Fluorinated Synthons

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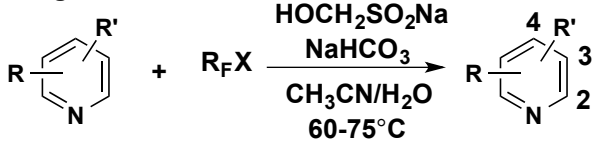
GM Focus: Interesting applications of fluorinated starting materials and reagents therein.

To Be Covered:
1. Rongalite: "The Confused Sulfinate Salt"
2. "The Nitrogen Walk"
3. Perfluoroheteroaromatics and "Mirror Image Logic"
4. N-Fluoropyridinium Salts and "The Fluorine Walk"
5. "The Negative Fluorine Effect" and the "chemical chameleon"

Not Covered:
General/"Traditional" Fluorination Reagents and techniques: i.e. Selectfluor,NFSI, DAST, XeF_2, AgF_2 (see Fluorination GM by S. Su (2008))

Rongalite: "The Confused Sulfinate"

J. of Flourine Chemistry, 64 (1993) 37-46



52-68%

General Isomer Distribution:
C2:C3:C4 = 1:4:4

Observed byproducts:
R_FH and R_FSO_2Na

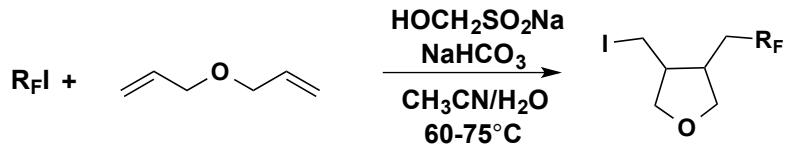
R_FX:
$C_6F_{13}I$
$C_7F_{15}I$
$C_8F_{17}I$
$Cl(CF_2)_6Br$

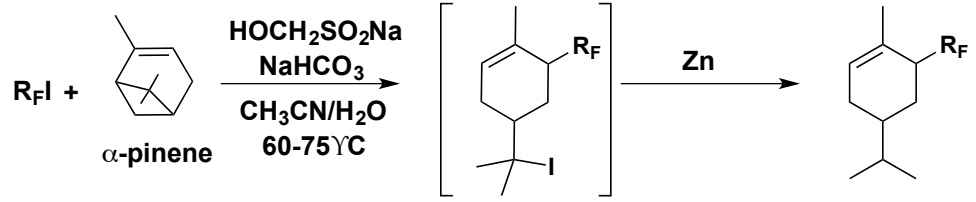
R, R'= H,CH_3
R_F=C_6F_{13}, C_7F_{15}, C_8F_{17}, $Cl(CF_2)_6$

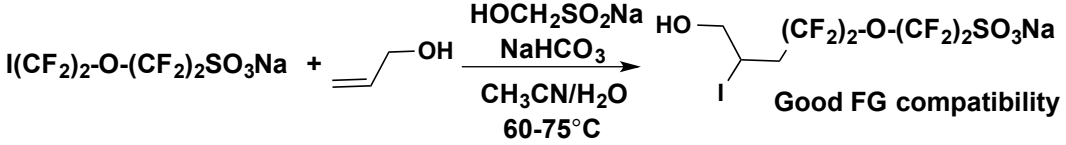
*Bicarb. kept rxn slightly basic and prevent dissociation of Rongalite.
*Also works on pyrroles (selective C2 substitution), quinolines and isoquinolines.
*Pyrazine and imidazole were problematic.

Rongalite With Olefins

Chin. J. Chem., 358 (1990)

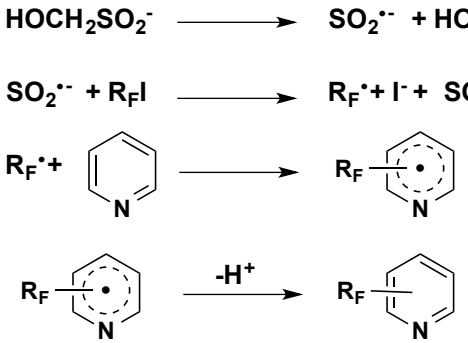






Good FG compatibility

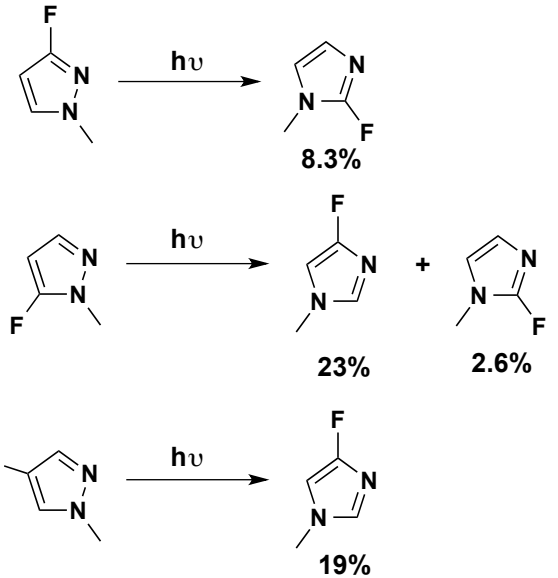
General Mechanism:



