

Fluorite crystals, CaF_2
 “The most colorful mineral in the world”

Primary text :

Chambers, R. D. Fluorine in organic chemistry. Blackwell, 2004.

‘Fun’ fluorine facts

- Highly toxic, pale yellow diatomic gas
- 13th most abundant element in crust
- 1529, named ‘Fluo’ for “flow” since ores were low melting
- Fluorocarbons are greenhouse gases with global-warming-potentials 100 – 200 000 x CO_2



Henri Moisson

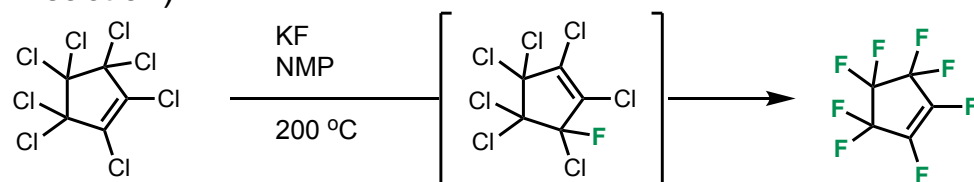
“In recognition of the great services rendered by him in his investigation and isolation of the element fluorine ... The whole world has admired the great experimental skill with which you have studied that savage beast among the elements.”

Important events in the history of fluorocarbons

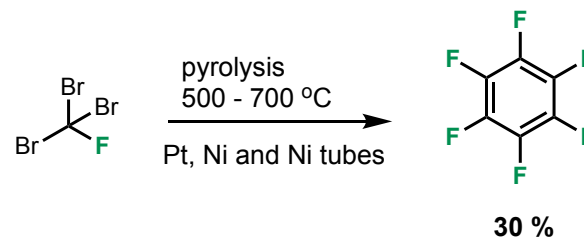
- 1890-1938 Pioneering work by Swartz / “fluorine martyrs”
- 1886 Moisson isolated F_2 , later wins Nobel
- 1930 Midgely/Henne discover fluorocarbon refrigerants
- 1937 Simons isolates CF_4 , C_2F_6 , C_3F_8 , C_4F_{10} , C_6F_{14}
- 1938 Plunkett accidentally discovers Teflon at Dupont
- 1940-1945 WWII drives discovery as stable materials intolerant to UF_6 in ^{235}U production

Industrial preparations of fluorocarbons

- Major source of fluorine is from fluorspar (CaF_2), and from phosphate rock (3.8 % F)
- HF produced by distillation (Bp 20 °C) from fluorspar and H_2SO_4
- Most fluorocarbons are produced from HF by either direct reaction, electrolyzing solutions, fluorination with F_2 or metal fluorides
- Reactive halides are easily displaced with fluoride (Swarts reaction)

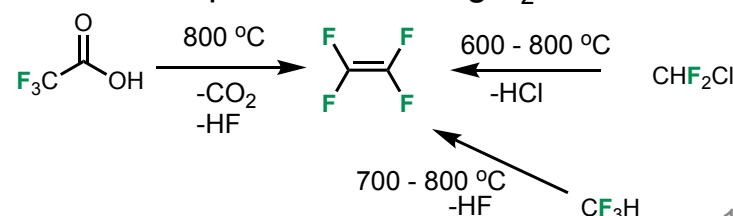


Chambers *et al.* *J. Chem. Soc., Perkin Trans 1*, 1997, 3623. 58 %



Wall *et al.* US2927138, 1960.

- The most important fluorocarbon, tetrafluoroethylene, has many methods of product involving F_2C : dimerization



Electronic effects

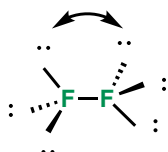
Factors comparing fluorocarbons with hydrocarbons

1. Electronegativity
2. Unshared electron pairs
3. Leaving groups / displacement of F-
4. C-F vs. C-H bond strengths
5. Size difference

	H	F	Cl
Electronegativity (Pauling)	2.20	3.98	3.16
Ionization energy (kcal/mol)	314	403	299
Electron affinity (kcal/mol)	17.7	79.5	83.3
Bond energy X-X (kcal/mol)	104	37.5	57.8
Bond length C-X (Angst.)	1.091	1.319	1.767
Van der Waals radius (Angst.)	1.20	1.47	1.75

- F+ not observed (unlike other halogens)
- Slightly larger radius than hydrogen
- Electron affinity and X-X bond strength is lower than chlorine b/c unshared electron repulsion

LP repulsion



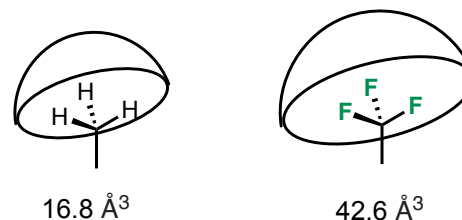
Fluorine forms very strong bonds

- B-F, Si-F, H-F and C-F are strongest bonds due to ionic bonding character
- Pauling proposed no-bond resonance, now used often

	C-F bond length (Å)	BDE (kcal/mol)	q_C	q_F
CH ₃ F	1.385	109.9	0.01	-0.23
CH ₂ F ₂	1.357	119.5	0.40	-0.23
CHF ₃	1.332	127.5	0.56	-0.21
CF ₄	1.319	130.5	0.72	-0.18

