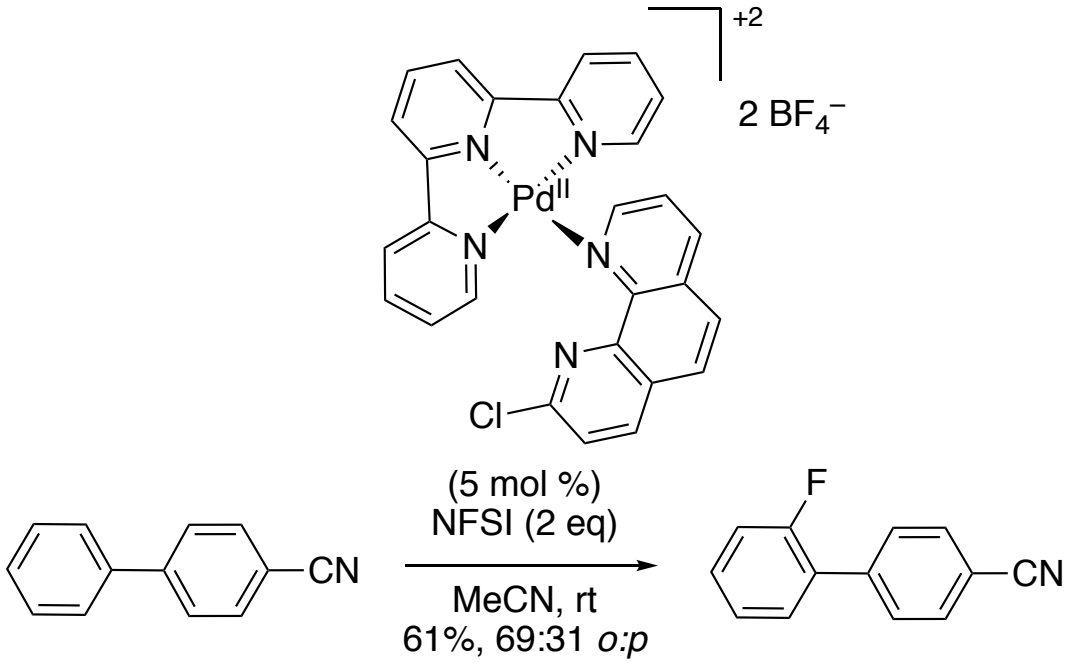
Palladium-Catalyzed Electrophilic Aromatic C–H Fluorination



Yamamoto, K; Li, J.; Garber, J. A. O.; Rolfes, J. D.; Boursalian, G. B.; Borghs, J. C.; Genicot, C.; Jacq, J.; van Gastel, M.; Neese, F.; Ritter, T.

Nature **2018**, *554*, 511-514

John Milligan

Wipf Group Meeting

Current Literature

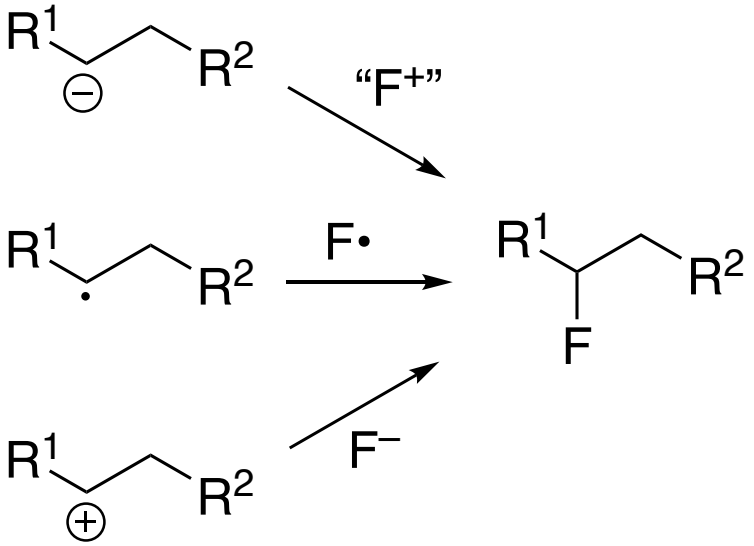
March 17, 2018

Fluorination

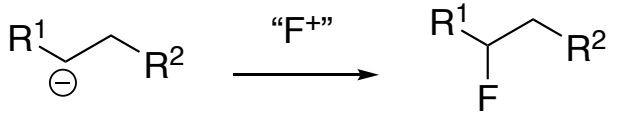
Electrophilic fluorination
(Selectfluor, NFSI, etc.)

Radical fluorination
(above reagents under
radical formation conditions)

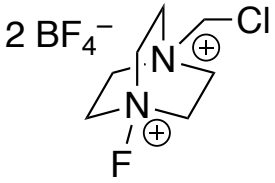
Nucleophilic fluorination
(HF•pyridine, F^- salts;
also deoxyfluorination reagents
such as DAST, Deoxofluor, PyFluor)



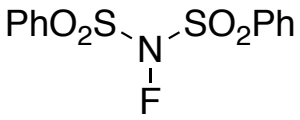
Electrophilic fluorination



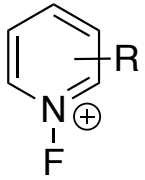
Representative reagents:



Selectfluor™



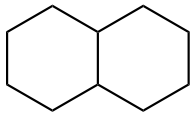
NFSI



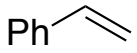
fluoropyridinium salts

XeF_2 (expensive)

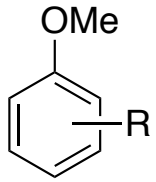
Representative substrates:



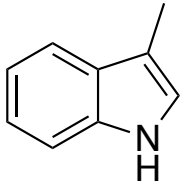
alkanes
(w/ heating)



