

Organofluorine Chemistry & Prof. Dr. Jinbo Hu Research



Presentation Plan

- *Introducing **Fluorine & Fluoroorganic Compounds***
- *Methods for the **Synthesis** of Complex **Organofluorine Compounds***
- ***Jinbo Hu's Contribution** to the Field:*
 - > *development of new fluorinating reagents and methods*
 - > *study and understanding of the fluorine effect in organic chemistry*

Fluorine on Earth

- Main natural sources of fluorine:



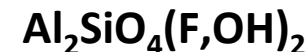
Fluorspar (or Fluorite)



Cryolite



Fluorapatite



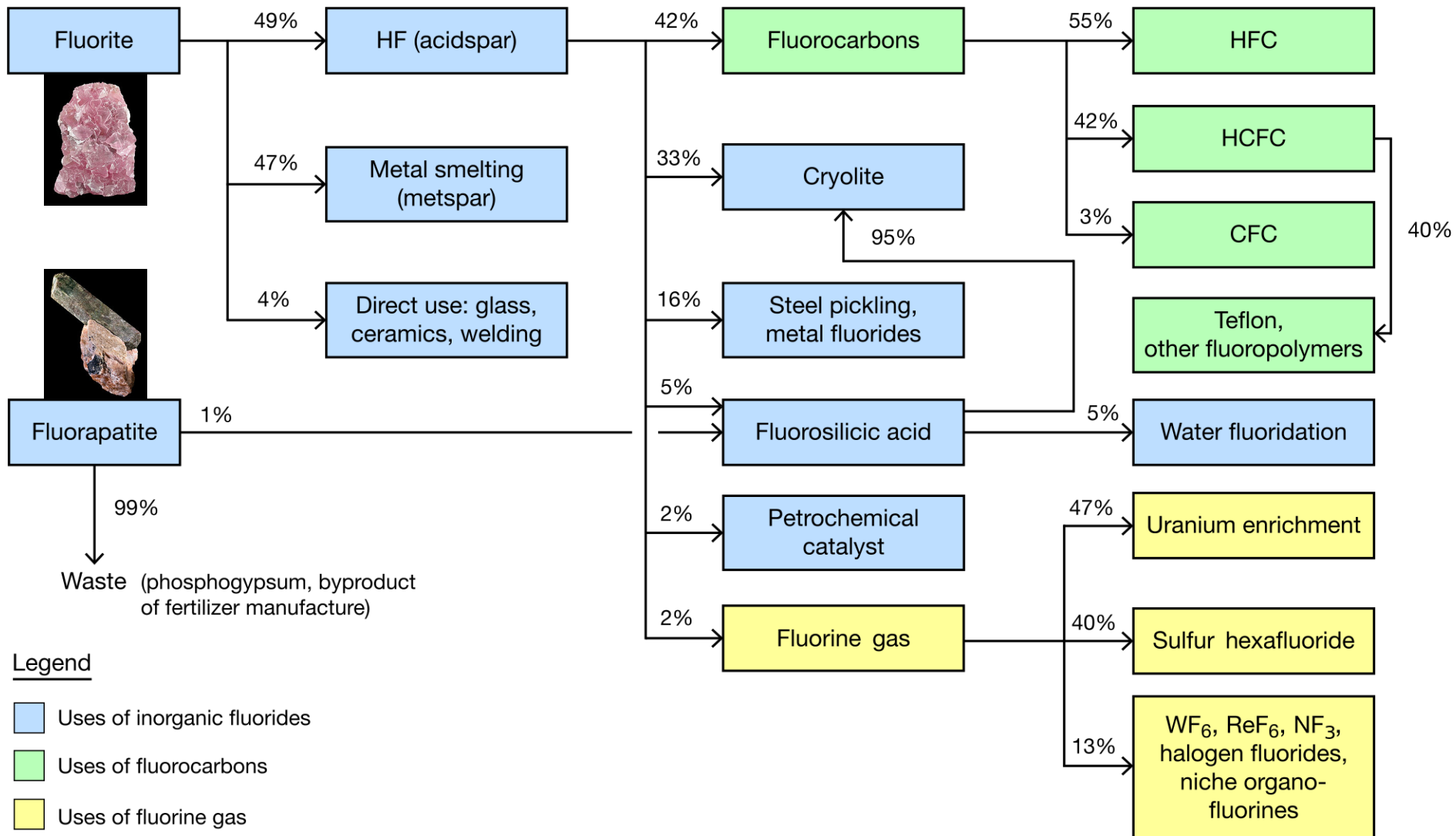
Topaz

- Main industrial uses of fluorine:

HF: from CaF_2 & $\text{Ca}_5(\text{PO}_4)_3\text{F}$

F₂: electrolysis HF-KF

Fluorine on Earth



Fluorocarbons as Natural Products

➤ ¹⁹F, the most abundant halogen (13th element) in earth's crust but:

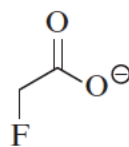
> ca. **3650** naturally occurring **organohalogen compounds**

> **Organochlorines**: 2150

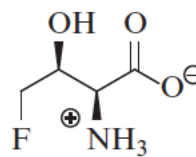
> **Organobromines**: 1850

> **Organoiodines**: 95

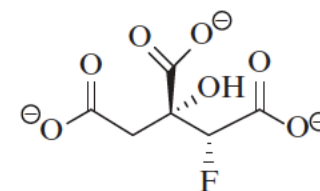
> **Organofluorines**: ca. **30**



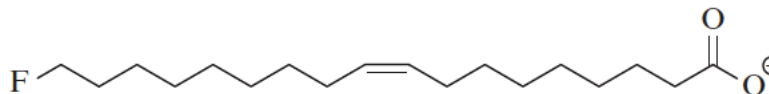
Fluoroacetate



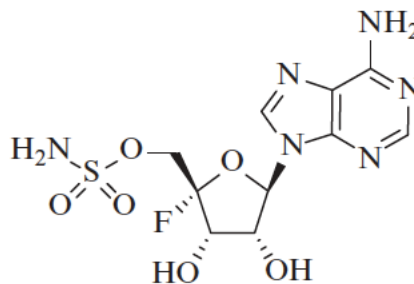
4-Fluoro-L-threonine



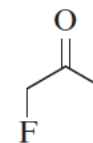
(2*R*,3*R*)-2-Fluorocitrate



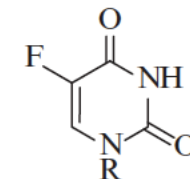
ω -Fluorooleic acid



Nucleocidin



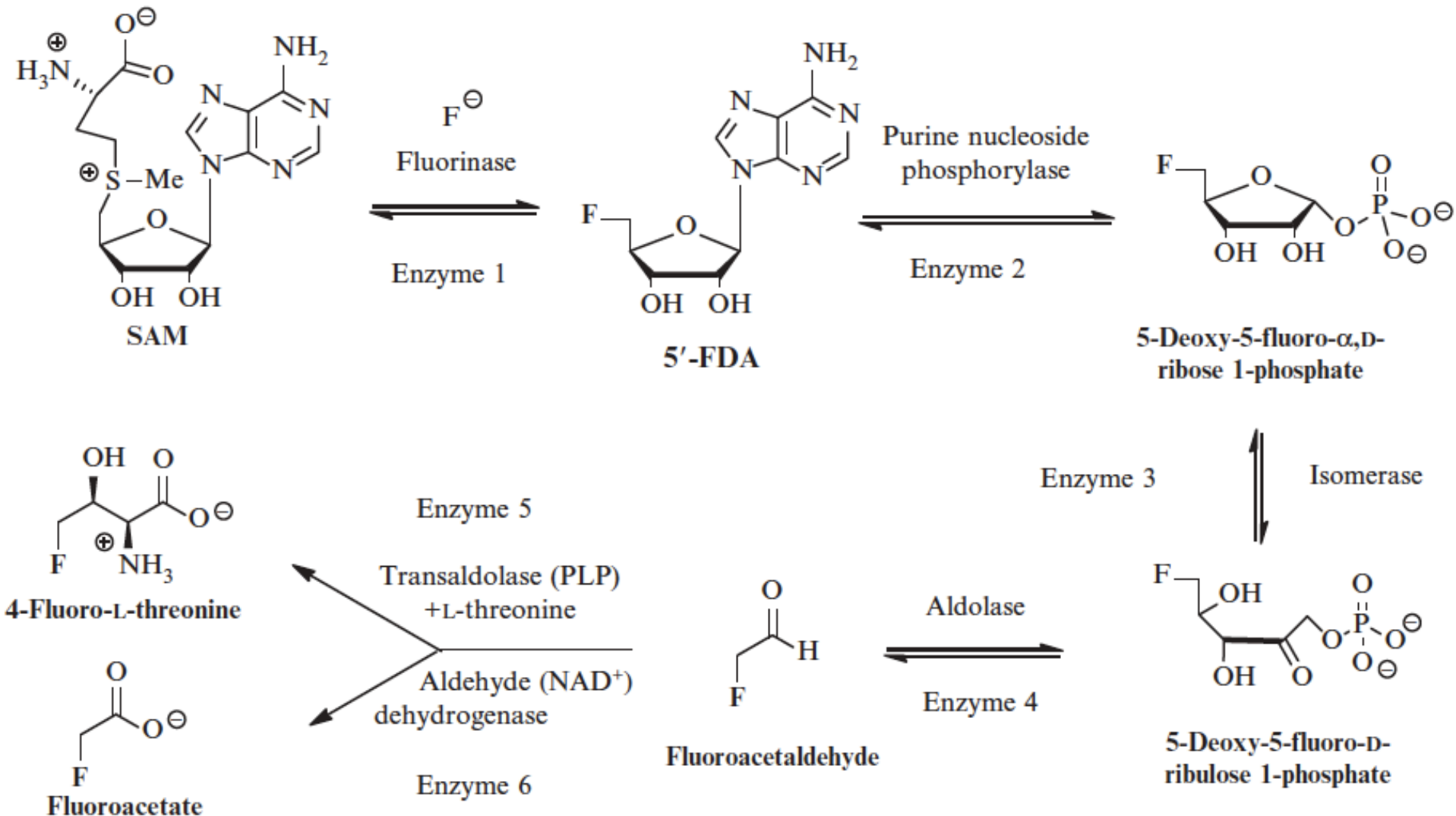
Fluoroacetone



5-Fluorouracils

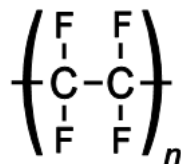
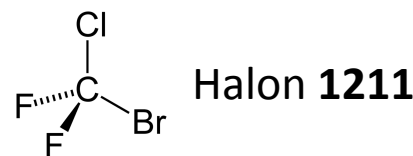
Most probably misidentified
fluorinated natural products

Biosynthesis of Fluorocarbons


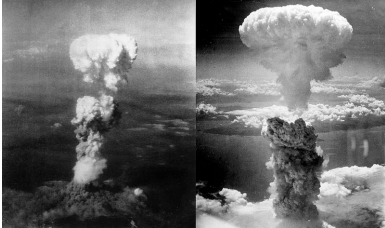
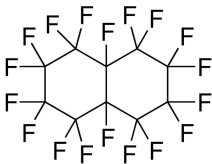


Historic Landmarks

Time	Key Event
1764	First synthesis of hydrofluoric acid from fluorspar and sulfuric acid by A. S. Marggraf, repeated in 1771 by C. Scheele
1886	First synthesis of elemental fluorine by H. Moissan (Nobel Prize in 1906) by electrolysis of an HF–KF system
1930s	Refrigerants (“Freon”, in Germany “Frigen”), fire extinguishing chemicals (“Halon”), aerosol propellants
1940s	Polymers (PTFE = “Teflon”), electrochemical fluorination (H. Simons)

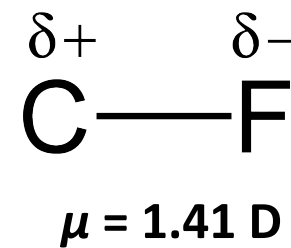
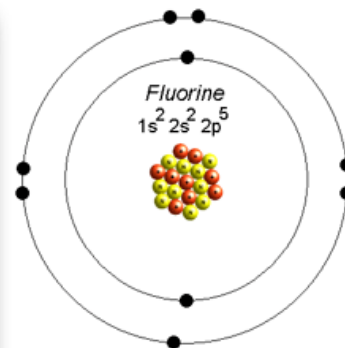
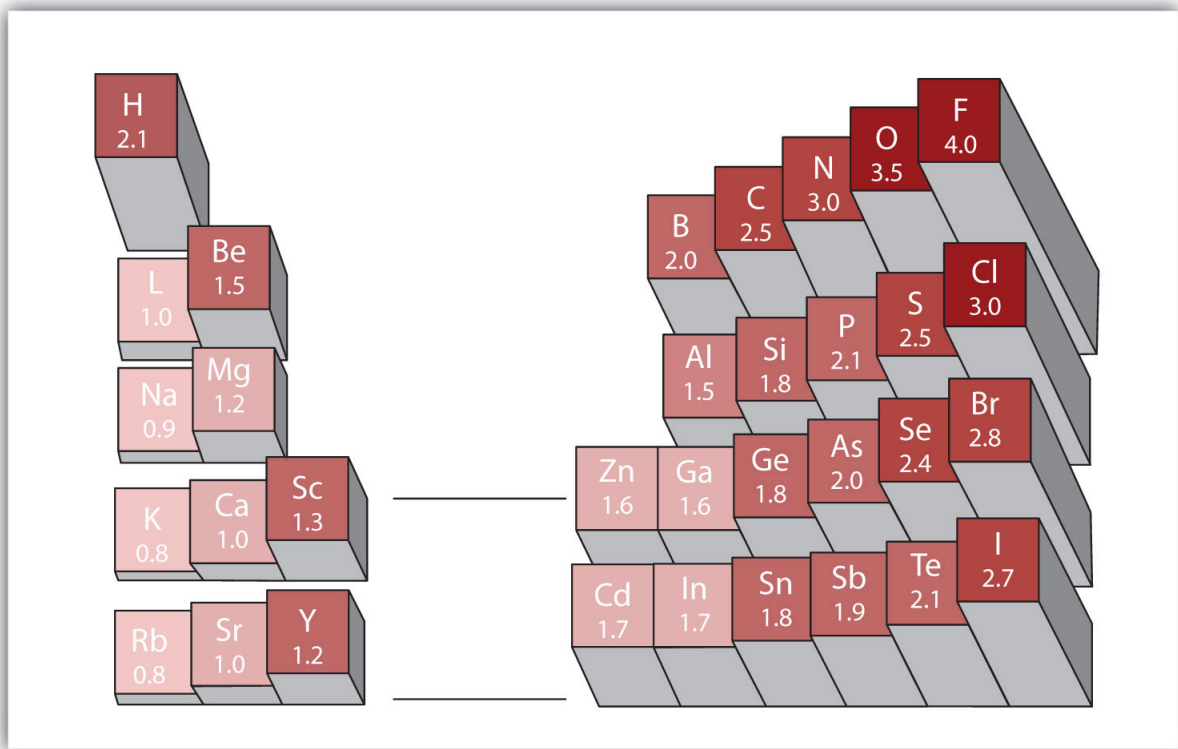


