

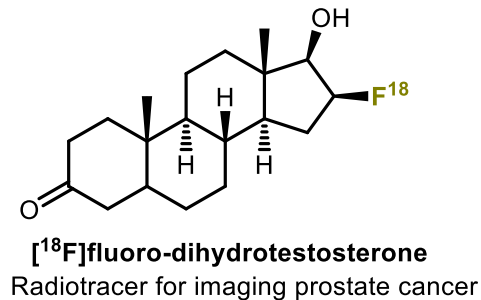
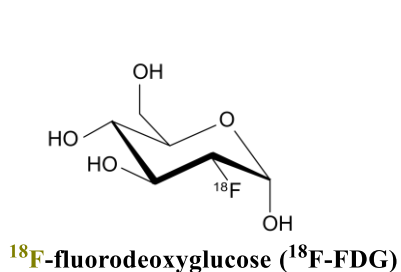
Late Stage Fluorination and its Medicinal Use

MSM Lab Group Seminar
26.09.2020

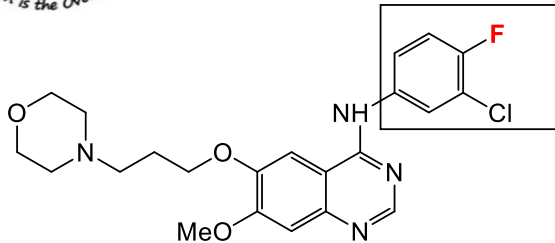


By
Dhananjay Pal
M.Sc. 2nd Year
Department of Chemistry
IIT Kharagpur

- ❖ Approximately 20% of commercial pharmaceuticals and 30% of agrochemicals contain at least one fluorine atom.
- ❖ Important role in drug design and diagnostics as F-18 have the most ideal half life 109.8 minutes.
- ❖ Enhance membrane permeability and increase bioavailability of Drugs.
- ❖ Stronger target binding ability and slower oxidative metabolism.
- ❖ The widespread use of [^{18}F]fluoro-2-deoxyglucose, [^{18}F]FDG in PET has an impact in Oncology.

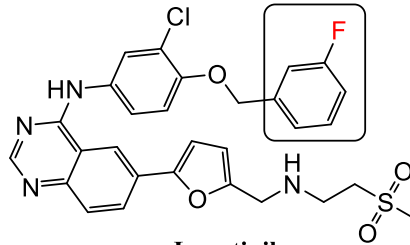


Some of the fluorinated drugs



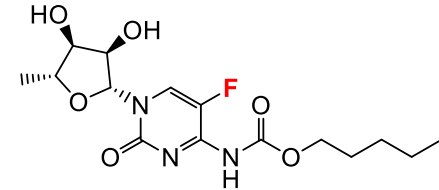
Gefitinib

Oral epidermal growth factor receptor (EGFR) used for certain breast, lung and other cancers treatment



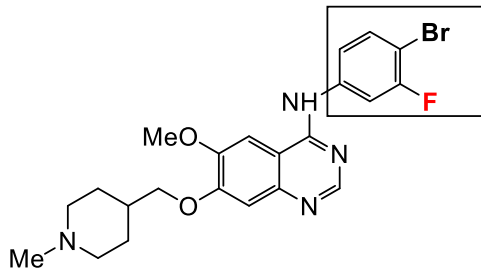
Lapatinib

Orally active drug for breast cancer and other solid tumours



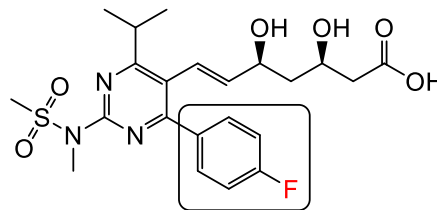
Capecitabine

Chemotherapy medication used to treat breast cancer, gastric cancer and colorectal cancer



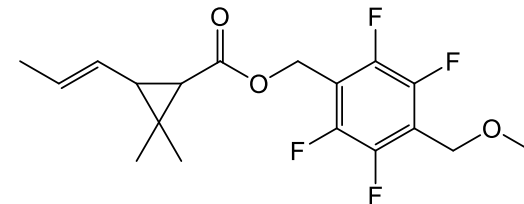
Vandetanib

Anti-cancer drug used for the treatment of certain tumours of the thyroid gland.



