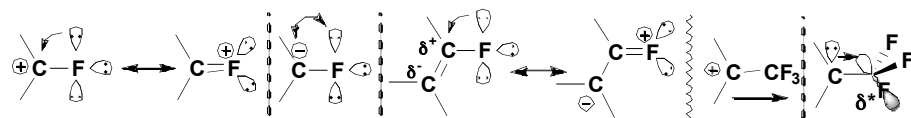


Introduction

- F_2 : Isolated in 1886 by Moissan; 13th most abundant element; only 13 naturally occurring organic compounds are known.
- The usefulness of fluorinated material was first realized during the "Manhattan Project" (manipulation of UF_6)
- Fluorine Effects:
 - Enhanced thermal stability (C-F 107 kcal/mol)
 - Increased lipophilicity to enhance bioavailability
 - Mimicking of enzyme substrate (comparable in size to H, 1.47Å vs 1.20Å)
 - Isoelectronic effects to $-O^-$ and $-OH$
 - The high electronegativity of fluorine frequently alerts chemical reactivity
 - Blocking effect in metabolic transformations



- Utility of some highly fluorinated compounds:
 - Coolants and aerosol propellants: CCl_2F_2 , $CF_2Cl-CFCl_2$, *cyclo*- C_4F_8
 - Fire extinguisher: CF_3Br , CF_2ClBr
 - Inhalation anaesthesia: THF- F_8 , Dioxane- F_8
 - Surfactants: C_7F_{15} to $C_{10}F_{21}-SO_3H$
 - Polymers: high melting point; high thermal and chemical stability
 - Blood substitutes: perfluorinated cycloalkanes, amines, and *O*-heterocycles
 - Perfluorinated solvents and reagents

Reviews

General Reviews:

- Chemistry of Organic Fluorine Compound II: A Critical Review* ACS, 1995.
- ACIEE* 1981, 20, 647.
- Organic Process Research & Development* 2008, 12, 305.
- Electrophilic Fluorination: *Tetrahedron* 2004, 60, 1435.
- Fluoroaromatic Compounds: *Aldrichimica Acta* 1988, 21, 3.
- DAST: *Synthesis* 2002, 2561.
- Selectfluor: *ACIEE* 2005, 44, 192.
- BrF_3 : *Acc. Chem. Res.* 2005, 38, 803.
- XeF_2 : *Tetrahedron* 1995, 51, 6605.
- Electrochemical Fluorination: *Tetrahedron* 1999, 55, 12431.
- gem*-Difluoromethylene Compounds: *Tetrahedron* 1996, 52, 8619.
- Trifluoromethylation: *Tetrahedron* 1992, 48, 6555.

Reaction Types

- Electrophilic Fluorination
- Nucleophilic Fluorination
- Fluorinated Synthons
- Electrochemical Fluorination

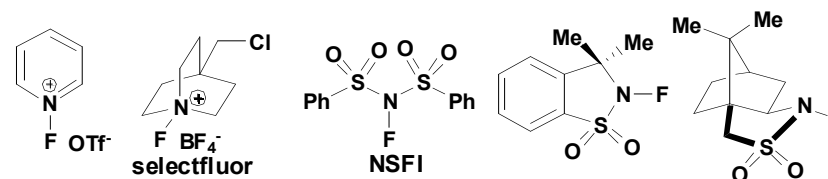
Fluorination Reagents

Inorganic Reagents: AgF_2 , CoF_3 , $CsSO_4F$, HgF_2 , $RbSO_4F$, $PbF_2(OAc)_2$, $Tl(O_2CCF_3)_3$

Ammonium Fluorides: $Et_3N \cdot 3HF$ (TREAT-HF), $(HF)_x \cdot Pyr$ (Olah's Reagent) PPHF

Hypofluorites: CH_3COOF , CF_3COOF , CF_3OF , $FOClO_3$

N-Fluoro Reagents:



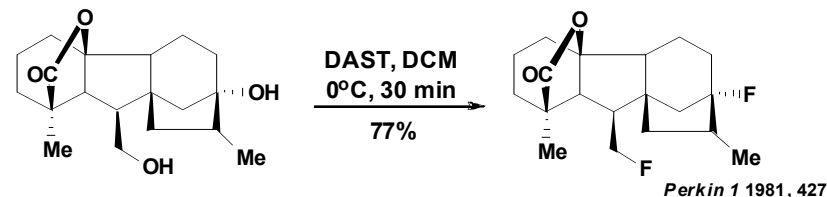
Fluoroaminosulfuranes: Et_2NSF_3 (DAST), $(Me_2N)_3S(Me)_3SiF_2$ (TASF)

Other Reagents: $PhIF_2$, BF_3 , XeF_2

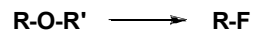
sp^3 -C-F



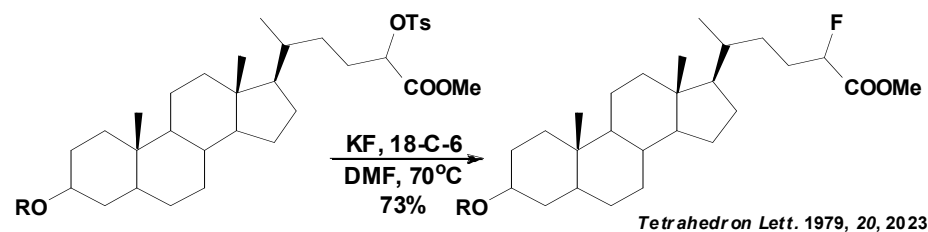
$R'=H$: DAST, SF_4/Et_3N or Pyr , $CHClCF_2NEt_2$, $(HF)_x \cdot Pyr$ (benzylic primary OH)



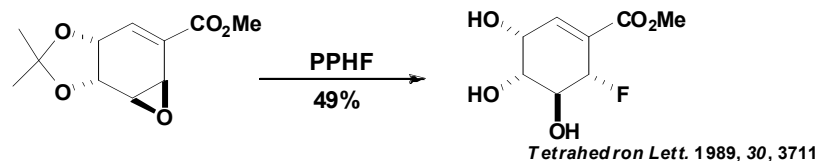
sp^3 -C-F



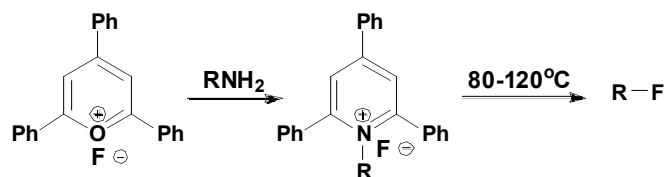
R' = -OTs and analogues: KF, CsF, TREAT-HF, TBAF



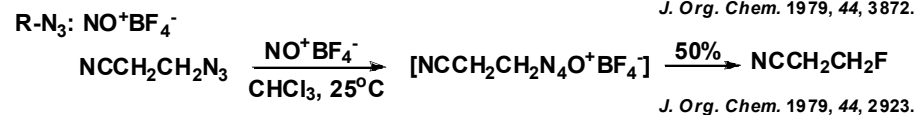
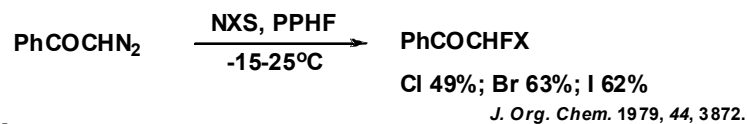
Epoxide Opening: CsF, KF, TREAT-HF, PPHF, DSAT, SF₄



R-NH₂: NaNO₂/PPHF (α -amino acids); 2,4,6-triphenylpyrium flouride (1° alkyl, benzylic)



