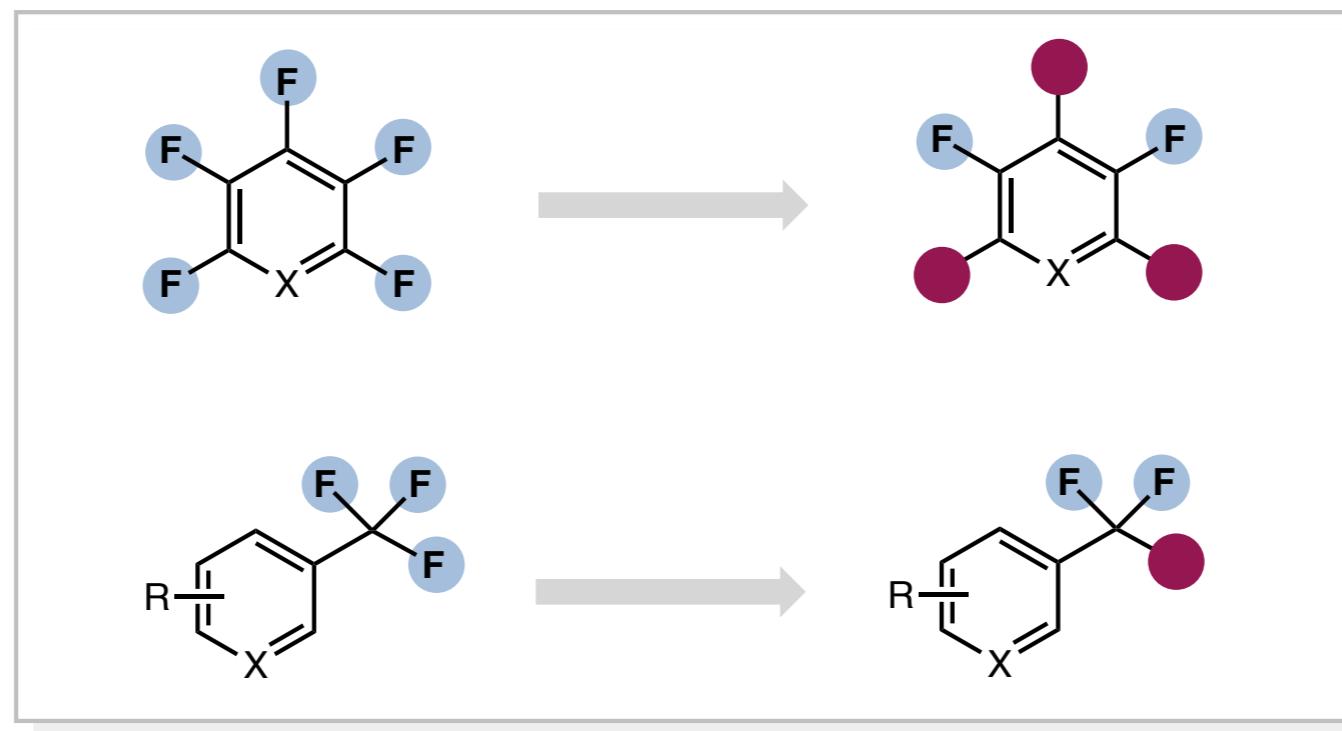


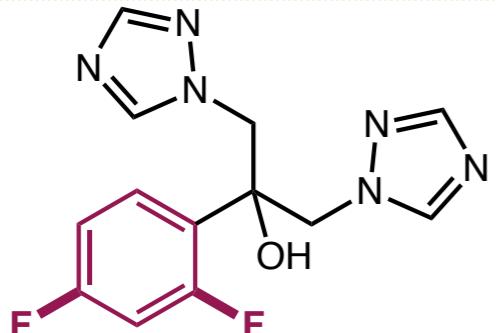
Selective C-F bond Functionalization in Multifluoroarenes and Trifluoromethylarens



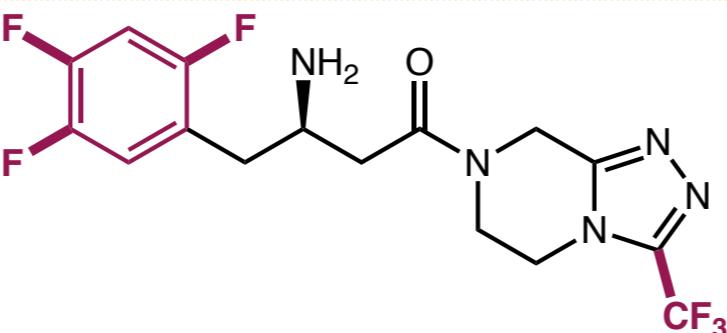
Xiangbo Zhao
Macmillan Group Meeting
October 9th, 2019

Strategies for the Synthesis of Organofluorine Compounds

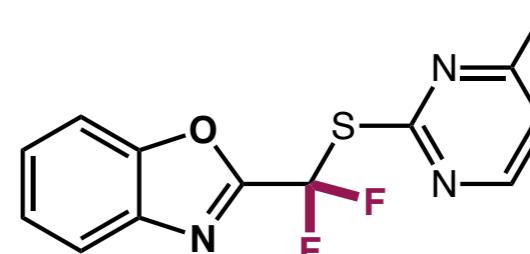
■ C-F bond formation & C-F bond cleavage



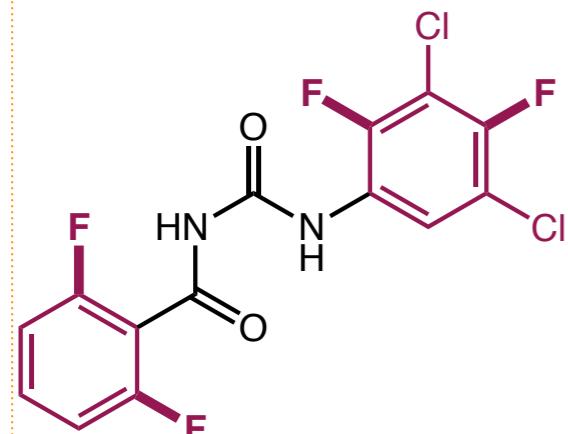
Fluconazole
antifungal



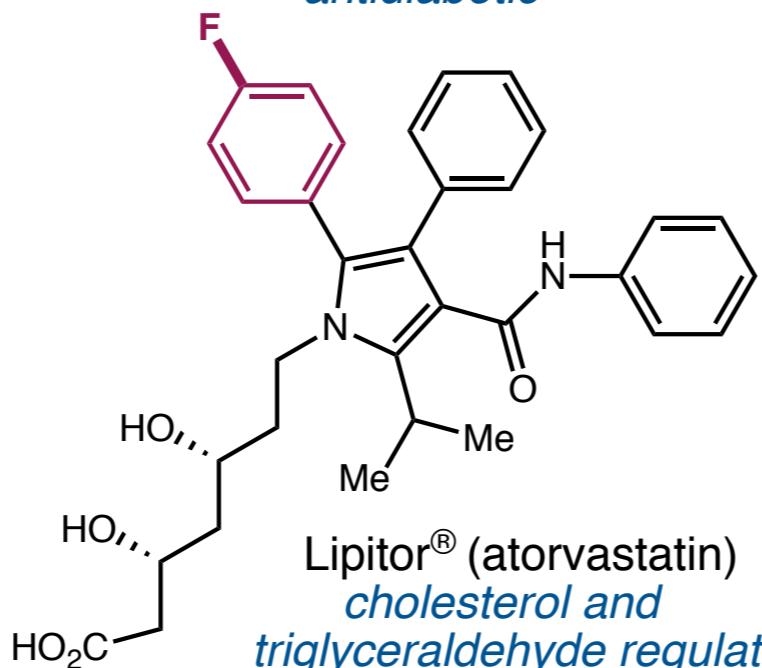
Januvia® (sitagliptin)
antidiabetic



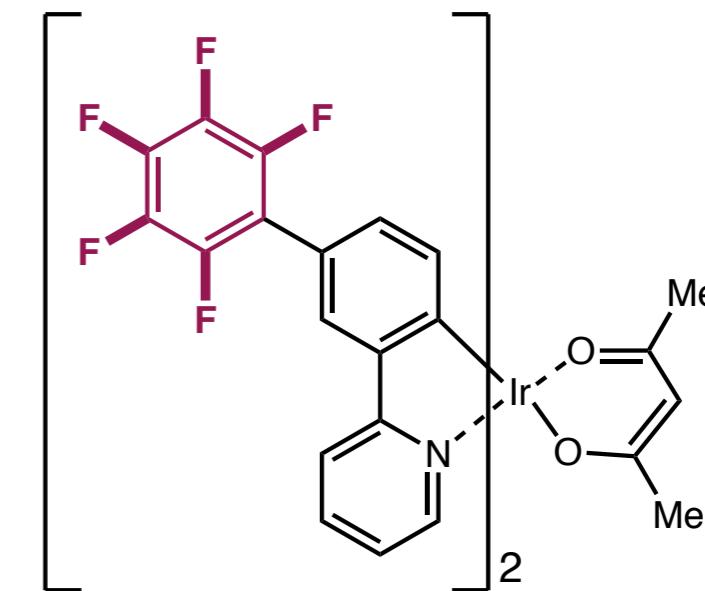
HIV-1 reverse
Transcriptase inhibitor



Teflubenzuron
insecticide



Lipitor® (atorvastatin)
*cholesterol and
triglyceraldehyde regulator*



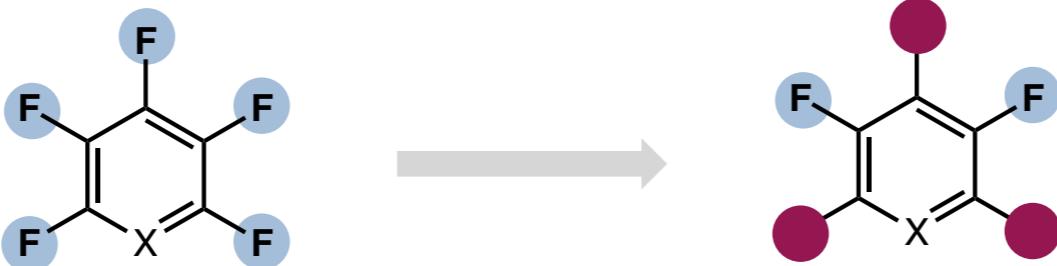
Organofluorine
Compounds

C-F (or F-containing moiety)
Bond Formation

Selective C-F bond Activation
and Functionalization

Content Outline

■ Selective C-F bond functionalization in aromatic fluorides



Nucleophilic
Substitution
 S_NAr

Defluorinative
Functionalization
Via Benzyne

Photocatalytic
reduction

■ Selective C-F bond functionalization in trifluoromethylarenes

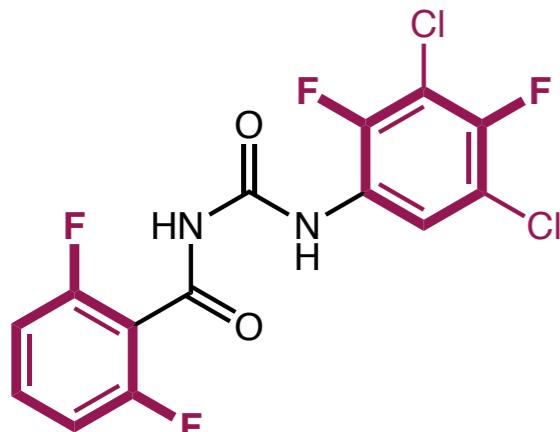


Anionic or Cationic
Mechanism

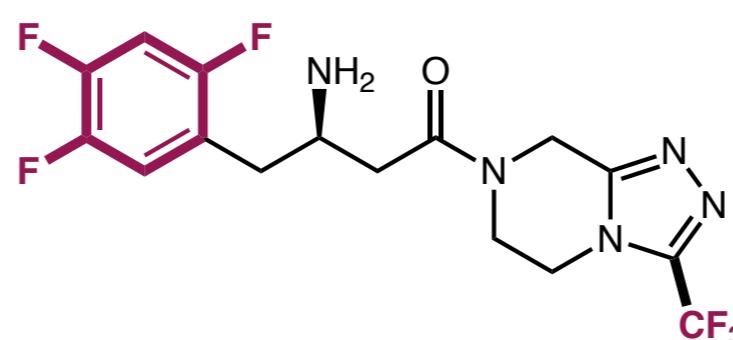
SET &
Photocatalysis

Selective C-F bond Functionalization of Multifluoroarenes

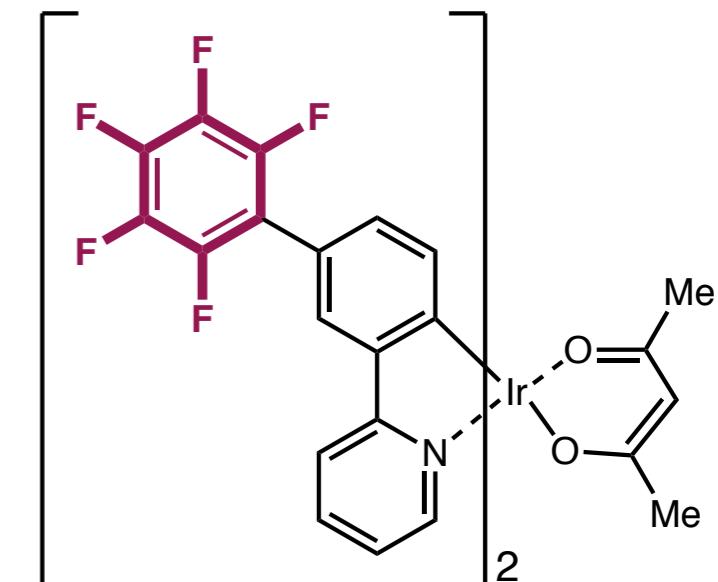
- Introduction of the alternative approach to partially fluorinated compounds



