

Fluorinated Drug Design, Synthesis, and Metabolism

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9-29-10



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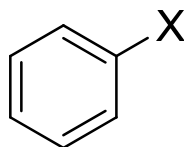


Physiochemical Properties

- Van der Waal radius: F = 1.47Å, H = 1.2Å, O = 1.57Å
- Bond length: C-F (1.39-1.43Å) vs C(sp³)-H (1.09-1.10Å). C-F bonds fall between C-C triple bonds (1.37-1.38Å) and C-C double bonds (1.45-1.46Å)
- High electronegativity leads to changes in pKa, dipole moments, reactivity, stability, etc
- C-F (116 kcal/mol) vs C-H (99 kcal/mol) providing increased oxidative and thermal stability
- Possible leaving group and has been utilized in forming bonds with nucleophilic active site amino acids
- Usually lipophilic yet still capable of weak H-bonding



C-F can reduce of the overall polarizability of a compound increasing its lipophilicity



Hansch hydrophobicity parameters for monosubstituted benzenes

X	π_x	X	π_x	X	π_x
F	0.14	OCH ₃	-0.02	CH ₃ C(O)NH	-1.63
Cl	0.71	OCF ₃	1.04	CF ₃ C(O)NH	0.55
OH	-0.67	CH ₃ C(O)	-1.27	CH ₃ SO ₂	-1.63
CH ₃	0.56	CF ₃ C(O)	0.08	CF ₃ SO ₂	0.55
CF ₃	0.88				



logP values of straight-chain alkanols

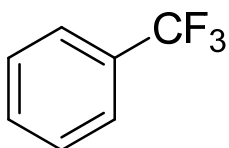
	X = H	X = F	
Alcohols	logP _H	logP _F	ΔlogP
<chem>X3C-CH2-OH</chem>	-0.32	0.36	0.68
<chem>X3C-CH2-CH2-OH</chem>	0.34	0.39	0.05
<chem>X3C-CH2-CH2-CH2-OH</chem>	0.88	0.9	0.02
<chem>X3C-CH2-CH2-CH2-CH2-OH</chem>	1.4	1.15	-0.25
<chem>X3C-CH2-CH2-CH2-CH2-CH2-OH</chem>	2.03	1.14	-0.89



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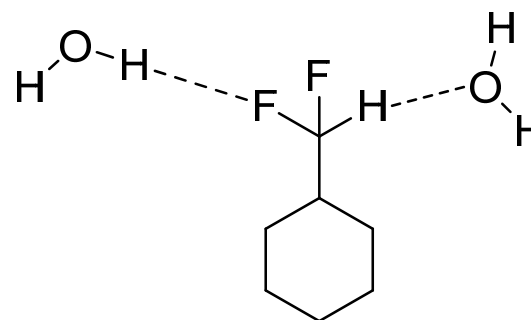


- CF_2 used as an electronic mimic for oxygen
- Can not be hydrolyzed as compared to the sensitive phosphate ester



CF_3 :

- Among the most lipophilic groups known
- Much more sterically demanding than $-\text{CH}_3$. Comparable to isopropyl although evidence exists to suggest the size to be closer to phenyl or *t*-butyl



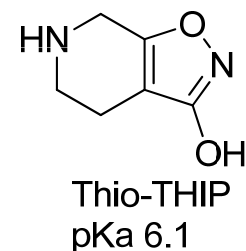
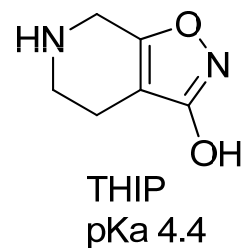
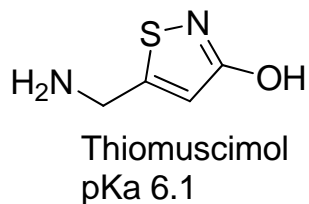
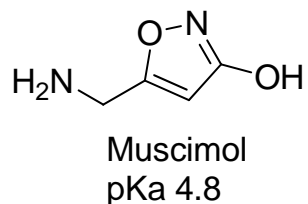
CF_2H :

- Used extensively as a bioisostere for $-\text{OH}$
- Capable of acting as both a H-bond donor and acceptor

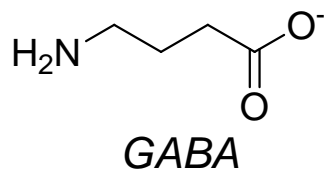


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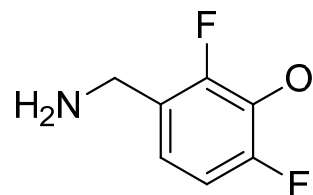
GABA Bioisosteres



GABA aminotransferase inhibitors:



VS



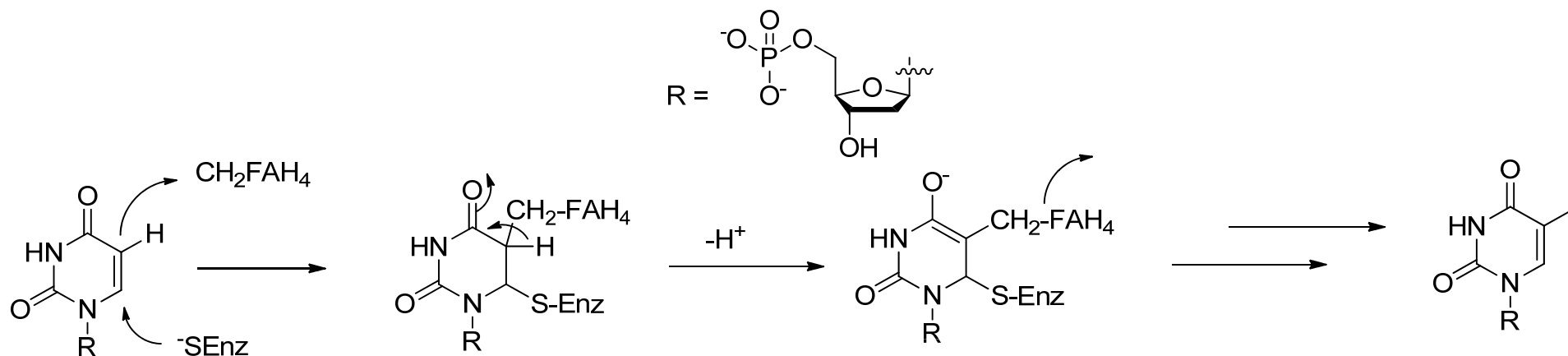
- pKa = 7.1
- Capable of hydrogen bonding
- Increased lipophilicity



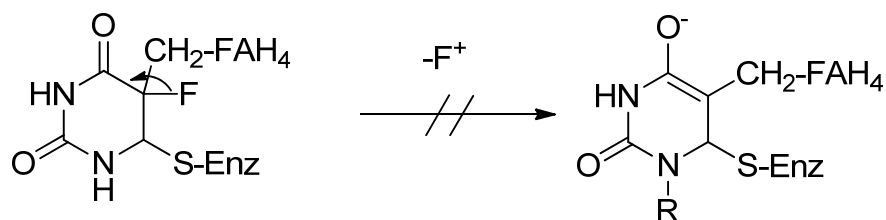
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Orthogonal Reactivity

Catch and trap method of inhibition of deoxyuridine monophosphate conversion to thymidylate



Fluorine can not be lost as F^+

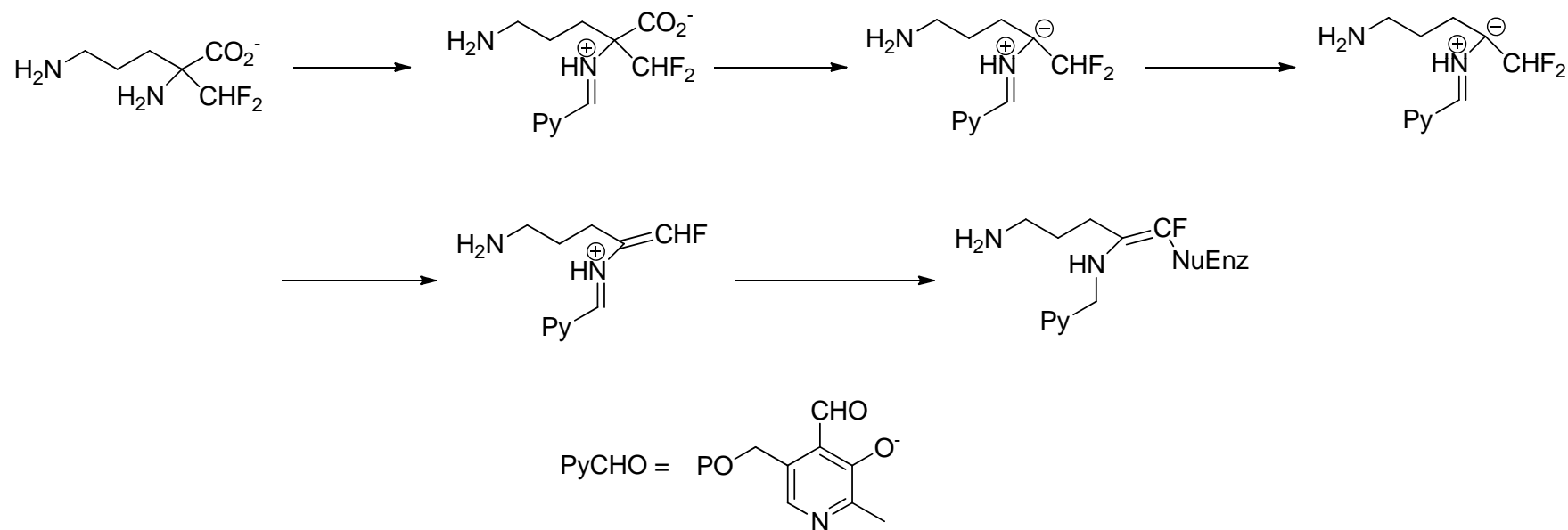




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Irreversible inhibition of ornithine decarboxylase by nucleophilic capture