Rosuvastatin

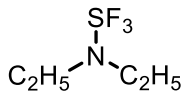
Used to prevent cardiovascular disease in those at high risk and treat abnormal lipids



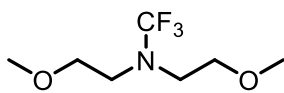
Metofluthrin

Used as an insect repellent

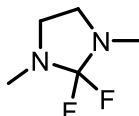
Nucleophilic fluorinating reagents:



DAST



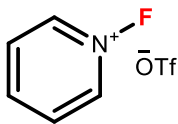
DEOXOFLUOR



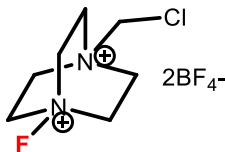
DFI

CsF, AgF, anhyd. Me₄NF

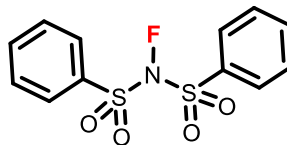
Electrophilic fluorinating reagents:



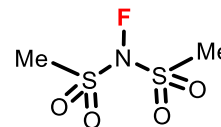
N-fluoropyridinium triflate



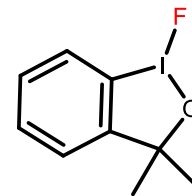
SELECTFLUOR



N-fluorobenzenesulfonimide(NFSI)

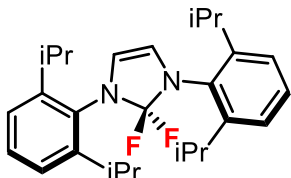


Me-NFSI

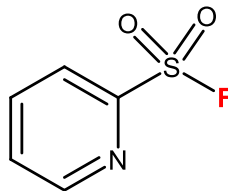


Fluorobenziodoxole

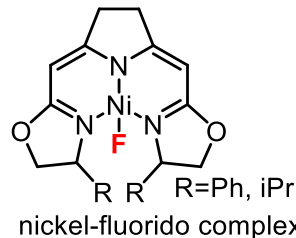
Deoxy-fluorinating reagent :



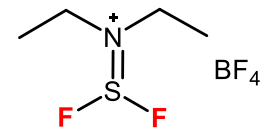
PhenoFlour



PyFlour

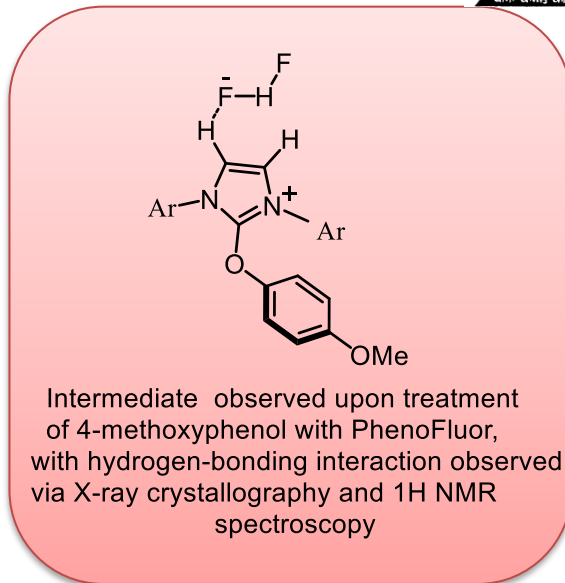
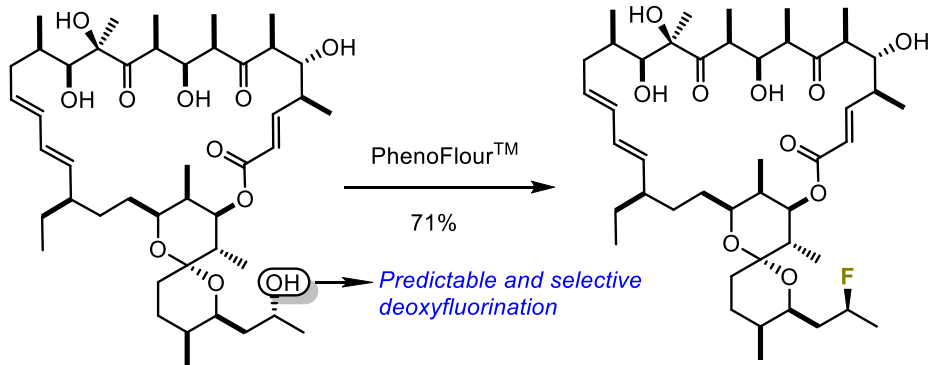
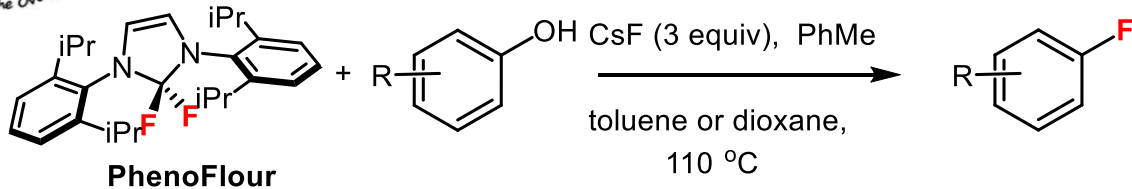