Sterics

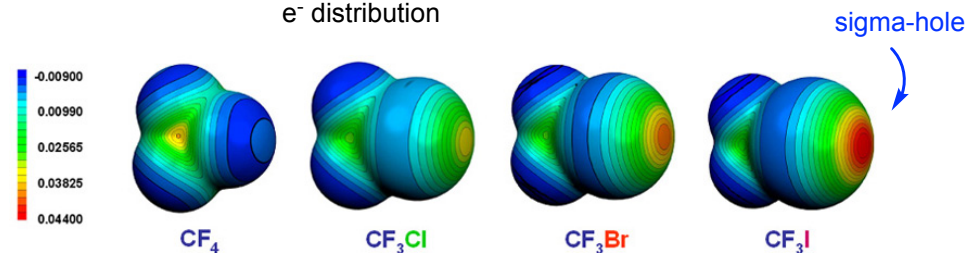
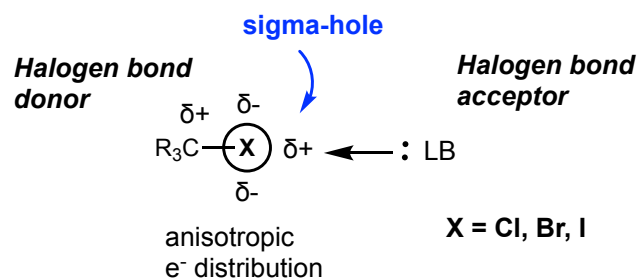
- C-F is very only slightly larger than C-H bond
- C-F is isosteric with C-O
- CF₃ occupies a significantly larger volume than CH₃



Seebach. *Angew. Chem., Int. Ed.*, **1990**, 29, 1320.

Halogen bonding : Fact or fiction ?

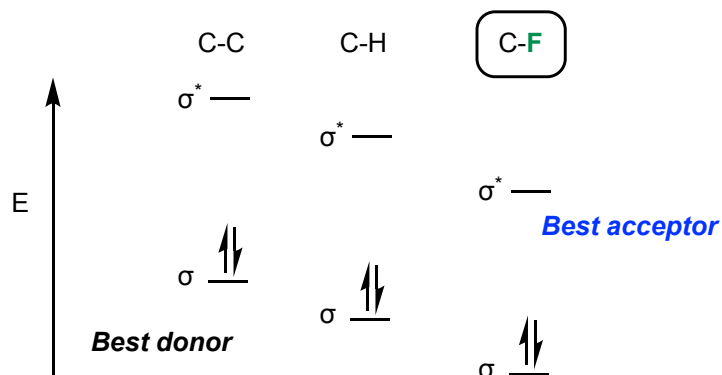
- There has been an ongoing debate on whether fluorine can form halogen bonding
- Consensus appears to suggest that no σ -hole is present, and therefore does not classify as a halogen bond



Eskandari and Lesani. *Chem. Eur. J.* **2015**, 21, 4739.

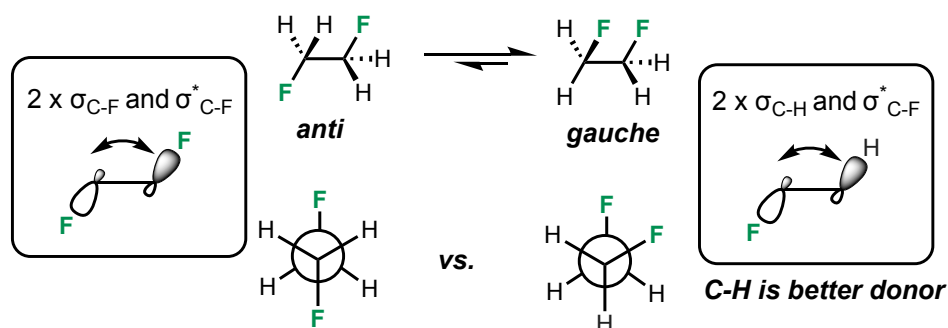
Hyperconjugation

- C-F bonds are strong hyperconjugative **acceptors** b/c of their low LUMO

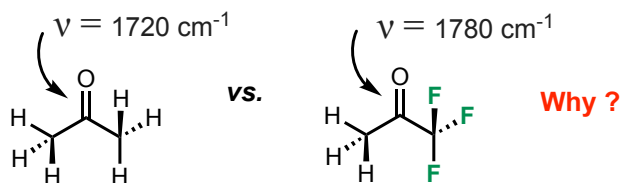
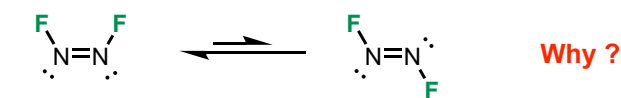


Gauche effect

- Vicinal fluorocarbons adopt gauche conformation to maximize hyperconjugation



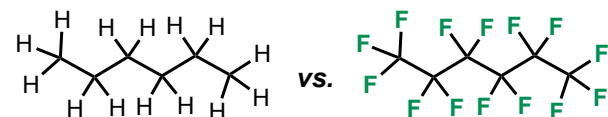
- Useful for explaining many phenomena



Lipophilicity, viscosity and volatility

- Low intramolecular attractive forces** b/c electroneg. of fluorine reduces polarizability and therefore the London-dispersion force
- Results in **low viscosities, low surface tension and heats of vaporization, higher volatility and lipophilicity**

Polarizability (for CH_3X , $\times 10^{-24} \text{ cm}^3$)	
H	2.59
F	2.97
Cl	4.72
Br	6.03

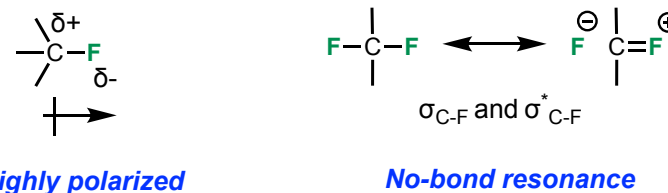


n-hexane
Bp = 68 °C
Density = 0.66 g/mL

n-perfluorohexane
Bp = 56 °C
Density = 1.68 g/mL

- Comparably **higher densities**

Saturated fluorocarbons



Highly polarized

No-bond resonance

Unsaturated fluorocarbons

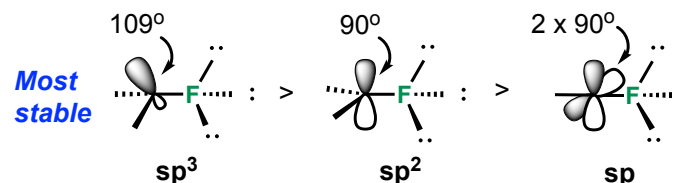
- Opposing contributions leads to variable reactivity



