Organofluorine Chemistry

Julien Lee Heberling
Shenvi Lab
Department of Chemistry
Scripps Research
Seminar
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Contents

Introduction

Etymology

Fluorine ⟹ Fluorspar ⟹ *fluo, fluere, fluxi, fluxum*
"to flow"

Fluorspar

Smelting

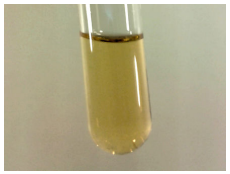
Banks, R. E. *J. Fluor. Chem.* **1986,** *33,* 3

Etymology

Fluorine: name given by Ampère (1812)

Phtorine: name later proposed by Ampère
from the Greek, *phtoros* (“destructive”)

- Chlorine → *chloros* “pale green”
- Bromine → *bromos* “stench”
- Iodine → *iodes* “violet”
- Astatine → *astatos* “unstable”



Liquid fluorine
(cryogenic)

Chlorine gas

Liquid bromine

Sublimating iodine

Astatine
(radioactive)

Regrettably the name fluorine stems from the occurrence of element number 9 as native calcium fluoride […] and conveys no hint of its aggressive nature. By contrast, the names chlorine, bromine, iodine […] and astatine do reveal obvious characteristics.

R. E. Banks

Banks, R. E. *J. Fluor. Chem.* **1986,** *33,* 3

Brief History

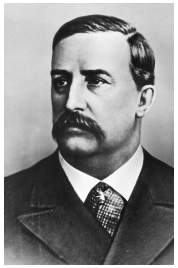
Georgius Agricola account on fluorspar

1530

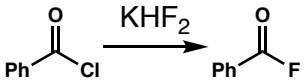
1771

Scheele synthesizes HF

Borodin first to synthesize organofluorine compound



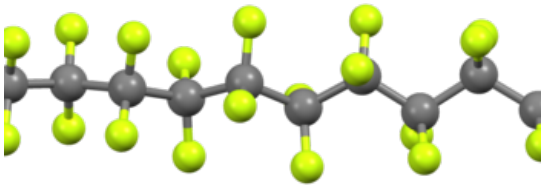
1863



1886

Moissan isolates F_2

Plunkett develops PTFE at DuPont

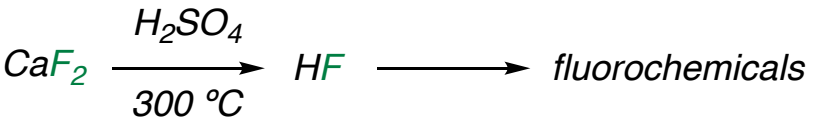


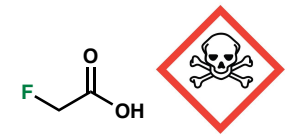
1938

Banks, R. E. *J. Fluor. Chem.* **1986,** *33,* 3
Okazoe, T. *Proc. Jpn. Acad.* **2009,** *85,* 276
edu.rsc.org/feature/the-discovery-of-fluorine/2020249.article
Dehnen, S.; Schafer, L. L.; Lectka, T.; Togni, A. *J. Org. Chem.* **2021,** *86,* 16213

Provenance and Use

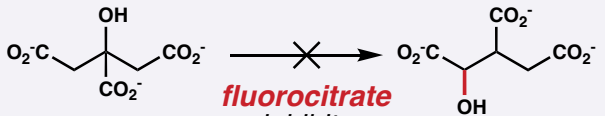
- Fluorine abundant in the form of fluorspar (CaF_2)
- Synthesis of HF, precursor to fluorinated products
- Fluorinase: only known enzyme to perform fluorination
- Only 5 known naturally-occurring organofluorine compounds





Fluoroacetic acid

TCA cycle arrested



- Metallurgical flux
- Optical lenses, glass etching
- PTFE (Teflon)
- Toothpaste for dental health
- Fluorine present in ≈ **20% of all pharmaceuticals**
- Fluorine present in ≈ **30 to 40% of agrochemicals**

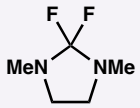
Fluoroapatite strengthens enamel

Klose, I.; *et al. Nature* **2024,** *635,* 359
Patel, C.; *et al. Science* **2023,** *381,* 302
Reichel, M.; Karaghiosoff, K. *Angew. Chem. Int. Ed.* **2020,** *59,* 12268
Lauble, H.; Kennedy, M. C.; Emptage, M. H.; Beinert, H.; Stout, C. D. *Proc. Natl. Acad. Sci.* **1996,** *93,* 13699
Dehnen, S.; Schafer, L. L.; Lectka, T.; Togni, A. *J. Org. Chem.* **2021,** *86,* 16213

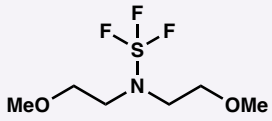
Common Fluorinating Reagents

Nucleophilic

DAST
Diethylaminosulfur trifluoride

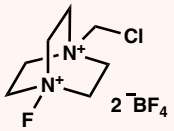


DFI
2,2-Difluoro-1,3-dimethyl-imidazolidine

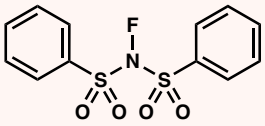


Deoxofluor

Electrophilic

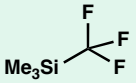


Selectfluor

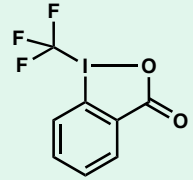


NFSI
N-Fluorobenzenesulfonimide

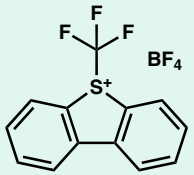
CF_3 transfer



Ruppert-Prakhash



Togni's reagent II



Umemoto's reagent I

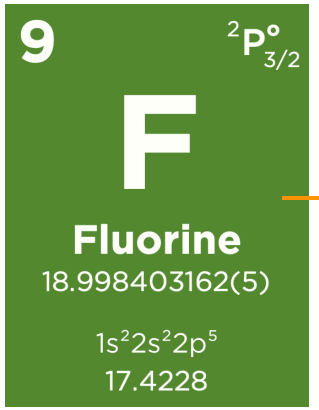
Physical Chemistry

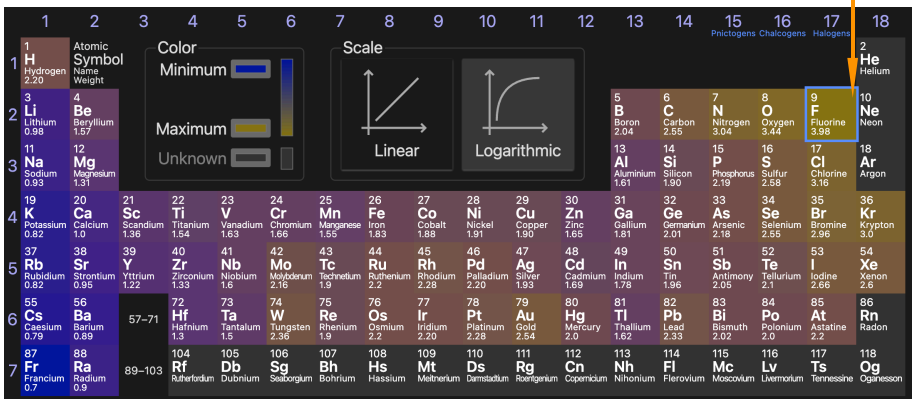
Physical Properties

- Lightest halogen
  - Group 7
  - Period 2

- -219.67 ºC = melting point
- -188.11 ºC = boiling point
- Pale yellow-green gas

- Most **electronegative** element on the periodic table

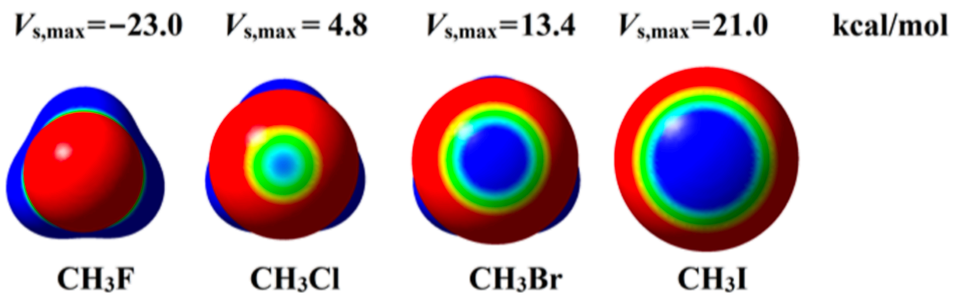




ptable.com
periodic-table.rsc.org/element/9/fluorine
Ibrahim, M. A. A.; Moussa, N. A. M. *ACS Omega* **2020,** *5,* 21824

