples below.

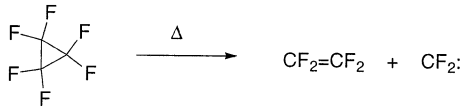


4. Chemistry of Fluorinated Cyclopropanes

Virtually all of the observed chemistry of fluorinated cyclopropanes and their derivatives exhibits a uniqueness that derives from the unique strain and polar characteristics of the respective fluorocyclopropane entities. This remarkable, reactive nature of fluorinated cyclopropanes is reflected in their rates of reactions, in the regiochemistry of their reactions, or simply because they facilitate novel chemistry.

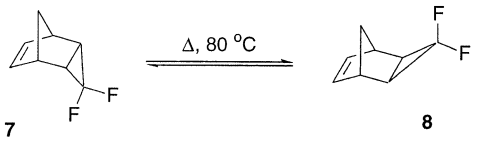
4.1. Unimolecular, Thermal, Homolytic Rearrangements

The first "chemistry" of fluorinated cyclopropanes to be reported was that of their thermolysis. A critical review of these early studies was published by O'Neal and Benson in 1968.[32] Included were their first estimates of the incremental strain of mono- through hexafluorocyclopropane, which were based upon the early (1964−65) kinetic work of Trotman-Dickenson.[81] Although such early work did not include *product identification*, it soon became apparent, as a result of the work of Mitsch,[82] Craig,[83] and Atkinson,[84] that the characteristic reaction of saturated fluorinated cyclopropanes was that of :CF_2 extrusion; i.e.[84]

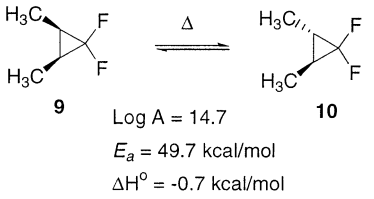


Thermal Stereomutation Processes. In the mid-70s, Staricco's group initiated their now long-standing program of study of unimolecular reactions of saturated fluorinated cyclopropanes. Included in their early work was a 1975 thermolytic study of *trans*-1,2-dichloro-3,3-difluorocyclopropane, **6**, which provided the first reported kinetic information for a thermal stereomutation reaction of a fluorinated cyclopropane.[85] This was followed shortly by

Jefford's[86] surprising report of the facile endo → exo isomerization of tricyclic compound **7**.

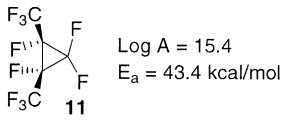


The latter result prompted Dolbier to initiate a systematic investigation directed at quantification of the kinetic effect of fluorine substituents on the thermal behavior of cyclopropane compounds. Two reviews of his work in this area have been published.[87,88] His first study was that of the thermal, cis−trans-epimerization of 1,1-difluoro-2,3-dimethylcyclopropane, **9**,[89] the activation energy of which



was 9.7 kcal/mol lower than that of the analogous hydrocarbon rearrangement, with **9** rearranging ∼1100 times faster than its non-fluorine-containing counterpart at 320 °C. The kinetic impact of the geminal fluorine substituents of **9** was consistent with the earlier mentioned kinetic studies of Trotman-Dickinson, Atkinson, and Mitsch (vide supra), which led O'Neal and Benson to conclude that the strain energy of fluorinated cyclopropanes was increased by ∼5 kcal/mol for each fluorine substituent.[32] Notably, the 0.7 kcal/mol preference for the trans-isomer **10** is less than that (1.3 kcal/mol) exhibited by the parent hydrocarbon system,[90] perhaps because of the greater C_2–C_3 bond length in the difluoro system.

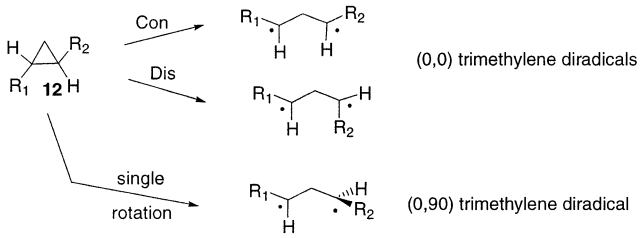
In addition to his study of dichloro system, **6**, Staricco also examined the cis−trans-isomerization bis-2,3-(trifluoromethyl)tetrafluorocyclopropane, **11**,[91]



which provided additional evidence regarding the kinetic influences of fluorine substitution on cyclopropane stereomutation.

Mechanism and Theory. Such "simple" C−C bond homolyses as those involved for the thermal interconversion of **9** and **10** proceed via the intermediacy of a trimethylene diradical. The nature of this fundamental process can be elucidated experimentally via the study of stereomutations, and they have been found to be anything but simple. For example, in principle, the chiral *trans*-2,3-disubstituted cyclopropane **12** can undergo two kinetically distinguishable stereomutations via C(1)−C(2) bond homolysis: (a) a coupled rotation of both C(1) and C(2) (either con- or disrotatory) via the so-called (0,0) trimethylene intermediate or (b) a single rotation of either C(1)

Scheme 2. Coupled versus Single Rotation Homolysis of Cyclopropanes



or C(2), where the (0,90) trimethylene would be formed, as depicted in Scheme 2. To the extent that the coupled rotation process is preferred, racemization would be preferred over diastereoisomerization (trans−cis-conversion). On the other hand, if single rotation is preferred, the two processes should occur at the same rate.

There has been a long and interesting history of both theoretical and experimental studies of the hydrocarbon cyclopropane system.[22,92−94] What has become clear from the most recent high-level calculations is that (a) the preferred (0,0) trimethylene intermediate is barely a minimum, existing in a very shallow energy well (less than 1 kcal barrier to ring closure), and (b) coupled rotation with conrotation is slightly favored (for unsubstituted cyclopropane) over both the single rotation process and the coupled disrotatory process ($\Delta G^{\ddagger} \sim 1.7$ kcal/mol), but such preference essentially disappears for alkyl-substituted cyclopropanes.[92] Numerous experiments have failed to confirm such predictions, with elegant experiments, containing deuterium as the only substituent, leading to conflicting results.[93,94]

In contrast, ab initio calculations by Getty, Hrovat, and Borden predicted a very different behavior for the stereomutations of *gem*-difluorocyclopropanes.[22,35] 1,1-Difluorocyclopropane is predicted to show a large preference for stereomutation by disrotation of C(2) and C(3). Such preference is predicted to be enhanced, not diminished, by alkyl substituents. Finally, since the s-trans,s-trans-(0,0)-conformation of 3,3-difluoropentane-2,4-diyl is computed to be 3−4 kcal/mol lower in energy than the s-cis-s-trans-(0,0)-conformation, the relative rates of coupled rotation in *cis*- and *trans*-1,1-difluoro-2,3-dialkylcyclopropanes via these two possible transition states are predicted to be useful for differentiating experimentally between con- and disrotation.

More specifically, an optically active *cis*-1,1-difluorocyclopropane was predicted to racemize much more rapidly than its trans-stereoisomer. As shown in Scheme 3, the *cis*-cyclopropane can undergo disrotatory ring opening to the preferred s-trans,s-trans-transition state for racemization, whereas disrotatory ring opening of the *trans*-cyclopropane gives the higher energy s-cis,s-trans-conformation of the diradical.

The remarkable stereochemical predictions of Borden were confirmed experimentally in 1998 via a kinetic study of the stereomutations of optically active *cis*- and *trans*-1,1-difluoro-2-ethyl-3-methylcyclopropane.[95] In this study, the cis-isomer was found to racemize more than 2 orders of magnitude

Scheme 3. Stereomutation of *gem*-Difluorocyclopropanes

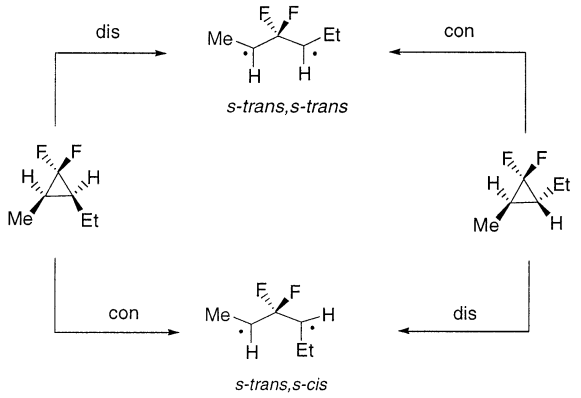
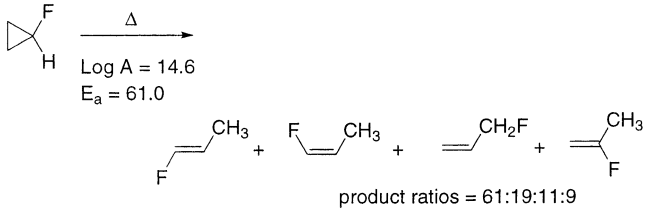


Table 2. Activation Energies for Thermal Extrusion of :CF_2

cyclopropane	log A	E_a, kcal/mol	ref
1,1 difluoro	14.1	56.4	96
1,1,2-trifluoro	14.4	50.5	96
1,1,2-trifluoro-2-trifluoromethyl	15.2	50.6	99
1,1,2,2-tetrafluoro	14.0	45.1	100
1,1,2,3-tetrafluoro-2,3-bis-trifluoromethyl	15.4	46.6	91
1,1,2,2,3-pentafluoro-3-pentafluoroallyl	14.8	42.7	82
hexafluoro	13.3	38.6	84

faster than its epimerization to the trans-isomer, thus demonstrating a preferred coupled rotation process. Since the cis-isomer also was shown to racemize more than 40 times faster than the trans-isomer, this coupled process was confirmed to be disrotatory in nature.

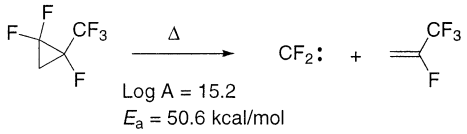
Saturated Cyclopropane Thermolyses−:CF_2 Extrusion Reactions. When saturated hydrocarbon cyclopropanes are heated to temperatures higher than those required for stereomutations, the most commonly observed reactions are those involving 1,2-H-shifts to form propenes. In contrast, H-shift processes are not common in pyrolyses of fluorinated cyclopropanes, with only the monofluorocyclopropane clearly behaving in this manner.[96,97]



Recently, Lauterwald and Heydtmann showed that small amounts of H-shift products, mostly 1,1-difluoropropene, were also formed during the pyrolysis of 1,1-difluorocyclopropane.[98]

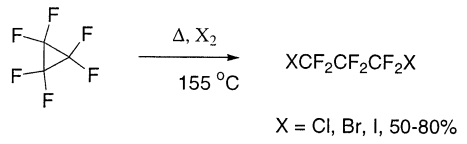
As indicated from the data in Table 2, the E_a required for unimolecular decomposition of fluorinated cyclopropanes decreases with increasing fluorine content. Although the early kinetic studies of 1,1-difluoro-, 1,1,2-trifluoro-, and 1,1,2,2-tetrafluorocyclopropanes were carried out without product analysis, subsequent studies have made it clear that the primary thermal process undergone by all of these compounds is :CF_2 extrusion, as exemplified by

the 1977 study of the pyrolysis of 1,1,2-trifluoro-2-trifluoromethylcyclopropane by Quero, Ferrero, and Staricco.[99]



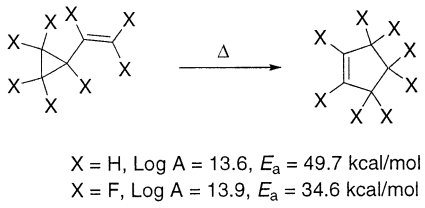
As will be seen in the discussion of fluorinated spiropentane pyrolyses (section II.4.1.5), even when structural rearrangements are possible, thermal extrusions of :CF_2 are often found to compete. For example, in Dolbier's geometric isomerization study of difluorocyclopropanes **9** and **10**, a competing process involving loss of :CF_2 was observed (k_{isom}/k_{extr} = 21.3 at 297° and 15.6 at 345 °C).

Although the mechanism for this extrusion process is generally considered to be a concerted loss of :CF_2, the possible intermediacy of a trimethylene intermediate (particularly in the case of the perfluoro system) has not been ruled out. Such conjecture is mainly based on the observation by Yang, Krusic, and Smart that pyrolysis of perfluorocyclopropane in the presence of halogens gives 1,3-dihalohexafluoropropane as the major products.[101]



Other highly fluorinated cyclopropanes, such as trifluoromethylpentafluoro-, bromopentafluoro-, and pentafluorocyclopropane, undergo similar, but non-regiospecific, ring-opening halogenation reactions.

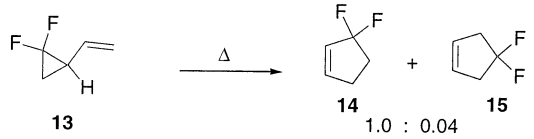
Vinylcyclopropane Rearrangements. The very first example of a structural rearrangement of a fluorinated cyclopropane system was Mitsch's study of perfluorovinylcyclopropane in 1966.[82]



Note the dramatic lowering of E_a for the vinylcyclopropane rearrangement of C_5F_8 when compared to that of the hydrocarbon![102] Mitsch discussed his results in terms of the usual diradical mechanism, and he attributed the lowered E_a to the greater strain of the perfluoro system.

Studies of 2,2-difluorovinylcyclopropanes are of particular interest, because the regiochemistry of their ring-opening rearrangements could provide insight into the relative stabilities of 1,1-difluoro- versus 2,2-difluorotrimethylene diradical species. Ever since the structural features of 1,1-difluorocyclopropanes, namely the lengthening of the distal C(2)−C(3) bond accompanied by the shortening of the proximal C(1)−C(2) bonds, had been elucidated (see section II.1), there had been speculation that such structural effects would be translated into reactions proceeding with preferential distal bond homolysis.