Polarized π -bond

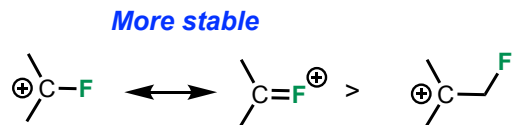
Pauli repulsion

Stability of hybridization

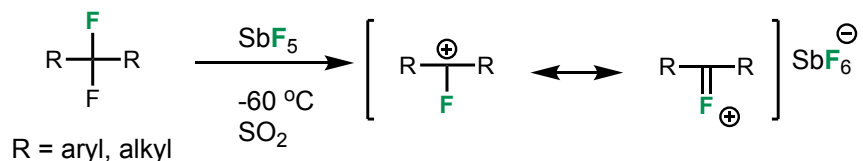


Carbocations

- Carbocations are stabilized when bearing fluorine by mesomeric stabilization and destabilized when alpha to fluorine

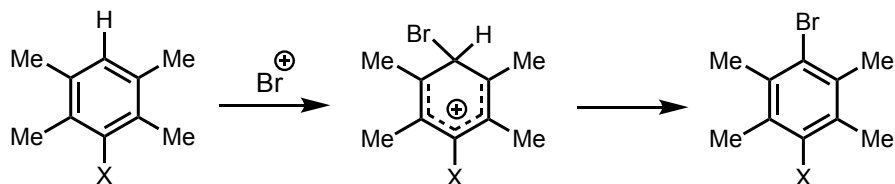


- George Olah discovered several long-lived carbocations stabilized by fluorine from strong LA

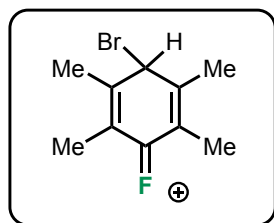


Olah *et al.* *J. Am. Chem. Soc.*, **1967**, 89, 1268.

- Electrophilic aromatic substitution also demonstrates the counterintuitive stabilization of fluorine



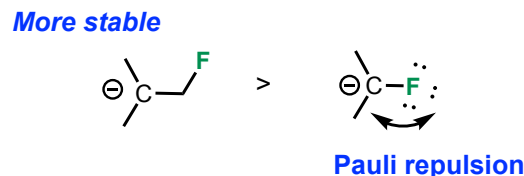
X	Rel. Rate
H	1
F	4.62
Cl	0.145
Br	0.062



Mare and Ridd, *Aromatic Substitution*, Butterworths, London, **1959**.

Carbanions

- Carbanions are destabilized when bearing fluorine by Pauli repulsion and stabilized when alpha to fluorine



- Base-catalyzed deuterium exchange experiments show fluorine is **least stabilizing halogen** when bound directly

Haloform	Rate of exchange ($10^5 k$)(l.mol ⁻¹ s ⁻¹)
CHF ₃	Too slow to measure
CHCl ₃	820
CHBr ₃	101 000
CHI ₃	105 000
CHCl ₂ F	16
CHBr ₂ F	3600
CHI ₂ F	8800

Hine *et al.* *J. Am. Chem. Soc.*, **1957**, 79, 1406.

- Carbanions bearing fluorine will often adopt a pyramidal structures to avoid repulsion



Burdon *et al.* *J. Chem. Soc., Perkin 1*, **1979**, 1205.

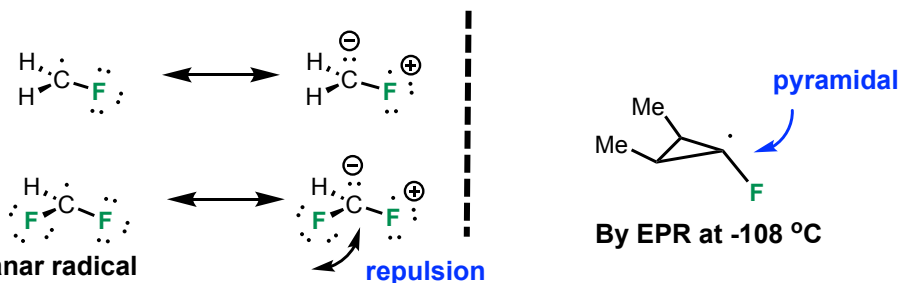
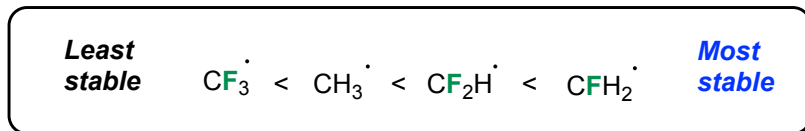
- Carbanions with alpha fluorines are stabilized

Structure	Rel. rate D/H exchange	Approx. pKa
	1	31
	6	30
	10 ⁵	20
	10 ⁹	11

Andreades, *J. Am. Chem. Soc.*, **1964**, 86, 2003.

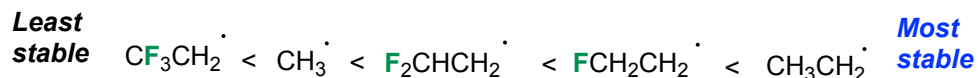
Carbon radicals

- Unlike other heteroatoms, fluorine offers little stabilization to bound radicals, likely due to repulsion



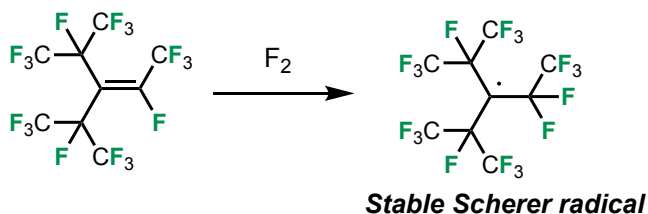
Pasto *et al.* *J. Org. Chem.*, **1987**, 52, 3062.
Kawamura *et al.* *J. Am. Chem. Soc.*, **1977**, 99, 8251.