Based on ability to eliminate Fluorine to give F⁻



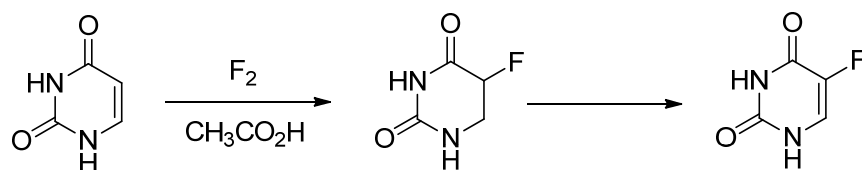
Metcalf, B. W.; Bey, P.; Danzin, C.; Jung, M. J.; Casara, P.; Vever, J. P. J. Am. Chem. Soc. 1978, 100, 2551–2553.



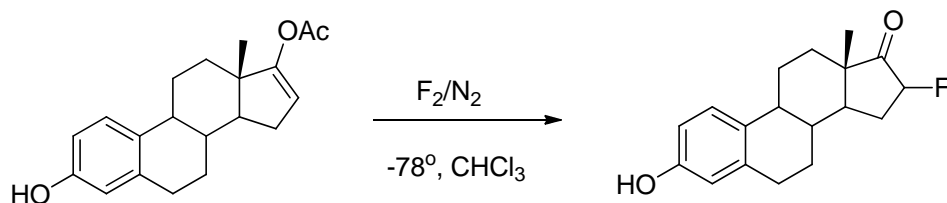
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Electrophilic Fluorination

- Elemental fluorine was first isolated by Henri Moissan in 1886
- Received Nobel Prize in 1906



Reactivity tamed by dilution with inert gas



Early O-F Reagents and others:



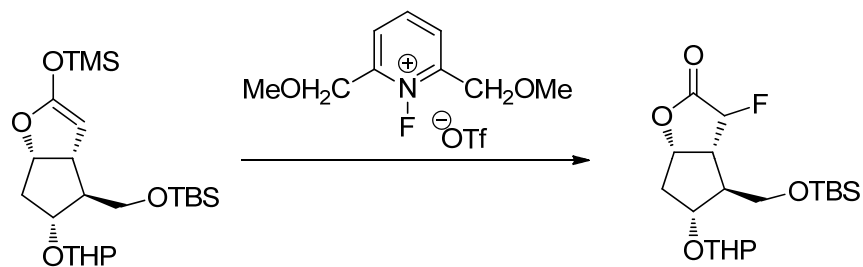
Cech, D.; Holy, A. *Collect. Czech. Chem. Commun.* **1976**, *1*, 3335–3342.



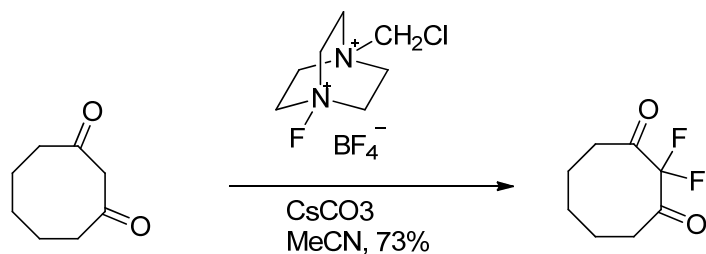
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N-Fluoro Reagents

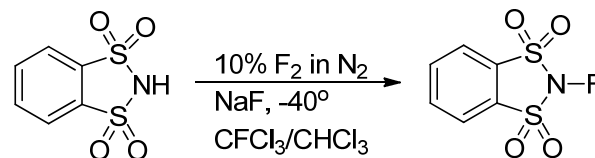
N-fluoropyridinium triflates:



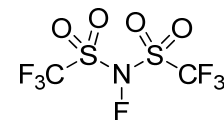
Selectfluor (F-TEDA-BF₄):



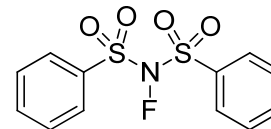
N-alkyl-N-fluorosulfonamides:



Perfluoroalkylsulfonamide:



N-Fluorobenzenesulfonimide (NSFI)



Bertozzi, C.R. *J Am Chem Soc.* **2008**, *130*, 11486-93.

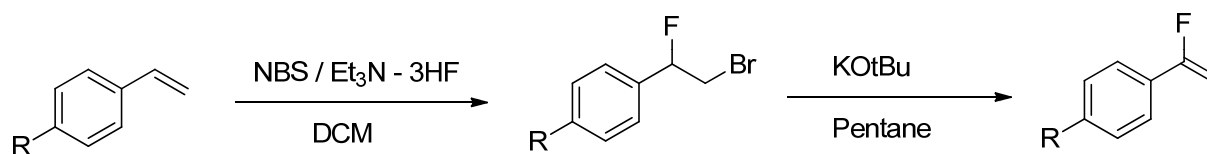
Lal, G. S.; Pez, G. P.; Syvret, R. G. *Chem. Rev.* **1996**, *96*, 1737-1756.