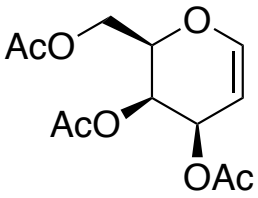
alkenes/ alkynes



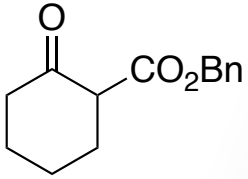
activated arenes



activated heterocycles



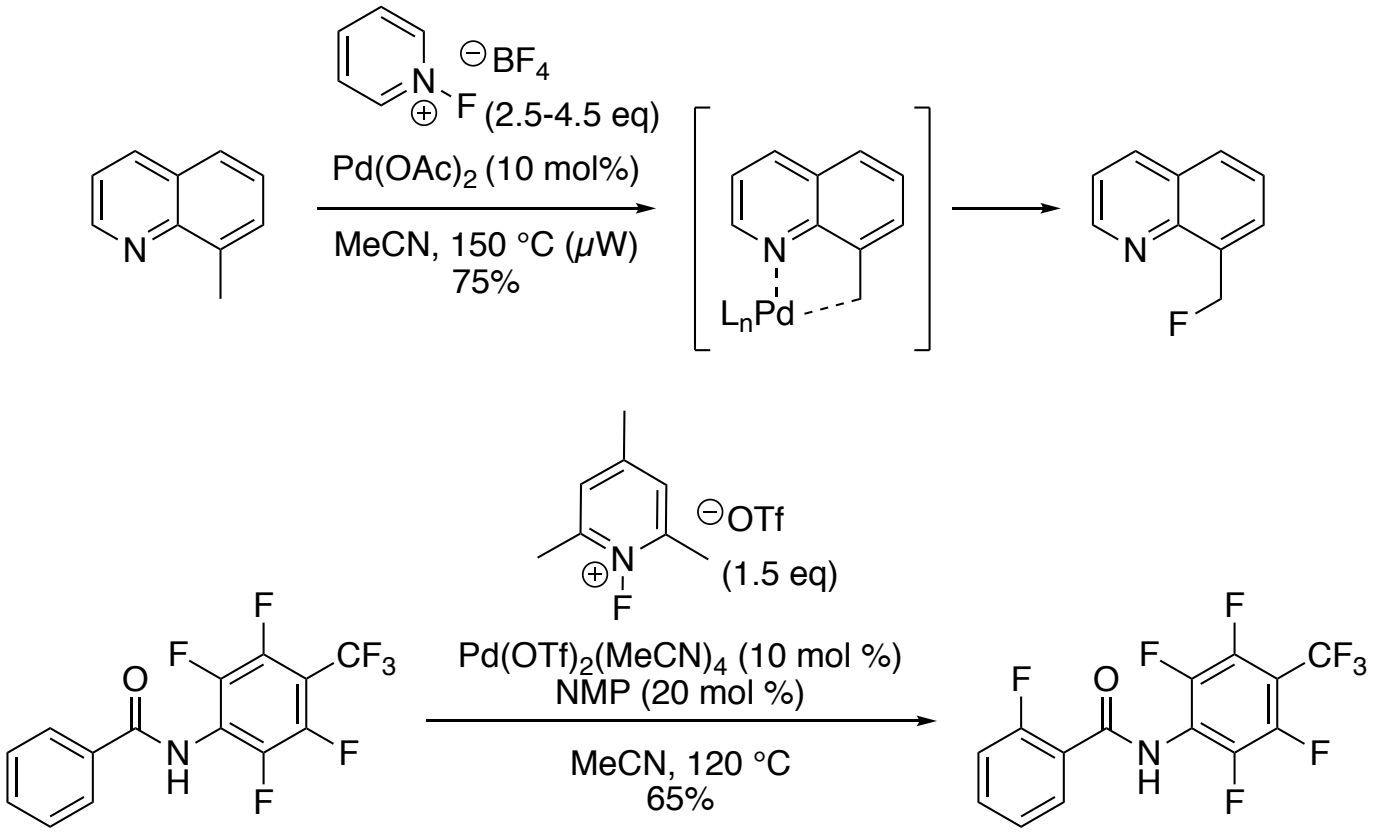
glycals/ enol ethers/ enamines



1,3-dicarbonyl compounds

Baudoux, J.; Cahard, D. *Org. Reactions.* **2007**, *69,* 347-672.

Catalytic, Electrophilic C–H Fluorination

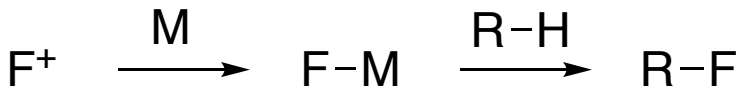


Hull, K. L.; Anani, W. Q.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 7134-7135.
Chan, K. S. L.; Wasa, M.; Wang, X.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2011**, *50*, 9081-9084.