- Adjacent fluorines (or other EWGs) are destabilizing, but steric crowding can lead to kinetically stable radicals



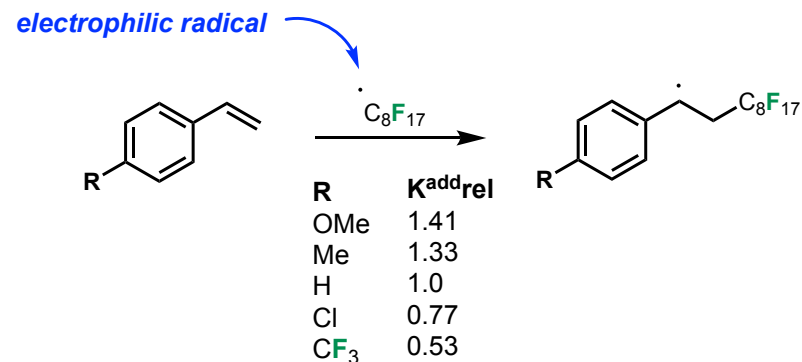
Pross *et al.* *Tetrahedron*, **1980**, 36, 1999.

- Steric crowding allows Scherer radical to be stable at rt with oxygen present ! Observed by EPR



Scherer *et al.* *J. Am. Chem. Soc.*, **1985**, 107, 718.

- Fluorocarbons produce electrophilic radicals



Avila *et al.* *J. Am. Chem. Soc.*, **1994**, 116, 99.

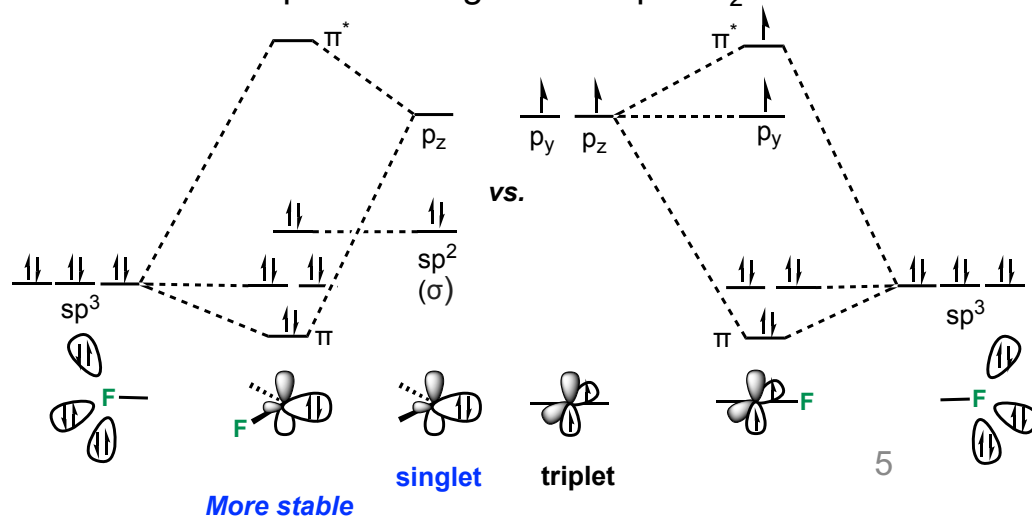
Carbenes

- Fluorine, a σ -acceptor and π -donor, leads to a very stable, singlet, ambiphilic carbenes
- Singlet state is energetically favored due to orbital mixing and Pauli repulsion

Worthington *et al.*
J. Phys. Org. Chem.
1997, 10, 755.

	$E_{\text{Triplet}} - E_{\text{singlet}}$ (kcal/mol)
H_2C :	-9
FHC :	15
F_2C :	57

- π -MO description of singlet and triplet F_2C :

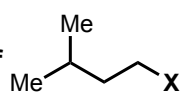


Reactivity

Displacement

- As a nucleophile, fluoride reactivity increases with decreasing lattice energy **Most nucleophilic** $\text{CsF} > \text{KF} > \text{NaF} \sim \text{LiF}$ (in aprotic solvents)

- Fluoride is generally a poor leaving group for $\text{S}_{\text{N}}2$ processes b/c of its low polarizability and strong C-F bonds

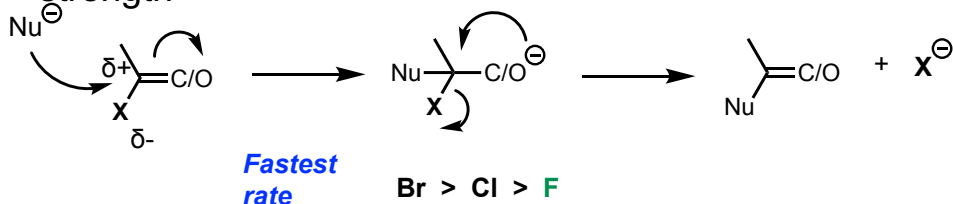
Rel. Rate of displacement of  at 18°C				
Reagent	X = F	X = Cl	C = Br	X = I
Piperidine	1	68.5	17 800	50 500
MeONa/MeOH	1	71	3 500	4 500

Tronov et al. *J. Russ. Phys. Chem. Soc.*, **1926**, 58, 1270.