FYI: Rongalite
$250/5KG= $0.05/g
Aldrich

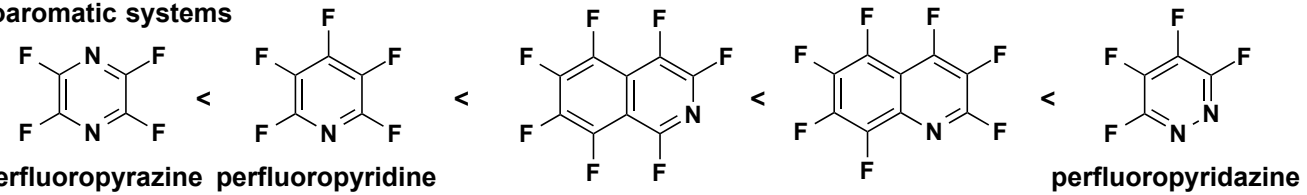
The "Nitrogen Walk"

J. Org. Chem. 1991,56, 6313-6320



Perfluorinated Heterocycles as Synthons?

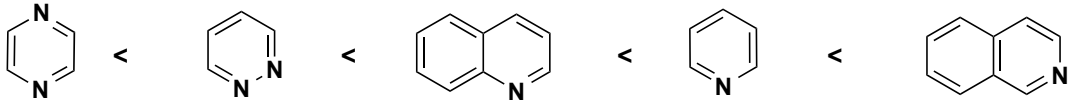
perfluoroheteroaromatic systems



perfluoropyrazine < perfluoropyridine < perfluoroisoquinoline < perfluoroquinoline < perfluoropyridazine

bp (°C) = 54 | bp (°C) = 84 | bp (°C) = 212 | bp (°C) = 212 | bp (°C) = 117

heteroaromatic systems



pyrazine < pyridazine < quinoline < pyridine < isoquinoline

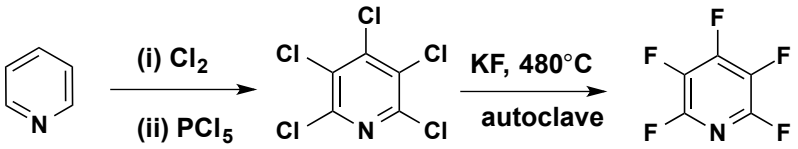
bp (°C) = 115 | bp (°C) =208 | bp (°C) = 238 | bp (°C) = 115.5 | bp (°C) = 243

Increasing base strength

*All perfluoroheteroaromatic compounds are weak bases - a fluorine atom placed *ortho* to the nitrogen atom significantly decreases the basicity of the system.

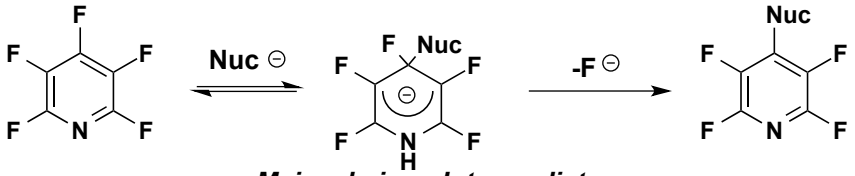
*Boiling points: Lower bp is attributed to lower intermolecular forces and low basicities of fluorocarbon systems that compensate for the increase in mass upon replacing hydrogen by fluorine.

General synthesis of perfluoroheteroaromatic heterocycles (many other methods available).



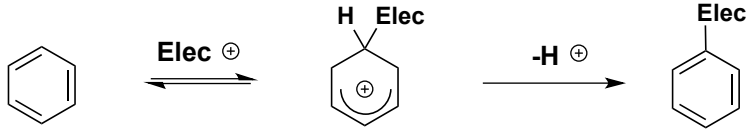
Petrov, V. *Fluorinated Heterocyclic Compounds*, New Jersey, 2009.