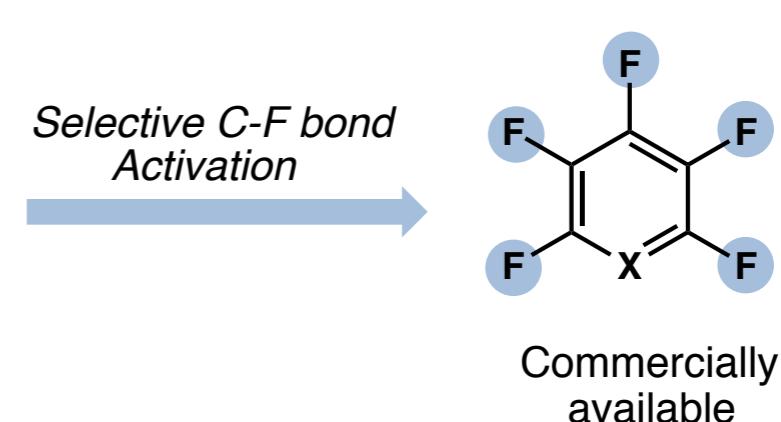
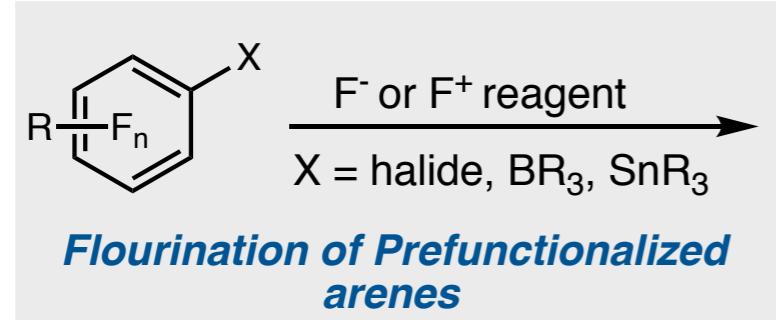
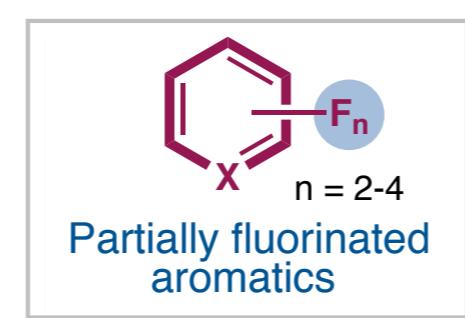
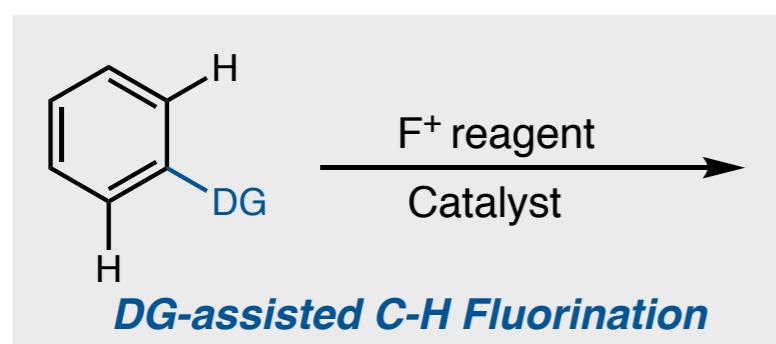
Teflubenzuron
insecticide



Januvia® (sitagliptin)
antidiabetic



An organic LED molecule

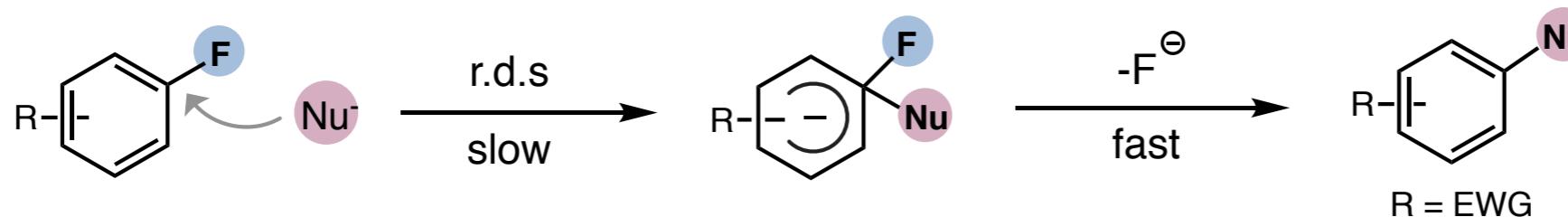


Senaweera, S.; Weaver, J. D. *Aldrichimica Acta* **2016**, *49*, 45.

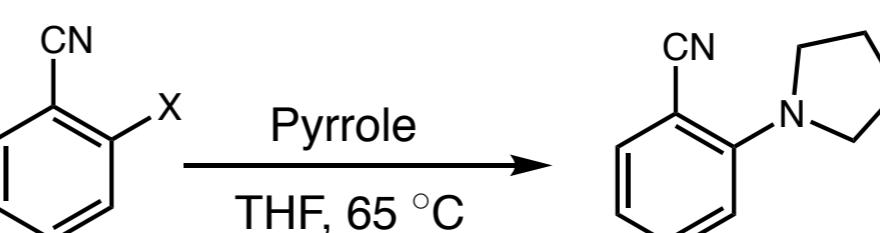
Amii, H.; Uneyama, K. *Chem. Rev.* **2009**, *109*, 2119.

Selective C-F Bond Functionalization in Aromatic Fluorides

■ Nucleophilic substitution of aromatic fluorides (S_NAr)

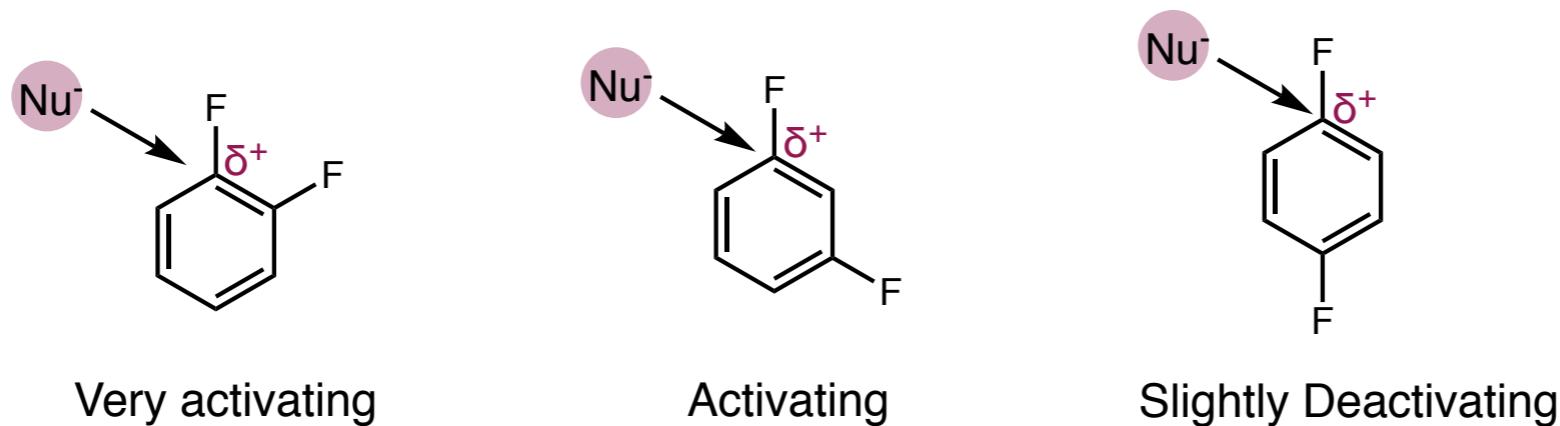


S_NAr	S_N2
<i>Aromatic Halides</i>	<i>Aliphatic Halides</i>
$F > Cl > Br > I$	$I > Br > Cl > F$
<u>Reactivity Order Comparision</u>	



X	Yield
F	100%
Cl	70%
Br	10%

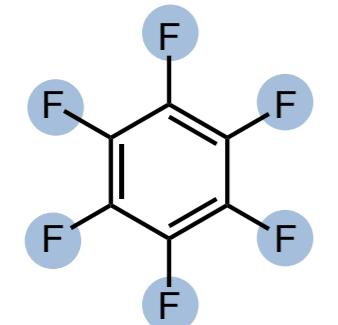
Thomas, S.; Collins, C. J.; Singaram, B. *J. Org. Chem.* **2001**, *66*, 1999.



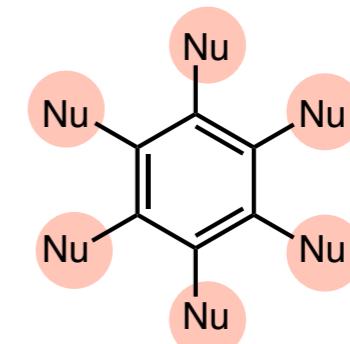
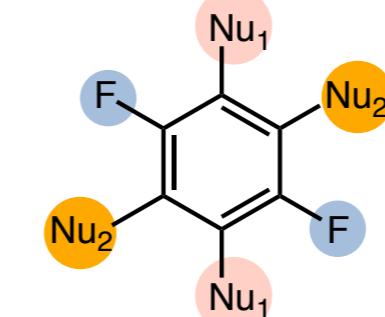
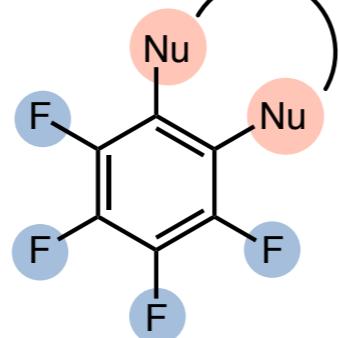
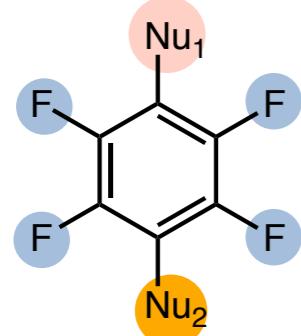
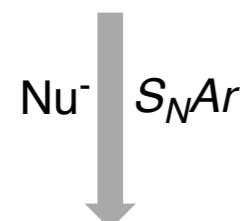
General Reactivity: Effects of Fluorine on Nucleophilic Substitution

Selective C-F Bond Functionalization in Aromatic Fluorides

■ Nucleophilic substitution of hexafluorobenzene



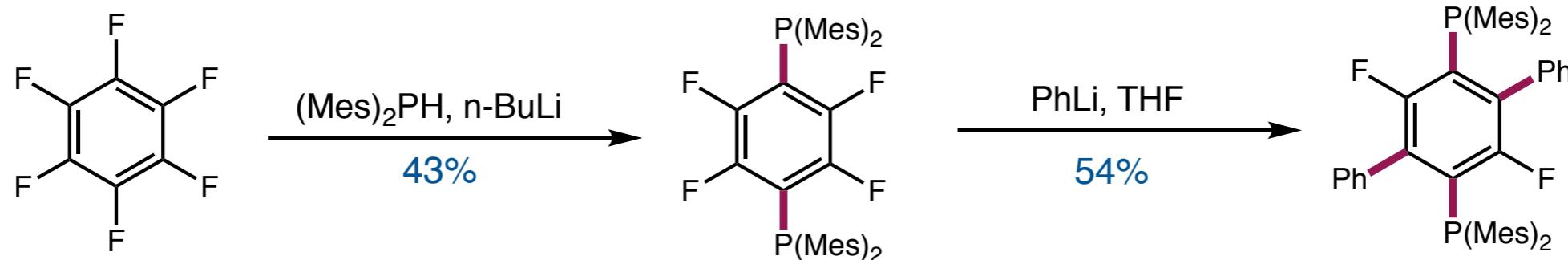
- ◆ Perfluoro-substitution dramatically lowers the energy of the π^* orbitals, making the aryl ring more susceptible to nucleophilic attack
- ◆ After monosubstitution, the second substitution occurs regioselectively at C-4 carbon, irrespective of the electronic nature of the first substituent.



Regioselectivity Pattern

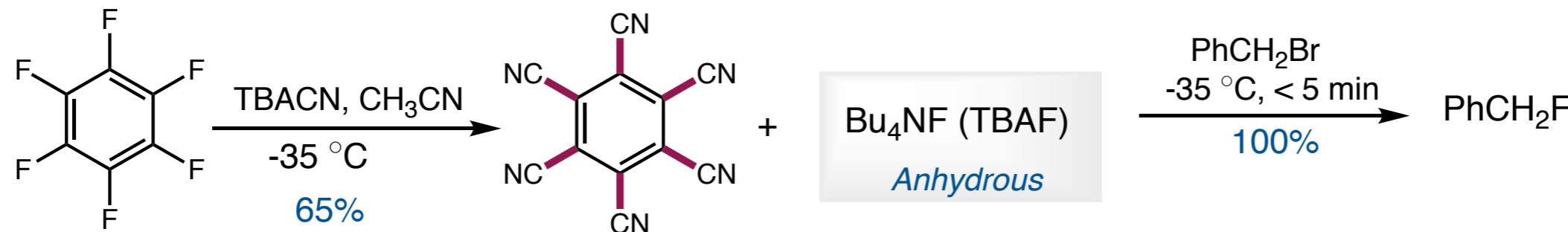
Selective C-F Bond Functionalization in Aromatic Fluorides

- One example of nucleophilic substitution of hexafluorobenzene



Sasaki, S.; Tanabe, Y.; Yoshifuji, Y. *Bull. Chem. Soc. Jpn.* **1999**, 72, 563.

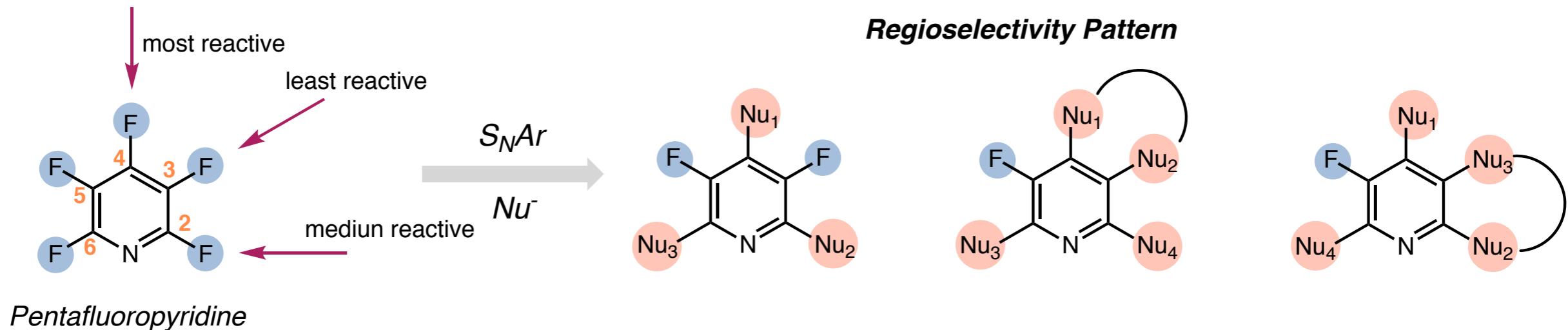
- An interesting application: the preparation of anhydrous TBAF



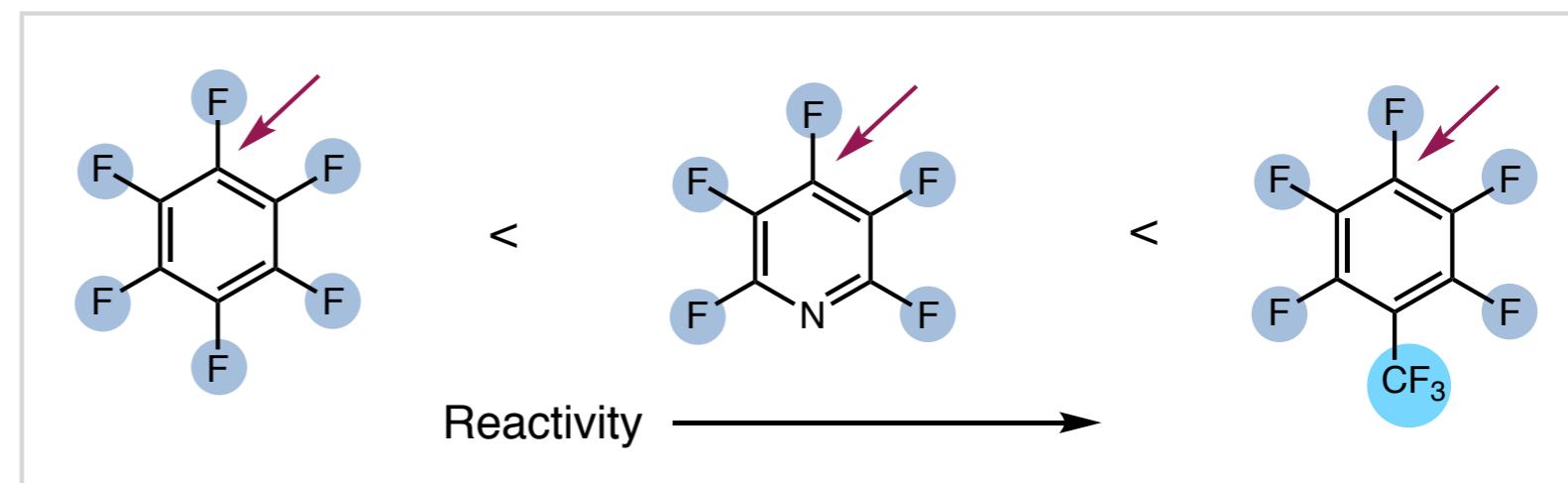
Sun, H.; DiMagno, S. G. *J. Am. Chem. Soc.* **2005**, 127, 2050.