Dolbier and Roth's studies of the thermolyses of the parent, 2,2-difluorovinylcyclopropane, **13**, and of 2,2-difluoro-(*trans*-1-propenyl)cyclopropane, **16**, demonstrated a distinct, but far from exclusive, preference for distal bond cleavage,[33,103] this after an initial erroneous report of preferred formation of **15**.[104]

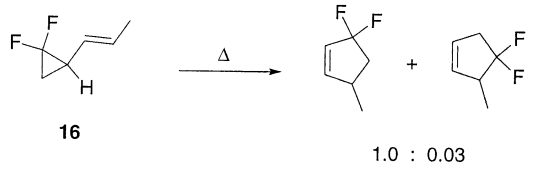


For reaction **13** → **14** + **15**: log A = 13.7, E_a = 40.3 kcal/mol[103]

For reaction **13** → **14**: log A = 12.7; E_a = 36.9 kcal/mol[33]

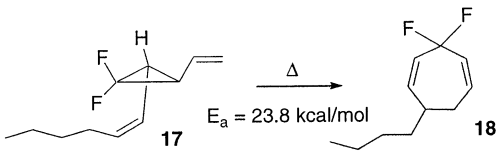
For reaction **13** → **15**: log A = 12.6; E_a = 40.5 kcal/mol[33]

Such preference was consistent with Borden's later

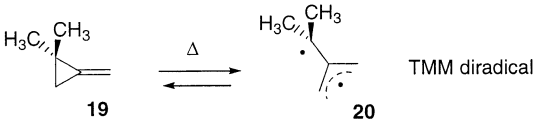


estimates of a difference of 3.9 kcal/mol between the (0,0)-conformation of 2,2-difluorotrimethylene and the (0,90)-conformation of the 1,1-difluorotrimethylene diradical.[35]

An interesting fluorinated *divinyl*cyclopropane system, **17**, has been examined kinetically. The E_a for its rearrangement to **18** is 9 kcal/mol lower than the rearrangement of an analogous non-fluorine-substituted compound.[105]

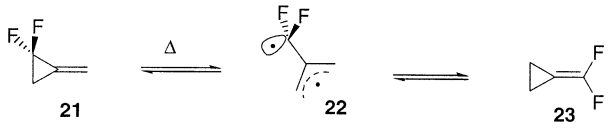


Methylenecyclopropane Rearrangements. Methylenecyclopropanes undergo thermal rearrangements via a single-rotation cleavage of the bond distal to the methylene group to form orthogonal trimethylenemethane (TMM) diradical intermediates, such as **20**, depicted below.[106,107]



With such a mechanism in mind, a system that should provide insight into the relative energetics for cleavage of the *proximal* bond of a *gem*-difluoro-

cyclopropane should be the 2,2-difluoromethylenecyclopropane system, **21**.[77]

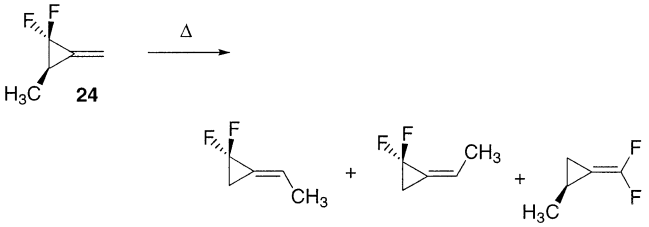


Log A = 13.2; E_a = 38.3 kcal/mol

With an E_a of 38.3, the impact of the fluorine substituents of **21** on proximal C−C bond cleavage (∼ 3 kcal/mol) was found to be considerably less than had been observed for distal bond cleavage of compounds **8** and **13** (∼9−10 kcal/mol).

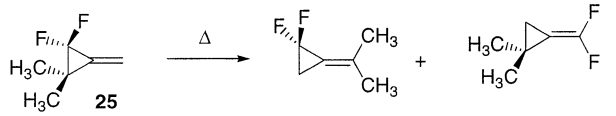
As has been pointed out by Borden,[108,109] the smaller kinetic advantage in the methylenecyclopropane system appears to derive from the strong preference of a CF_2 radical center, such as that present in **22**, for a pyramidal geometry, which raises the enthalpies of the transition structures for the rearrangement of **21** by an amount that substantially offsets the additional strain present in **21**. A study of the degenerate rearrangement of a deuterium-labeled **21**, where the CF_2 carbon acts as the "pivot" carbon of the TMM diradical, would provide definitive insight regarding the true barrier for C(2)−C(3) bond homolysis.

A study of the rearrangements of 2,2-difluoro-3-methyl- and 2,2-difluoro-3,3-dimethylmethylenecyclopropane, **24** and **25**, indicates that fluorine and methyl exhibit similar propensities to determine the pivot carbon.[110] Therefore, it would not be surprising



kinetic ratio: 1.5 : 0.64 : 1

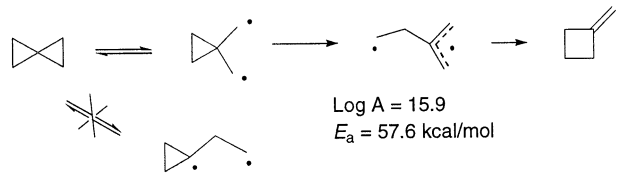
if the degenerate rearrangement of **25** were to have a kinetic advantage similar to the $\Delta\Delta G^{\ddagger}$ of 2.4 kcal/mol observed for the degenerate versus structural rearrangements of the deuterium-labeled **19**, i.e., 2,2-dimethyl-3,3-dideuteriomethylenecyclopropane.[107]



Kinetic ratio (201 °C) = 1 : 1.1
Thermodynamic ratio (243 °C) = 2.6 : 1

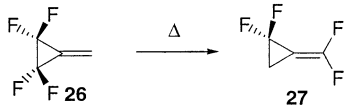
2,2,3,3-Tetrafluoromethylenecyclopropane (**26**) was found to rearrange 7900 times as fast as 2,2-difluoromethylenecyclopropane (**21**), which reflects a difference in their respective E_a values of 8.7 kcal/mol.[80] Therefore, the second CF_2 group has a much greater impact on the reactivity of **26** than the 3 kcal/mol impact derived from the single CF_2 group of **21**. This large difference probably derives from two factors:

Scheme 4



Log A = 15.9
E_a = 57.6 kcal/mol

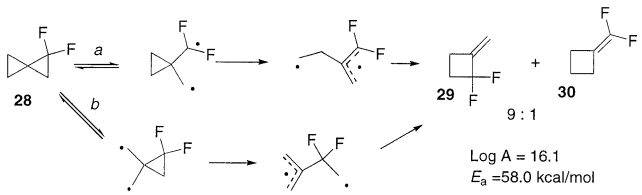
(a) the nonincremental effect of the two CF_2 groups on the strain of **26** and (b) the loss of the "degenerate" mode of rearrangement, which was "invisible" for **21**. In contrast, each homolysis of **26** must lead to rearrangement to **27**.

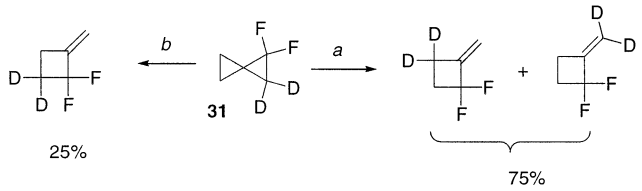


Log A = 12.6
E_a = 29.6 kcal/mol

Spiropentane → Methylenecyclobutane Rearrangements. The thermal unimolecular rearrangement of spiropentane to methylenecyclobutane is an interesting and complex reaction, the mechanism of which has been investigated in detail. Rearrangement of the parent hydrocarbon has been shown to proceed exclusively via initial peripheral C(1)−C(2) bond cleavage, as depicted in Scheme 4.[111]

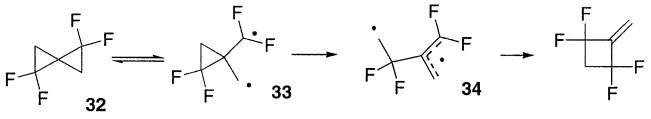
Studies of the various fluorinated spiropentanes have provided considerable additional insight into details of the rearrangement mechanism as well as into the kinetic influences of fluorinated cyclopropanes.[112] For example, consistent with the methylenecyclopropane results (section II.4.1.3), the two geminal fluorine substituents of 1,1-difluorospiropentane (**28**) exerted little overall kinetic effect on the homolysis of the proximal C(1)−C(2).[113] The observed regioselectivity of the reaction did not allow one to distinguish between the two possible peripheral homolysis mechanisms, a and b. However, simple analysis of the product ratios from thermal rearrangement of deuterium-labeled analogue **31** allowed determination of the ratio of mechanisms a and b to be 3:1.





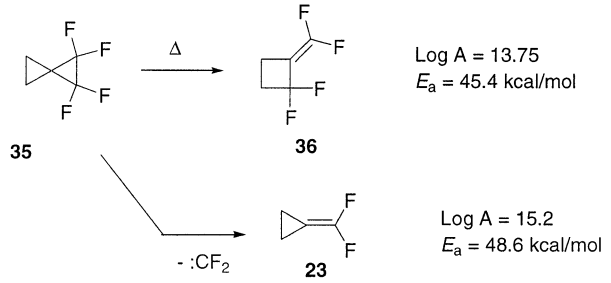
Thermolysis of 1,1,4,4-tetrafluorospiropentane (**32**) exhibited a modest 10-fold rate enhancement relative to **28**, which is consistent with the preequilibrium formation of diradical **33**, followed by enhancement

of the kinetically significant conversion to diradical **34** by distal bond cleavage of the second ring.[114]



Log A = 14.8; E_a = 51.7 kcal/mol

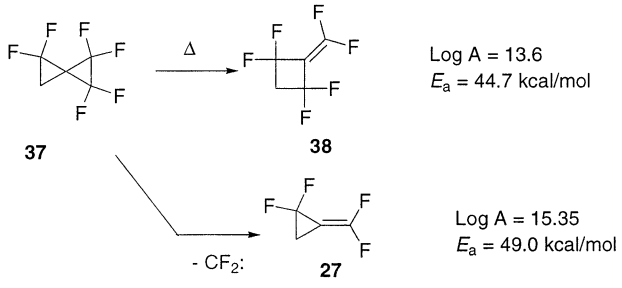
Extrusion of :CF_2 is the preferred unimolecular reaction of 1,1,2,2-tetrafluorospiropentane, although rearrangement of **35** to **36** is highly competitive (40% of the reaction). Extrusion of :CF_2 from **35** occurs at



:CF_2 extrusion/rearrangment (270 °C) = 1.49

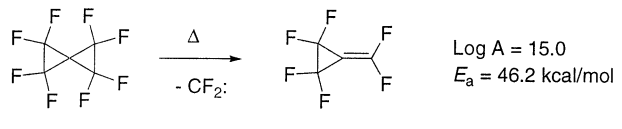
virtually the same rate as its extrusion from tetrafluorocyclopropane (see Table 2). The rearrangement of **35** occurs at a rate 140 times faster than the difluoro system (**28**) at 340 °C, an enhancement that is comparable to the difference between the tetrafluoro- and difluoromethylenecyclopropanes (section II.4.1.4).

Extrusion of :CF_2 and rearrangement are again competitive processes in the thermolysis of hexafluorospiropentane (**37**).[112] In this case, rearrangement plays a larger role than was the case for **35**, mainly because the third CF_2 group specifically facilitates rearrangement.



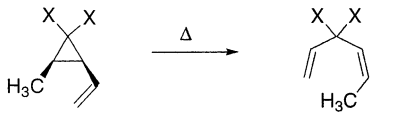
CF_2: extrusion/rearrangment (270 °C) = 1.03

Perfluorospiropentane (**39**) underwent exclusive :CF_2 extrusion upon thermolysis, with a facility modestly greater than that exhibited by **35** and **37**.



The relative reactivities of the various fluorinated spiropentanes, as well as the regiospecificity exhibited in their rearrangements and their relative propensities to undergo extrusion versus rearrangement, are all consistent with the previously discussed kinetic effects of geminal fluorine substituents on cyclopropane reactivity. One should consult the original papers for numerous other more subtle kinetic observations that were reported in the studies of this interesting series of compounds.

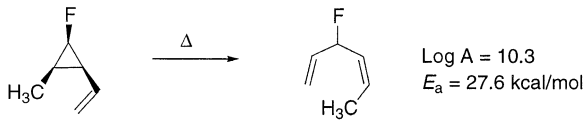
Sigmatropic Rearrangements. Additional evidence for distal bond weakening for *gem*-difluorocyclopropanes has been obtained through a study of some pericyclic processes. Thermal homo 1.5-hydrogen shifts have been observed for a number of *cis*-2-alkyl-1-vinylcyclopropane systems, with rearrangement of the parent system (**40**) having been reported in 1964−65.[115,116] The observed low A factor along with the low E_a led the authors to propose a pericyclic mechanism involving concerted H-transfer and cyclopropane ring-cleavage.