Physical Properties: Electronegativity

		χ (Pauling)
N	→	3.04
O	→	3.44
F	→	3.98
Cl	→	3.16
Br	→	2.96
I	→	2.66



Methylhalide electrostatic potentials
$V_{s,max}$ = maximum positive electrostatic potential

periodic-table.rsc.org/element/9/fluorine
Ibrahim, M. A. A.; Moussa, N. A. M. *ACS Omega* **2020,** *5,* 21824

Physical Properties: Bond Enthalpy

Bond enthalpy (kJ · mol^{-1})

Bond identity	X = F		X = Cl	X = Br	X = I
X–X	155	<	242	193	151
C–X	485	>	339	285	218
H–X	565	>	431	366	299

periodic-table.rsc.org/element/9/fluorine
periodic-table.rsc.org/element/17/chlorine
periodic-table.rsc.org/element/35/bromine
periodic-table.rsc.org/element/53/iodine

Physical Properties: Bond Enthalpy

C–X bond enthalpy (kJ · mol^{-1})

X = F	X = H	X = C	X = N	X = O
485	413	347	305	358

*Fluorine forms **strongest** bond to carbon*

periodic-table.rsc.org/element/9/fluorine
periodic-table.rsc.org/element/1/hydrogen
periodic-table.rsc.org/element/6/carbon
periodic-table.rsc.org/element/7/nitrogen
periodic-table.rsc.org/element/8/oxygen

Physical Properties: Atomic Radius

Atomic radius (Van der Waals) (pm)

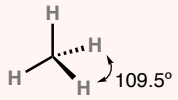
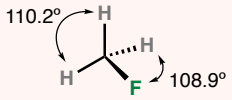
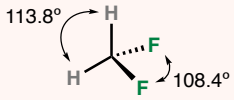
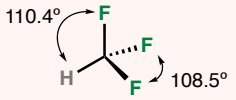
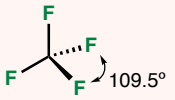
X = N	X = O		X = F		X = Cl	X = Br	X = I
155	152	>	135	<	175	183	198

period 2

group 7

pubchem.ncbi.nlm.nih.gov/ptable/atomic-radius/

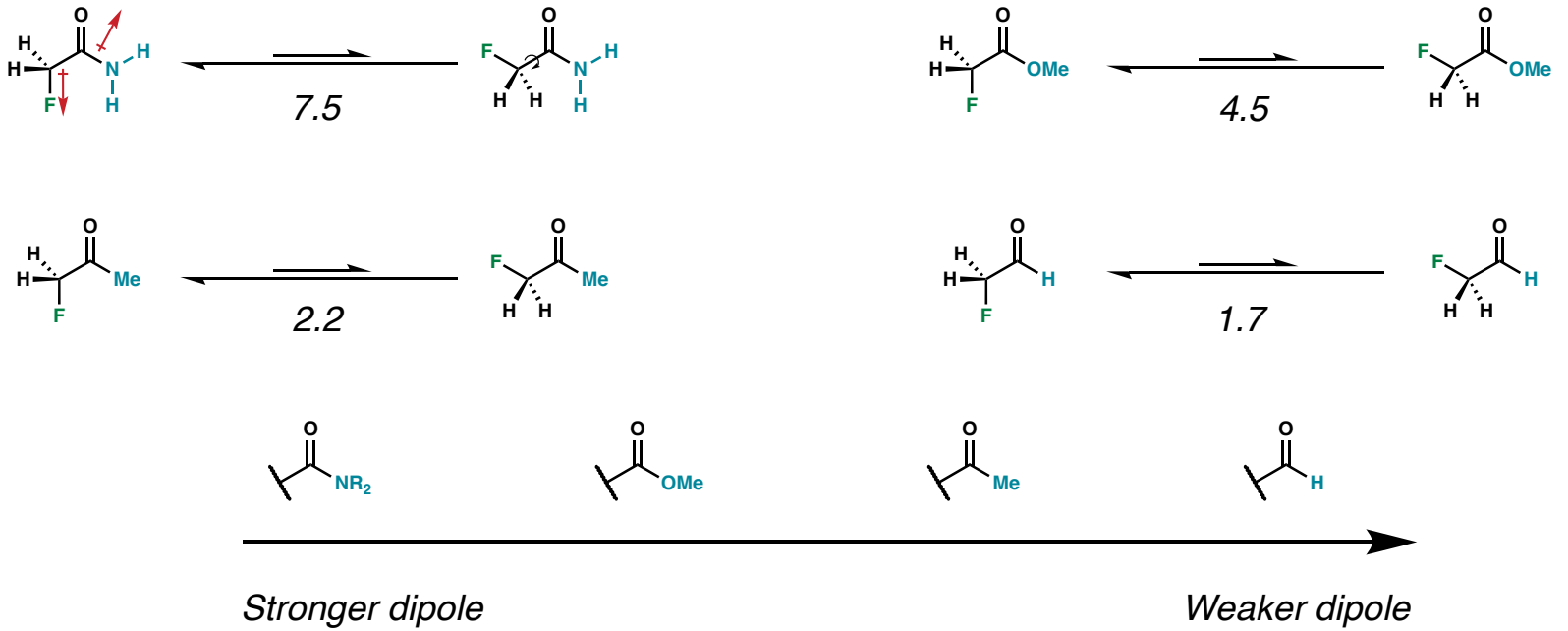
Physical Properties: Bond Angle & Length

					
C–F bond length (pm)	——	139	136	133	132
Dipole moment (μ) (D)	0	1.85	1.97	1.65	0

O'Hagan, D. *Chem. Soc. Rev.* **2008,** *37,* 308

Physical Properties: Dipole-Dipole Interactions

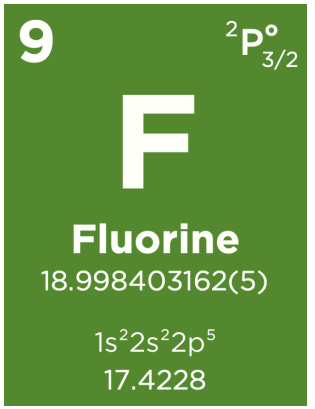
Values refer to ΔE (kcal • mol^{-1})



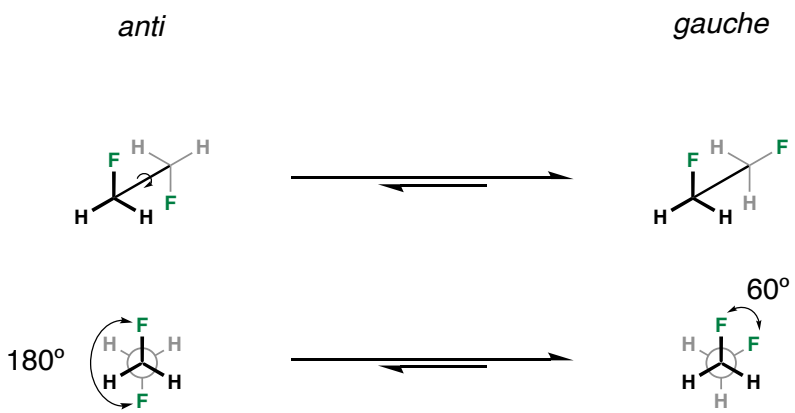
O'Hagan, D. *Chem. Soc. Rev.* **2008,** *37,* 308