Perfluoroheteroaromatics: "Mirror Image" Chemistry



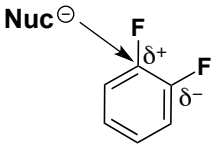
Meisenheimer Intermediate

"Mirror Image" to:

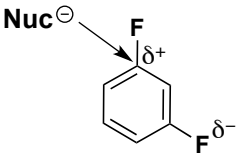


Wheland Intermediate

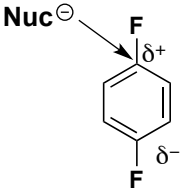
General Reactivity: Effects of Fluorine on Nucleophilic Substitution



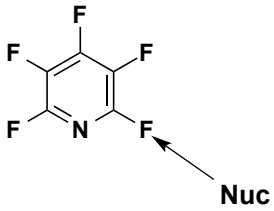
Very Activating



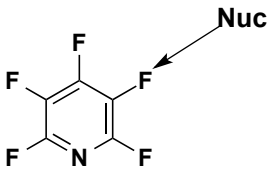
Activating



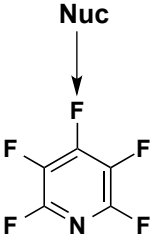
Slightly Deactivating



ortho N activating
1 ortho F activating
2 meta F activating
1 para F deactivating



meta N not activating
2 ortho F activating
1 meta F activating
1 para F deactivating

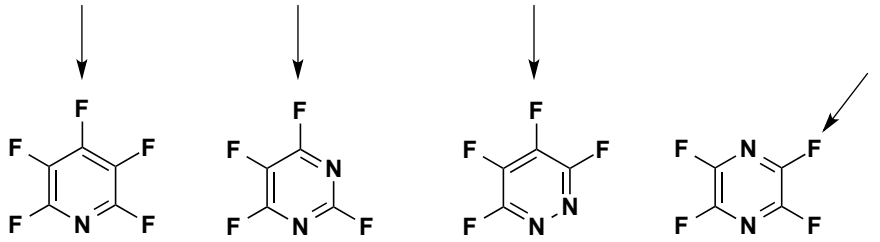


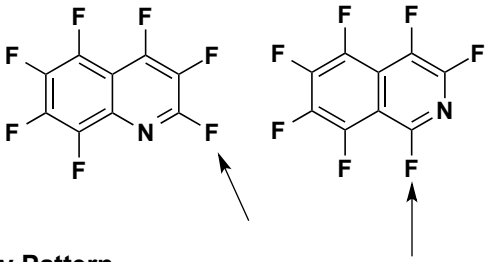
para N activating
2 ortho F activating
2 meta F activating

Petrov, V. *Fluorinated Heterocyclic Compounds*, New Jersey, 2009.

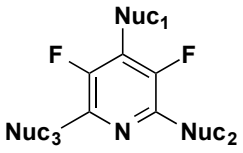
Nucleophilic substitution of perfluorinated heteroaromatic systems occurs at sites that:
1) are para to the ring nitrogen
2) maximize the number of activating ortho and meta F atoms
3) minimize the number of F atoms para to the site of attack

