Classics and Moderns in Fluorine Chemistry

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University of Oxford
Chemistry Research Laboratory

BOSS XV
Tetrahedron Chair
July 2016

UNIVERSITY OF OXFORD

Lecture 1: Late Stage Fluorination of Arenes: *The Never Ending Story*

Lecture 2: F-Csp^3 Bond Construction: *Challenges and Solutions*

Lecture 3: Catalytic Reactions for Tri- and Difluoromethylation: *The State of Play*

Lecture 4: The Art of ^{18}F-Labelling for Applications in Positron Emission Tomography

Late Stage Fluorination of Arenes: The Never Ending Story

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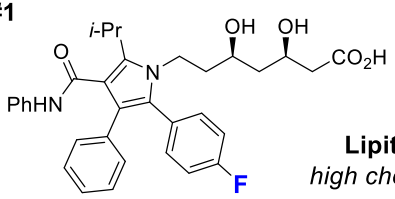
Contents

- Properties of Fluorine
- Applications in Drug Discovery
- Fluorinating Reagents
- Fluorination of Arenes

Applications of Organofluorine Chemistry

25 % of Pharmaceuticals

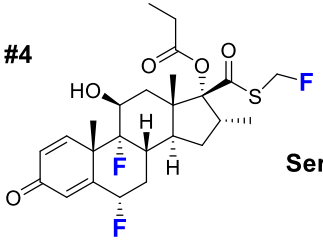
#1



$13288 Million

Lipitor (Atorvastatin)
high cholesterol treatment

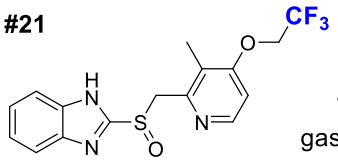
#4



$8098 Million

Seretide (Fluticasone&Salmeterol)
B2-Stimulants+Corticoids

#21



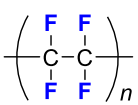
$3778 Million

Takepron (Lansoprazole)
gastric acid secretion regulator

ranking from 2003

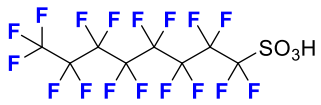
Material Chemistry

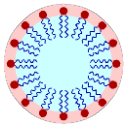
Fluoropolymers



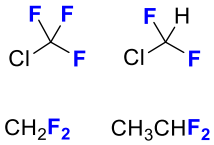
PTFE

Surfactants



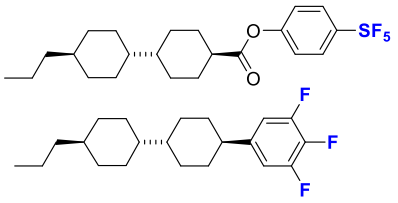


Refrigerants



CH_2F_2 CH_3CHF_2

Liquid Crystals

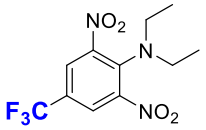


Electrical Insulator : SF_6

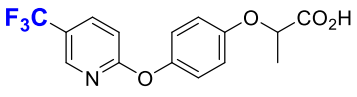
Nuclear Reactor : UF_6

Fluorine
9
F
18.998

30 % of Agrochemicals



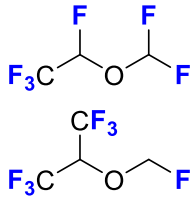
Trifluralin



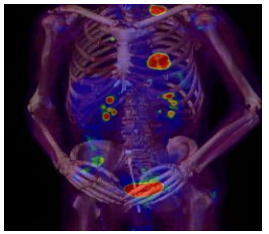
Fluazifop

Medical Applications

Anaesthesia



^{19}F: NMR & ^{18}F: PET



O'Hagan *J. Fluorine Chem.* **2014**, *167*, 16; **Gouverneur** *Chem. Soc. Rev.* **2008**, *37*, 320; **Liu** *Chem. Rev.* **2014**, *114*, 2432.

Properties of Fluorine

Atom	Pauling's electronegativity χ_p	Electron Affinity (kcal/mol)	Ionisation Potential (kcal/mol)	Van der Waals Radii (Å)	Atom Polarisability (Å^3)
H	2.20	17.7	313.6	1.20	0.667
F	**3.98**	**79.5**	**401.8**	**1.47**	**0.557**
Cl	3.16	83.3	299.0	1.74	2.18
Br	2.96	72.6	272.4	1.85	3.05
I	2.66	70.6	241.2	1.98	4.70
C	2.55	29.0	240.5	1.70	1.76
N	3.04	- 6.2	335.1	1.55	1.10
O	3.44	33.8	314.0	1.52	0.82

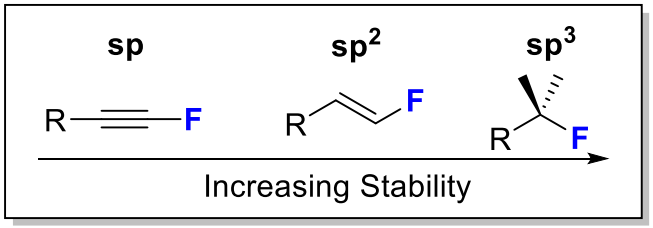
X	Bond Length C-X (Å)
H	1.09
F	1.35
Cl	1.77
O	1.43
S	1.82
C	1.54
Si	1.85

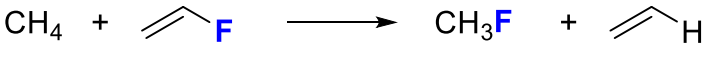
D^0(C-X)	Bond Dissociation Energy kcal/mol
CH_3-H	104.3
CH_3-F	108.3
CH_3-Cl	82.9
CH_3-Br	69.6
CH_2F-F	119.5
CHF_2-F	127.5
CF_3-F	130.5

Pauling *The Nature of the Chemical Bond and the Structure of Molecules and Crystals: An Introduction to Modern Structural Chemistry*, Cornell University Press, Ithaca, NY, **1939**; **Bondi** *J. Phys. Chem.* **1964**, *68*, 441; **Bégué** *Bioorganic and Medicinal Chemistry of Fluorine*, Wiley, NY, **2008**.

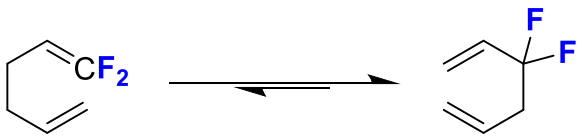
Properties of Fluorine

[A]





favoured by 7.9 kcal/mol



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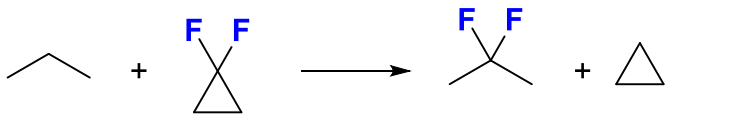
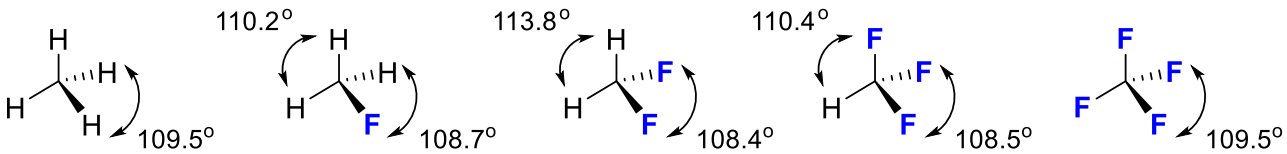


favoured by 11.2 kcal/mol

[B]



C-F bond length (Å)	**-**	**1.39**	**1.36**	**1.33**	**1.32**
C-F bond energy (kcal/mol)	**-**	**107**	**109.6**	**114.6**	**116**

[A] Dolbier *J. Am. Chem. Soc.* **1987**, *109*, 3046; **Wiberg** *Acc. Chem. Res.* **1996**, *29*, 229; **Houk** *Angew. Chem. Int. Ed.* **2006**, *45*, 1442;
[B] Hu *J. Phys. Chem. A* **2001**, *105*, 2391

Properties of Fluorine

[A]

Substituent	σ_{taft}	σ inductive	σ resonance
F	**3.10**	**0.52**	**-0.46**
Cl		0.47	-0.24
Br		0.44	-0.22
NO_2		0.56	+0.22
OH		0.29	-0.43
CH_3		0.04	-0.15
CH_2F	1.17		
CHF_2	2.0		
CF_3	**2.6**	**0.42**	**+0.10**

[B]

Hansch hydrophobicity Parameters (π_X)	
X in C_6H_5-X	π_X
F	**0.14**
CF_3	**0.88**
Cl	0.71
OH	-0.67
Me	0.56
OCF_3	**1.04**

[C]

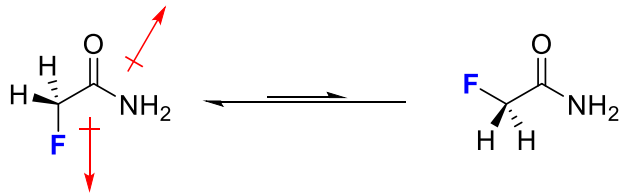
Compound	pK_a	*Compound*	pK_a	*Compound*	pK_a
CH_3COOH	4.76	CH_3CH_2COOH	4.87	$(CH_3)_2CHOH$	17.1
CH_2FCOOH	2.59	CF_3CH_2COOH	3.06	$(CF_3)_2CHOH$	9.3
$CH_2ClCOOH$	2.87	C_6H_5COOH	4.21	$(CH_3)_3COH$	19.0
$CH_2BrCOOH$	2.90	C_6F_5COOH	1.70	$(CF_3)_3COH$	5.4
CHF_2COOH	1.33	CH_3CH_2OH	15.93	C_6H_5OH	9.99
CF_3COOH	0.50	CF_3CH_2OH	12.39	C_6F_5OH	5.5

pK$_a$ → **HCF_3** = 30.5 **$HCCl_3$** = 24.4 **$HCBr_3$** = 22.7

[A] McDaniel *J. Org. Chem.* **1958**, *23*, 420; **Hansch** *Chem. Rev.* **1991**, *91*, 165; **[B] Ojima** *Fluorine in Medicinal Chemistry and Chemical Biology. Blackwell Publishing,* **2009**; **[C] Uneyama** *Organofluorine Chemistry, Blackwell publishing* **2006**; **Schlosser** *Angew. Chem. Int. Ed.* **1998**, *110,* 1496.

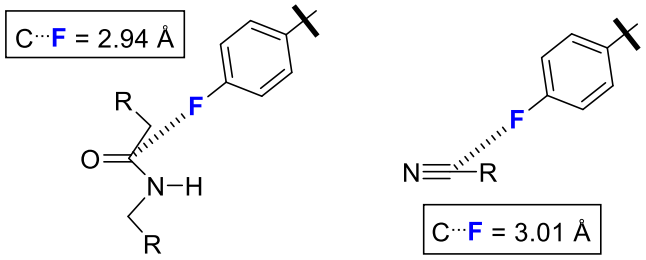
Properties of Fluorine

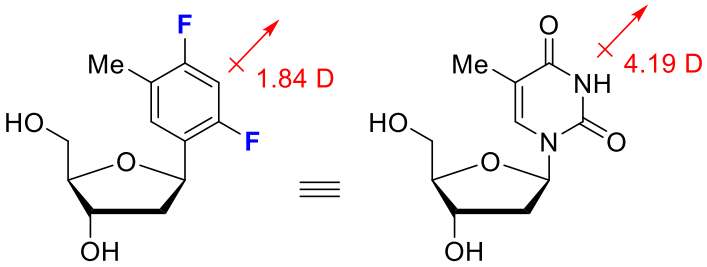
[A] Dipole-dipole interactions



trans 0.0 kcal/mol

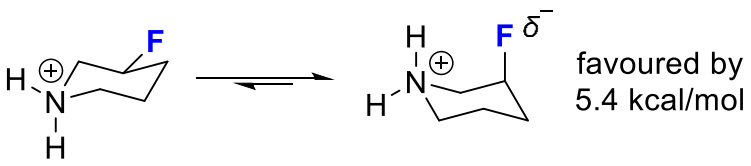
cis 7.5 kcal/mol



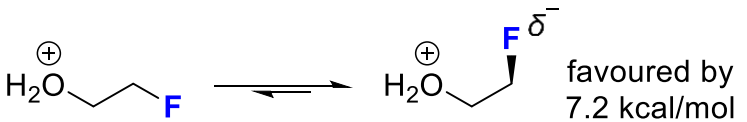


Polar hydrophobic analogues of amides and thymine

[B] Charge-dipole interactions



favoured by 5.4 kcal/mol

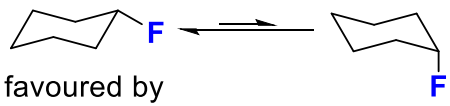


favoured by 7.2 kcal/mol

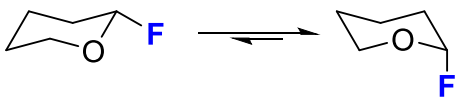
[A] O'Hagan *J. Chem. Soc., Perkin Trans. 2* **1999**, 2409; **Abraham** *Tetrahedron* **1986**, *42*, 2101; **Pannecoucke** *Org. Biomol. Chem.* **2007**, *5*, 1151; **Diederich**, *ChemBioChem* **2004**, *5*, 666; *Org. Biomol. Chem.* **2004**, *2*, 1339. **[B] Snyder** *Chem. Eur. J.* **2005**, *11*, 1579. **O'Hagan** *Org. Biomol. Chem.* **2004**, *2*, 732.

Properties of Fluorine

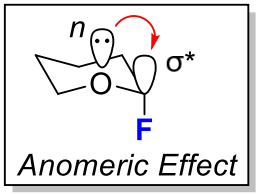
[A]



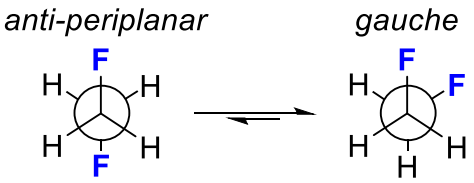
favoured by
0.2-0.3 kcal/mol



favoured by
6 kcal/mol



[B]



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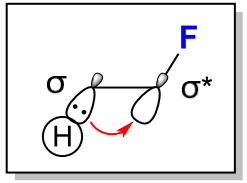
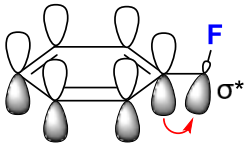
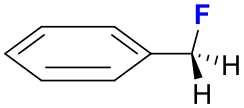
0.5-0.9 kcal/mol



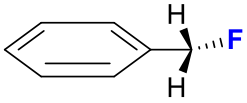
Gauche conformation provides two stabilising $\sigma_{C\text{-}H}$ - $\sigma^*_{C\text{-}F}$ interactions

[C]



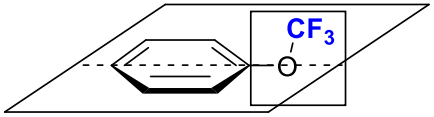


C-F orthogonal
lowest energy structure

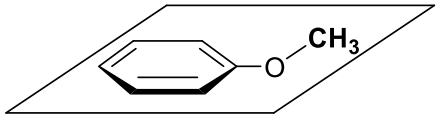


C-F planar

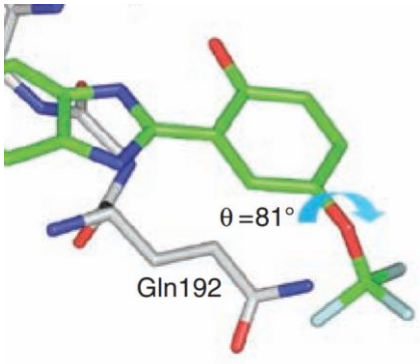
[D]



C-OCF_3 orthogonal



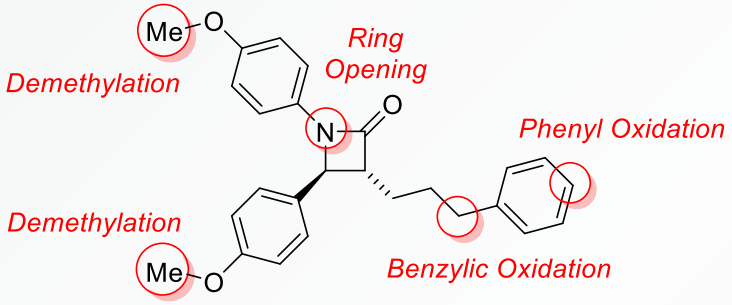
C-OCH_3 planar



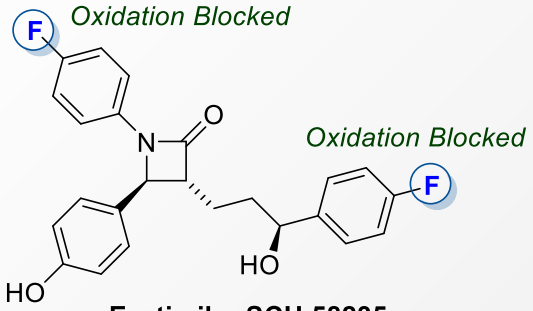
O'Hagan *Chem. Soc. Rev.* **2008**, *37*, 308; **[A] Pinto** *Can. J. Chem.* **2006**, *84*, 692; **[B] MacDougall** *J. Phys. Chem.* **1990**, *94*, 6956; **O'Hagan** *J. Chem. Soc., Perkin Trans. 2* **2000**, 605; **[C] Tozer** *Chem. Phys. Lett.* **1999**, *308*, 160; **[D] Leroux** *Beilstein J. Org. Chem.* **2008**, *4*, 13; **Müller**, **Diederich** *Science* **2007**, *317*, 1883.