Historic Landmarks

Time	Key Event
1941–1954	Manhattan Project: highly resistant materials for isotope separation plants, lubricants for gas centrifuges, coolants  
1950s	Fluoropharmaceuticals, agrochemicals, artificial blood substitutes, respiratory fluids, chemical weapons  Fluosol, 49mL O ₂ /100 mL
1987	The Montreal Protocol initiates the phasing-out of CFC
1990s	Fluorinated liquid crystals for active matrix liquid crystal displays (AM-LCD)

Unique Properties of Fluorocarbons

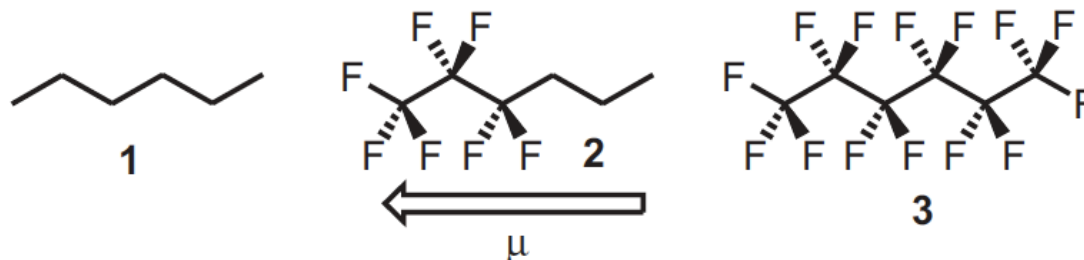
- Linked to the properties of fluorine: high(est) electronegativity



X	H	F	Cl	Br	I	C
Electronegativity	2.20	3.98	3.16	2.96	2.66	2.55
Dipole moment, μ , C-X	(0.4)	1.41	1.46	1.38	1.19	—

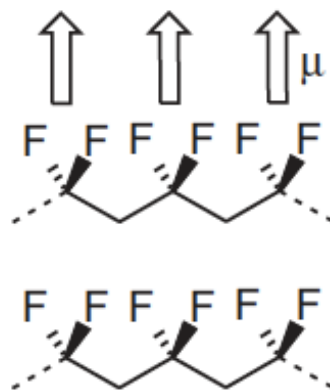
Unique Properties of Perfluorocarbons

➤ Physicochemical properties:

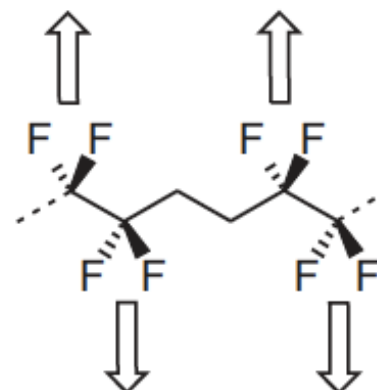


Property	1	2	3
b. p. (°C)	69	64	57
γ^{25} (dyn cm ⁻¹)	17.9	14.3	11.4
ϵ	1.89	5.99	1.69

poly(vinylidene
difluoride)
PVDF



poly(ethylene-co-
tetrafluoroethylene)
ETFE

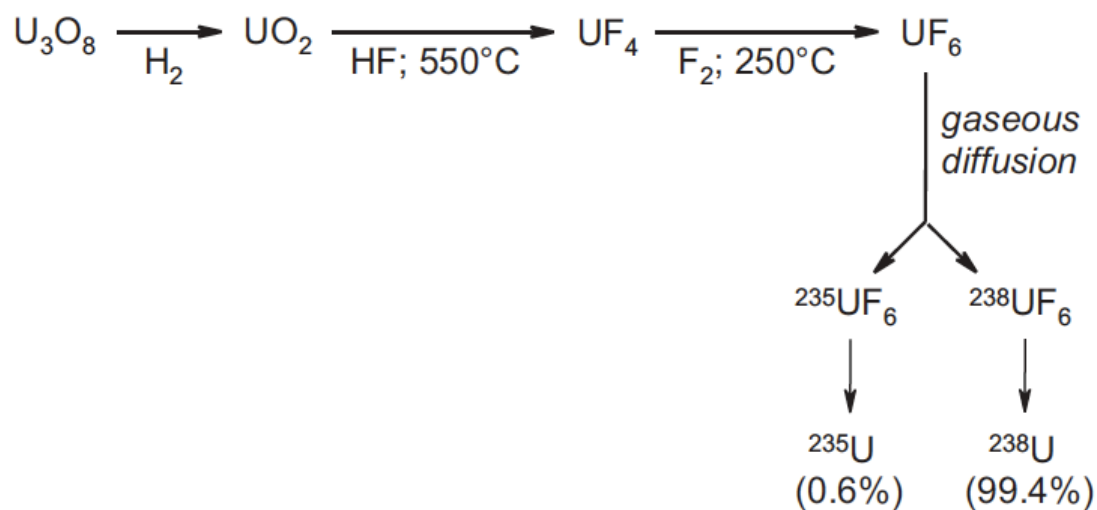
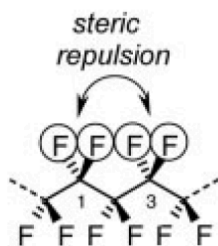
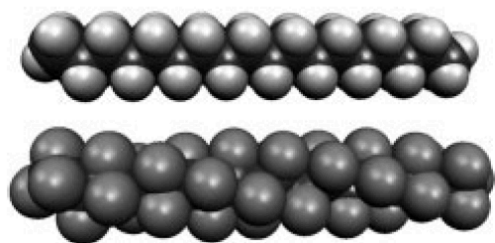


Unique Properties of Perfluorocarbons

➤ Characteristics of the carbon-halogens & carbon-carbon bonds:

> C–F bond is extremely stable

X	H	F	Cl	Br	I	C
Bond length C–X (pm)	109	138	177	194	213	–
Binding energy C–X (kcal/mol)	98.0	115.7	77.2	64.3	50.7	~83
Van der Waals radius (pm)	120	147	175	185	198	–



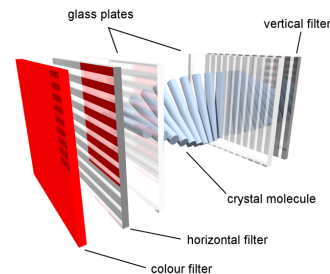
Properties of Fluorocarbons: Summary

➤ Properties:

> (bio)chemical inertness, hydrophobicity, non-flammability, low friction coefficient, ...

➤ Applications:

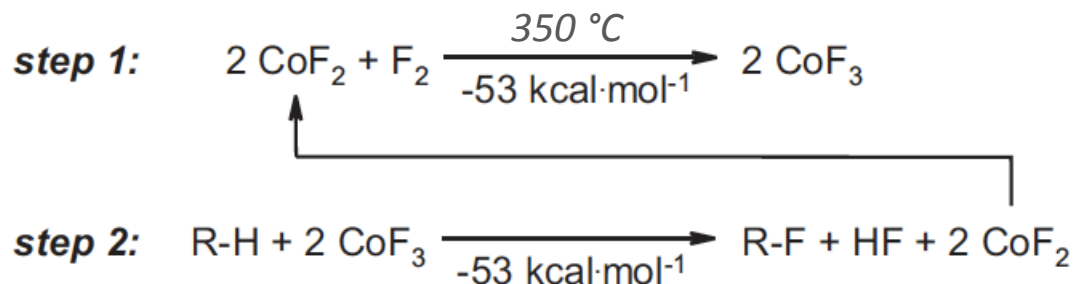
> Lubricants, Electronics, Materials, Biomedical, ...



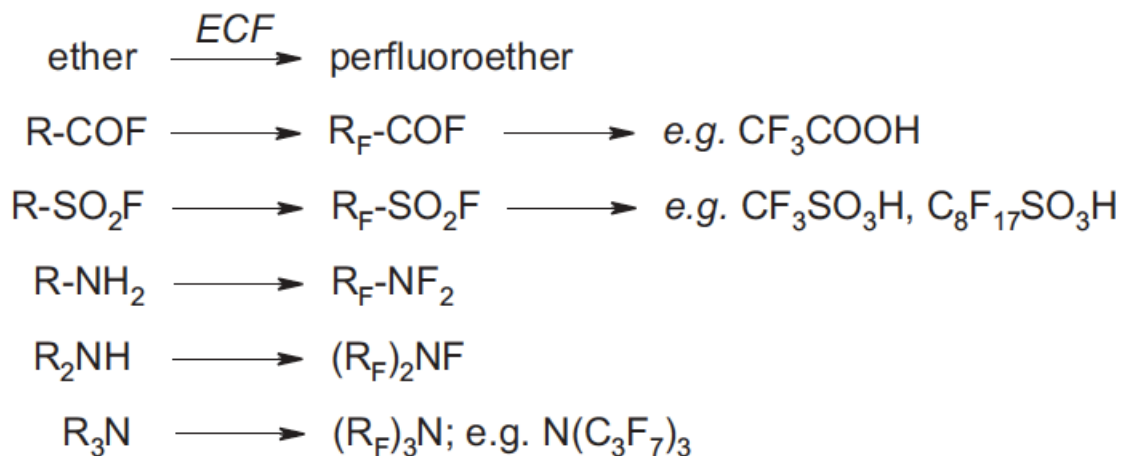
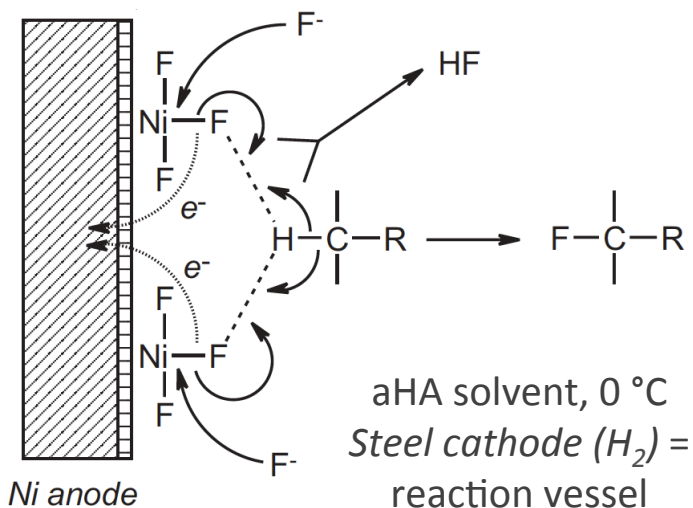
Direct C–F Bonds Formation

➤ Mostly using fluorine gas F_2 or anhydrous hydrofluoric acid **aHA** (bp 20 °C)

> the “**Flutec**” process



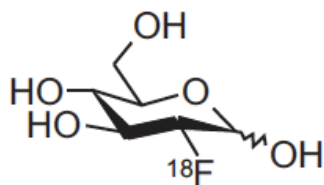
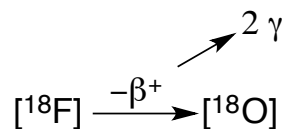
> the **Simons electrochemical fluorination (ECF)** process



Complex Organofluorine Compounds

➤ Mainly in *rational drug design*:

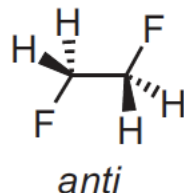
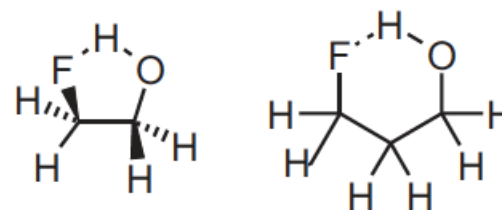
- > Generally increased lipophilicity
- > Hydrogen bonding (¹⁹F = HBA)
- > Stereoelectronic effects
- > Metabolic stabilisation
- > ¹⁸F labelling



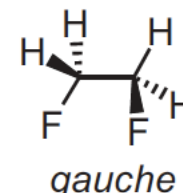
[¹⁸F]FDG: *glucose metabolism*
(*oncology, cardiology, brain*)

$t_{1/2} = 120 \text{ min}$

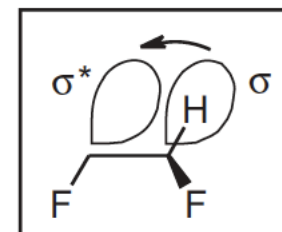
$\pm 2 \text{ kcal/mol}$



anti



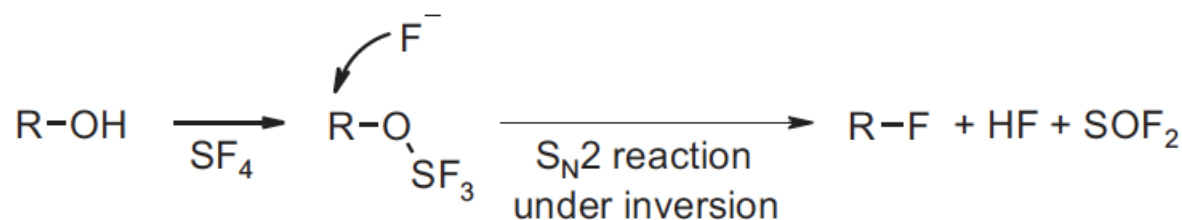
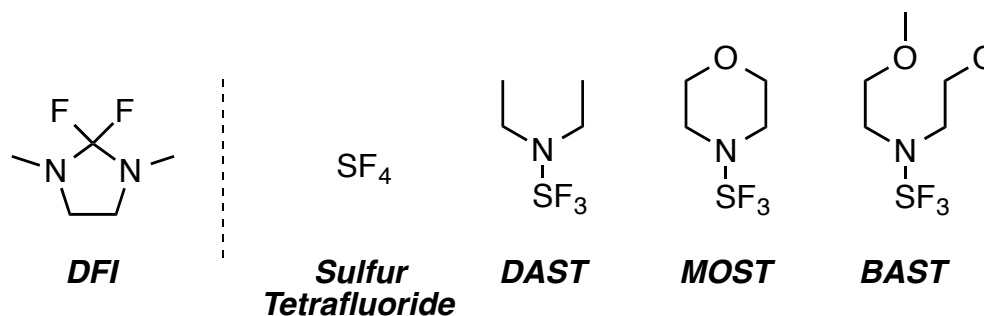
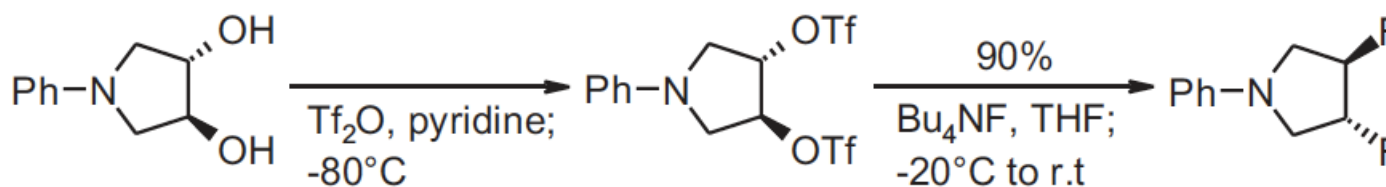
gauche