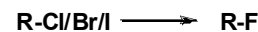
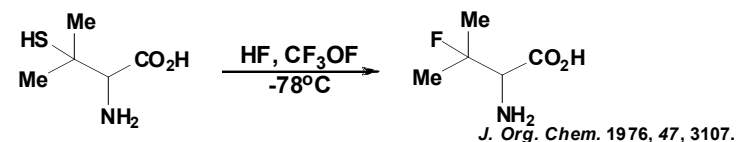
R-CHN₂: Diazoalkanes-- acyl fluoride/HF/KF; Dizaoketonss-- HF.Pyr, NXS/HF.Pyr



sp^3 -C-F



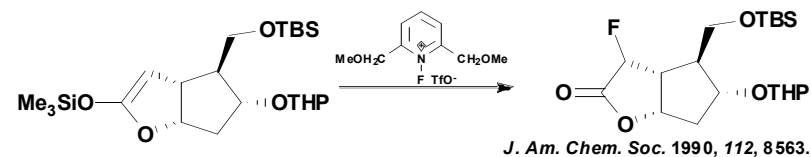
HF/CF₃OF, HF/F₂, HF/NCS



spray-dried KF, CsF, AgF, AgBF₄, TBAF, HgF₂



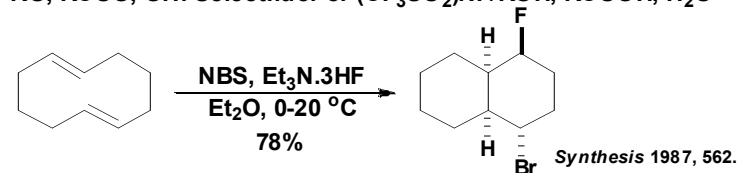
Formation of α -fluoro carbonyl compounds:



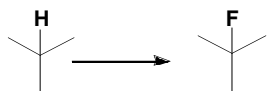
Alkene fluorination



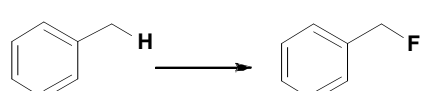
A = H: HF, HF.Pyr, polyvinylpyridium poly(hydrogen fluoride)
 A = F: TREAT-HF or PPHF/Selectfluor or (CF₃SO₂)NF, XeF₂, CsSO₄F
 A = Cl, Br, I: NXS/TREAT-HF or PPHF
 A = RO, RCOO, OH: Selectfluor or (CF₃SO₂)NF/ROH, RCOOH, H₂O



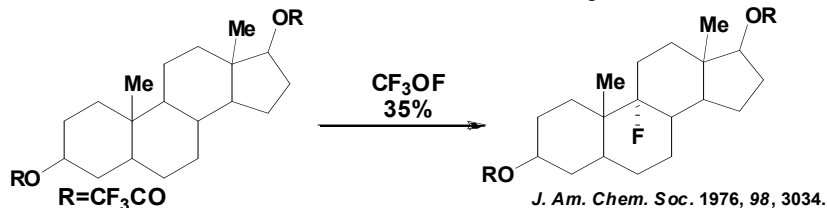
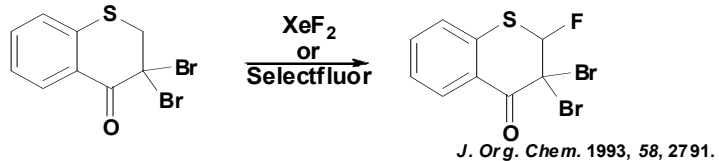
sp^3 -C-F