- Lewis acids/Bronsted acids activated C-F bonds, as well as hydrogen bonding solvents increase rate of displacement due to strong H-F hydrogen bonding

Addition / Elimination

- Bond polarization allows facile additions, and the lower rate of fluoride elimination relates to the higher bond strength

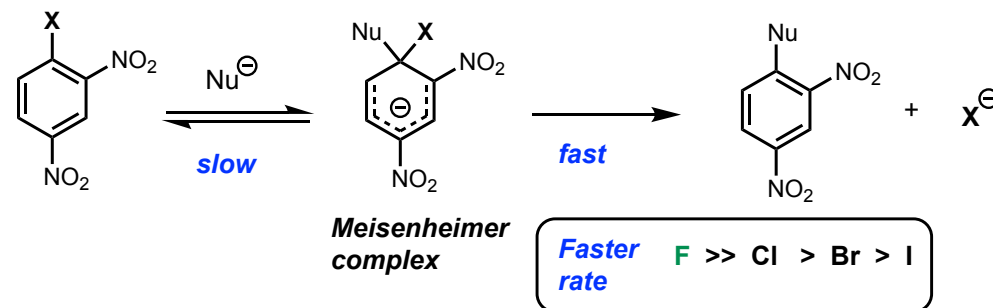


Swain et al. *J. Am. Chem. Soc.*, **1953**, 75, 246.

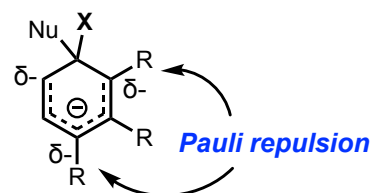
Nucleophilic aromatic substitution

- Two-step mechanism of addition of nucleophiles to electron-poor arenes. Recent work suggesting a concerted mechanism is not operative.

Kwan et al. *Nature Chemistry*, **2018**, 10, 917.



- Generally, O/N nucleophiles react faster than C/S b/c Hard-Soft-Acid/Base
- meta*-fluorine stabilizes the Meisenheimer complex best



Comparison of $k_{\text{F}}/k_{\text{H}}$

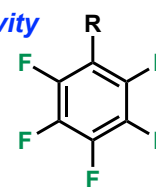
MeO ⁻ /MeOH, 58 °C	<i>ortho</i> -F	<i>meta</i> -F	<i>para</i> -F
Benzene derivatives	57	106	0.43
Pyridine derivatives	79	30	0.33

One R = F Chambers et al. *J. Chem. Soc., Perkin Trans. 1*, **1988**, 255.

- Regioselectivity can be predicted

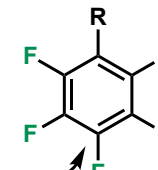
Regioselectivity of subst. of

R	Site
H	<i>para</i>
Me	<i>para</i>
CF ₃	<i>para</i>
NH ₂	<i>meta</i>
OH	<i>meta</i>



For R = H, Me, CF₃

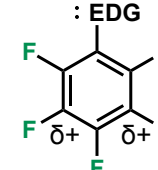
para



most activating fluorine interactions
(2 x *meta* + 2 x *ortho*)

For R = EDG

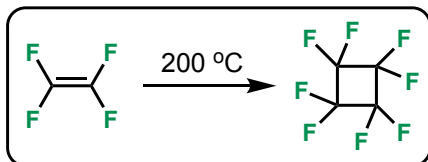
meta



EDG directing overrides reactivity

Cycloadditions

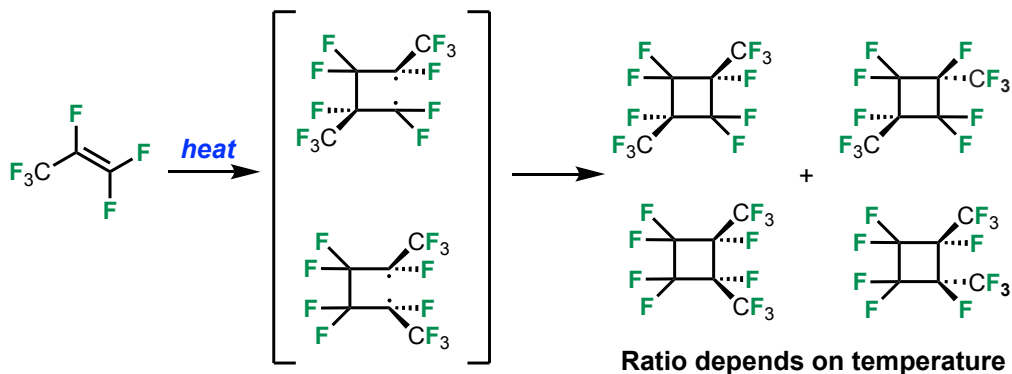
- Fluorocarbons have an unusual propensity to form **4-member rings**



SM	Prd	ΔH (kcal/mol)	E_a (kcal/mol)	K_{eq} at 315 °C
		-8	33	9000
		12	47	0.0056
2 sp^2 C-F	6 sp^2 C-F			

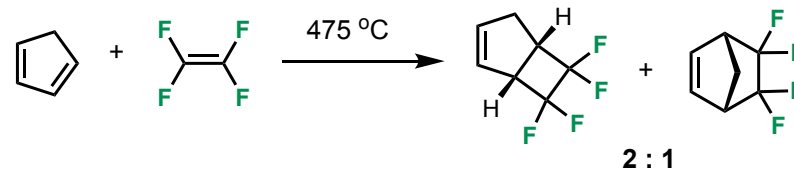
Cheswick. *J. Am. Chem. Soc.*, **1966**, 88, 4800.

- Mechanism is stepwise ($[2\pi+2\pi]$ are thermally disallowed) and involves formation of a diradical intermediate; is not stereospecific



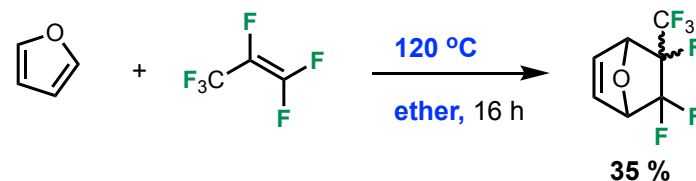
Hauptschein, *J. Am. Chem. Soc.*, **1958**, 80, 842.