C-F Bonds Formation

➤ Nucleophilic fluorination

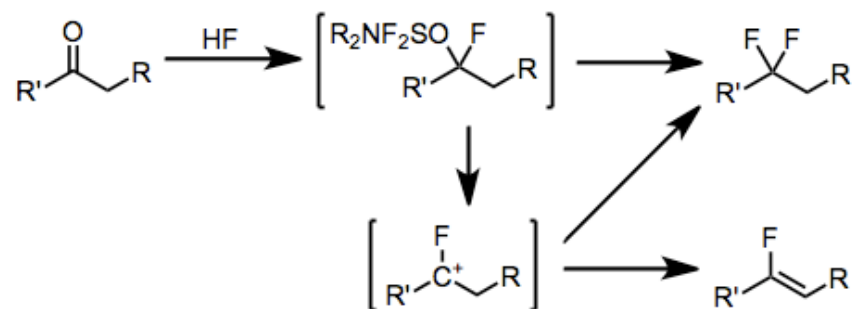
> Hydroxyl group displacement



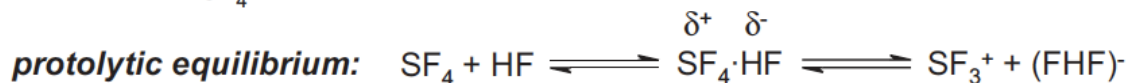
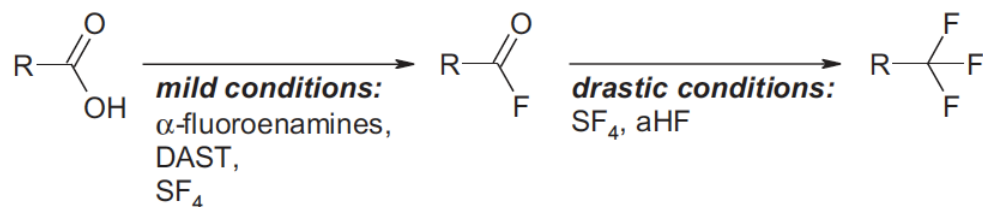
Direct C–F Bonds Formation

➤ Nucleophilic fluorination

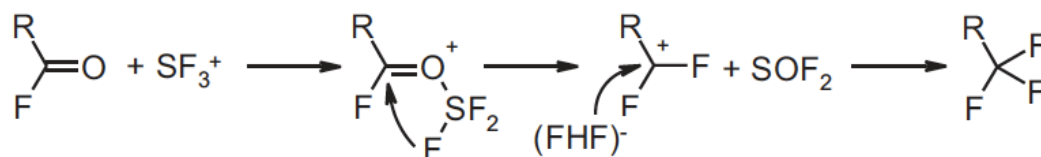
> Carbonyls into gem-Difluoromethylene



> Carboxyl into Trifluoromethyl



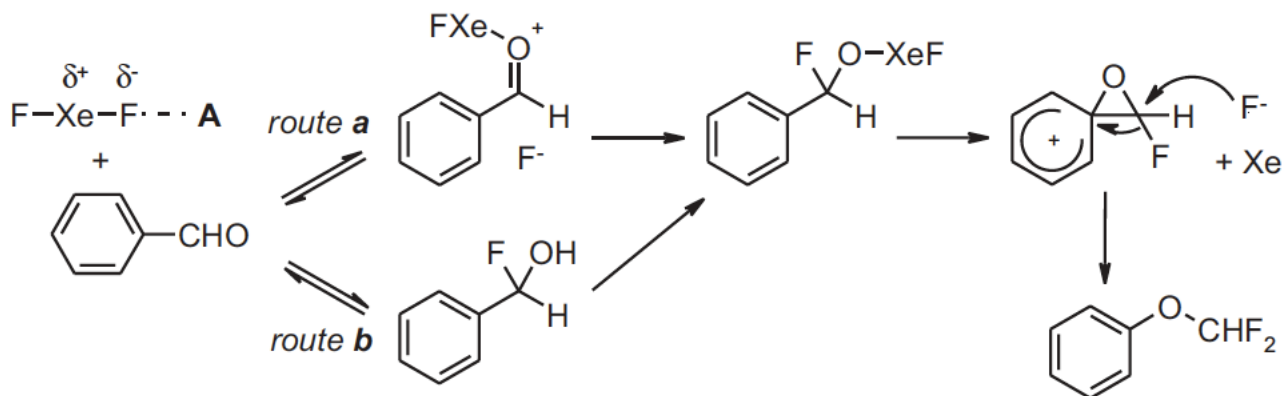
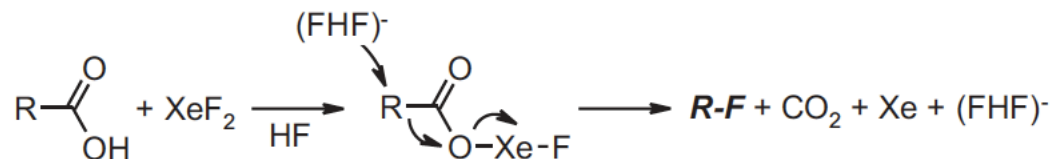
fluorination:



Direct C–F Bonds Formation

➤ Nucleophilic fluorination

> Xenon difluoride

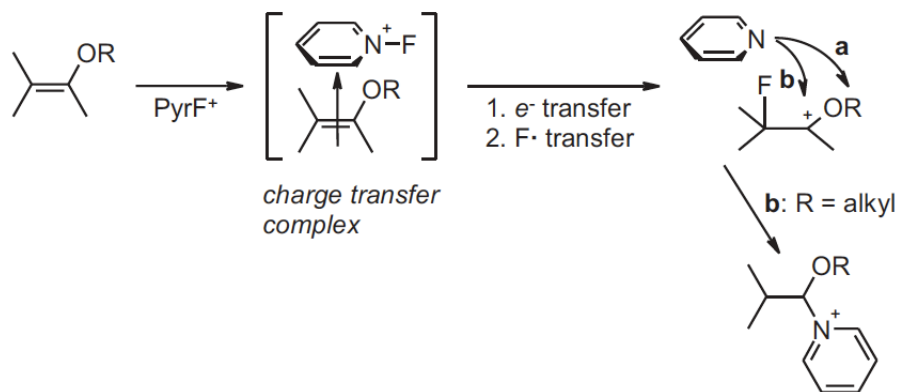
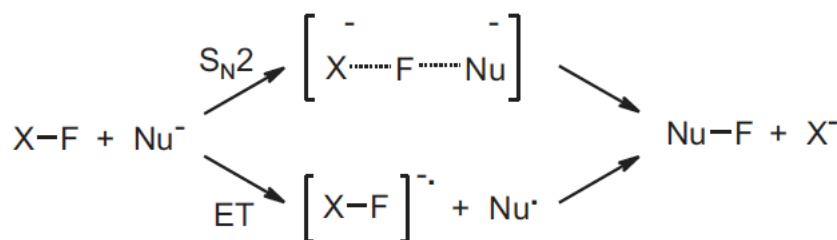
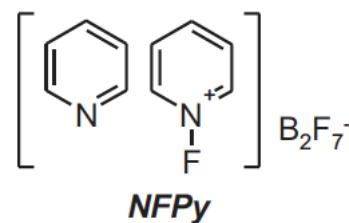
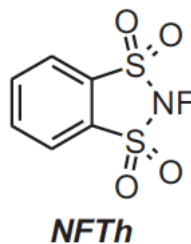
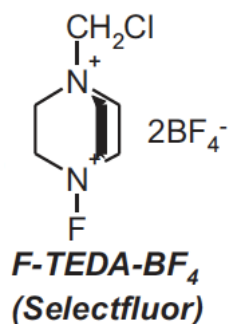


A: cat. SiF₄

Direct C–F Bonds Formation

➤ Electrophilic fluorination

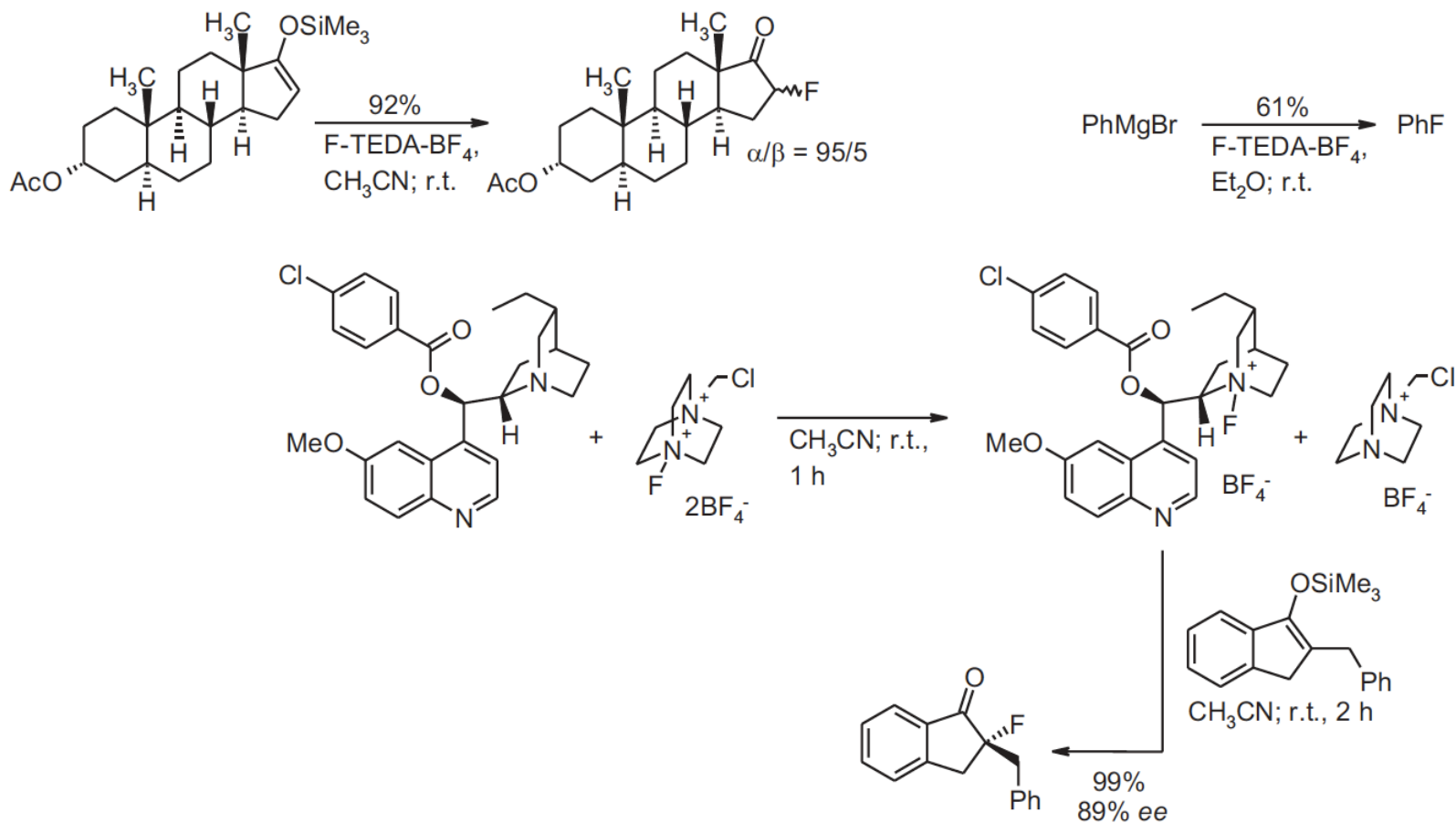
> “NF”-Reagents (from F₂/N₂)



Direct C–F Bonds Formation

➤ Electrophilic fluorination

> “NF”-Reagents, examples



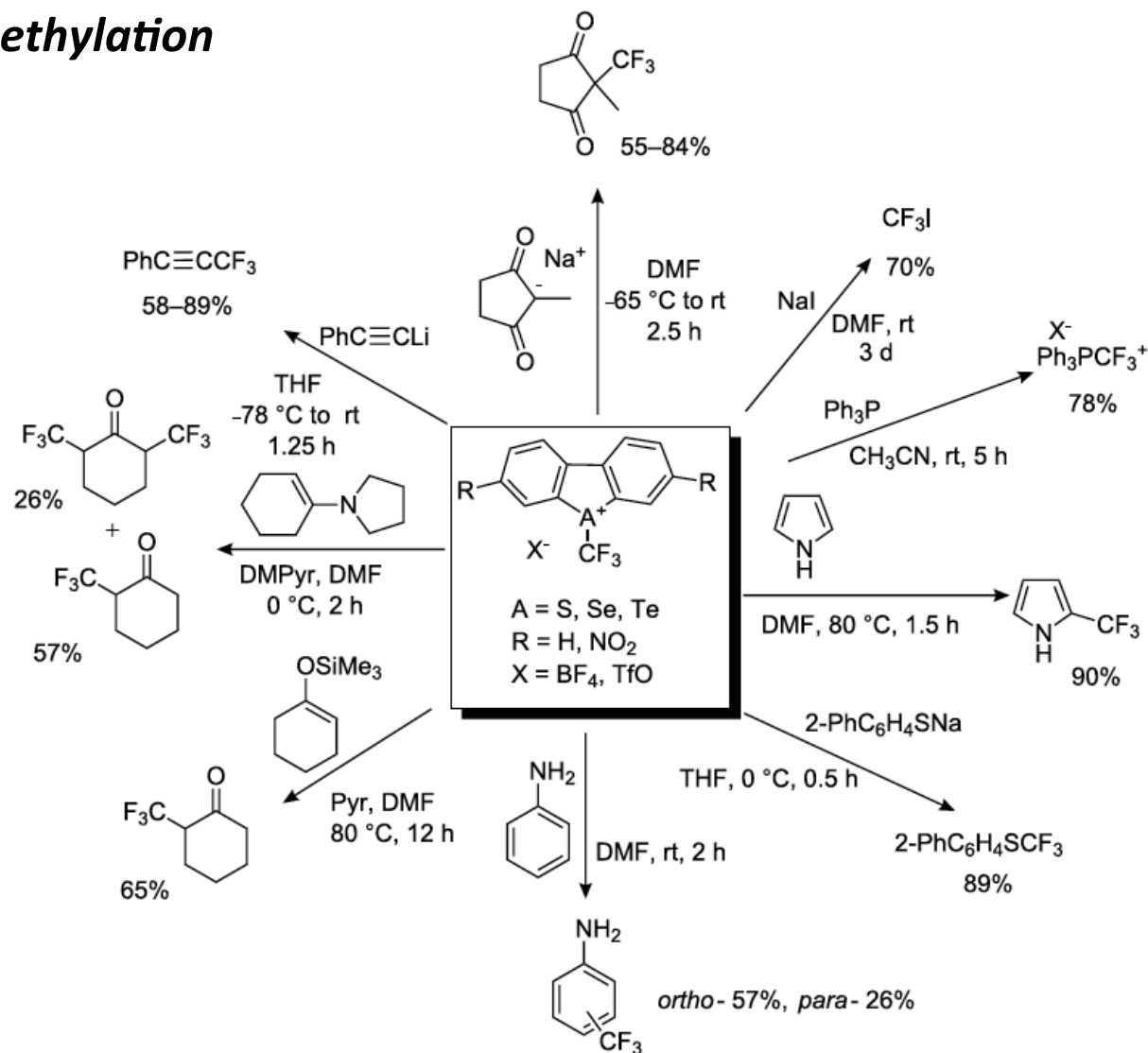
T. Umemoto, S. Fukami, G. Tomizawa, K. Harasawa, K. Kawada, K. Tomita, *J. Am. Chem. Soc.* **1990**, *112*, 8563–8575.