Physical Properties: Key Takeaways

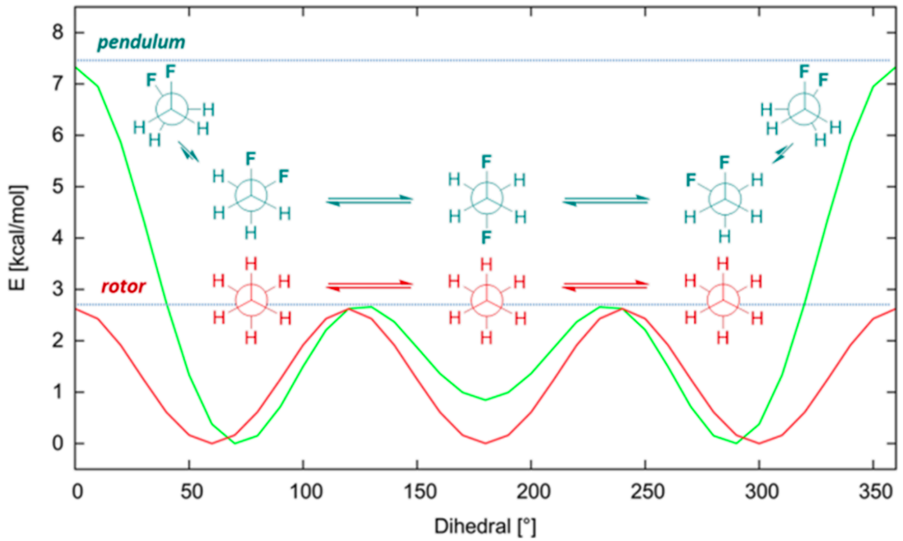
- Occupies small space, low steric encumbrance
- High electronegativity
- Strong C–F bond



Conformation: the *Gauche* Effect

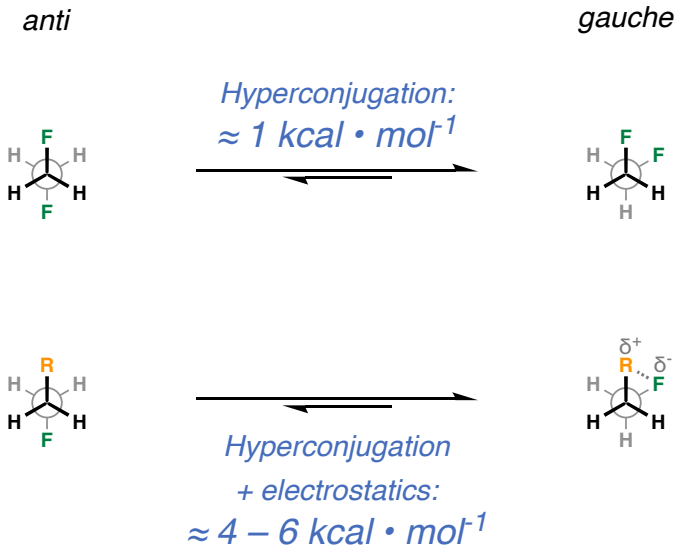


$\Delta E \approx -1.0$ kcal • mol^{-1}

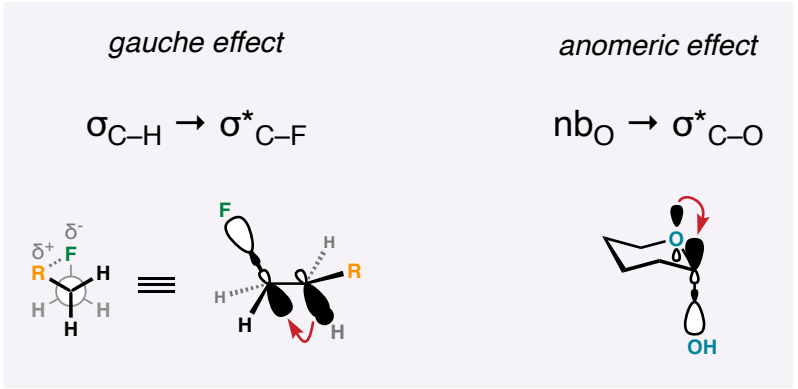


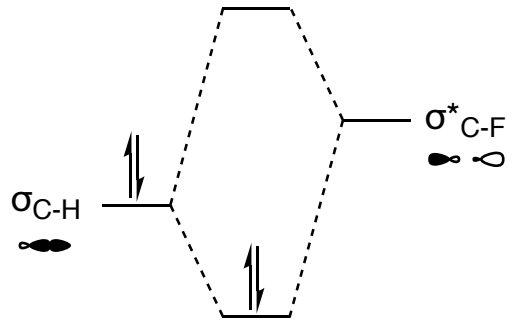
Van Schaick, E. J. M.; Geise, H. J.; Miljhoff, F. C.; Renes, G. *J. Mol. Struct.* **1973,** *16,* 23
Aufiero, M.; Gilmour, R. *Acc. Chem. Rev.* **2018,** *51,* 1701
Thiehoff, C.; Rey, Y. P.; Gilmour, R. *Isr. J. Chem.* **2017,** *57,* 92

Conformation: the *Gauche* Effect



R = CO_2Me, CONHMe, OH, NH_3^+, SOR'





Aufiero, M.; Gilmour, R. *Acc. Chem. Rev.* **2018,** *51,* 1701
Thiehoff, C.; Rey, Y. P.; Gilmour, R. *Isr. J. Chem.* **2017,** *57,* 92
Zimmer, L. E.; Sparr, C.; Gilmour, R. *Angew. Chem. Int. Ed.* **2011,** *50,* 11860

β-Fluoroamine Acidity: Through-Bond

pK_a	10.7	9.0	7.3	5.7

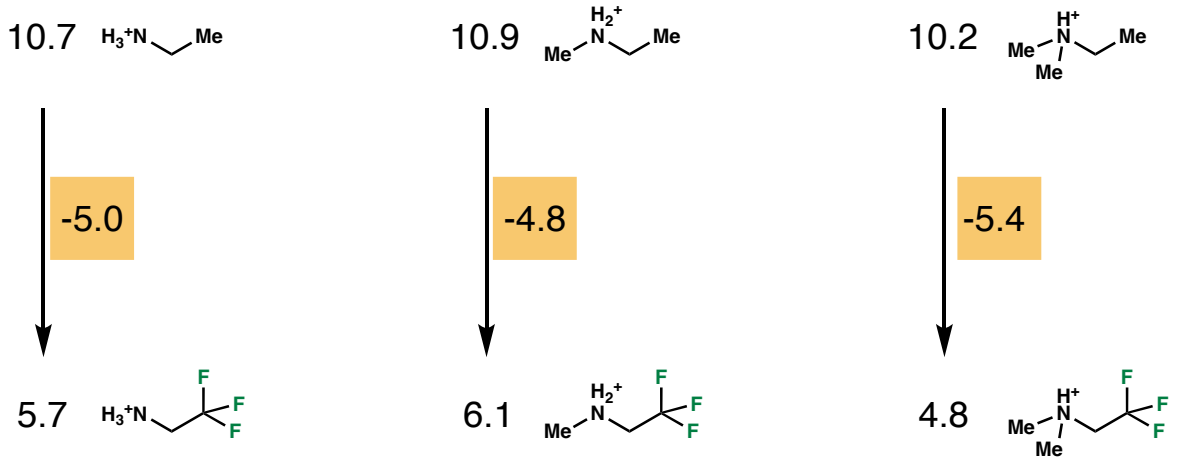
more basic → *more acidic*

- *pK_a lowered by ≈ 1.5 per β-fluorine added*
- *Inductive effect observed all the way through δ substitution*

Hagmann, W. K. *J. Med. Chem.* **2008,** *51,* 4359
Müller, K.; Faeh. C.; Diederich, F. *Science* **2007,** *317,* 1881
Morgenthaler, M.; *et al. ChemMedChem* **2007,** *2,* 1100

β-Fluoroamine Acidity: Through-Space

Values refer to pK_a



Hagmann, W. K. *J. Med. Chem.* **2008,** *51,* 4359
Morgenthaler, M.; *et al. ChemMedChem* **2007,** *2,* 1100