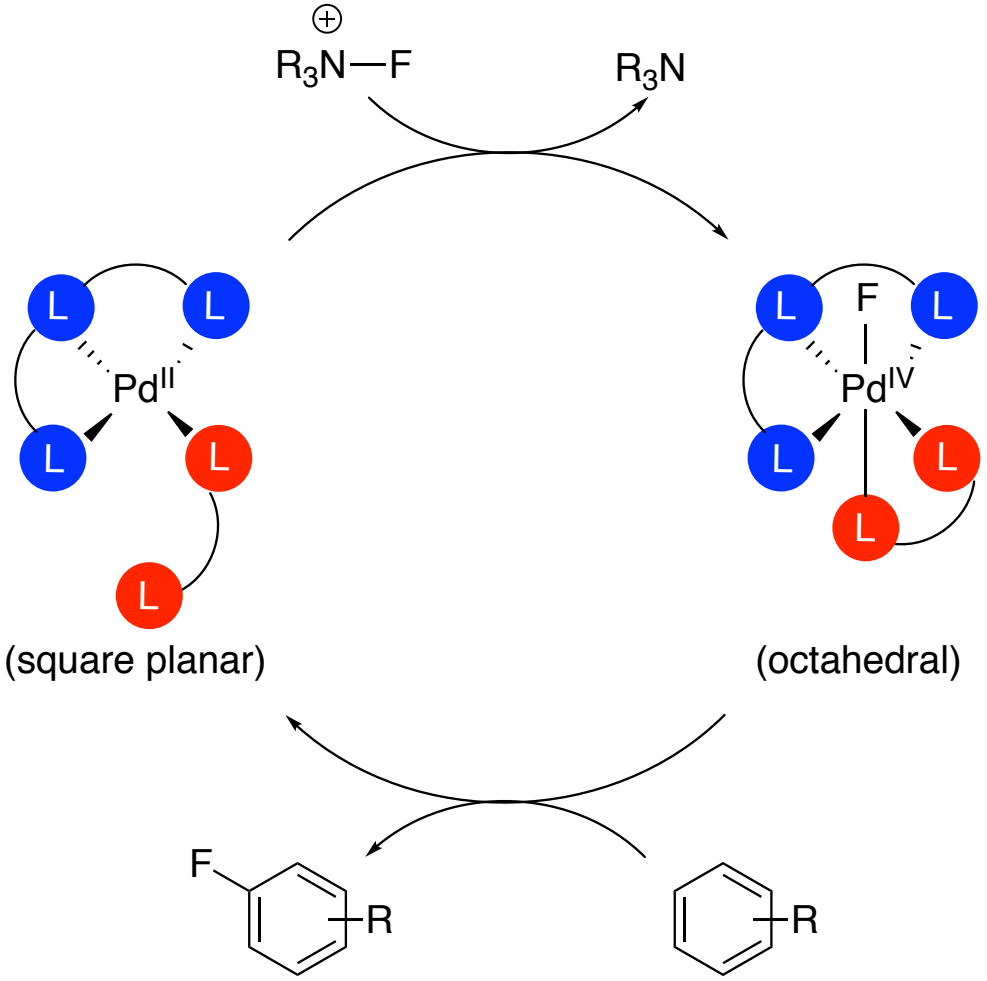
Concept of Current Work

Previous Approaches: Fluorination of a C–M bond

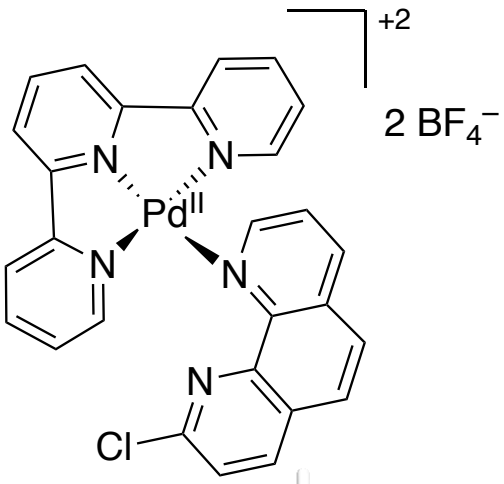
This Work: Formation of a highly electrophilic M–F species

