How to Introduce Fluorine Element into the Organic Molecules by Building C–C Bond and C–F Bond

Hundreds of Fluoro-pharmaceuticals

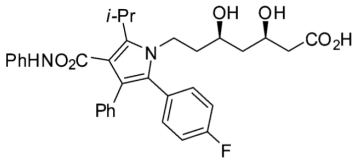
12/09/2023
ZHANG Yanghao

Contents

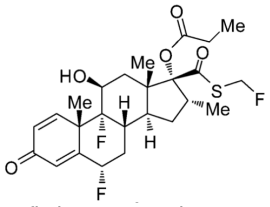
1. Introduction

1.1. Applications of Fluorinated Compounds

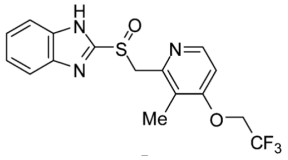
Common Fluorine-containing Drugs



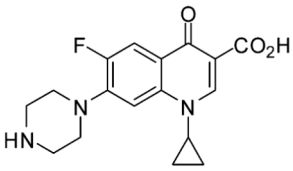
atorvastatin
anti-hyperlipidemic



fluticasone propionate
reduce inflammation

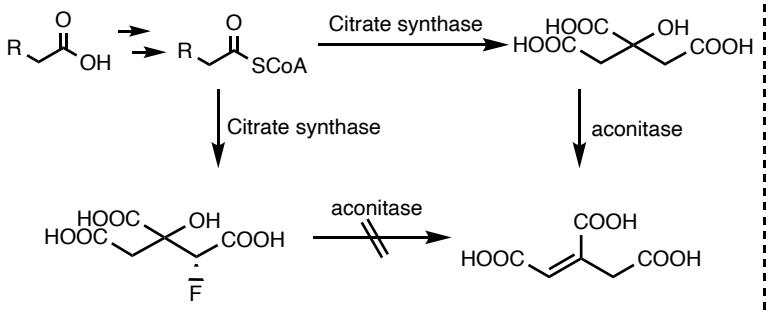


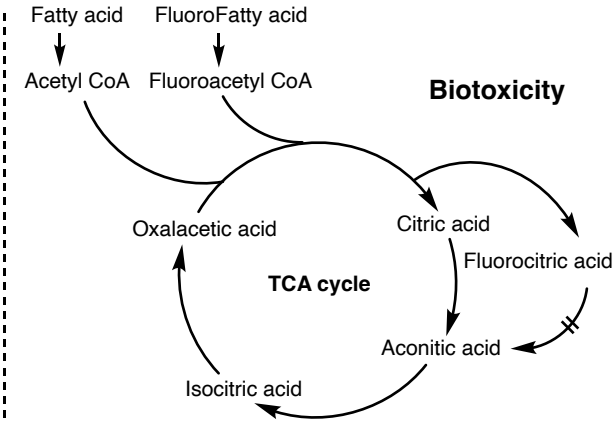
lansoprazole
suppresses stomach acid secretion



ciprofloxacin
anti-microbial

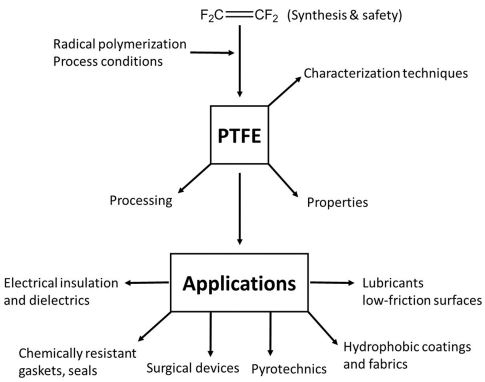
Mimic Effect and Block Effect in Medicinal Chemistry

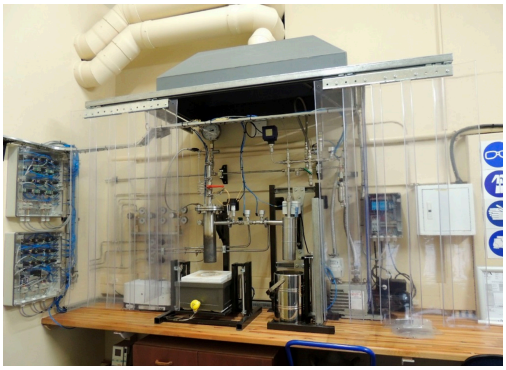




Common Fluorine-Containing Materials

PTFE





Synthesis of PTFE and Applications **Kilogram-scale PTFE Pyrolysis Reactor**

Artificial blood

- **Chemical Inertness**
- **Excellent Oxygen Carrying Capacity**
- **Good Biocompatibility**

1.2. Early Synthesis of Organofluorine Compounds

1886 year, Moissan successfully produced F_2 (1)(2)(3)(4)

(1986 year, France established the Moissan Medal)

Moissan Medal

$$KHF_2 + KF \xrightarrow{\text{electrolysis}} H_2\uparrow + F_2\uparrow$$

1930 year, T.Midgly & A.L.Henne produced Freon 12 (5)

$$CCl_4 + HF + SbCl_5 \longrightarrow CF_2Cl_2$$

1934 year, Schloffer & Scherev produced Freon 22 (6)

$$HCCl_3 + HF \longrightarrow CHF_2Cl + HCl \qquad CHF_2Cl \xrightarrow{650^oC} CF_2{=}CF_2$$

1938 year, Roy J. Plunkett discovered polytetrafluoro-ethylene (PTFE), better known as Teflon™ (7)

$$CF_2{=}CF_2 \longrightarrow \{CF_2{-}CF_2\}_n$$

Teflon™

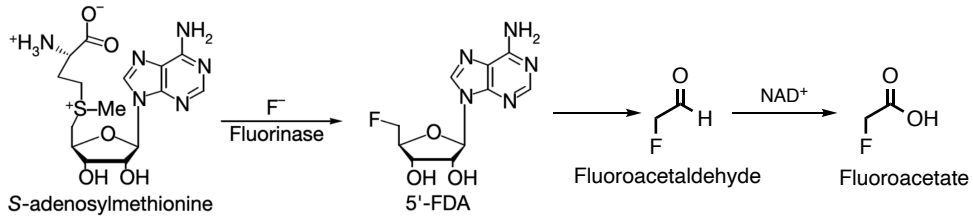
1947 year, Fowler discovered the method of synthesis perfluo-rinated compounds (8)

$$CoF_2 + F_2 \longrightarrow CoF_3 \qquad C_6H_{14} + CoF_3 \longrightarrow C_6F_{14} + HF$$

1949 year, Simons process has been discovered (9)

$$R_3C{-}H + HF \xrightarrow{\text{electrolysis}} R_3C{-}F + H_2\uparrow$$

2002 year, O'Hagan developed a method of synthesizing organo-fluorine molecule (10)



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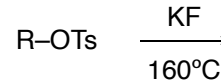
(1) Liu, H. *et al. Chem. Rev.* 2014, **114**, 2432. (2) Liu, H. *et al. Chem. Rev.* 2016, **116**, 422. (3) M. Ameduri, B. *et al. Chem. Rev.* 2019, **119**, 1763. (4) Fechete, I. *Comptes Rendus Chimie.* 2016, **19**(9)*:* 1027. (5) Thomas, M. *et al. Industrial & Engineering Chemistry.* 1930*,* **22**(5): 542. (6) Schloffer, F. *et al.* DE1934I0050715, 1939. (7) Plunkett, R. J. *et al. J. Am. Chem. Soc.* 1938, **60**, 2847. (8) Fowler, R. D. *et al. Ind. Eng. Chem.* 1947, 39, 3, 292.(9) Simons, J. H. *et al. J. Electrochem. Soc.* 1949, **95,** 55. (10) O'Hagan, D. *et al. Nature* 2002, **416**, 279.