β-Fluoroamine Acidity: Through-Space

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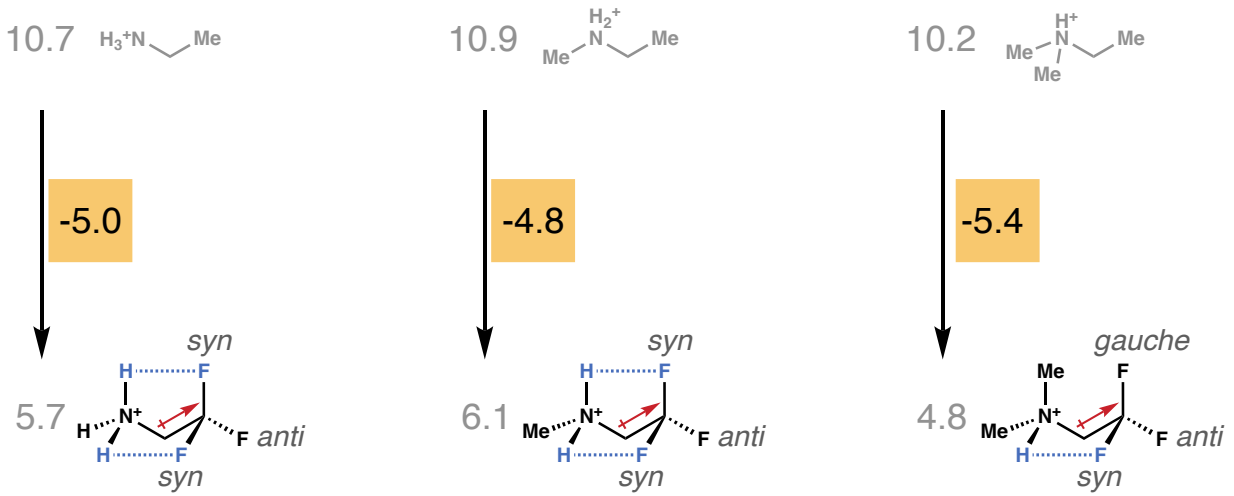
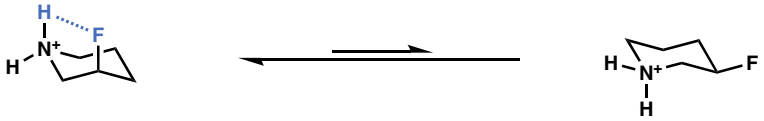


F inductively destabilizes positive charge → lowers pK_a

F syn or anti to proton mitigates inductive destabilization

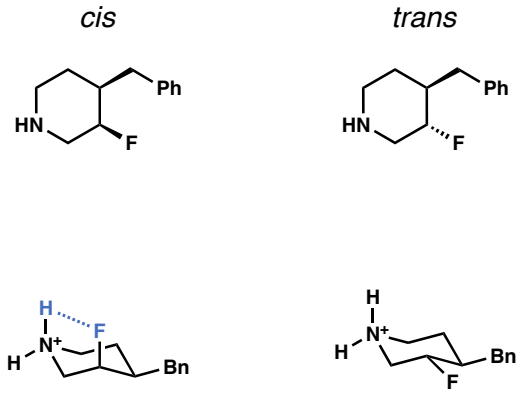
Hagmann, W. K. *J. Med. Chem.* **2008,** *51,* 4359
Morgenthaler, M.; *et al. ChemMedChem* **2007,** *2,* 1100

β-Fluoropiperidine Acidity: Through-Space



96% $\Delta E = 1.9$ kcal • mol^{-1} 4%

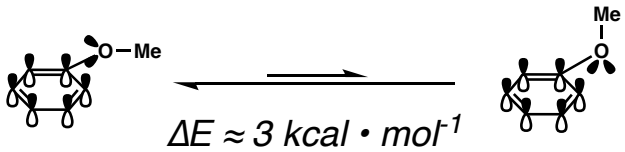
(by NMR)



pK_a 9.3 < 8.8

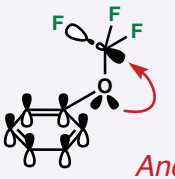
Lankin, D. C.; Chandrakumar, N. S.; Rao, S. N.; Spangler, D. P.; Snyder, J. P. *J. Am. Chem. Soc.* **1993,** *115,* 3356
Hagmann, W. K. *J. Med. Chem.* **2008,** *51,* 4359
Morgenthaler, M.; *et al. ChemMedChem* **2007,** *2,* 1100
O'Hagan, D. *Chem. Soc. Rev.* **2008,** *37,* 308
Sun, A.; Lankin, D. C.; Hardcastle, K.; Snyder, J. P. *Chem. Eur. J.* **2005,** *11,* 1579

Aromaticity



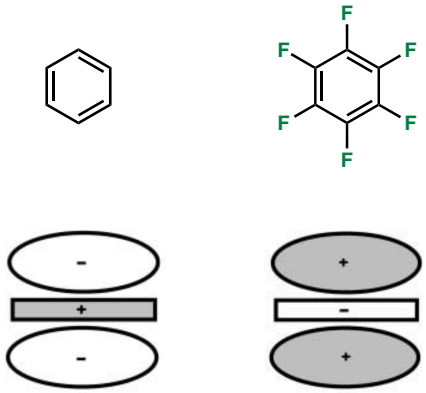
OMe ***in plane & conjugated*** *in π system*

$nb_O \rightarrow \sigma^*_{C-F}$



Anomeric effect

OCF_3 ***out plane***

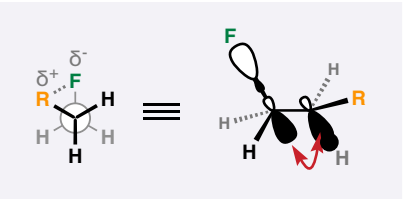


Electron density inverted in hexafluorobenzene

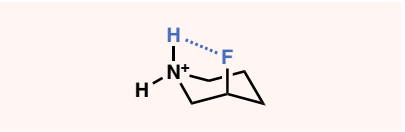
Leroux, F.; Jeschke, P.; Schlosser, M. *Chem. Rev.* **2005,** *105,* 827
Müller, K.; Faeh. C.; Diederich, F. *Science* **2007,** *317,* 1881
Meyer, E. A.; Castellano, R. K.; Diederich, F. *Angew. Chem. Int. Ed.* **2003,** *42,* 1210

Conformational Effects: Key Takeaways

- Low-lying σ^*_{C-F} bond gives rise to *gauche* effect

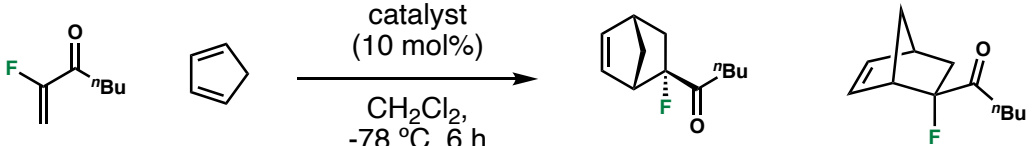


- High electronegativity of fluorine enables additional electrostatic interactions



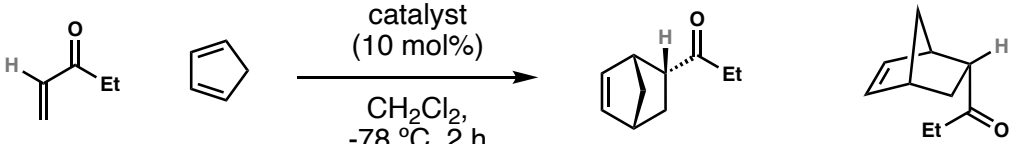
Implications in Synthesis & Beyond

Lewis Acid Catalyzed Diels-Alder Reaction



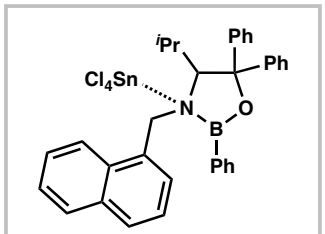
exo / endo = 83 / 17

exo favored



exo / endo = 1 / 99

endo favored

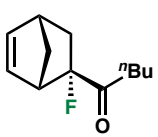


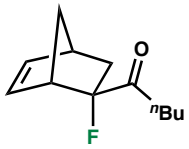
oxazaborolidine catalyst

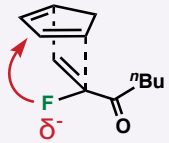
Shibatomi, K.; Futatsugi, K.; Kobayashi, F.; Iwasa, S.; Yamamoto, H. *J. Am. Chem. Soc.* **2010,** *132,* 5625
Essers, M.; Ernet, T.; Haufe, G. *J. Fluor. Chem.* **2003,** *121,* 163
Cahard, D.; Bizet, V. *Chem. Soc. Rev.* **2014,** *43,* 135