40, X = H: Log A = 11.0; E_a = 31.2 kcal/mol
41, X = F: Log A = 10.3; E_a = 23.4 kcal/mol

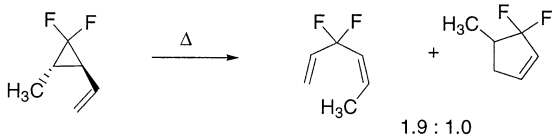
Since the bond cleaved would be the one *distal* to the *gem*-difluoro substituents of *cis*-2,2-difluoro-3-methyl-1-vinylcyclopropane (**41**), one would expect the ring opening to receive the full kinetic benefit of the fluorine substituents (such as that which was experienced for the vinylcyclopropane rearrangements discussed in section II.4.1.3), and that is indeed what is observed, with **41** rearranging at a rate 6900 times faster than **40** at 100 °C.[117]

This pericyclic system was also utilized to determine the effect of a *single* fluorine substituent on distal bond cleavage. Thus *cis*,*cis*-2-fluoro-3-methyl-1-vinylcyclopropane (**42**) was observed to rearrange via the homo-1,5-hydrogen shift mechanism at a rate only 11.2 times faster than the hydrocarbon system, which is another indication that geminal fluorine substituents exert an impact much more than would be predicted simply on the basis of the impact of a single fluorine substituent.[118]



42

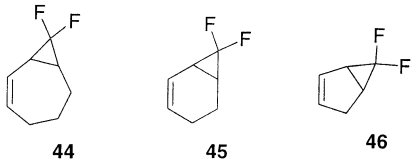
Thermolysis of *trans*-2,2-difluoro-3-methyl-1-vinylcyclopropane (**43**), which because of molecular constraints cannot undergo the pericyclic hydrogen shift process, proceeded at a rate considerably slower than that of its cis-isomer (**41**): k_{rel} = 1/2805 at 200 °C, and it underwent competitive vinylcyclopropane and H-shift rearrangement processes.[117]



43

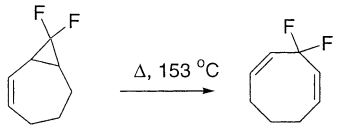
1.9 : 1.0

Bicyclic Difluorovinylcyclopropane Systems. A series of three difluorobicyclic vinylcyclopropane compounds, **44**−**46**, were examined thermolytically, with the initial expectation that they should provide additional examples of pericyclic 1,5-H shift reactions or vinylcyclopropane rearrangements.



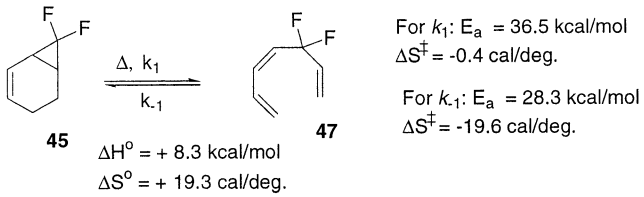
44 **45** **46**

In fact, only one bicyclooctene system, **44**, underwent an expected type of reaction, rearranging with the substantial rate enhancement expected, relative to its hydrocarbon counterpart, for distal bond cleavage.[117] The other two underwent unique reactions that provided unexpected insight with respect to hitherto unobserved aspects of difluorocyclopropanes' reactivity.



44 k_{rel} = ~1,500

Unlike its hydrocarbon analogue, which was stable up to temperatures exceeding 290 °C, bicycloheptene system **45** underwent a relatively low-temperature equilibration with acyclic triene **47**, with an equilibrium constant of 1.14 at 160 °C.[119] Such a reaction is

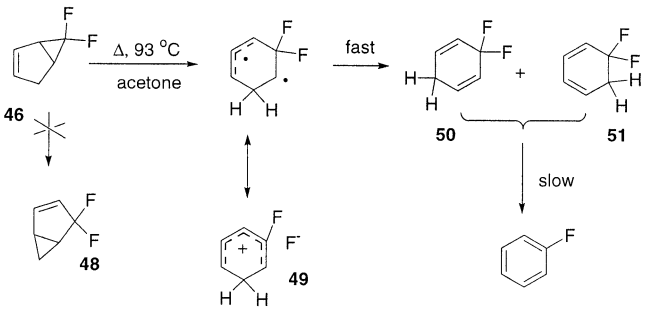


45 **47**

best envisioned as a intramolecular retro-Diels−Alder reaction. The kinetic parameters that were observed for the above reversible Diels−Alder reaction represent what is perhaps the most clear-cut and dramatic examples of the precise relationship of the transition state of a Diels−Alder reaction to both the starting materials and the adduct. The fact that virtually all of the entropy that is lost in forming product is lost in reaching the cycloaddition transition state is demonstrated by the observed activation parameters.

Numerous investigations have shown that vinylcyclopropane rearrangements are to be expected when bicyclo[3.1.0]hex-2-enes undergo thermal isomerization. In this respect, the thermal conversion of 6,6-difluorobicyclo[3.1.0]hex-2-ene (**46**) should have the additional advantage of both a kinetic and a thermodynamic impetus. It is therefore surprising that interconversion of **46** and **48** was not observed to occur at 70 °C in the gas phase, but rather only dehydrofluorinative aromatization to form fluorobenzene (Scheme 5) was seen.[120,121] When the reaction

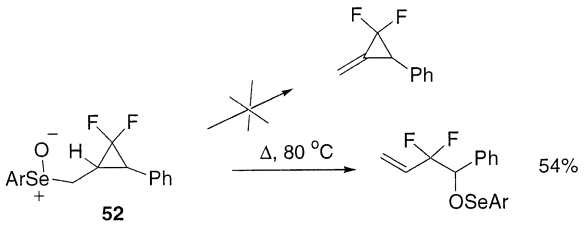
Scheme 5



46 **48** **49** **50** **51**

was carried out at 93 °C in acetone solution, almost no fluorobenzene was formed after 30 min, but instead, two intermediate 1,2-H-shift products, **50** and **51**, were formed. It is amazing that H-shift products should be formed rather than observing the simple valence tautomerism to **48**. Nevertheless, such results can be rationalized in terms of the importance of the dipolar, hyperconjugative resonance form **49**. To the extent that the diradical has cationic character, the observed 1,2-H-shifts should be made facile.[10]

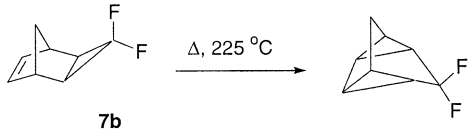
Other Thermal Rearrangements. In section 3.4, the synthesis of 2,2-difluoromethylenecyclopropanes via selenoxide elimination reaction was discussed. In contrast to the normal elimination reaction, which occurs when nonactivating substituents, such as CH_2-OBn, are at the 3-position, a ring-opening rearrangement reaction occurs preferentially when the 3-position bears a phenyl substituent, as is the case for **52**.[78]



52

4.2. Thermal Bimolecular Reactions

Because of the long, weak distal bond of 1,1-difluorocyclopropane systems, there have been many unsuccessful attempts (virtually all unpublished) to induce such compounds, that is, saturated *gem*-difluorocyclopropanes and 2,2-difluorovinylcyclopropanes, to undergo cycloaddition-type reactions across the distal bond, but to our knowledge, the only example thus far reported has been Jefford's intramolecular [2 + 2] reaction of fluorinated tricyclic compound **7b**.[86] In recent years, there have been

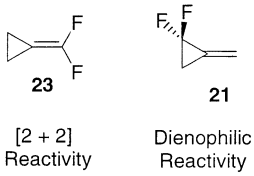


7b

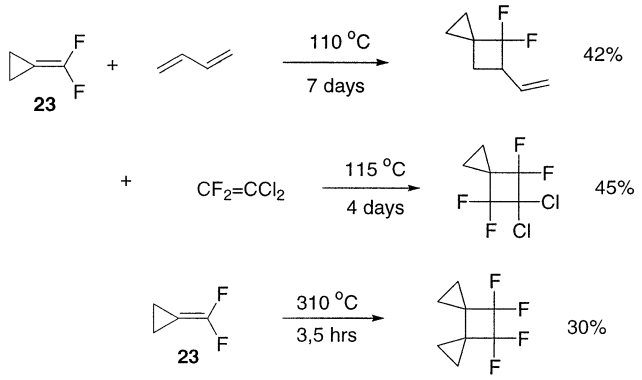
numerous examples published of transition metal catalyzed [5 + 2] cycloadditions between *hydrocarbon* vinylcyclopropanes and alkenes and alkynes,[122] but thus far such techniques have not been applied to fluorine-containing vinylcyclopropanes.

Methylenecyclopropane Cycloadditions. Methylenecyclopropanes have two possible modes of cycloaddition chemistry: (a) direct cycloaddition to the strained methylene group and (b) by trapping of the "TMM-diyl" intermediate formed from thermolysis of a methylenecyclopropane.

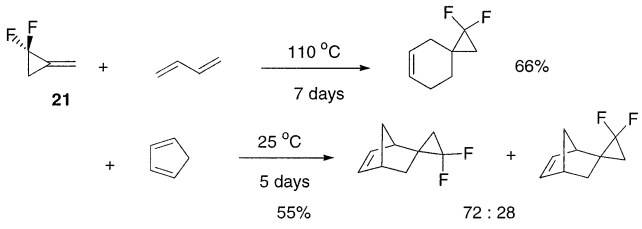
Direct Cycloaddition. Fluorinated methylenecyclopropanes should have a distinct advantage with respect to the direct mode of cycloaddition. Since 1,1-difluoroalkenes are recognized to have good [2 + 2] cycloaddition reactivity[123,124] and methylenecyclopropanes a modest [2 + 2] reactivity, (difluoromethylene)cyclopropane (**23**), which combines both attributes, should be a good [2 + 2] partner. On the other hand, olefins bearing allylic fluorine substituents have been found to have significant *dienophilic reactivity*.[125] Hence, 2,2-difluoromethylenecyclopropane (**21**) should be a good dienophile in [2 + 4] cycloadditions. Both of these expectations have been borne out in practice.[126]



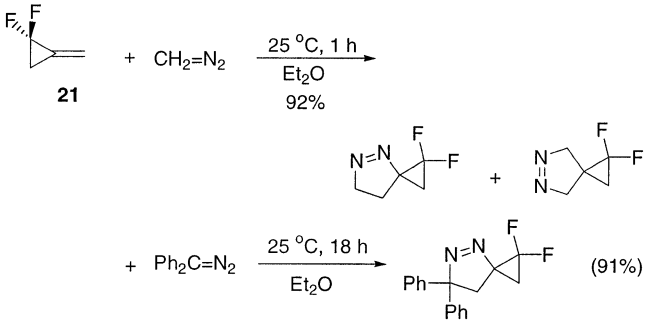
Thus (difluoromethylene)cyclopropane (**23**) was found to have a modest reactivity with respect to [2 + 2] cycloadditions, as indicated by the examples below.[126]



As predicted, 2,2-difluoromethylenecyclopropane (**21**) exhibits moderate dienophilic reactivity, as exemplified by the reactions below.[126]

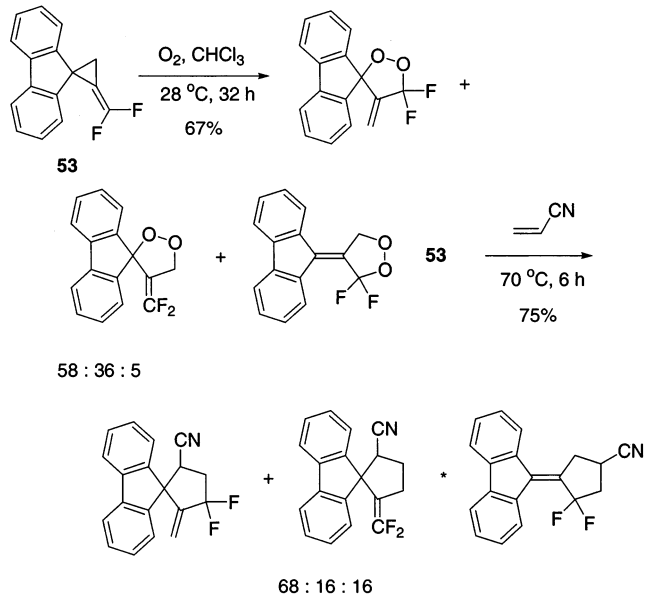


Not surprisingly, **21** also exhibits significant dipolarophilic reactivity as well, reacting smoothly with diazomethane and diphenyldiazomethane to give excellent yields for 1,3-dipolar cycloaddition.[127] The regiospecificity exhibited in the second reaction undoubtedly is sterically derived.



TMM-diyl Reactivity. Berson and later Little and co-workers have demonstrated a wide variety of intra- and intermolecular "cycloaddition" reactions of TMM-diyls of highly strained methylene cyclopropanes,[128,129] but there have been few reports of relatively "simple" methylenecyclopropanes undergoing such trapping reactions.[130−132]

Fluorines seem to help in that regard. When a fluorinated methylenecyclopropane bears sufficiently stabilizing groups at the pivot carbon, there can be sufficient diyl present, in some systems even at room temperature, for TMM-diyl trapping to occur. For example, bubbling O_2 at room temperature or heating acrylonitrile in a $CHCl_3$ solution of methylenecyclopropane (**53**) in each case leads to good yields of isomeric adducts derived from trapping of the diyl species.



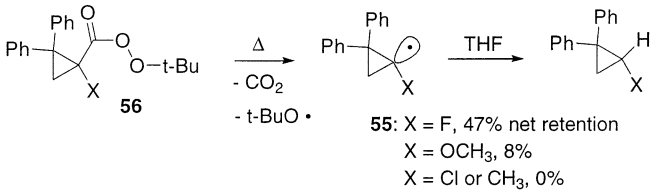
The nonfluorinated analogue reacted similarly, but much more slowly, and the analogous diphenyl compound was unreactive under the same conditions. Because of the enforced coplanarity of the two phenyls of the fluorenyl group, this group has been shown to be a much better radical stabilizer than two phenyl substituents, which require a substantial loss of entropy to reach coplanarity.[133]

4.3. Radical Chemistry

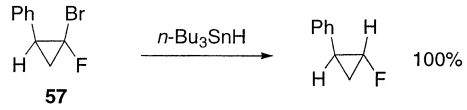
A discussion of the chemistry of fluorinated cyclopropane radicals can be broken down into two classes of relevant radical systems, one being those where

the radical is directly on the cyclopropane ring, the other being systems where the radical is contiguous to the cyclopropane ring. Radicals located more distant from the cyclopropane ring behave completely independent of the cyclopropane moiety and are therefore not relevant to this discussion.