Selective C-F Bond Functionalization in Aromatic Fluorides

Nucleophilic substitution of pentafluoropyridine

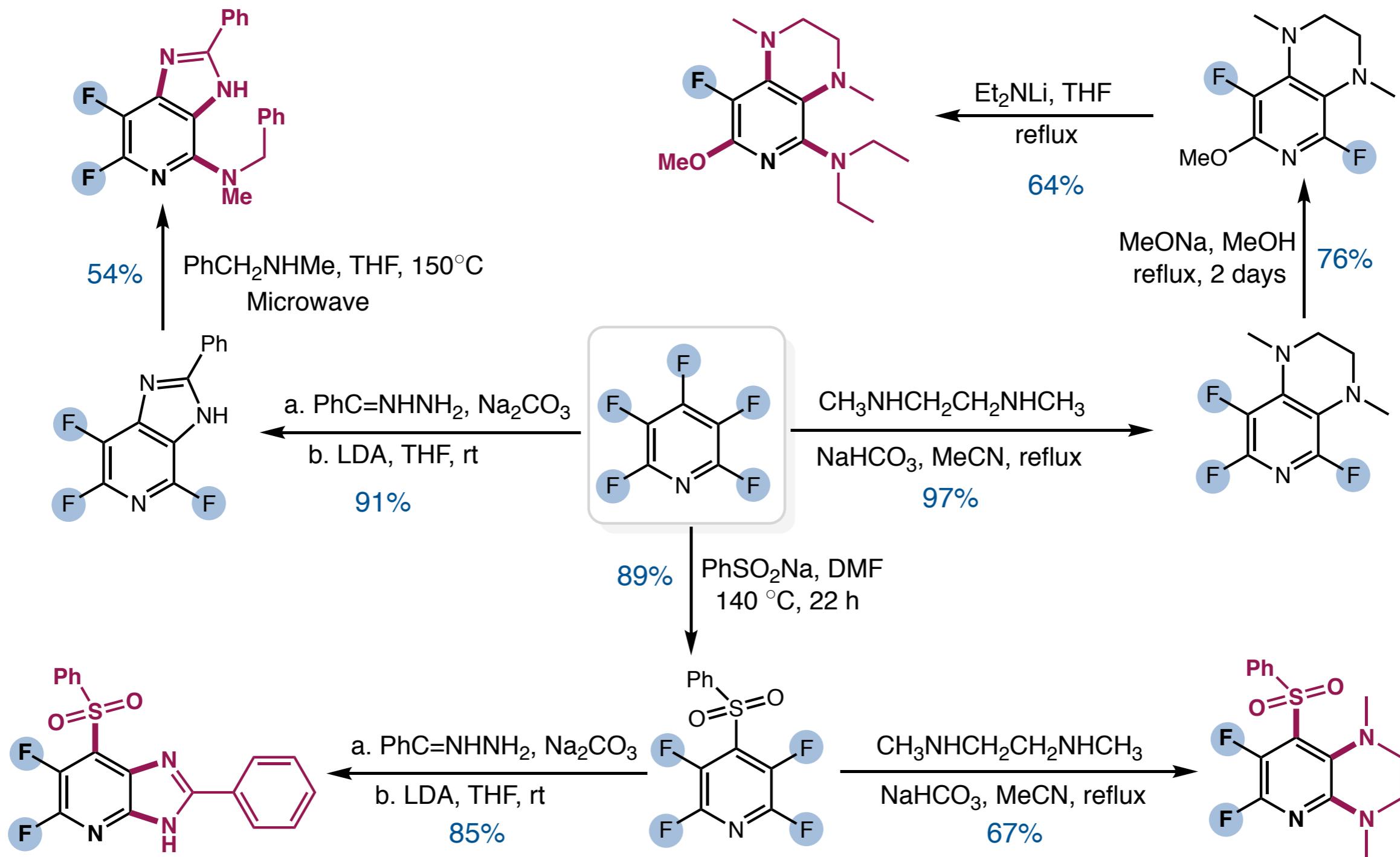


- ◆ Nucleophilic substitution occurs regioselectively stepwise
- ◆ First carbon-4, then carbon-2, finally carbon-3.
- ◆ Three kinds of different nucleophiles can be introduced stepwise.



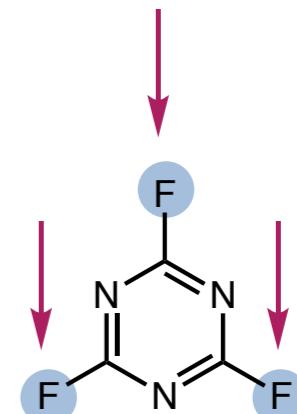
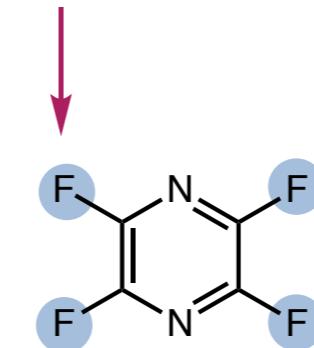
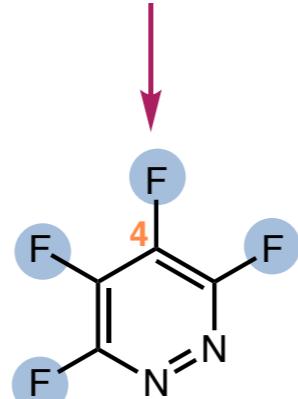
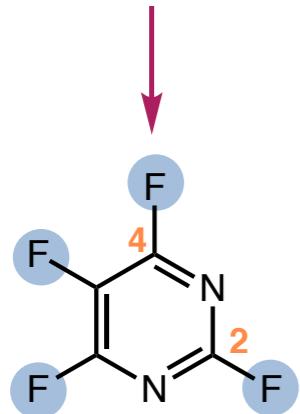
Selective C-F Bond Functionalization in Aromatic Fluorides

■ Some applications of nucleophilic substitution of pentafluoropyridine

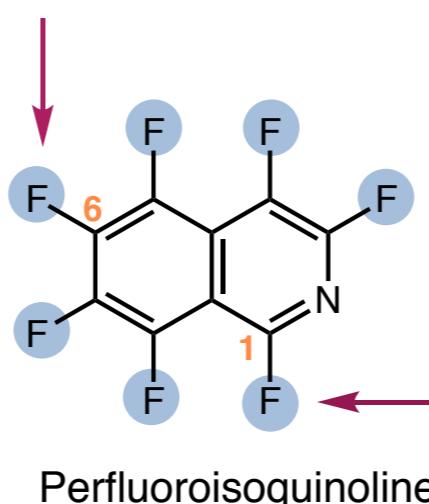
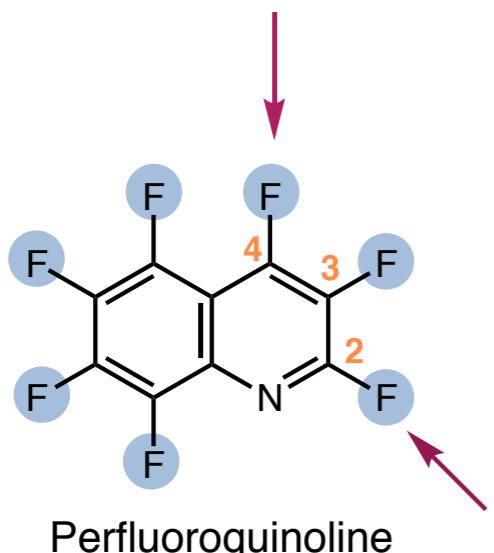


Selective C-F Bond Functionalization in Aromatic Fluorides

■ Nucleophilic substitution of perfluoroheteroaromatic systems



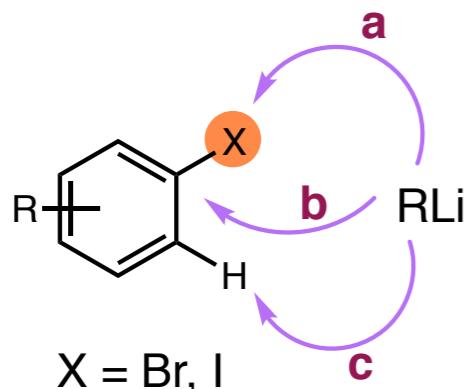
*Difficult to get mono only
(highly activated)*



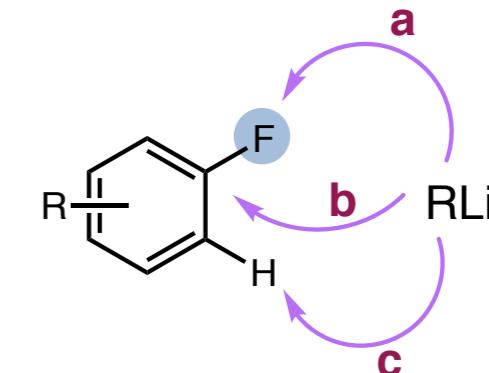
- ◆ Favored sites of attack for S_NAr occurs at sites that are para or ortho to the ring nitrogen

Selective C-F Bond Functionalization in Aromatic Fluorides

■ Defluorinative functionalization via benzenes

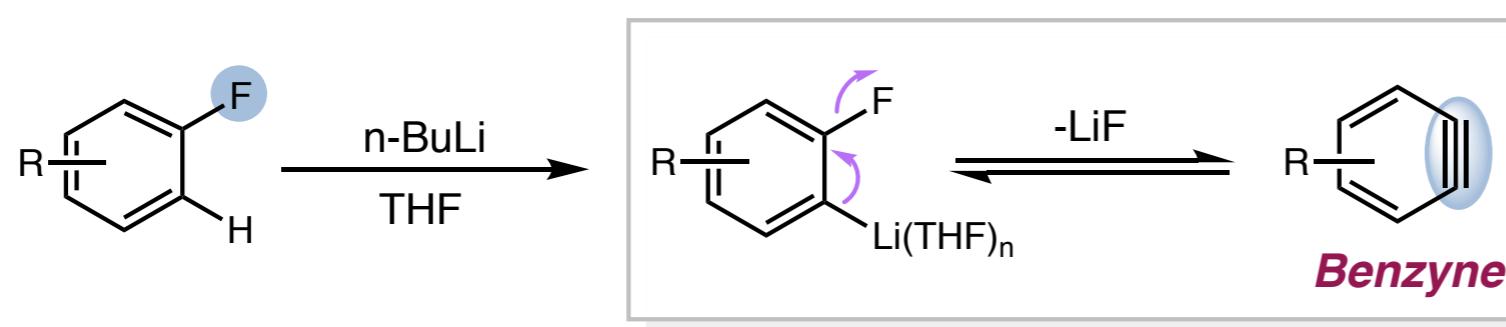


- a. Lithium-halogen exchange
- b. Nucleophilic replacement
- c. Deprotonation

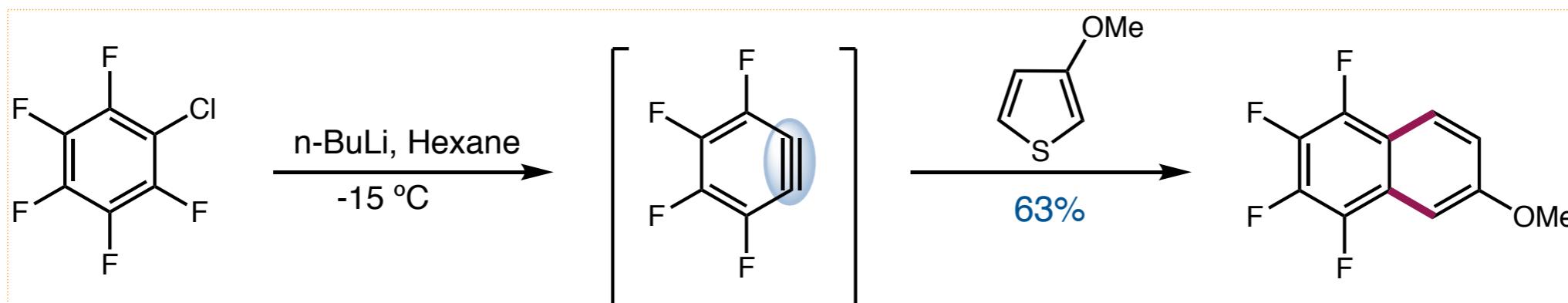


Lithium halogen exchange favoured

Ortho-hydrogen deprotonation favoured



- ◆ Elimination of LiX follows the order of $\text{LiBr} < \text{LiCl} < \text{LiF}$.