nickel-fluorido complex



XtalFluor E

Fluorination by PhenoFlour

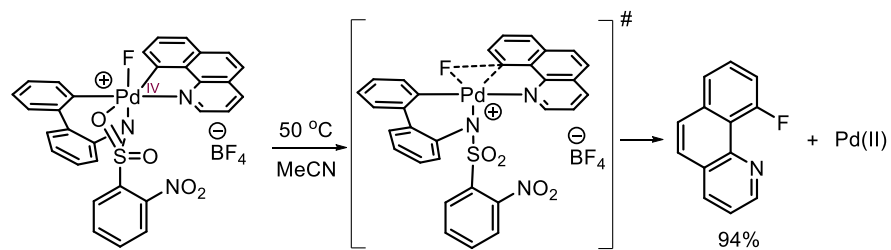
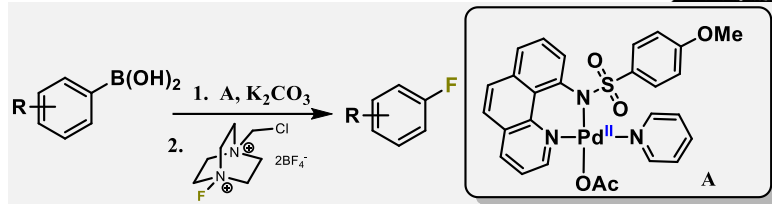
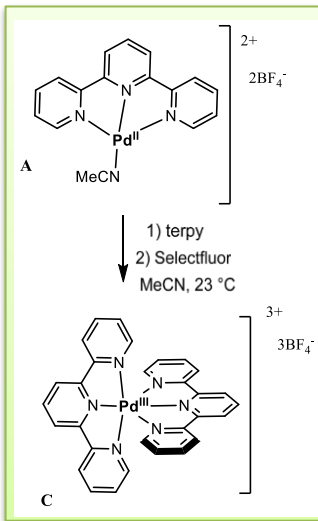
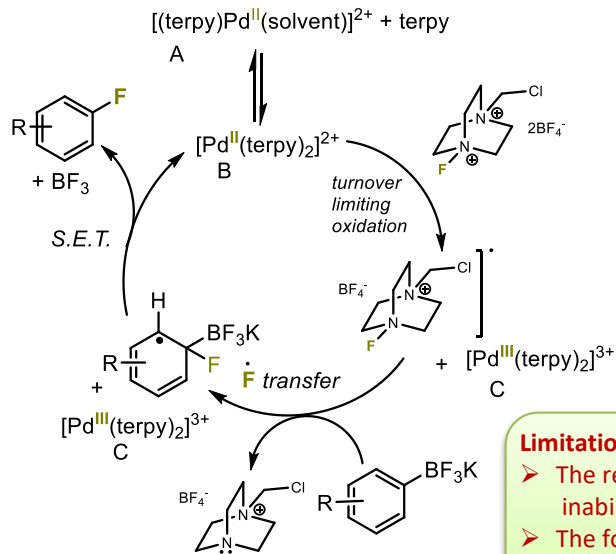
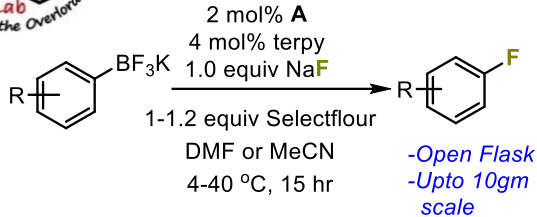


Disadvantages of PhenoFlour

- Not suitable for large-scale use due to the reagent's mass, catalytic turnover should be conceptually possible.
- PhenoFlour provides for a practical synthesis of aryl fluorides, but is currently applicable only to substrates that contain the requisite phenol functionality.