- 6-member rings are less common, and often contaminated with [2+2] adducts

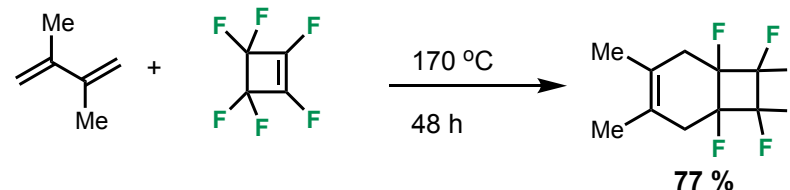


Drisdale et al. *J. Am. Chem. Soc.*, **1958**, 80, 245.

- Fluorine does not significantly lower the LUMO of alkenes, but fluorinated substituents and strain does

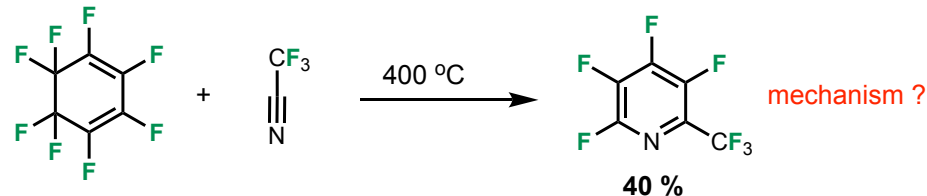


Albekov et al. *Bull. Acad. Sci. USSR (Div. Chem. Sci.)*, **1988**, 37, 777.



Burton et al. *J. Fluorine Chem.*, **1983**, 22, 397.

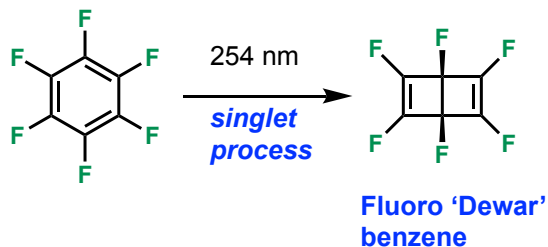
- Cycloadditions involving heteroatoms are also possible



Anderson et al. *J. Chem. Soc. (C)*, **1969**, 2559

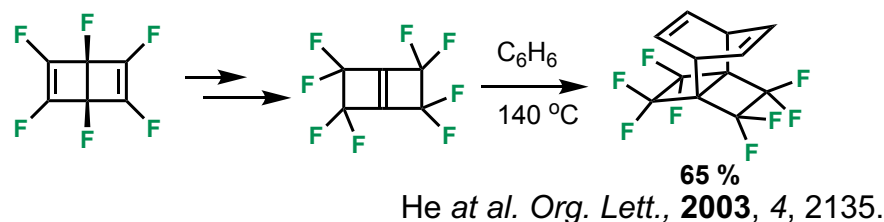
Photochemistry

- Unsurprisingly, fluoroalkenes undergo a number of bizarre photochemical processes
- Lemal has been a leading figure in the development, based on Fluoro "Dewar" benzene

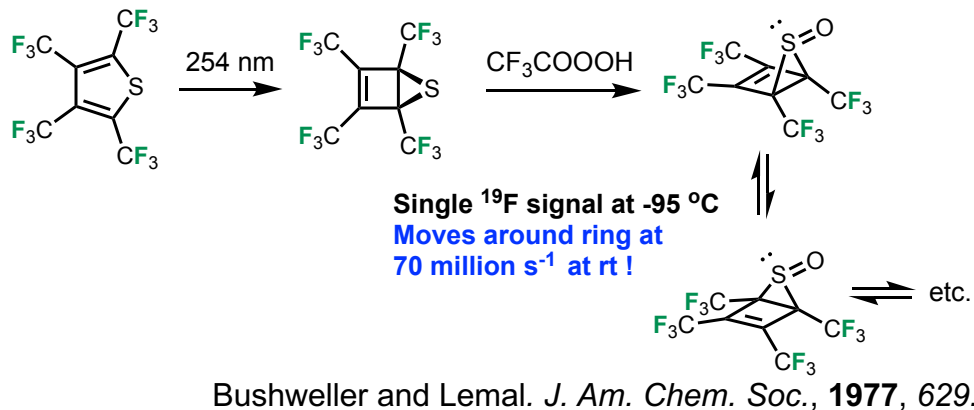


David M. Lemal
Prof. emeritus Dartmouth
Ph.D with Woodward

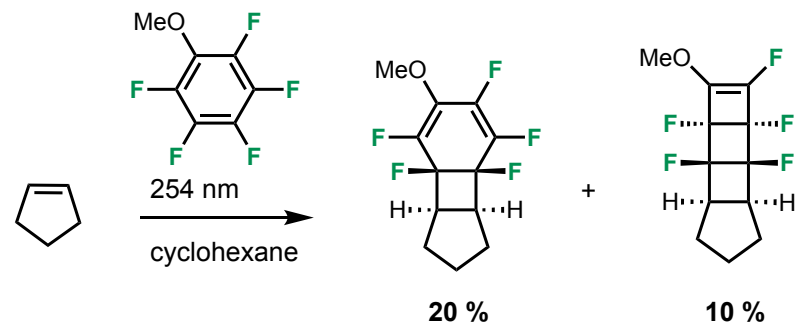
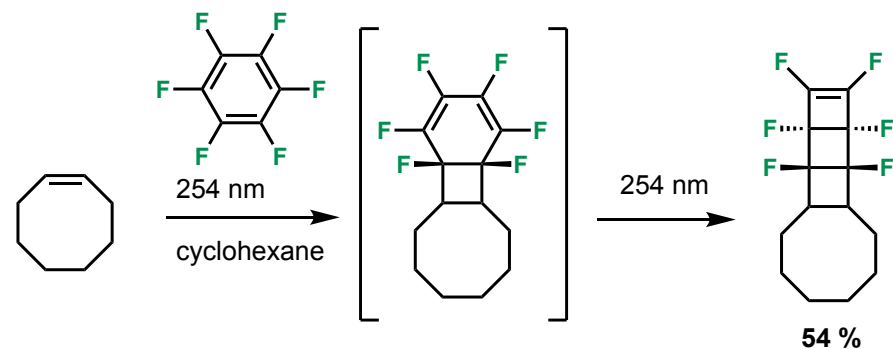
- Perfluorobicyclo[2.2.0]hex-1(4)-ene reacts with benzene