2. Nucleophilic, Electrophilic Fluorination

2.1. Common Nucleophilic Fluorination

Common Nucleophilic Fluorination Reagents

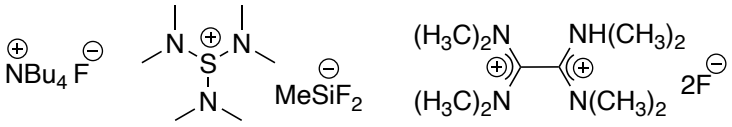
Metal Fluoride Salts



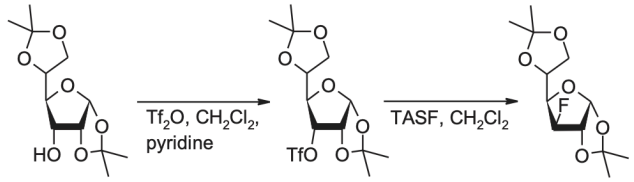
CsF > RbF > KF > NaF > LiF

Fluorination activity sequence

Naked Fluoride

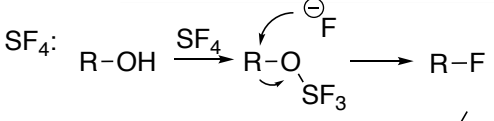


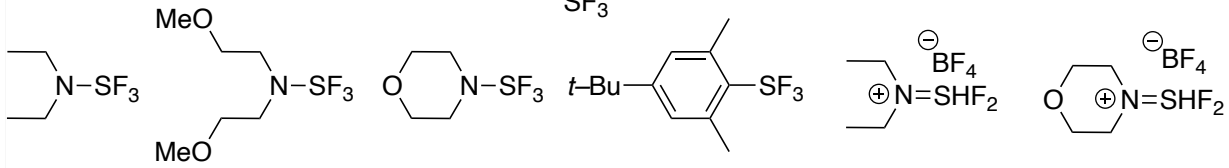
TBAF TASF $TDAE^{+}\ 2F^{-}$



(1)

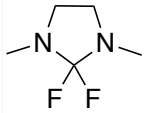
SF_4, DAST and derivatives



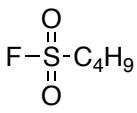


DAST Deoxo-Fluor/BAST MOST Fluolead XtalFluor–E XtalFluor–M

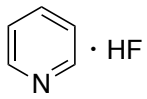
Other Types



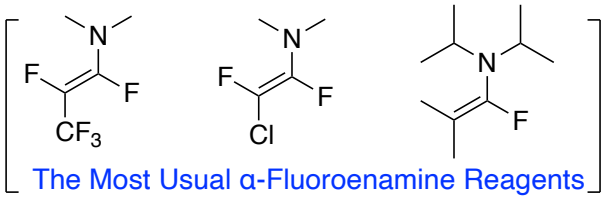
DFI



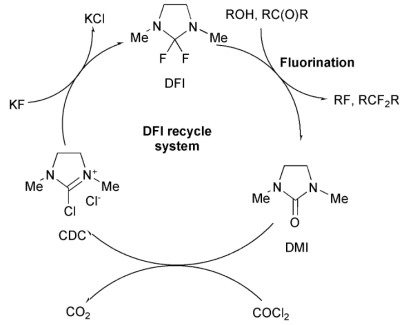
PBST

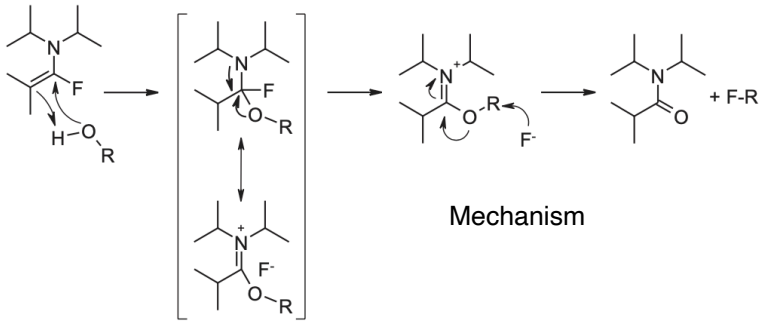


Olah's Reagent

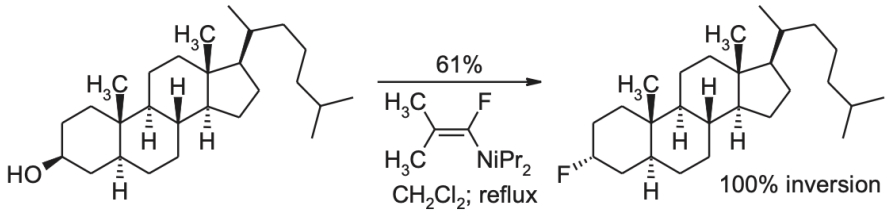


The Most Usual α-Fluoroenamine Reagents





Mechanism



(2)

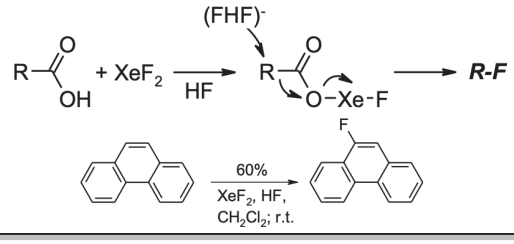
(1) Szarek, W. A. *J. Chem. Soc., Chem. Commun.* 1985, 663.
(2) Muneyama, F. *et al. Tetrahedron Lett.* 1989, **30**, 3077.

2.2. Common Electrophilic Fluorination(1)(2)(3)(4)

Common Electrophilic Fluorination Reagents

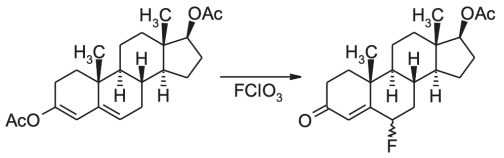
Earlist Electrophilic Fluorination

XeF_2 (Xenon Difluoride)

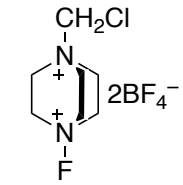


Perchloryl Fluoride and Hypofluorides

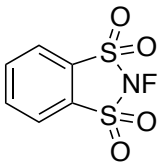
$KClO_4 + 2HF + SbF_5 \xrightarrow{40\text{-}50°C} FClO_3 + KSbF_6 + H_2O$