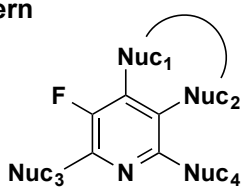
Favored sites of attack for S_NAr

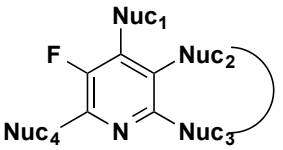


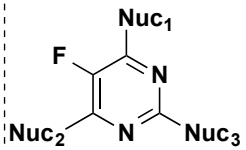


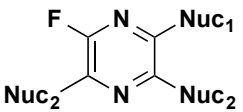
Regioselectivity Pattern



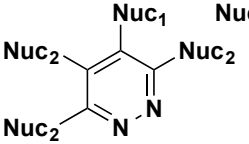




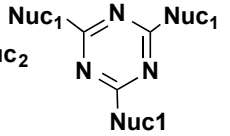




position of Nuc_2 is dependent on Nuc_1



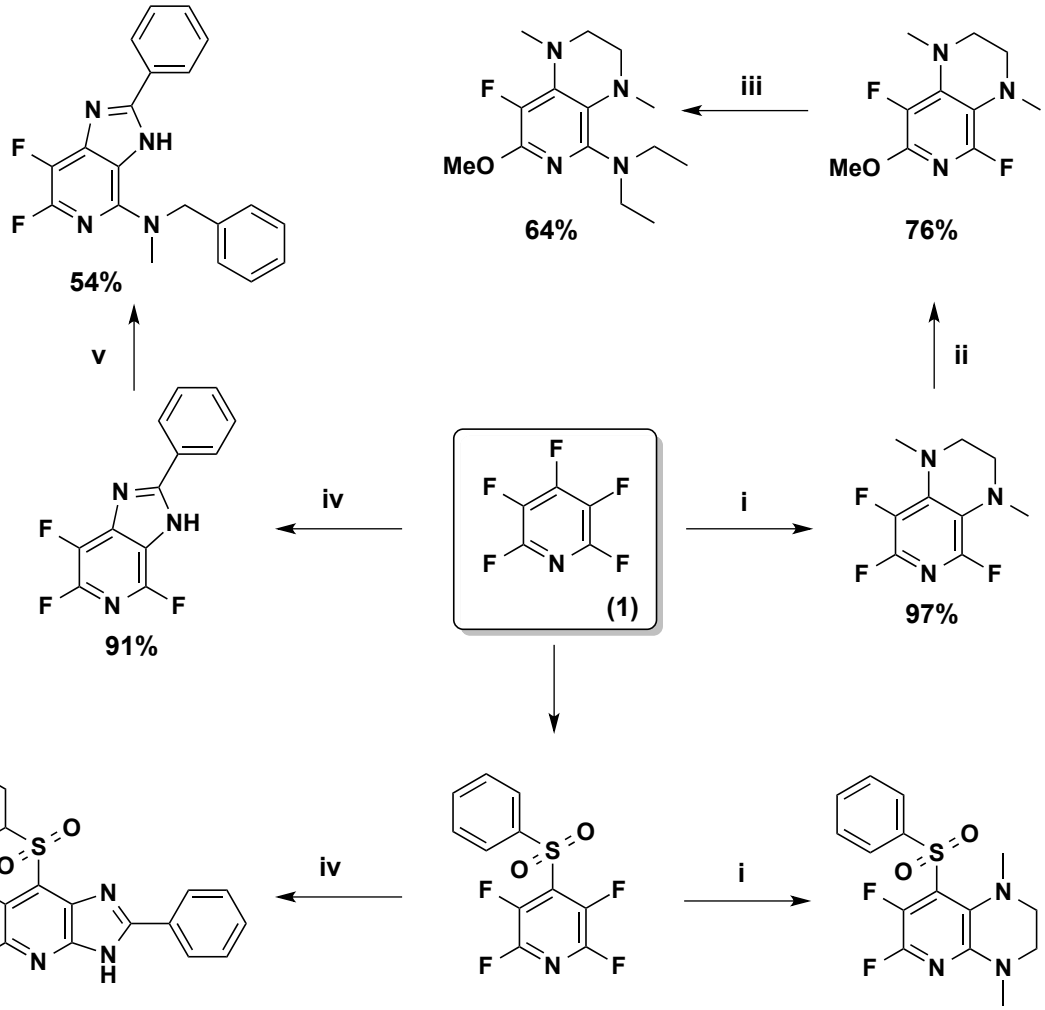
can get mono, bis, or tri



difficult to get mono only (highly activated)

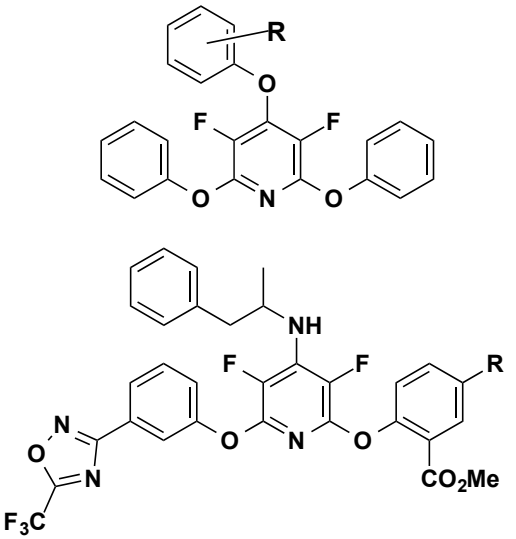
"Mirror Image Logic" Examples

*a reaxys search showed 1134 reactions with (1) as starting material

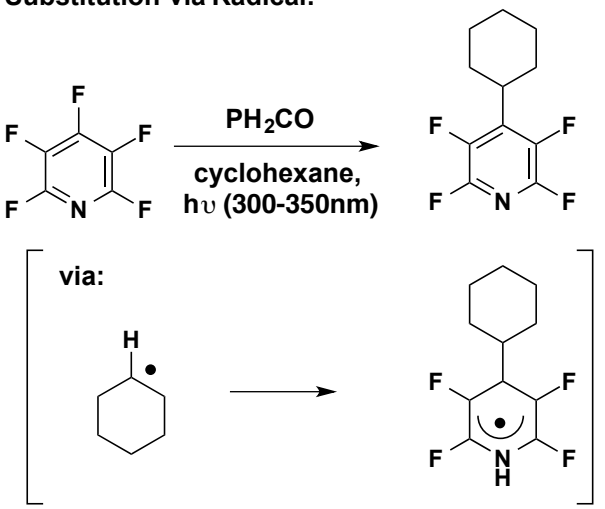


Petrov, V. *Fluorinated Heterocyclic Compounds*, New Jersey, 2009.