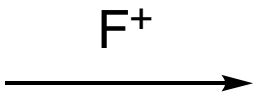


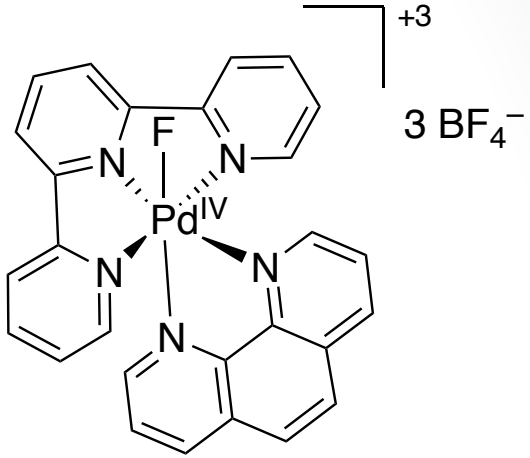
Concept of Current Work

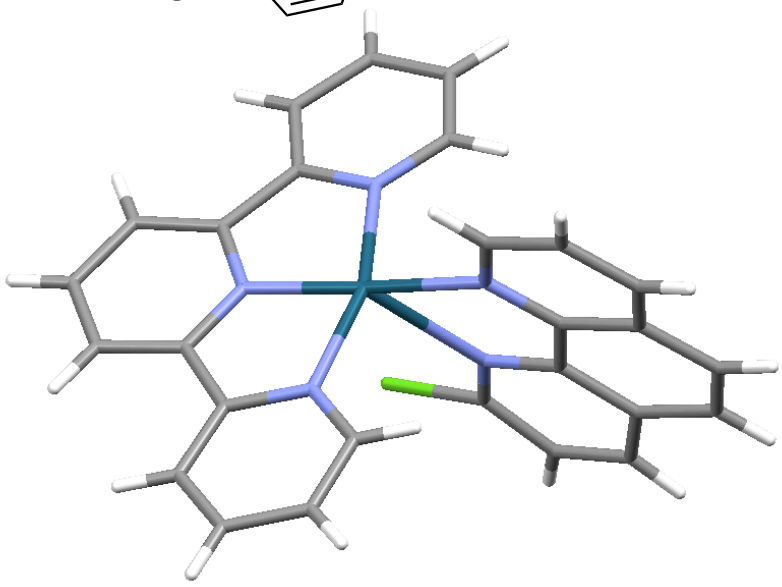


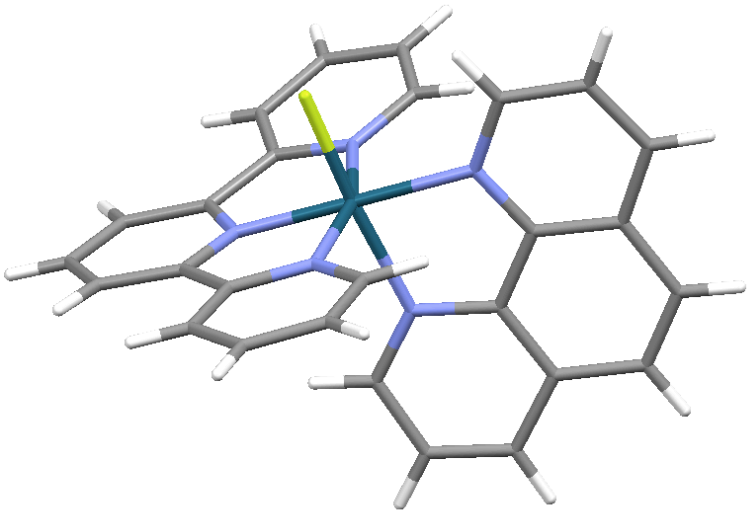
Palladium complexes





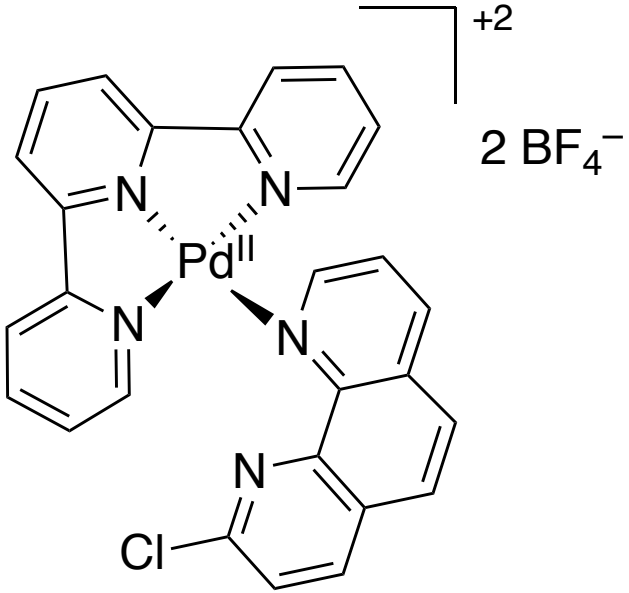


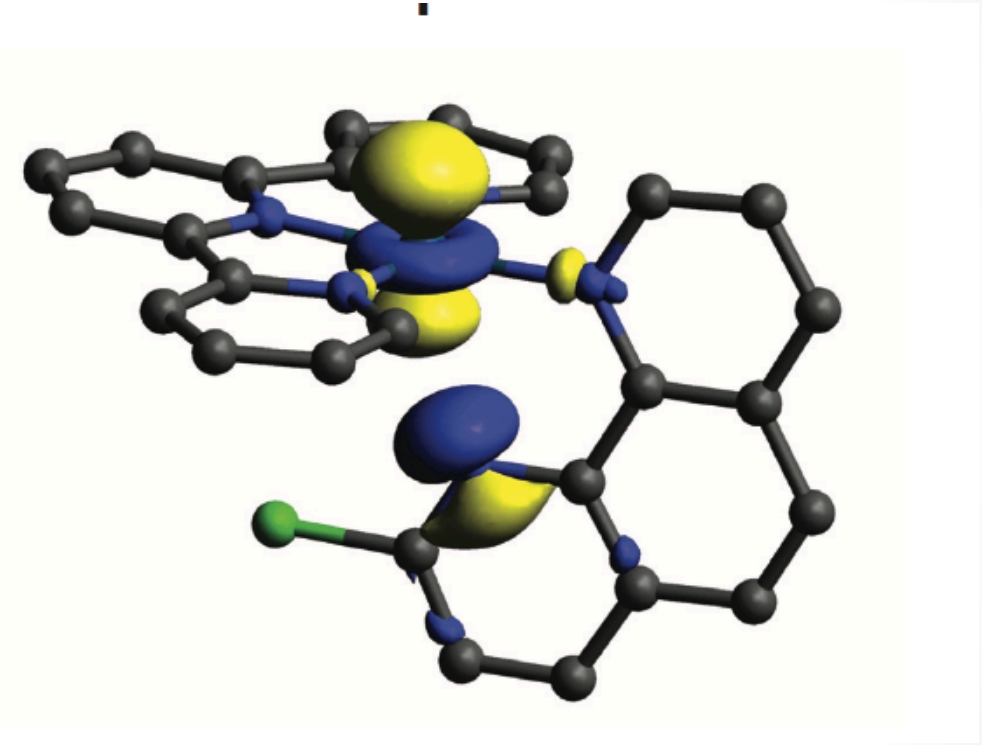




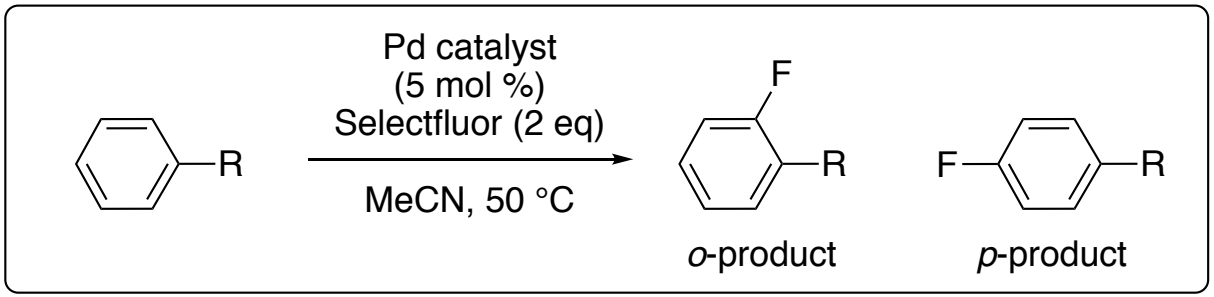
CCDC #1465063, 1536794

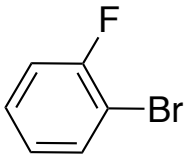
Catalyst HOMO



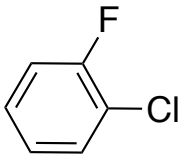