Fluorine and Drug Design

[A] Ezetimibe (Cholesterol lowering)

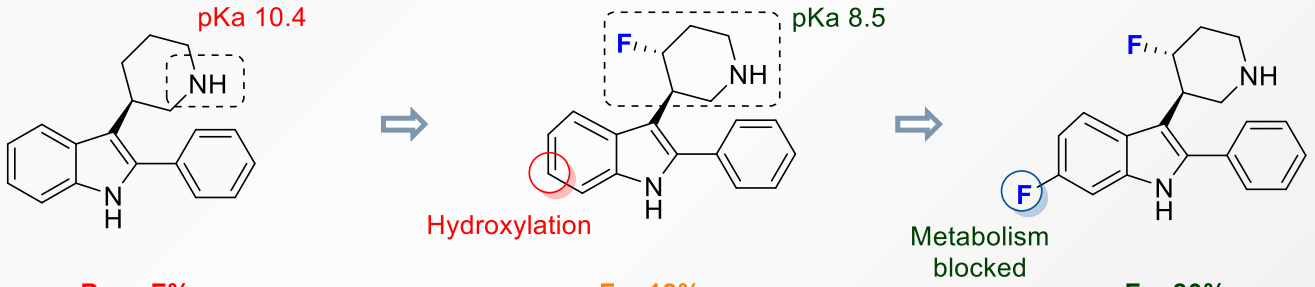


SCH 48461
moderate cholesterol absorption inhibitor
(ED_{50} = 2.2 mg/Kg/day)



Ezetimibe-SCH 58235
50 times more potent than SCH 48461
(ED_{50} = 0.04 mg/Kg/day)

[B] $5HT_{2A}$ antagonists



Bioavailability (F)

Poor F%
(K_i= 0.99 nM)

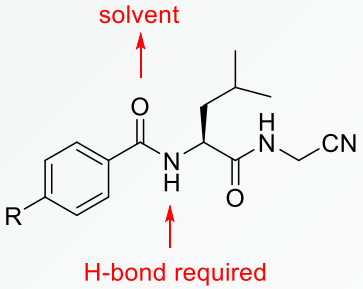
F = 18%
(K_i= 0.43 nM)

F = 80%
(K_i= 0.06 nM)

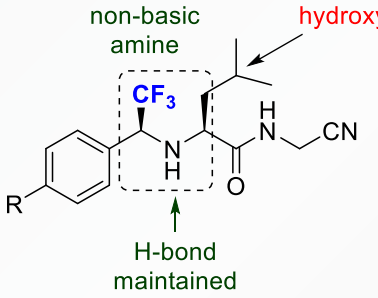
[A] Rosenblum *J. Med. Chem.* **1998**, *41*, 973; **[B] Rowley** *J. Med. Chem.* **2001**, *44,* 1603.

Fluorine and Drug Design

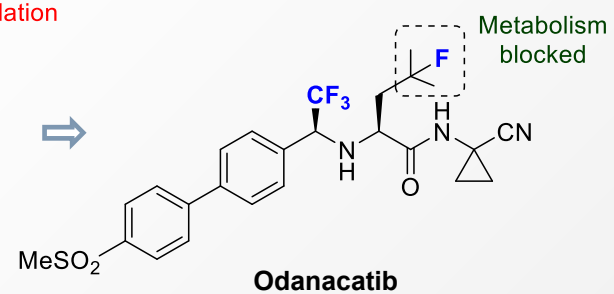
[A] Odanacatib (Cathepsin K inhibitors)



• Peptidic nature



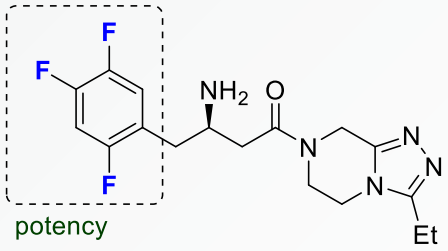
• 10-20x > potency
• Improved "amide" stability
• Short $t_{1/2}$ in cyno



Odanacatib

• Improved metabolism
• Good selectivity

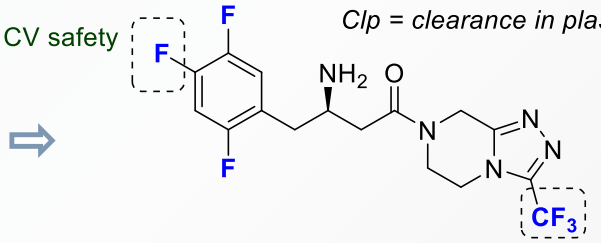
[B] Sitagliptin - JANUVIA™ (DPP-4 inhibitors)



LogD	Clp ml/min/kg	$T_{1/2}$ h	F
1.8	16	3.9	9%

Clp = clearance in plasma; F = bioavailability

CV safety

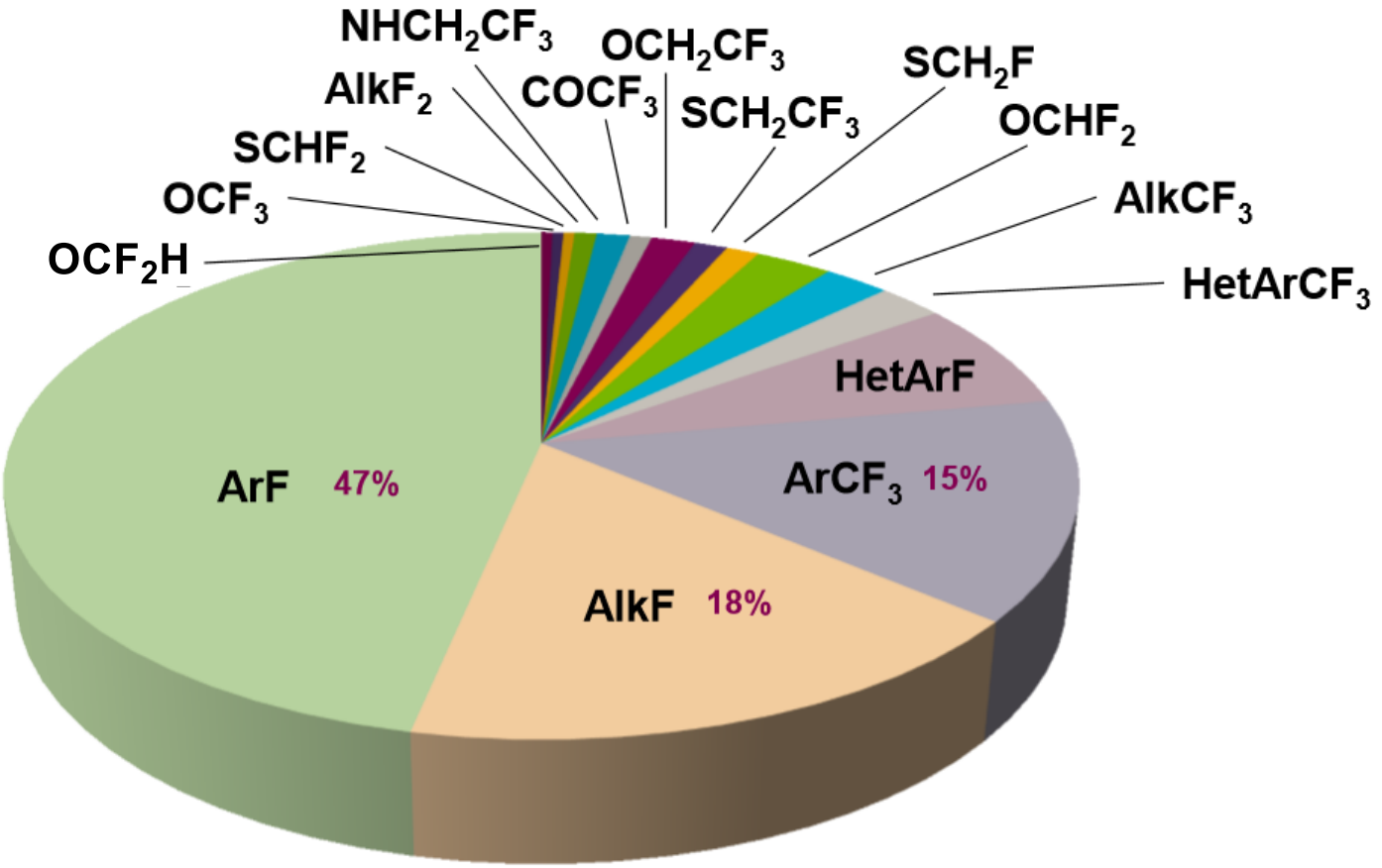


LogD	Clp ml/min/kg	$T_{1/2}$ h	F
2.5	6	3.9	68%

• Improved absorption and bioavailability

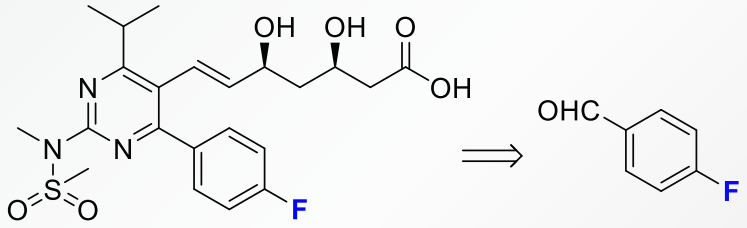
[A] Zanda *Chem. Eur. J.* **2003**, *9*, 4510; **Black** *Bioorg. Med. Chem. Lett.* **2008**, *18*, 923**; [B] Kim** *J. Med. Chem.* **2005**, *48*, 141; **Kim** *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3373.

Diversity of Fluorine in Pharmaceuticals

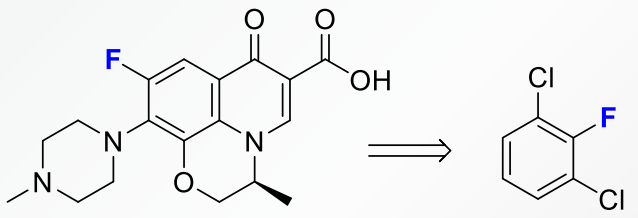


Gouverneur *Angew. Chem. Int. Ed.* **2009**, *48*, 8610; **Njardarson** *J. Chem. Ed.* **2013**, *90*, 1403; **Ritter** *Chem. Rev.* **2015**, *115*, 612.

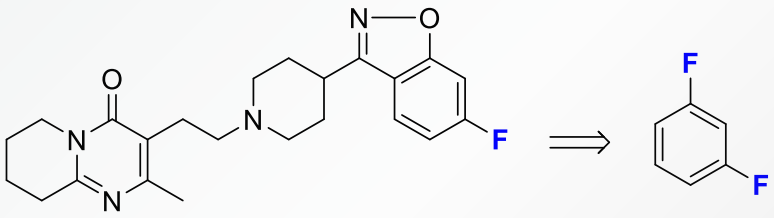
Selected Top-Selling Drugs Containing Fluorine



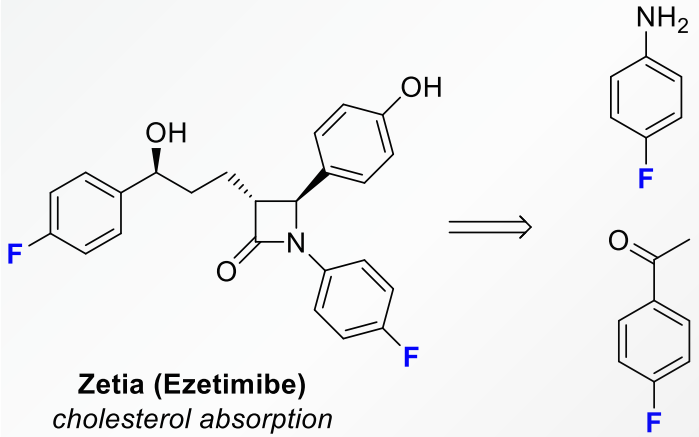
Crestor (Rosuvastatin)
Cholesterol lowering
$1.7 billion (#17) / Astra Zeneca



Levaquin (Levofloxacin)
Antibiotic
$1.5 billion (#22) / Janssen



Risperdal (Risperidone)
Anti-psychosis
$1.2 billion (#28) / Janssen

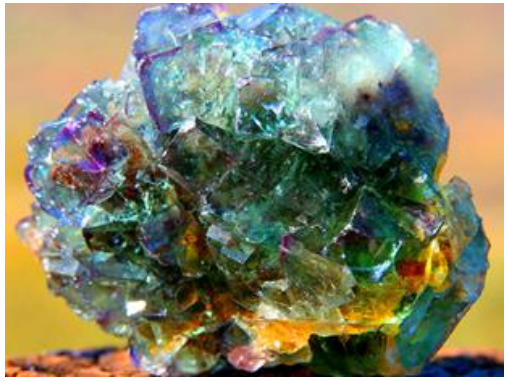


Zetia (Ezetimibe)
cholesterol absorption
$1.2 billion (#30) / Merck

O'Hagan *J. Fluorine Chem* **2010**, *131*, 1071.

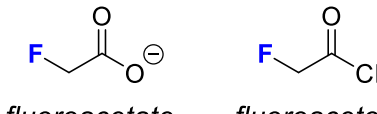
Fluorine in Nature

Fluorine : 13th most abundant element in the Earth's crust ⇨

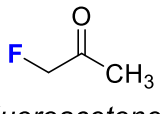


Fluorite (Fluorospar) - CaF_2

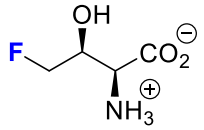
Fluorine-containing natural products



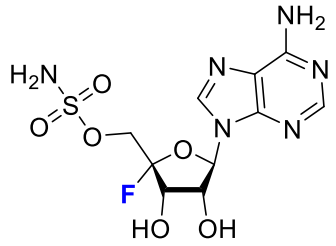
fluoroacetate



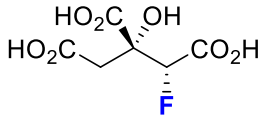
fluoroacetone



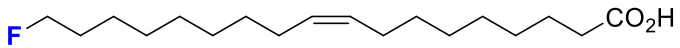
4-fluorothreonine



nucleocidin

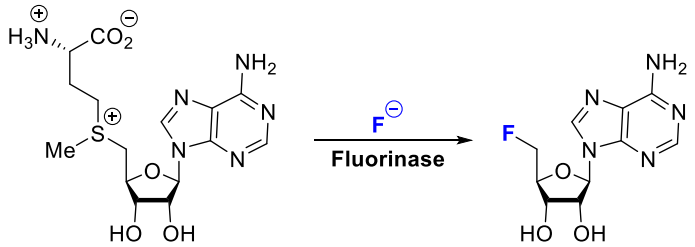


(2R, 3R)-fluorocitrate



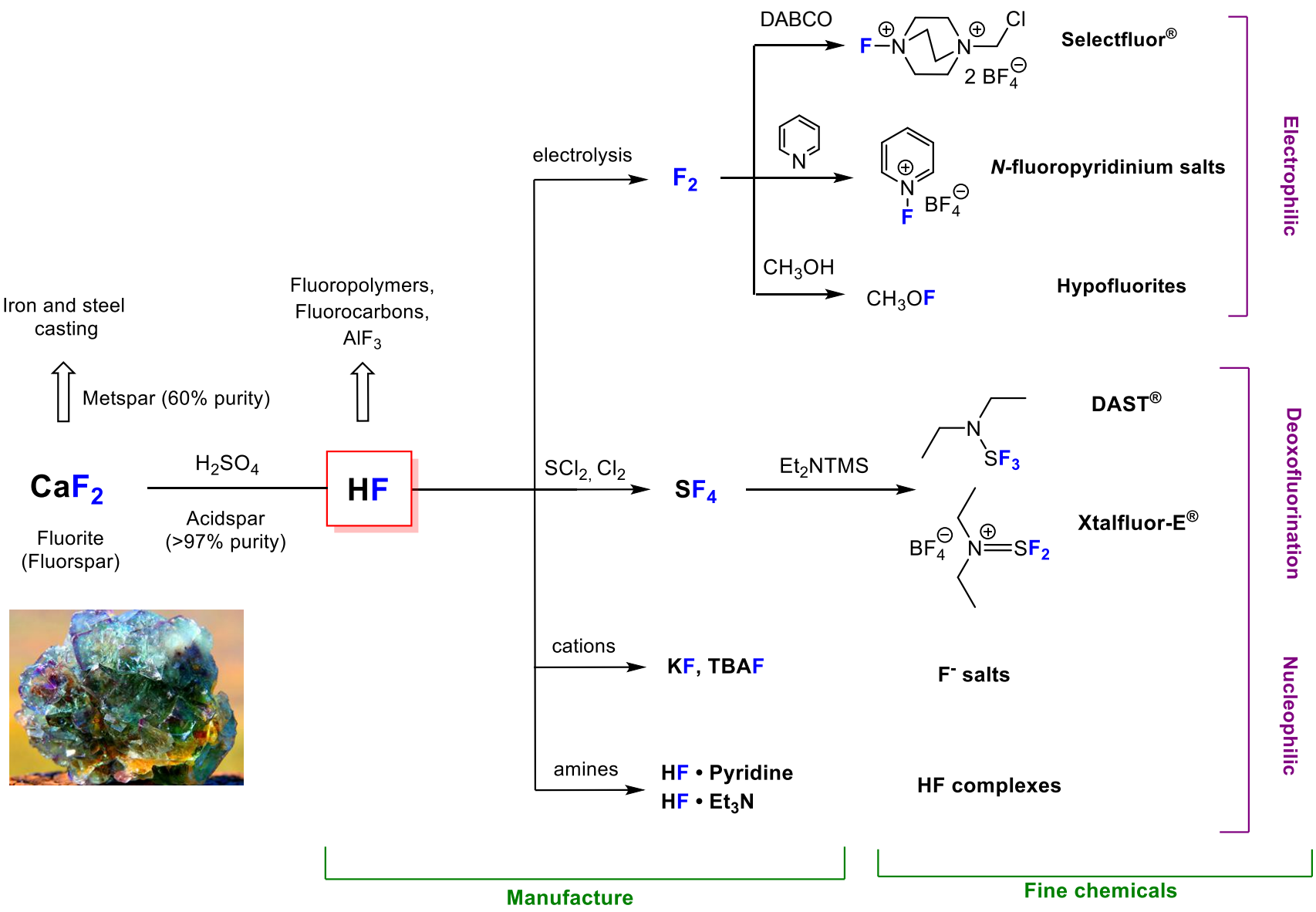
fluoro-oleic acid

Fluorinase enzyme (2002)



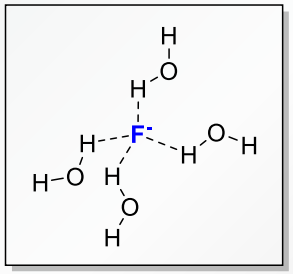
O'Hagan *J. Fluorine Chem.* **1999**, *100*, 127; *Nature* **2002**, *416*, 279.