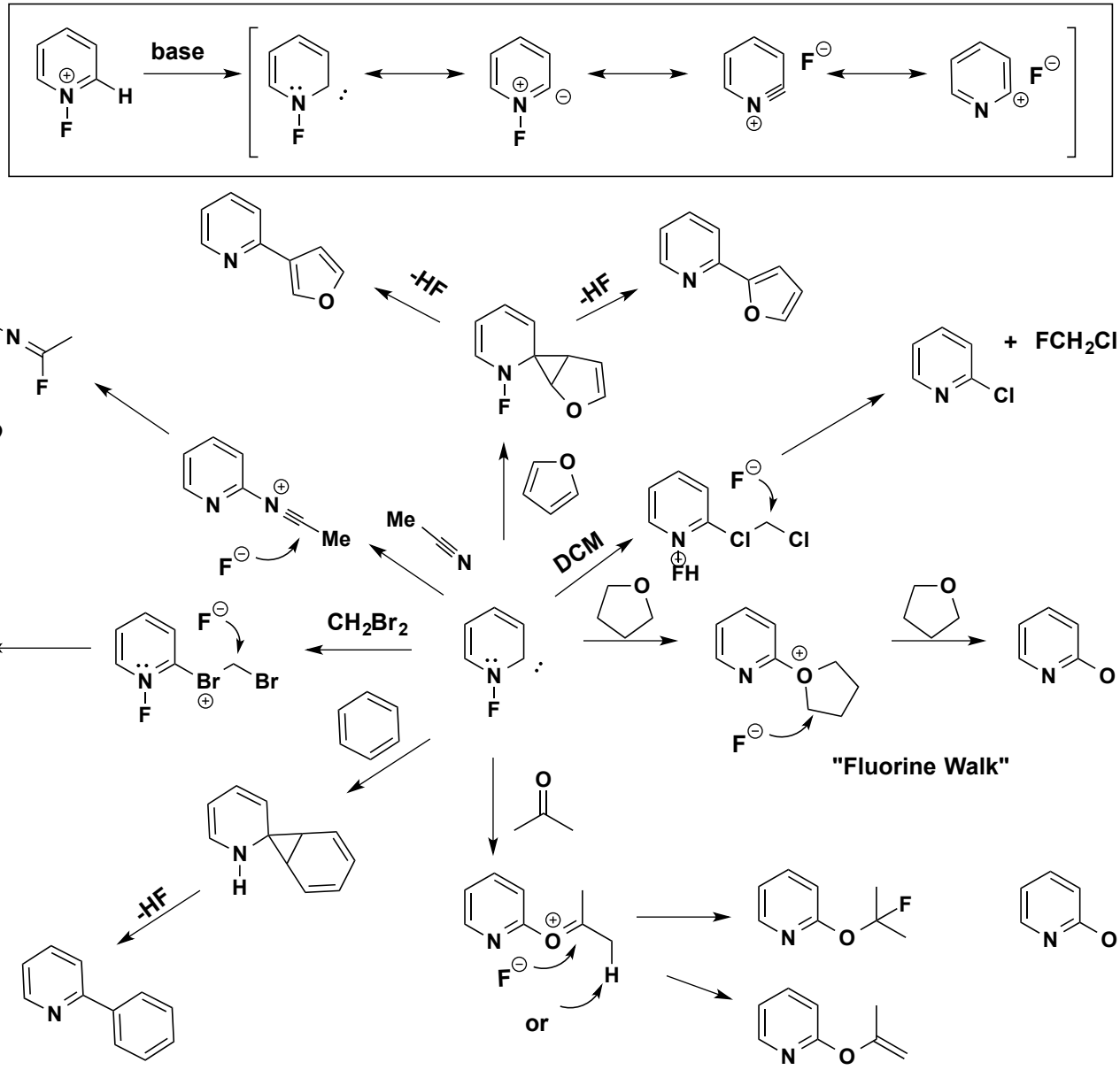
Biologically active compounds using "Mirror Logic" (used by Novartis and others)



Substitution via Radical:



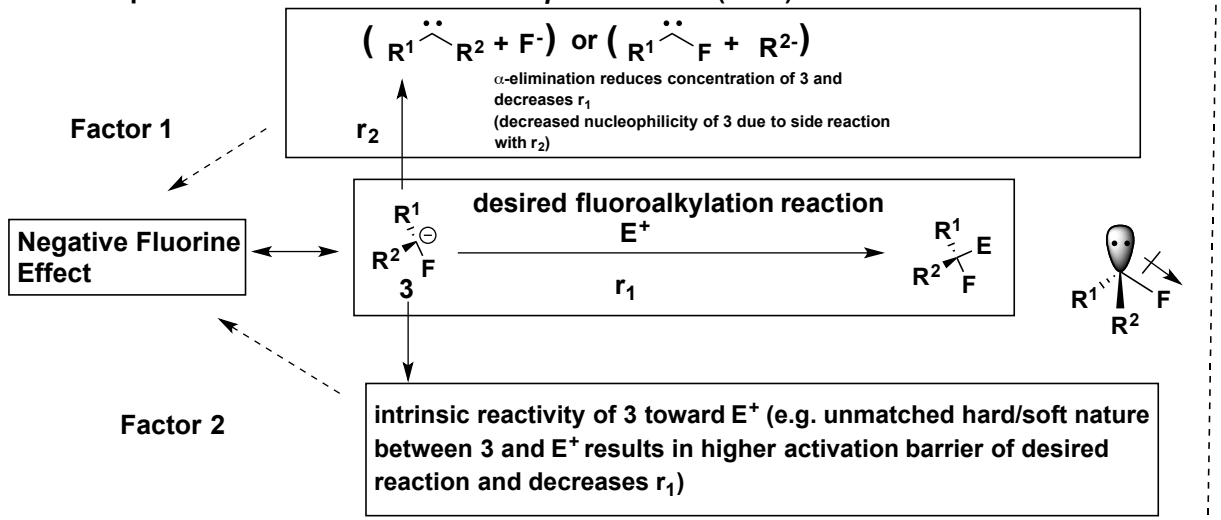
Carbenes from N-Fluoropyridinium Salts: Featuring the "Fluorine Walk"?