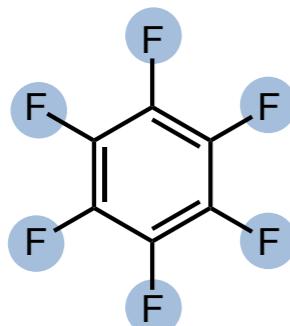


Masson, E.; Schlosser, M. *Eur. J. Org. Chem.* 2005, 4401

Yudin, A. K.; Zheng, J.; Lough, A. *Org. Lett.* 2000, 2, 41

Selective C-F bond functionalization in Aromatic Fluorides

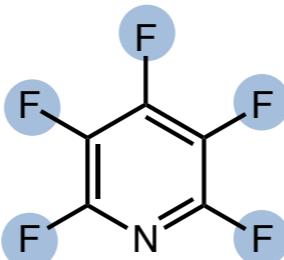
■ C-F bond reduction of aromatic fluorides via low-valent metals



Hexafluorobenzene

$E_{1/2} \text{Ar}^{0/-1} = -2.81 \text{ V}$

$\text{BDE}_{(\text{C}-\text{F})} = 145 \text{ kcal/mol}$



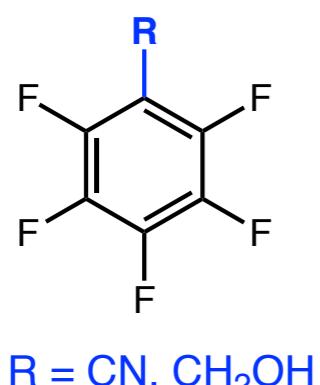
Pentafluoropyridine

$E_{1/2} \text{Ar}^{0/-1} = -2.12 \text{ V}$

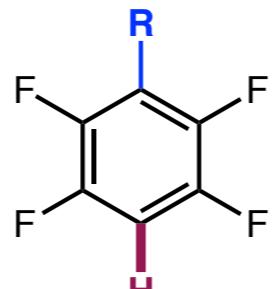
$\text{BDE}_{(\text{C}-\text{F})} = 127 \text{ kcal/mol}$

- ◆ Li, Na, K in liquid ammonia
- ◆ Lithium naphthalene
- ◆ Activated Mg powder
- ◆ CeCl_3 , LiAlH_4

Hydrodefluorination
almost no selectivity

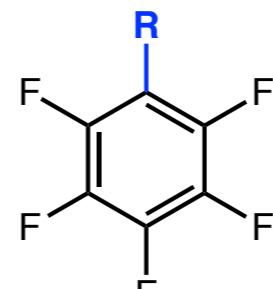


$\xrightarrow[\text{rt, 10 h}]{\text{Zn (6.0 eq)} \text{ aq. NH}_3}$



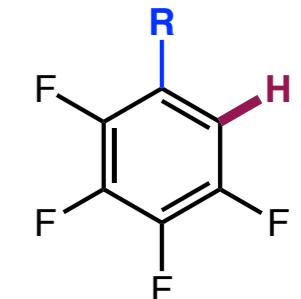
> 70% yield

$\text{R} = \text{CN, CH}_2\text{OH}$



$\xrightarrow[\text{rt, 10 h}]{\text{Zn (6.0 eq)} \text{ aq. NH}_3}$

$\text{R} = \text{NHAc, CO}_2\text{H}$



> 70% yield

- ◆ Large excess of reductants
- ◆ Limited substrate scope

Amii, H.; Uneyama, K. *Chem. Rev.* **2009**, *109*, 2119.

Laev, S. S.; Shteingarts, V. D. *Tetrahedron Lett.* **1997**, *38*, 3765.

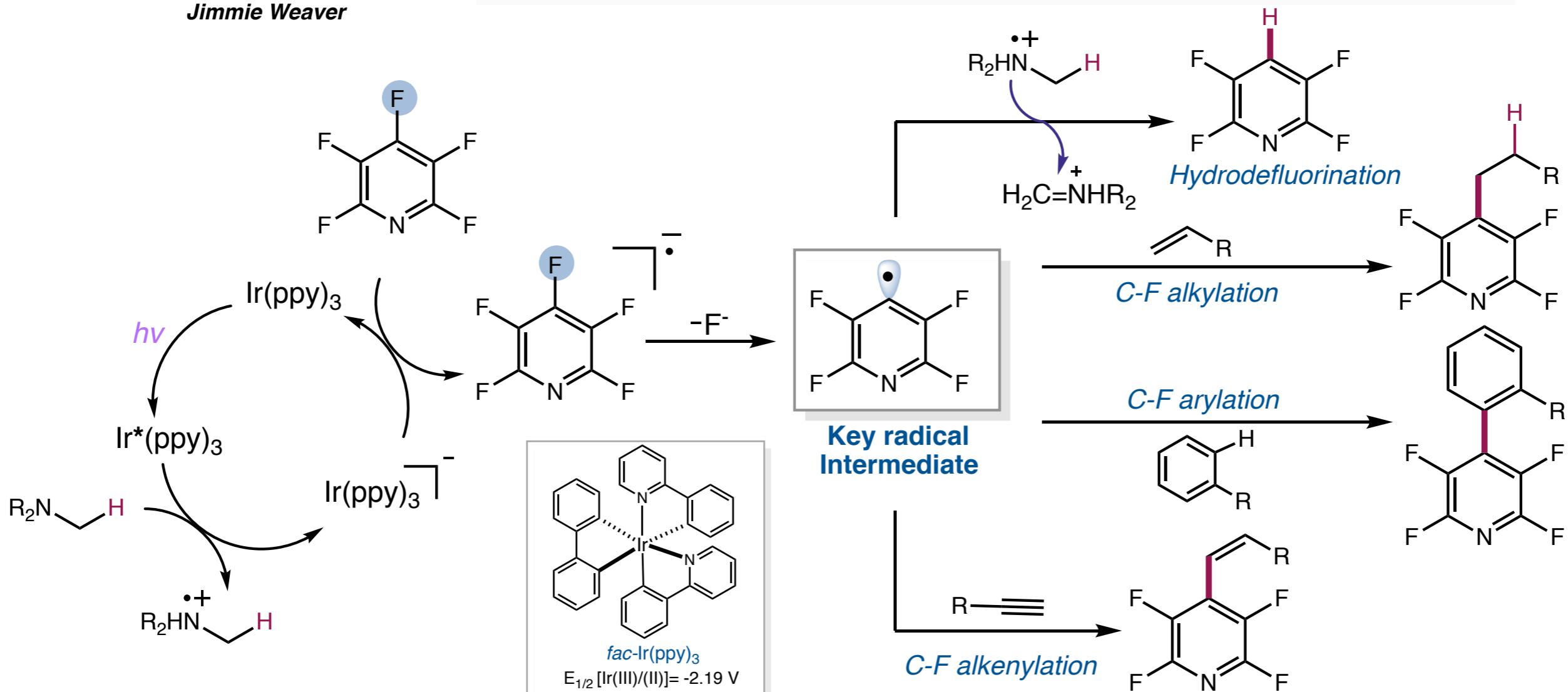
Photocatalytic C-F reduction and Functionalization in Aromatic Fluorides

■ Introduction of Weaver group's work on photocatalytic C-F functionalization



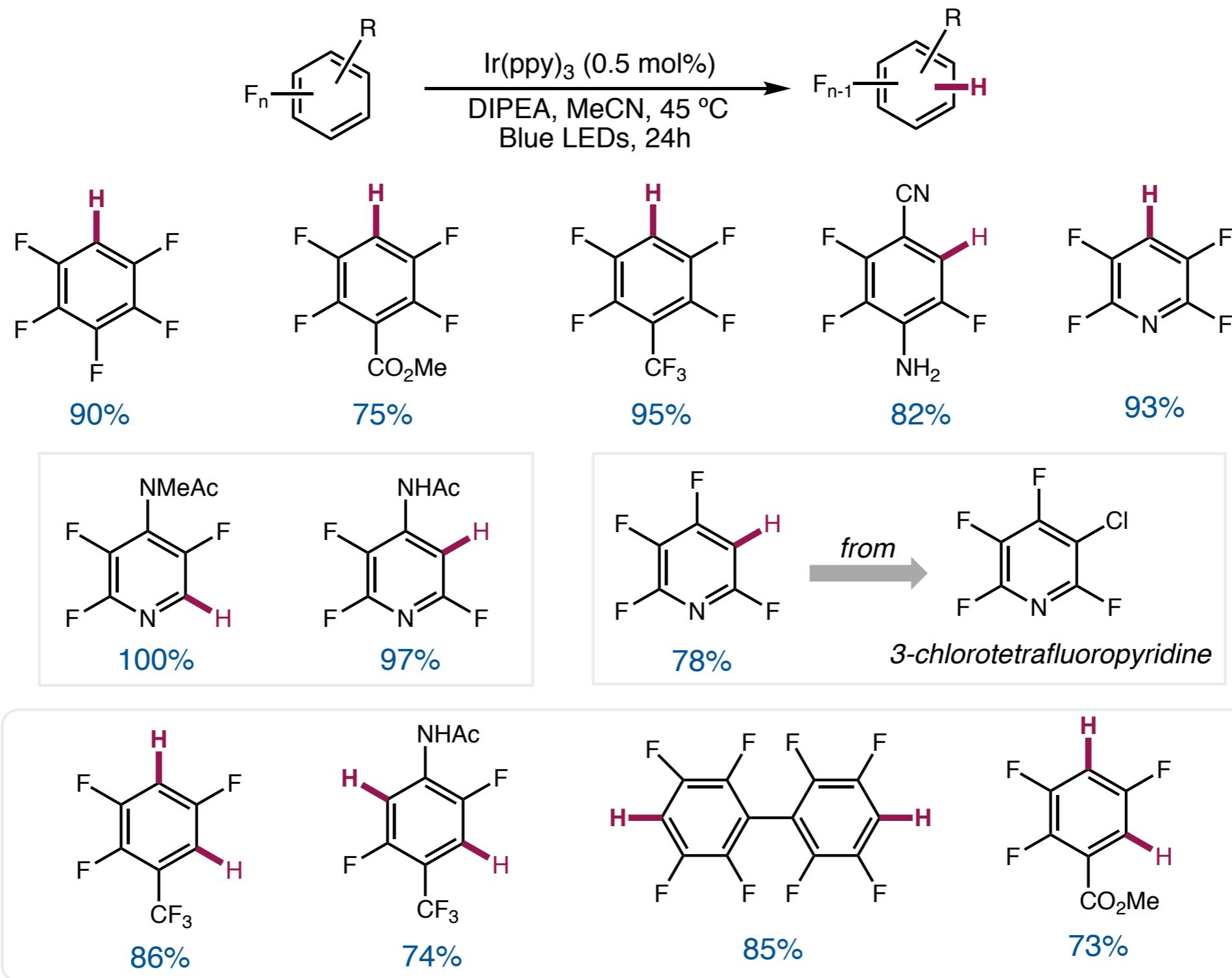
Jimmie Weaver

- ◆ Photocatalysis can make perfluoroaryl radical catalytically and in a controlled manner *in situ*.
- ◆ The outer sphere nature of the electron transfer might avoid the problematic catalyst–fluoride intermediates and lead to higher TONs.



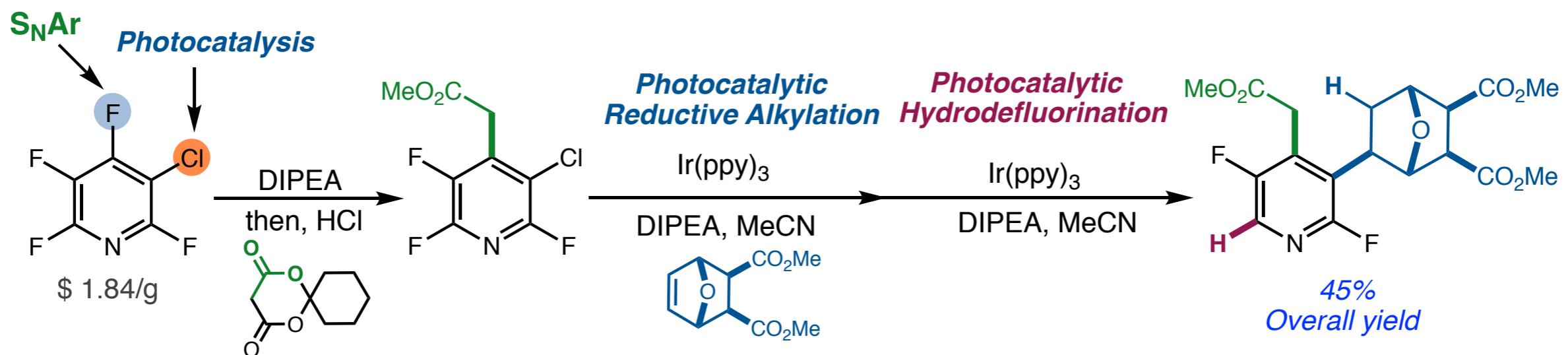
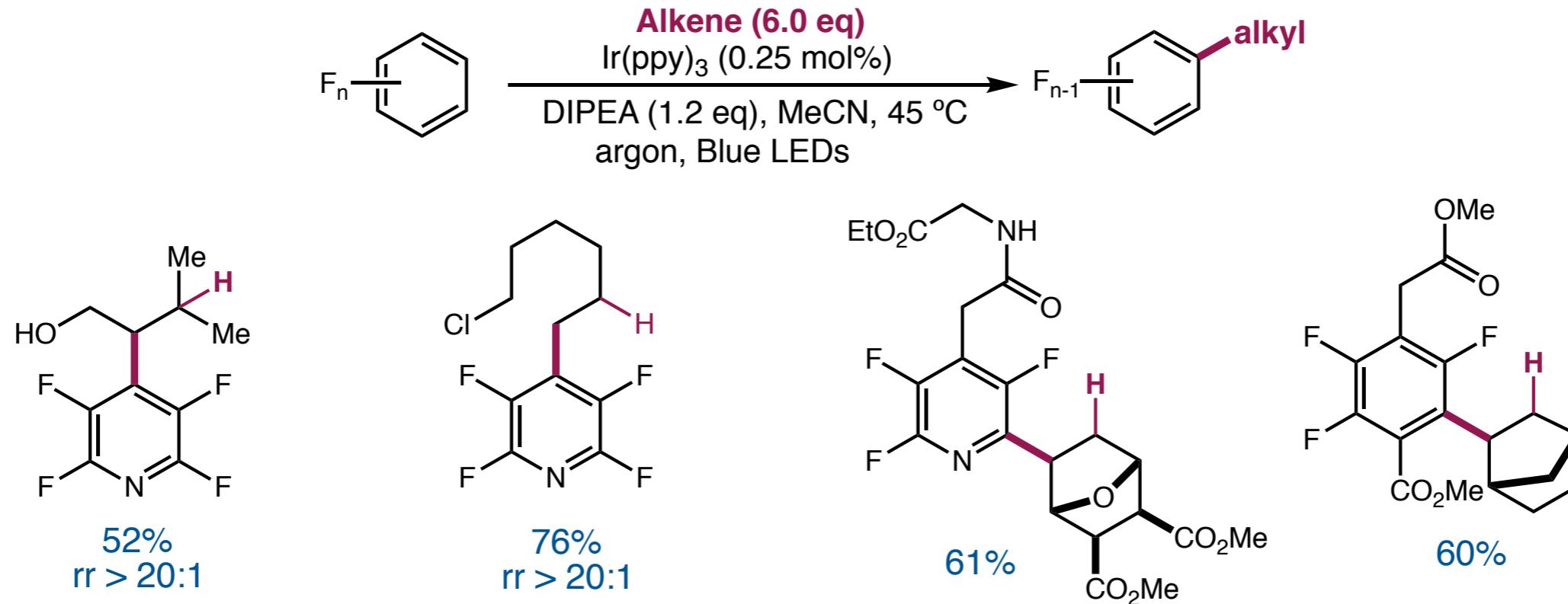
Photocatalytic C-F reduction and Functionalization in Aromatic Fluorides