Cyclopropyl Radicals. Cyclopropyl radicals bearing fluorine substituents on any carbon but the radical carbon have no particularly unique structure or reactivity characteristics, other than an increased electrophilicity due to the presence of an electronegative substituent such as fluorine. On the other hand, the 1-fluorocyclopropyl radical has been the subject of considerable study, with its most interesting characteristic being its configurational stability.[134] The cyclopropyl radical already is σ (that is pyramidal) in nature,[135] and addition of a fluorine substituent to the radical center serves to enhance such character and increase the inversion barrier.[136] Walborsky was the first to report such behavior in his stereochemical study of the thermal decomposition of *tert*-butyl peresters of chiral 1-substituted-2,2-diphenylcyclopropanecarboxylic acids (**55**).[137]

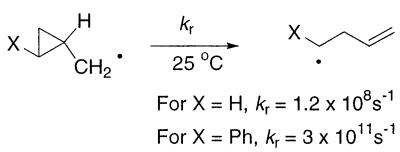


Indeed, if a faster H-transfer agent, such as *n*-Bu_3SnH, is used to trap radical **55**, as in the reduction of bromofluorocyclopropane **57**, complete retention of

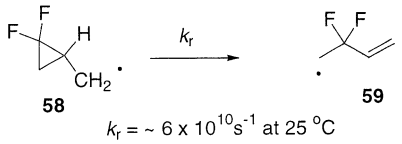


configuration is observed.[61] Other kinetic studies have served to confirm the strong σ-character and significant barrier to inversion of the 1-fluorocyclopropyl radical.[138]

Cyclopropylcarbinyl Radicals. The rearrangement of the cyclopropylcarbinyl radical to the allylcarbinyl radical belongs to a class of so-called "clock reactions" that have been developed for use as "probes" of radical intermediacy for the last 20 years.[139,140] This rearrangement has attracted particular attention in recent years because its family of derivatives provides ultrafast mechanistic probes of radical intermediacy and lifetime,[141] with rate constants ranging from 1.2×10^8 s^{-1} for the parent to 3×10^{11} s^{-1} for the 2-phenylcyclopropylcarbinyl radical.[142]



The 2,2-difluorocyclopropylcarbinyl radical, **58**, also undergoes an extraordinarily fast and regiospecific unimolecular ring opening distal to the geminal fluorine substituents to form the 2,2-difluoro-3-butenyl radical, **59**, so fast that the only bimolecular

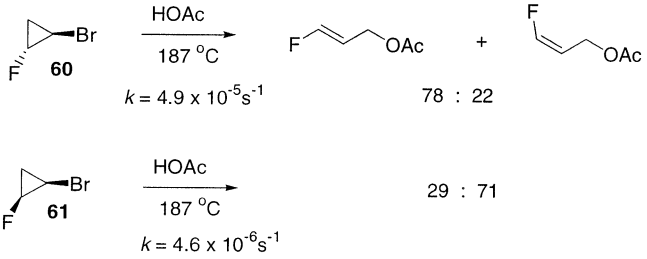


trap that was able to provide a detectable (1 part in 100) product from trapping of the **58** was the nitroxyl radical, TEMPO, which traps with diffusion control. Using competition kinetics with TEMPO as the trapping agent, a rate constant of 1.3×10^{11} s^{-1} at 93 °C (or $\sim 6 \times 10^{10}$ s^{-1} at room temperature) was determined.[143] A computational paper has also appeared that examines the impact of from one fluorine substituent to perfluorination on the activation barriers for cyclopropylcarbinyl radical ring opening.[144] Interestingly, the perfluoro and the hydrocarbon radical systems are calculated to have virtually identical barriers to ring opening, although the enthalpies of reaction differ tremendously (−19 vs −4.5 kcal/mol, respectively). The lowest calculated barrier is 1.6 kcal/mol, that of the 2,2-difluorocyclopropylcarbinyl radical (**58**).

With its modest steric demand, this ultrafast radical clock reaction of **58** should prove useful as a probe of reactions that potentially involve radical intermediates. Enhancing its use in this regard is the fact that this probe can also clearly distinguish between radical and carbocation intermediates (section II.4.4.2).

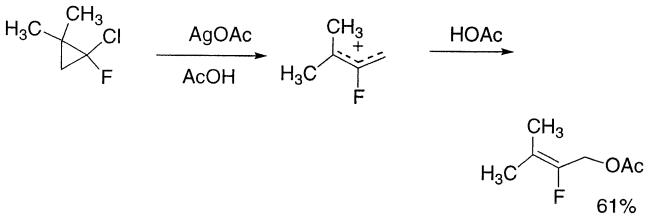
4.4. Carbocation Chemistry

The Cyclopropyl Cation. One of the most commonly observed reactions of halocyclopropanes is their solvolysis to form cyclopropyl cations, which invariably produce products derived from their rearrangement to allylic cations. In fact, these reactions almost surely do not actually involve cyclopropyl cations as distinct intermediates but rather proceed via a concerted, pericyclic ring opening synchronous with heterolytic cleavage of the cyclopropyl−halogen bond, as was elegantly demonstrated by DePuy and Schleyer, when they demonstrated that such solvolyses proceeded with disrotatory C(2)−C(3) bond cleavage.[145,146] The fact that this orbital symmetry controlled, stereospecific process also involved torquoselectivity was demonstrated by the relative stereoselectivities exhibited during the solvolyses of *trans*- and *cis*-2-fluorocyclopropyl bromides, **60** and **61**.[147]

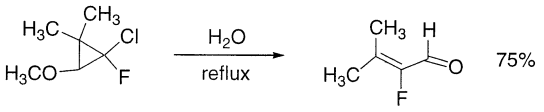


Trans-isomer **60** is more reactive, which is consistent with the known torquoselective preference for a fluorine substituent to rotate outward in an electrocyclic ring-opening process.[148] Although the results appear to be indicative of a lack of stereospecificity in the solvolytic ring openings, this is not likely the case. The partial loss of stereochemistry probably derives from the partial intermediacy of CH_2=CHCHFX species (X = Br or OAc) in the reaction.

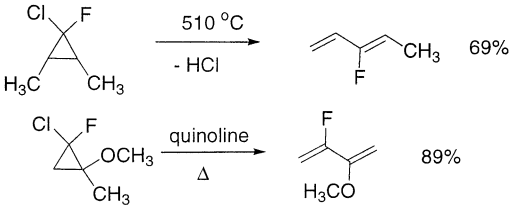
More commonly in the literature, the fluorine substituent on a cyclopropyl cation has been at the 1-position, and such reactions have long been utilized for synthetic purpose since Schlosser's report of the acetolysis of geminal chlorofluorocyclopropanes in 1974.[149−151] Since then, Schosser's and Wakselman's



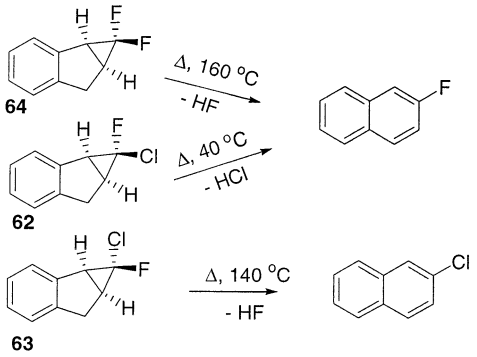
groups have elaborated on this chemistry to provide synthetic methods for analogous aldehydes and ketones, as exemplified below.[152−155]



Geminal chlorofluorocyclopropanes have also been used as precursors of dienes, with two different strategies having proved successful in this regard.[156,157]



A study of the thermal dehydrohalogenative aromatization reactions of a series of benzobicyclo[3.1.0]-hexenes provided considerable mechanistic insight into the factors governing the reactivity of halogenated cyclopropanes in their ionization processes.[121] For example, *endo*-chloro compound **62** was found to

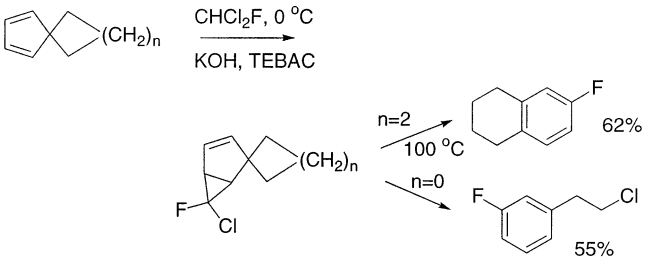


undergo loss of chloride ion at temperatures >40 °C, to form 2-fluoronaphthalene, whereas its *endo*-fluorine epimer **63** did not lose Cl^- and required temperatures >140 °C to undergo specific fluoride loss to form 2-chloronaphthalene. Surprisingly, the two reactions were found to have similar enthalpies of activation (25.7 and 24.7 kcal/ mol, respectively), with the main cause of their difference in reactivities deriving from drastically different entropies of activation (+ 2.3 versus −15.6 cal/deg, respectively). The 6,6-difluoro analogue **64** had a similarly low $\Delta H^{\ddagger}$ (24.2 kcal/mol) but an even larger negative $\Delta S^{\ddagger}$ (−24.6 cal/deg), such that 160 °C was required for its dehydrofluorinative aromatization reaction to occur. There have been a number of additional studies of these and similar reactions,[59,155] among them a study by Volchkov and co-workers in which **63** is reported to convert to 2-*fluoro*naphthalene.[59]

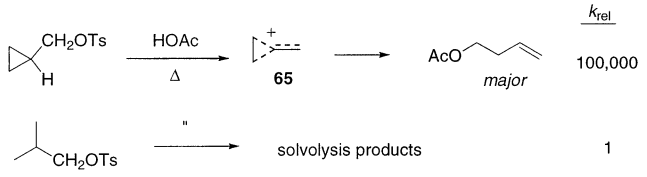
A similar difference in epimeric reactivity was noted by Jefford with respect to the two :CFCl adducts of norbornene. Only the *endo*-F adduct could be isolated, whereas the *endo*-Cl adduct lost Cl^- upon attempts at isolation.[86]

Nefedov and co-workers have devised a useful variation of this chemistry to synthesize various fluoroaromatic compounds.[158] As exemplified for the synthesis of fluorobenzene, they generate a fluorinated carbene :CFX in the presence of cyclopentadiene in a high-temperature, gas phase, flow process that presumably proceeds via the 6,6-dihalobicyclo-[3.1.0]hexane intermediate, which then undergoes ring opening loss of HX under the pyrolytic conditions to produce fluorobenzene in yields as high as 75%.[156]

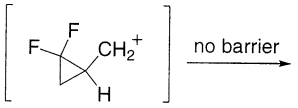
Last, Nefedov and co-workers have utilized carbocation rearrangements of the chlorofluorocarbene adducts of spirocyclopentadienes to prepare fluoroaromatics.[156]



The Cyclopropylcarbinyl Cation. The cyclopropylcarbinyl cation (**65**) proved to be one of the most interesting and controversial carbocation systems encountered during the "age" of carbocation chemistry.[159] Reactions that proceeded via this "nonclassical", delocalized, and highly stabilized primary carbocation exhibited extraordinary rate enhancements, as exemplified by the comparison below.[160,161]



Because β-fluorine substituents destabilize carbocations, whereas α-fluorines are stabilizing, it was predicted (with support from calculations)[144] that reactions involving the 2,2-difluorocyclopropylcarbinyl cation, **66**, would undergo rearrangement via



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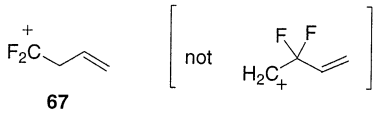
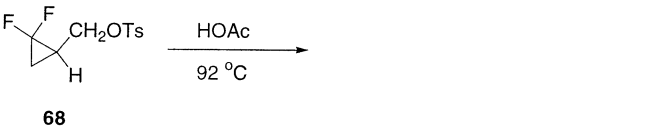


67

regiospecific cleavage of the proximal bond to form the 1,1-difluorobut-3-enyl cation, **67**. Indeed a solvolysis study of tosylate derivative **68** clearly demonstrated the expected regiochemistry for ring opening.[162] The unrearranged product was shown to derive from solvent participation (S_N2 character) in the solvolytic process. Interestingly, virtually the entire rate enhancement derived from the cyclopropycarbinyl nature of the substrate was erased by the presence of the fluorines in **68**, which rearranged at essentially the same rate as isobutyl tosylate.