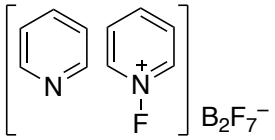
"NF"–Reagents



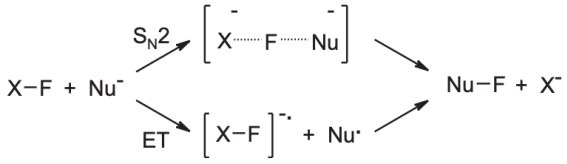
F–TBDA–BF_4
Selectfluor™

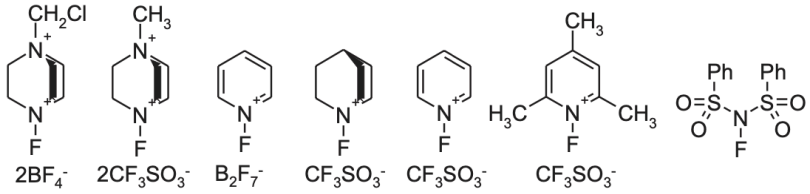


NFTh



NFPy

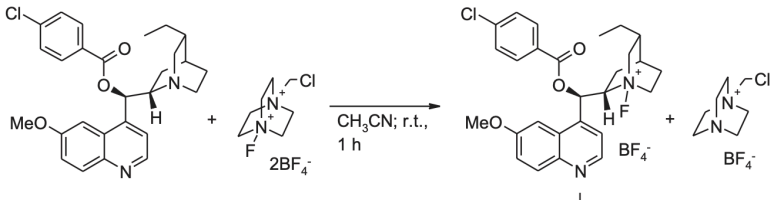


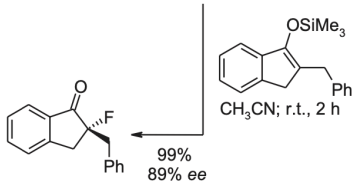


$E_{p,red}$ (V vs. SCE)	-0.04	-0.09	-0.34	-0.37	-0.47	-0.37	-0.78

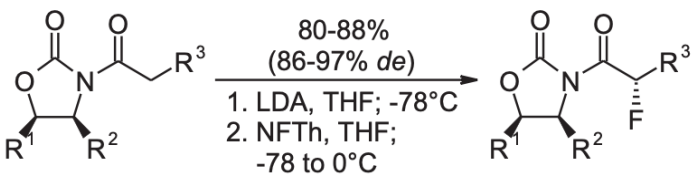
increasing fluorinating power

Asymmetric Electrophilic Fluorination

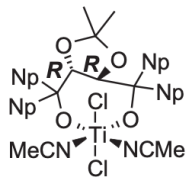




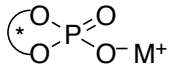
(1)(2)(3)(4)



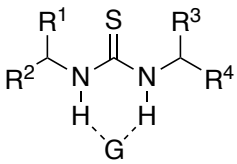
Chiral Catalysts



TADDOL complexes

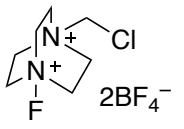


CPA

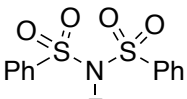


Takemoto catalyst
G: Fluorination Reagents

Fluorination Reagents



Selectfluor™



NFSI

$Et_3N \cdot nHF$

etc…

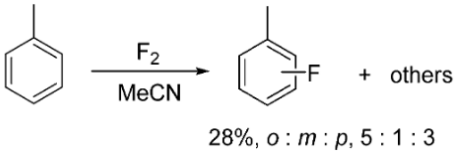
(1) Evans, D. A. *et al. J. Am. Chem. Soc.* 1990, **112**, 10, 4011. (2) Takeuchi, Y. *J. Am. Chem. Soc.* 2000, **122**, 10728. (3) Roques, N. Tetrahedron Lett. 2001, **42**, 1867. (4) Togni, A. *Angew. Chem. Int. Ed.* 2000, **39**, 4359.

3. Radical Fluorination

3.1. Early Radical Fluorination

First Generation

F_2 [1]



Initiation

$F_2 \longrightarrow 2F\cdot$

$R\text{–}H + F_2 \longrightarrow R\cdot + F\cdot + HF$

Propagation

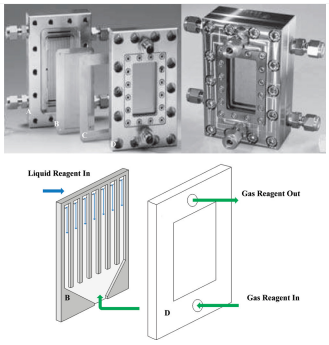
$R\text{–}H + F\cdot \longrightarrow R\cdot + HF$

$R\cdot + F_2 \longrightarrow R\text{–}F + F\cdot$

Overall Reaction

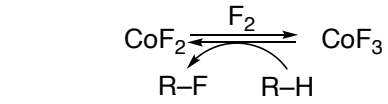
$R\text{–}H + F_2 \longrightarrow R\text{–}F + HF$

Mechanism

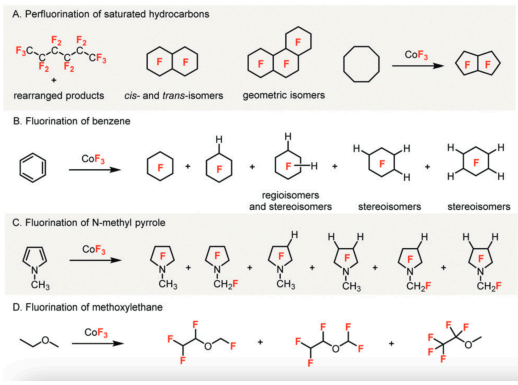


Reaction Equipment

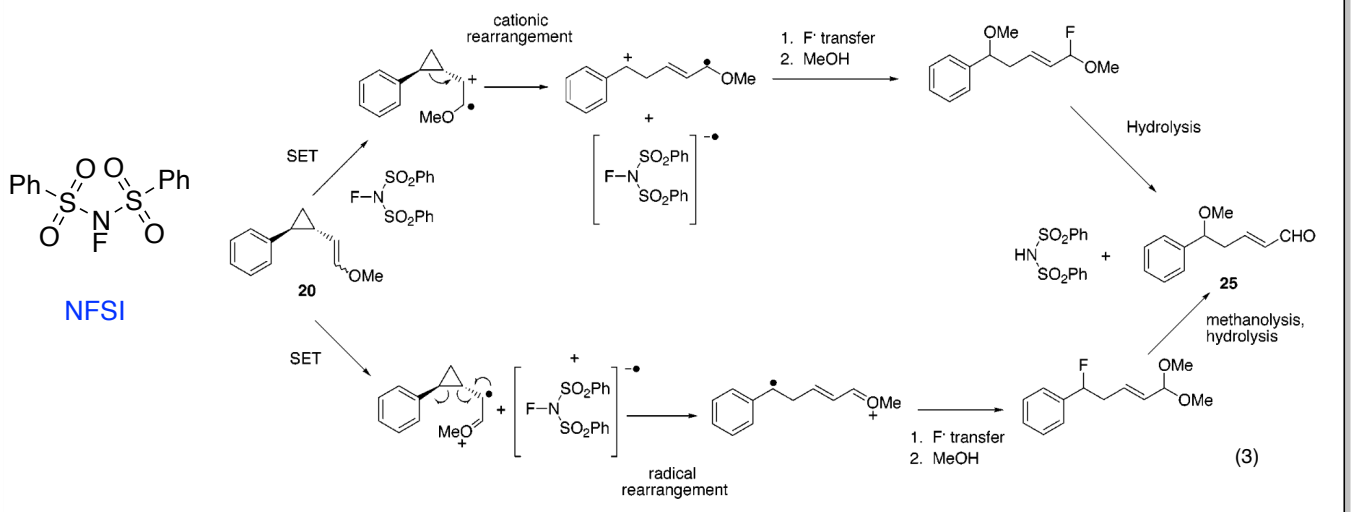
CoF_3 [2]



$R\text{–}H + CoF_3 \longrightarrow [R\text{–}H]^{\bullet+} \xrightarrow{-H^+} R\cdot \xrightarrow{CoF_3} R\text{–}F$