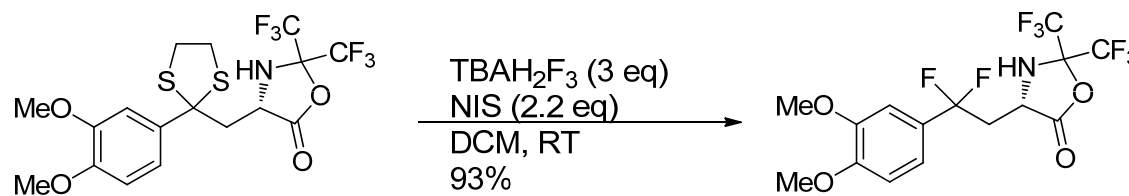
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Nucleophilic Fluorination

- Fluoride is strongly solvated in protic solvents
- Tight ion pairs form in aprotic solvents which is overcome by large counterions
- HF reactivity is suppressed via complexation with an amine



Oxidative-Desulfurization Method:

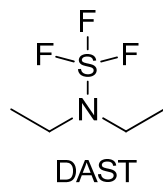


Ernet, T.; Haufe, G. *Tetrahedron Lett.* **1996**, *37*, 7251–7252.



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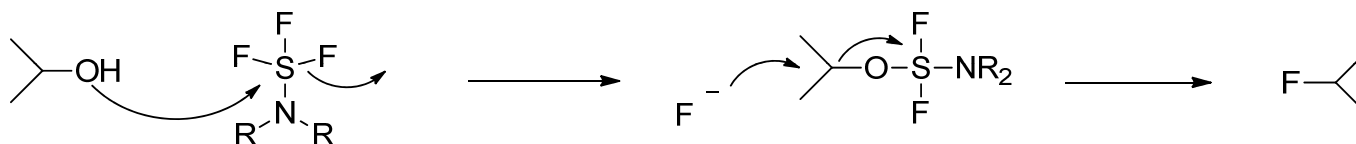
DAST



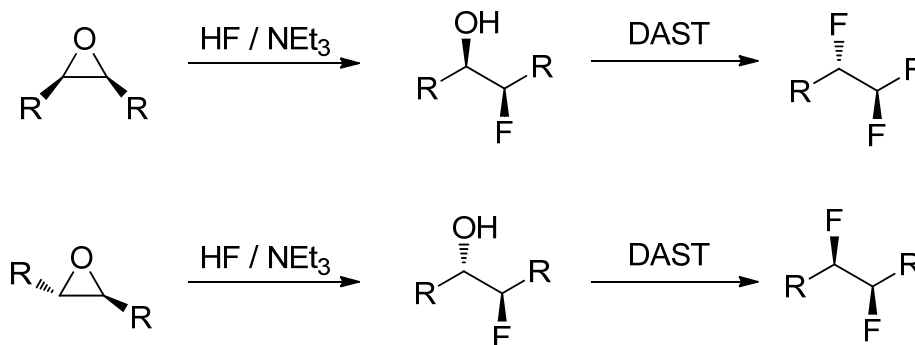
(Diethylaminosulfur trifluoride)



- Increased nucleophilicity through ion pair with soft lewis acid
- Deoxofluor compensates for thermal instability of DAST (reported to detonate at 90°C)



- Mechanism allows for stereospecific addition of fluorine by inversion of the existing chiral center

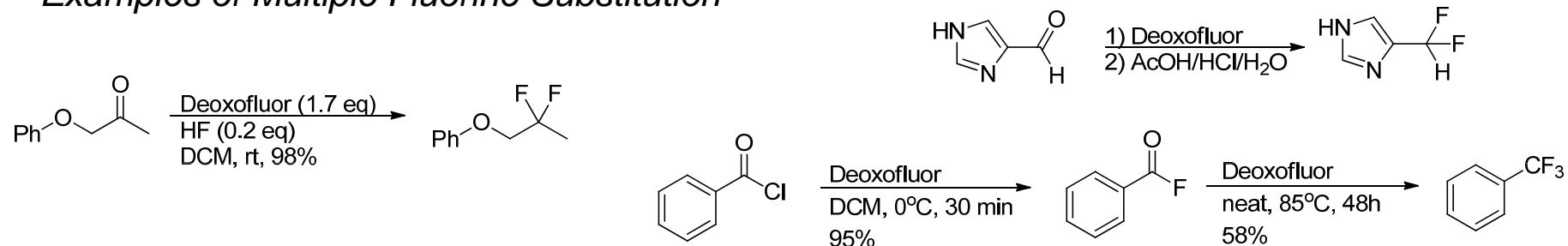


Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574–578.