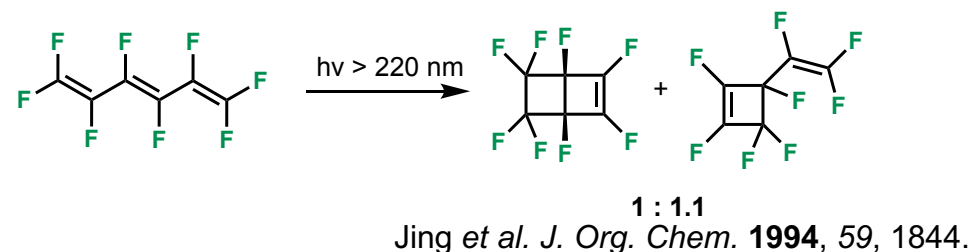
- Bizarre behavior of Dewar thiophene-S-oxide



- Hexafluorobenzene will perform photocycloadditions with cyclic alkenes that form fluoroladderenes



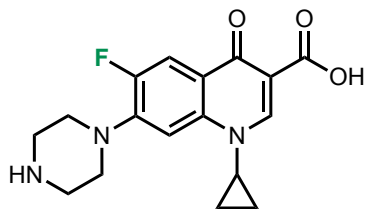
- Many examples exist of polyenes forming cyclobutenes and polycyclobutenes



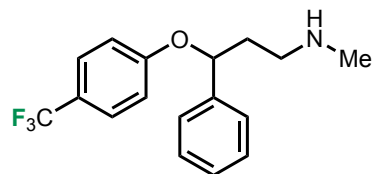
Applications

Pharmaceuticals

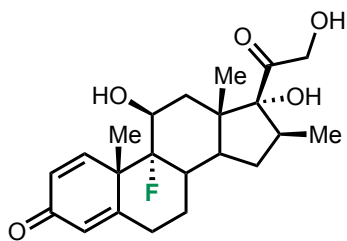
- Fluorinated analogues of biological molecules have become a popular methods of modifying pharmaceutical agents
- Fluorine effects several necessary drug properties :
 - Absorption
 - Membrane transport
 - Target binding (active site)
 - Metabolism
- Size (compared with H) is not a dominant factor
- Generally, F enhances the lipophilicity, acidity, solubility and stability of drug molecules, or be displacement and covalently attached (suicide inhibitor)



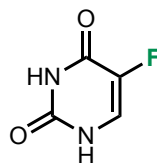
Ciprofloxacin
(antibacterial)



Prozac
(anti-depressant)



Betamethasone
(anti-inflammatory)



5-Fluorouracil
(anti-cancer)
Likely suicide inhibitor

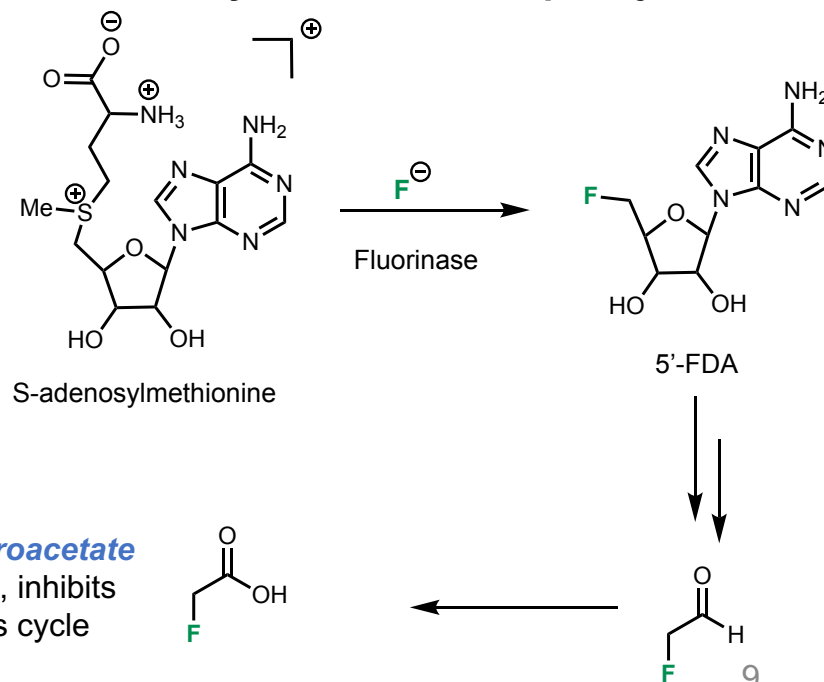
Why has nature rarely used fluorine ?

- Surprisingly rare use of fluorine despite abundance
- Only 12 natural compounds contain C-F bonds
- Likely causes :
 - Difficulty in forming C-F bonds
 - Subsequent enzymatic transformations in plant/animals are inhibited by the presence of C-F bonds

Proposed causes for unreactivity of fluorine

- F mostly present as insoluble salts
- F⁻ is highly hydrated / weak nucleophilicity
- F⁺ too difficult to form

One fluorinase enzyme exists in *Streptomyces cattleya*



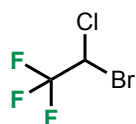
O'Hagan *et al.* *Nature*, 2002, 416, 279.