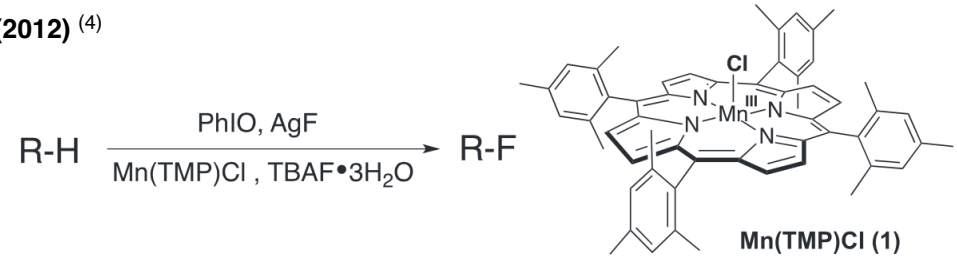


Second Generation

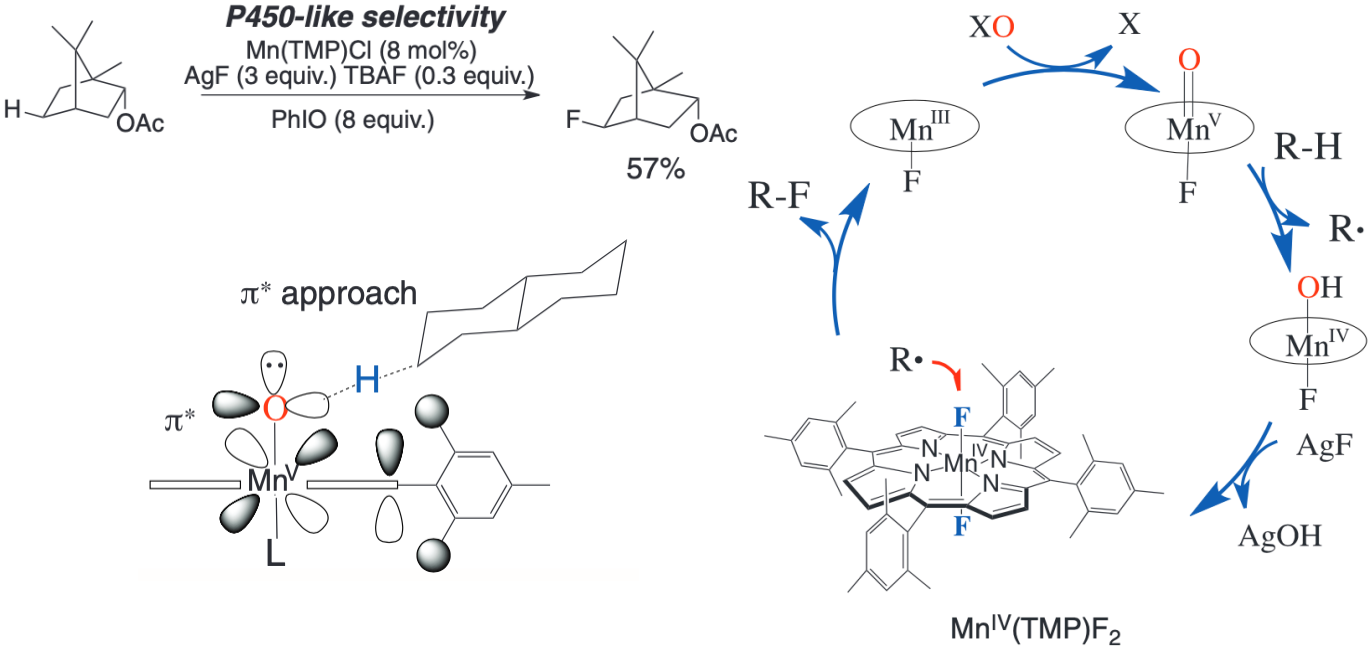


3.2. Radical Fluorination by Metal Catalyst

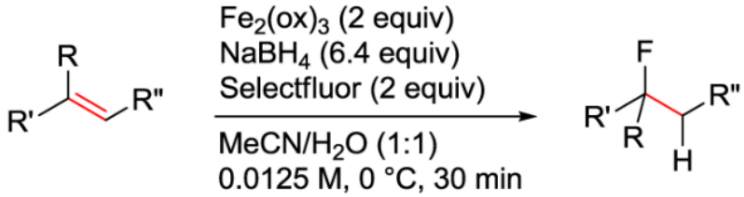
Mn (2012) [4]

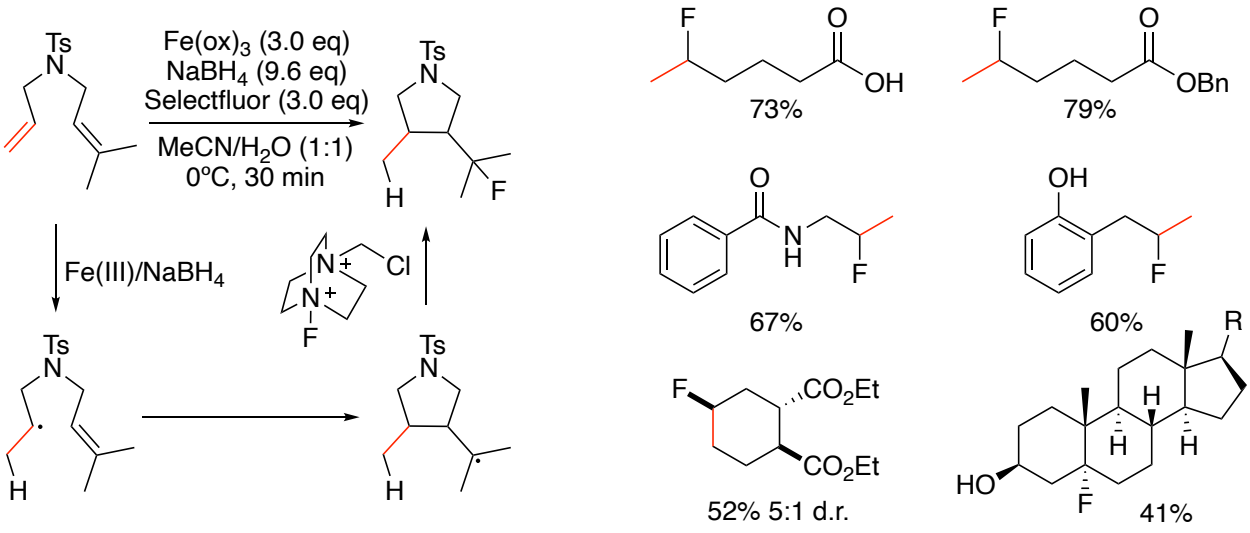


(1) Sandford, G. *et al. Org. Process. Res. Dev.* 2012, **16**, 844. (2) Ye, K.-Y. *et al. Chem. Commun.*, 2020, **56**, 8512. (3)Wong, C.-H. *et al. J. Org. Chem.* 1999, **64**, 5264. (4) Groves, J. T. *et al. Science* 2012, 337, 1322.