Substrate Scope

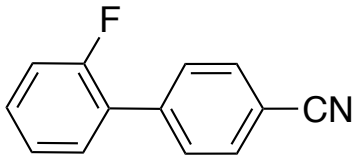




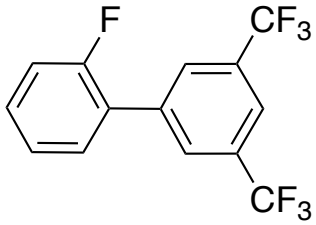
49%, 52:48 *o:p*



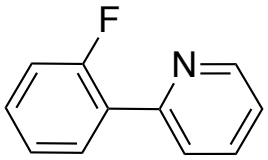
51%, 59:41 *o:p*



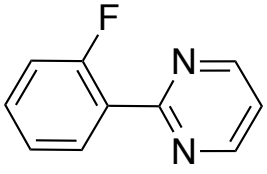
61%, 69:31 *o:p*



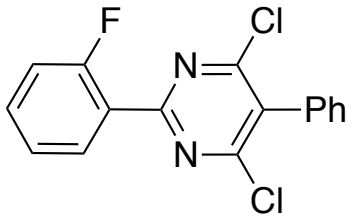
85%, 69:31 *o:p*



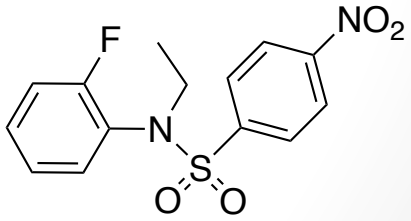
55%, 77:23 *o:p*



46%, 67:33 *o:p*

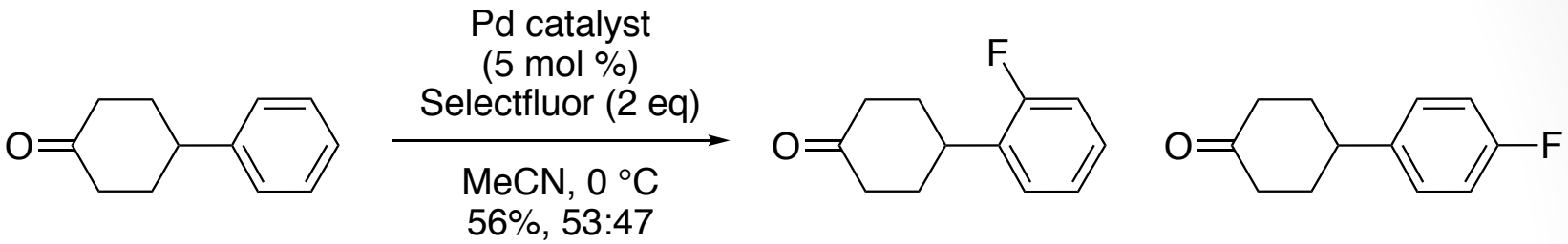