So, The development of a catalytic reagent with reactivity analogous to that of PhenoFlour would be a major advance !!

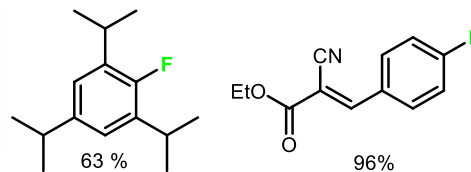
Palladium-catalyzed fluorination



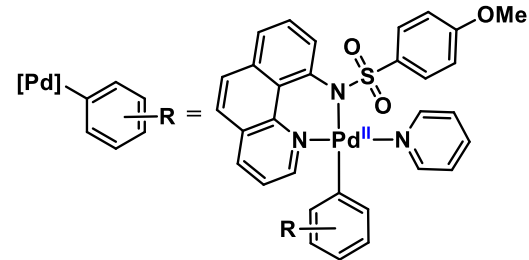
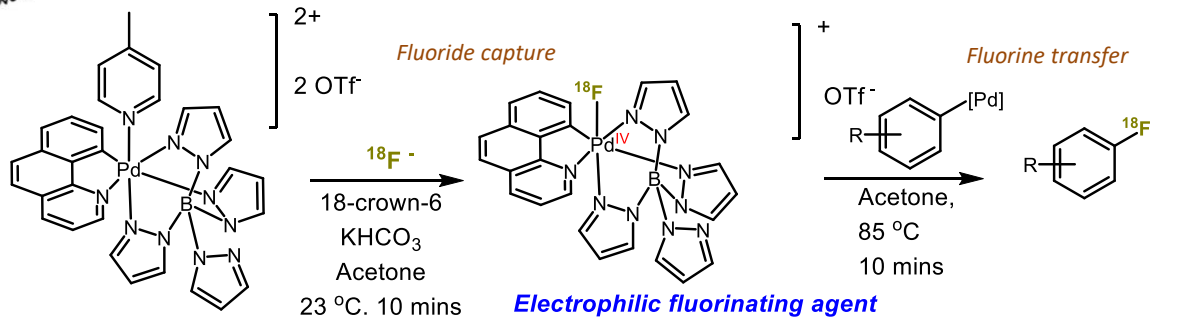
- Pd-mediated electrophilic fluorination of arenes
- Well defined C-F reductive elimination from Pd(IV) fluoride A featuring a hemilabile pyridyl-sulfonamide ligand to promote reductive elimination via a five-coordinate transition state.

Limitations :

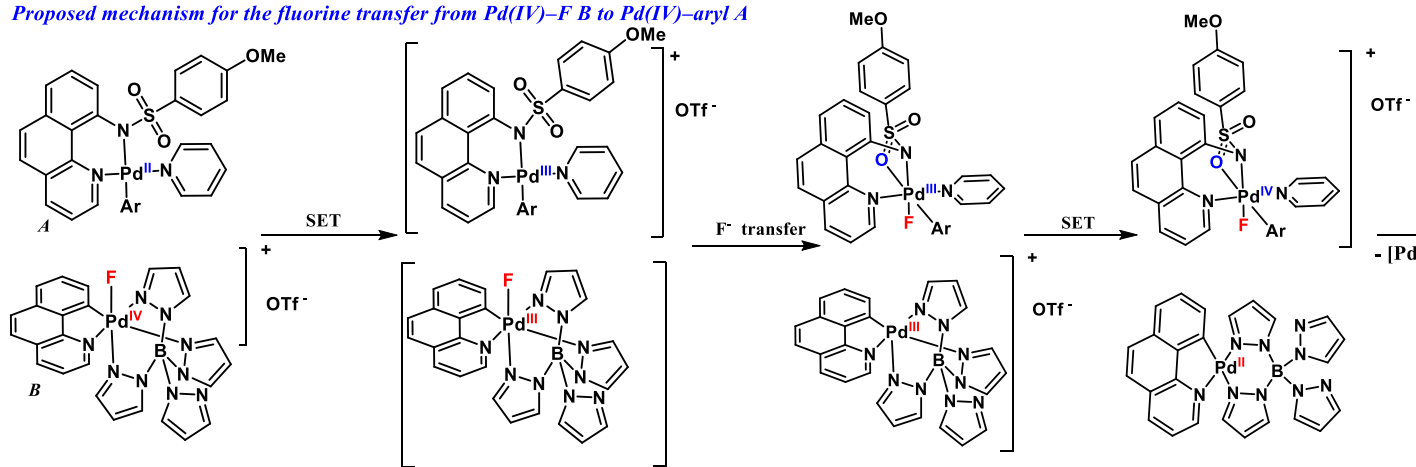
- The reaction include the inability to fluorinate heterocycles
- The formation of constitutional isomers for some electron-poor substrates