N. Shibata, E. Suzuki, Y. Takeuchi, *J. Am. Chem. Soc.* **2000**, *122*, 10728–10729.

Fluorinated Building Blocks

➤ Electrophilic trifluoromethylation

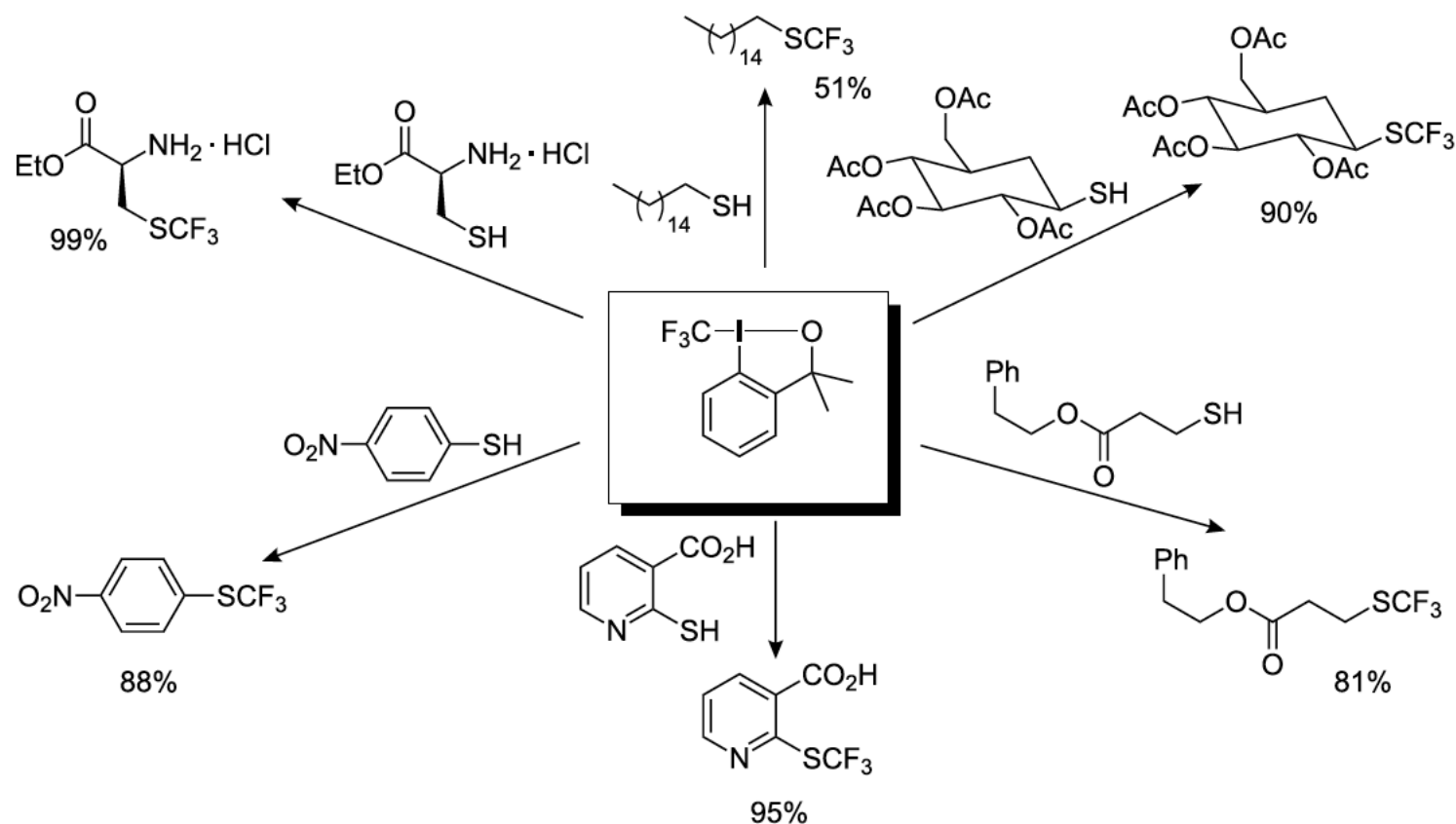
> Umemoto reagents



Fluorinated Building Blocks

➤ Electrophilic trifluoromethylation

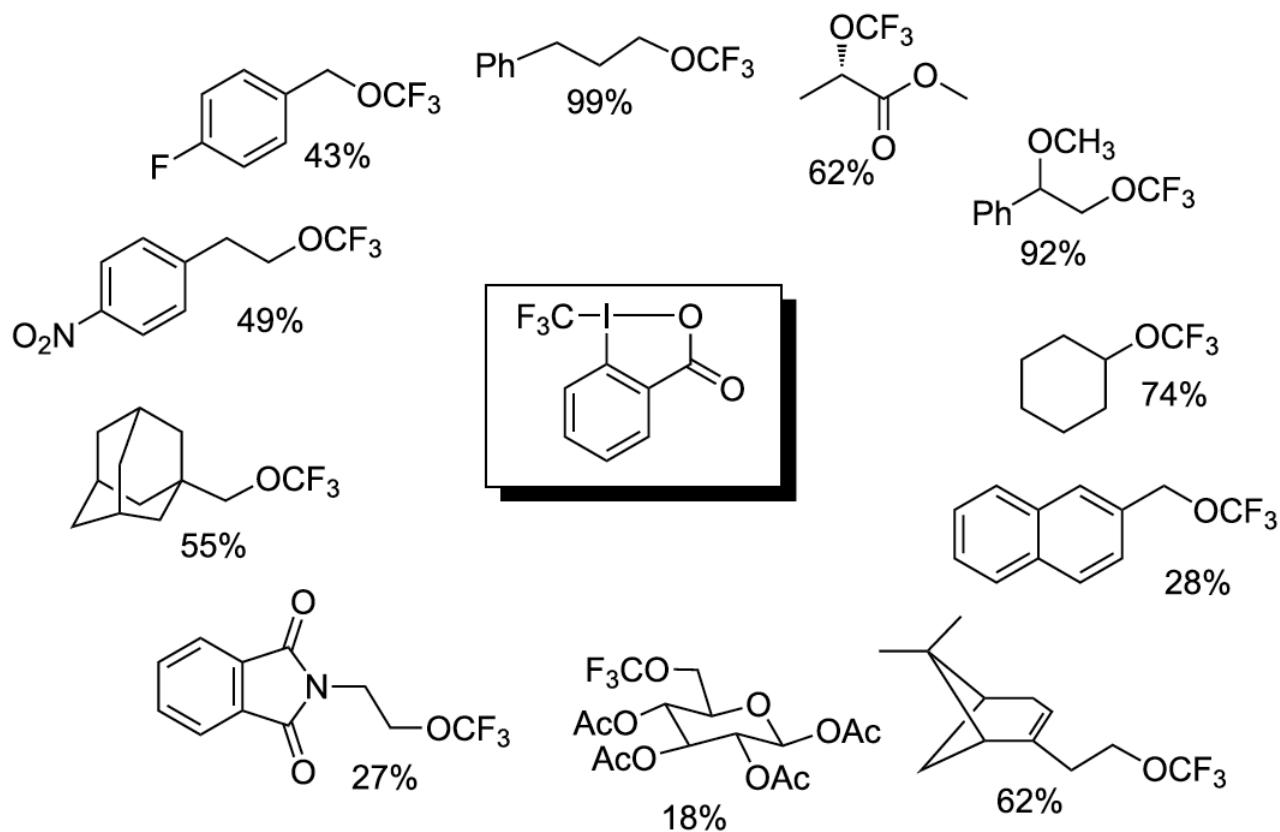
> Togni reagent



Fluorinated Building Blocks

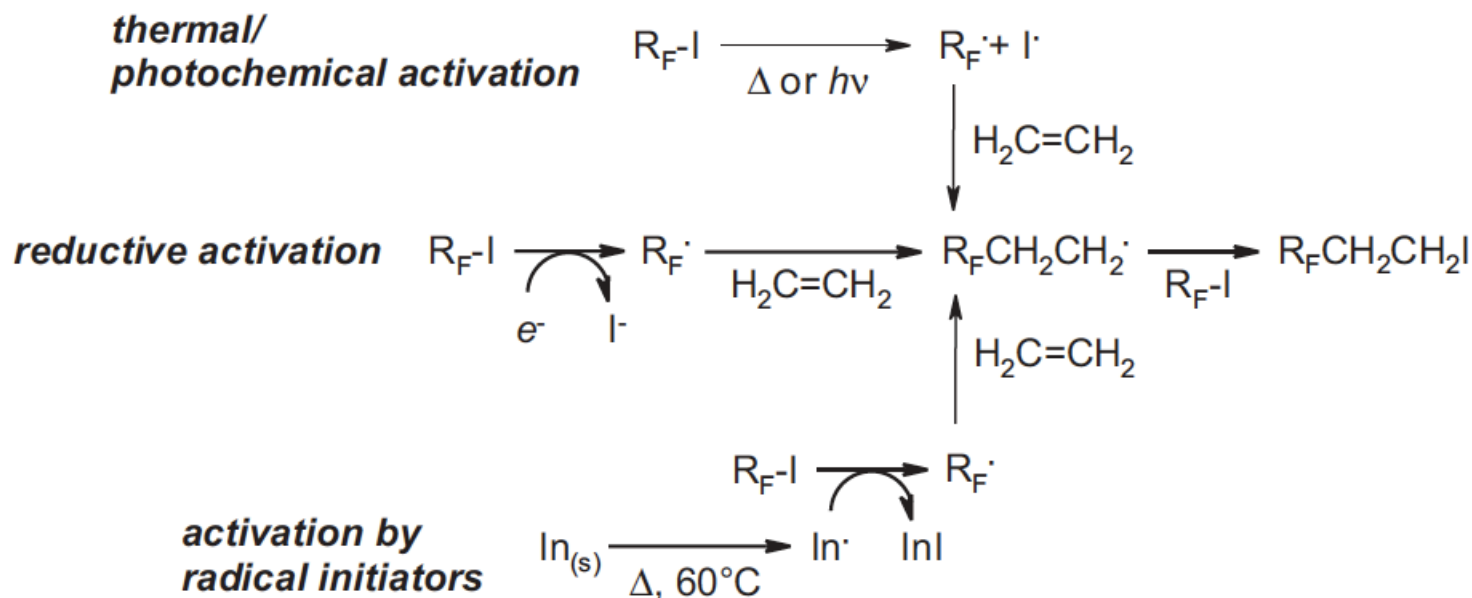
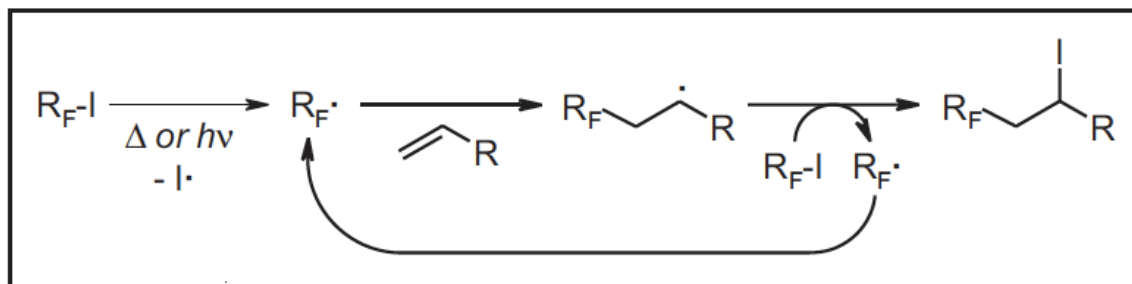
➤ Electrophilic trifluoromethylation

> Togni reagent & ZnX₂



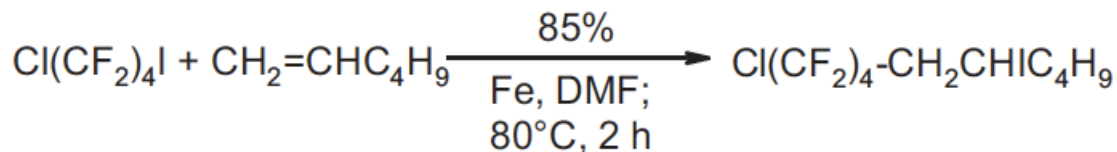
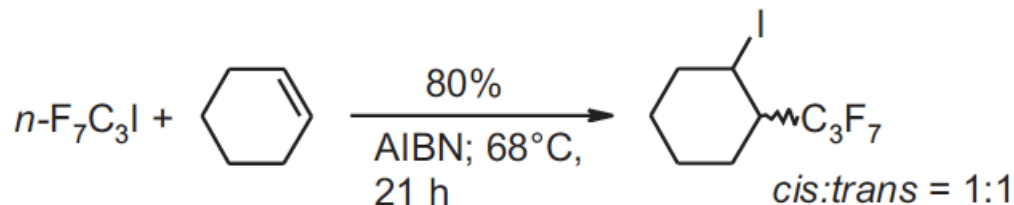
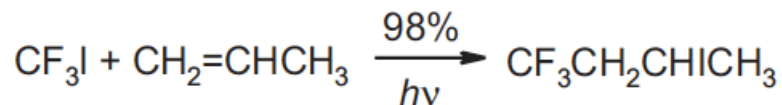
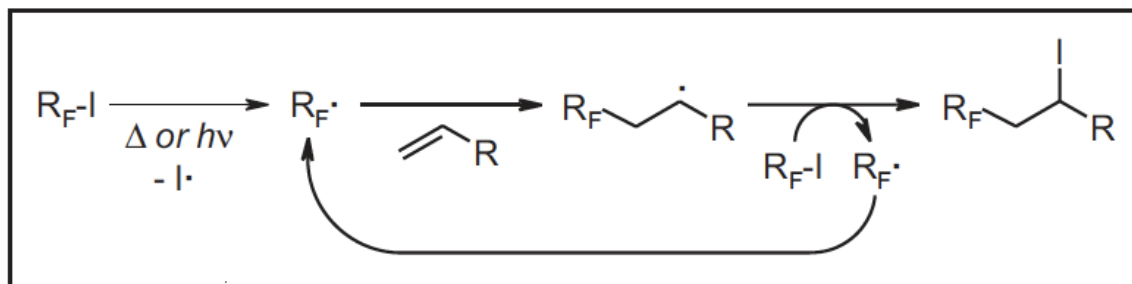
Fluorinated Building Blocks