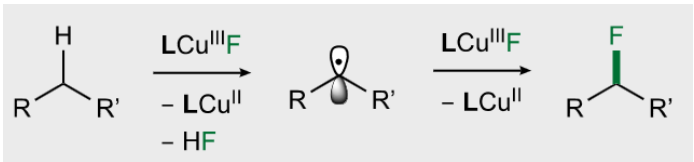


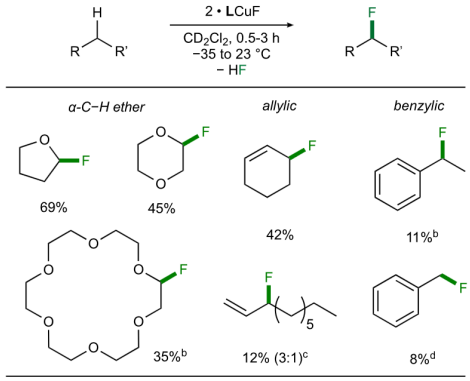
Fe (2012) (1)

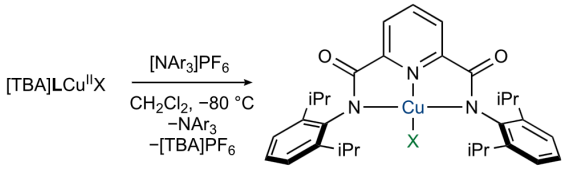




Cu (2020) (2)

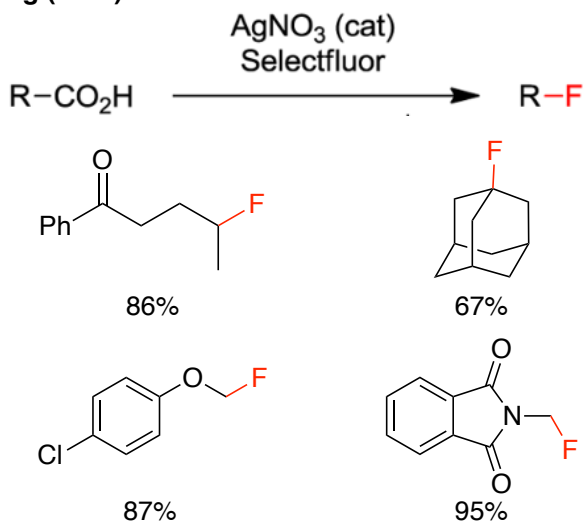


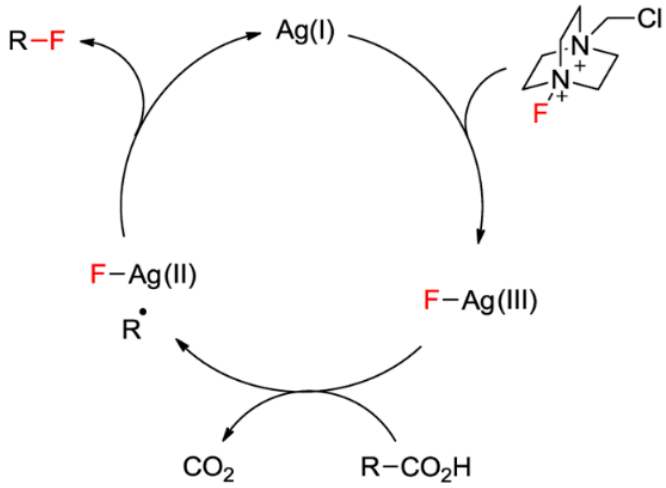




(1) Barker, T. J. *et al. J. Am. Chem. Soc.* 2012, **134**, 13588.
(2) Boger, D. L. *et al. J. Am. Chem. Soc.* 2020, **142**, 8514.

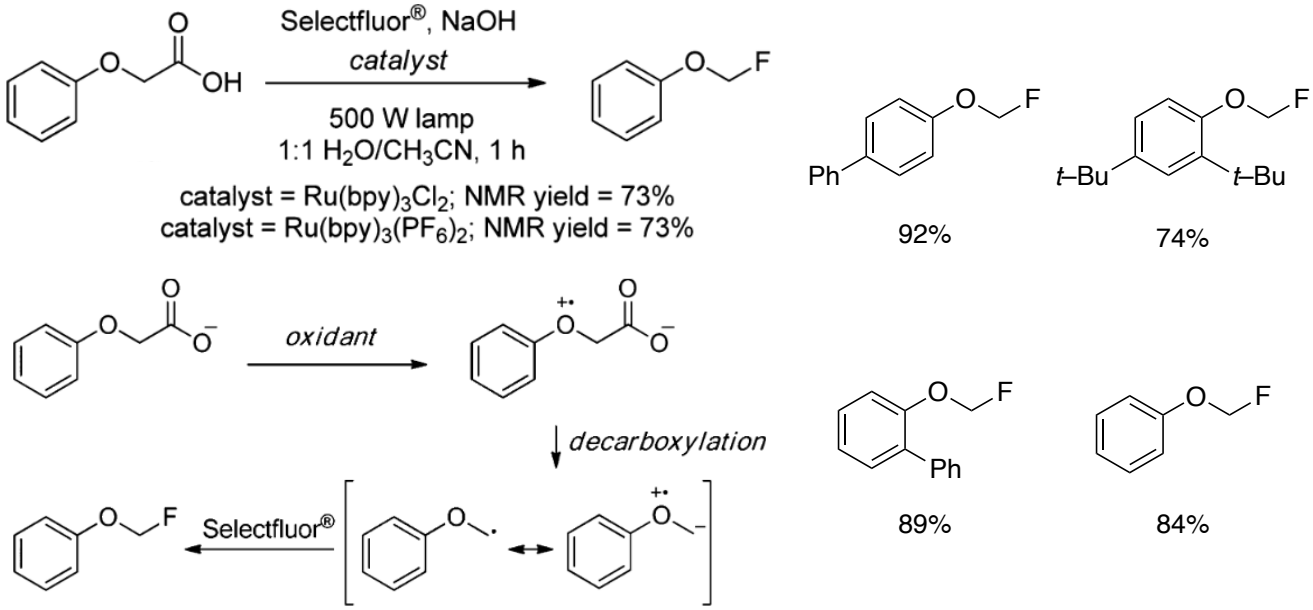
Ag (2012) [1]



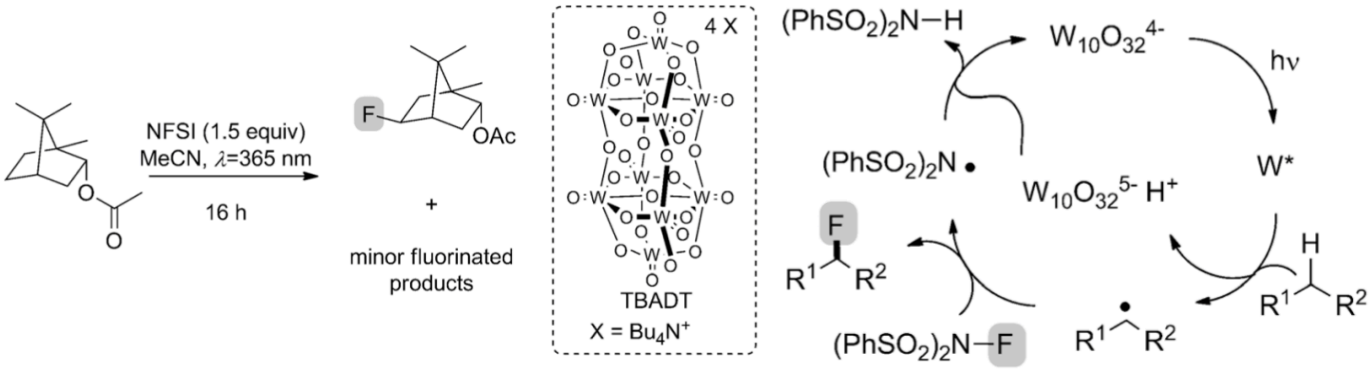


3.3. Radical Fluorination by Photocatalysis

Ru PI (2014) [2]