Fluorinating Reagents



Sandford *Green Chem.* **2015**, *17*, 2081.

Nucleophilic Fluorinating Reagents



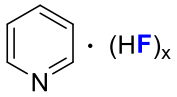
$\Delta G_{hyd}(F^-)$ = -104.3 kcal/mol

KF CsF

AgF

$[R_4N]^{\oplus}\ F^{\ominus}$

R = Me : **TMAF**
R = *n*Bu : **TBAF**



Hydrogen fluoride pyridine

Olah *J. Org. Chem.* **1979**, *44*, 3872

$Et_3N \cdot (HF)_3$

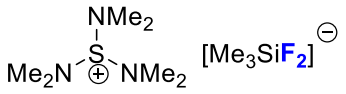
TREAT-3HF

Franz *J. Fluorine Chem.* **1980**, *15*, 423

$[nBu_4N]^{\oplus}\ [Ph_3MF_2]^{\ominus}$

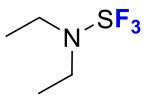
M = Sn or Si

DeShong *J. Am. Chem. Soc.* **1995**, *117*, 5166



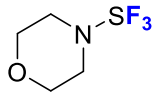
TASF

Middleton *U.S. Patent 3 940 402* **1976**



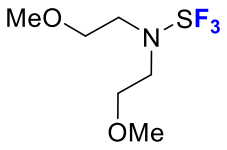
DAST

Middleton *J. Org. Chem.* **1975,** *40*, 574



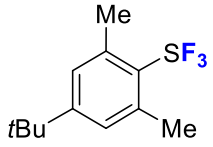
Morpho-DAST

Markovskii *Zh. Org. Khim+* **1975,** *11*, 74



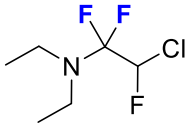
Deoxo-Fluor®

Lal *J. Org. Org. Chem.* **1999,** 64, 7048



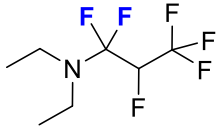
Fluolead™

Umemoto *J. Am. Chem. Soc.* **2010**, *132*, 18199



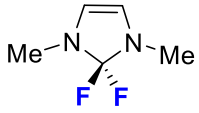
Yarovenko's reagent

Yarovenko *Zh. Obshch. Khim+* **1959**, 29, 2159



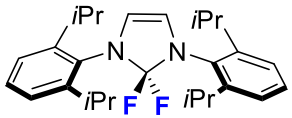
Ishikawa's reagent

Ishikawa *Bull. Chem. Soc. Jpn.* **1979**, *52*, 3377



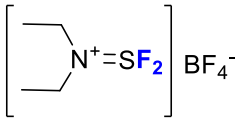
DFI

Hayashi *Chem. Commun.* **2002**, 1618



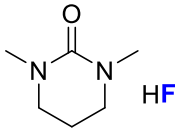
PhenoFluor®

Ritter *J. Am. Chem. Soc.* **2011**, *133*, 11482



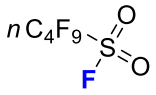
Xtalfluor-E

Couturier *J. Org. Chem.* **2010,** *75*, 3401



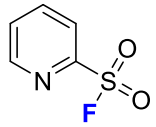
DMPU-HF

Bo Xu *J. Am. Chem. Soc.* **2014**, *136*, 14381



Nonaflyl fluoride

Vorbrüggen *Bull. Soc. Chim. Belg.* **1994**, *103*, 453



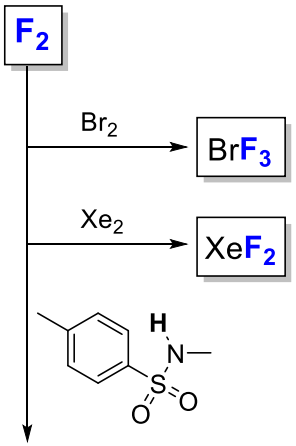
PyFluor ®

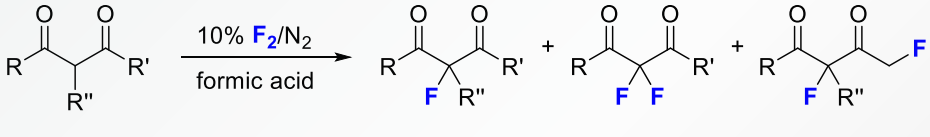
Doyle *J. Am. Chem. Soc.* **2015**, *137*, 9571

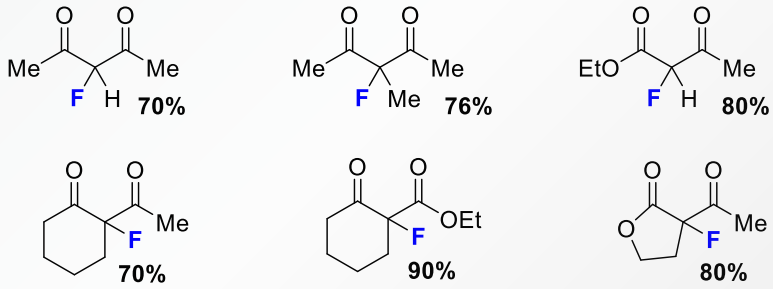
Electrophilic Fluorinating Reagents

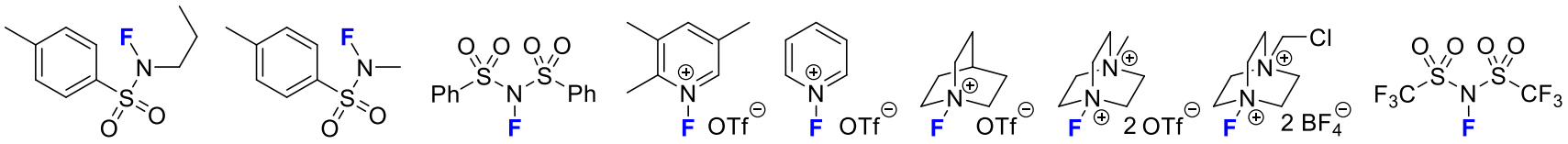
Henri Moissan
Nobel Prize 1906

(Bond Energy 38 kcal/mol)









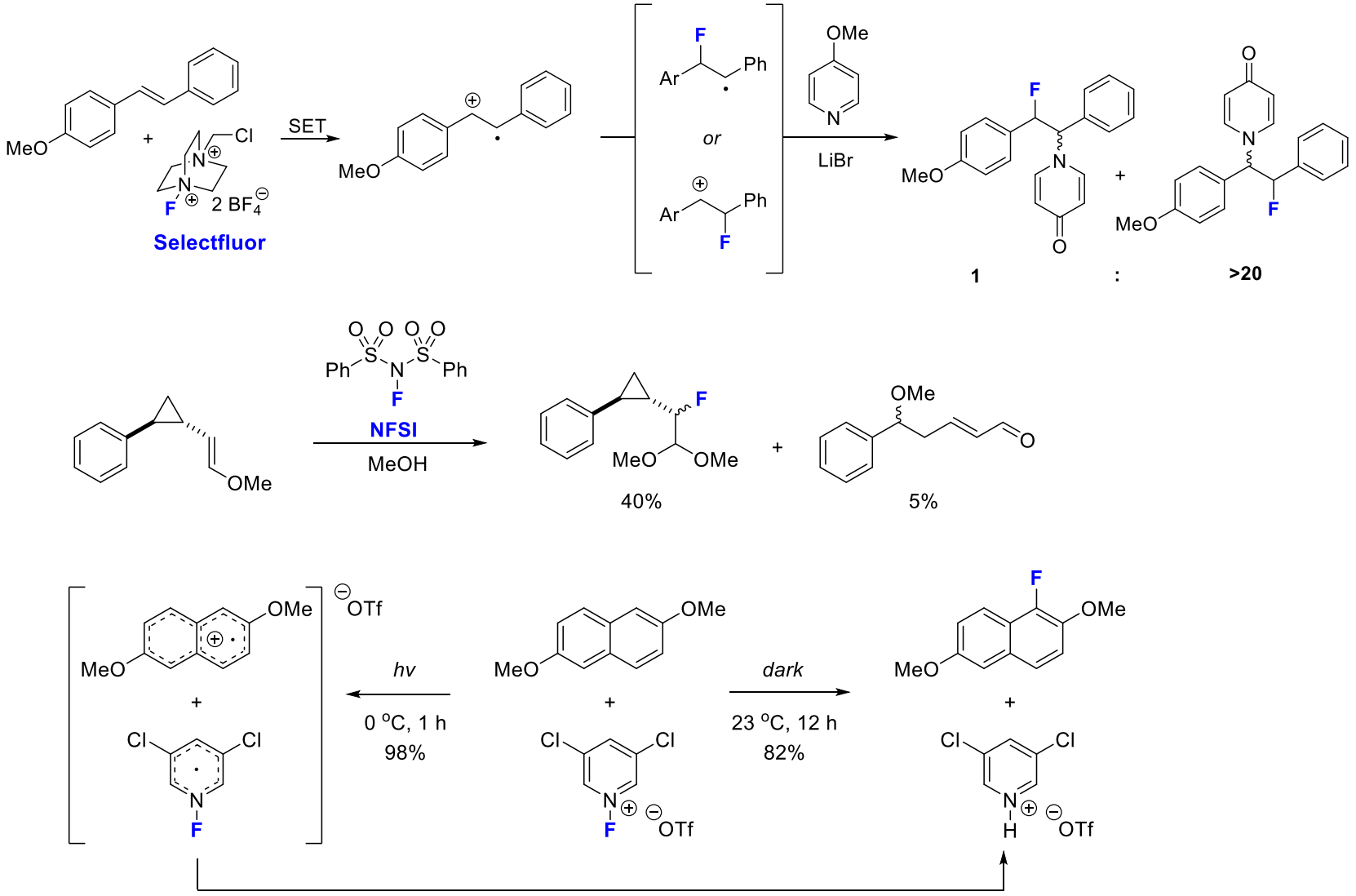
Increasing reduction potential correlates with increasing fluorinating power

- Nucleophilic Displacement : $R_2N\text{-}F + Nu^{\ominus} \longrightarrow [R_2N\text{---}F\text{---}Nu] \longrightarrow R_2N^{\ominus} + Nu\text{-}F$

- SET : $R_2N\text{-}F + Nu^{\ominus} \longrightarrow [R_2N\text{–}F^{\ominus\bullet}\ \ Nu^{\bullet}] \longrightarrow R_2N^{\ominus} + Nu\text{-}F$

Rozen *Eur. J. Org. Chem.* **2005**, *12*, 2433; **Chambers** *Tetrahedron* **1996**, *52*, 1; **Sandford** *Tetrahedron* **1998**, *54*, 2867; **Syvret** *Chem. Rev.* **1996**, *96*, 1737.

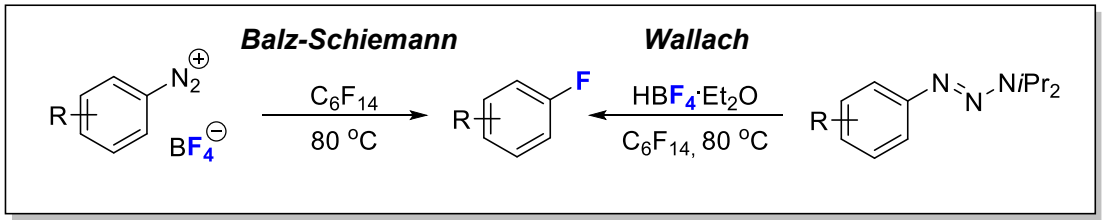
Experimental Evidence for SET Mechanisms

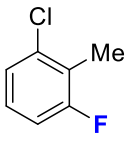


Ritter *Chem. Rev.* **2015**, *115*, 612.

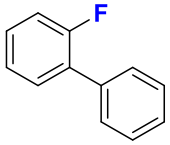
Fluorination of Arenes *via* Diazonium Salts and Arynes

[A]

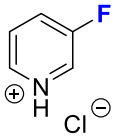




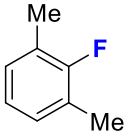
81% (BS)



75% (W)

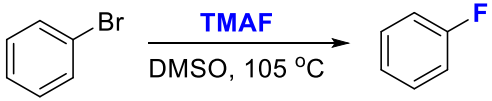


55% (W)
71% (BS)

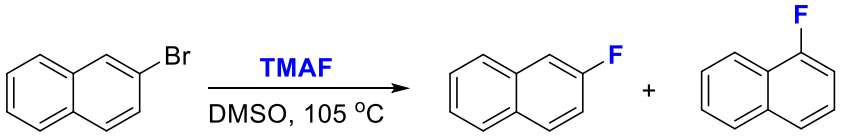


90% (W)

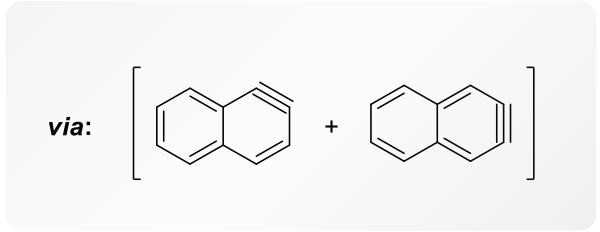
[B]



65%



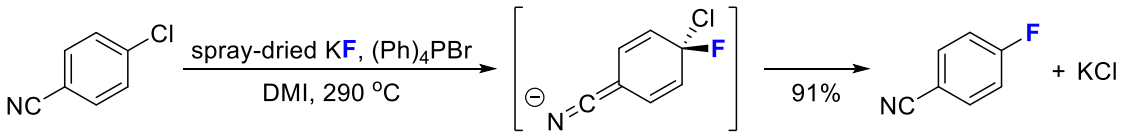
65% (1.5 : 1 mixture of regioisomers)



[A] **Balz** & **Schiemann** *Ber. Dtsch. Chem. Ges B* **1927**, *60*, 1186; **Wallach** *Justus Liebigs Ann. Chem.* **1888**, *243*, 219; **Bräse** *Angew. Chem. Int. Ed.* **2010**, *49*, 5986; **[B]** **Grushin** *Organometallics* **2008**, *27*, 4825.