➤ Radical processes



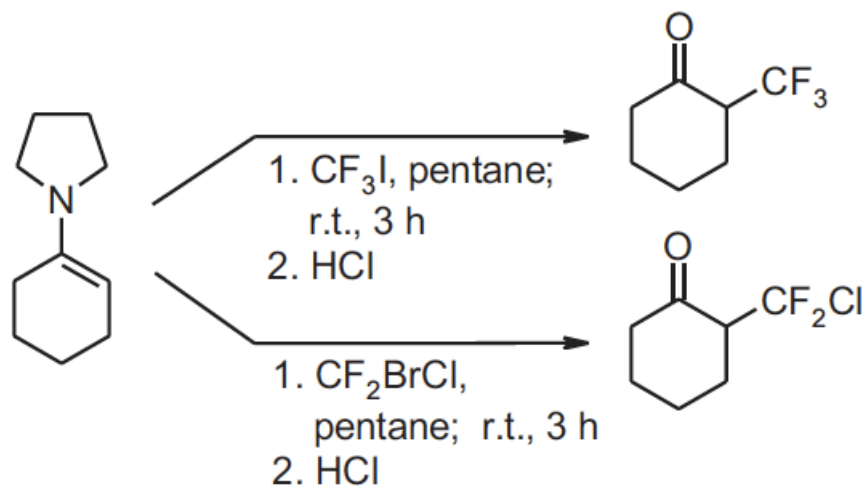
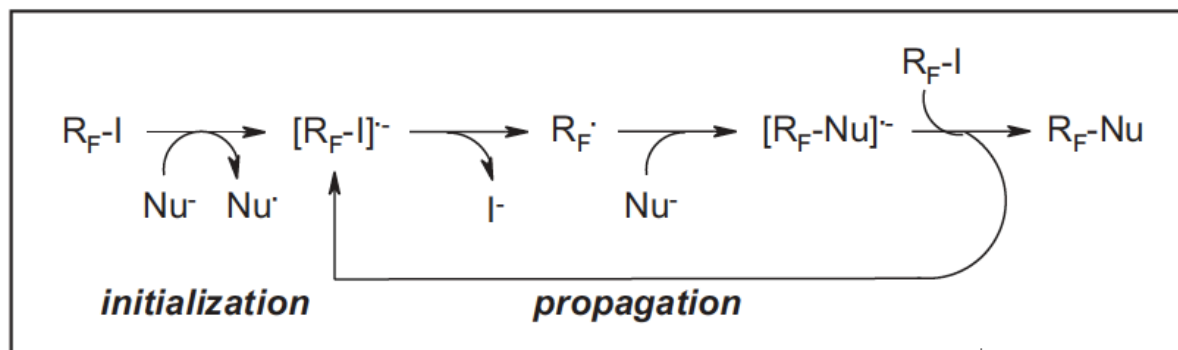
Fluorinated Building Blocks

➤ Radical processes



Fluorinated Building Blocks

➤ Radical processes



Fluorinated Building Blocks

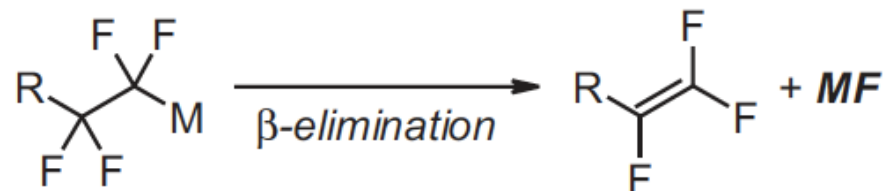
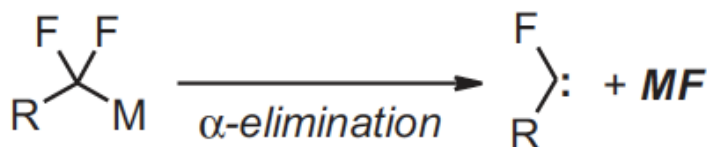
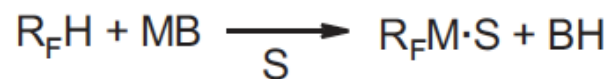
➤ Nucleophilic processes

> Fluorinated Carbanions: Metallic Compounds

metallodehalogenation



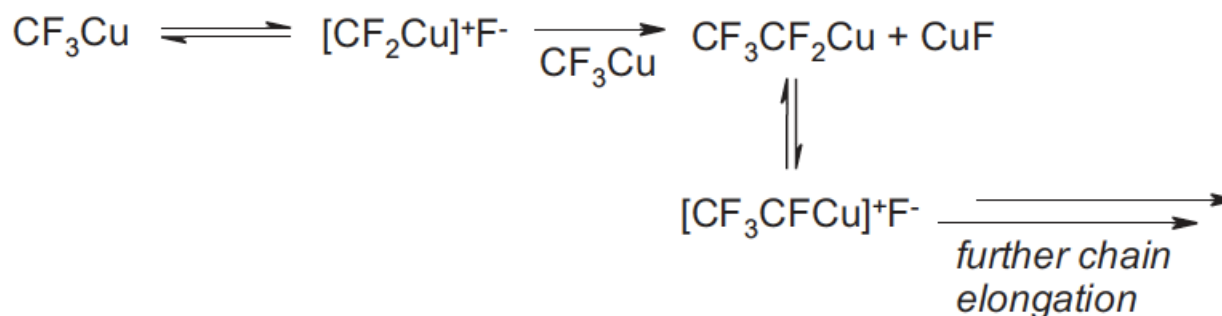
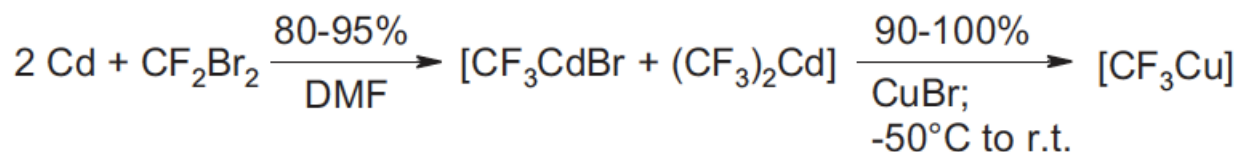
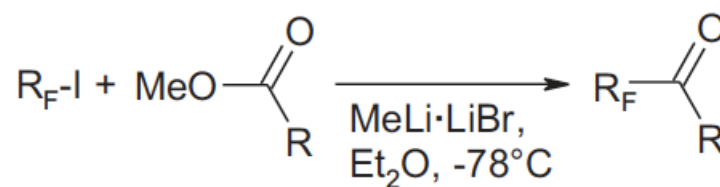
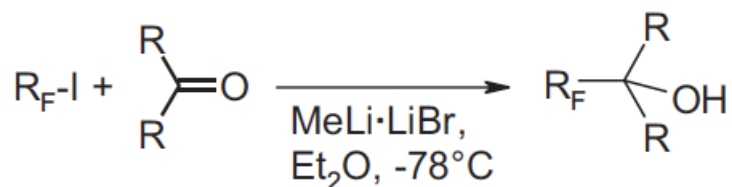
metallodeprotonation



Fluorinated Building Blocks

➤ Nucleophilic processes

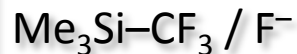
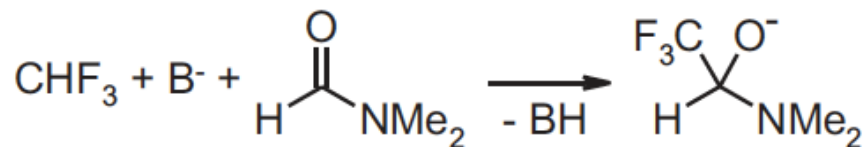
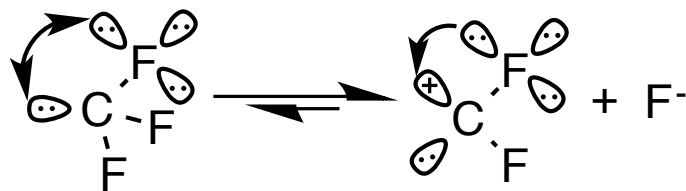
> Fluorinated Carbanions: Halogen-Metal Exchange & Transmetalation



Fluorinated Building Blocks

➤ Nucleophilic processes

> Fluorinated Carbanions: Deprotonation

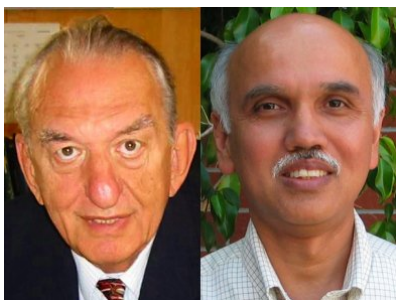
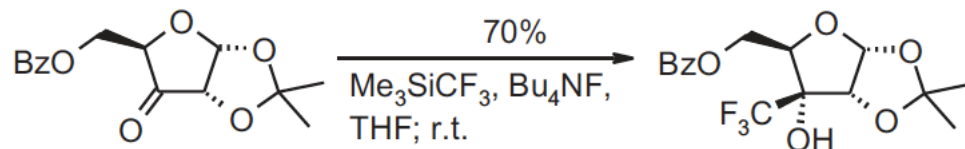
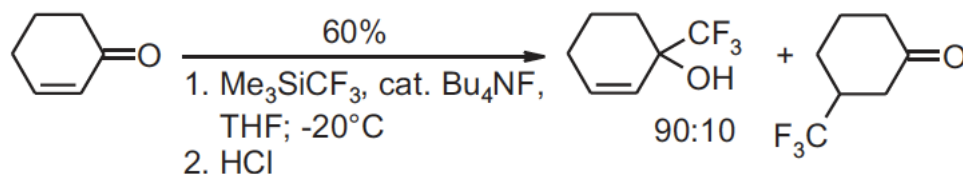


“Ruppert-Prakash”

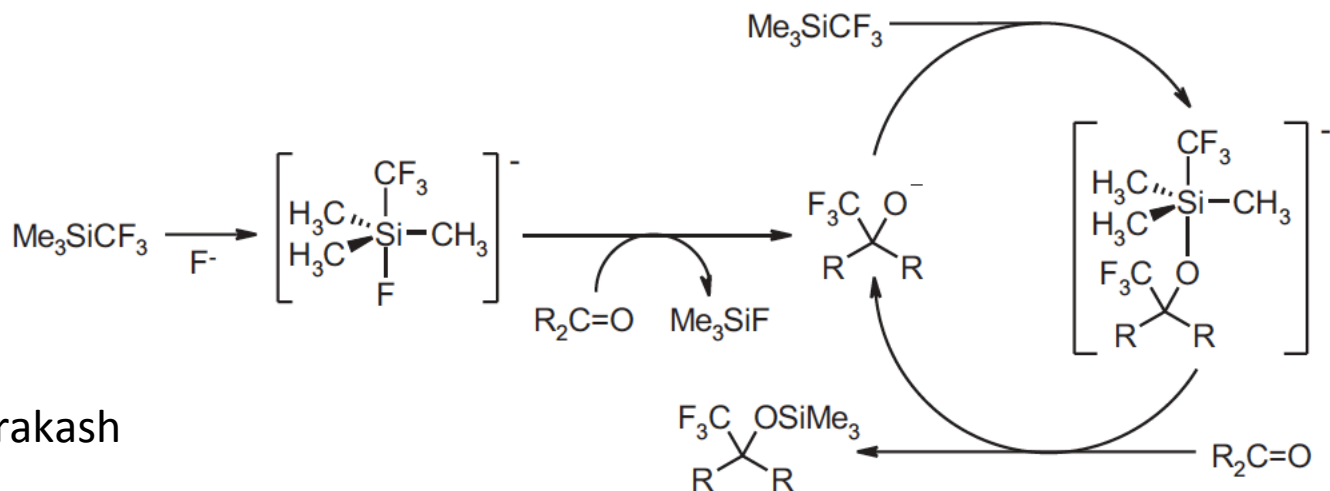
Fluorinated Building Blocks

➤ Nucleophilic processes

> Fluorinated Carbanions: Ruppert-Prakash reagent



G.A. Olah G.K. Surya Prakash





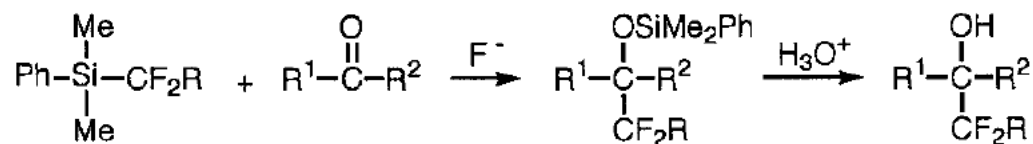
Jinbo Hu

- Date of birth:** February 9, 1973
- Position:** Research Professor, CAS Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences (CAS)
- E-mail:** jinbohu@sioc.ac.cn
- Homepage:** http://sourcedb.sioc.cas.cn/cn/expert/200906/t20090621_1750777.html
- Education:** 1994 Undergraduate studies in chemistry, Hangzhou University
1997 MSc with Prof. R.-W. Peng, Shanghai Institute of Metallurgy, Chinese Academy of Sciences
2002 PhD with Profs. G. K. S. Prakash and G. A. Olah, University of Southern California
2002–2005 Postdoctoral fellow with G. K. S. Prakash and G. A. Olah
- Awards:** **2007** Chinese Chemical Society Young Chemist Award; **2008** Distinguished Young Investigator Foundation (sponsored by The National Natural Science Foundation of China); **2009** RSC Fluorine Prize; **2012** Chen Jia-Geng Science Award for Young Scientists
- Current research interests:** New efficient methods for selective fluoroalkylation, fluorination, and defluorination; synthesis of fluorinated functional materials; probing the unique “fluorine effect” in organic chemistry; isotope separation
- Hobbies:** Walking, traveling, reading history books, spending time with my family

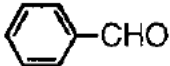
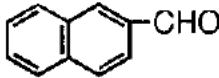
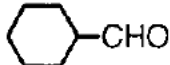
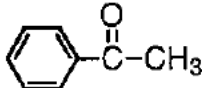
Nucleophilic Fluoroalkylation