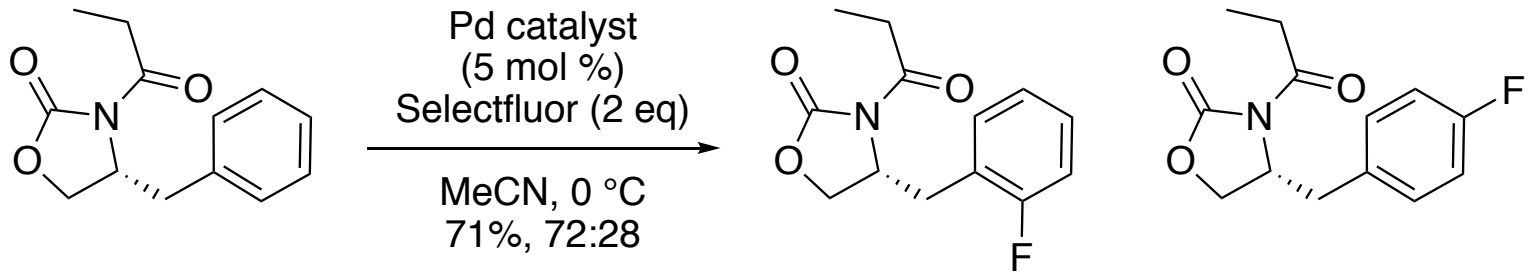
51%, 59:41 *o:p*

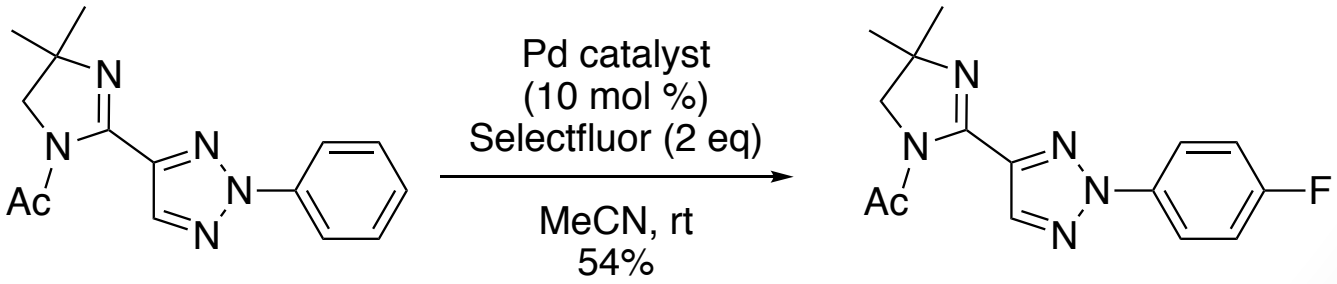


60%, 49:51 *o:p*

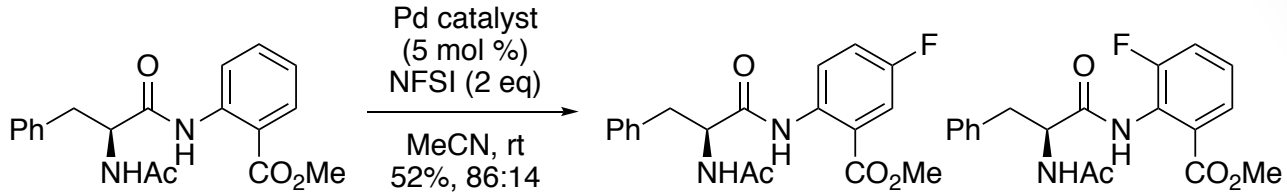
Functional Group Tolerance

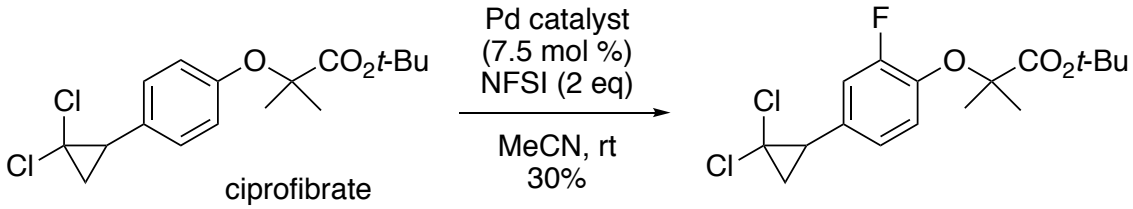




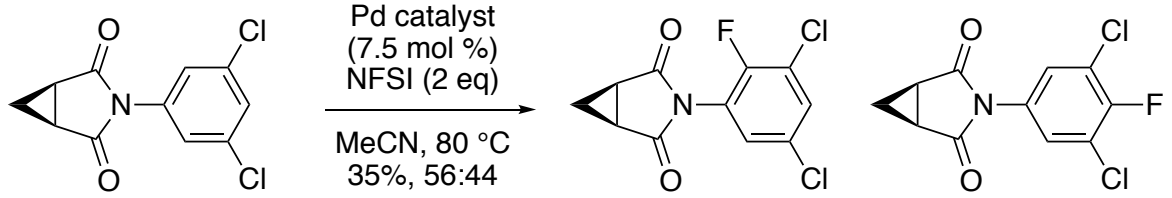


NFSI reactions

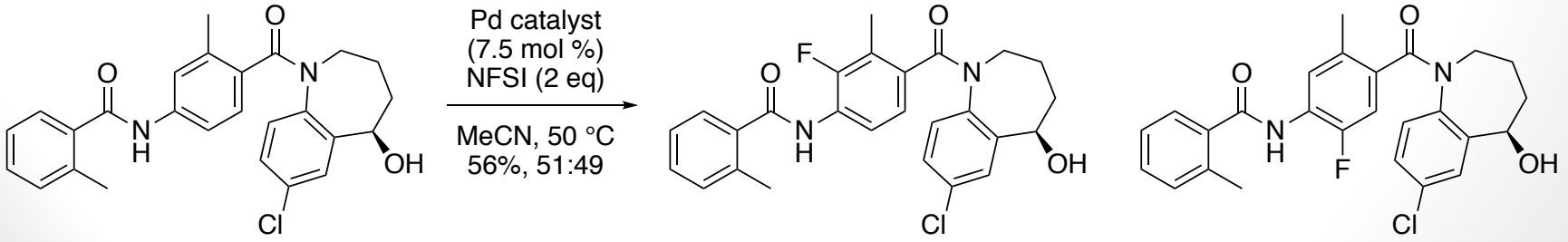




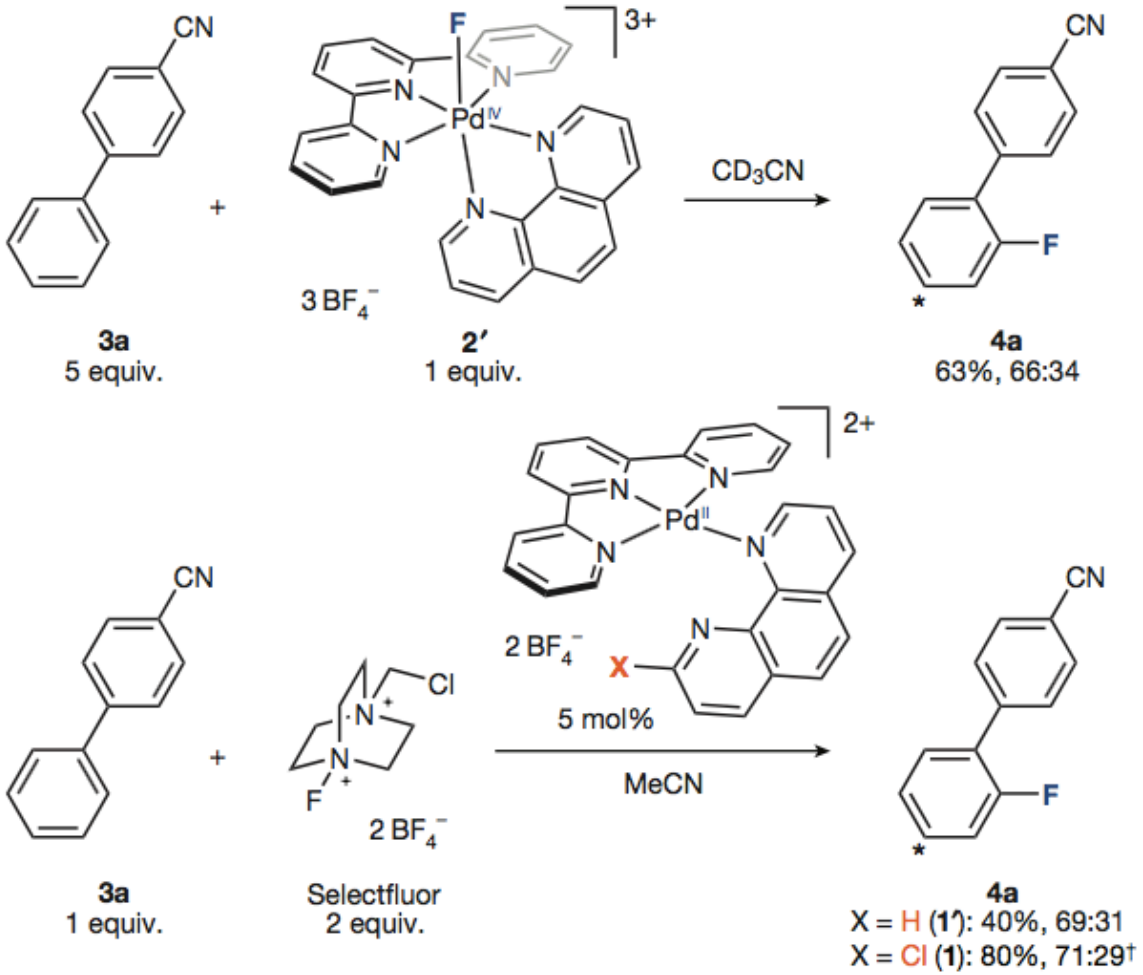
ciprofibrate



procymidone



Comparison Study



3a
5 equiv.

2′
1 equiv.