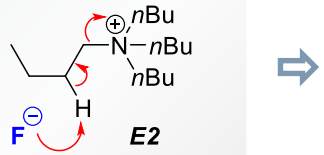
Fluorination of Arenes: Halogen Exchange

[A]

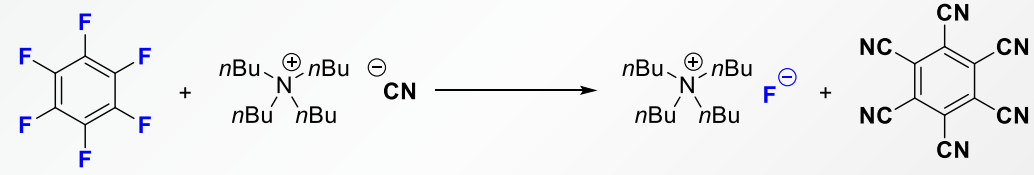


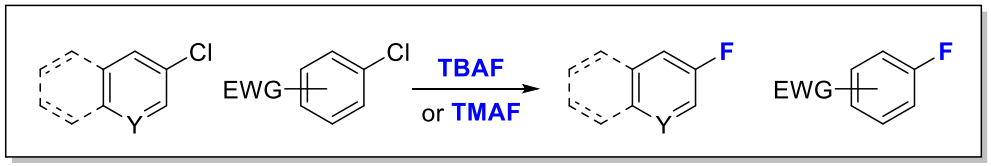
[B]

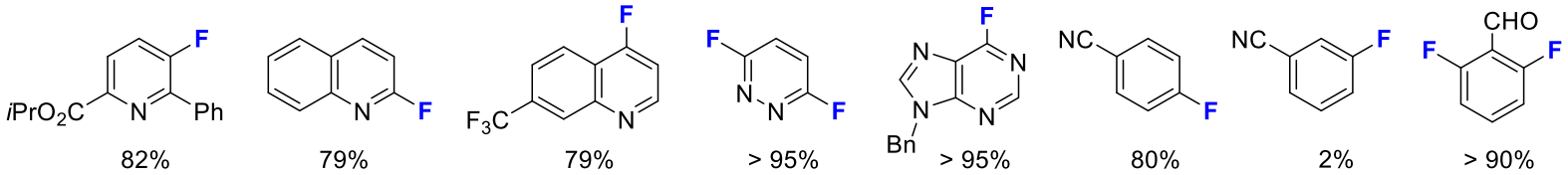
drying is problematic



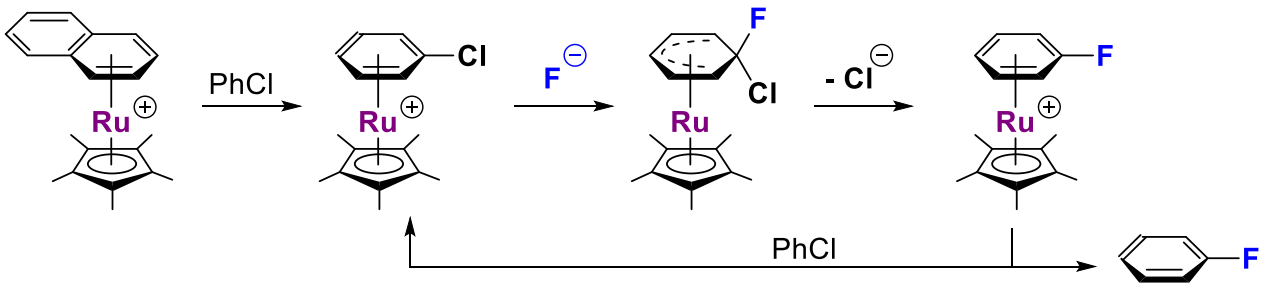
anhydrous TBAF : **DiMagno** *J. Am. Chem. Soc.* **2005**, *127*, 2050







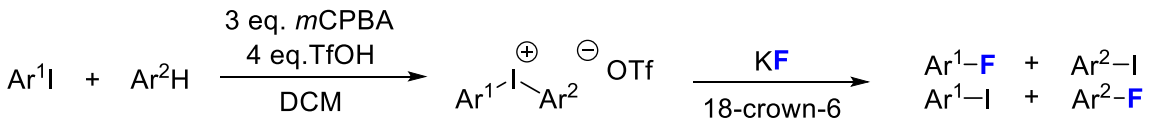
[C]

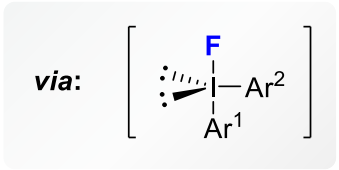


[A] Clark *Chem. Soc. Rev.* **1999**, *28*, 225; **Kimura** *J. Fluorine Chem.* **1991**, *52*, 341; **[B] DiMagno** *Angew. Chem. Int. Ed.* **2006**, *45*, 2720; **Sanford** *J. Org. Chem.* **2015**, *80*, 12137; **[C] Grushin** *Chem. Commun.* **2015**, *51*, 13527.

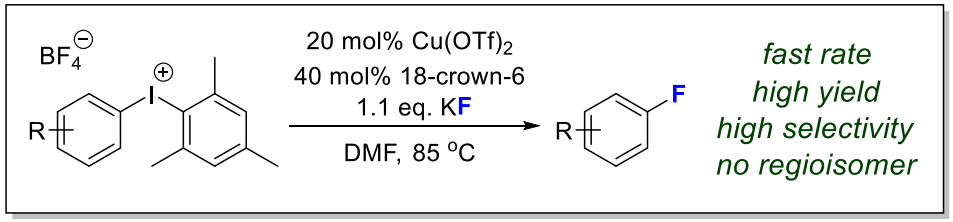
Fluorination of Diaryliodonium Salts and Anilines

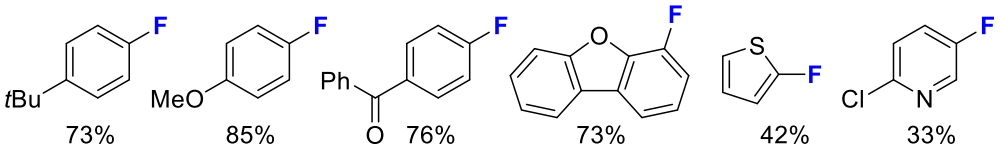
[A]

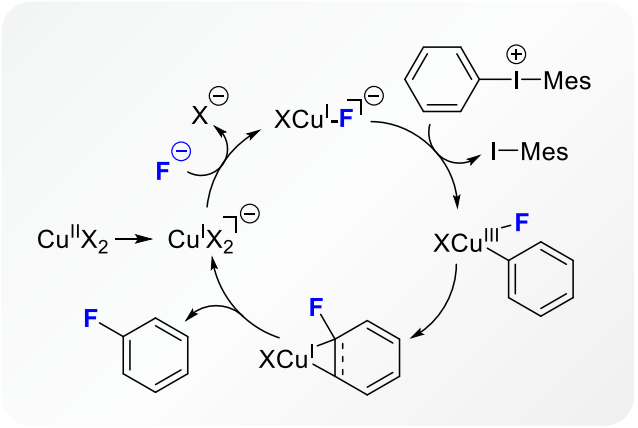




Copper catalysis

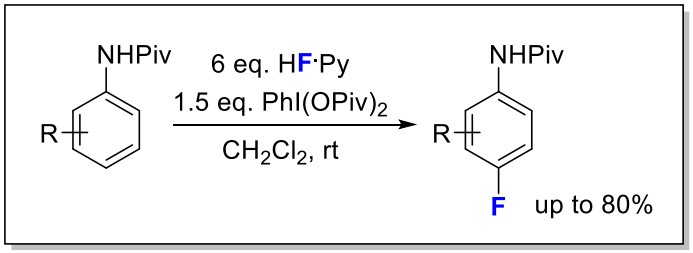


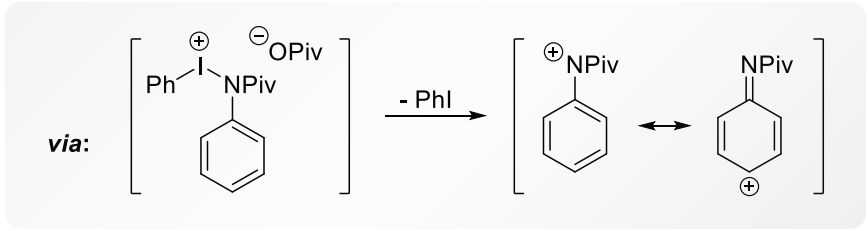




Without Cu : Selective for fluorination of mesityl in most cases

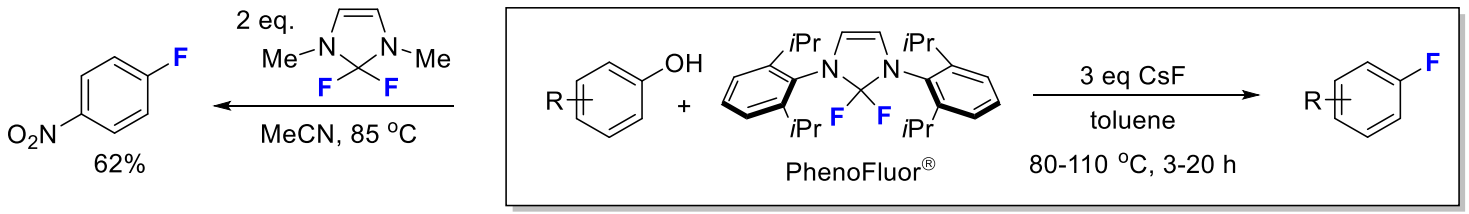
[B]

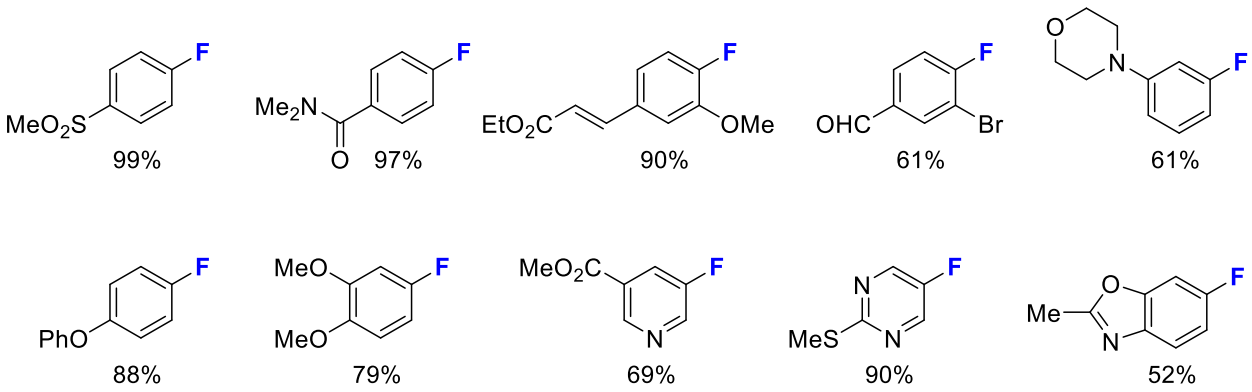


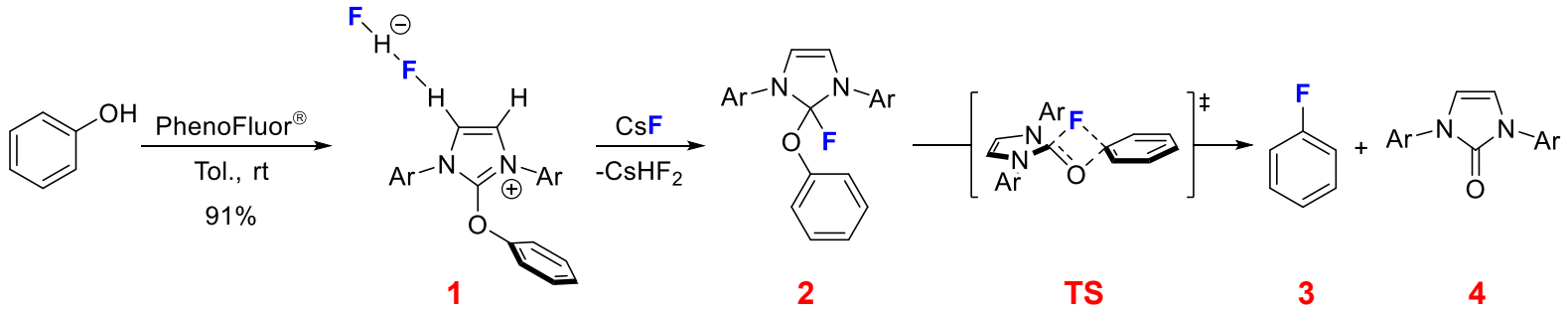


[A] Olofsson *Synlett* **2008**, *4*, 592; **Grushin** *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1983**, *33*, 1957; **Sanford** *Org. Lett.* **2013**, *15*, 5134; *Organometallics* **2014**, *33*, 5525; **[B] Li** *J. Org. Chem.* **2013**, *78*, 728.

Deoxyfluorination of Phenols

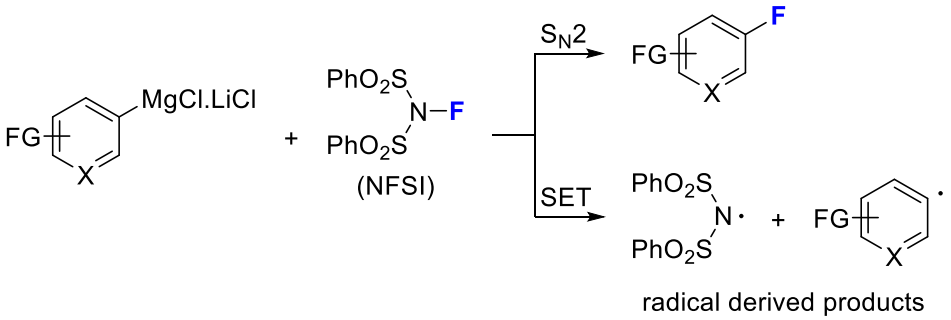


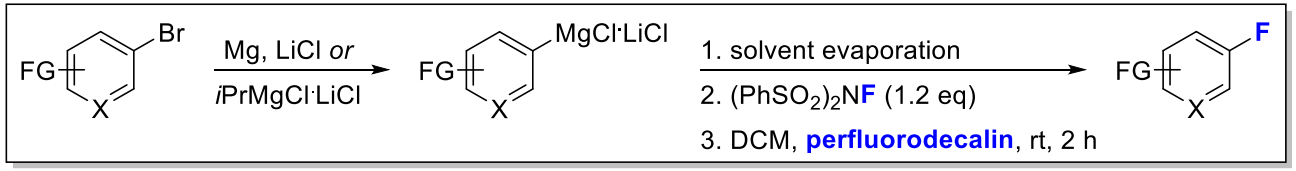


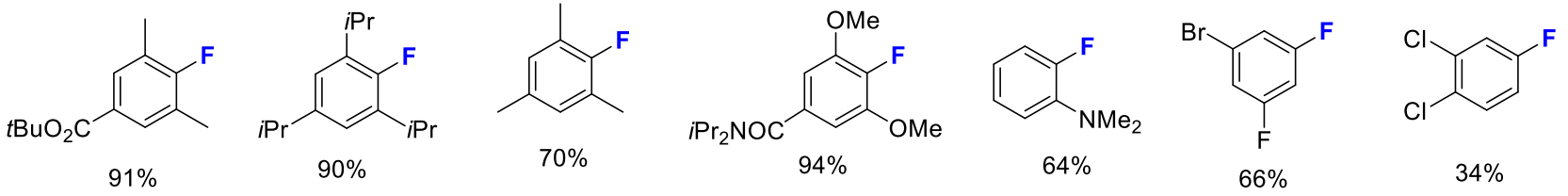


Hayashi *Chem. Commun.* **2002**, 1618; **Ritter** *J. Am. Chem. Soc.* **2011**, *133*, 11482; *Org. Lett.* **2015**, *17*, 544; *Nature* **2016**, *adv. art.*;
Aliphatic alcohols: **Ritter** *J. Am. Chem. Soc.* **2013**, *135*, 2470.

Fluorination of (Hetero)arenes from Grignard Reagents

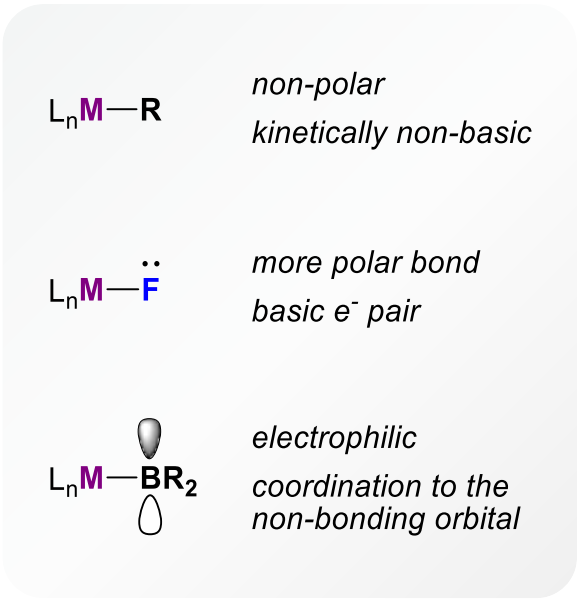


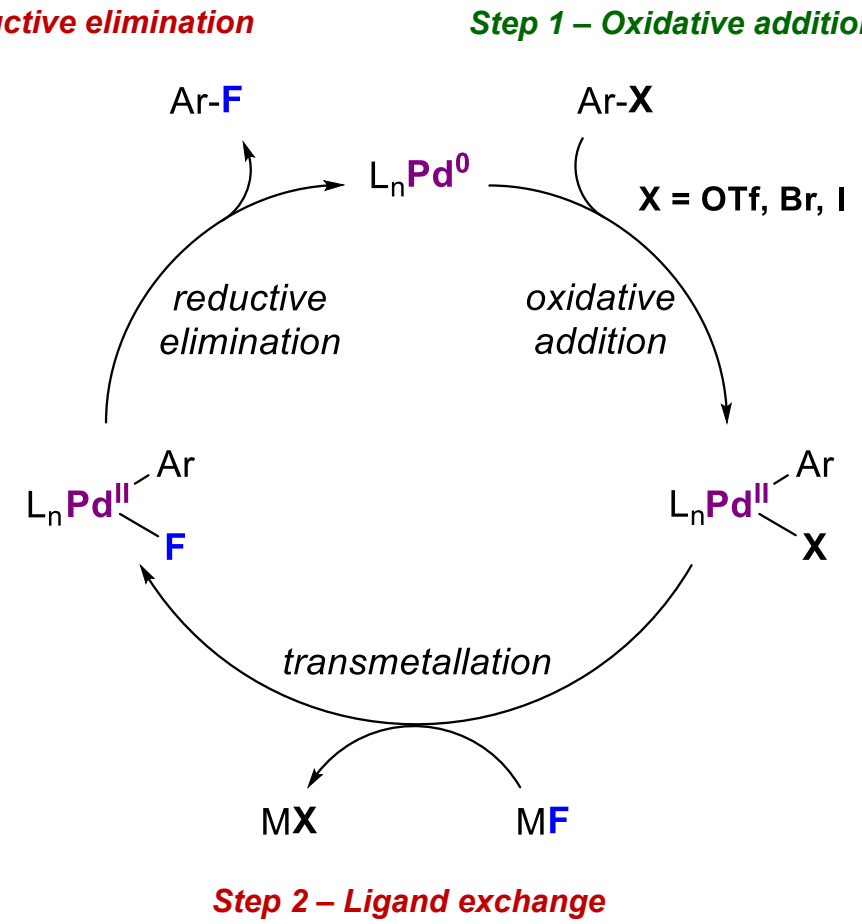




Knochel *Angew. Chem. Int. Ed.* **2010**, *49*, 2215; **Beller** *Angew. Chem. Int. Ed.* **2010**, *49*, 2219.