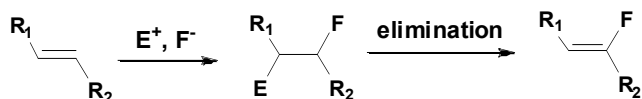
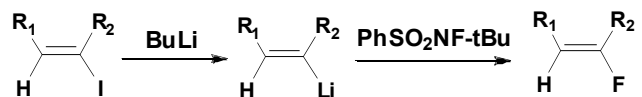
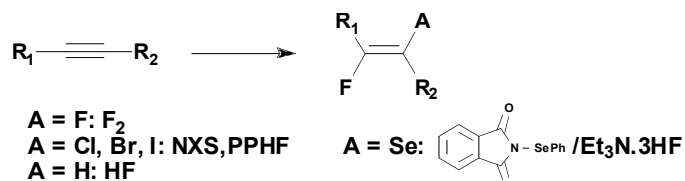
F_2 , XeF_2 , $CsSO_4F$, CF_3OF ,
 $NO_2BF_4/HF.Pyr$



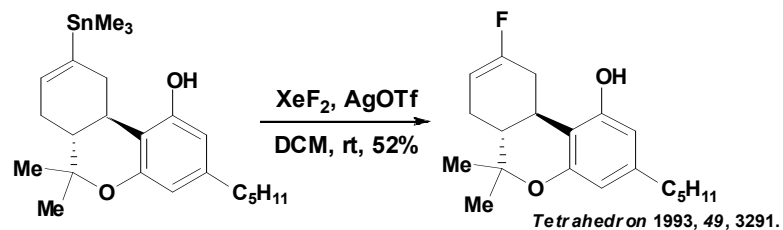
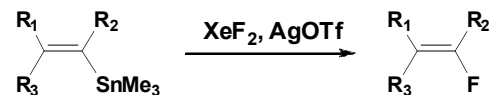
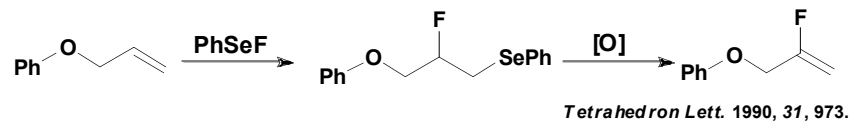
CF_3OF , $CsSO_4F$, $AgF/TiO_2/h\nu$



sp^2 -C-F

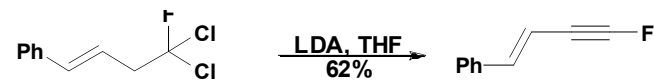


sp^2 -C-F



sp -C-F

generated via fluorinated synthons

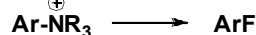
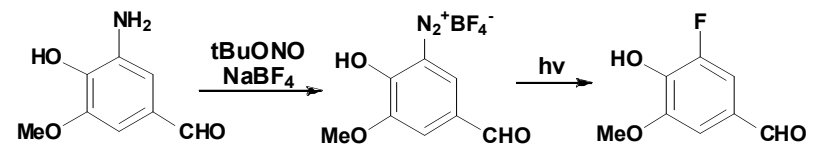


J. Fluorine Chem. 1988, 41, 425.

Ar-F



Balz-Schiemann reaction: $NaNO_2/HCl/HBF_4$, $tBuONO/NaBF_4/h\nu$

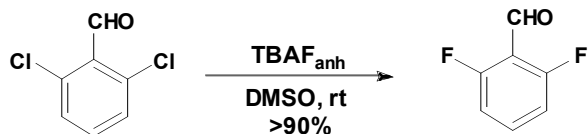
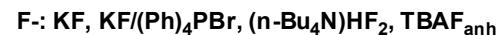
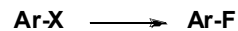


KF/CsF in DMSO

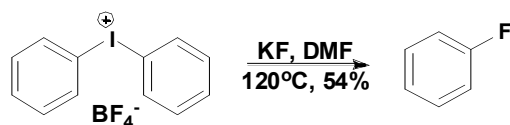
Ar-F



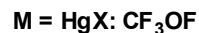
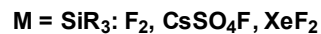
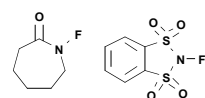
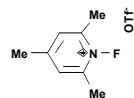
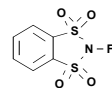
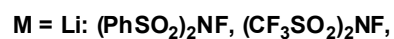
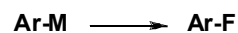
J. Fluorine Chem. 1990, 48, 189.