Lewis Acid Catalyzed Diels-Alder Reaction

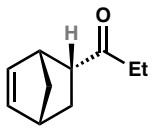
exo

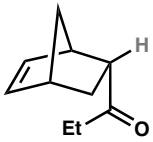


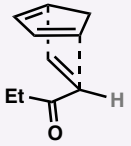




endo



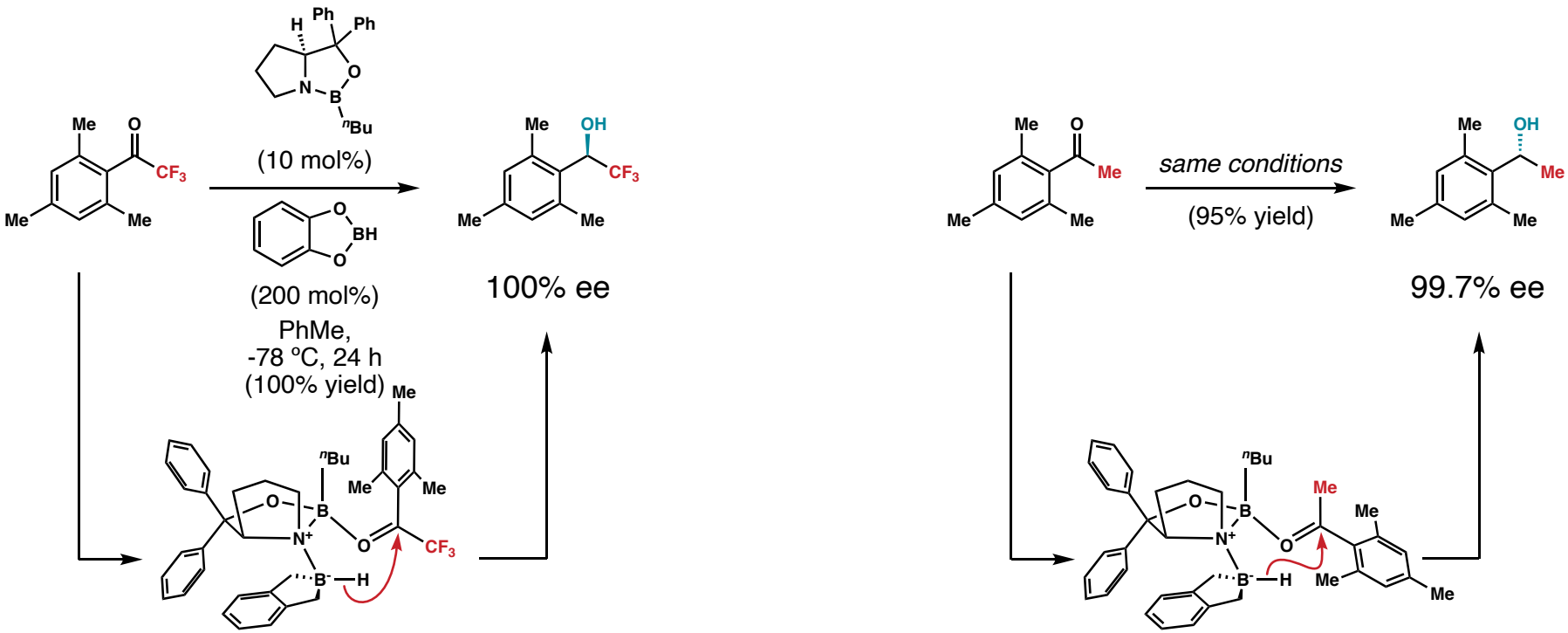




Fluorine adds electron density into diene π system

Shibatomi, K.; Futatsugi, K.; Kobayashi, F.; Iwasa, S.; Yamamoto, H. *J. Am. Chem. Soc.* **2010,** *132,* 5625
Essers, M.; Ernet, T.; Haufe, G. *J. Fluor. Chem.* **2003,** *121,* 163
Cahard, D.; Bizet, V. *Chem. Soc. Rev.* **2014,** *43,* 135
Scott A. Snyder Lecture Notes *The Diels-Alder Reaction*

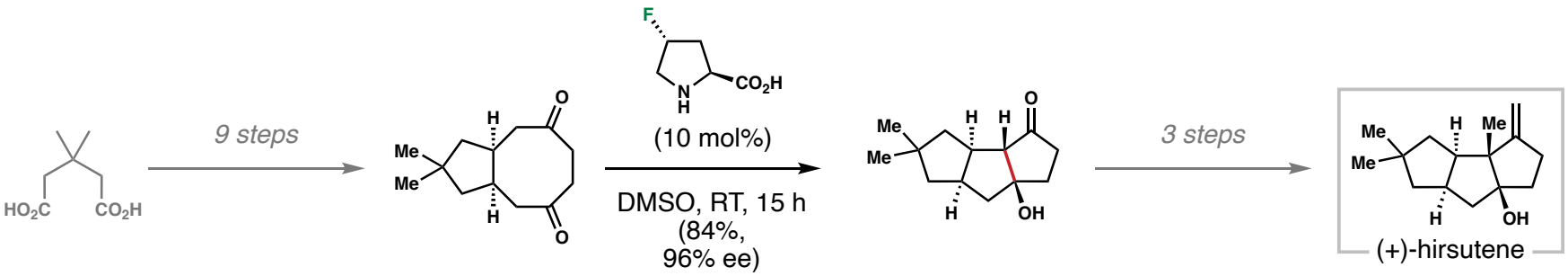
CBS Reduction

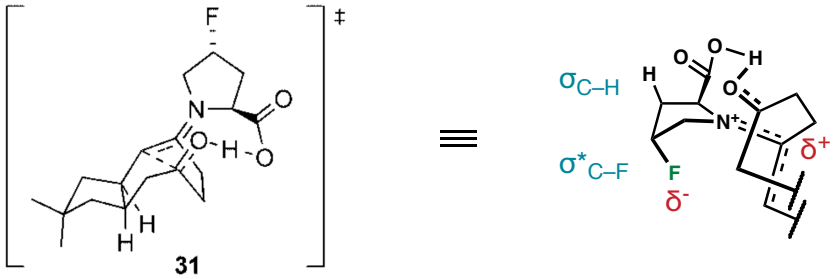


- *Anti orientation between sterically encumbered group & engaged O lone pair*
- *Electronic repulsion between boronate & CF_3 (Corey et al.)*

Corey, E. J.; Cheng, X.-M.; Cimprich, K. A.; Sarshar, S. *Tetrahedron Lett.* **1991,** *32,* 6835
Cahard, D.; Bizet, V. *Chem. Soc. Rev.* **2014,** *43,* 135

Organocatalysis: Hirsutene



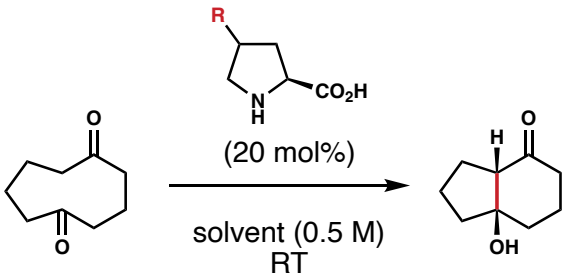


Desired conformation defined by gauche & electrostatic effects

Chandler, C. L.; List, B. *J. Am. Chem. Soc.* **2008,** *130,* 6737
Zimmer, L. E.; Sparr, C.; Gilmour, R. *Angew. Chem. Int. Ed.* **2011,** *50,* 11860

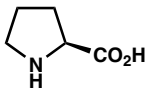
Organocatalysis: Hirsutene

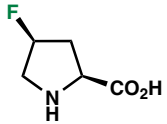
Model substrate catalyst screen

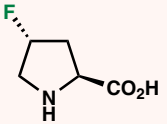


entry	R	solvent	time [h]	conversion [%][a]	er[b]	ee (%)
1	H	DMF	16	60	77:23	54
2	*trans*-OH	DMF	24	50	82:18	64
3	*trans*-OTBS	DMF	15	60	39:61	22 (favoring undesired)
4	*trans*-O*t*-Bu	DMF	2	95	80:20	60
5	*trans*-F	DMF	24	75	90:10	80
6	*cis*-F	DMF	24	50	79:21	58
7	*trans*-F	CH_3CN	24	50	56:44	12
8	*trans*-F	DMSO	24	75	91:9	82