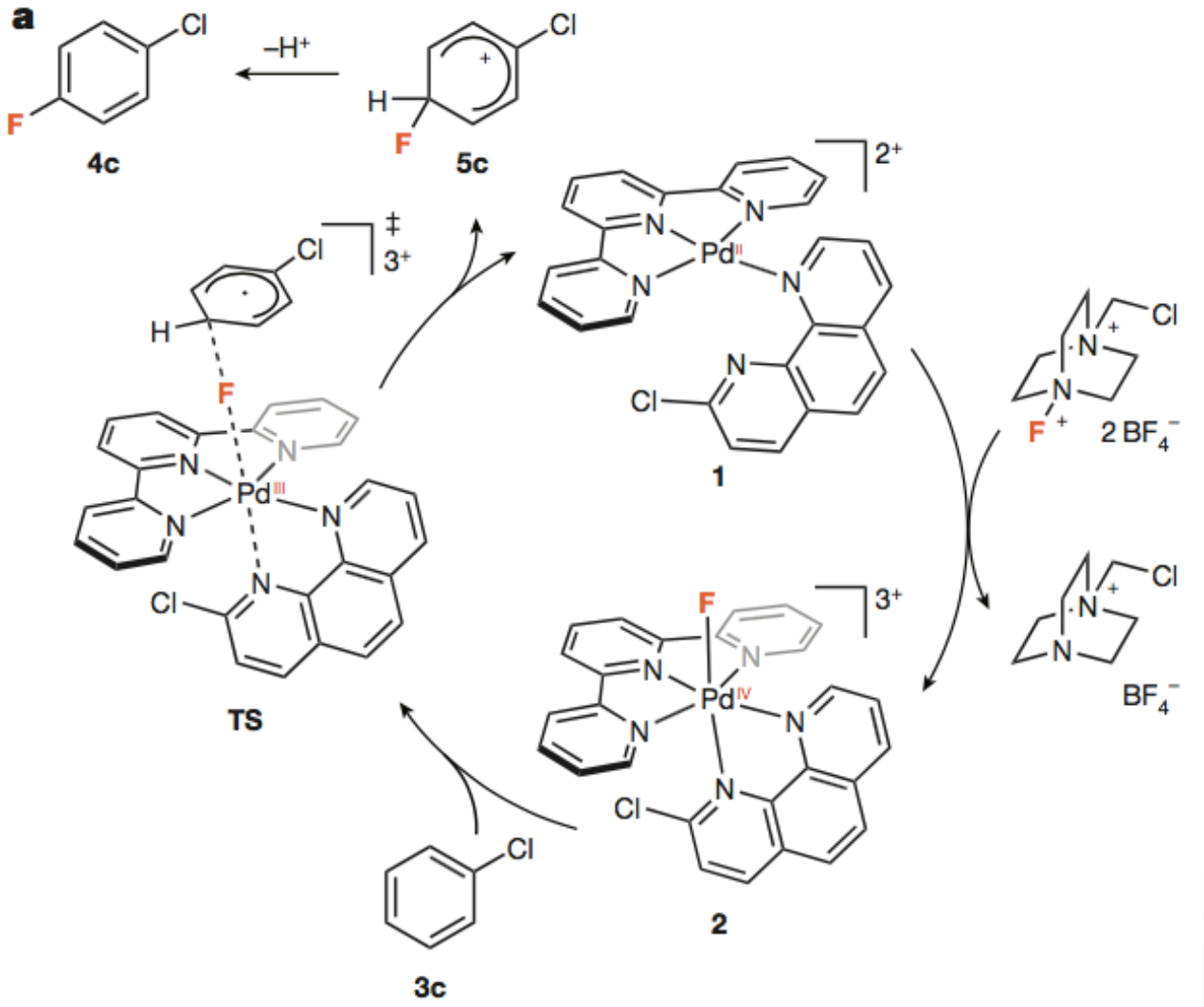
4a
63%, 66:34

3a
1 equiv.

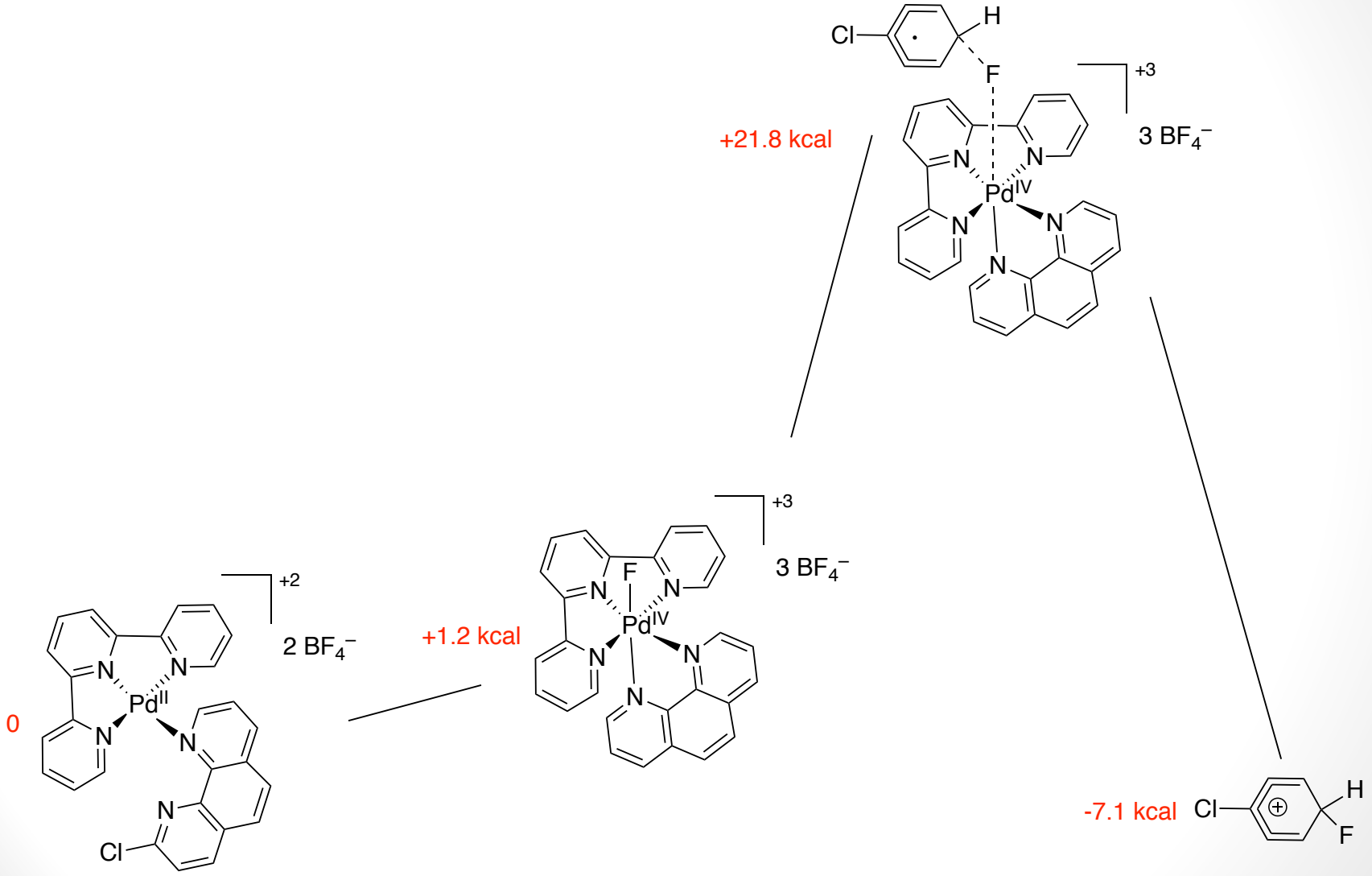
Selectfluor
2 equiv.