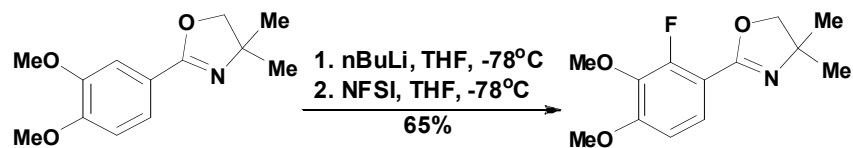
ACIEE 2006, 45, 2720.



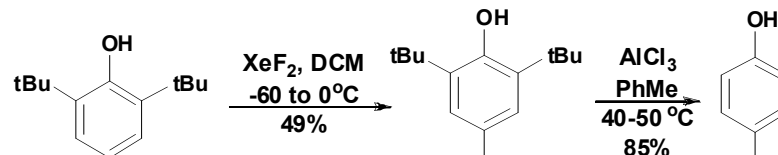
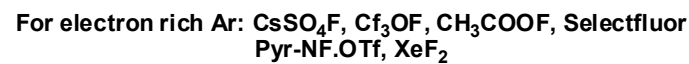
J. Fluorine Chem. 1982, 21, 385.



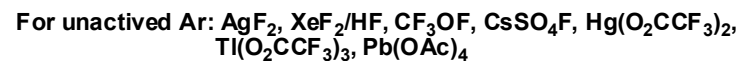
Ar-F



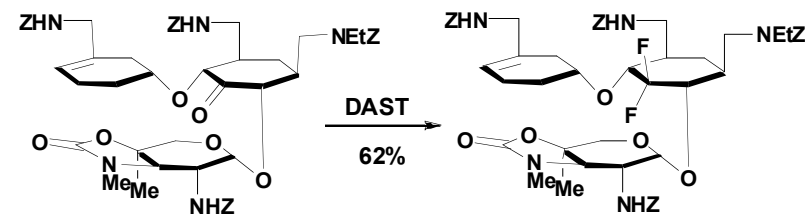
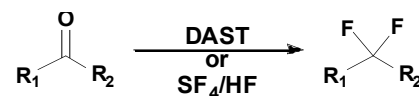
Tetrahedron Lett. 1994, 35, 3465.



Biosci. Biotech. Biochem. 1994, 58, 594

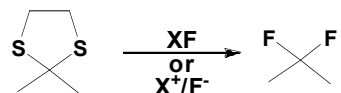


gem-CF₂

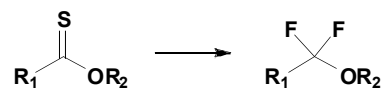


Carbohydrates Research 1993, 238, 147.

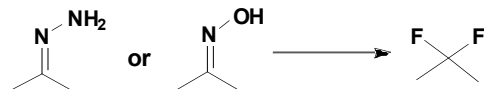
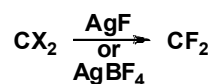
gem-CF₂



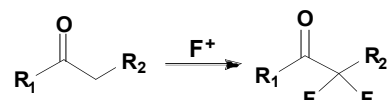
Conditions: BrF, IF, NXS/PPHF, NOBF₄/PPHF