➤ $-CF_3$ addition regarded as solved: $TMS-CF_3 / F^-$

> Approach not efficient with $-CHF_2$ or $-CH_2F$



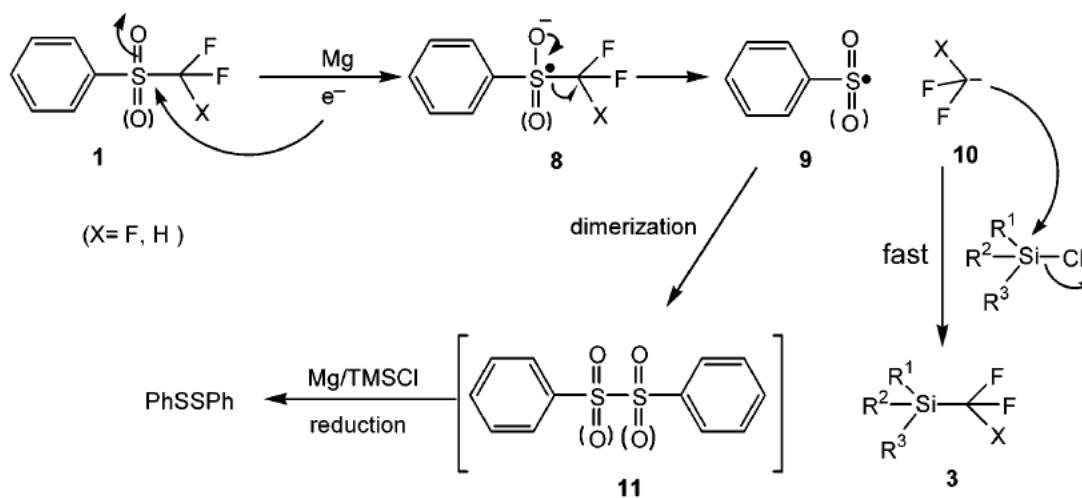
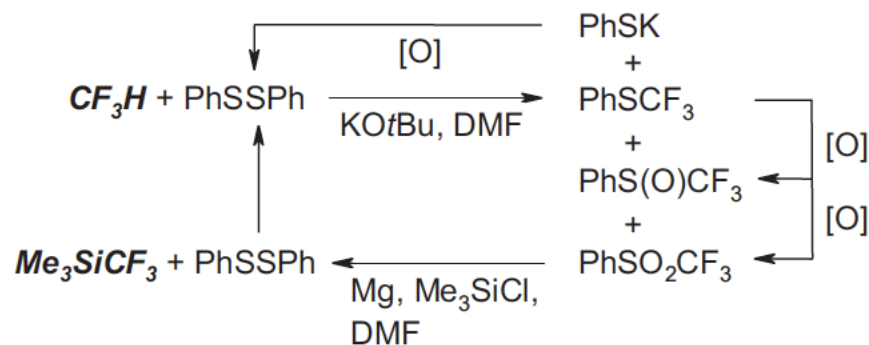
R= H, Br, Et, *i*-Pr, α -Hex

Substrate	KF (mol%)	Time (h)	Yield (%)
	5	6	82
	5	12	77
$\text{CH}_3(\text{CH}_2)_5-\text{CHO}$	50	6	56
	50	12	43
	50	12	20

Nucleophilic Fluoroalkylation

➤ Removable Activation Group (RAG)

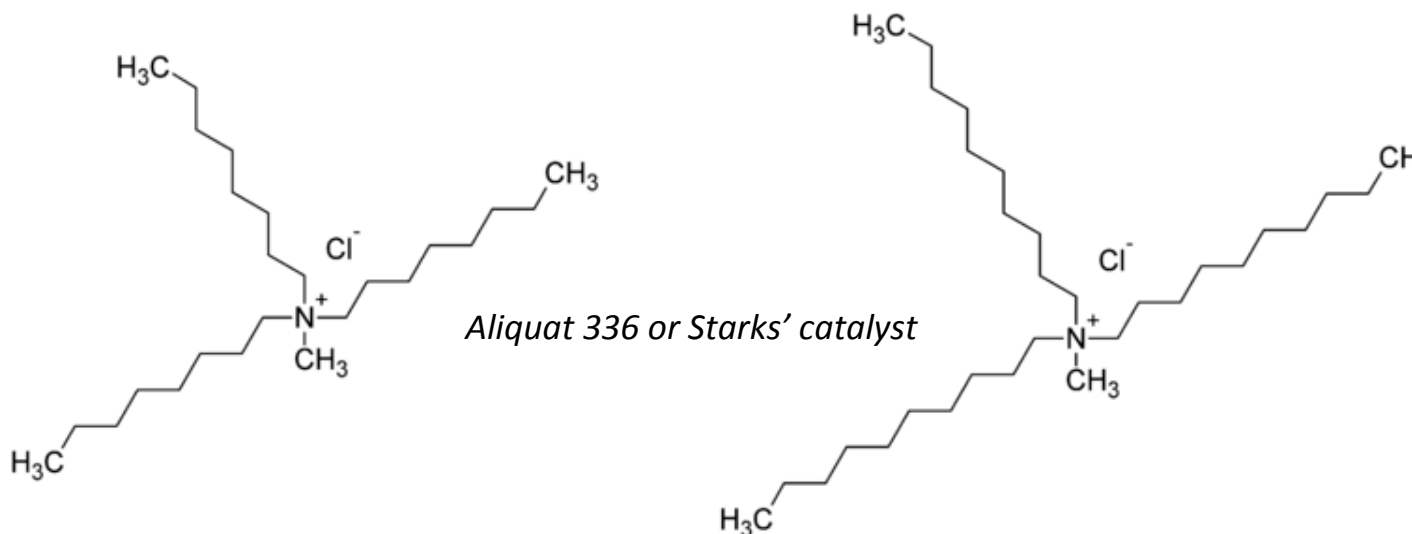
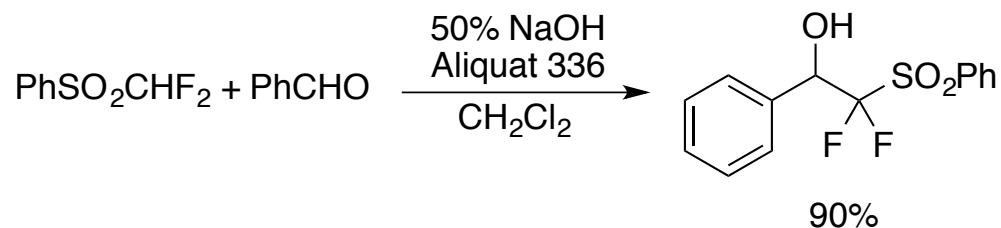
> Sulfone functionality: work done with Prakash & Olah



Nucleophilic Fluoroalkylation

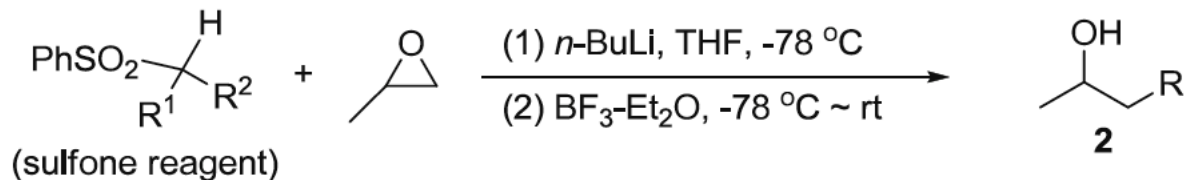
➤ Removable Activation Group (RAG)

> Sulfone functionality: seminal example by Stahly

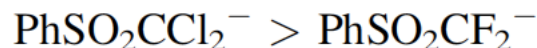
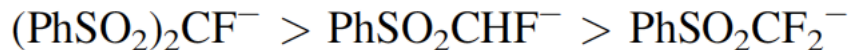


Nucleophilic Fluoroalkylation

➤ *Sulfone Reagents: Structure-Reactivity Relationship*

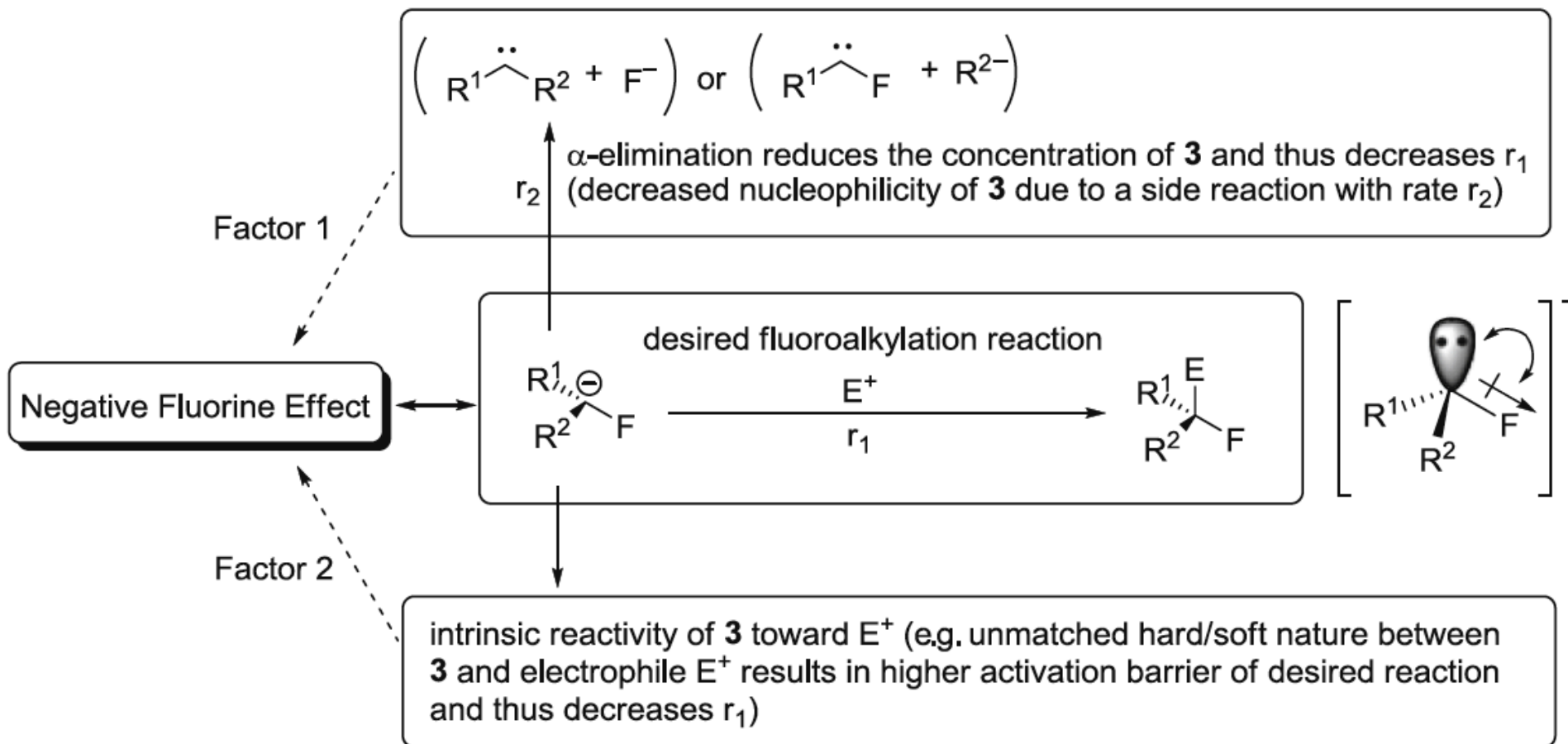


2a	R = PhSO ₂ CF ₂	0%
2b	R = PhSO ₂ CCL ₂	72%
2c	R = PhSO ₂ CHF	67%
2d	R = PhSO ₂ CHCl	71%
2e	R = (PhSO ₂)CF	91%



> *The more Fluorine atoms, the more difficult is the transformation*

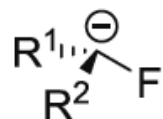
The « Negative Fluorine Effect »



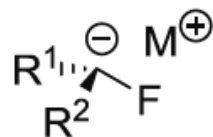
Modulating the Fluoroalkylation Reactions



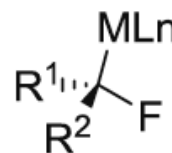
Method A:
Changing the number of fluorine atoms



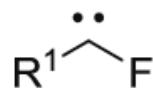
Method B:
Slightly changing the neighboring groups
(R^1 , R^2)



Method C:
Changing the metal counterion (M^+)



Using C-M covalent bond
to tune the reactivity

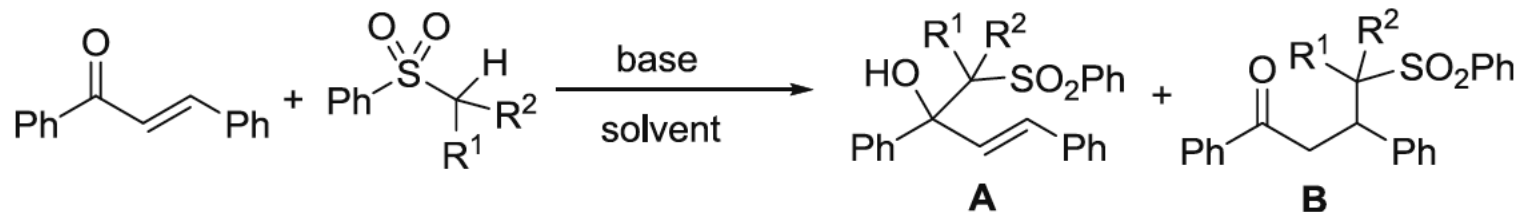
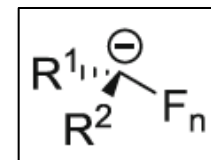