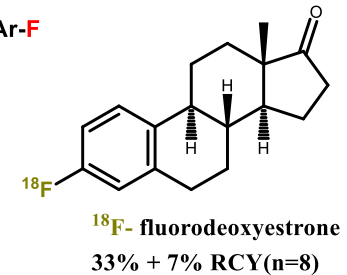
Palladium-catalyzed fluorination



Proposed mechanism for the fluorine transfer from Pd(IV)-F B to Pd(IV)-aryl A



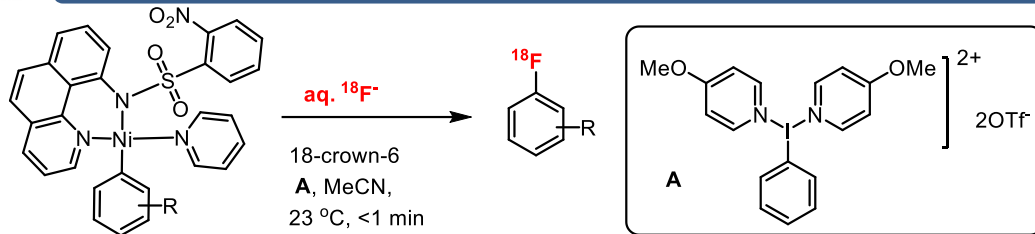
- Two step procedure
- Very fast intermediate Pd(IV)-F formation
- Unusual SET/fluoride transfer/SET mechanism in Fluorine transfer



Ni-mediated fluorination

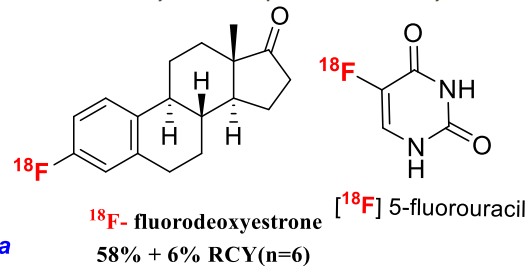
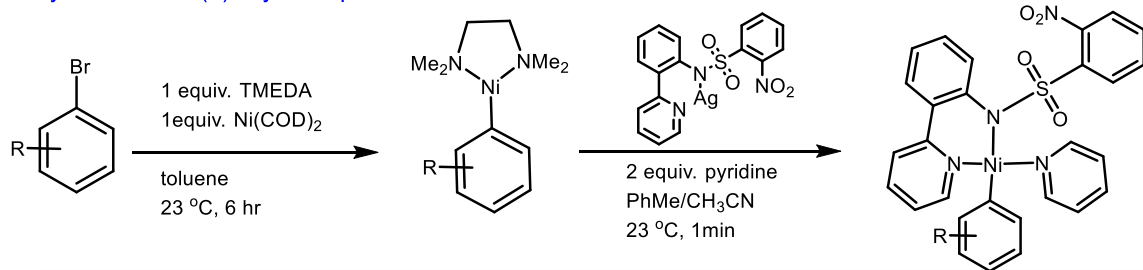
One-step Ni-mediated C-¹⁸F bond formation using aqueous ¹⁸F and oxidant