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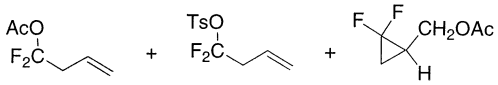
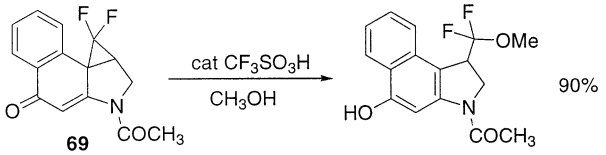


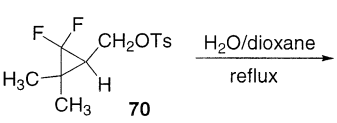
39 : 4.4 : 56.5

There have been other studies of the regiochemistry of such cationic ring openings, including Boger's study of the acid-catalyzed, ring-opening reaction of spirocyclohexadienone, **69**, which ring-opened with proximal bond cleavage exclusively.[163]



69

Preferential *distal* bond cleavage was reported by Schlosser in his solvolysis reaction of tosylate **70**.[164]



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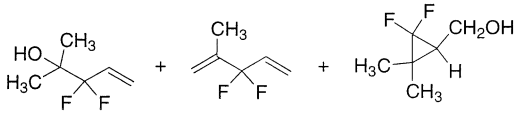
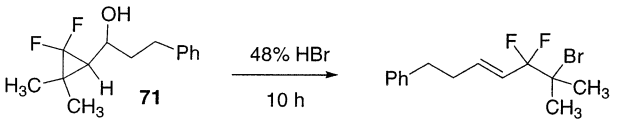


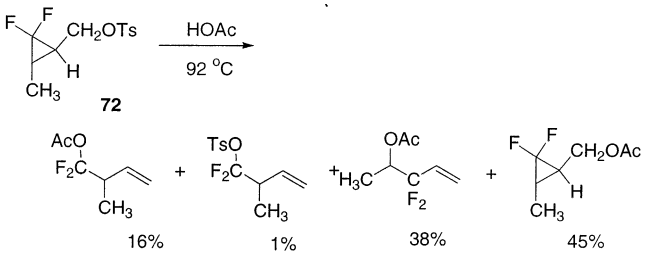
31 : 57 : 10

Apparently, the prospect of forming a tertiary carbocation is sufficient to divert the reaction to distal cleavage. In a related study, Kobayashi observed a similar distal cleavage reaction in the ring-opening reaction of alcohol **71** with 48% HBr.[165]



71

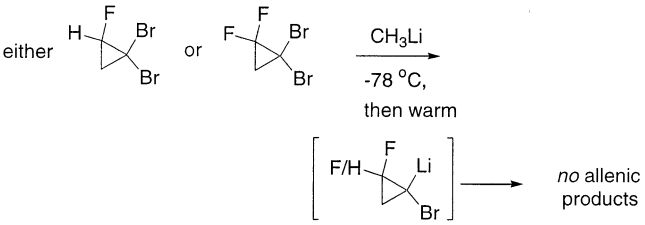
In recent unpublished work, Dolbier has found that a *single* methyl group at the 3-position (as in tosylate **72**) induces distal and proximal bond cleavages to become competitive in a solvolytic process.[166]



72

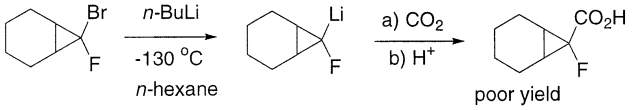
4.5. Carbanion Chemistry

Cyclopropyl Anions. There has been little chemistry reported of reactions involving fluorinated cyclopropyl anions. When the fluorine substituent is β to the anion, apparently fluoride ion is too easily lost for productive chemistry to be observed. For example, it is not possible to synthesize either fluoroallene or difluoroallene by the organometallic carbenoid method that has proved so useful for making hydrocarbon allenes.[167]



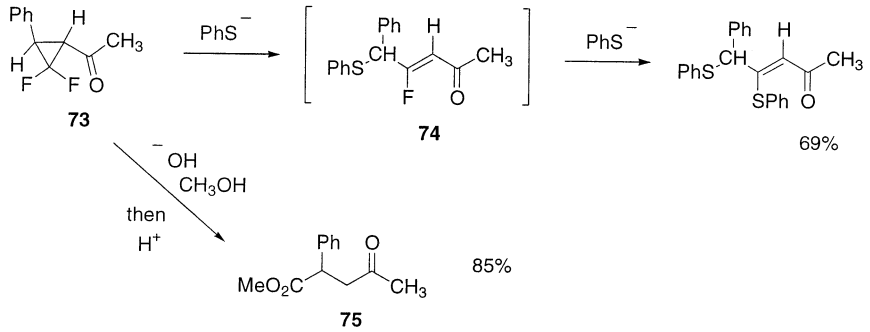
It has been possible to utilize β-eliminations to synthesize fluorinated cyclopropenes, as will be described in that section of the review devoted to fluorinated cyclopropenes.

On the other hand, although little utilized, it has been possible to generate α-fluorocyclopropyl anions in a similar manner and use such carbanion intermediates for synthetic purpose.[138]

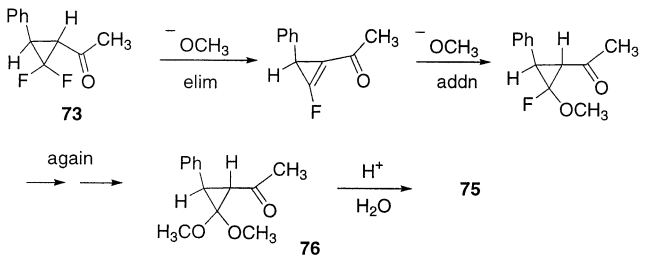


Ring-Opening Carbanionic Chemistry. In 1980, Kobayashi reported that 2,2-difluorocyclopropyl ketones, such as **73**, undergo a Michael-like, distal, ring-opening reaction with nonbasic nucleophiles, i.e., phenyl thiolate.[168] It was suggested that the reaction proceeds by simple "nucleophilic attack of the thiolate anion on C(3) to afford the intermediary β-fluoro enone (**74**)" (Scheme 6). However, it is also possible that an $S_{RN}1$ type mechanism is involved, since the

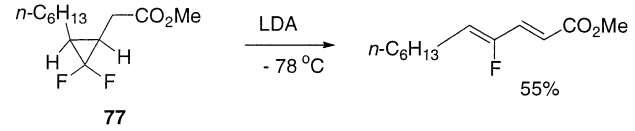
Scheme 6



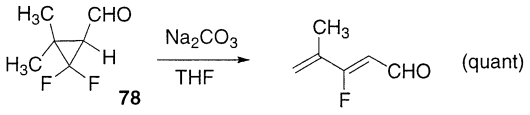
reaction of **73** with basic nucleophiles proceeds very differently, forming non-fluorine-containing **75**. It is likely that formation of **75** proceeds via a series of elimination−addition steps, followed by hydrolysis of intermediate **76**.



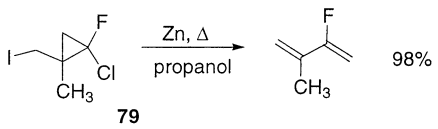
In contrast, when the carbonyl is one carbon removed from the difluorocyclopropyl group, as in substrate **77**, a distal, ring-opening, 1,4-elimination reaction is observed to occur.[169] Similar reactions were also observed for nitriles and sulfones.

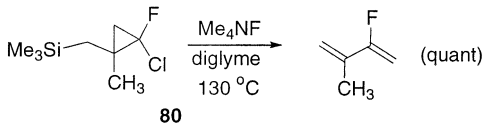


Schlosser noted that the lability of 2,2-difluorocyclopropyl carboxaldehyde, **78**, probably derives from the great facility of its related 1,4-elimination reaction.[164]



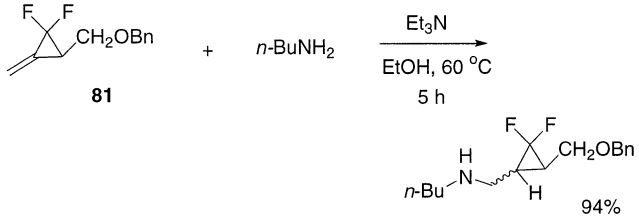
Schlosser's group has elaborated on related 1,4-eliminations as a general route to 2-fluoro-1,3-butadienes, as exemplified by the reactions of **79** and **80** below.[170−172]



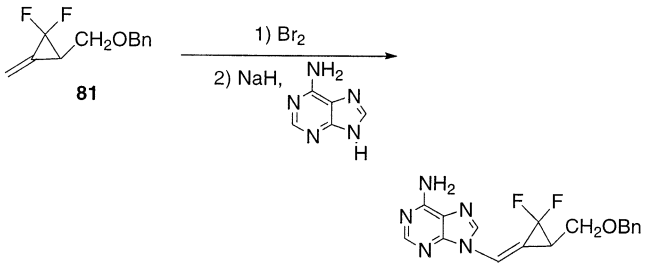


4.6. Other Reactions

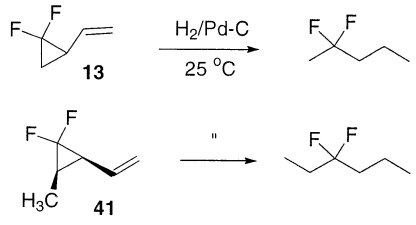
Nucleophilic Addition Reactions of 2,2-Difluoromethylenecyclopropanes. It was found that the geminal fluorine substituents of 2,2-difluoromethylenecyclopropanes, such as **81**, provide sufficient electron-withdrawing activation to give such compounds high reactivity as *Michael acceptors*.[78]



A similar reactivity also allowed Zemlicka's synthesis of nucleoside-substituted difluoromethylenecyclopropanes via a series of addition−elimination reactions:[79]



Hydrogenations. When *gem*-difluorocyclopropanes undergo catalytic hydrogenation, the distal bond is regiospecifically cleaved, as exemplified by the hydrogenations of **13** and **41**.[33]



III. Fluorinated Cyclopropenes

1. Introduction

For the purposes of this review "fluorinated cyclopropenes" will again be defined as cyclopropene systems containing at least one fluorine substituent on a cyclopropene ring. By contrast with the cyclopropane ring system, the first substantiated cyclopropene derivative, 2,3-diphenylcyclopropenedicarboxylic acid, was prepared by Darling and co-workers

in 1931 by base-catalyzed elimination of nitrous acid from the corresponding nitrocyclopropane.[173] The modern era of cyclopropene chemistry, however, originates from Breslow's synthesis of the triphenylcyclopropenium cation in 1957.[174,175] This synthesis is germane to this review in that the first fluorine-substituted cyclopropene derivative may well have originated, in situ, from the manner of generation of the cation. Thus, treatment of 3-cyano-1,2,3-triphenylcyclopropene with boron trifluoride etherate containing traces of water gave predominantly triphenylcyclopropenium tetrafluoroborate, which may be reasonably construed as arising from reaction of a preformed, covalent, 3-fluoro-1,2,3-triphenylcyclopropene intermediate with boron trifluoride. It must be stated that the author of this report did not mention such a conjecture, but it remains a viable explanation for the formation of the tetrafluoroborate salt. As we shall see, simpler cyclopropenium tetrafluoroborates are obtained by treatment of covalent fluorocyclopropenes with boron trifluoride.

With Breslow's synthesis of 3-cyano-1,2,3-triphenylcyclopropene by reaction of diphenylacetylene (tolane) with the carbene phenylcyanomethylene, the era of the [2 + 1] cycloaddition route to cyclopropenes was inaugurated, while Darling's elimination route to cyclopropenes was reintroduced somewhat later. These two synthetic routes to cyclopropenes constitute the bulk of approaches to fluorinated cyclopropenes, especially when coupled with halogen exchange, as discussed in the following section. The third general route to cyclopropenes involving electrocyclization of vinylcarbenes, which may be called the Wiberg method, has received only limited attention.

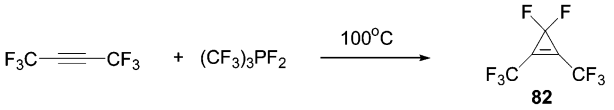
2. Synthesis

Of the eight possible ring substituted fluorinated cyclopropenes (and their derivatives) there are two monosubstituted, three disubstituted, two trisubstituted, and, of course, one tetrasubstituted example(s). When otherwise unsubstituted, there are only three of these three-membered ring systems known and reasonably characterized: 3-fluoro-, 3,3-difluoro-, and perfluorocyclopropene. The largest class of substituted fluorinated cyclopropenes belongs to the 3,3-difluoro system, which is not surprising in view of the many varied sources of difluorocarbene. Central to this latter class, the parent 3,3-difluorocyclopropene is of special interest as it relates to the hydrocarbon cyclopropene in structure and reactivity. The synthetic routes to representative examples of the above classes of fluorinated cyclopropenes by the carbene and non-carbene approach are briefly presented below.

2.1. Fluorocarbene Methods

In this section we consider only the direct reaction of fluorinated carbenes with alkynes, although as we shall see in section 2.2.2, certain fluorinated cyclopropanes, available by reaction of alkenes with the appropriate halocarbene (vide supra), are important precursors to fluorinated cyclopropenes.

Difluorocarbene. The first preparation of an authentic example of a fluorinated cyclopropene was reported by Mahler in 1962.[176] Heating a gas phase mixture of hexafluoro-2-butyne with the difluorocarbene source $(CF_3)_3PF_2$ at 100 °C resulted in the formation of perfluoro-1,2-dimethylcyclopropene (**82**).