4a
X = H (**1′**): 40%, 69:31
X = Cl (**1**): 80%, 71:29†

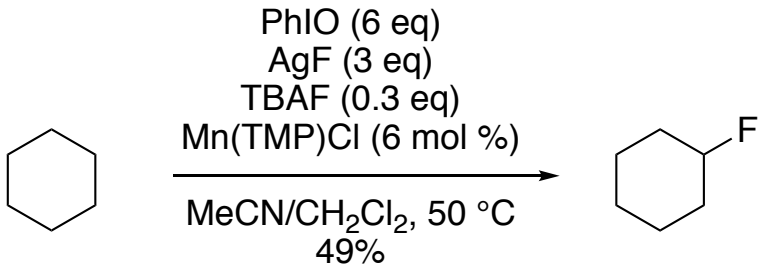
Mechanism: Electron Transfer

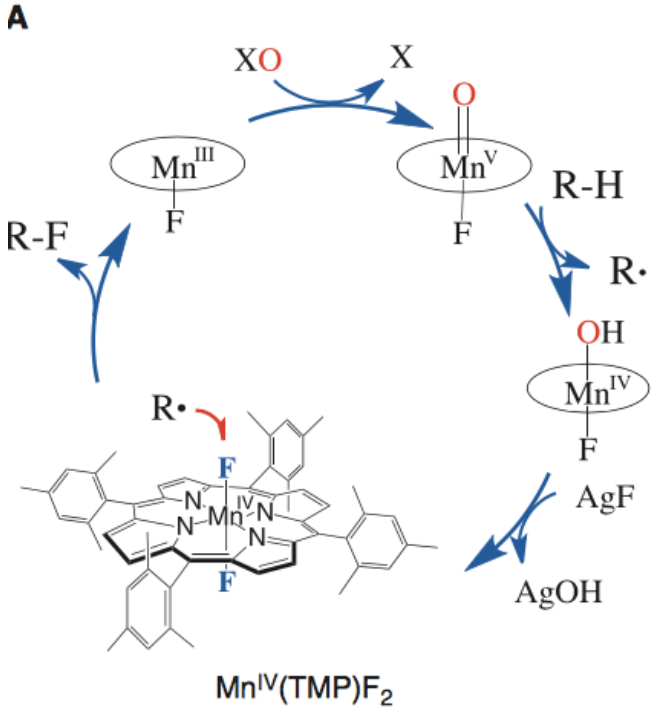


Computational Mechanistic Studies



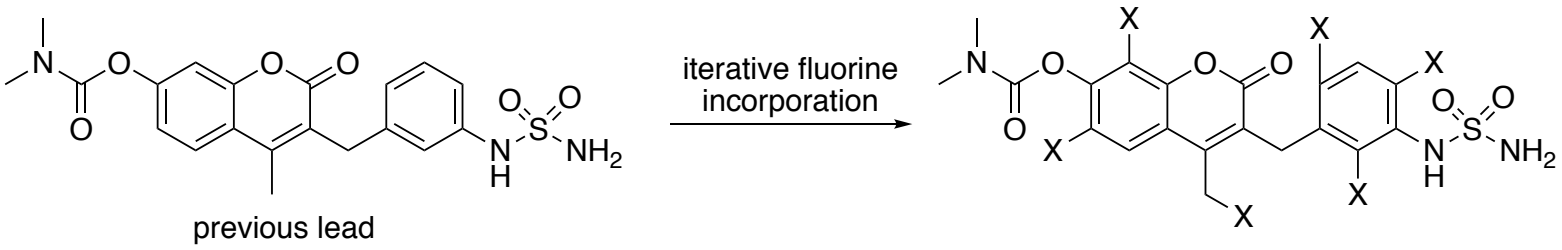
Comparison: Radical-Based C-H Fluorination



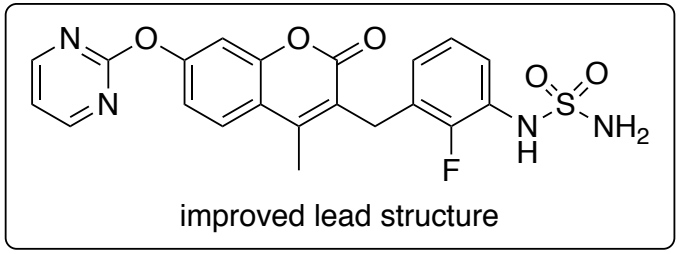


Liu, W.; Huang, X.; Cheng, M.; Nielsen, R. J.; Goddard, W. A. III.; Groves, J. T. *Science* **2012**, *337*, 1322-1325.

Potential Application: Fluoride Scanning



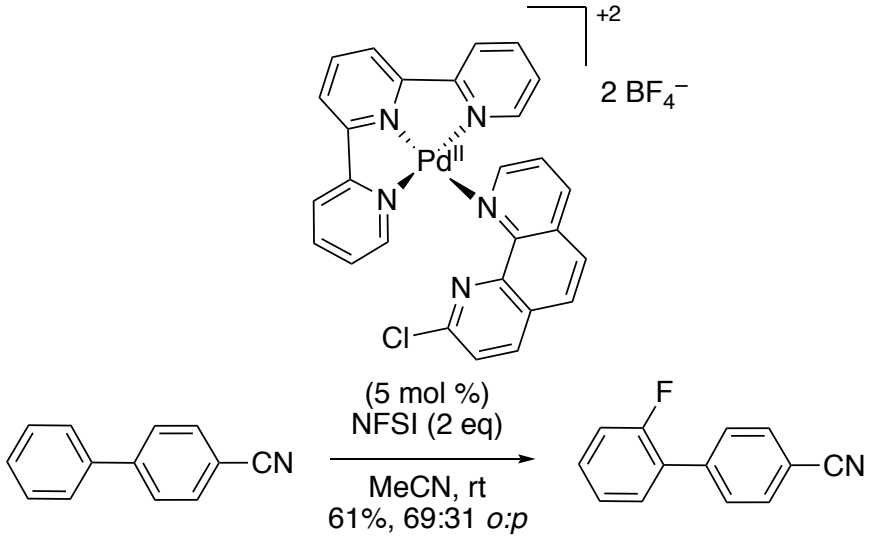
previous lead



improved lead structure

Hyohdoh, I. *et al. ACS Med. Chem. Lett.* **2013**, *4*, 1059-1063.

Summary



- This new method enables the electrophilic fluorination previously unsuitable substrates
- Amenable for late stage fluorination
- Future opportunities: Design of catalysts with high selectivity