Method D:
Enhancing the generation of carbene species

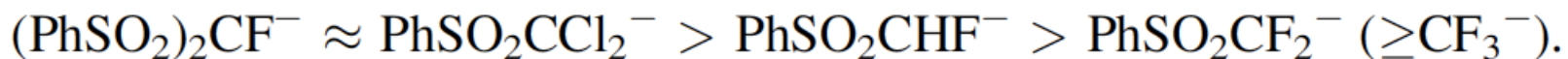
Method A: Changing the Number of ¹⁹F

➤ Influence of the Number of Fluorine Atoms

> HSAB study



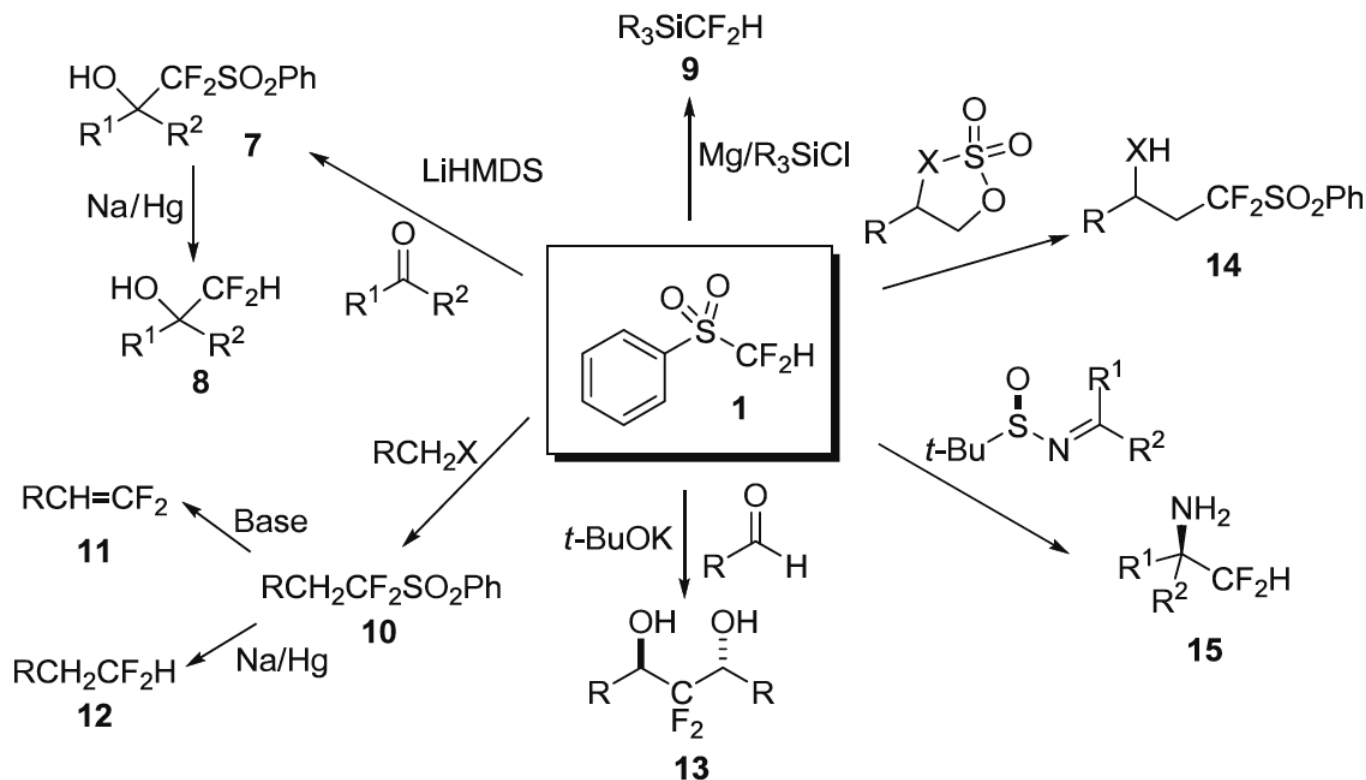
Sulfone	R ¹	R ²	Yield (A+B)	A:B
1	F	F	97	100:0
4	F	H	98	42:58
5	F	SO ₂ Ph	98	0:100
6	Cl	Cl	95	0:100



Method A: Changing the Number of ¹⁹F

➤ Influence of the Number of Fluorine Atoms

> 2 Fluorine atoms, the PhSO₂CF₂H reagent

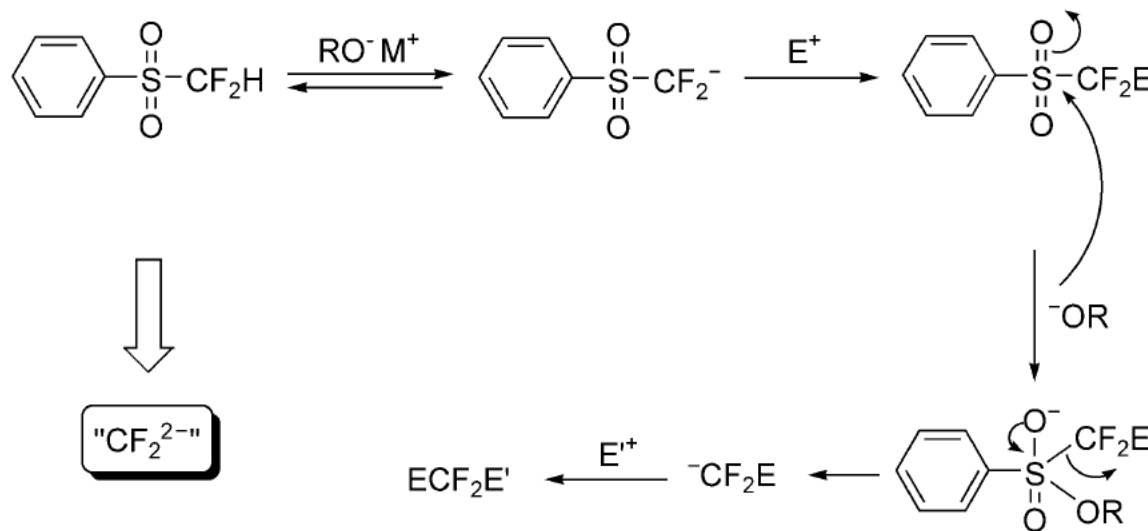
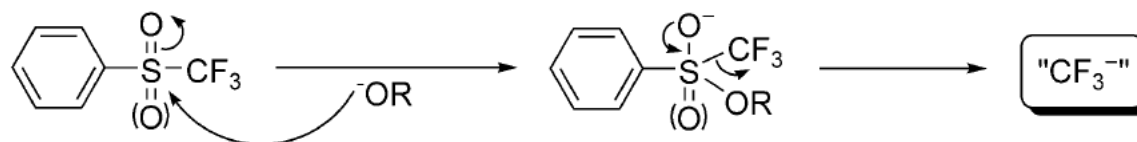
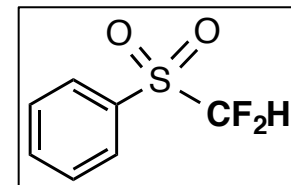


C. Ni, J. Liu, L. Zhang, J. Hu, *Angew. Chem. Int. Ed.* **2007**, *46*, 786–789. G. K. S. Prakash, J. Hu, Y. Wang, G. A. Olah, *Org. Lett.* **2004**, *6*, 4315–4317. G. K. S. Prakash, J. Hu, Y. Wang, G. A. Olah, *Angew. Chem. Int. Ed. Engl.* **2004**, *116*, 5315–5318. G. K. Surya Prakash, J. Hu, Y. Wang, G. A. Olah, *Eur. J. Org. Chem.* **2005**, 2218–2223. Y. Li, J. Hu, *Angew. Chem. Int. Ed. Engl.* **2005**, *44*, 5882–5886.

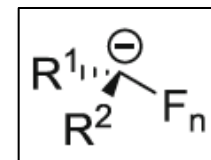
Method A: Changing the Number of ¹⁹F

➤ PhSO₂CF₂H

> Addition to aldehydes, *t*-BuOK as a base.

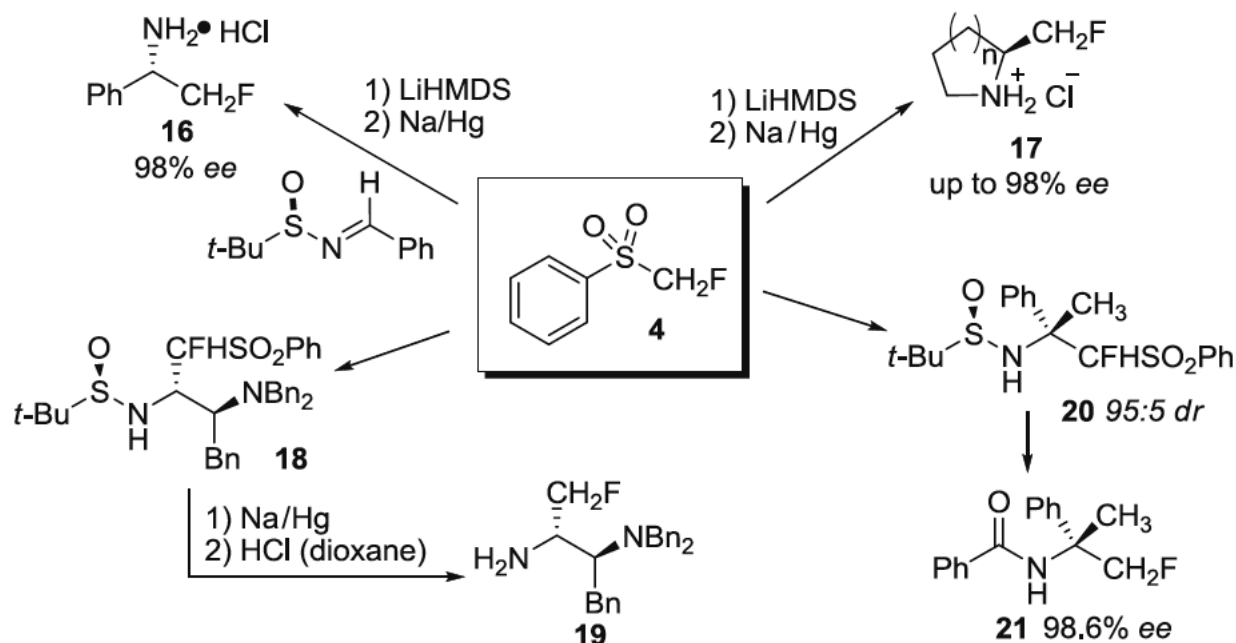


Method A: Changing the Number of ¹⁹F



➤ Influence of the Number of Fluorine Atoms

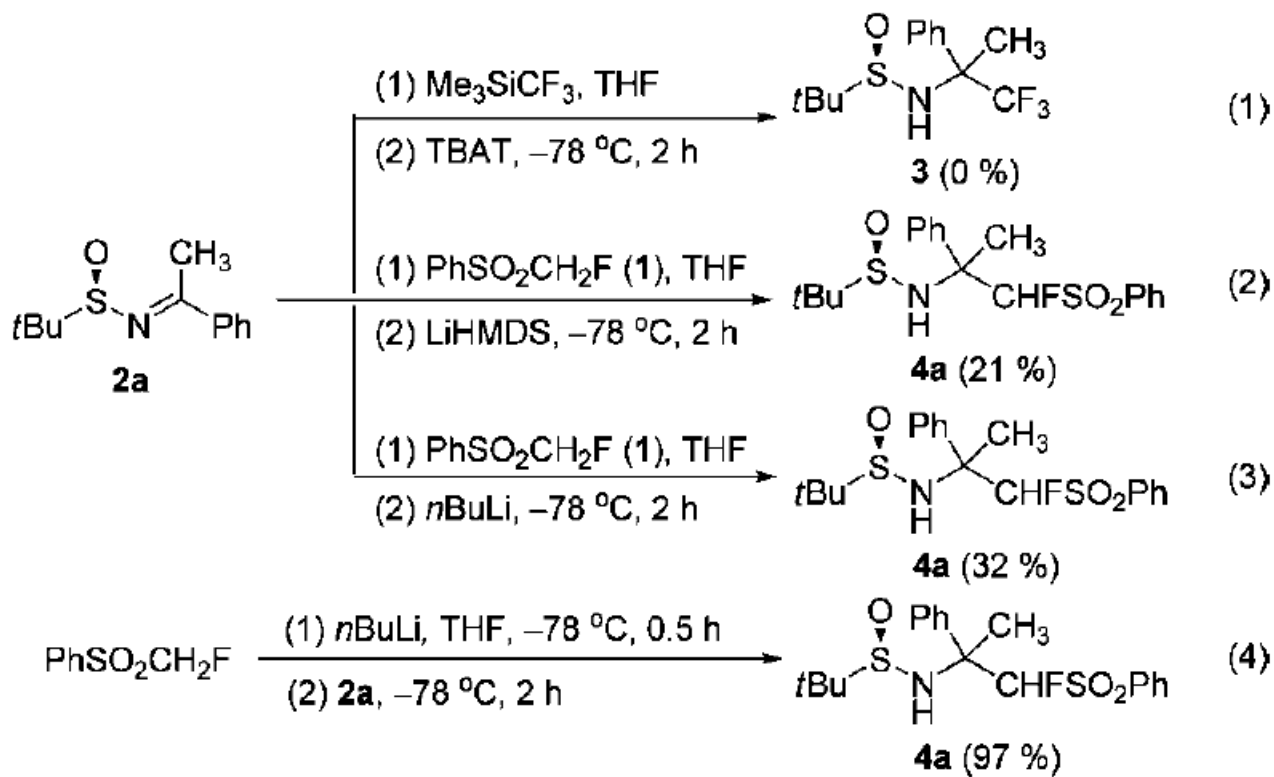
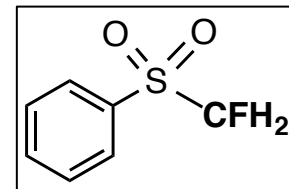
> 1 Fluorine atom, the more reactive $\text{PhSO}_2\text{CFH}_2$ reagent



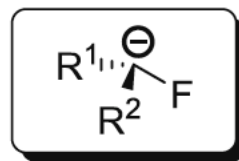
Method A: Changing the Number of ¹⁹F

➤ PhSO₂CFH₂

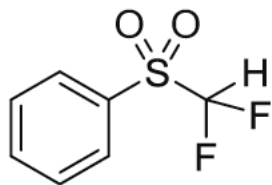
> Addition N-tert-Butylsulfinyl Ketimines



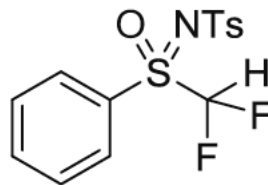
Method B: Changing the Neighboring Groups