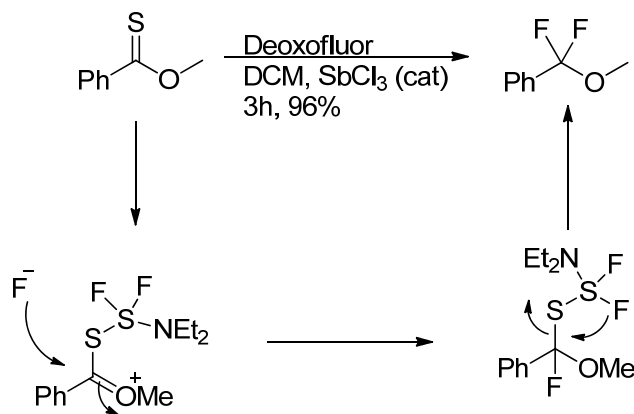
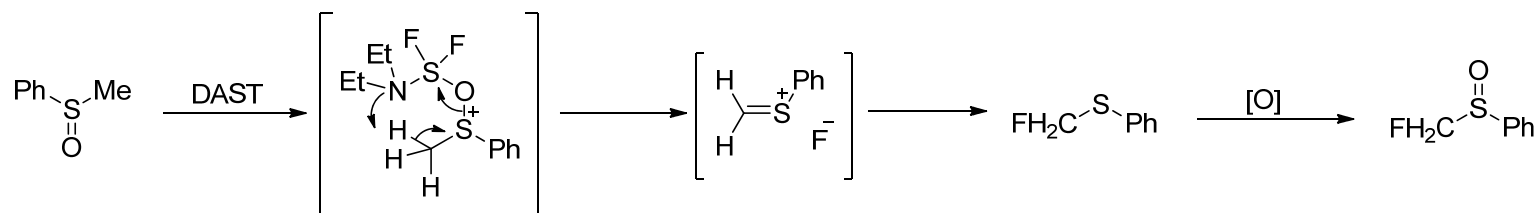


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Examples of Multiple Fluorine Substitution



Fluoropummerer

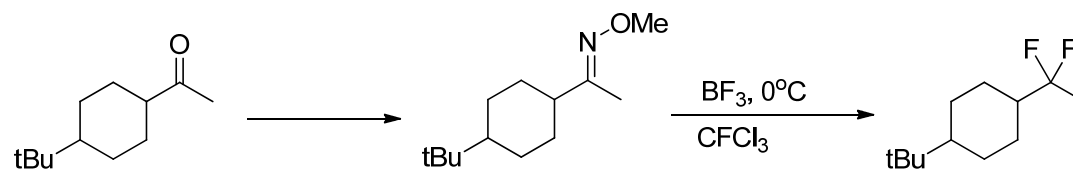
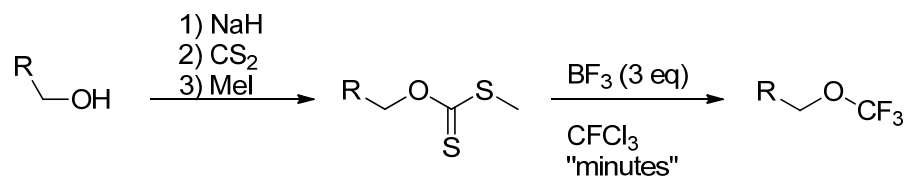


McCarthy, J. R.; Peet, N. P.; LeTourneau, M. E.; Inbasekaran, M. J. *Am. Chem. Soc.* **1985**, *107*, 735–737.