- one-pot method
- Fast procedure



After less than 1 min after addition, the fluorination reactions were analyzed by radioTLC and HPLC for radiochemical yield and product identity

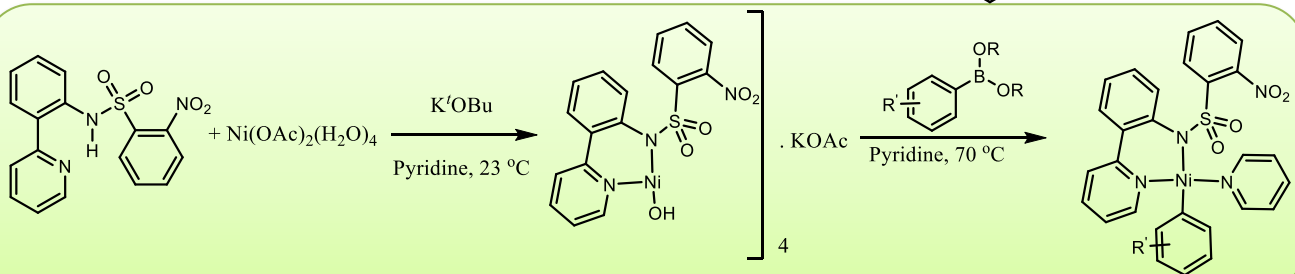
Synthesis of Ni(II) Aryl Complexes



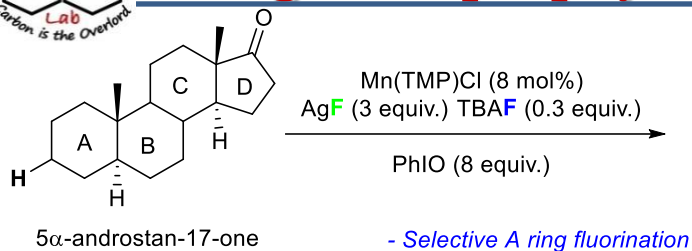
Successful for the synthesis of

- Electron-rich
- Electron-poor
- Ortho-, meta-, and para-substituted
- Densely functionalized aryl fluorides
- Alkenyl fluorides

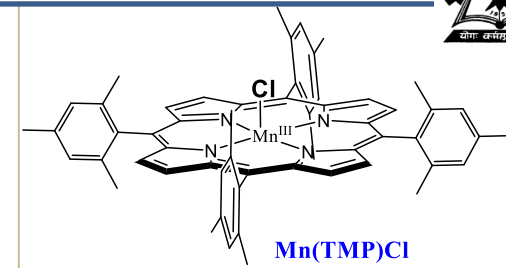
❖ Tertiary amines are currently not tolerated, presumably due to the unproductive reaction of oxidant



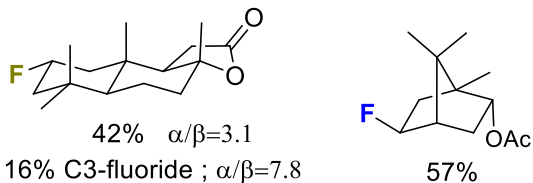
Manganese porphyrin-catalyzed selective C-H fluorinations