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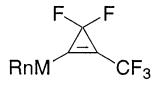
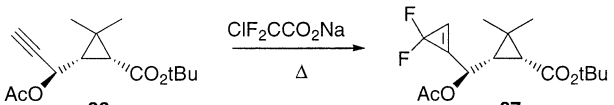
Following Mahler's report there has been a slow but steady growth in the number of applications of this approach to the synthesis of fluorinated cyclopropenes, often with a spurt of activity following the development of a more convenient or less hazardous source of difluorocarbene. For example, 4 years later the somewhat less hazardous and more readily available compound trifluoromethyltrimethylstannane was employed as the difluorocarbene generator at 140 °C for the preparation of the novel 3,3-difluoro-2-trifluoromethylcyclopropenylarsane, -silane, and -germane systems **83**−**85**, the first compounds of their type in the cyclopropene series.[177]



83; R=CH_3, n=2, M=As
84, R=CH_3, n=3, M=Si
85, R=CH_2CH_3, n=3, M=Ge

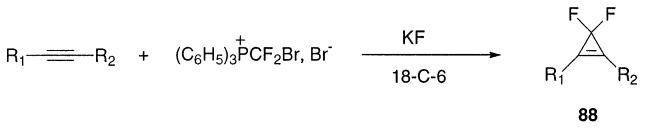
Following the same protocol, the first difluorocyclopropenation of monosubstituted alkynes, 3,3,3-trifluoropropyne and related perfluoroalkyl acetylenes, was achieved.[178] Somewhat later, Crabbe and coworkers reported the first examples of difluorocyclopropenation of nonfluorinated monoalkyl substituted alkynes in a steroid series using sodium chlorodifluoroacetate as the $:CF_2$ source.[179] Although the yields in these reactions were low, this was likely the result of facile hydrolysis of the initial difluorocyclopropenes to the corresponding cyclopropenones on aqueous workup. That the fault may not lie with the carbene source in this case is indicated by the much later report of the smooth conversion of alkyne **86** to cyclopropene **87** employing CF_2ClCO_2Na (diglyme/60 °C).[180]



86 **87**

Before proceeding, mention should be made of the development in the mid-1960s, by the DuPont group, of hexafluoropropene oxide (HFPO) as an effective difluorocarbene source and their use of this reagent for the subsequent synthesis of perfluorinated 1-methyl- and 1,2-dimethylcyclopropenes.[181−183] The reactivity of HFPO derives from the fact that fluorine substituents destabilize an oxirane ring in a manner similar to a cyclopropane.[184] This $:CF_2$ precursor was also instrumental in the synthesis of perfluorocyclopropene (vide infra). Despite its efficacy, HFPO has slipped into disuse as a consequence of the development of more convenient and less hazardous protocols for difluorocarbene generation. Thus, for example,

Bessard and Schlosser[185] used a modified version of the Burton reagent to effect conversion of simple alkyl and phenyl acetylenes to the respective 3,3-difluorocyclopropenes **88** in acceptable yields (46−

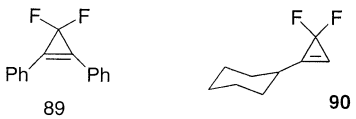


88

$R_1 = C_3H_7; C_6H_{13}; C_8H_{17}; C_6H_5; R_2 = H$
$R_1 = R_2 = C_3H_7; R_1 = C_6H_5, R_2 = CH_3$

80%). These authors point out that, under these conditions, 4-octyne is more reactive than *cis*-4-octene by a factor of 10 in competition experiments, a surprising result considering the lore on dichlorocarbene cycloadditions.[186]

Finally, the reported generation and trapping of difluorocarbene at temperatures as low as −5 °C from decomposition of bis(trifluoromethyl)cadmium, generated in situ by reaction of dimethylcadmium with trifluoromethyl iodide, has recently appeared.[187] Two 3,3-difluorocyclopropenes, **89** and **90**, were reportedly



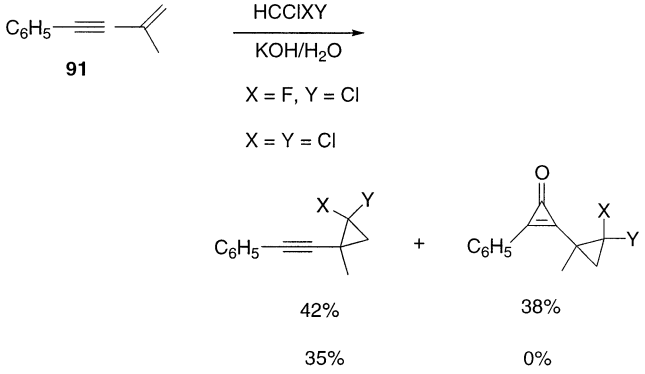
89

90

obtained in greater than 95% yields based on ^{19}F NMR analysis of the reaction mixture. Subsequent elaboration of the scope of this procedure has not been recorded; however, the method holds promise for the preparation of labile difluorocyclopropenes.

With one exception, all of the above cyclopropene derivatives prepared by the [2 + 1] cycloaddition reaction with difluorocarbene are in the 3,3-difluorocyclopropene classification. Not surprisingly, the parent member of this class, 3,3-difluorocyclopropene, has not been prepared by this carbene route. To circumvent the problems with using acetylene as the reactive alkyne in cyclopropenation, bis(trimethylsilyl)acetylene, an acetylene equivalent, could be employed. Indeed, this reaction was explored with Seyferth's reagent, $C_6H_5HgCF_3$, as the difluorocarbene source.[188] A reasonably pure product was obtained in low yield. The mass spectrum clearly supported the 1,2-bis(trimethylsilyl)-3,3-difluorocyclopropene structure, but decomposition occurred before full characterization could be obtained. Considering the newer reagents for generating difluorocarbene developed in the last 25 years, this reaction should be reinvestigated as a potentially more viable route to 3,3-difluorocyclopropene than those discussed in section 2.1.4.

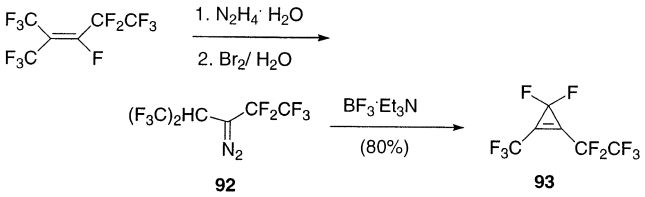
Chlorofluorocarbene. Only one example of a cycloaddition of :CFCl to an alkyne has been reported. A problem in the case of this carbene is the paucity of methods for generating it under nonaqueous conditions, since the preformed 3-chloro-3-fluorocyclopropenes are rapidly hydrolyzed to the corresponding cyclopropenones in aqueous solution. Thus, when chlorofluorocarbene is generated under phase transfer conditions (50% aqueous KOH/CH_2Cl_2) in the presence of alkynes, the only products isolated



91

are cyclopropenones.[189] An instructive example regarding the alkyne/alkene relative reactivity of chlorofluorocarbene compared to dichlorocarbene is the internal competitive reaction of eneyne **91** with the two carbenes under the same phase transfer conditions. From this and related results the authors conclude that chlorofluorocarbene is more reactive toward alkynes. Nevertheless, for the synthesis of fluorinated cyclopropenes, the phase transfer generation of :CFCl in aqueous solution is clearly unsuitable. Dolbier's method ($Ti/CHFCl_2$)[60] has apparently not been examined with alkynes.

Perfluorovinylcarbenes. Application of the electrocyclization of vinylcarbenes for the synthesis of cyclopropenes, as first demonstrated by Wiberg,[190] has received ample synthetic attention in the hydrocarbon series. By contrast. there appears to be just three reported examples of this protocol being used in the fluorocarbon series; however, only one of these procedures is synthetically useful. In this case the diazo compound **92**, prepared in two steps from



92 93

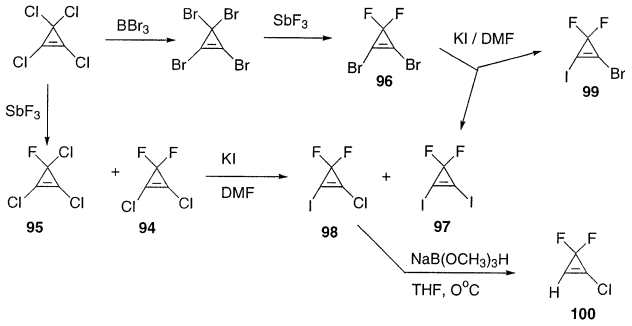
perfluoro 2-methyl-2-pentene, provides the perfluorocyclopropene **93** in 80% yield upon treatment with triethylamine−boron trifluoride.[191] Apparently, Lewis acid-assisted elimination of HF precedes decomposition of the diazo compound to subsequently generate a vinylcarbene intermediate that cyclizes to **93**. Although only one example was reported, the method would appear to be amenable to the synthesis of a number of fluorinated cyclopropenes, including 3,3-difluorocyclopropene. In the other two examples, low to trace amounts of perfluorinated 1,2-dialkylcyclopropenes were obtained,[192,193] which again may be accounted for on the basis of intermediate vinyl carbene formation.

2.2. Non-Carbene Methods

The primary preparative methods briefly summarized in this section are the halogen exchange reactions of the archetypal tetrachlorocyclopropene[194] and the eliminative methods, i.e., dehalogenation/dehydrohalogenation, of fluorinated halocyclopro-

panes. In addition, there are a few extraneous methods collected under the heading of miscellaneous. The reaction of fluorinated halocyclopropenes with nucleophiles other than halogen is discussed in a later section.

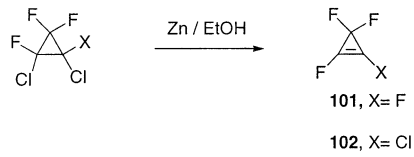
Halogen Exchange. The preparation of tetrachlorocyclopropene by West and co-workers[194] may now be viewed as pivotal in the annals of cyclopropene chemistry, rivaling even that of Breslow's synthesis of the triphenylcyclopropenium cation, at least from a synthetic perspective. As a result of halogen-exchange reactions with BBr_3 and/or SbF_3, these workers produced the second examples of fluorinated cyclopropenes, namely **94**−**96**. In a later report, Sepiol and Soulen reported the preparation of 1,2-diodo-3,3-difluorocyclopropene (**97**) as well as the 1-chloro- and 1-bromo-2-iodo-3,3-difluorocyclopropenes, **98** and **99**.[195] Reductive removal of the iodine in **98** by means of sodium trimethoxyborohydride provided the trihalogenated cyclopropene **100**.[196]



Since the minor product **95** from treatment of tetrachlorocyclopropene with antimony trifluoride is less volatile than the major product **94**, it is possible to separate the two by distillation, but the monofluoro cyclopropene prepared by this route is usually contaminated by the difluoro component. According to a recent report,[197] this problem can be alleviated by performing the exchange reaction with KF in methylene chloride in the presence of 18-crown-6. Although the yield of **95** is modest (43%), the isolated material is uncontaminated with **94**.

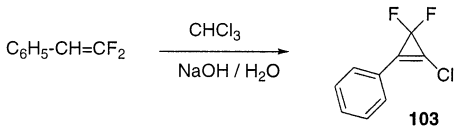
While at the time of its initial preparation **95** was the first example of a monofluorinated cyclopropene, subsequently the parent molecule, 3-fluorocyclopropene, was prepared, also by a chloride for fluoride exchange reaction utilizing 3-chlorocyclopropene, prepared by the method of Breslow.[198] Passage of the chlorocyclopropene as a gas through a short column of silver difluoride/potassium fluoride (six passes) afforded the fluorocyclopropene as a gas that was condensed at liquid nitrogen temperatures.[199] 3-Fluorocyclopropene is reportedly an extremely unstable compound, yet it was possible to characterize the structure by NMR and IR. Interestingly, the NMR spectrum revealed an exceedingly large geminal HF coupling constant (110 Hz), which may suggest, according to the authors, an unusually large FCH bond angle. Or perhaps the large *J* value may derive from the quite different orbital characteristics of the CH and CF bonds. Indeed, calculations (vide infra, see Table 3) suggest that the FCH bond angle is smaller than that of fluorocyclopropane.

Dehalogenation/Dehydrohalogenation of Halocyclopropanes. Tetrafluorocyclopropene (**101**),



the ultimate fluorinated cyclopropene, has been prepared in low yields by photochemical oxidation of perfluoro-1,3-butadiene[200] and perfluorocyclobutene,[201] whereas base-catalyzed dehydrohalogenation of 1-chloro-1,2,2,3-tetrafluorocyclopropane or pentafluorocyclopropane is reported to afford **101** in yields ranging from 10 to 30%, depending on the base and conditions employed.[181] Tetrafluorocyclopropene is a colorless, flammable, and explosive (in air) gas (bp −13 °C), but yet it is thermally quite stable in the absence of oxygen. It is very reactive with nucleophiles, which explains the low yields in the dehydrohalogenation preparative methods. Sargeant and Krespan found that dehalogenations of 1,2-dichloro-1,2,3,3-tetrafluorocyclopropane with zinc dust in ethanol circumvent the problem and provide yields of **101** in the 70% range.[181] Similar observations to those of Sargeant and Krespan were made by Camaggi and Gozzo,[201] who also prepared 1-chloro-2,3,3-trifluorocyclopropene (**102**) by dehalogenation of 1,2,2-trichloro-1,3,3-trifluorocyclopropane. It should be mentioned that this trifluorocyclopropene (**102**) has also been prepared by the halogen-exchange method of West and co-workers.[202]

Other pertinent examples of the dehydrohalogenation method to make fluorinated cyclopropene include the isolation of 3,3-difluorocyclopropene in low overall yield (10%) by passing 1-chloro-2,2-difluorocyclopropane through an ascarite (NaOH on asbestos) column at room temperature (not recommended for synthetic purposes)[203] and the base-promoted elimination of HCl from the dichlorocyclopropane adduct formed in situ from the addition of dichlorocarbene to 2,2-difluorostyrene under phase transfer conditions (40% aqueous NaOH, benzyltriethylammonium chloride).[204] The yield of cyclopropene **103** was 55%. It is noteworthy that hydrolysis to the corresponding cyclopropenone was not a major obstacle.