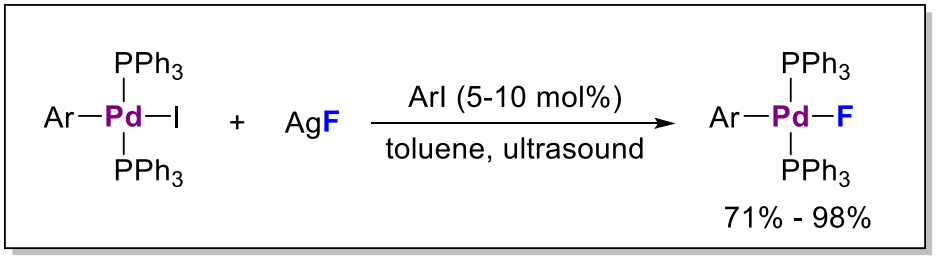
Palladium for Catalytic Fluorination



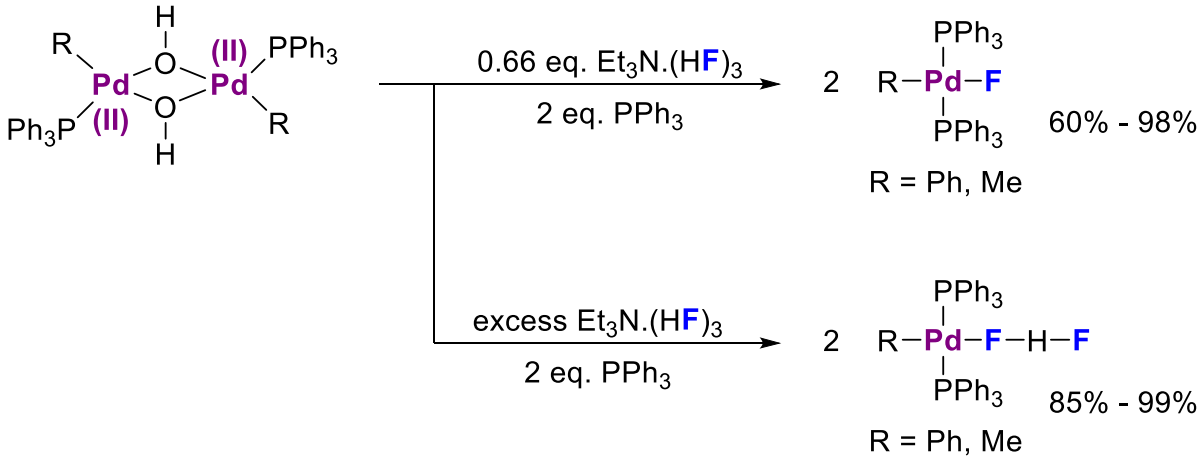


Palladium for Catalytic Fluorination

Step 2: Preparation of Pd(II) fluoride Complexes



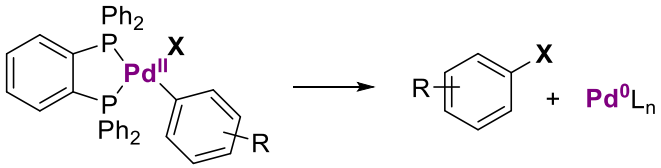
Ar = Ph
4-MeC_6H_4
4-$MeOC_6H_4$
1-naphthyl
4-ClC_6H_4
4-$CF_3C_6H_4$
4-$O_2NC_6H_4$



Grushin *J. Am. Chem. Soc*, **1997**, *119*, 4769; *Chem. Eur. J.* **2002**, *8*, 1006.

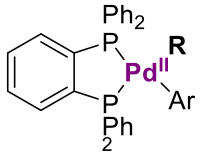
Palladium for Catalytic Fluorination

Step 3: Reductive elimination – C-X vs C-F bond formation



rate of reductive elimination:
X = PR_2 > SR > NR_2

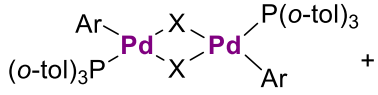
Reductive elimination to form **C-X** bond occurs more rapidly with more nucleophilic heteroatoms
C-P > C-S > C-N > C-O
(more favorable attack of lone pair **X** on ipso C-aryl)



Ar—**R**

R =	k_{rel} (110 °C)
Me	>600
Bn	>250
$CH_2C(O)Ar$	31
CH_2CF_3	1.7
CH_2CN	1
CF_3	nr

σ effect is predominant
Aryl-palladium-alkyl complexes undergo slow reductive elimination when alkyl contains an electron withdrawing group



+ 4 P*t*Bu$_3$ $\underset{}{\overset{C_6D_6,\ 70\ ^oC}{\rightleftharpoons}}$ 2 ArX + 2 (P*t*Bu$_3$)$_2$Pd

K_{eq} = 9 x 10^{-2} (Cl), 2.3 x 10^{-3} (Br), 3.7 x 10^{-5} (I)

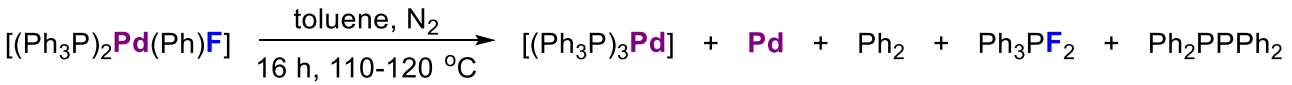
for higher halogen, equilibrium disfavors reductive elimination

excess phosphine leads to formation of aryl chloride or aryl bromide

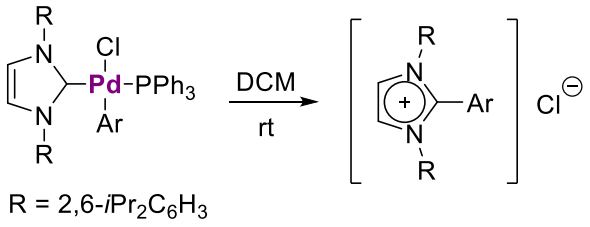
Hartwig *Inorganic Chemistry* **2007**, *46*, 1936; *J. Am.Chem. Soc.* **2001**, *123*, 1232.

Palladium for Catalytic Fluorination

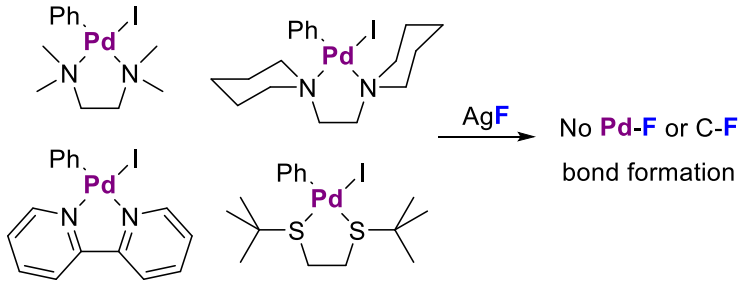
[A] Thermolysis of Pd^{II} fluoride species



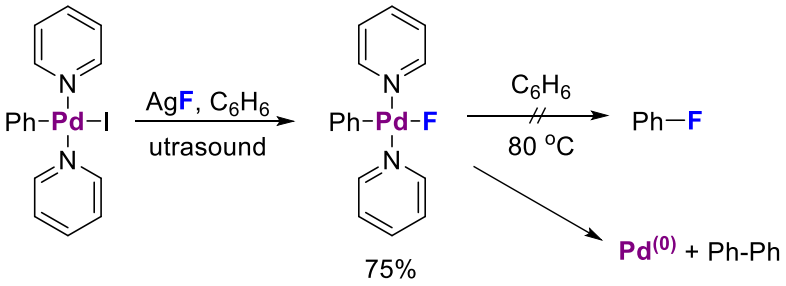
[B] NHC Ligands



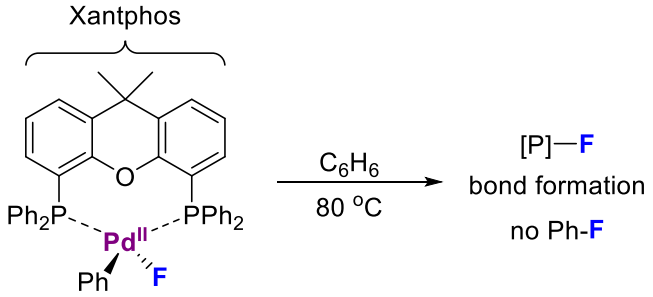
[C] N,N- and S,S- Bidentate Ligands



[D] Pyridine Ligands



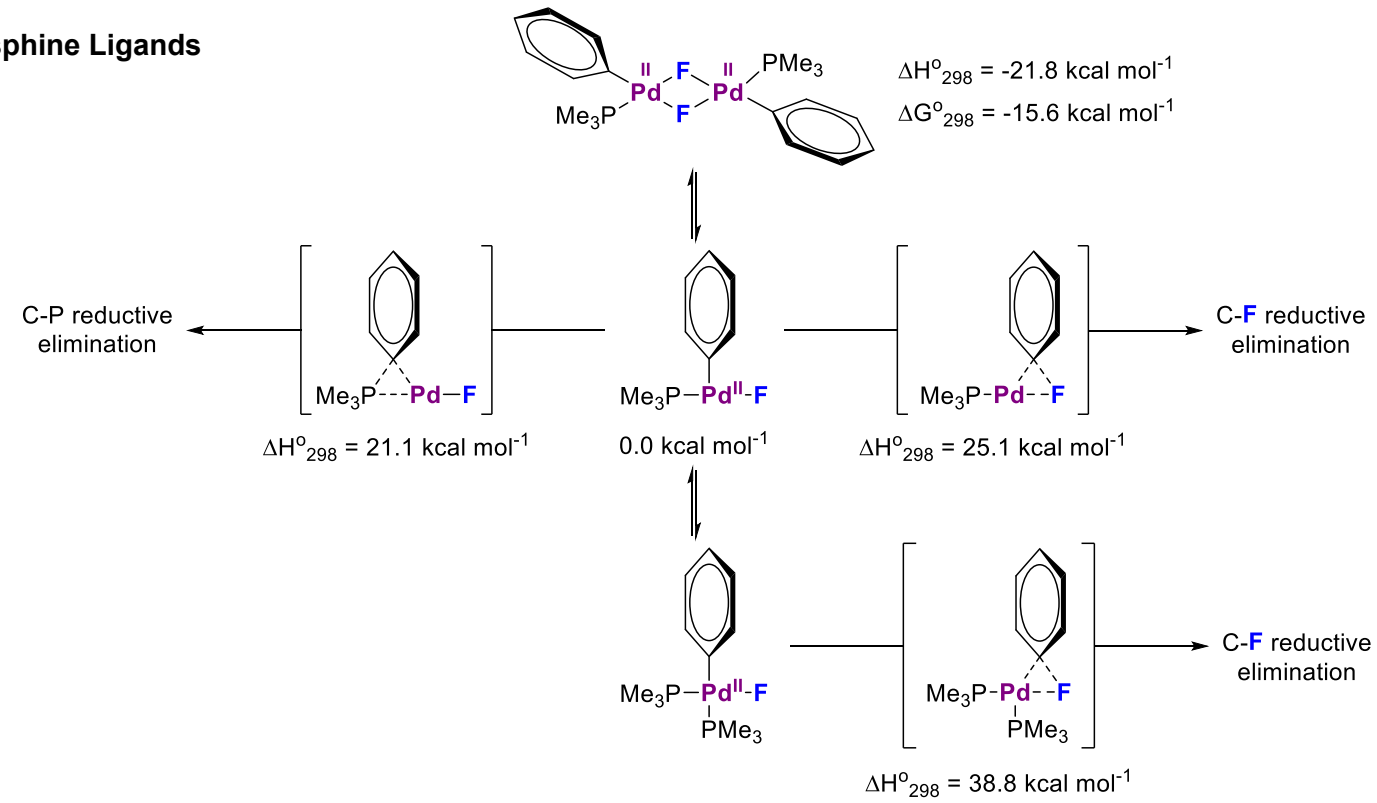
[E] Xantphos



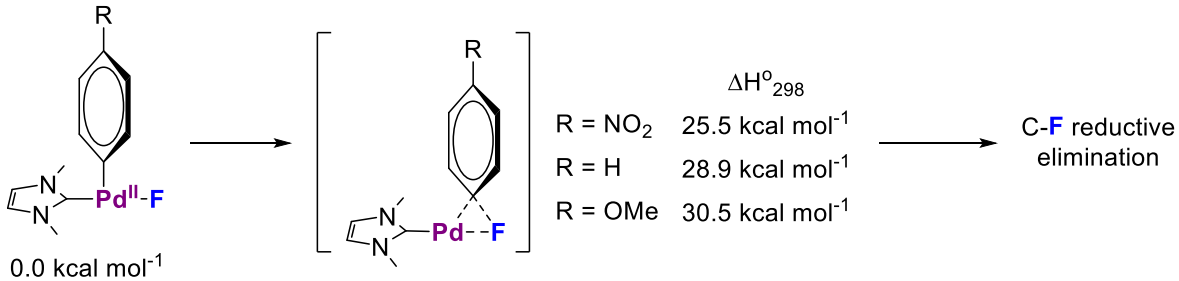
[A] Grushin *Acc. Chem. Res.* **2010**, *43*, 160; *Organometallics* **2000**, *19*, 1888; **[B] Grushin** *Organometallics* **2003**, *22*, 1591; **[C] Grushin** *Organometallics* **2008**, *27*, 4825; **[D] Grushin** *J. Am. Chem. Soc.* **2009**, *131*, 918; **[E] Grushin** *J. Am. Chem. Soc.* **2006**, *128*, 12644.

Palladium for Catalytic Fluorination

- Phosphine Ligands

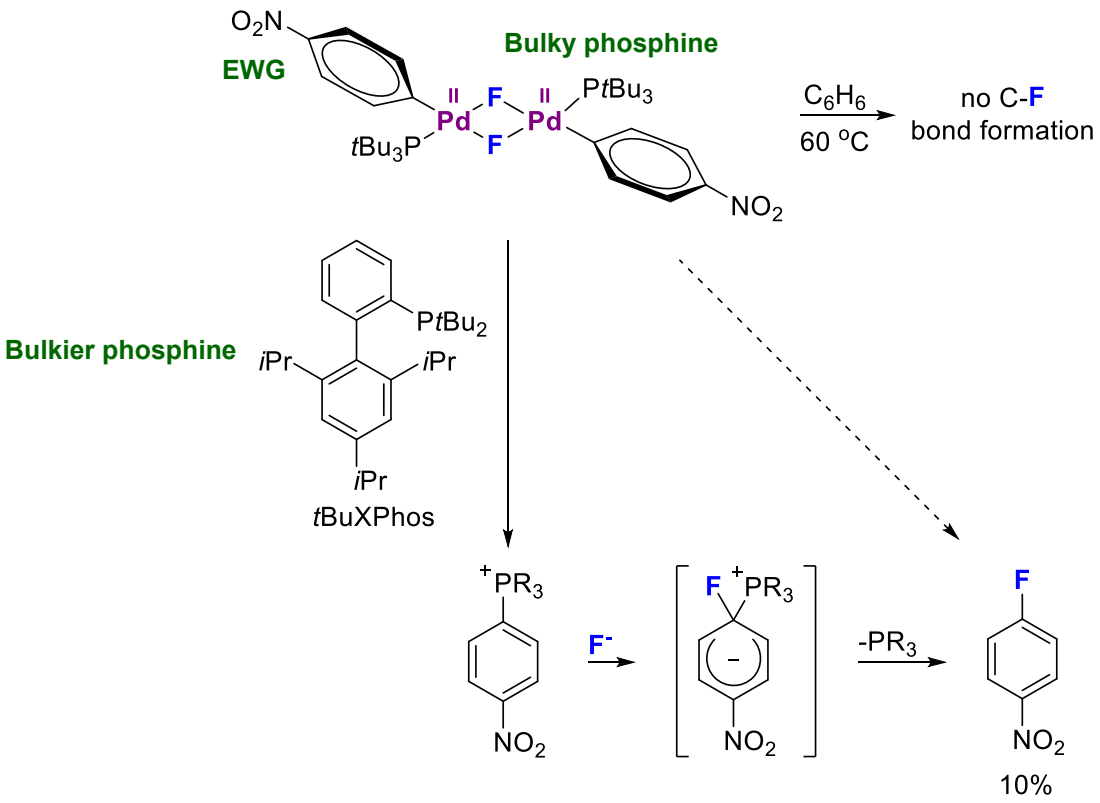


- NHC Ligands



Yandulov *J. Am. Chem. Soc.* **2007**, *129*, 1342.