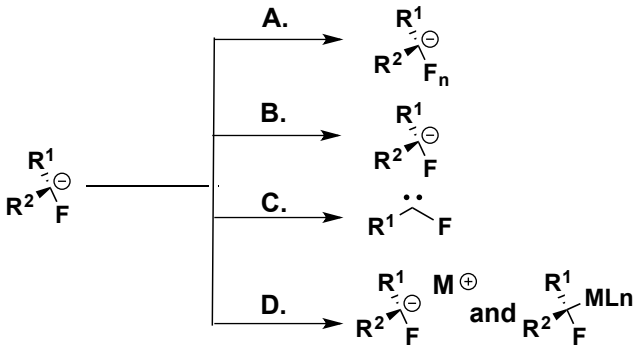
Tetrahedron Lett. 1987, 28(24), 2705-2708.

The Negative Fluorine Effect (NFE)

NFE Overview: "Fluorine substitution on the carbanionic C poses a negative effect in many nucleophilic fluorination reactions." *Top Curr Chem* **(2012) 308:25-44**



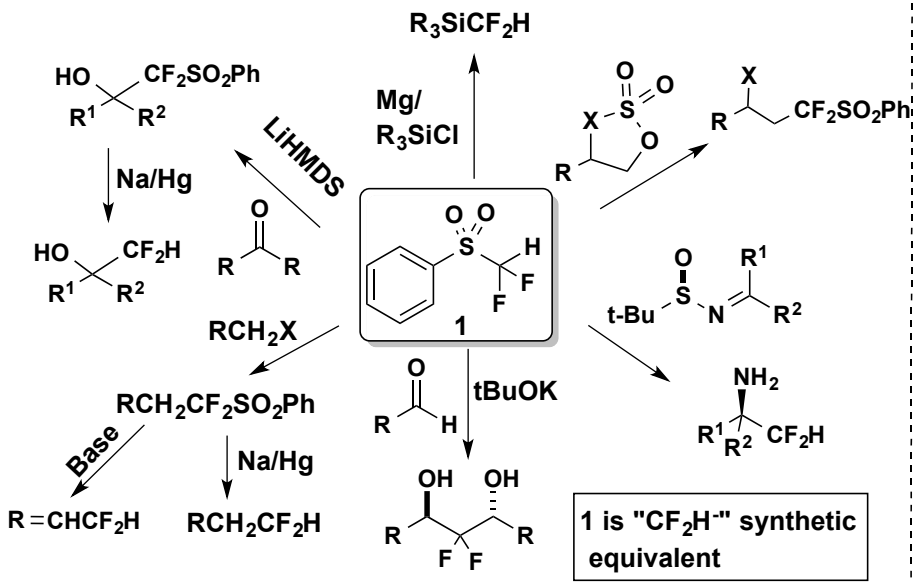
Taming NFE



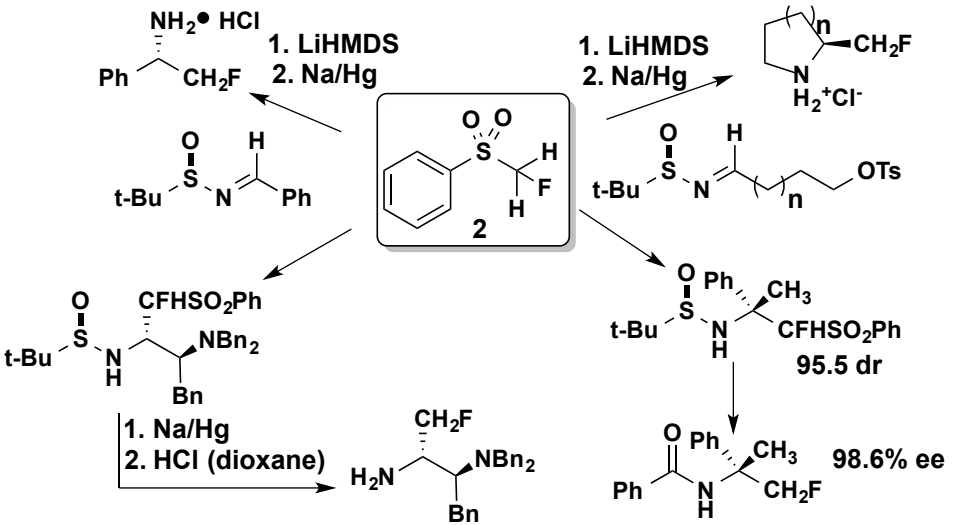
4 Methods for Modulating the NFE

A. Change fluorine atoms
B. Slightly change neighboring groups (R^1,R^2)
C. Enhance generation of carbene species
D. Change the metal counterion $M^{\oplus}$ or covalent bond to M

Method A: Nucleophilic Difluoromethylation Reactions with 1



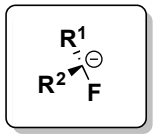
Method A: Nucleophilic Monofluoromethylation Reactions with 2



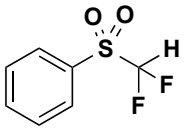