BF₃ Fluorinations

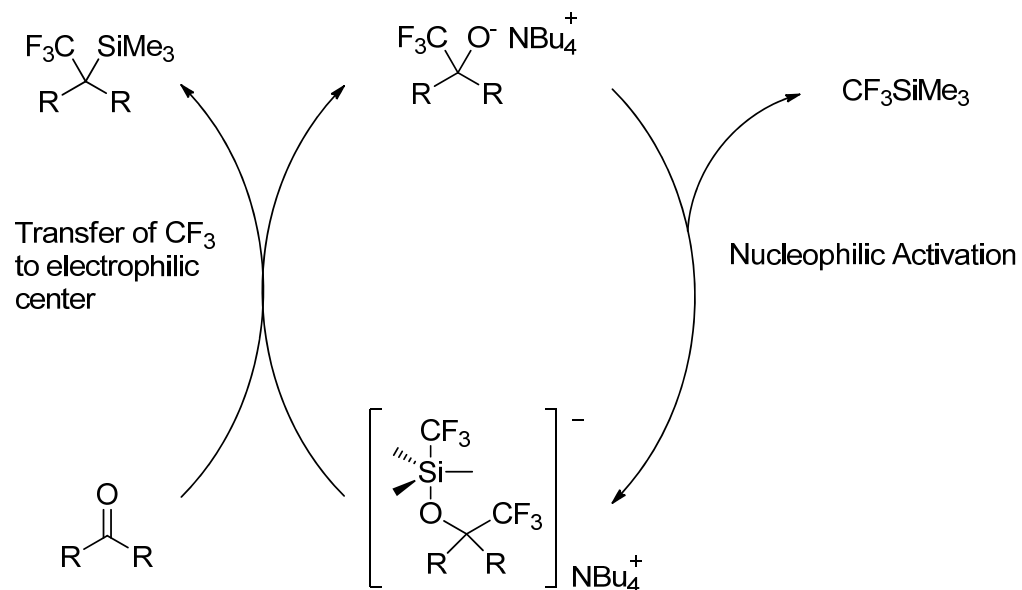
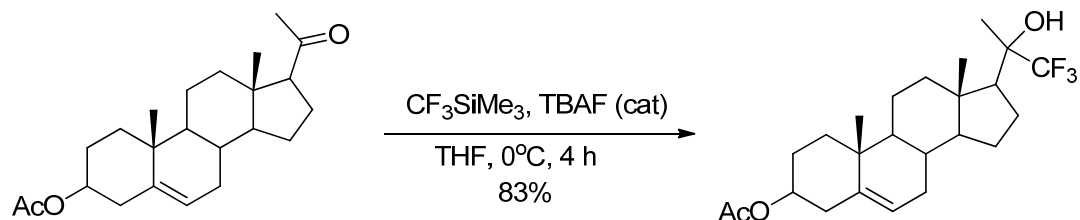
- Undergoes strong, uncontrollable reactions in H₂O or any hydroxylic solvent
- Reactivity relies on a soft acid (Br) and soft base (S or N) interaction positioning the fluorine for intramolecular transfer to the activated electrophile





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Trifluoromethylation



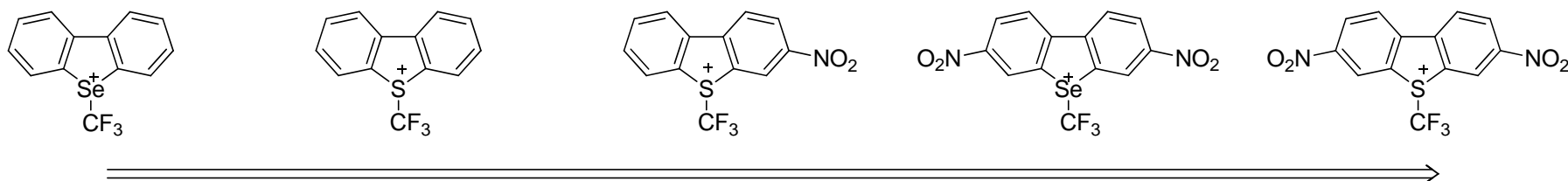
Prakash, G. K. S.; Yudin, A. K. *Chem. Rev.* **1997**, *7*, 757–786.

Singh, R. P.; Shreeve, J. M. *Tetrahedron* **2000**, *56*, 7613–7632.

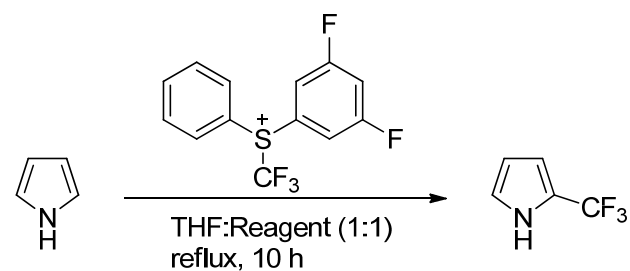
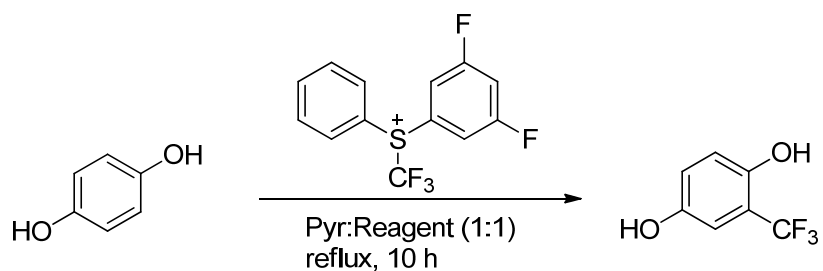


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Electrophilic Trifluoromethylating Reagents:



(Displayed in order of reactivity from left to right)



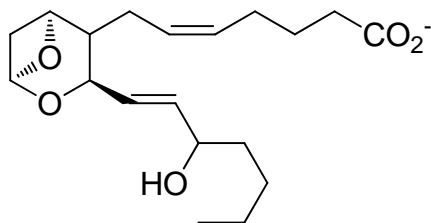
Billard, T.; Bruns, S.; Langlois, B. R. Org. Lett. 2000, 2, 2101–2103.