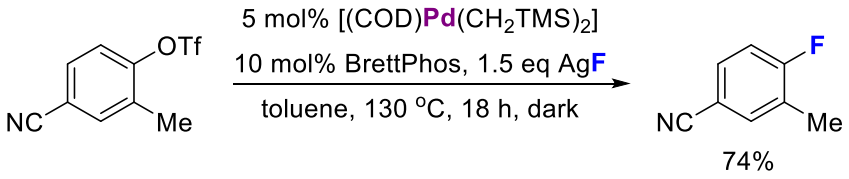
Palladium for Catalytic Fluorination

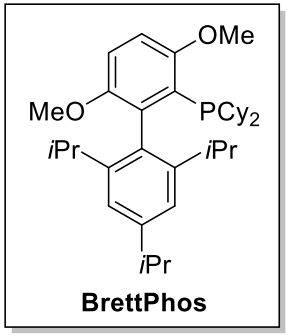


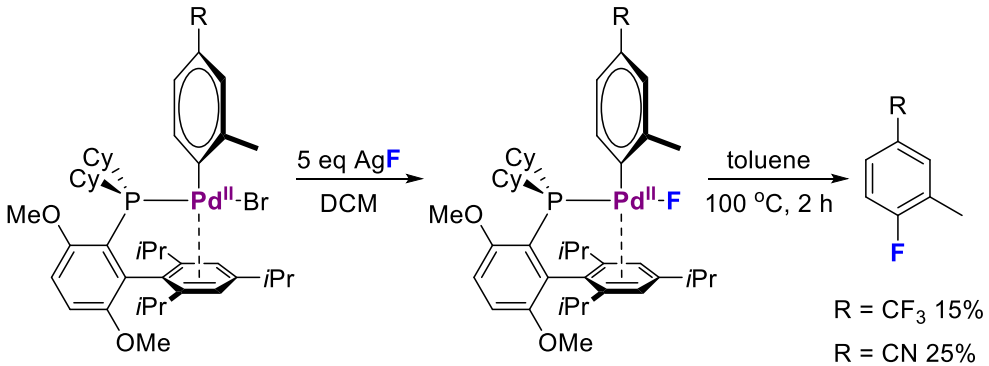
Grushin *Organometallics* **2007**, *26,* 4997; **Yandulov** *J. Am. Chem. Soc.* **2007**, *129*, 1342.

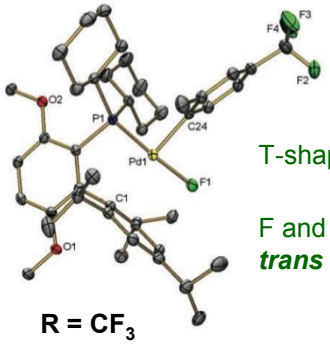
Palladium for Catalytic Fluorination

- BrettPhos







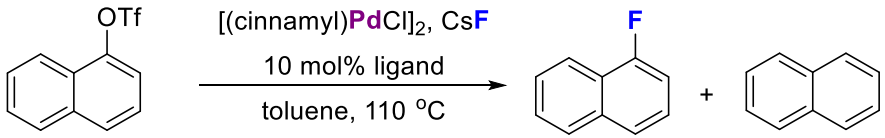


R = CF_3

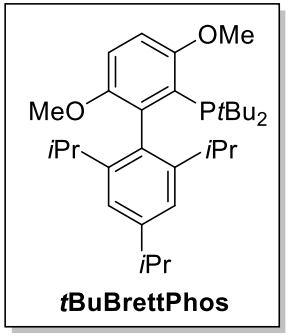
T-shape ***monomeric*** complex

F and P ligand occupy ***trans*** coordination sites

- *t*BuBrettPhos

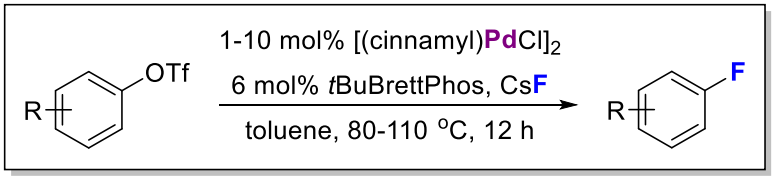


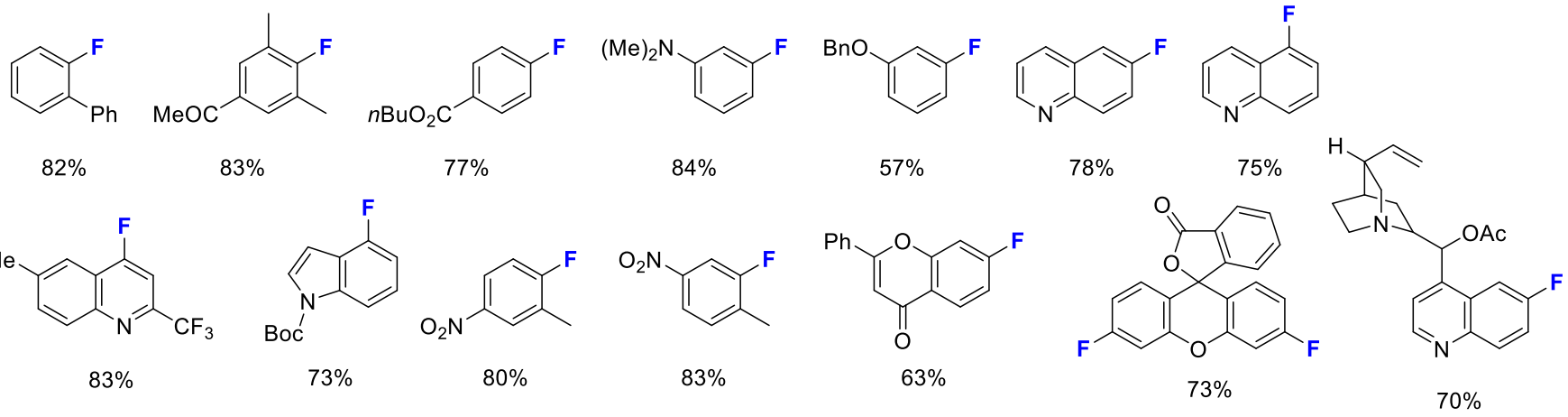
BrettPhos	30%	5%
***t*BuBrettPhos**	**71%**	**1%**



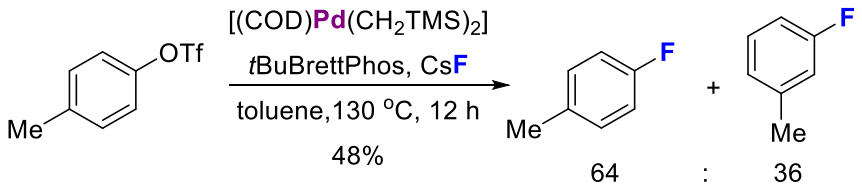
Buchwald *Science* **2009**, *325*, 1661.

Palladium for Catalytic Fluorination





Formation of regioisomers

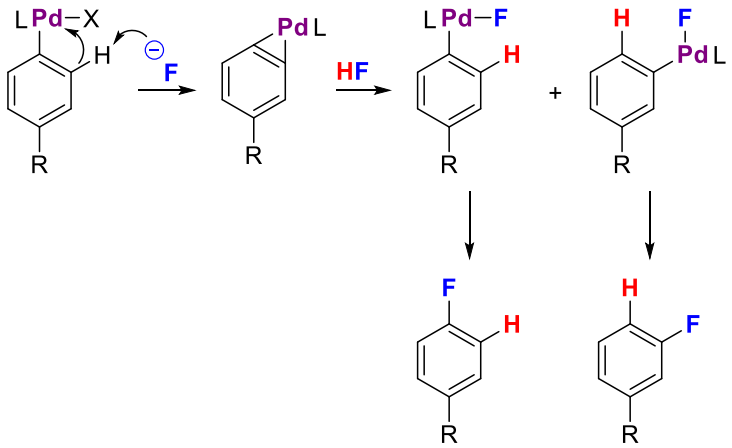


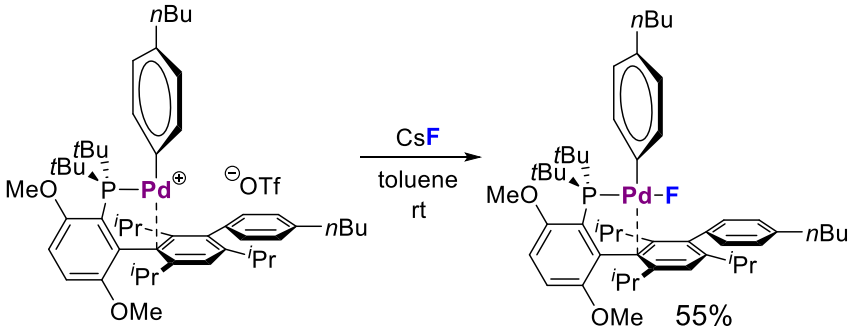
Next Challenges
- Regioisomers formation
- Reduction by-products
- Lewis basic groups
- Highly electron-rich substrates
- Heteroaryl substrates

Buchwald *Science* **2009**, *325*, 1661.

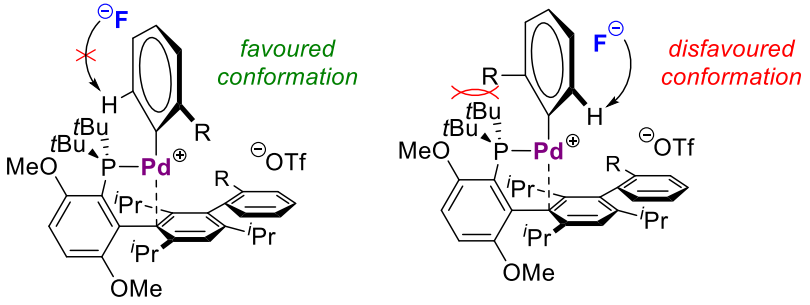
Palladium for Catalytic Fluorination

[A] *t*BuBrettPhos

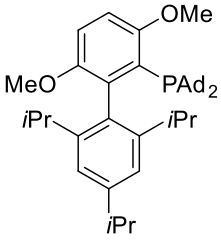




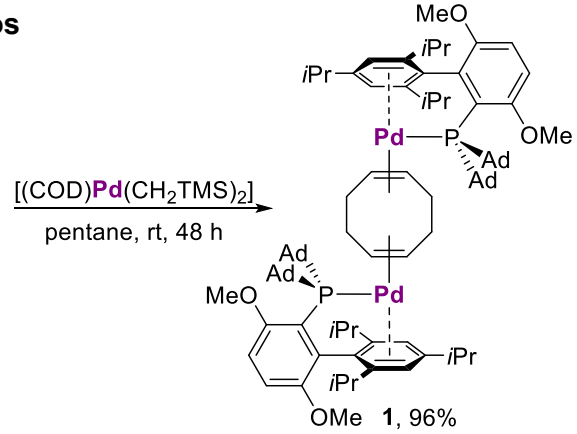
Shielding effect of *t*Bu groups decelerates *ortho*-deprotonation:

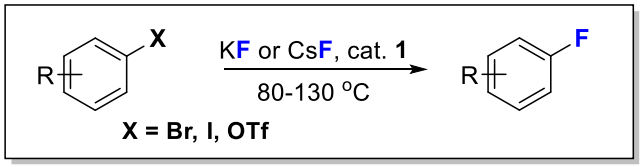


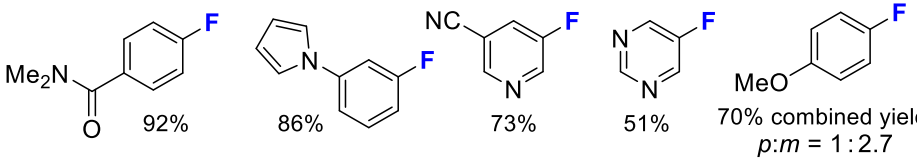
[B] AdBrettPhos



AdBrettPhos

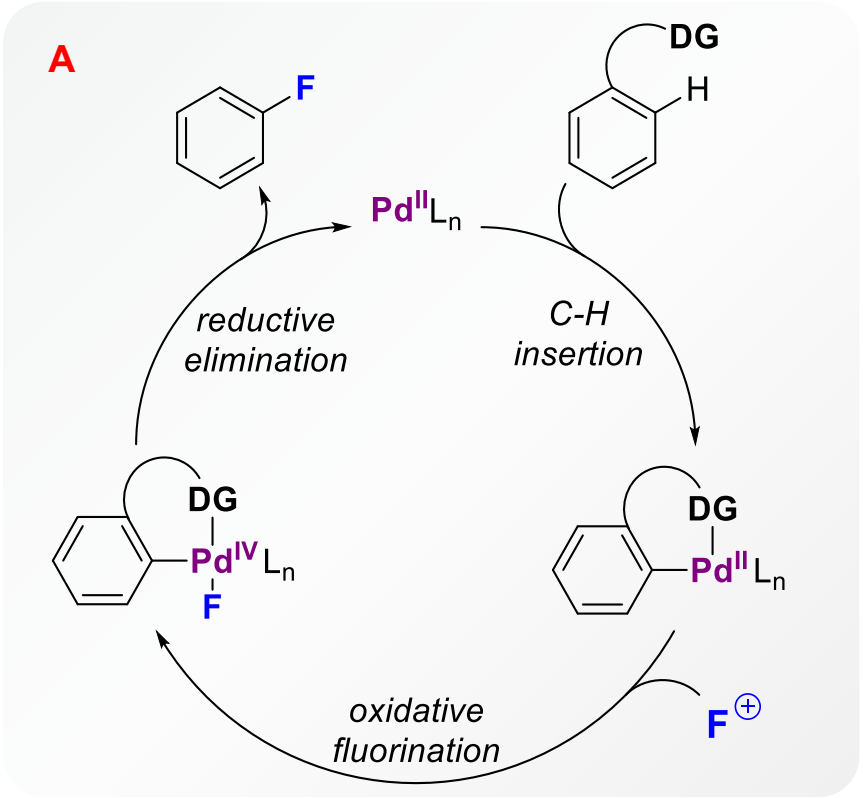


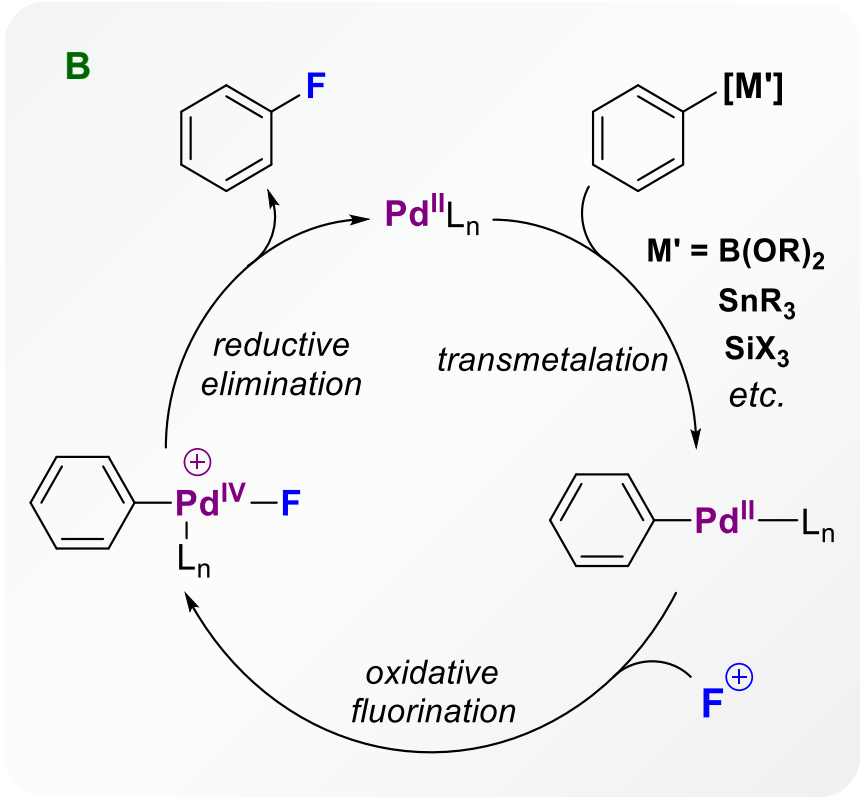




[A] Buchwald *J. Am. Chem. Soc.* **2014**, *136*, 15757; **[B] Buchwald** *Org. lett.* **2013**, *15*, 5602; *J. Am. Chem. Soc.* **2014**, *136*, 3792; *J. Am. Chem. Soc.* **2015**, *137*, 13433.