Weaver group's work: Photocatalytic hydrodefluororation



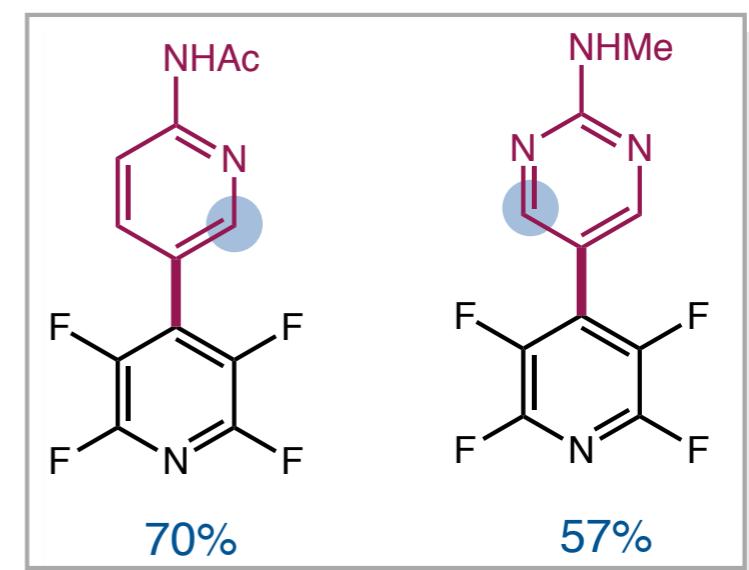
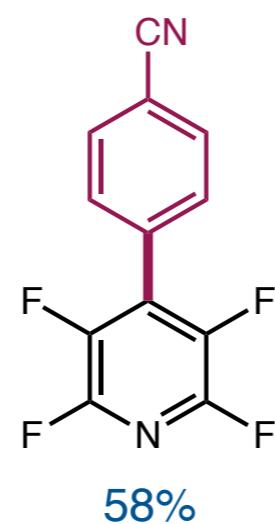
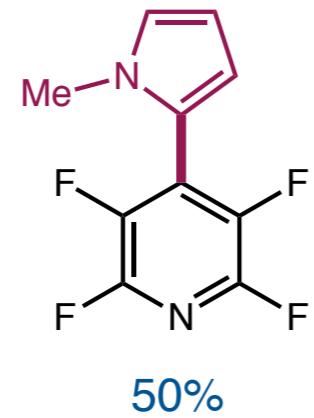
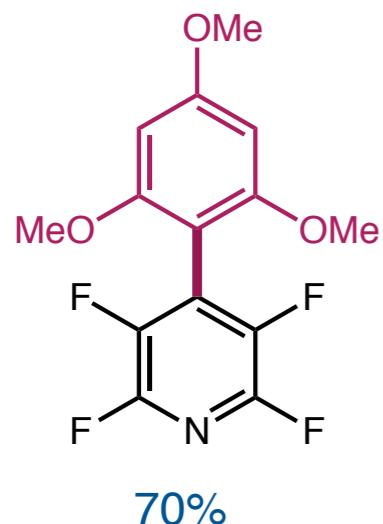
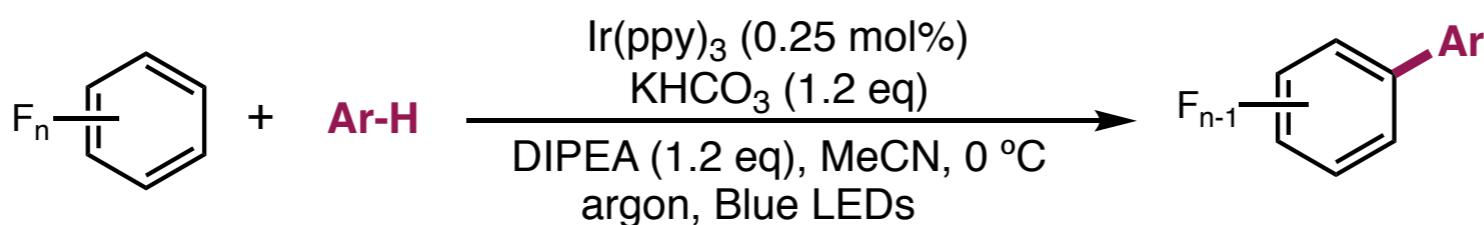
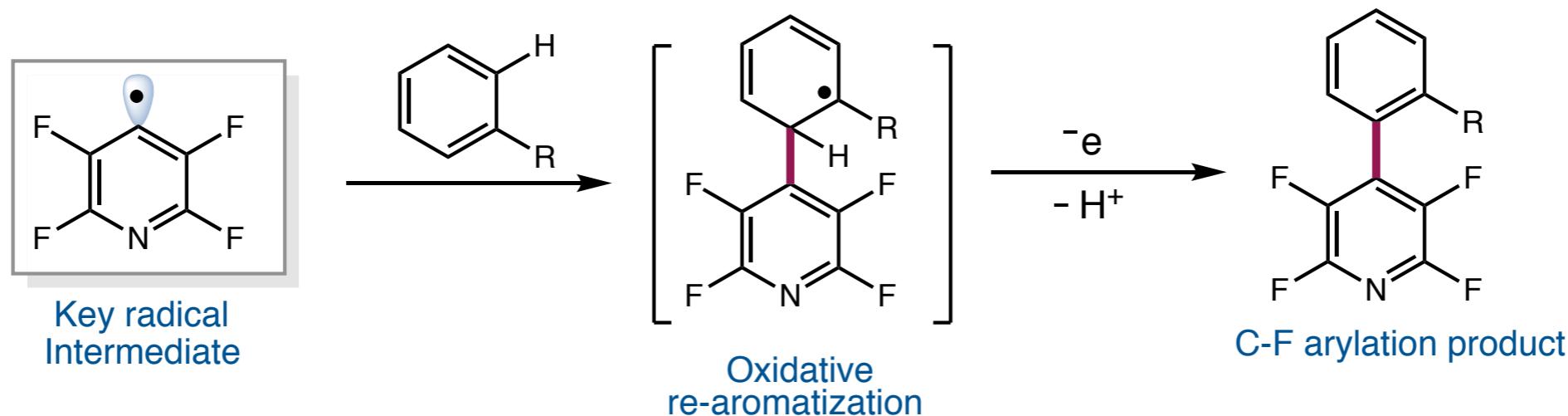
Photocatalytic C-F reduction and Functionalization in Aromatic Fluorides

■ Weaver group's work: Photocatalytic Alkylation of Fluoroarenes



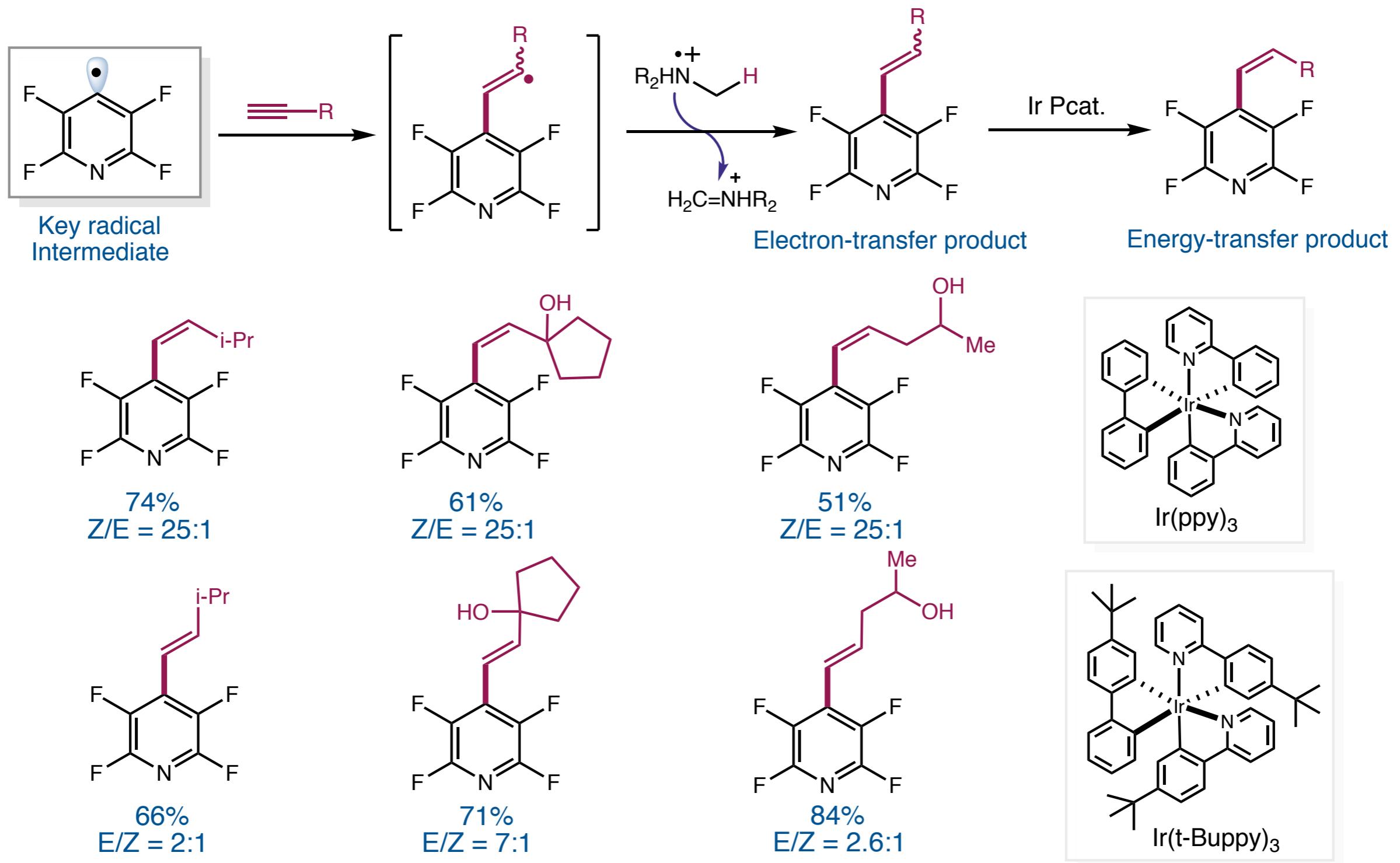
Photocatalytic C-F reduction and Functionalization in Aromatic Fluorides

■ Weaver group's work: Photocatalytic Arylation of Fluoroarenes



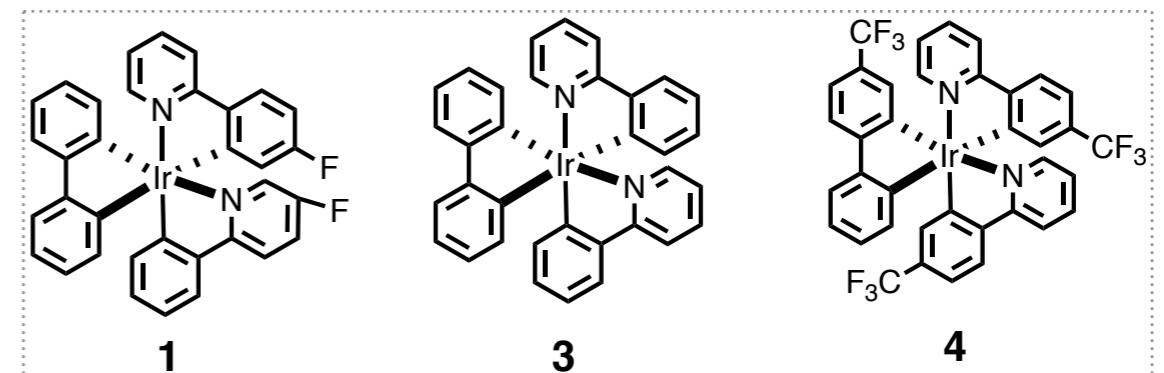
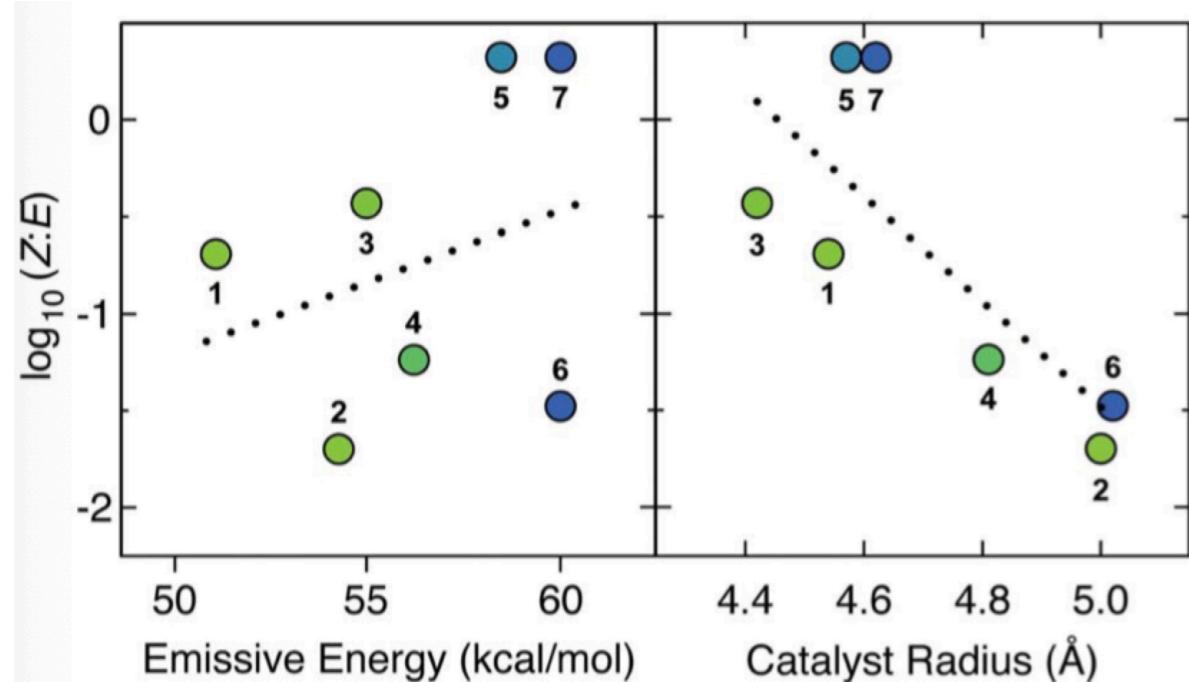
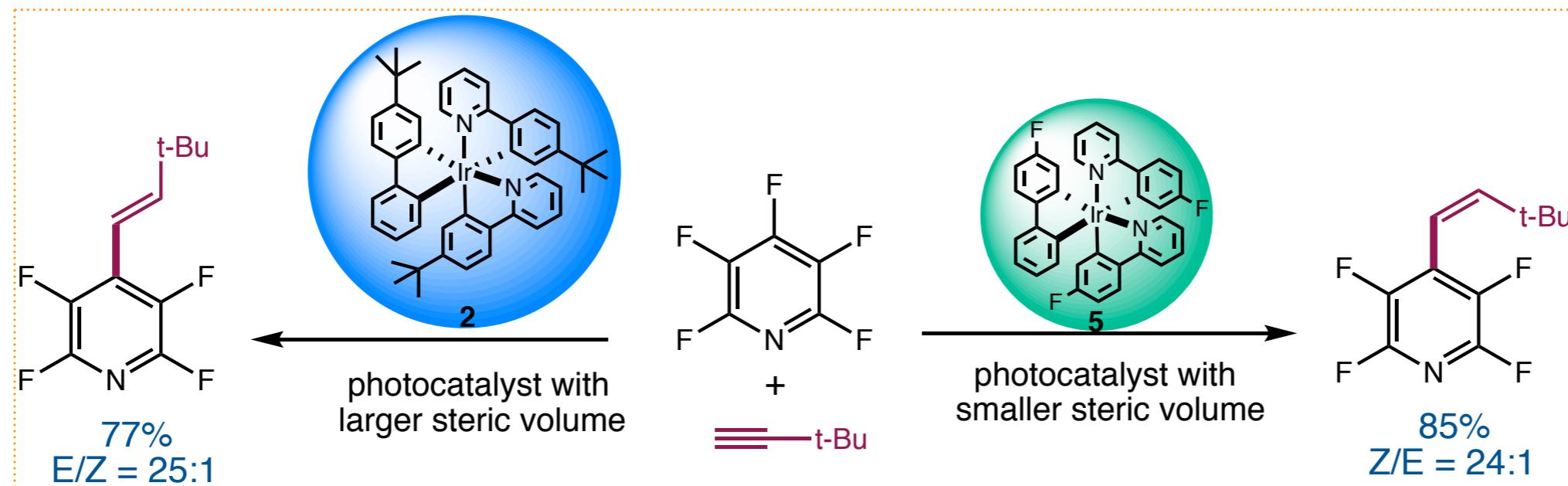
Photocatalytic C-F reduction and Functionalization in Aromatic Fluorides