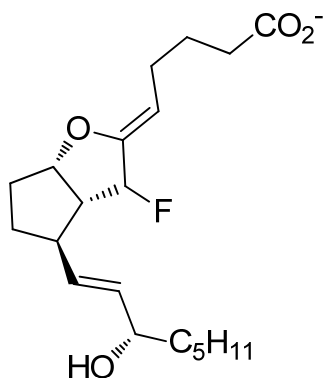
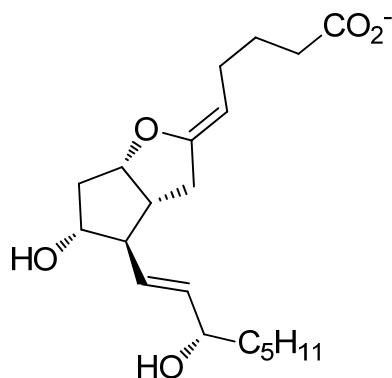
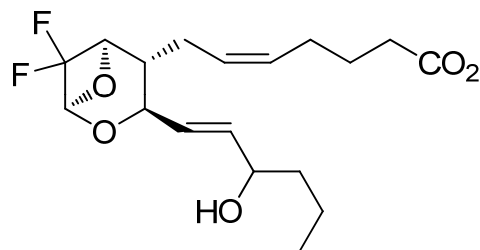
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Effects of Fluorine on Rates of Drug Metabolism

Thromboxane A₂



- Half life in biological conditions = 32s
- CF₂ reduces the rate carbonium ion formation and acid hydrolysis resulting in 10⁸ slower metabolic rate



Prostacyclin

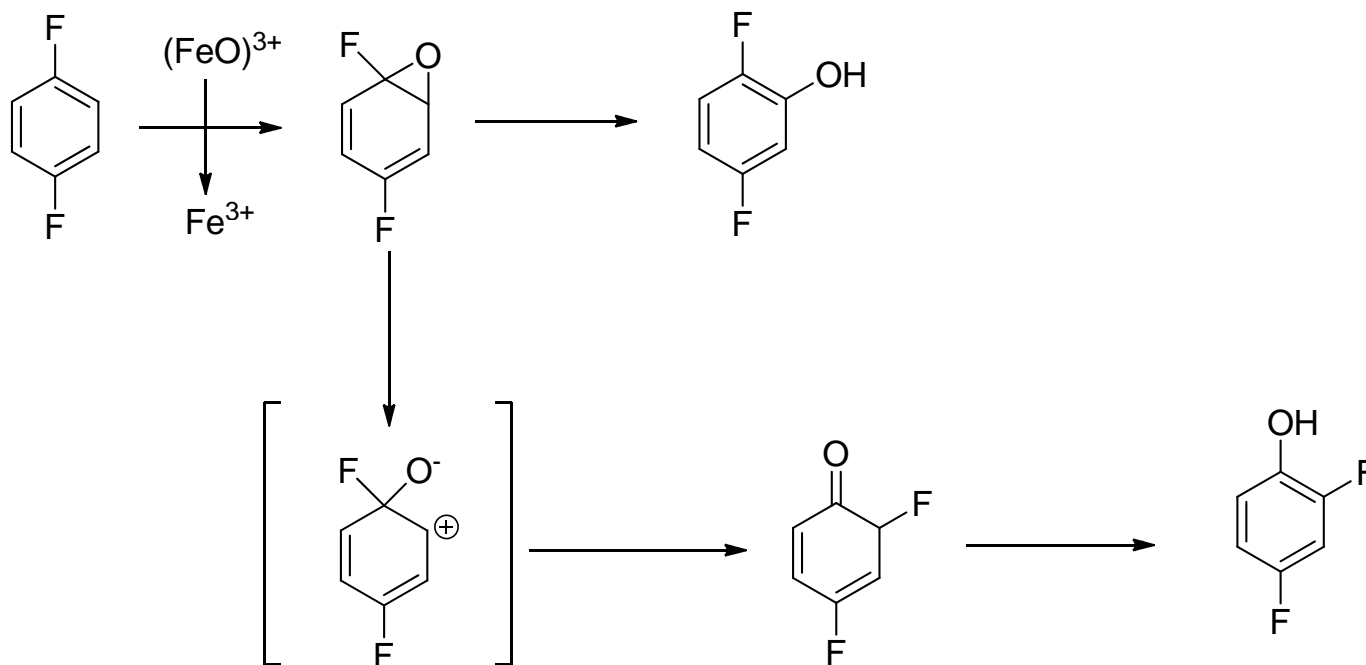
- Fluorine substitution deactivates the enol ether toward acid hydrolysis
- 150 fold increase in biological half life



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Prevention of Metabolic Bioactivation

- Fluorination of aromatic systems is used to both prevent site specific oxidation and lessen the aptitude for cytochrome p450 oxidation
- Likely aromatic sites of p450 oxidation can now be predicted via computational methods
- Though oxidation is possible of fluorobenzenes, the rate is much less for tri- and tetra-substituted systems