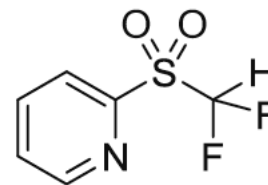
slightly changing the neighboring groups (R^1 , R^2) results in dramatically different chemistry



sulfone



sulfoximine

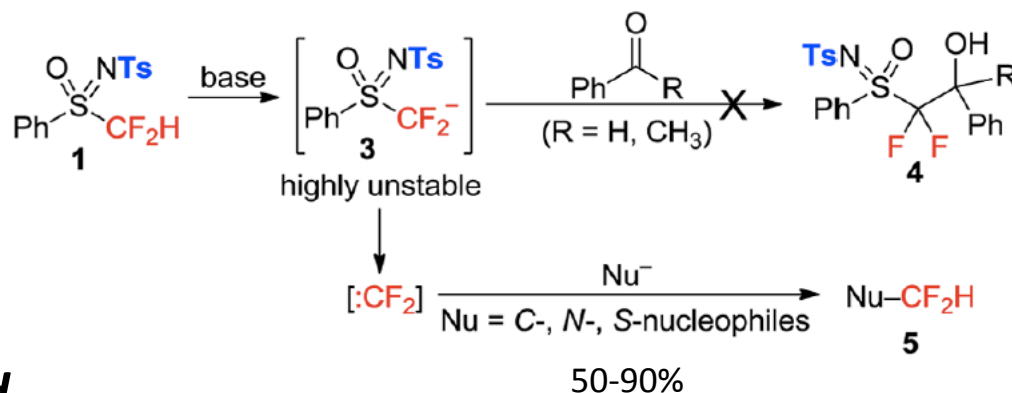


2-pyridyl sulfone

Method B: Changing the Neighboring Groups

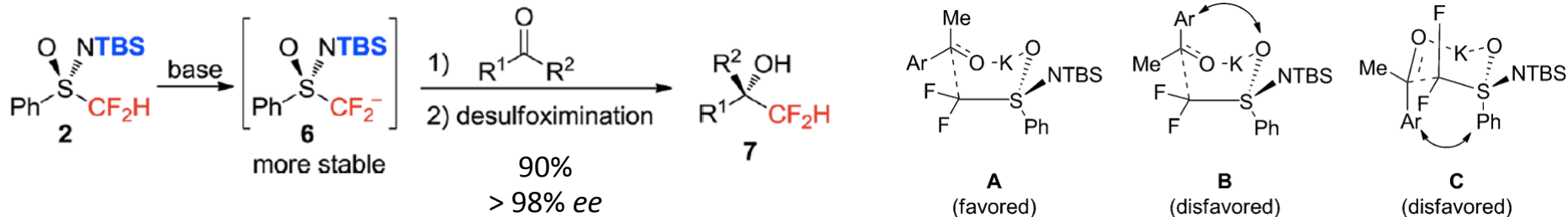
➤ PhSO(NTs)CF₂H

> EWG-ability maintained, better LG-ability



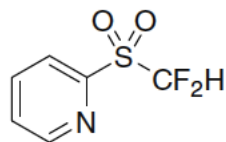
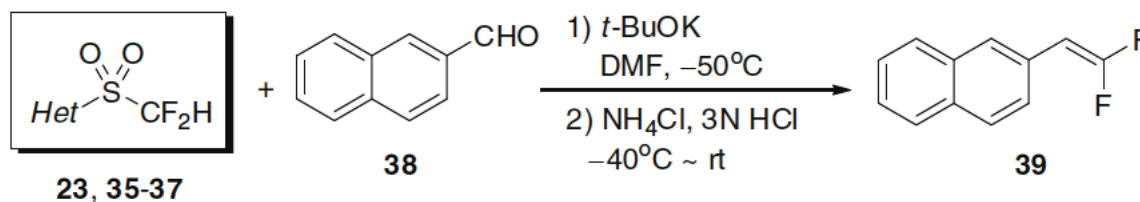
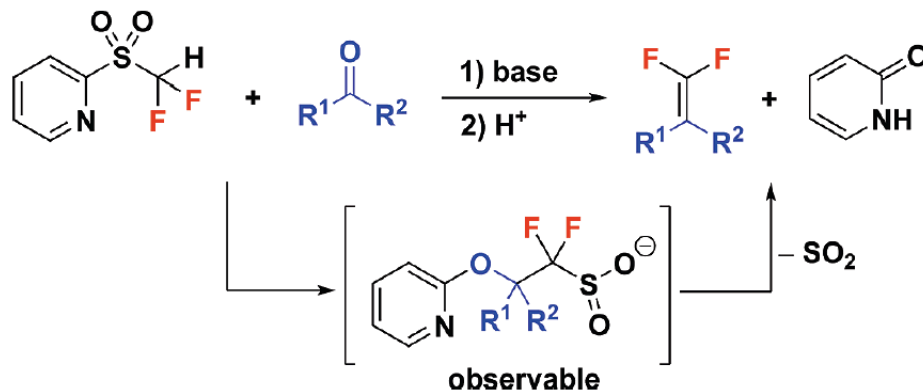
➤ PhSO(NTBS)CF₂H

> From electrophilic to nucleophilic



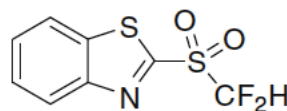
Method B: Changing the Neighboring Groups

➤ Het-SO₂CF₂H



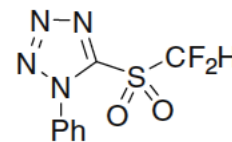
23 (2-PySO₂CF₂H)

92% yield



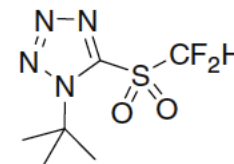
35 (BTSO₂CF₂H)

42% yield



36 (PTSO₂CF₂H)

trace



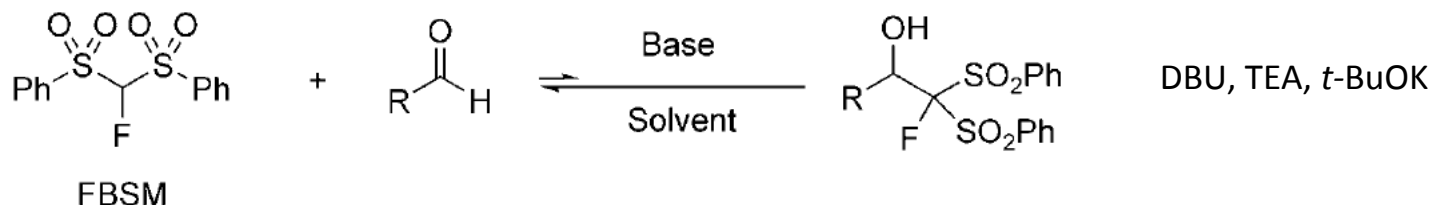
37 (TBTSO₂CF₂H)

0% yield

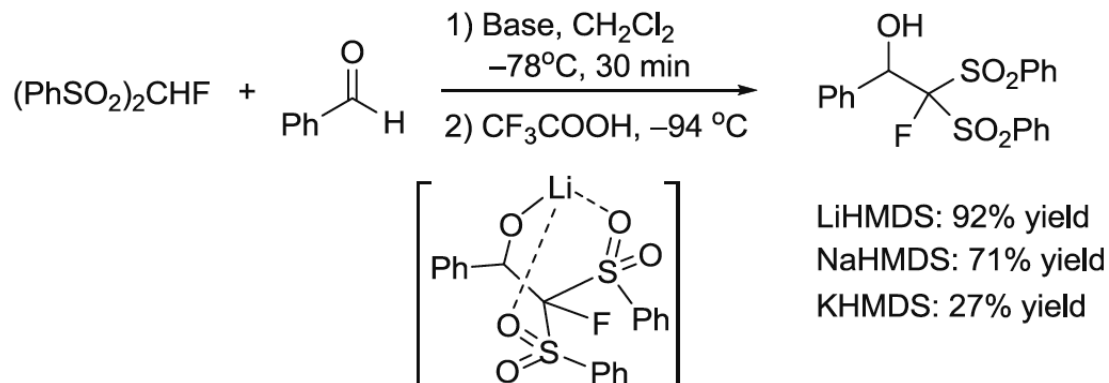
Method C: Influence of the Metal

➤ Influence of the Cation in Base-promoted reaction

Shibata & co-workers

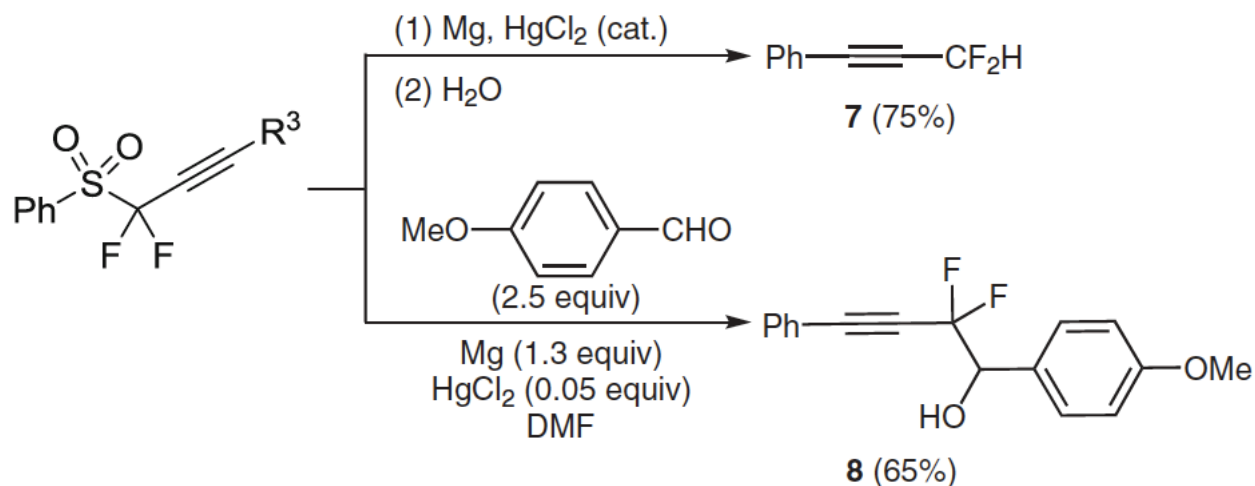
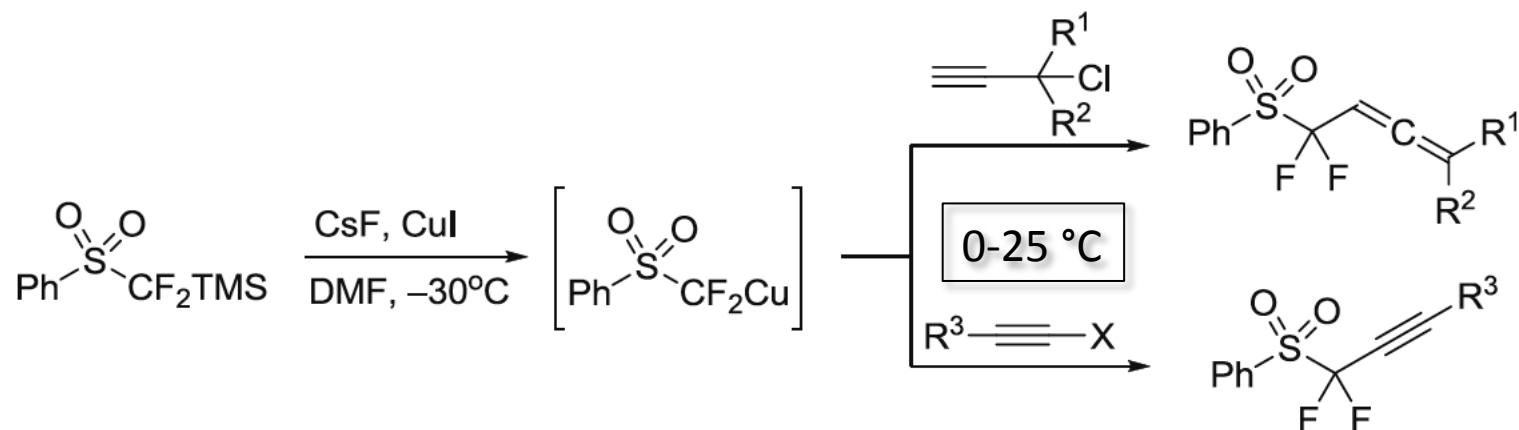


Hu et al.



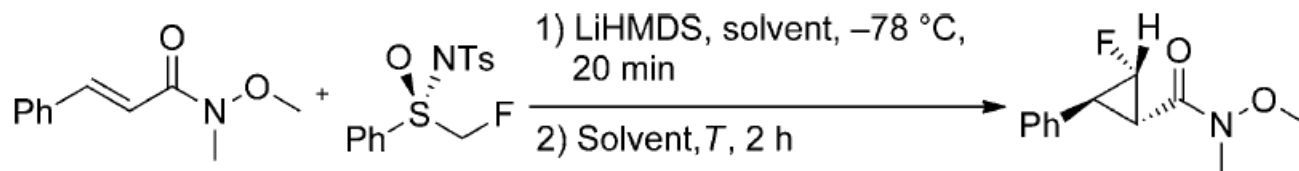
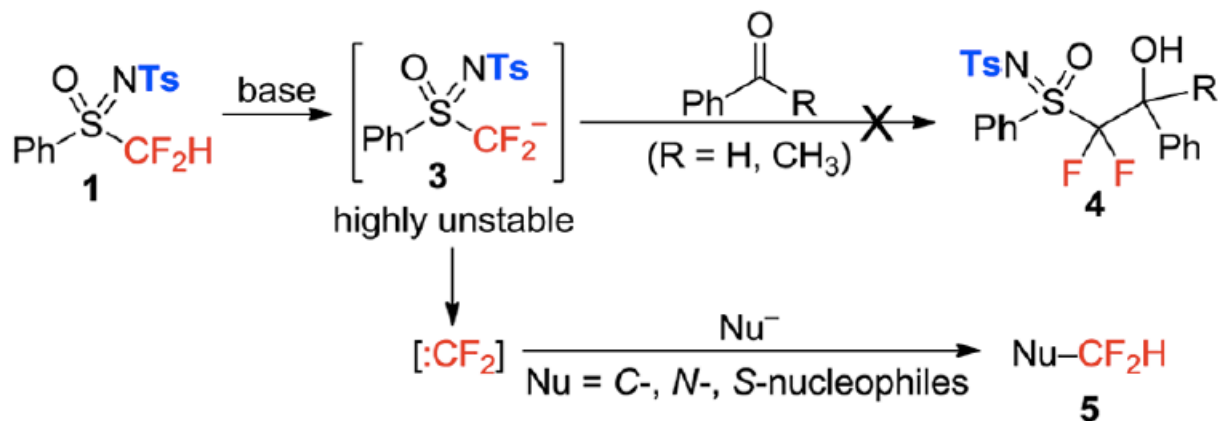
Method C: Influence of the Metal

➤ Organocopper Compounds



Method D: Formation of Carbene Species

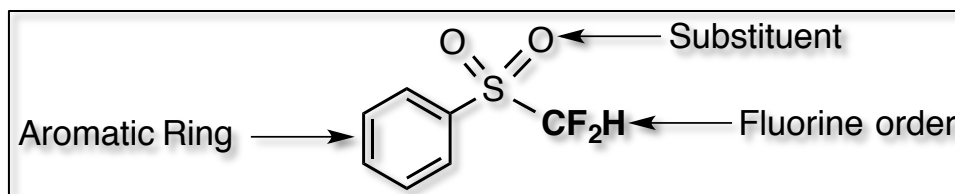
➤ Taking Advantage of the Fluoro-anion Unstability



13 examples
80-90%
> 90% ee



- 71 articles, last accepted 12.2013
- Deep systematic investigation of arylsulfones as fluoroalkyl sources



- Currently focusing on:
 - > Carbene/Cyclopropanation
 - > Stereoselective transformation