Miscellaneous. In a manner reminiscent of the previously discussed synthesis of tetrafluorocyclopropene, perfluoromethylenecyclopropane (**104**), an

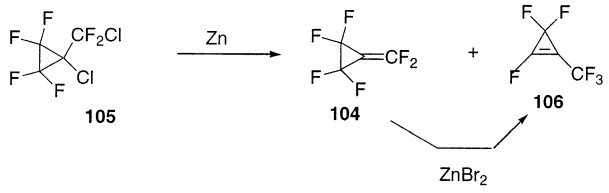
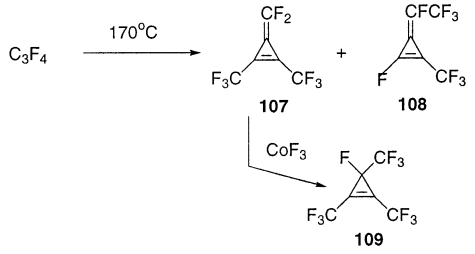


Table 3. Some Experimental/Computed Structures for Fluoro-Substituted Cyclopropenes

	∠X−C−Y, deg	∠$C_{1-}C_3-C_2$, deg	*r*(C=C), Å	*r*(C−C), Å	method[a]
R = X = Y = H	114.66	50.38[b]	1.296	1.509	MW[210]
R = X = H, Y = F	108.0	52.42	1.288	1.458	HF/6-311G*[208]
R ≃ H, X = Y = F	105.48	54.60	1.321	1.438	MW[211]
R = X = Y = F	105.4	53.2	1.307	1.461	ED/MW/LC[207]
R = X = Y = Cl			1.320	1.479	ED[212]

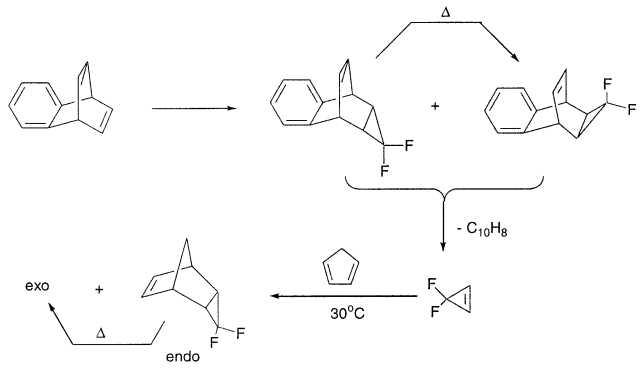
[a] ED = gas-phase electron diffraction; MW = microwave spectroscopy; LC = liquid crystal NMR spectroscopy. [b] Calculated (HF/6-311G*).

extremely reactive and toxic compound, was prepared by zinc dehalogenation of cyclopropane **105**.[183] Accompanying **104** was a small amount of the isomeric cyclopropene **106**, formed either by elimination of ClF or by zinc ion-promoted isomerization of **104**. Indeed, treatment of **104** with zinc bromide resulted in quantitative isomerization to cyclopropene **106**, whose chemistry was similar to that tetrafluorocyclopropene and, of course, 1,2-bis(trifluoromethyl)-3,3-difluorocyclopropene. Perfluoromethylenecyclopropenes have also been prepared and isolated[201] or spectroscopically observed by matrix isolation techniques.[205] In the former report, Camaggi and Gozzo observed a unique, and still unexplained, thermal dimerization of tetrafluorocyclopropene to afford the isomeric perfluorodimethylmethylenecyclopropenes, **107** and **108**, in a 7:1 ratio, respectively. Addition of F_2 to the



exocyclic double bond of the major isomer produced the interesting perfluoro-1,2,3-trimethylcyclopropene, **109**. The chemistry of compounds **107**−**109** has received very little attention, possibly due to the daunting task of preparing and handling tetrafluorocyclopropene.

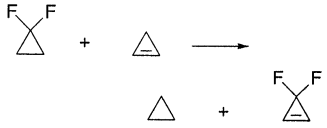
As mentioned earlier, 3,3-difluorocyclopropene is a molecule of special interest and has been the subject of considerable study, both experimental and theoretical, regarding the structural effects of the fluorine substituents as recounted in the following section. The problem has been its synthesis. Jefford and co-workers[206] addressed this problem by what they refer to as a molecular relay strategy involving difluorocarbene with an appropriate relay unit. Thus, addition of this carbene to benzobarrelene afforded a mixture of the endo and exo [2 + 1] adducts (50% yield) which on pyrolysis at 200 °C, separately or as the mixture, generated a mixture of naphthalene and 3,3-difluorocyclopropene by [2 + 4] retrocycloaddition. The cyclopropene was not isolated in pure form but was characterized in solution (C_6D_6) by ^1H and ^{19}F NMR and subsequently trapped by reaction with excess cyclopentadiene to provide mainly the endo-cycloadduct, which slowly isomerized to the exo-



isomer.[86] The authors note that the cycloaddition reaction is surprisingly slow, with some unreacted cyclopropene remaining after 48 h at 30 °C. This is in striking contrast to the hydrocarbon cyclopropene, which reacts rapidly with cyclopentadiene at 0 °C. Further discussion on this reactivity difference will be reserved for the section on reactivity.

3. Structure

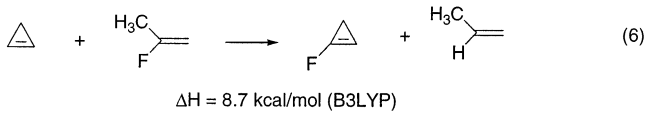
Experimental structural data for fluorinated cyclopropenes is largely confined to the 3,3-difluoro- and perfluorocyclopropene examples. In the latter case, extensive structural data has been obtained by a combination of methods including gas-phase electron diffraction (ED), microwave spectroscopy (MW), and liquid-crystal NMR spectroscopy (LC).[207] Additional structural data was obtained by single-crystal X-ray diffraction at 156 K of C_3F_4 (mp 196−199 K), which was in good agreement with the gas phase and NMR results. Complementary to these experimental results (see Table 3), various ab initio calculations[207,208] have provided reasonably accurate information on essentially all of the fluorinated cyclopropenes, including the as yet unknown 1,2-difluoro- and 1-fluorocyclopropene.[209] As seen in Table 3, fluorine substitution at the methylene carbon of cyclopropene results in significant lengthening of the C=C bond and shortening of the C−C single bonds, analogous to similar effects seen in the cyclopropane system (see Table 1). In contrast, however, Wiberg[11] has shown that fluorine substitution on the cyclopropene methylene carbon is less destabilizing than that on cyclopropane (e.g., isodesmic equation 5). In fact, rather



ΔH = -9.3 kcal/mol (B3LYP) (5)

than increasing the strain energy, as in cyclopropane, fluorine substitution at C-3 in cyclopropene would appear to actually stabilize the three-membered ring.

Fluorine substitution on the cyclopropene double bond, as in 1,2-difluoro- and 1-fluoro-cyclopropene, presents a different scenario, based on ab initio calculations by Panchencko and co-workers[208] and DFT calculations for 1-fluorocyclopropene.[209] For example, in the latter system the distal (C2−C3) bond is lengthened to 1.559 Å and the proximal (C1−C3) bond is shortened to 1.472 Å compared to the observed 1.509 Å bond distance in cyclopropene. Panchencko reached similar conclusions for the 1-fluoro system, as well as for the 1,2-difluorocyclopropene. Interestingly, as indicated in isodesmic equation 6, the 1-fluoro substituent apparently increases



(6)

ΔH = 8.7 kcal/mol (B3LYP)

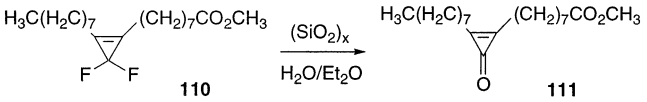
the strain energy in the system. It is remarkable that the same F-substituent effects on bond strengthening−bond weakening, first observed in the cyclopropane series, hold forth even when transmitted through an unsaturated framework.

4. Reactions

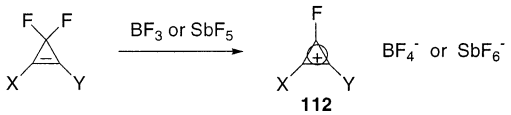
The reactivity of fluorinated cyclopropenes is inherently predicated on the well-established reaction profiles of the cyclopropene family of compounds. Presence of a highly strained double bond leads to the expectation of enhanced addition reactivity, whether electrophilic, nucleophilic, or pericyclic in nature. These addition reactions often lead to retention of the three-membered ring, as for example in the addition of chlorine to 1,2-dichloro-3,3-difluorocyclopropene to yield the corresponding tetrachlorodifluorocyclopropane.[194] A second pathway of reactivity, which may be predominant in the case of 3-halo-substituted cyclopropenes, is ionization to the aromatic cyclopropenyl cation, followed by reaction with nucleophiles, such as water, in which case cyclopropenones or ring-opened products are formed (vide supra). A fairly complete, but brief, summary of each of these reaction types follows.

4.1. Cyclopropenone/Cyclopropenyl Cation Formation

Whereas the reaction of dichlorocarbene with alkynes invariably leads to the corresponding cyclopropenones,[213] the more stable difluorocarbene adducts may be isolated, as discussed previously, assuming that aqueous workup is not prolonged. Nevertheless, to illustrate the facility of conversion of simple dialkyl 3,3-difluorocyclopropenes to their corresponding cyclopropenones, consider the hydrolytic conditions for difluorosterculic acid (**110**); a wet ether solution of **110** was filtered through silica gel to afford the cyclopropenone **111** in 89% yield on evaporation of solvent.[185]



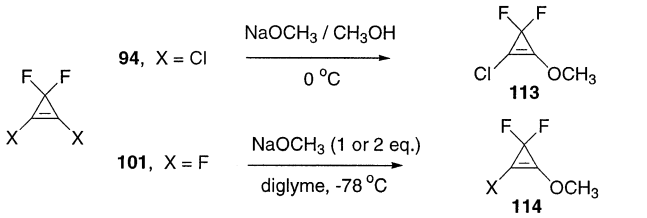
Illustrating the ease of loss of a fluoride ion from the 3,3-difluorocyclopropene system promoted by a Lewis acid, a series of monofluoro-, difluoro-, and trifluoro-cyclopropenyl salts (**112**) have been prepared from their appropriate covalent precursors utilizing BF_3 and SbF_5 in liquid sulfur dioxide,[181,202,203] While each of these salts was characterized by IR and NMR spectroscopy, they appear to be less stable than the corresponding trichlorocyclopropenium salts. In particular, the trifluorocyclopropenium salts (**112**; X = Y=F) were reportedly[181] difficult to handle without decomposition. No further chemistry has appeared on these interesting cations since the initial reports.



X = Y = Cl or Br or F
X = F, Y = Cl or Br
X = Y = H

4.2. Reactions with Nucleophiles

In addition to the previously mentioned examples of halogen exchange of 3,3-difluorodihalocyclopropenes at the vinylic carbons by iodide ion, there are several related examples of vinylic halogen displacement by other nucleophiles. Although 1,2-dichloro-3,3-difluorocyclopropene is relatively stable in methanol solution at reflux, addition of 1 equiv of sodium methoxide at 0 °C eventually resulted in formation of the monoether **113** in 63% isolated yield.[214]

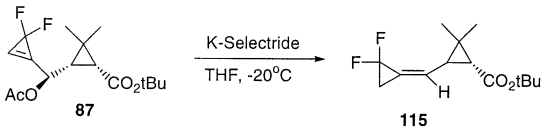


a, X = OCH_3 ; b, X = F

Addition of a second equivalent of methoxide ion to **113** resulted in ring-opening reactions, rather than formation of the bis ether derivative **114a**; however, Smart was able to obtain and isolate **114**(**a** or **b**) by use of an aprotic solvent (diglyme) and lower temperature (−78 °C).[215] Not surprising, these ethers are very moisture sensitive. When treated with SbF_5 at −78 °C, ethers **113** and **114** were cleanly converted to the corresponding cyclopropenium hexafluoroantimonates, **112** (X = OCH_3; Y = F, OCH_3, Cl).

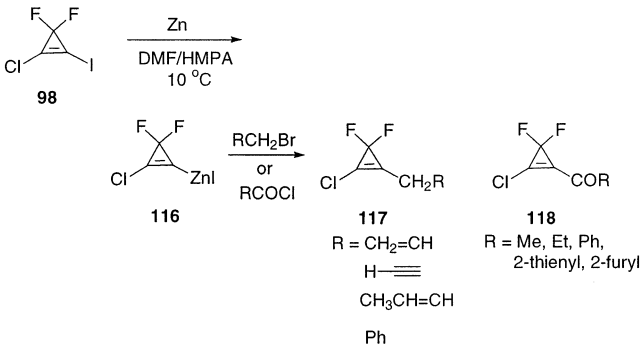
Following the above work, Soulen and co-workers reported[216] the low-yield preparation of 1,2-dithiocyano-3,3-difluorocyclopropene from treatment of the difluorodichlorocyclopropene with the less basic, more nucleophilic thiocycanate anion. In one of the few

examples of the reaction of tetrahalocyclopropenes with carbon nucleophiles, excess phenyllithium reacted with tetrafluorocyclopropene to provide a reasonable yield of tetraphenylcyclopropene.[201] By contrast, reaction of tetrachlorocyclopropene with excess phenylmagnesium bromide gave, at best, a 10% yield of the tetraphenylcyclopropene.[217] A recent example of nucleophilic addition to the vinyl unit of a 3,3-difluorocyclopropene with concomitant elimination of an exocyclic leaving group (acetate), essentially an S_N2' reaction, to produce a methylenecyclopropane system is the report by Babin and co-workers of the conversion of **75** to **103** by means of K-selectride in THF (72% yield).[180]



87 **115**

An alternative tactic for nucleophilic substitution at the vinylic carbon of a perhalocyclopropene would be to reverse the electronic sense of the overall addition/elimination process just described by incorporating an anionic center at a vinylic carbon, followed by reaction with an appropriate electrophile. The first application of this process in the halocyclopropene series was reported in 1997.[218] Preparation of the reasonably stable 1-chloro-3,3-difluorocyclopropenylzinc reagent **116** was accomplished by reaction of activated zinc dust with the iodide **98** in a



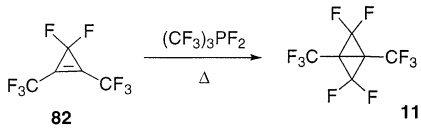
98 **116** **117** **118**

mixed solvent system, DMF−HMPA, at 10 °C. Subsequent alkylation−acylation of this zinc reagent with allylic bromides or acyl chlorides in the presence of a catalytic amount of CuBr (required) provided excellent yields of the respective allylated/acylated cyclopropenes **117** and **118**. Although simple alkyl halides, e.g. MeI and PrBr, failed to react in this zinc/copper(I) procedure, the method offers excellent synthetic promise, especially for cyclopropenyl ketones like **118**, which are difficult to prepare by other methods.

4.3. Cycloaddition Reactions

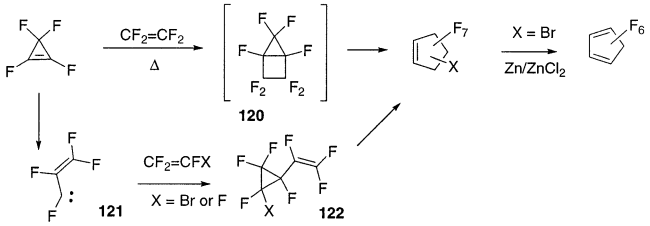
Similar to their hydrocarbon relatives, the perhalogenated cyclopropenes are reactive components in cycloaddition reactions. Of the possible [*m* + *n*] cycloadditions, there are reports of the [2 + 1] (one example), [2 + 2] (two examples), and [4 + 2] (many examples) type that will be summarized in the following sections. No examples of higher order of cycloadditions have appeared.