Catalyst (DMF solvent)







ee

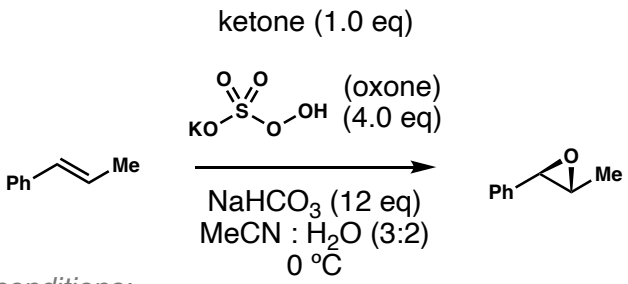
54%

58%

80%

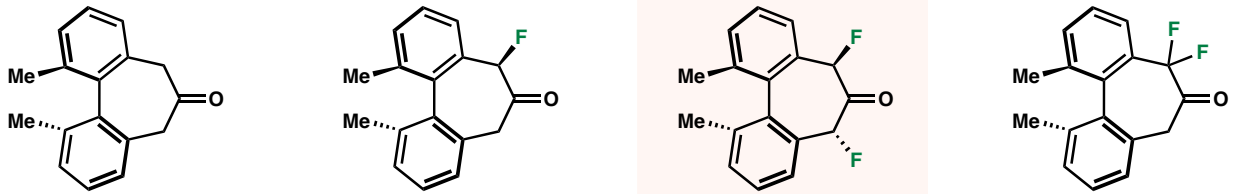
Chandler, C. L.; List, B. *J. Am. Chem. Soc.* **2008,** *130,* 6737
Zimmer, L. E.; Sparr, C.; Gilmour, R. *Angew. Chem. Int. Ed.* **2011,** *50,* 11860

Organocatalysis: Epoxidation

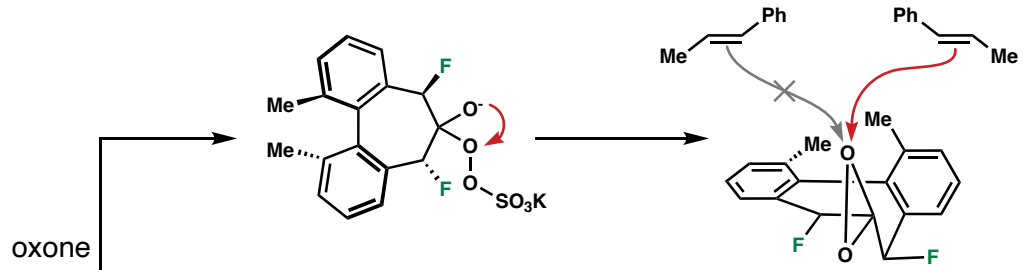


Final conditions:

ketone (30 mol%)
oxone (4.0 eq)
K_2CO_3 (12 eq)
MeCN : H_2O (3:2)
0 °C



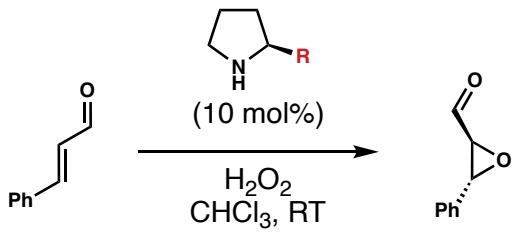
Conversion	6% (8 h)	33% (11 h)	100% (8 h)	100% (6 h)
ee	ND	79%	87%	85%

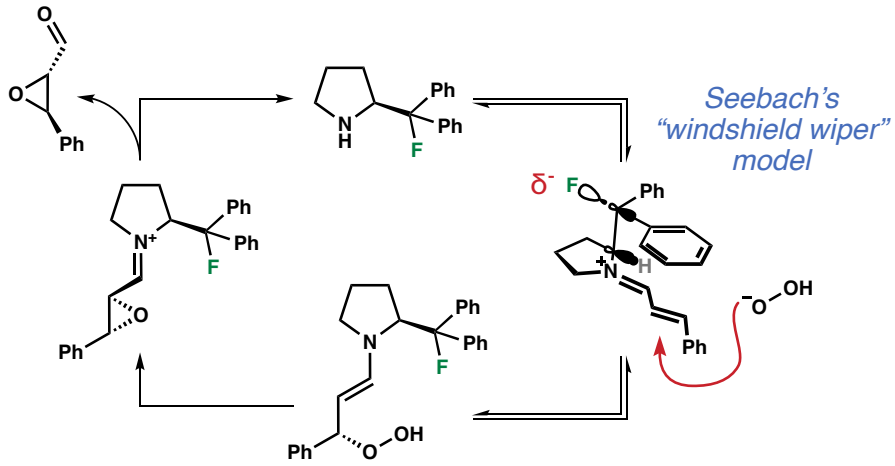


Fluoro substituents improve catalyst reactivity via inductive effect

Denmark, S. E.; Matsuhashi, H. *J. Org. Chem.* **2002,** *67,* 3479
Aufiero, M.; Gilmour, R. *Acc. Chem. Rev.* **2018,** *51,* 1701

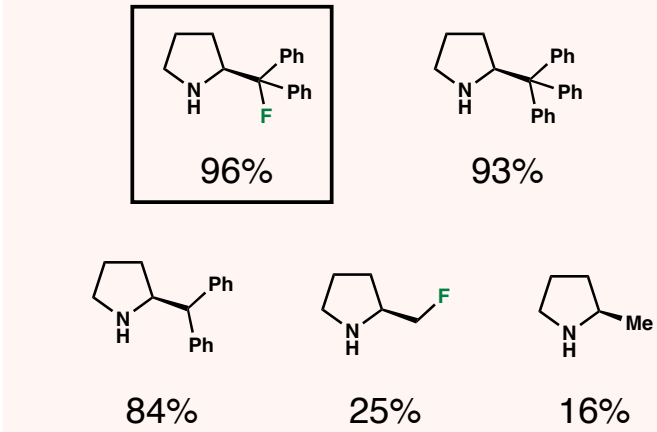
Organocatalysis: Epoxidation





Seebach's "windshield wiper" model

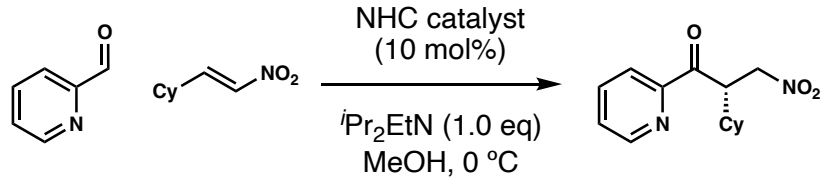
Catalyst (ee values)

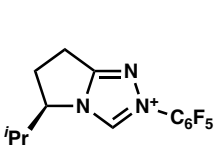


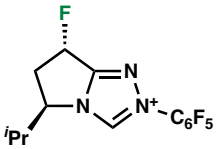
Stereochemistry determined by π stacking interactions + gauche conformer due to fluorine

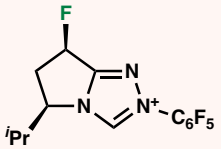
Tanzer, E.-M.; Zimmer, L. E.; Schweizer, W. B.; Gilmour, R. *Chem. Eur. J.* **2012,** *18,* 11334
Aufiero, M.; Gilmour, R. *Acc. Chem. Rev.* **2018,** *51,* 1701