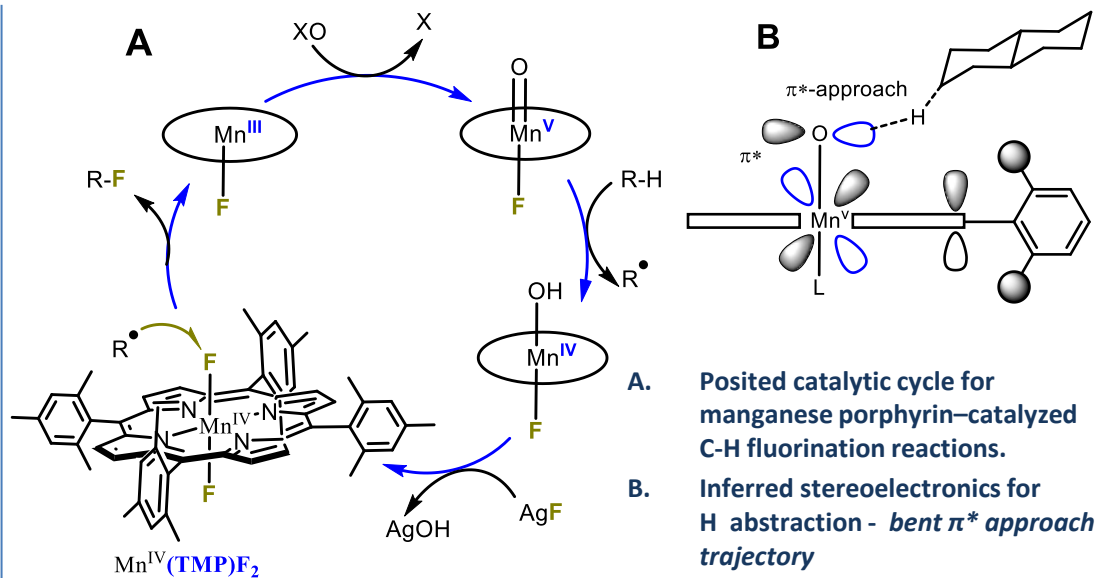
- Selective A ring fluorination



- Ultra-dry conditions are not required
- C-H bond cleavage is the rate-limiting step in the reaction (from KIE)

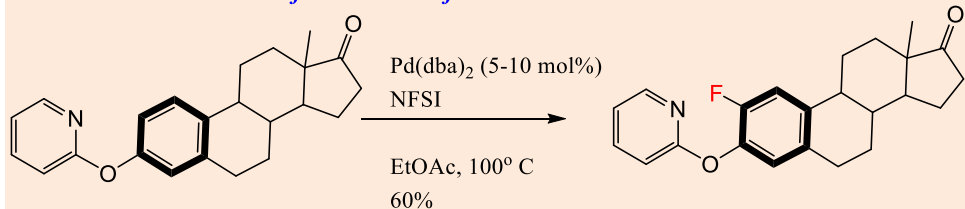


- Fluoride binding to separately prepared $\text{Mn}^{\text{IV}}(\text{O})(\text{TMP})$ was indicated by an ultraviolet (UV) spectral shift (423 to 427 nm)



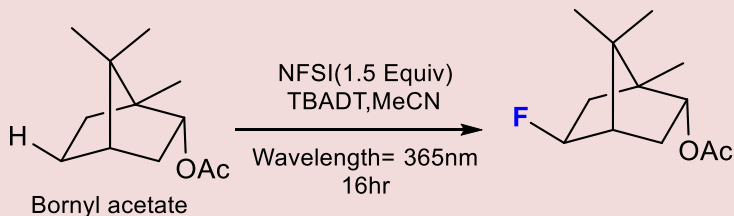
Few more Example of C-H fluorination

C-H fluorination of estrone derivative

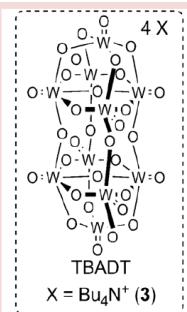


Shao-Jie Lou *et al.* *ACS Catalysis*, **2015**, 5(5), 2846-2849.

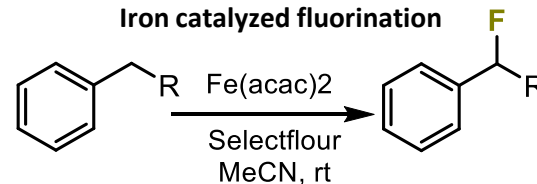
TBADT-catalyzed fluorination of Bornyl acetate



Halperin *et al.* *Angew. Chem. Int. Ed.* **2014**, 53, 1-5

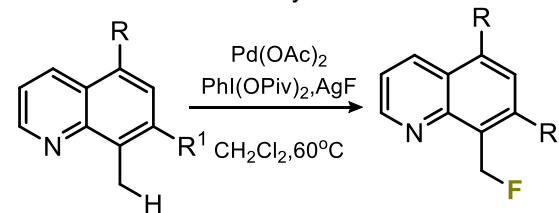


Iron catalyzed fluorination



Lectka *et al.* *Org. Lett.*, **2013**, 15, 1722.

Palladium catalyzed fluorination



Sanford *et al.* *Org. Lett.* **2012**, 4094.

Thank You
everyone....