■ Weaver group's work: Photocatalytic Alkenylation and Energy Transfer



Photocatalytic C-F reduction and Functionalization in Aromatic Fluorides

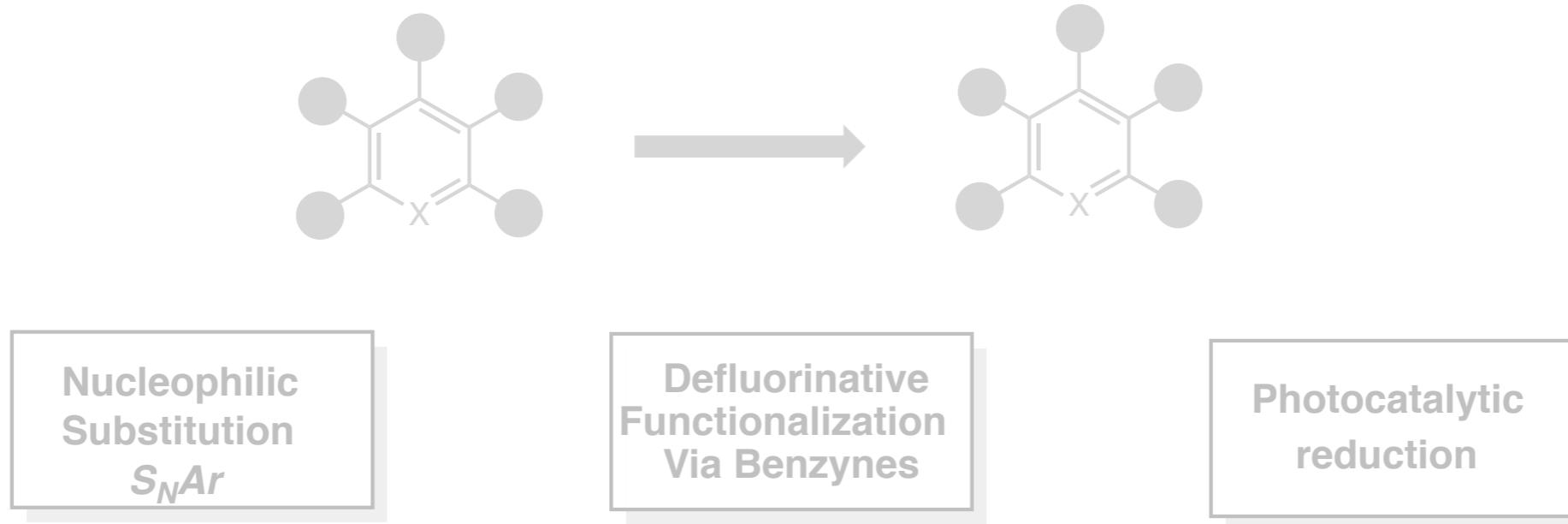
■ Weaver group's work: Photocatalytic Alkenylation and Energy Transfer



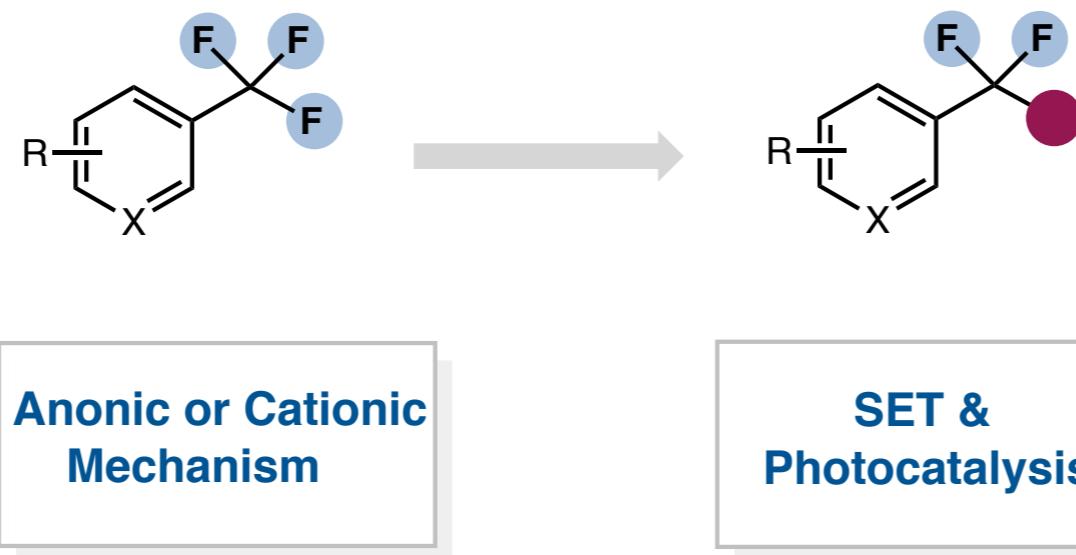
- ◆ The plot of Log(Z:E) vs the photocatalyst's emissive energy revealed no correlation
- ◆ The plot of log(Z:E) as a function of the radius of the catalyst shows a linear correlation

Content Outline

■ Selective C-F bond functionalization in aromatic fluorides

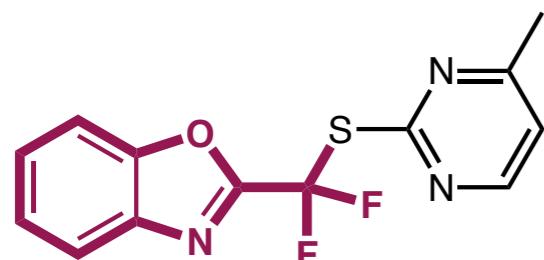


■ Selective C-F bond functionalization in trifluoromethylarenes

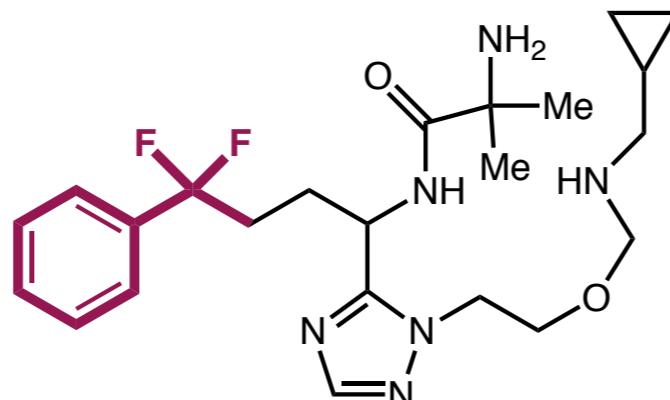


Selective C-F bond functionalization of Trifluoromethylarenes

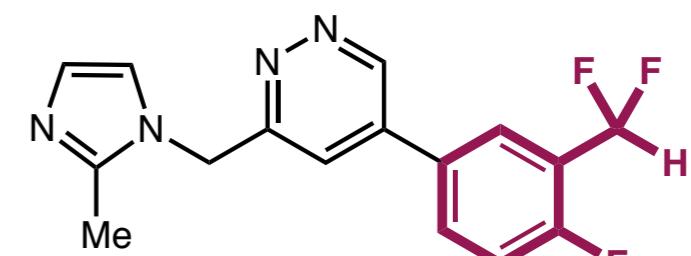
■ Introduction of the transformation challenge from ArCF_3 to ArCF_2R



HIV-1 reverse
Transcriptase inhibitor

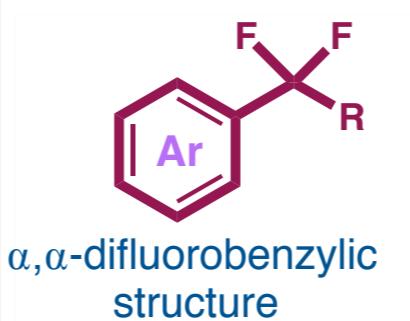


Growth hormone secretagogue

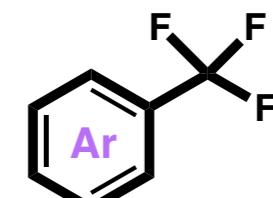


NR2B antagonist

- ◆ Enhanced bioavailability, metabolic stability.
- ◆ Serving as bioisosteres of aryl ethers
- ◆ Lipophilic hydrogen bond donors (ArCF_2H).



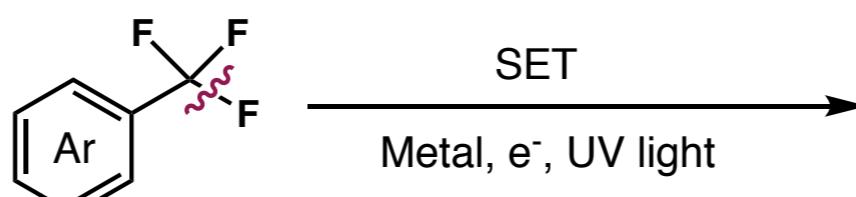
Single C-F bond
Cleavage



Trifluoromethylarenes
widely available

BDE (kcal/mol)

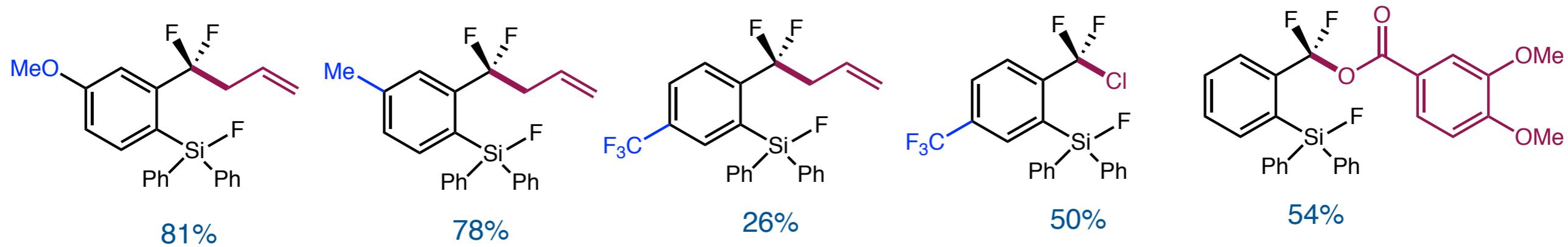
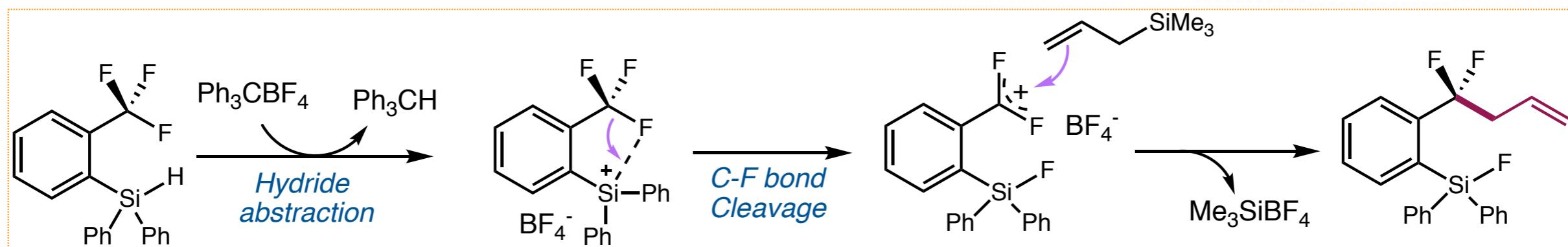
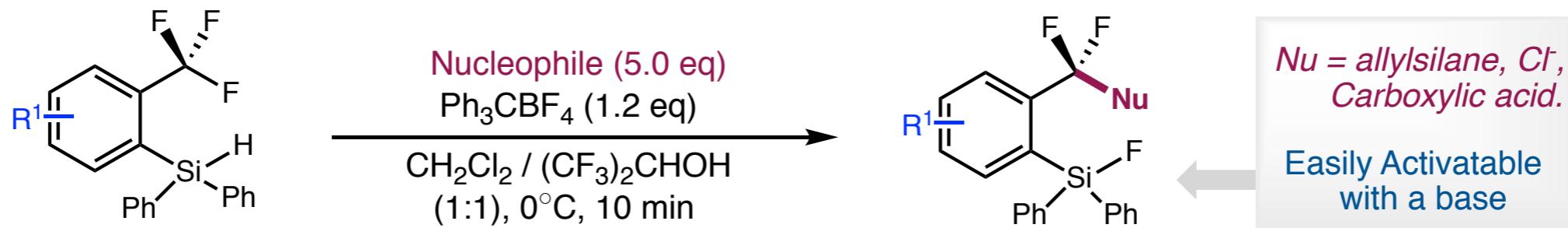
$\text{PhF}_2\text{C}-\text{F}$	115
$\text{PhFHC}-\text{F}$	106
$\text{PhH}_2\text{C}-\text{F}$	99