NHC: Stetter Reaction





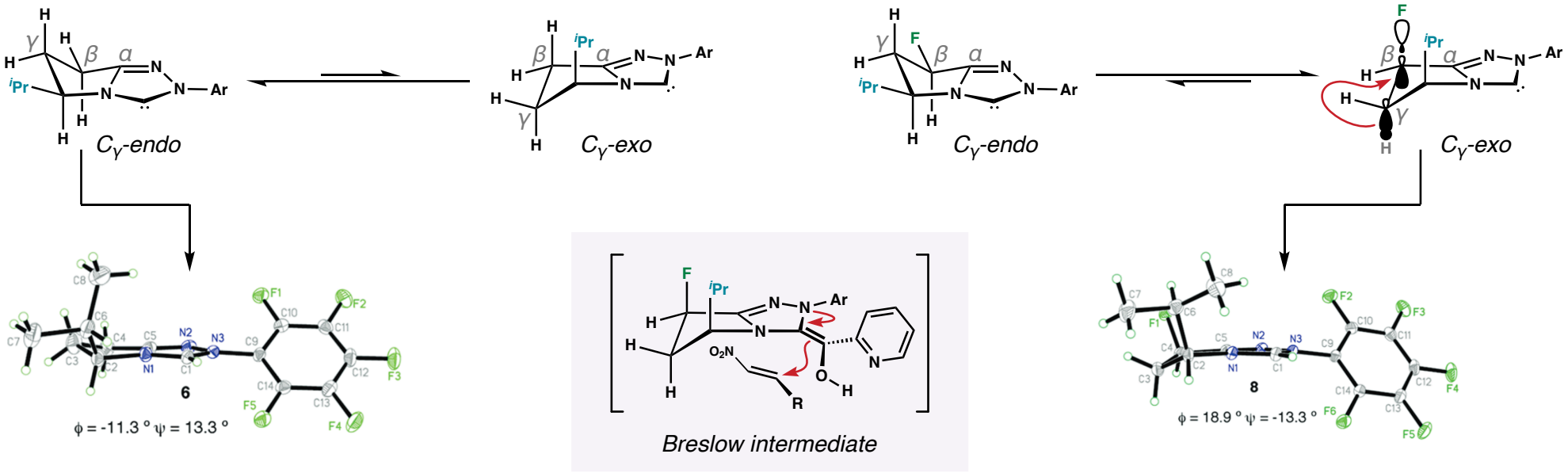




yield	90%	22%	95%
ee	88%	88%	95%

DiRocco, D. A.; Oberg, K. M.; Dalton, D. M.; Rovis, T. *J. Am. Chem. Soc.* **2009,** *131,* 10872
Aufiero, M.; Gilmour, R. *Acc. Chem. Rev.* **2018,** *51,* 1701

NHC: Stetter Reaction



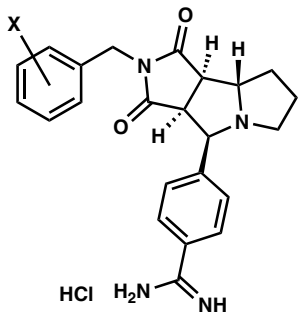
Determined by X-Ray

*Fluoro-NHC favors **C_γ-exo conformer** leading to improved ee*

DiRocco, D. A.; Oberg, K. M.; Dalton, D. M.; Rovis, T. *J. Am. Chem. Soc.* **2009,** *131,* 10872
Aufiero, M.; Gilmour, R. *Acc. Chem. Rev.* **2018,** *51,* 1701

Fluorinated Thrombin Inhibitors

Thrombin inhibitor

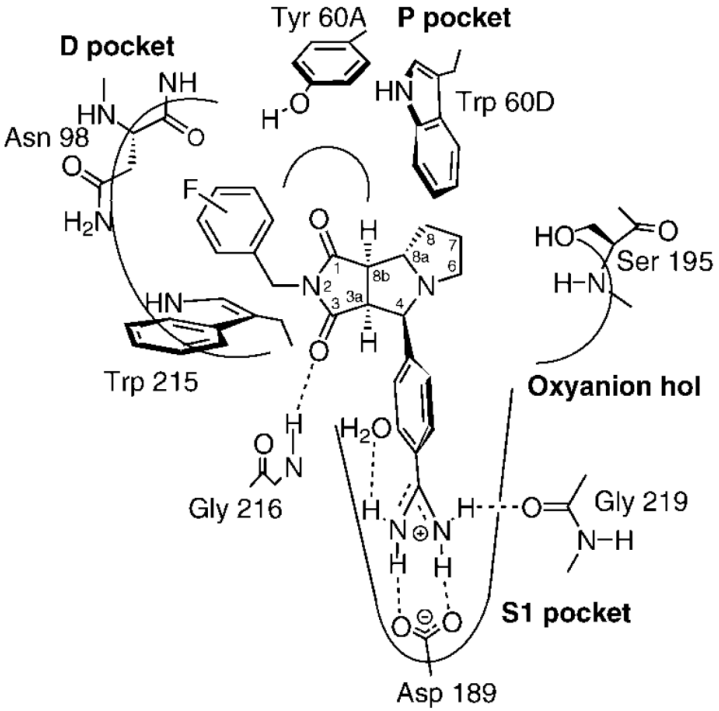


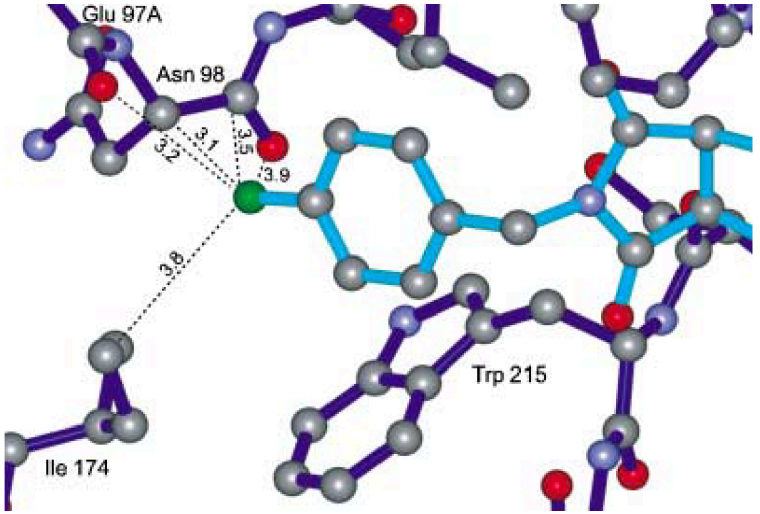
** = (K_i[trypsin]/K_i[thrombin])

X	K_i (μM)	Selectivity vs trypsin**
H	0.31	15
2-F	0.50	9.8
3-F	0.36	26
4-F	**0.057**	**67**
2,6-F_2	0.61	9.0
3,5-F_2	0.59	25
F_5	0.27	44

Olsen, J. A.; *et al. Angew. Chem. Int. Ed.* **2003,** *42,* 2507
Müller, K.; Faeh. C.; Diederich, F. *Science* **2007,** *317,* 1881
Hagmann, W. K. *J. Med. Chem.* **2008,** *51,* 4359

Fluorinated Thrombin Inhibitors





X-ray

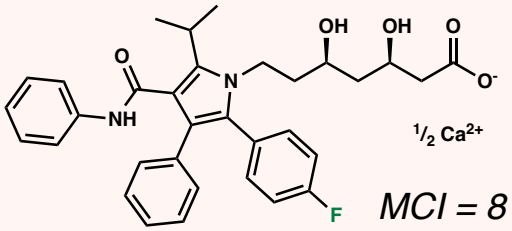
*4-fluorosubstituent significantly enhances binding of the inhibitor to **Asn 98***

C=O backbone binding through dipole interactions (3.5 Å)
α-CH hydrogen bonding (2.1 Å)

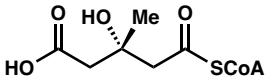
Olsen, J. A.; *et al. Angew. Chem. Int. Ed.* **2003,** *42,* 2507
Müller, K.; Faeh. C.; Diederich, F. *Science* **2007,** *317,* 1881
Hagmann, W. K. *J. Med. Chem.* **2008,** *51,* 4359

Atorvastatin: HMGR Inhibitor

Atorvastatin

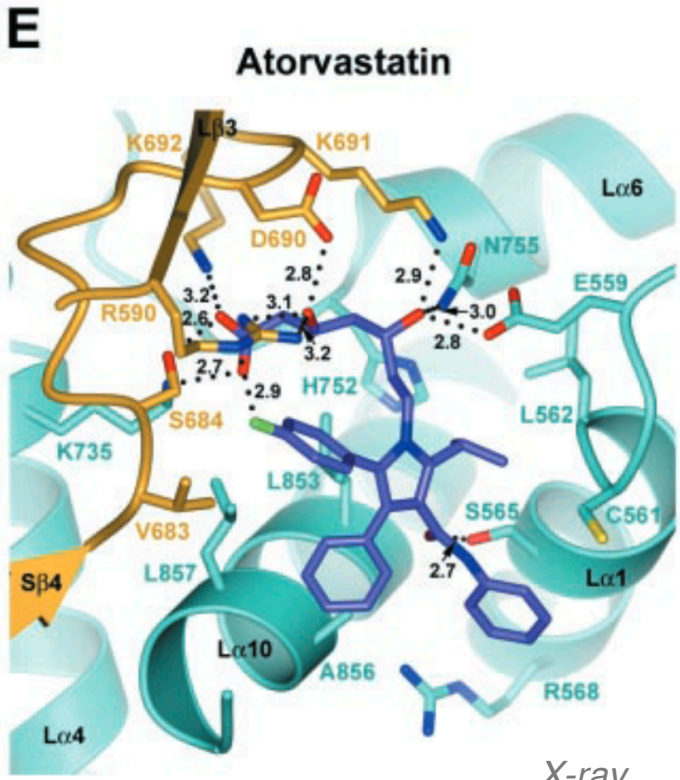


MCI = 8 nM



HMG-CoA

- *Inhibits HMGR (HMG-CoA reductase), prevents cholesterol synthesis*
- *Potency superior to –OH (2x), –OMe (10x), & –H (5x)*
- *Interacts with Arg^{590} guanidinium sidechain (2.9 Å)*