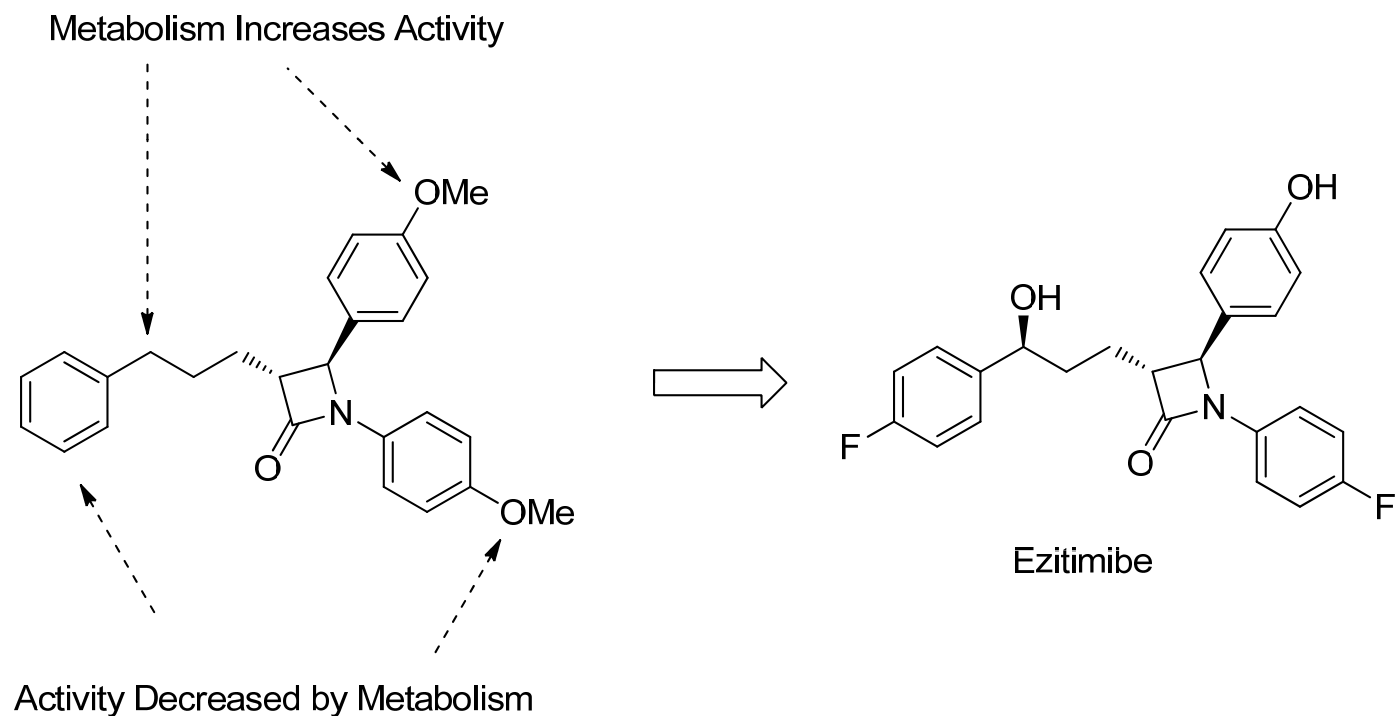


Koerts J, Soffers AEMF, Vervoort J, De Jager A, Rietjens IMC. *M. Chem. Res. Toxicol.* 1998, 11, 503–12



Ezetimibe

- licensed drug used to block cholesterol absorption
- Synthetic studies showed fluctuating activity based on sites of oxidation

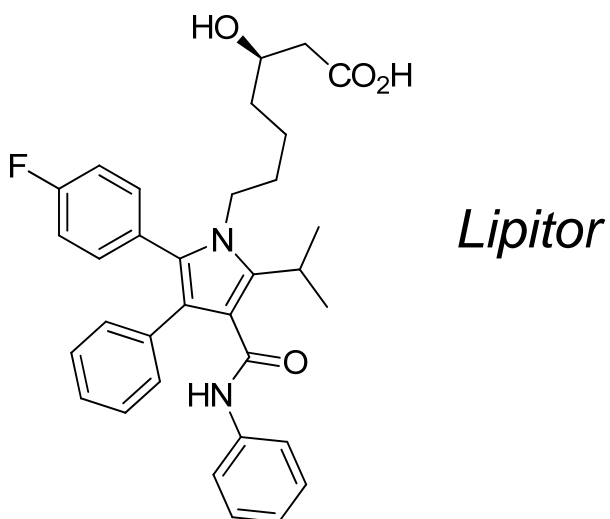




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Intermolecular Effects of Fluorine Substitution

- X-ray structure of Lipitor cocrystallized with HMG-CoA reductase shows guanidinium stacking with the fluorophenyl substituent with polar interactions between N and F
- Favorable C-F interaction demonstrated with H-bond donors in peptide substrates (peptide backbone, His, Tyr, Ser, Thr)
- “Hydrophobic hydration” of fluorinated compounds gives rise to positive entropies of binding upon desolvation of ordered H₂O shells



Biffinger, J. C.; Kim, H. W.; DiMugno, S. G. ChemBioChem 2004, 5, 622–627.