Refrigerants

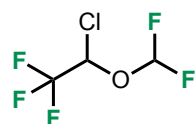
- Chlorofluorocarbons (CFCs) were introduced 60 years ago to replace NH_3 and SO_2 gases
- Peak 1974, 900 000 tones of CFCs produced, principally CF_2Cl_2 and CHFCl_2
- However, the Montreal protocol in 1987 severely reduced CFC production b/c of they decompose O_3 into O_2

Anesthetics

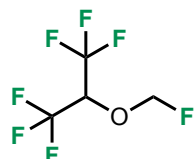
- Fluothane was the most common anesthetic in 1980, much better than the risks of older anesthetics (diethyl ether, chloroform etc.)
- Now, Isoflurane, Sevoflurane and Desflurane are used in the general quest for less readily metabolized systems and faster recovery times of the patients



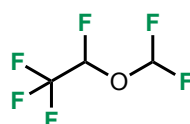
Fluothane



Isoflurane



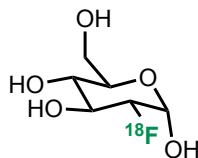
Sevoflurane



Desflurane

Imaging technique

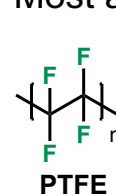
- ^{19}F -MRI (NMR) can be used
- Isotopic ^{18}F half-life is 109 minutes, decays by positron emission (measure by PET)
- PET is especially useful for *in-vivo* studies (non-invasive)
- E.g. 2-fluorodeoxyglucose is used to measure glucose metabolism



PET
scanning
agent

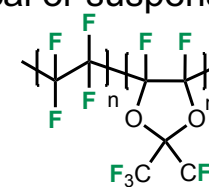
Polymers

- Fluoropolymers have become multi billion dollar industry because of their unique properties and longevity
- Most fluoropolymers are known for their :
 - Chemical resistant**
 - Thermal stability**
 - Low dielectric constant**
 - Low flammability**
 - Low surface energy**
- Most are prepared by radical or suspension polymerization



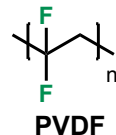
PTFE

Cookware,,
waterproof
clothing, medical
devices



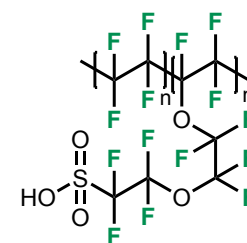
Teflon AF

Optically clear,
used in
corrosive
environments



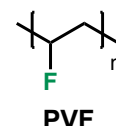
PVDF

Weather-
resistant
coatings



Nafion

Membranes in
chlor-alkali
cells



PVF

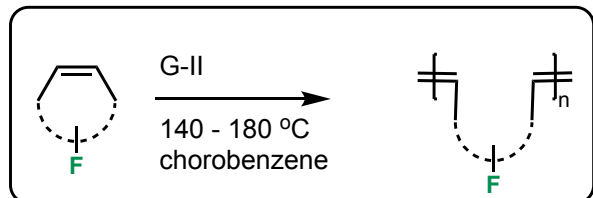
Coatings,
flexible films

Global Fluoropolymers Market, 2014 – 2020 (Kilo Tons) (USD Billion)

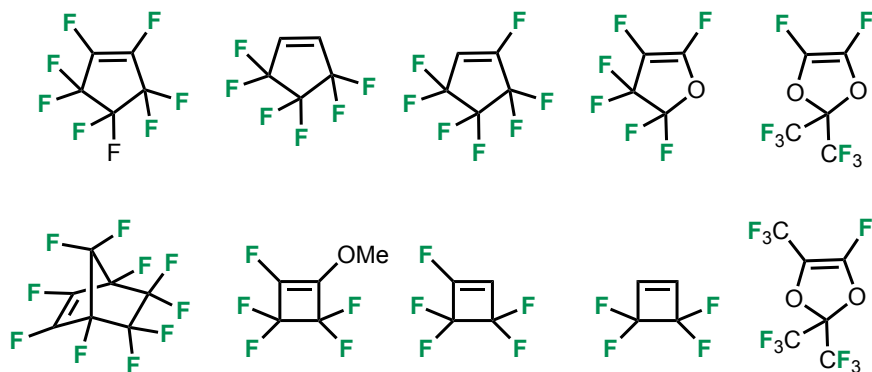


ROMP polymers of fluoroalkenes

- Surprisingly, Ru metathesis catalysts at high temp. is successful at preparing fluoropolymers

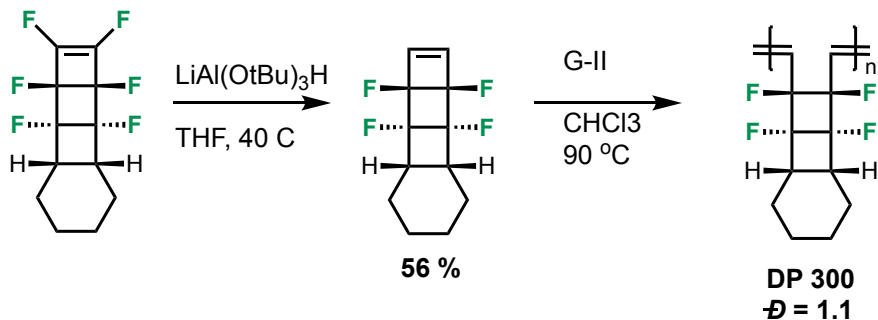


Monomers :



Takahira et al. (ASAHI glass). US2017/0335051. 2017.

- This method was recently extended to fluoroladderenes at modest temperature



The end !