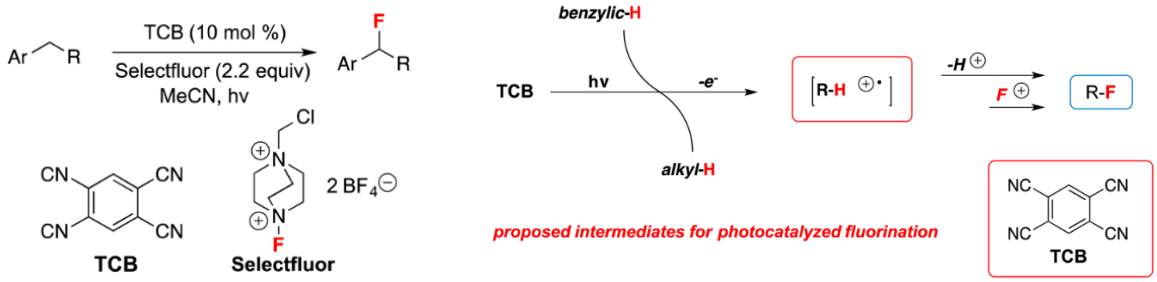


W PI (2014) [3]

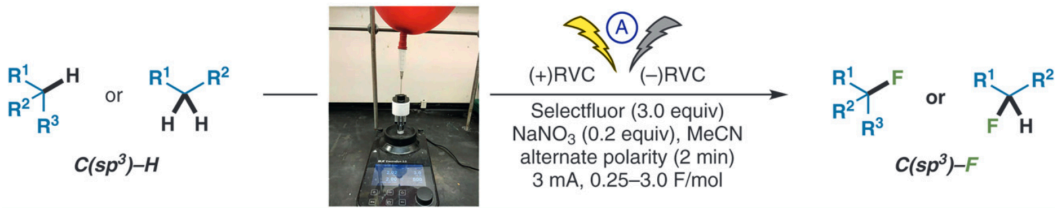


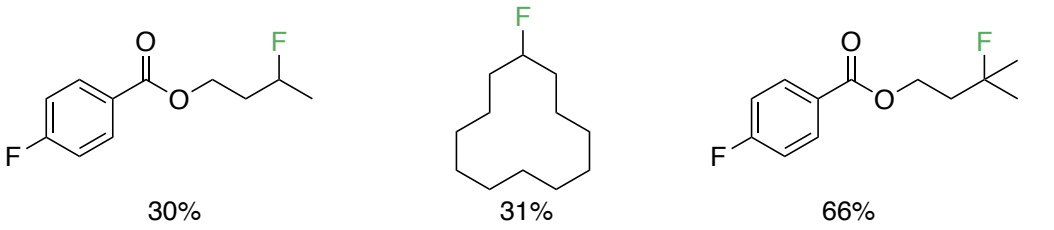
(1) Li, C.-Z. *et al. J. Am. Chem. Soc.* 2012, **134**, 10401.
(2)Montserrat, R.-B. *et al. J. Am. Chem. Soc.* 2014, **136**, 2637.
(3) Britton, R. *et al. Angew. Chem. Int. Ed.* 2014, **53**, 4690.

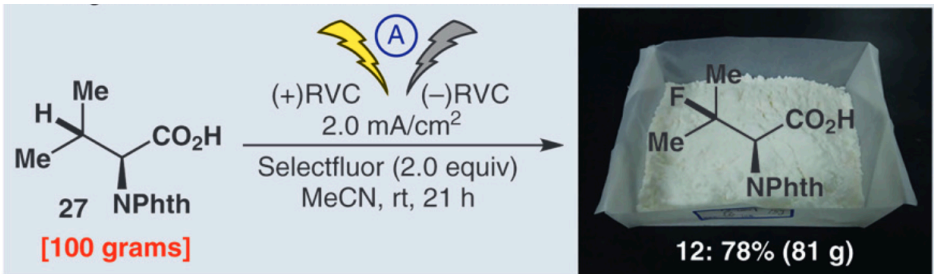
TCB PI (2014) [1]



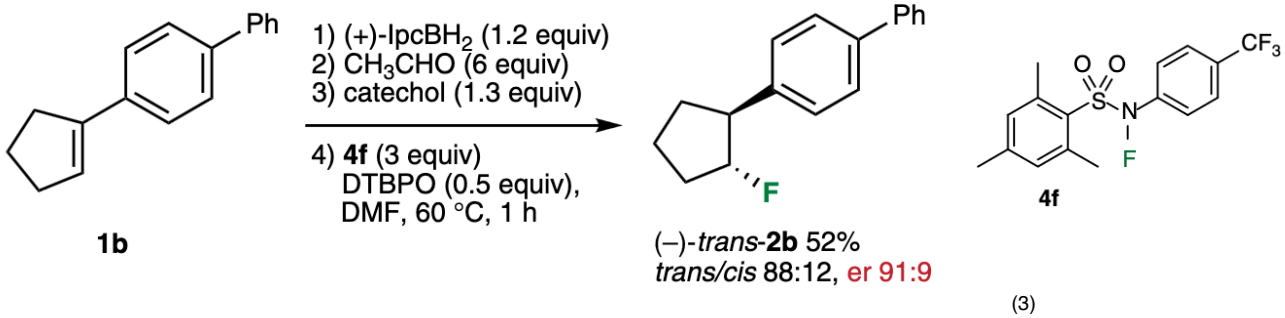
3.4. Radical Fluorination by Electrocatalysis [2]





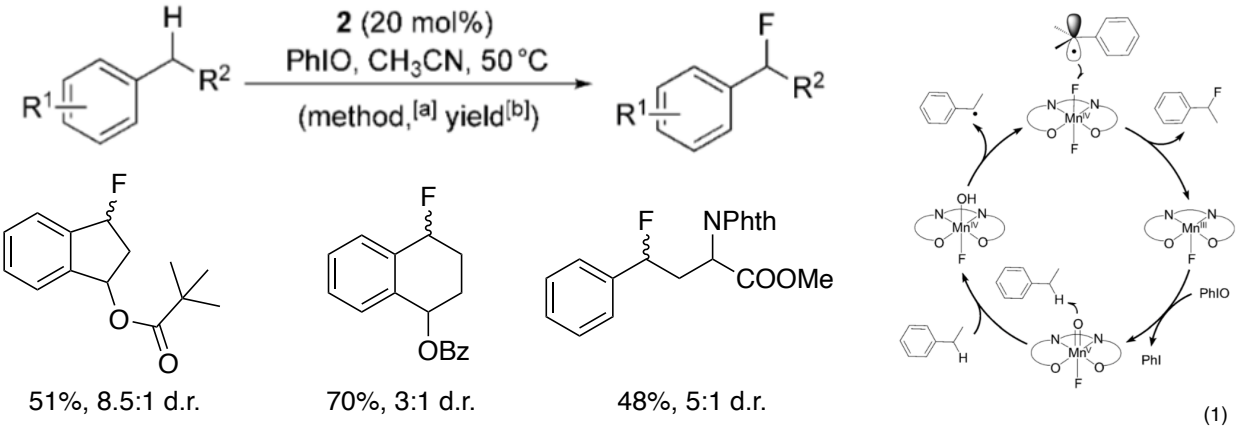


3.5. Asymmetric Radical Fluorination



(3)

(1) Lectka, T. *et al. Org. Lett.* 2014, **16**, 6338.
(2) Baran, P. S. *et al. Synlett* 2019, **30**, 1178.
(3) Renaud, P. *et al. Nat Commun.* 2018, **9**, 4888.