Conditions: DAST, BF₃, NBS or NIS/F⁻



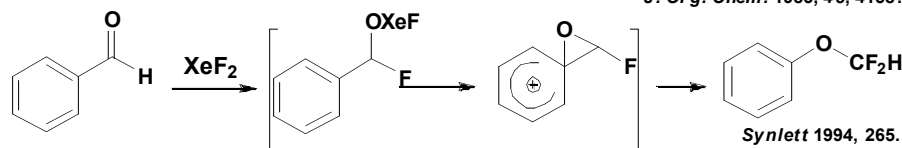
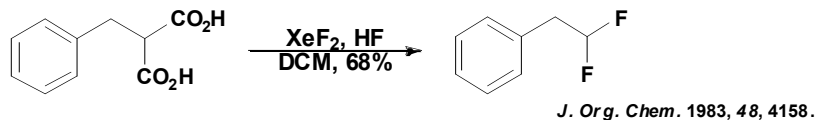
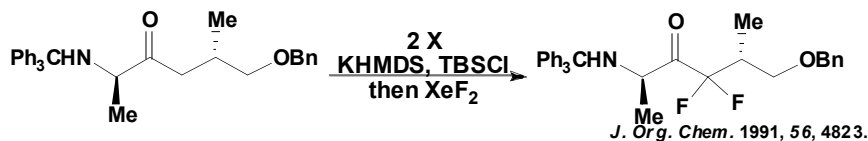
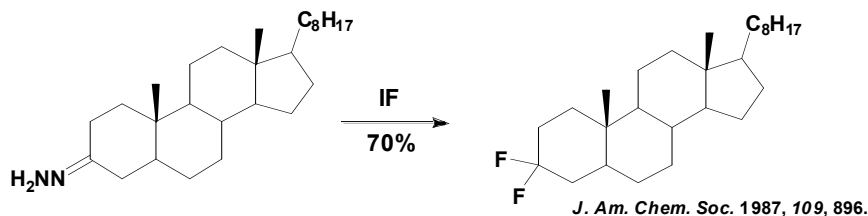
Conditions: IF, NIS or NBS/PPHF



Conditions: PPHF

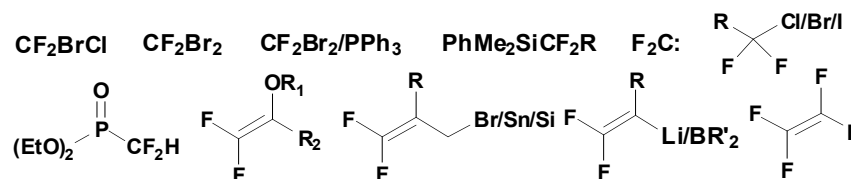


Conditions: PPHF/NXS



gem-CF₂

Difluoromethylene Synthons:



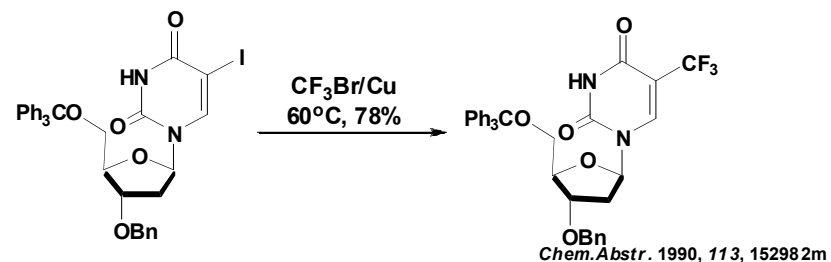
Ar-CF₃

Ar-CX₃ to Ar-CF₃

X = Cl: SbF₃, HF_{anh}, AlCl₃/FCCl₃, HF/CCl₄
CX₃ = CS₂H: XeF₂; CX₃ = CO₂H: DSAT, SF₄/HF

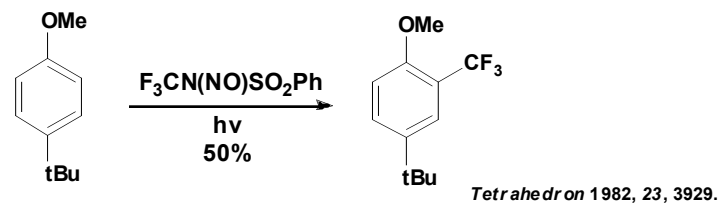
The use of CuCF₃ with Ar-Cl/Br/I

Preparation: Cu(I)/CF₃SiR₃, Cu(I)/(CF₃)ZnX, Cu/ICF₃, Cu/BrCF₃, Cu/(CF₃)₂Hg, Cu(I)/CF₃CO₂M, Cu/CF₃N(NO)SO₂CF₃, Cu/CF₃SO₂Cl, Cu/CF₂Br₂