Org. Lett. 2006, 1693-1696

The Negative Fluorine Effect: Changing Neighboring Groups

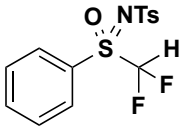
Method B:



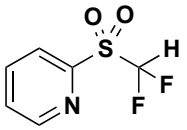
*The sulfone functionality is a "chemical chameleon" that is ideal for various types of reactions.



sulfone



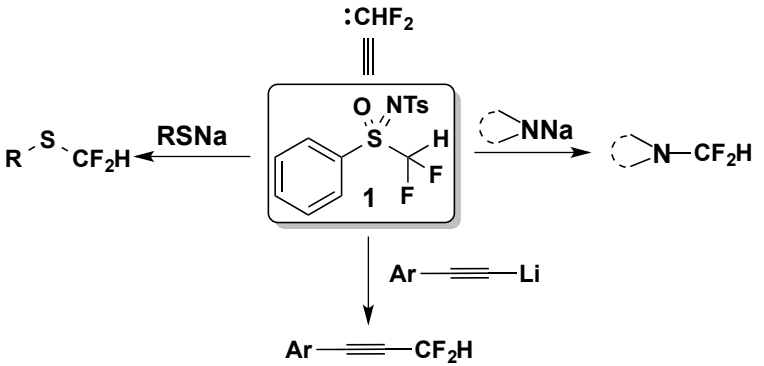
sulfoxime



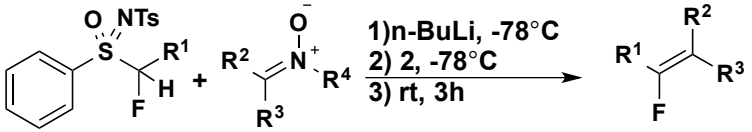
2-pyridyl sulfone

*Slightly changing R groups results in dramatically different chemistry.

Difluoromethylation of S-,N-, and C-Nucleophiles with 1.



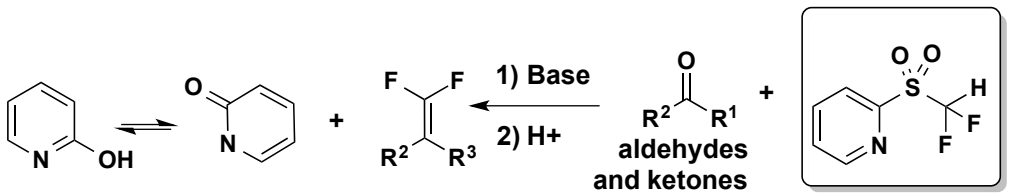
Fluorinated alkenes from nitrones.



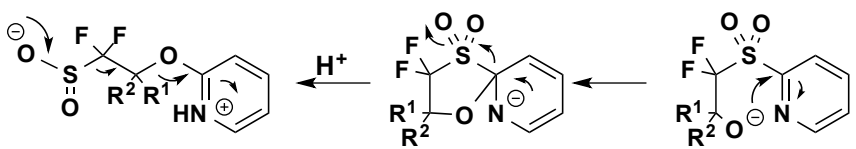
R^1 = aryl

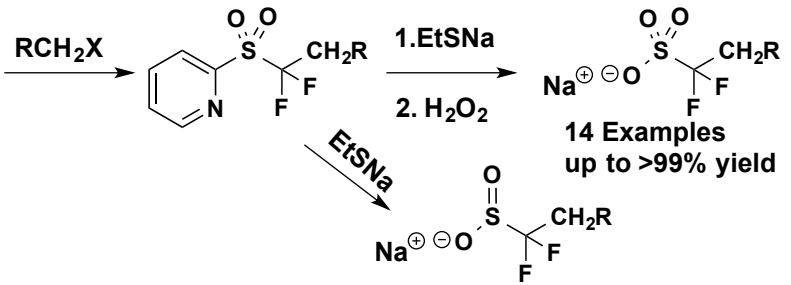
2

24 examples
up to 94% yield
up to 99:1 Z/E



Via:



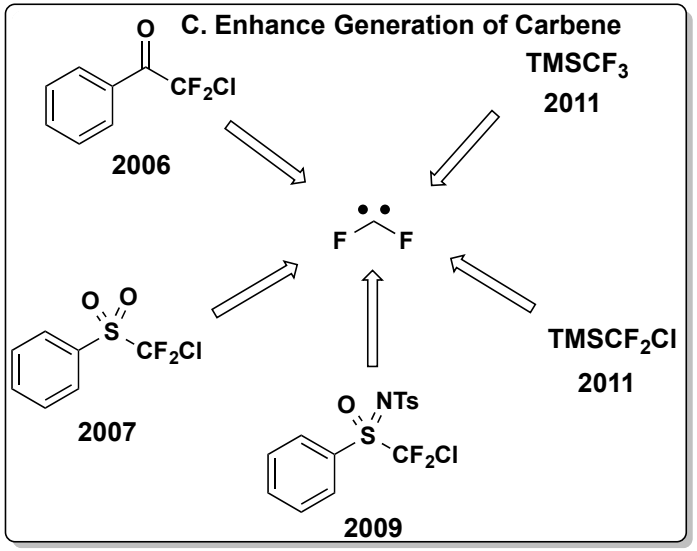


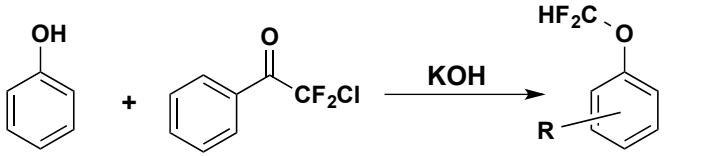
Angew. Chem. Int. Ed. 2011, 50, 2559 –2563

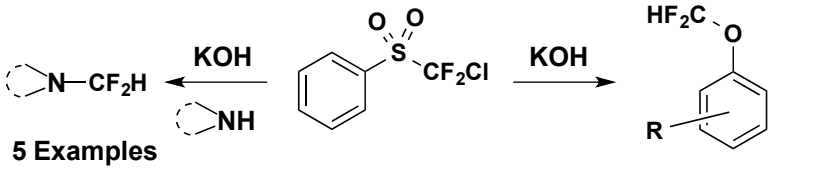
Angew. Chem. Int. Ed. 2013, 52, 3949 –3952

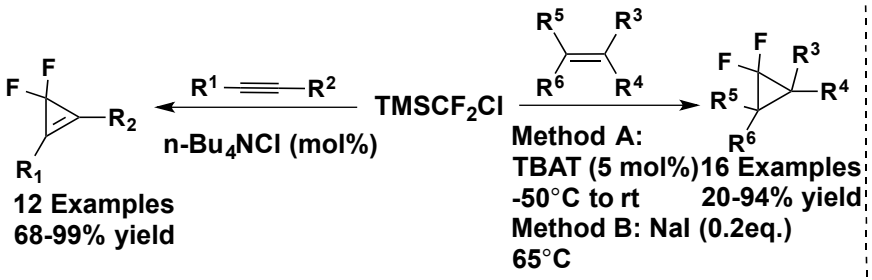
Org. Lett. 2010, 1444-1447

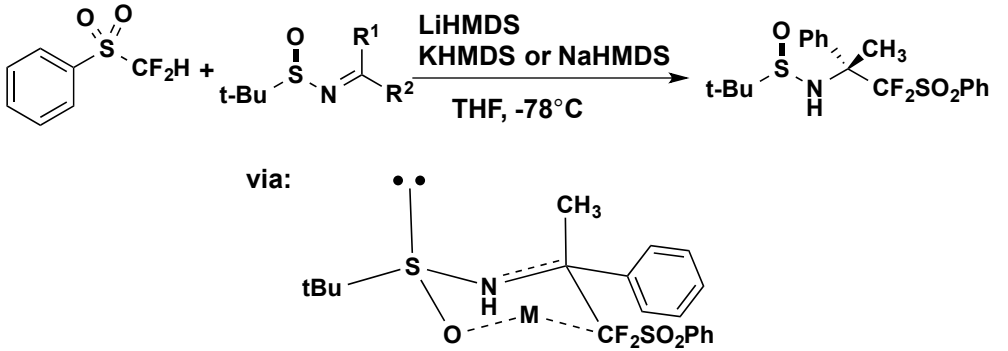
The Negative Fluorine Effect: Carbene, Counterion, M-X











Org. Lett., 2008, 5377-5380