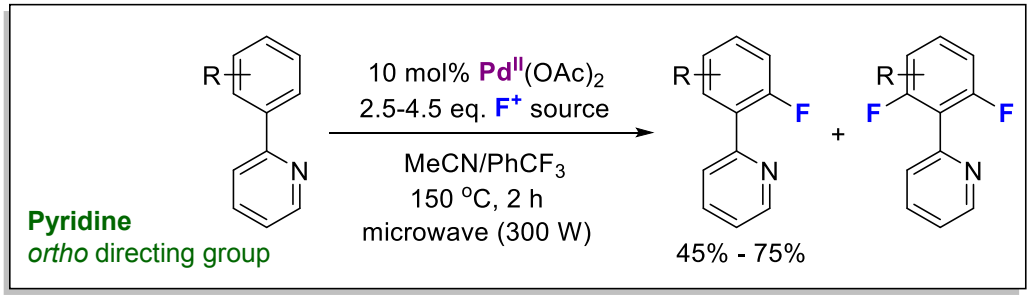
High Valent Palladium for Catalytic Fluorination

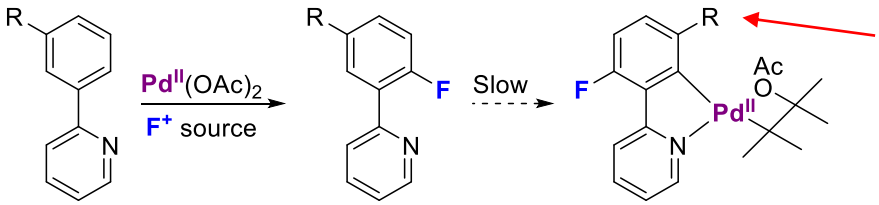




High Valent Palladium for Catalytic Fluorination

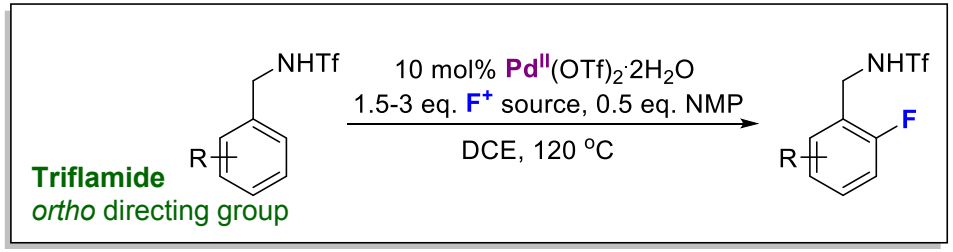
[A]

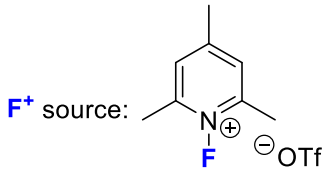




- ortho' or meta' blocking groups required to avoid difluorination
- Harsh reaction conditions

[B]



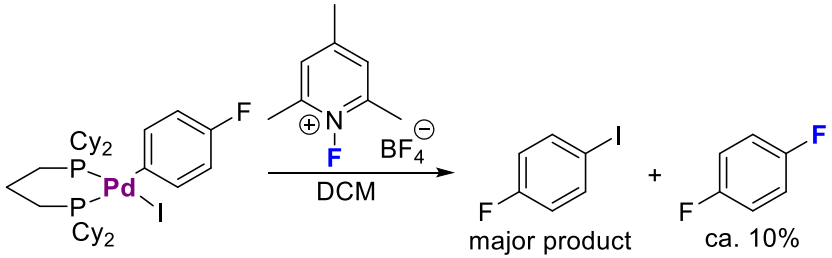


- milder conditions to Sanford
- Pd(OTf)$_2$ instead of Pd(OAc)$_2$ to prevent acetoxylation

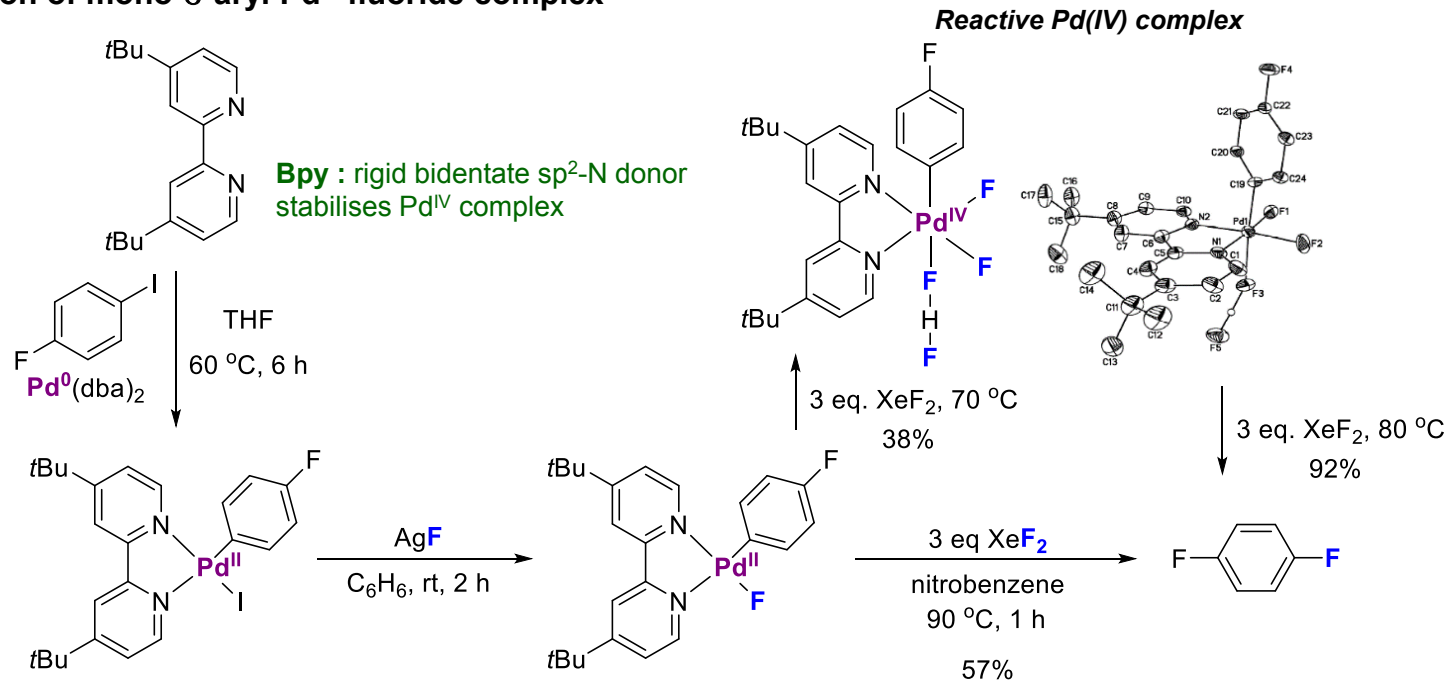
[A] Sanford *J. Am. Chem. Soc.* **2006**, *128*, 7134; **[B] Yu** *J. Am. Chem. Soc.* **2009**, *131*, 7520.

High Valent Palladium for Catalytic Fluorination

[A] Reactivity of Aryl Pd^{II} iodide complexes toward electrophilic NF reagents



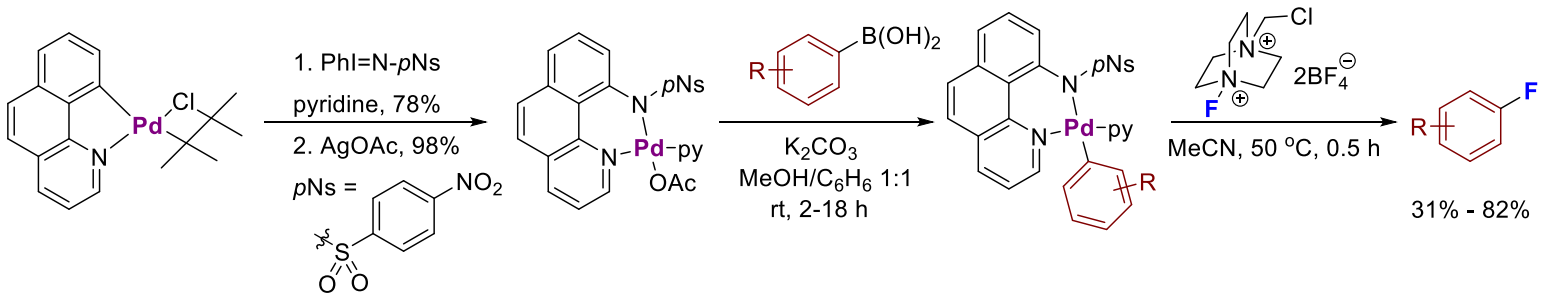
[B] Isolation of mono-σ-aryl Pd^{IV} fluoride complex



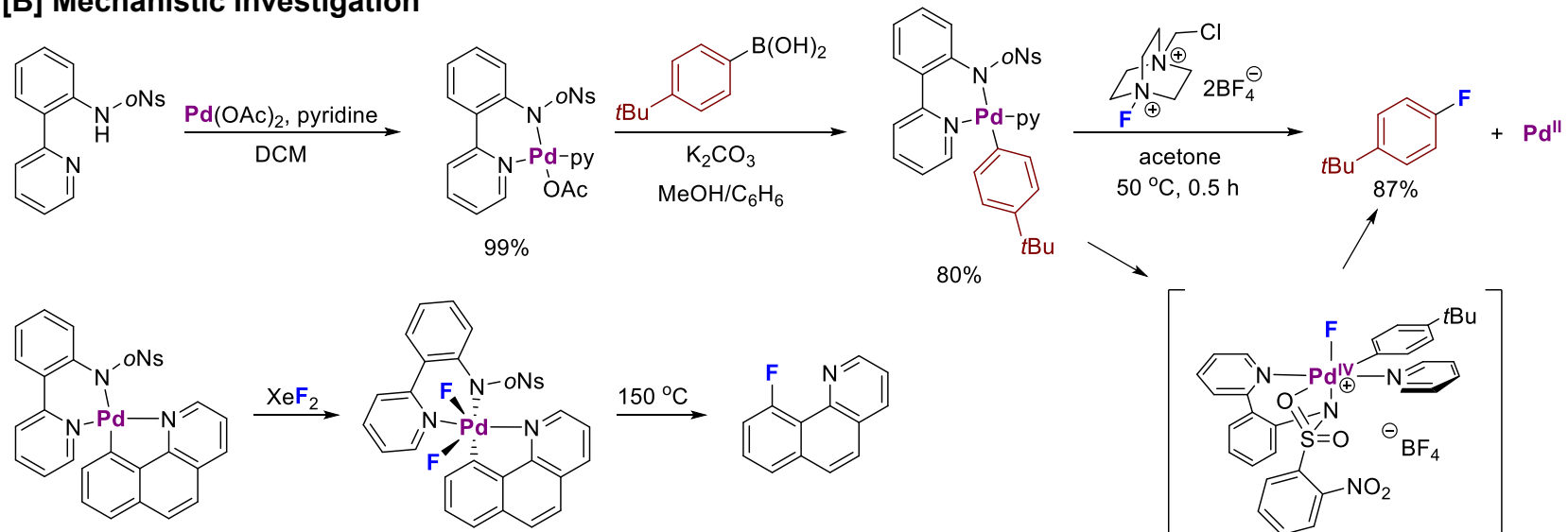
[A] Vigalok *Inorg. Chem*. **2008**, *47*, 5; **[B] Sanford** *J. Am. Chem. Soc*. **2009**, *131*, 3796.

High Valent Palladium for Catalytic Fluorination

[A] Pd-Mediated Fluorination of Arylboronic Acids



[B] Mechanistic Investigation

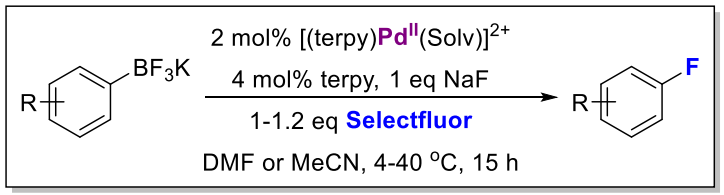


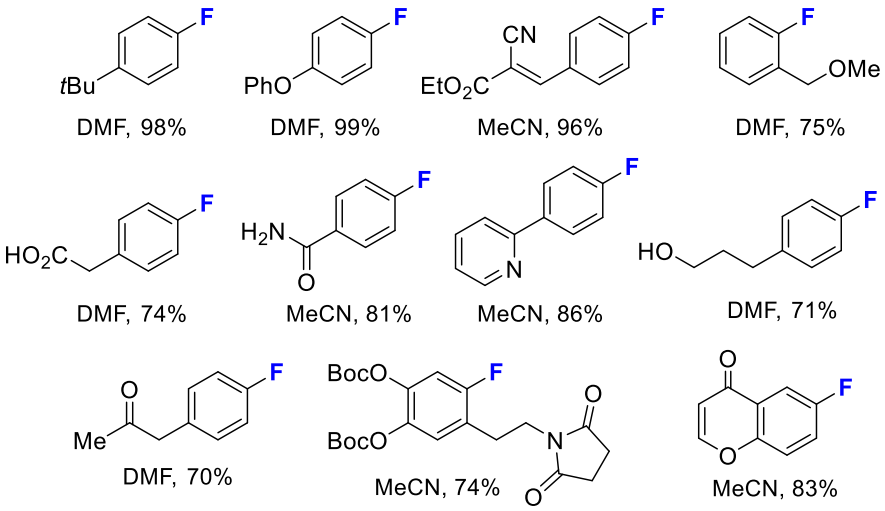
Reactive Pd(IV) intermediate isolated and X-ray characterised

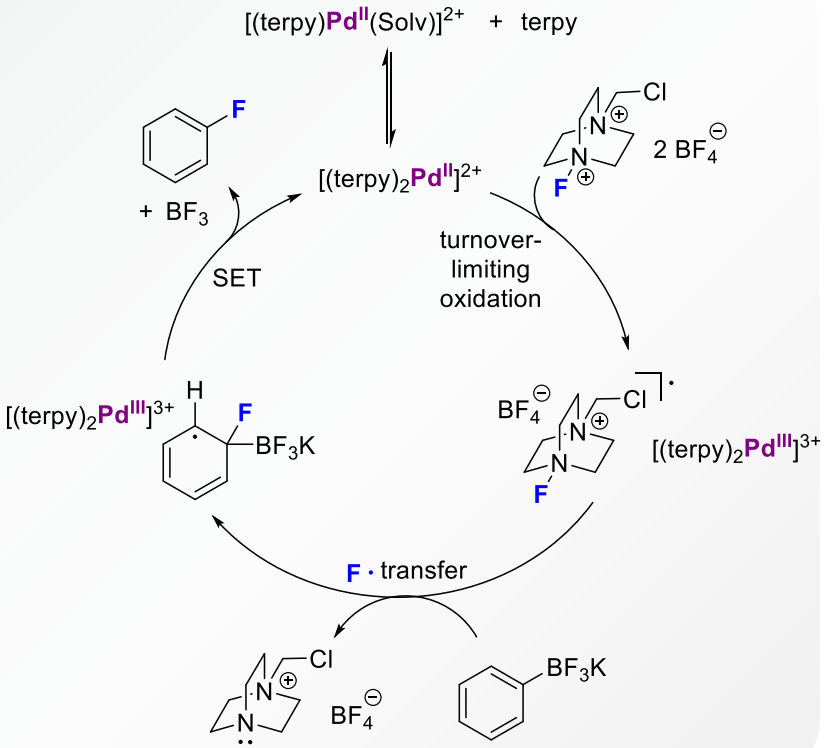
putative Pd^{IV} intermediate with monodentate aryl substituent

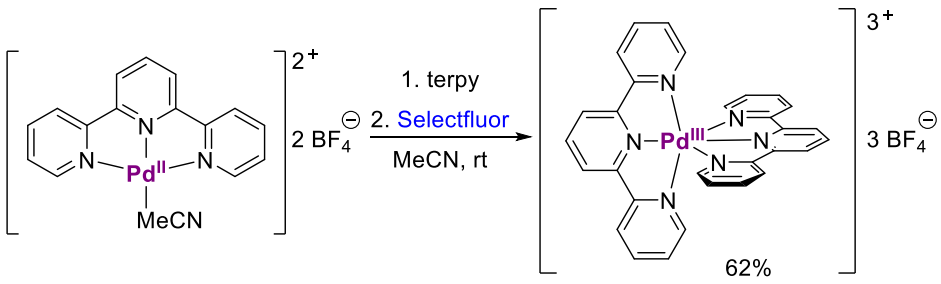
[A] Ritter *J. Am. Chem. Soc.* **2008**, *130*, 10060; **[B] Ritter** *Angew. Chem. Int. Ed.* **2008**, *47*, 5993.