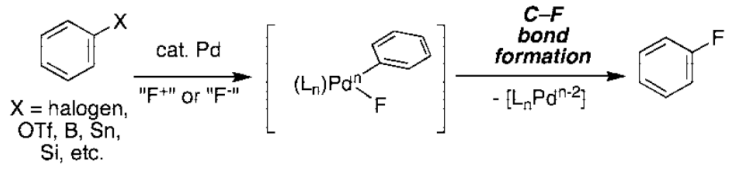


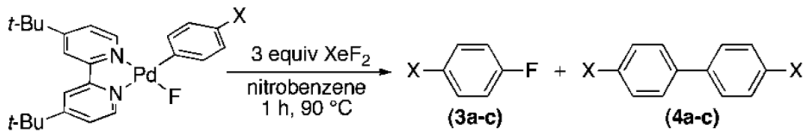
51%, 8.5:1 d.r. 70%, 3:1 d.r. 48%, 5:1 d.r.

(1)

4. Transition Metal Catalysizd Fluorination

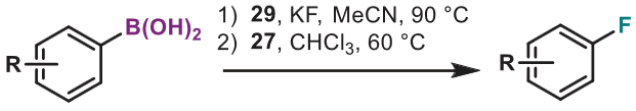
Pd (2009) (2)



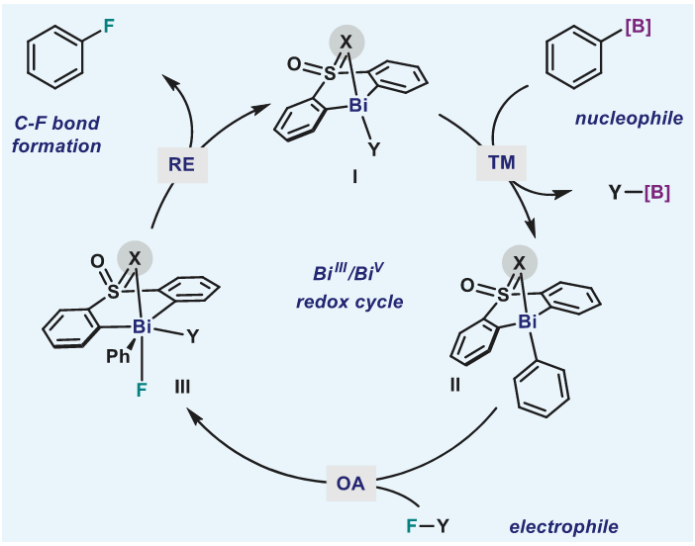


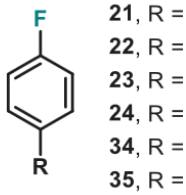
entry	X	complex	% **3**	% **4**
1	F	**2a**	57	7
2	CF_3	**2b**	60	3
3	OMe	**2c**	45	6

Bi (2020) (3)

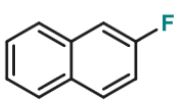


20, R = ^{t}Bu, 84%, 85%
21, R = CF_3, 82%, 35%§
22, R = CN, 75%‡, 71%
23, R = Cl, 70%, 57%§
24, R = OMe, 90%‡, 21%§
34, R = F, 88%, 50%§
35, R = CO_2Et, 67%, 98% (96%)¶
36, R = TMS, 73%, 77%

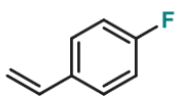




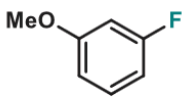
37
75%, 74%



38
95%, 75%



39
90%, 49%

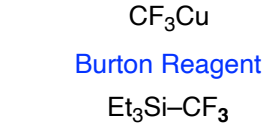


40
73%, 93%

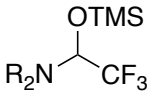
(1) Groves, J. T. *et al. Angew. Chem.* 2013, **125**, 6140.
(2) Sanford, M.S. *et al. J. Am. Chem. Soc.* 2009, **131**, 11, 3796.
(3) Cornella, J. *et al. Science* 2020, **367**, 313.

5. Polyfluoromethylation

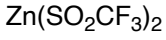
Common Polyfluoromethylating Reagents (1)(2)(3)



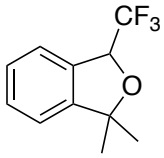
Ruppert-Prakash Reagent



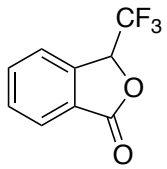
Langlois Reagent



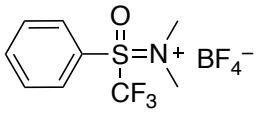
Baran Reagent



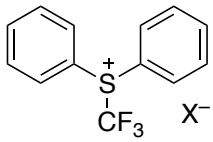
Togni Reagent I



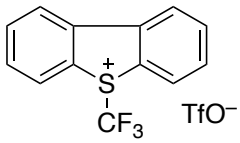
Togni Reagent II



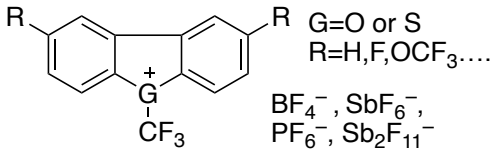
Shibata Reagent



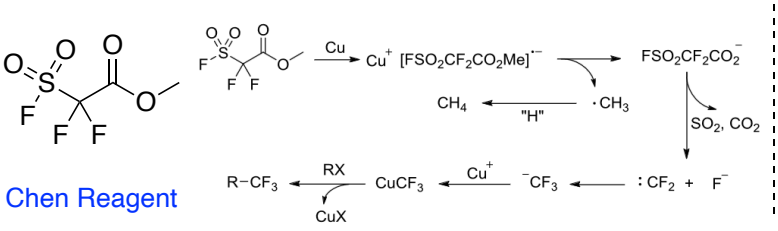
Yapoulskii Reasgent



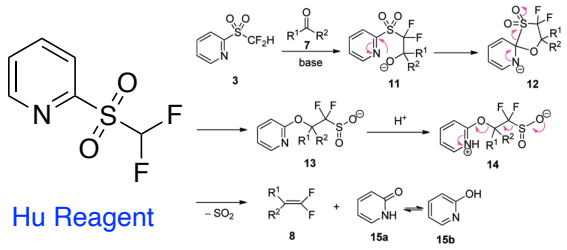
Shreeve Reasgent



Umemoto Reasgent I~IV

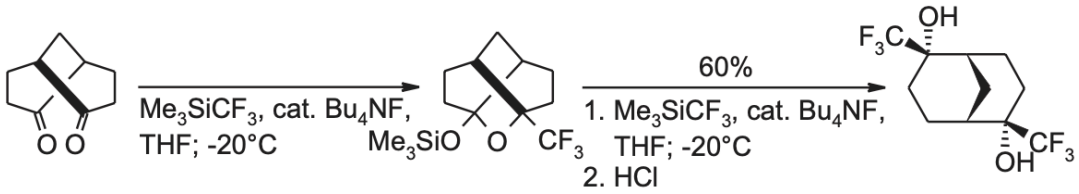


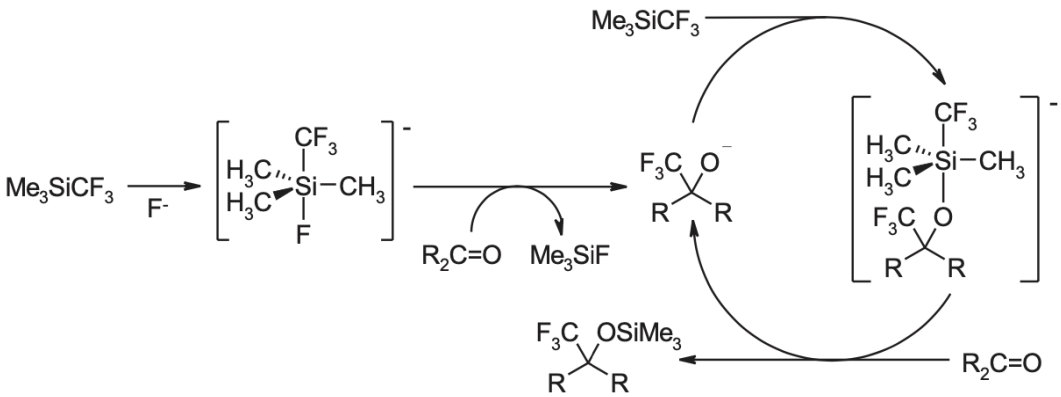
Chen Reagent



Hu Reagent

Burton & Prakash Type (4)