large excess of reductants
poor selectivity, limited scope

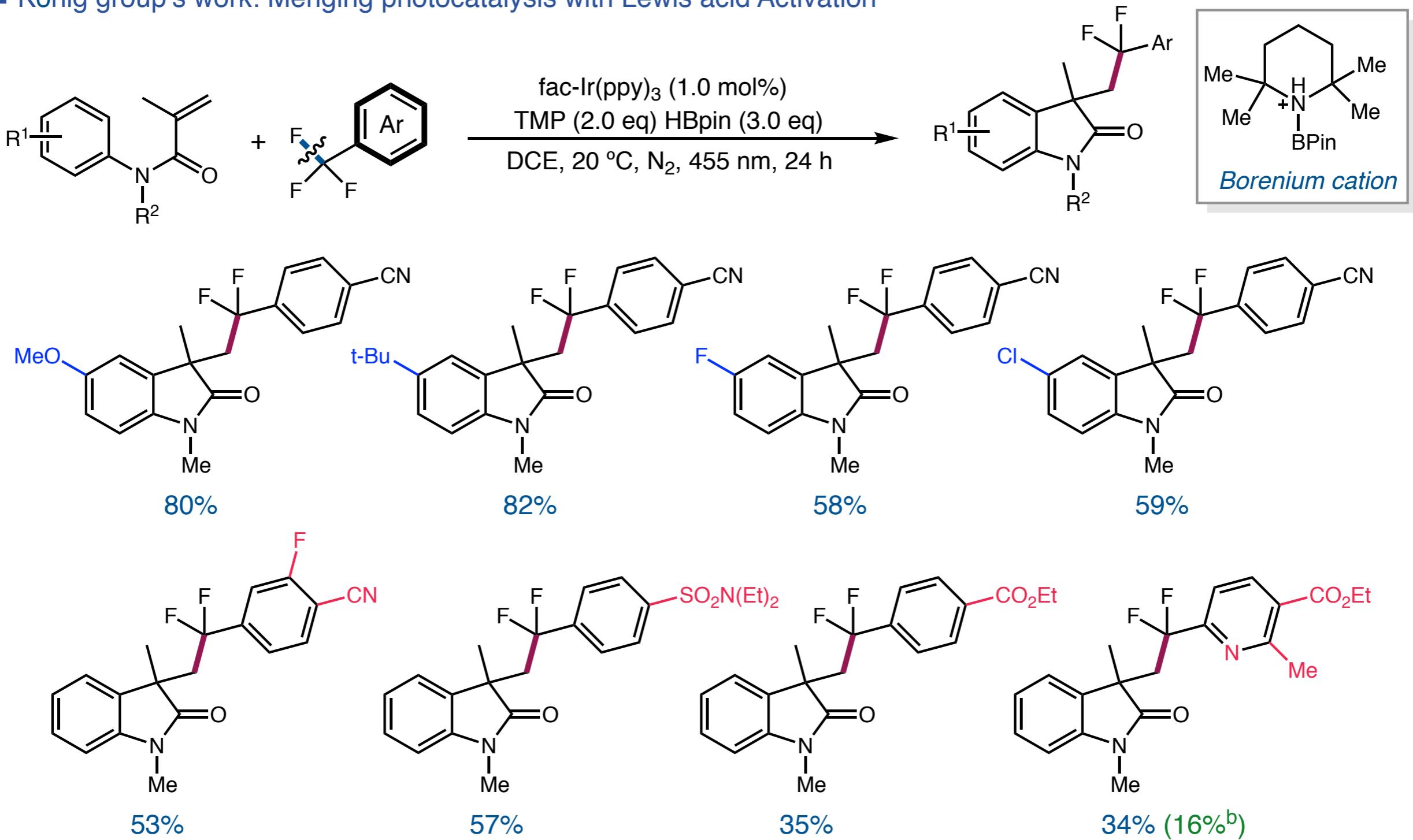
Selective C-F bond functionalization of Trifluoromethylarenes

- Yoshida group's work: Ortho-silylum cation mediated C-F bond cleavage of trifluoromethylarenes



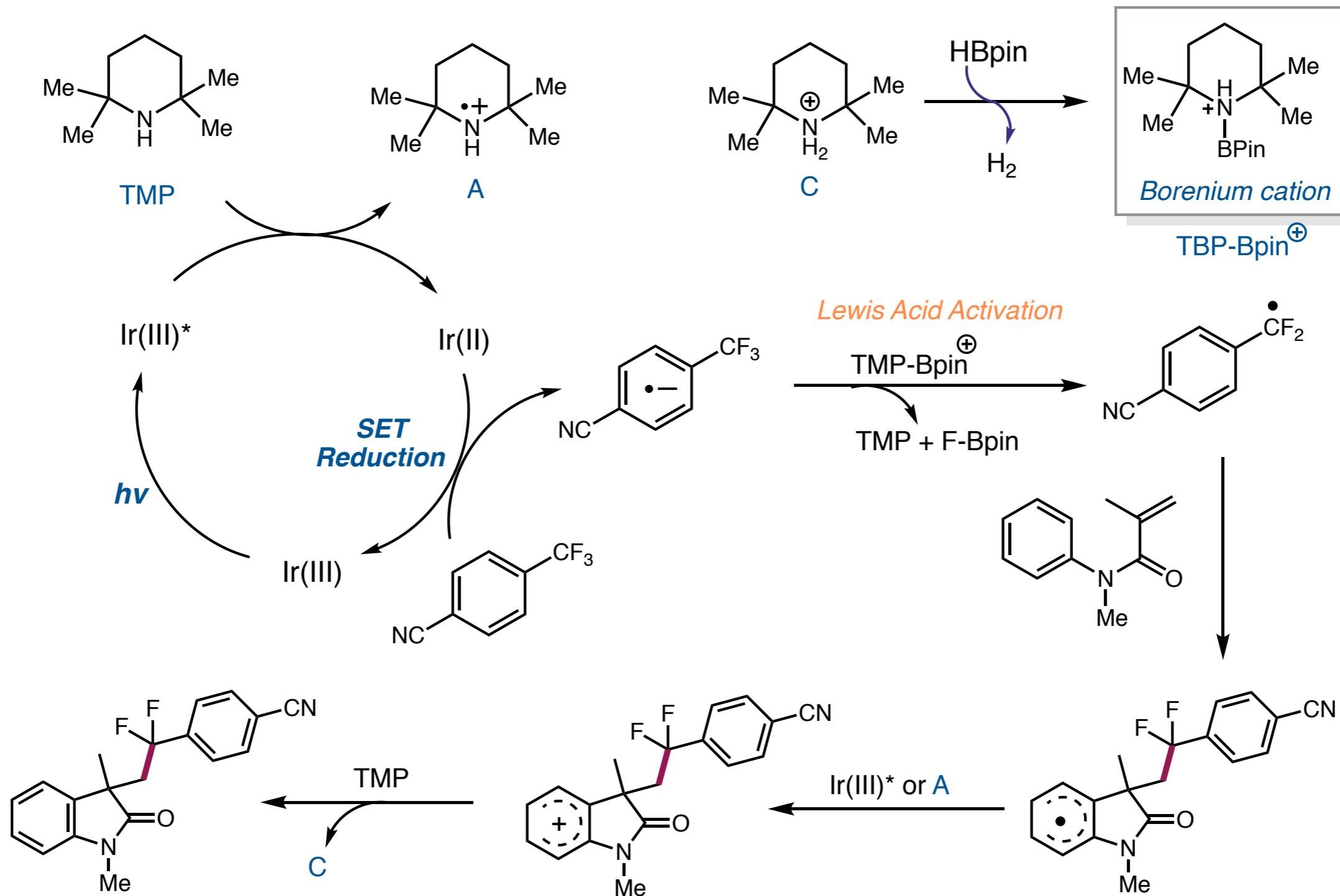
Photocatalytic C-F bond Functionalization in Trifluoromethylarenes

■ König group's work: Merging photocatalysis with Lewis acid Activation



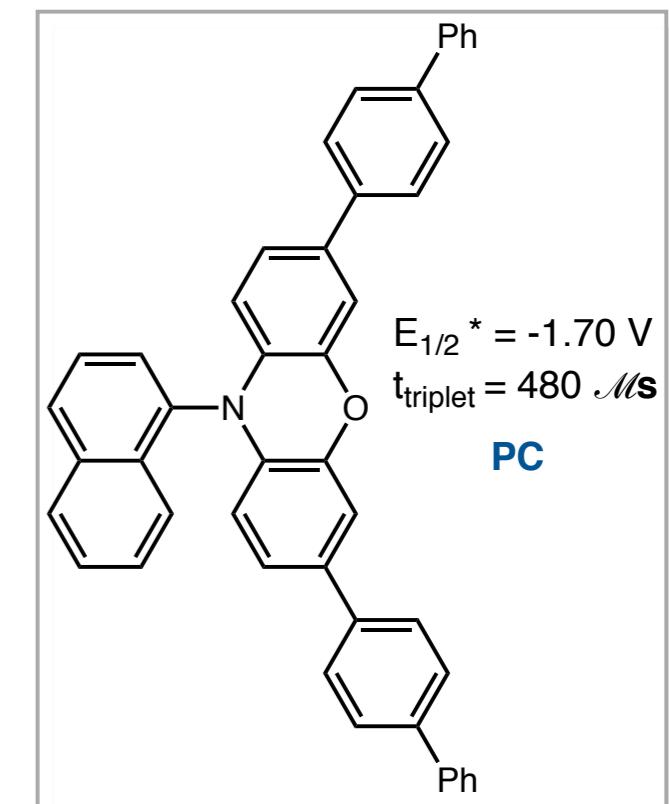
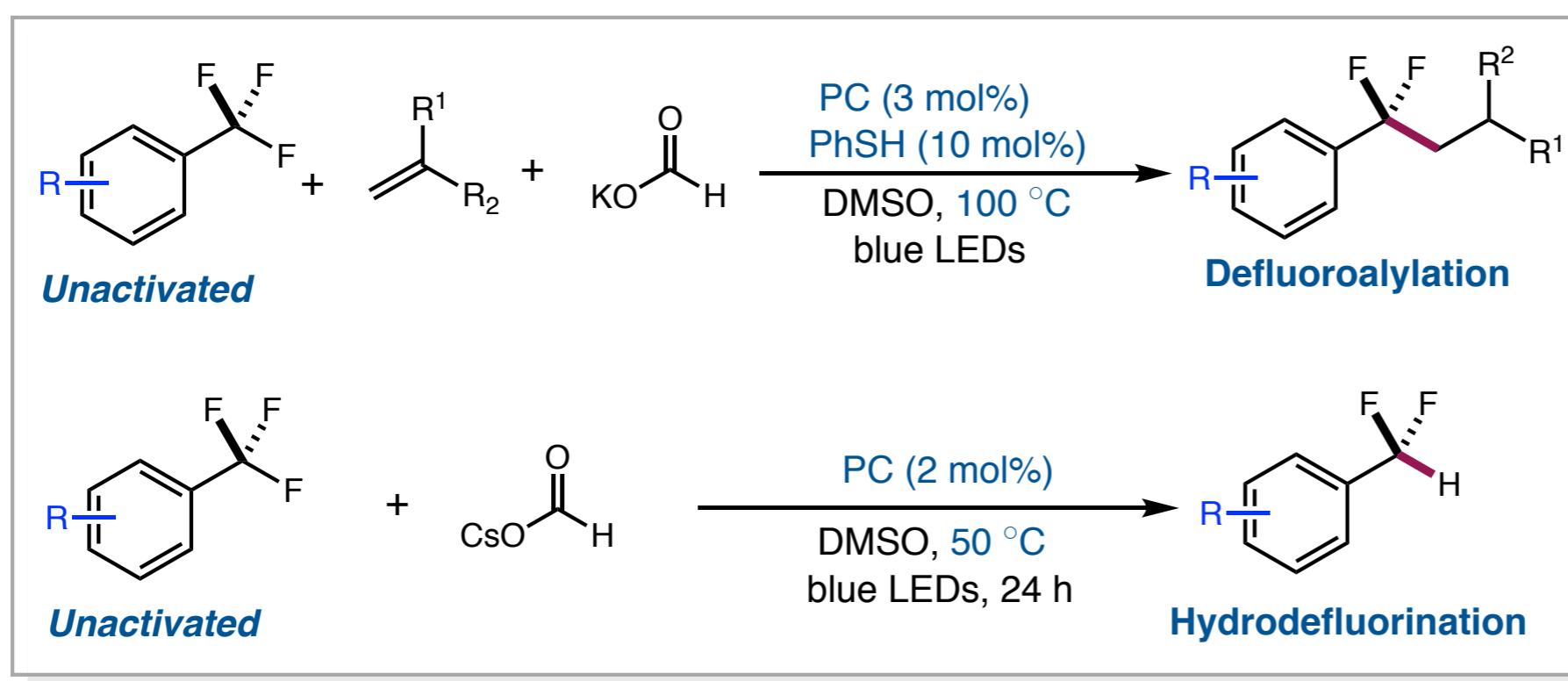
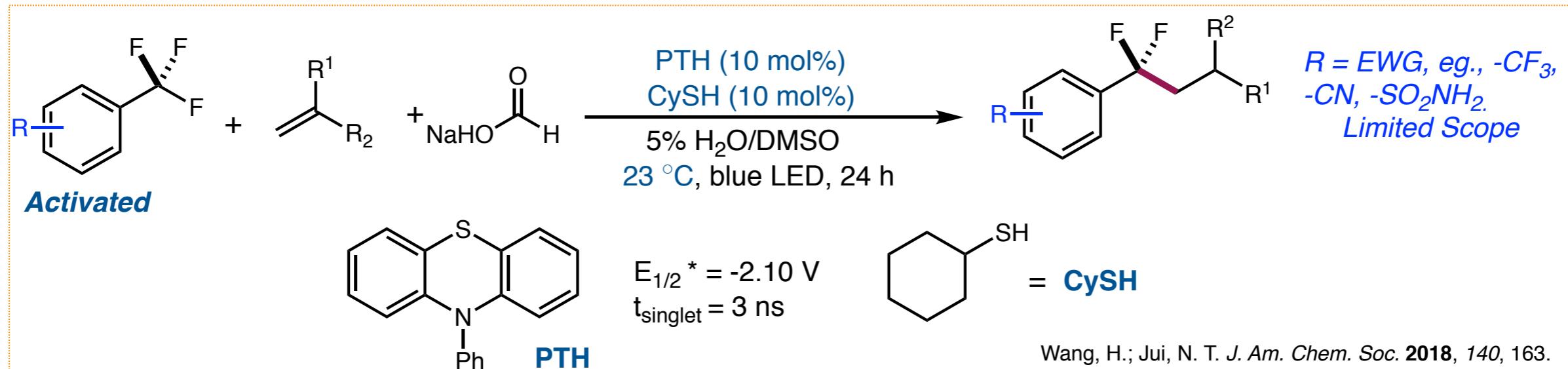
Photocatalytic C-F bond Functionalization in Trifluoromethylarenes