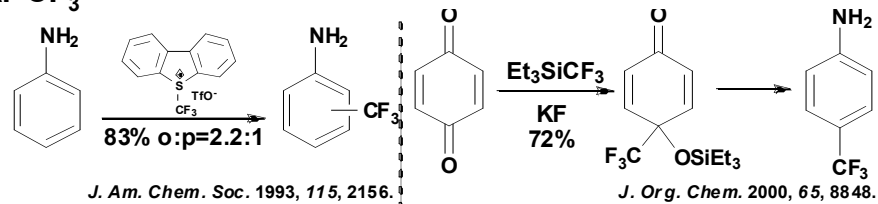


The use of F₃C•

Preparation: ICF₃, BrCF₃, Hg(CF₃)₂/hv, F₃CSO₂Na/tBuOOH, F₃CCO₂H/XeF₂, F₃CN(NO)SO₂Ph/hv, F₃CN=NCF₃/hv



Ar-CF₃

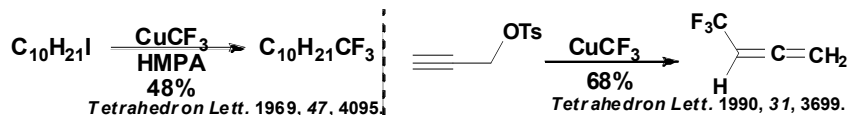


Alkane, alkene, and alkyne CF₃

-CX₃ to -CF₃

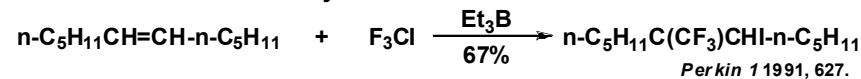
The use of CuCF₃

Aliphatic Cl/Br/I, vinyl Br/OH, benzyl OH

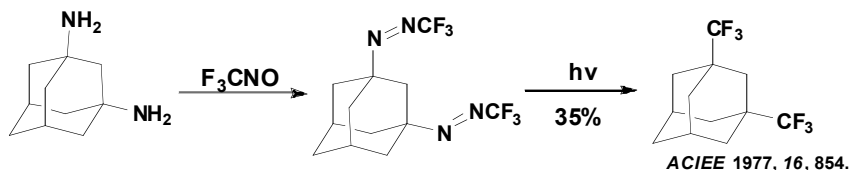


The use of F₃C•

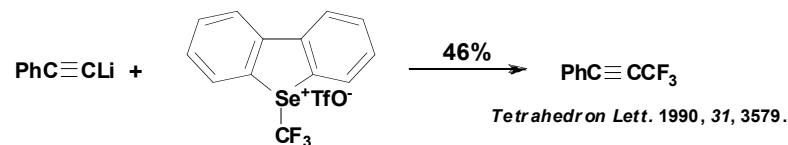
Addition to alkenes and alkynes



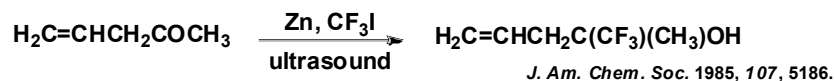
F₃CNO



Other Methods

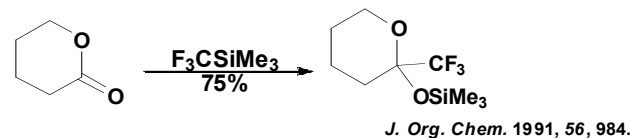