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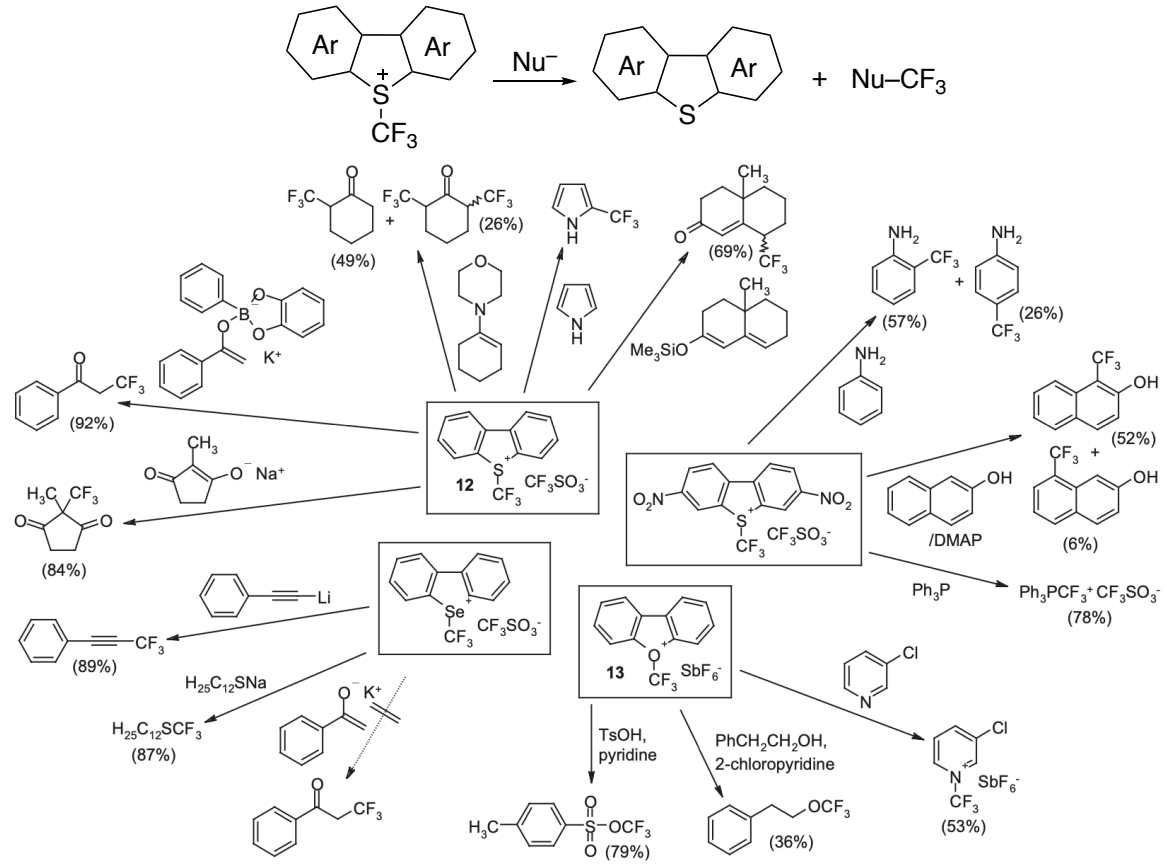
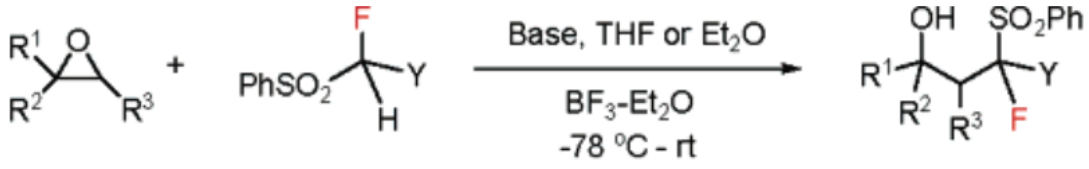
(1) Burton, D. J. *et al. J. Am. Chem. Soc.* 1986, **108**, 832.
(2) Kobayashi, Y. *et al. J. Chem. Soc., Perkin Trans. I.* 1980, 2755.
(3) Olah, G. A. *et al. J. Am. Chem. Soc.* 1989, **111**, 393.
(4) Langlois, B. R. *Synthesis* 2003, 185.

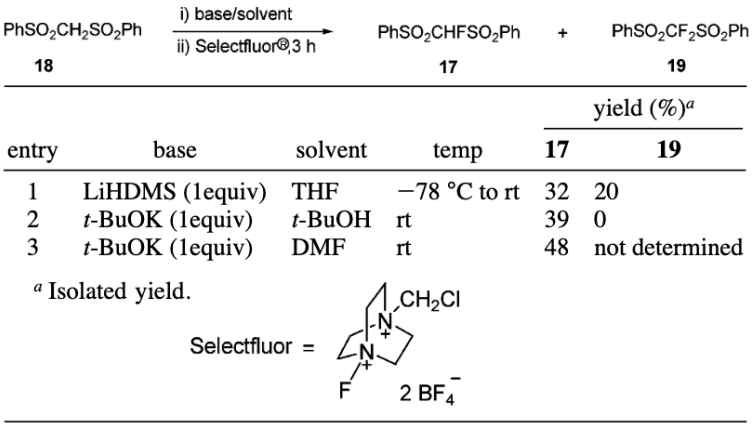
Electrophilic Type [1]



Negative Fluorine Effect [2][3]



Y = F 0 %
Y = H 10-78 %



entry	base	solvent	temp	yield (%)[a] 17	19
1	LiHDMS (1equiv)	THF	−78 °C to rt	32	20
2	*t*-BuOK (1equiv)	*t*-BuOH	rt	39	0
3	*t*-BuOK (1equiv)	DMF	rt	48	not determined

[a] Isolated yield.

Selectfluor =

kinetic stability:
$CH_3^- > CH_2F^- > CHF_2^- > CF_3^-$

C–H Type	CF_3–H	CHF_2–H	CH_2F–H	CH_3–H
C–H ionization (ΔH_{calcd}, kcal/mol)	368.9	391.3	406.3	416.8

(1) T. Umemoto, *MEC Reagent Brochure*, DAIKIN Fine Chemicals Research Center, Tokyo, 1997.
(2) Hu, J. B. *et al. Top Curr. Chem.* 2012, **308**, 25.
(3) Hu, J. B. *et al. J. Org. Chem.* 2006, **71**, 18