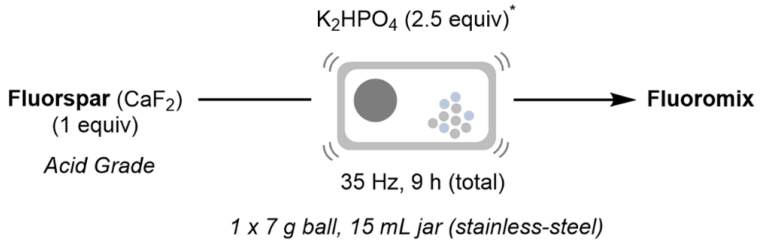


X-ray

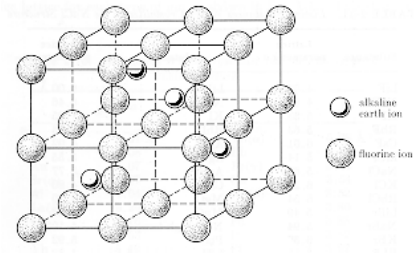
Istvan, E. S.; Deisenhofer, J. *Science* **2001,** *292,* 1160
Roth, B. D.; *et al. J. Med. Chem.* **1990,** *33,* 21
Müller, K.; Faeh. C.; Diederich, F. *Science* **2007,** *317,* 1881

Fluorspar Directly to Organofluorides

$CaF_2 + K_2HPO_4 \rightarrow [CaHPO_4 + 2\,KF]$

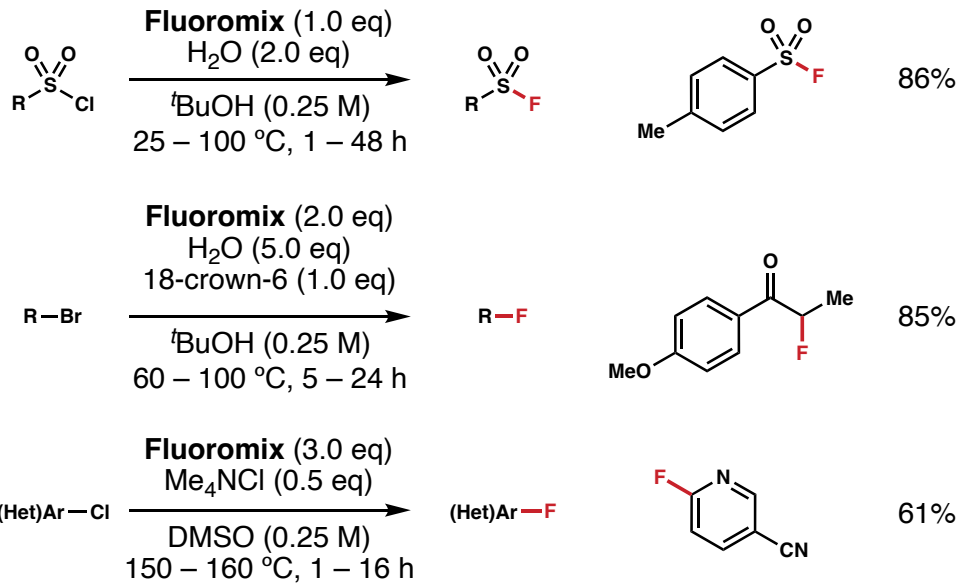


- *Form calcium phosphate salt*
  → *higher lattice energy, thermodynamically driven*
- *$Ca_3(PO_4)_2$ ΔU_L = 3534 kJ • mol^{-1}*



High lattice energy
ΔU_L = 2640 kJ • mol^{-1}

Selected examples



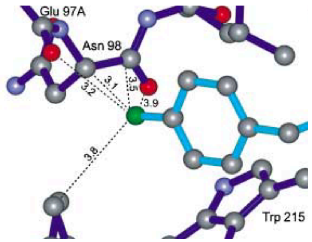
Patel, C.; *et al. Science* **2023,** *381,* 302

Summary

Forms the strongest bond to carbon
Bond enthalpy: 485 kJ • mol^{-1}

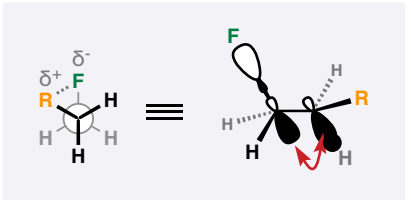
Most electronegative element
$\chi = 3.98$

Useful properties in medicinal chemistry via electrostatic interactions

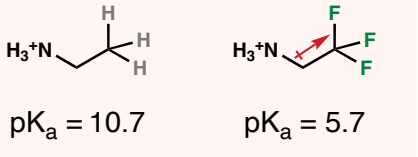


9
$^2P^\circ_{3/2}$
F
Fluorine
18.998403162(5)
$1s^2 2s^2 2p^5$
17.4228

Through-space:
low-lying σ^*_{C-F} bond gives rise to the *gauche* effect



Through-bond:
withdrawing nature of F significantly alters substrate reactivity & acidity



$pK_a = 10.7$ $pK_a = 5.7$

Supplementary Material

Physical Properties: Covalent Radius

Covalent radius (pm)

X = N	X = O		X = F		X = Cl	X = Br	X = I
70	66	>	64	<	99	114	133

period 2

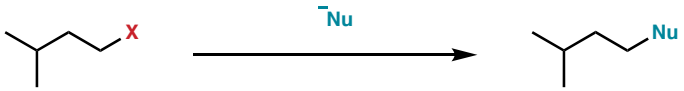
group 7

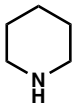
**Single bond, tetrahedral (CN = 4) structure

Dean, J. A. *Lange's Handbook of Chemistry (15th ed.);* New York: McGraw-Hill, 1999 (section 4.35)

Fluoride as Leaving Group

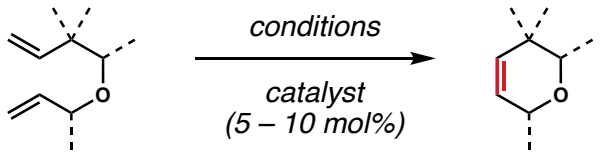
Relative rates at 18 ºC



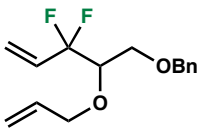
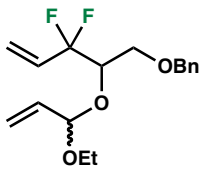
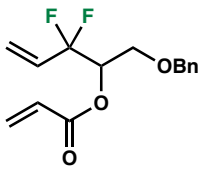
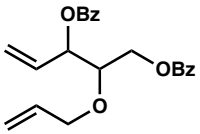
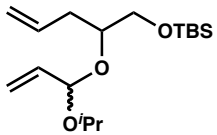
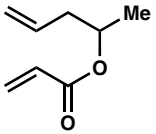
Nu =	X = F	X = Cl	X = Br	X = I
	1	68.5	17800	50500
NaO—Me	1	71	3500	4500

O'Hagan, D. *Chem. Soc. Rev.* **2008,** *37,* 308
Chambers, R. D. *Fluorine in Organic Chemistry;* Blackwell Publishing Ltd., Oxford, 2006 (p. 129)

Olefin Metathesis



- *Yields decrease with increased oxidation state*
- *Effect accentuated in the gem-difluoro species*

**Bibliographic data*						
Yield (%)	97	68	0	90	88	81
Time (h)	24	72	168	1	2	not reported
Temperature (°C)	RT	40	40	40	40	40

Percy, J. M.; Pintat, S. *Chem. Comm.* **2000,** 607
Audouard, C.; Fawcett, J.; Griffiths, G. A.; Percy, J. M.; Pintat, S.; Smith, C. A. *Org. Biomol. Chem.* **2004,** 528
Fustero, S.; Simón-Fuentes, A.; Barrio, P.; Haufe, G. *Chem. Rev.* **2015,** *115,* 871