F₃CMX

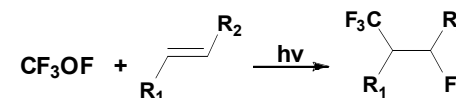
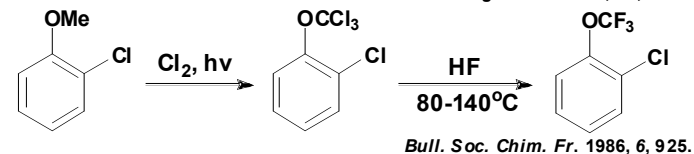
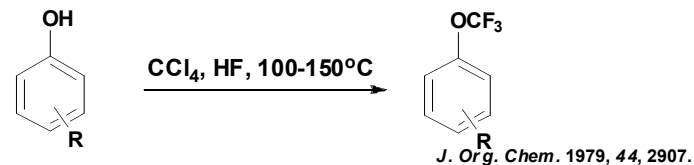
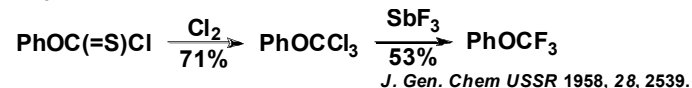


Alkane, alkene, and alkyne CF₃

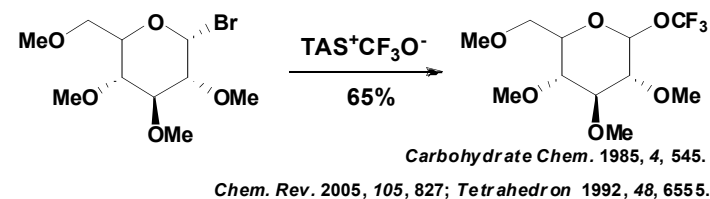
F₃CSiR₃



RO-CF₃

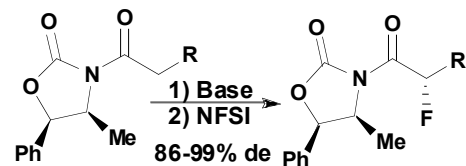


(Me₂N)₃S⁺CF₃O⁻ (TAS⁺CF₃O⁻)

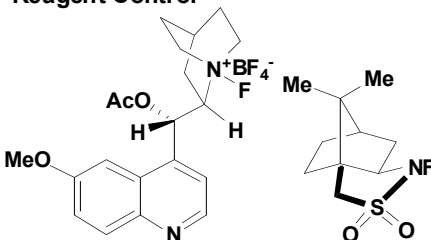


Enantioselective Monofluorination

Substrate Control

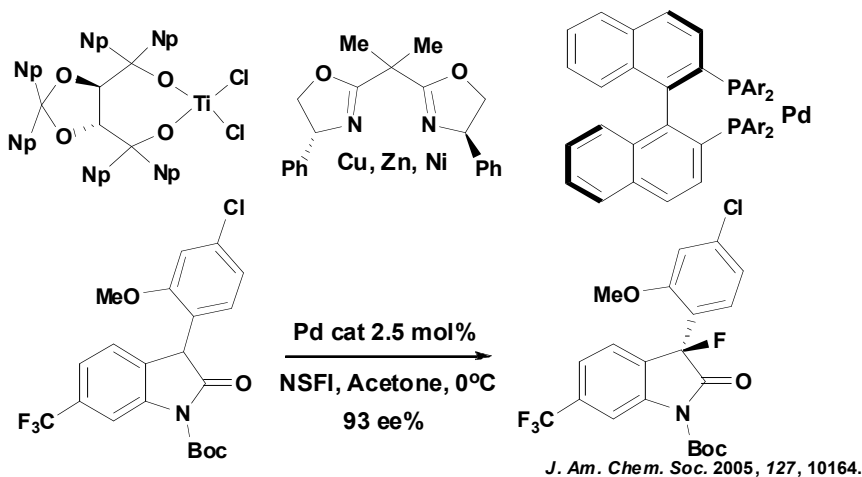


Reagent Control



Catalyst Control

Metal-Mediated Catalyst Control



Organocatalysis