[2 + 1] And [2 + 2] Cycloadditions. In his original synthesis of perfluoro-1,2-dimethylcyclopropene (**82**) Mahler observed a minor product that he was able to confirm as the perfluorinated dimethylbicyclo[1.1.0]butane **119** by further reaction of cyclo-



82 **119**

propene **82** with the same :CF_2 source.[176] Unfortunately, the thermal rearrangement of this bicyclobutane was not investigated. It is noteworthy that similar bicyclobutane products were not observed in the other cases of difluorocarbene additions to alkynes, perhaps because of the expected weakening of the intercyclic bond flanking two geminal difluoromethylene groups. Examples of this effect were observed in the [2 + 2] cycloaddition reactions of tetrafluorocyclopropene.[181] Thus, heating a mixture of this cyclopropene with tetrafluoroethylene in a sealed tube at 135 °C provided an almost quantitative yield of perfluorocyclopentene, most reasonably explained as proceding via the bicyclo[2.1.0]pentane **120**, al-



120 **121** **122**

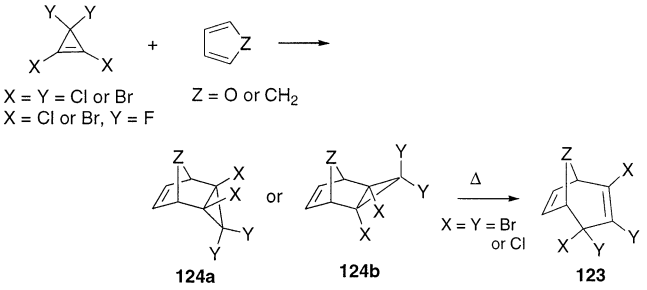
though another mechanistic pathway should be considered. Thermal ring cleavage to the vinylcarbene **121**, followed by cyclopropanation of TFE to give **122** (X = F), and subsequent vinylcyclopropane rearrangement should lead directly to perfluorocyclopentene without the requirement of a fluorine migration. A decade and a half later, in their pursuit of perfluorocyclopentadiene, Lemal and co-workers reinvestigated this purported [2 + 2] cycloaddition employing bromotrifluoroethylene with tetrafluorocyclopropene and obtained a mixture of 3-bromo- and 4-bromoheptafluorocyclopentene.[219]

Subsequent treatment of this mixture of bromocyclopentenes with $Zn/ZnCl_2$ in diglyme at 140 °C completed the synthesis of C_5F_6. Again the vinylcarbene mechanism is consistent with the formation of the bromocyclopentene isomers.

[4 + 2] Cycloadditions. The facility of Diels−Alder [4 + 2] cycloadditions of cyclopropenes is now well-appreciated,[220] and the perhalogenated cyclopropenes are no exception. The stereochemical proclivity of these cycloadditions, endo or exo, particularly in regard to cyclic dienes, is subject to some confusion in the literature as a result of structure misassignments and the usual problem of properly recognizing kinetic versus thermodynamic consequences. Attempted theoretical unraveling of the stereochemical features of these cycloadditions has

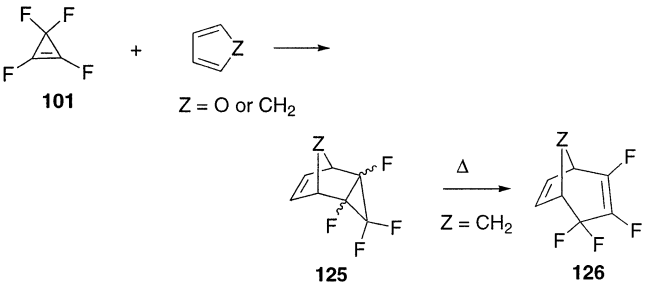
not been particularly illuminating and thus will be largely ignored in this summary.

The seminal report on the Diels−Alder reactions of perhalogenated cyclopropenes was that of Law and Tobey in 1968.[221] Primarily they investigated the reactions of tetrachloro-, tetrabromo-, 3,3-difluoro-1,2-dichloro-, and 1,2-dibromocyclopropene with furan and cyclopentadiene. Whereas the stereochemistry of cycloaddition could not be established for the tetrachloro and tetrabromo adducts because of facile rearrangement to the bicyclic allylic adducts **123**, the



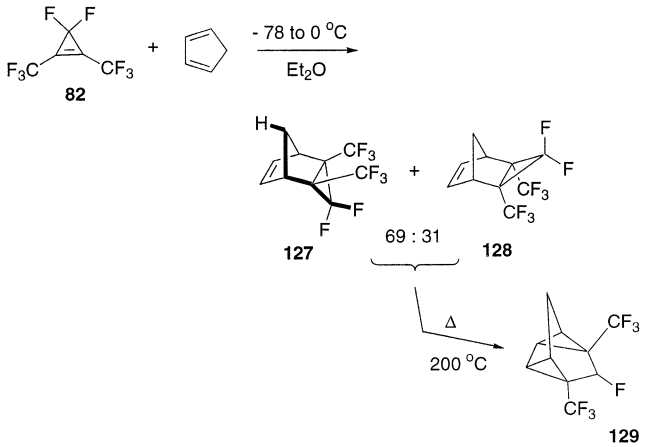
stereochemistry of the 3,3-difluoro-1,2-dihalo adducts **124** was assigned the endo configuration **124a**, based largely on analogy to previous lore in the cyclopropene series.[190,222] It should be mentioned that at the time these cycloadditions of perhalocyclopropenes, especially the perbromo and perchloro examples, were surprising in view of previously disclosed failures of 3,3-disubstituted (methyl or phenyl) cyclopropenes to undergo cycloaddition with cyclopentadiene or 1,3- butadienes,[222,223] presumably for steric reasons. Further examination of the structure of adducts **124** by several groups has unambiguously established the stereochemistry of the isolated adducts as exo, i.e., **124b**, largely by X-ray crystallography.[188,224,225] The cycloadducts of tetrachlorocyclopropene and 3,3-difluoro-1,2-dichlorocyclopropene with 1- substituted and 1,4-disubstituted 1,3-butadienes have been similarly determined to have the exo configuration.[224,226,227]

Almost simultaneously with the Law and Tobey report,[202] Sargeant reported the [4 + 2] cycloaddition reactions of perfluorocyclopropene (**101**) and perfluoro-1,2-dimethylcyclopropene (**82**) with cyclopentadiene and furan at room temperature.[182] In the case of **101**, both tricyclic adducts **125** (X = O or CH_2) were



assigned the endo structure, but again the evidence (NMR chemical shifts) is unconvincing. An argument could be made for reversing these structural assignments on the basis of the prevailing stereochemical evidence for perhalocyclopropene cycloadducts, but proof is lacking. Also lacking is an appreciation of the remarkable instability of the cyclopentadiene adduct **125** (X = CH_2) toward the now familiar cyclopropyl−allyl rearrangement. Thus, as Sargeant reports,[182] this adduct quantitatively rearranges on prolonged standing, or on attempted distillation, to the tetrafluorobicyclo[3.2.1]heptadiene **126**. Similar rearrangements occur in the cycloadductions of cyclopentadiene or furan with tetrachlorocyclopropene and tetrabromocyclopropene; however, the corresponding adducts with the 3,3-difluorodihalocyclopropenes show no propensity for this isomerization, even on heating. Furthermore, the related adducts of **82** did not exhibit this reactivity profile. Bond-weakening/bond-strengthening effects of fluorine aside, the answer may lie in the well-known ability of fluorine to stabilize electron-deficient centers better than chlorine or bromine.

The situation regarding the stereochemical assignments for the cycloadducts of **82** with cyclopentadiene and furan are, perhaps, more amenable to reinterpretation. In addition, the reported enhanced reactivity of **82** compared to **101**, as well as to the perhalocyclopropenes previously discussed, offers the opportunity to address the question of kinetic versus thermodynamic control in adduct formation, a point which has not been adequately examined experimentally. The significance of the reactivity of **82** is that its reaction with cyclopentadiene could be conducted at −78 °C in ether solvent. Removal of solvent at 0 °C revealed a 69:31 ratio of two isomeric adducts, the major of which was assigned the exo configuration. On the basis of the reported, but unassigned, bridge proton−fluorine coupling constant of 8.5 Hz for the major isomer, but absent in the minor isomer, the stereochemical assignments for the two adducts should be reversed. This $^5J_{FH}$ coupling, highlighted in structure **127**, is characteristic for an *endo*-3,3-



difluorotricyclo[3.2.1.$0^{2,4}$]octane structure.[86] Further to the point, the major isomer (endo) rearranged on heating to the minor isomer (*exo*-**128**). Despite the author's argument to the contrary, this only makes sense for an endo to exo stereomutation analogous to that observed by Jefford[86] for the difluorocarbene adducts of norbornadiene. Heating a mixture of **127** and **128** to 200 °C gave the tetracycle **129**, but no products of a cyclopropyl−allyl rearrangement were observed.

The reaction of furan with cyclopropene **82** at room temperature reportedly gave a quantitative yield of a single adduct that again was assigned the endo configuration. Since furan invariably yields exo adducts, even with cyclopropene, it is likely that this adduct has the exo structure. Other dienes that yield only, or predominantly, exo cycloadducts with perhalocyclopropenes include isobenzofurans,[188,227−230] 6,6-dimethyl- and 6,6-diphenylfulvene,[225] [2.2]furanophane,[231] and norbornadiene.[182,221]

Given the stereochemical results for the isolated cycloadducts of cyclopentadiene, furan, and the substituted 1,3-butadienes, there remains the question as to whether these adducts are of kinetic or thermodynamic origin. In the furan systems the preponderance of evidence supports kinetic determination of exo cycloadduction; however, the case for cyclopentadiene and related cyclic dienes is less clear. A complicating factor for cyclopropene dienophiles **82**, **94**, and **96**, bearing geminal fluorine groups at the 3-position, is the facile stereomutation of the endo adduct to the more stable exo isomer, as observed by Jefford[86] and earlier by Sargeant[182] (vide supra). In fact, under suitable conditions for kinetic control, both Sargeant and Jefford observed endo stereoselectivity for the reaction of **82** and 3,3-difluorocyclopropene, respectively, with cyclopentadiene. Since the Diels−Alder reactions of **94** and **96** were conducted under what now may be assessed as conditions of thermodynamic control, the conclusion may be drawn that cyclopentadiene reacts initially with perhalocyclopropenes by the endo pathway, followed by subsequent isomerization of the endo adduct as dictated by the halogen substitution pattern and reaction conditions.

Finally, the effect of halogen, particularly fluorine, substitution on the reactivity of the respective cyclopropenes should be mentioned. It is well-known that substitution at C3 tends to stabilize the cyclopropene ring, whereas substitution at the double bond carbons provides minimal stabilization.[223] In addition, electron-withdrawing groups, e.g. CO_2R, CN, OR, at the 3-position provide increased stability and diminished dienophilic reactivity; therefore, it is not surprising that perhalocyclopropenes, with the exception of perfluoro-1,2-dimethylcyclopropene (**82**), are less effective dienophiles than cyclopropene. Within the halogenated series, steric effects appear to be unimportant, since C_3Br_4 is slightly more reactive with furan than C_3Cl_4.[221] Also, replacing geminal Br or Cl by F results in a decrease in reactivity by a factor of 3 for each case. Law and Tobey attributed the decrease in reactivity for $C_3X_2F_2$(X = Br or Cl) to a decrease in ring strain as a result of increased s-character in the ring C−C bonds.[202] Essentially the same conclusion was reached by Wiberg some 30 years later on the basis of ab initio calculations (see isodesmic equation 4 and Table 3).[11] Taken together, the geminal fluorine effect and the effect of polar substitution at the methylene carbon adequately account for the sluggish reactivity of 3,3-difluorocyclopropene with cylopentadiene.[206]

4.4. Thermally Induced Ring Openings

Cyclopropenes undergo well-characterized thermal ring-opening reactions to produce a variety of products depending on substitution type.[232,233] Confirmation that these unimolecular reactions proceed through the reversible formation of a vinylcarbene intermediate has been obtained by experimental and computational means.[234−236] In the perhalocyclopropene series only tetrachlorocyclopropene has been unambiguously shown to thermally generate the analogous perchlorovinyl carbene intermediate through an elegant series of trapping experiments.[237] As discussed previously, there is credible suspicion that tetrafluorocyclopropene undergoes similar ring opening homolysis to produce the perfluorovinylcarbene, albeit at a higher temperature, consistent with the greater thermal stability of the fluorinated cyclopropene.

Pertinent to this discussion, a computational study of the thermal ring-opening reactions of 1-fluorocyclopropene has been recently reported.[209] As discussed previously, the distal bond (C2−C3) is lengthened while the proximal bond (C1−C3) is shortened, suggesting potential enhanced reactivity for cleavage of the distal bond, despite the fact that such cleavage would lead to a less stabilized vinylcarbene intermediate. Nevertheless, calculations revealed that distal bond homolysis had a slightly lower barrier to cleavage than the proximal bond (2 kcal/mol). Furthermore, no vinylcarbene was detected in the automerization process. That is, the homolysis of the distal bond occurs with a 180° rotation of the methylene group to re-form the cyclopropene through a single transition state. Therefore, 1-fluorocyclopropene is predicted to undergo a concerted automerization process, an unprecedented conclusion, but yet to be verified experimentally. On the other hand, thermolysis of 1,2-difluorocyclopropene would be expected to proceed through the usual two-step process due to fluorine stabilization of the carbene intermediate.

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