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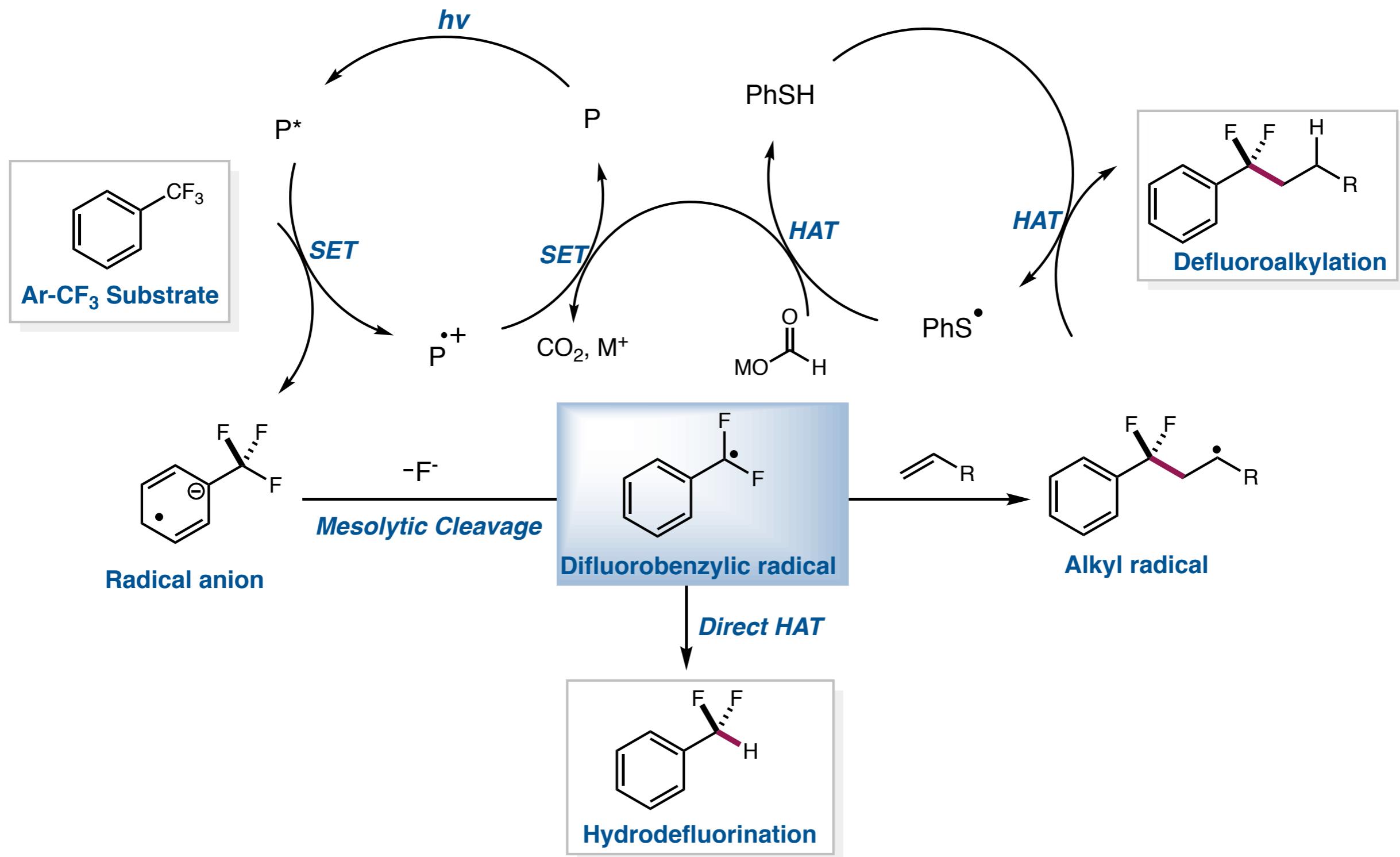
Photocatalytic C-F bond Functionalization in Trifluoromethylarenes

■ Jui group's work: Photocatalytic defluoroalkylation and hydrodefluorination of trifluoromethylarenes



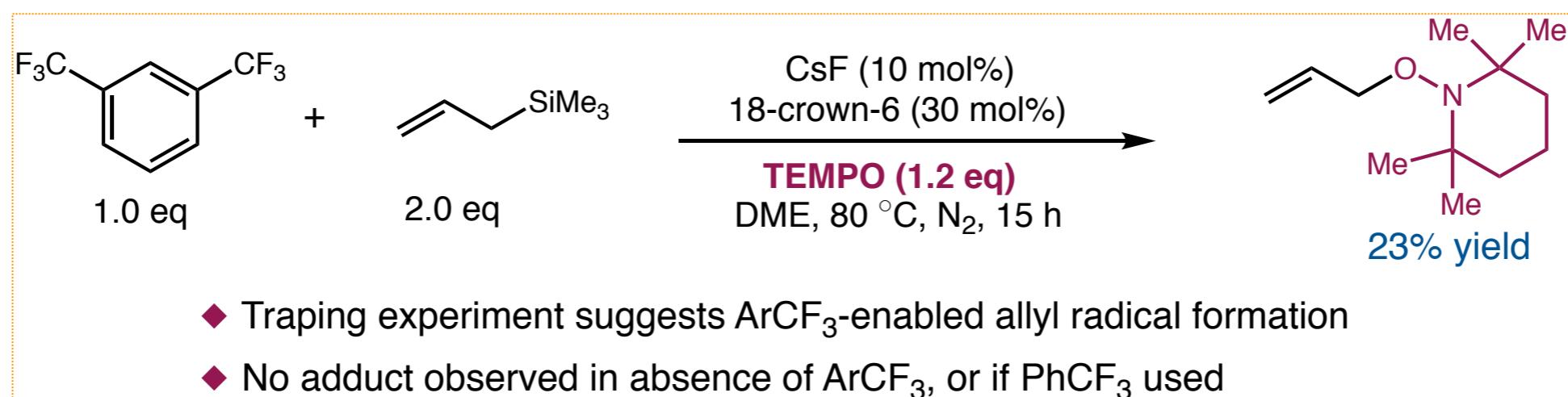
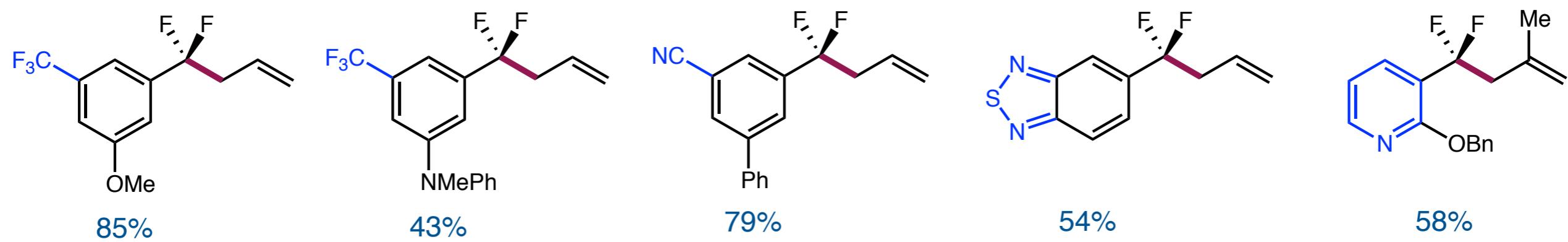
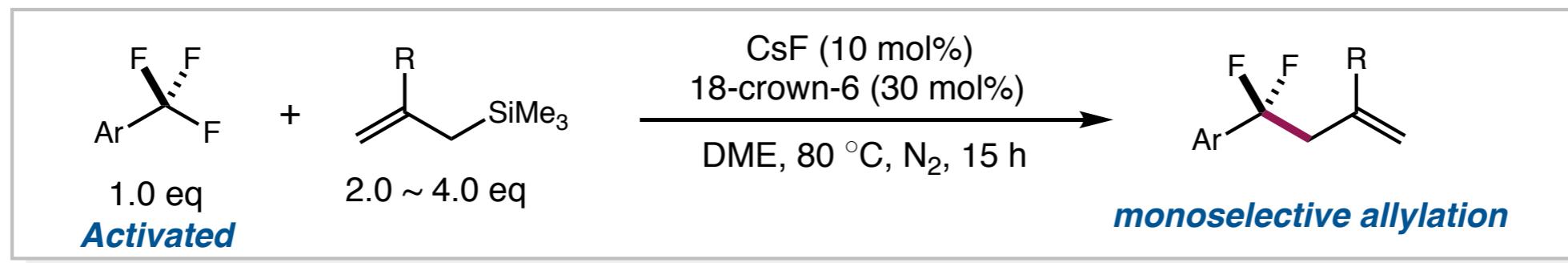
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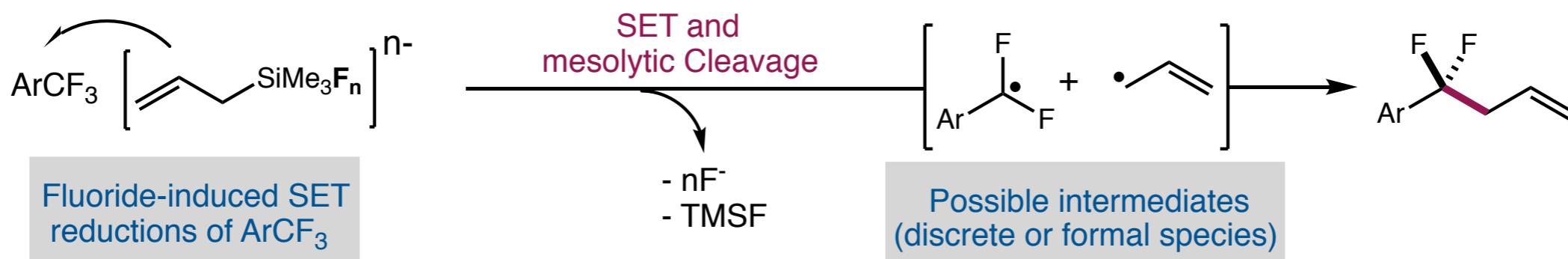
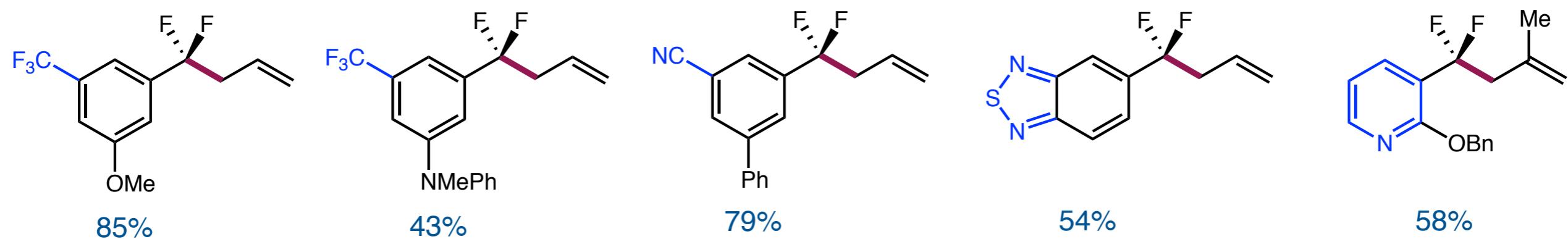
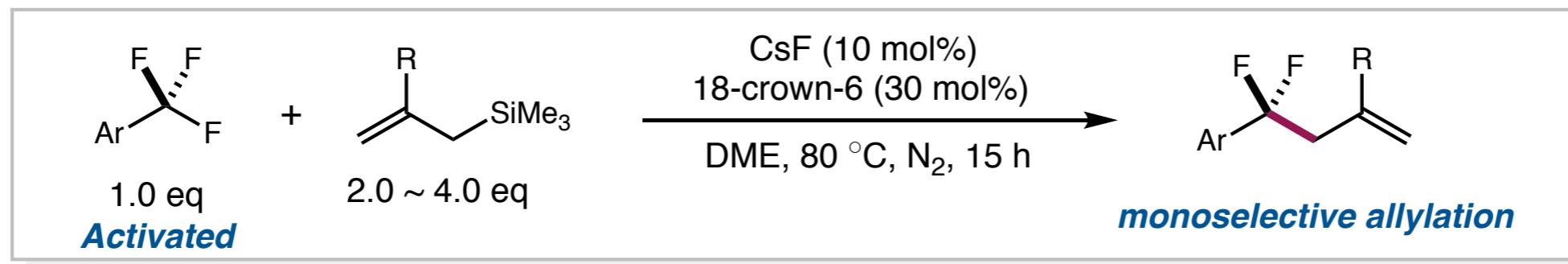
SET Mediated Selective Defluoroallylation Trifluoromethylarenes

- Bandar group's work: Fluoride-Induced direct ArCF_3 coupling with allylsilane



SET Mediated Selective Defluoroallylation Trifluoromethylarenes

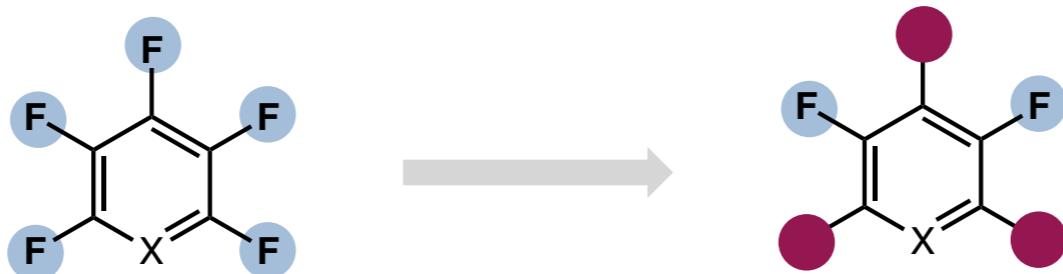
- Bandar group's work: Fluoride-Induced direct ArCF_3 coupling with allylsilane



- ◆ Reactivity correlates with ArCF_3 reduction potential
- ◆ No yield decrease in strict absence of light

Summary and Outlook

■ Selective C-F bond functionalization in aromatic fluorides



**Photocatalytic
reduction**

■ Selective C-F bond functionalization in trifluoromethylarenes



**Photocatalytic
reduction**

**Transition-Metal
Catalysis**

Chem. Rev. **2015**, *115*, 931
Chem. Rev. **2009**, *109*, 2119
J. Fluorine Chem. **2015**, *179*, 14