High Valent Palladium for Catalytic Fluorination



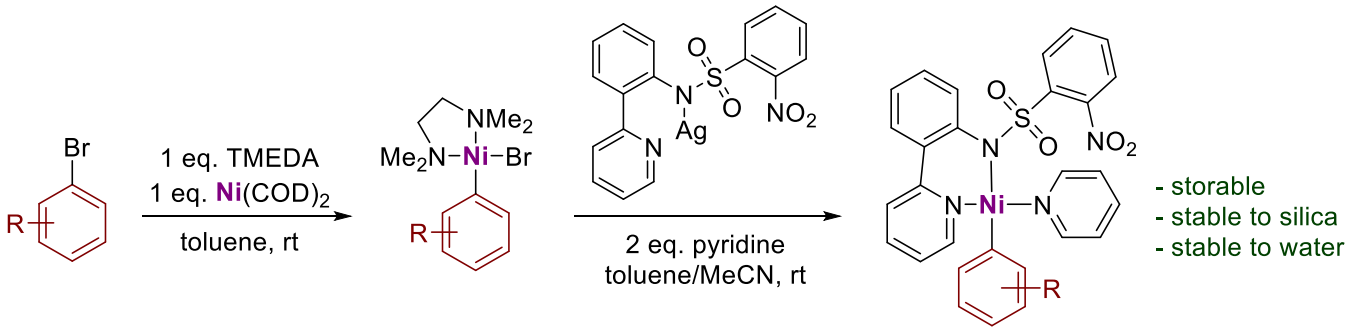


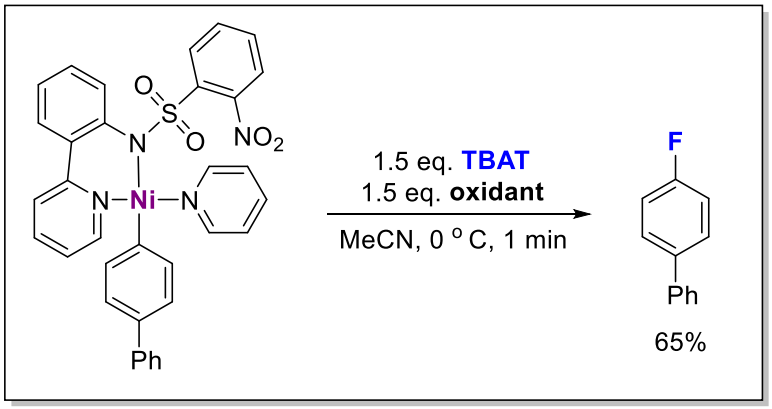


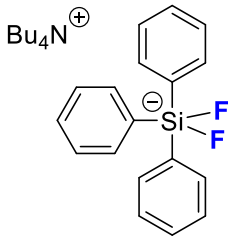


Ritter *J. Am. Chem. Soc.* **2013**, *135*, 14012.

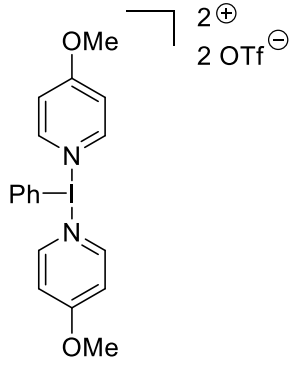
Oxidative Fluorination of Aryl Nickel(II) Complexes







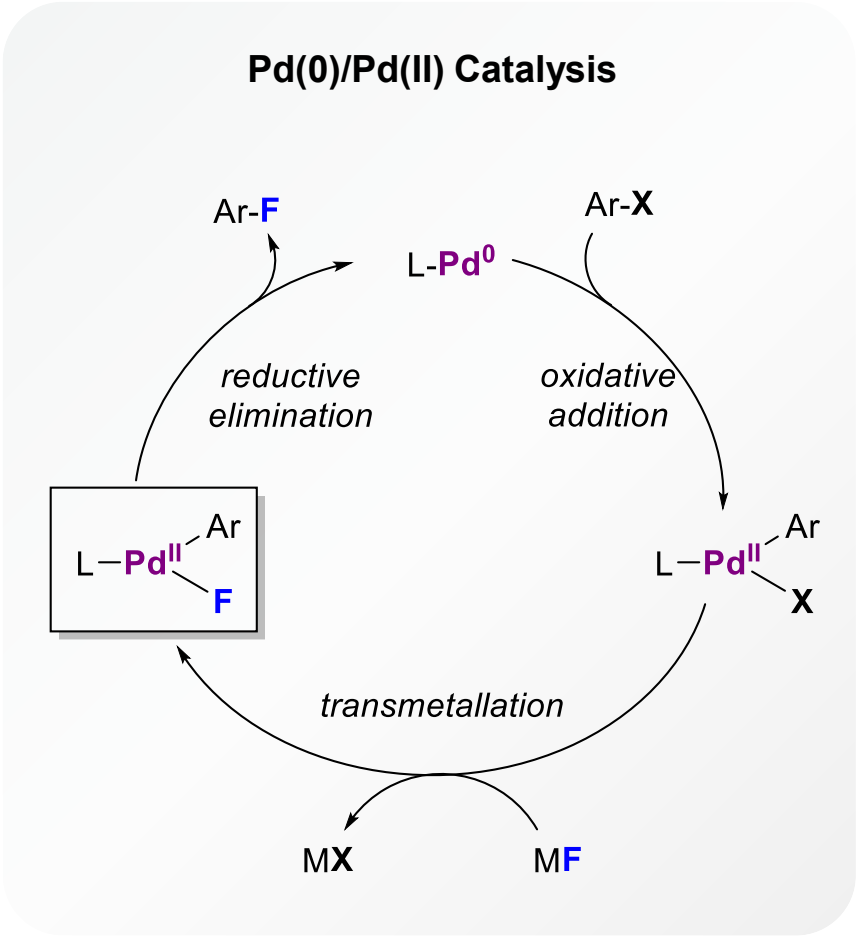
TBAT

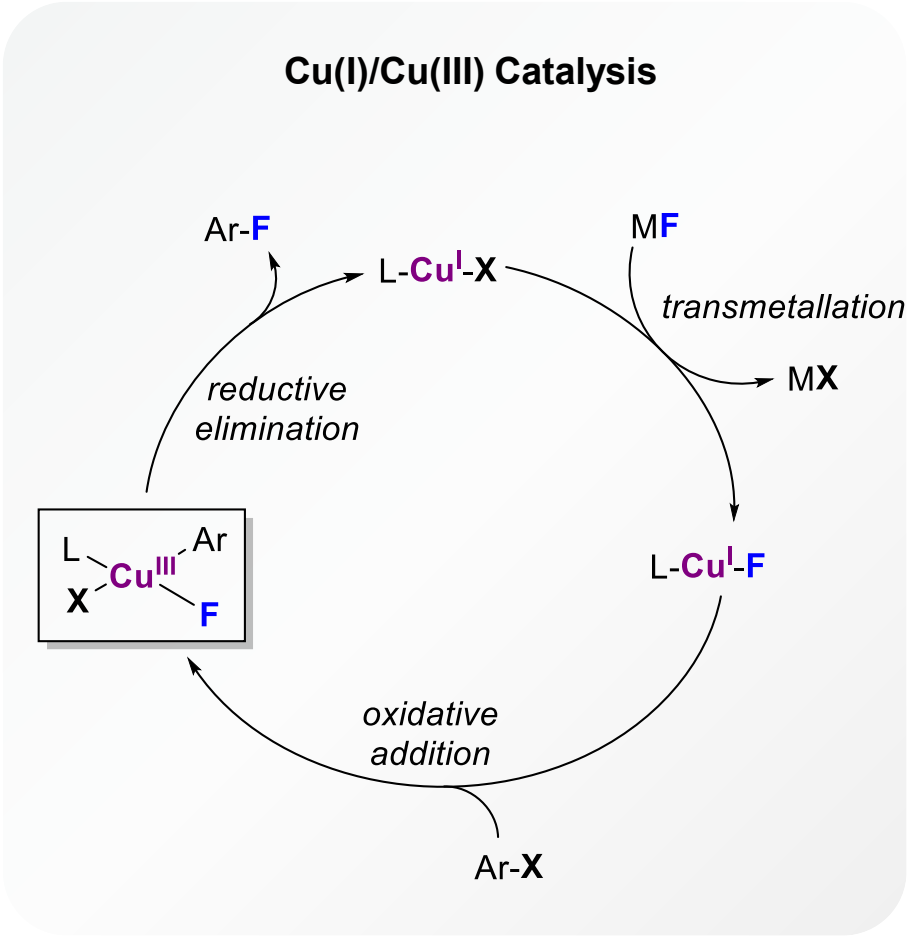


oxidant

Ritter *J. Am. Chem. Soc.* **2012**, *134*, 17456.

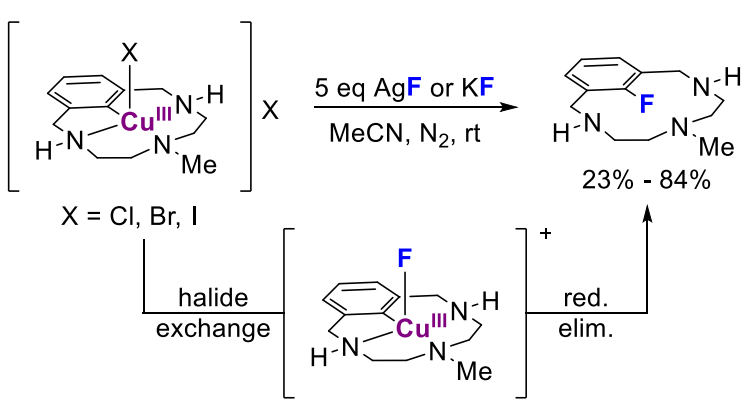
High Valent Copper for Catalytic Fluorination

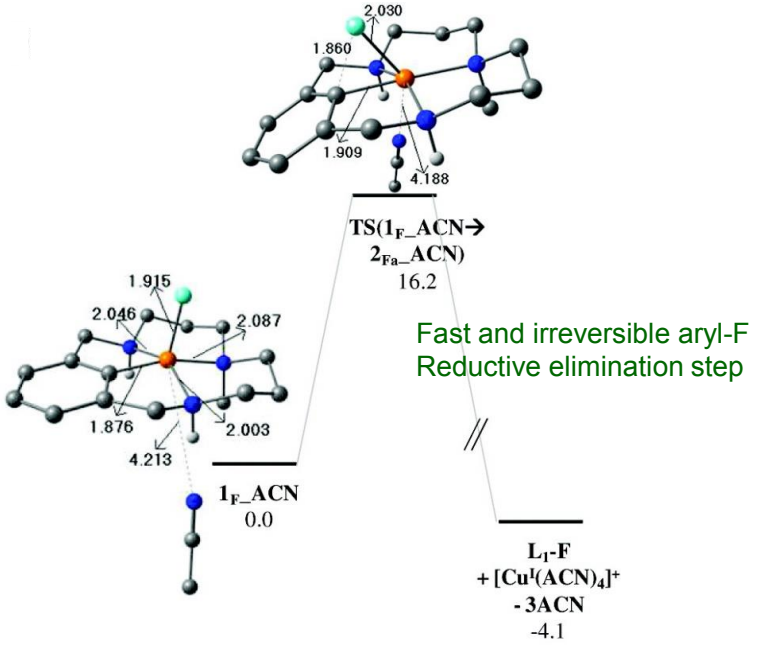




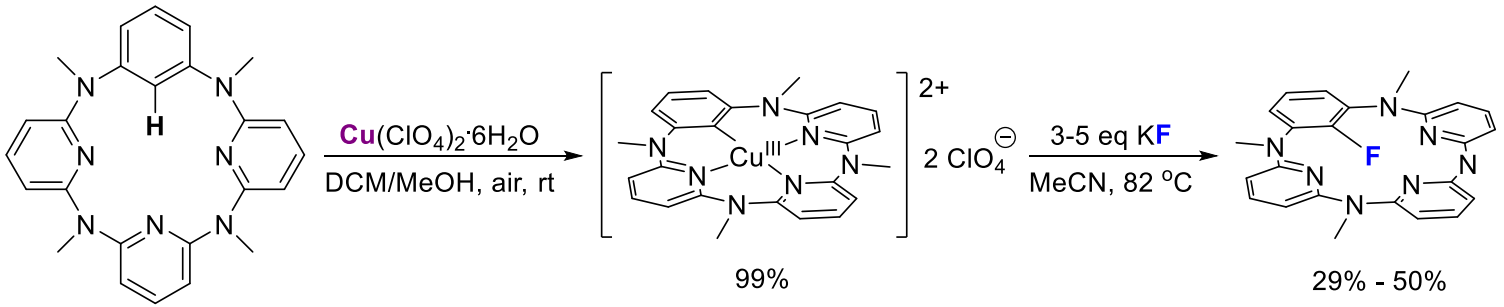
High Valent Copper for Fluorination

[A]





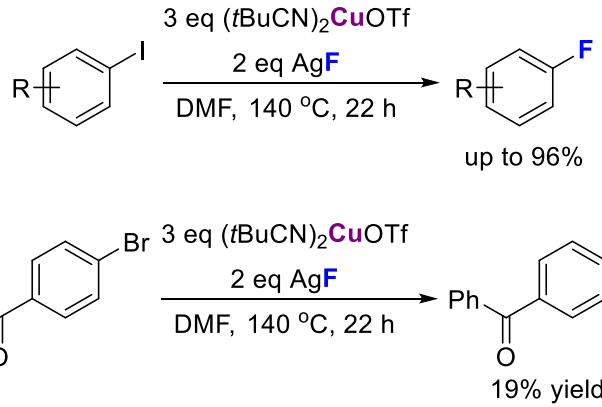
[B]

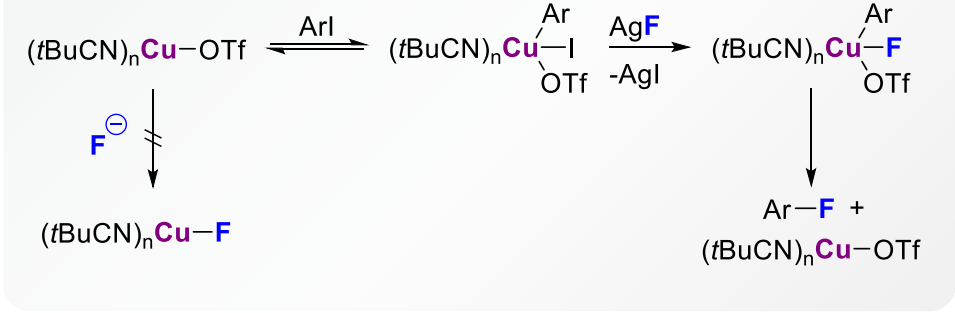


[A] Ribas *J. Am. Chem. Soc.* **2011**, *133*, 19386; **[B] Wang** *J. Org. Chem.* **2012**, 77, 3336.

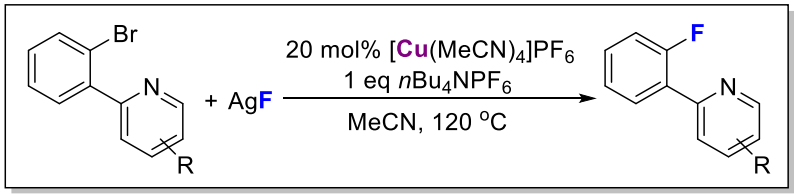
High Valent Copper for Catalytic Fluorination of Aryl Halides

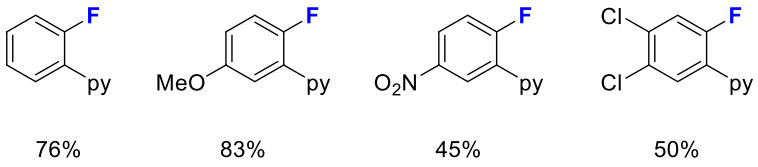
[A]

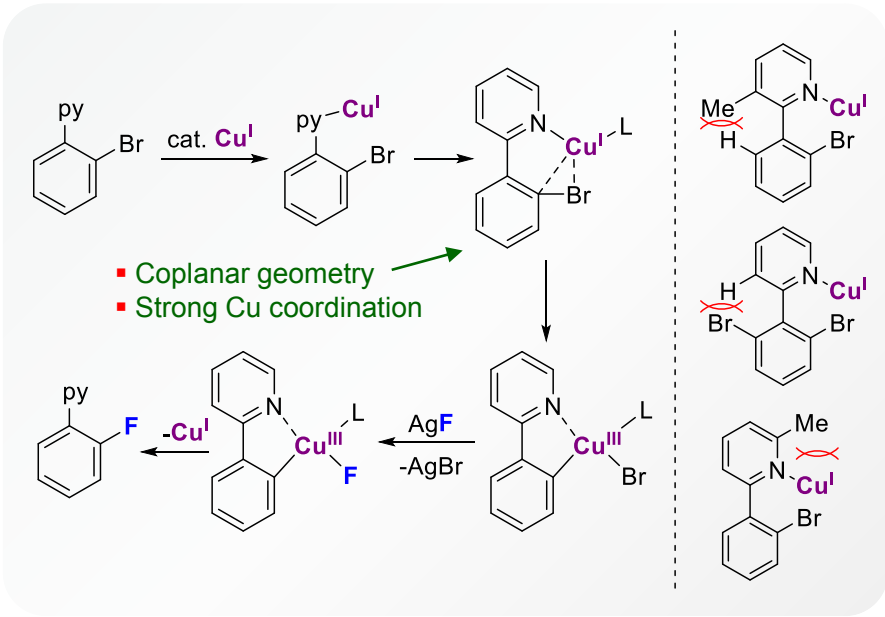




[B] With pyridine directing groups

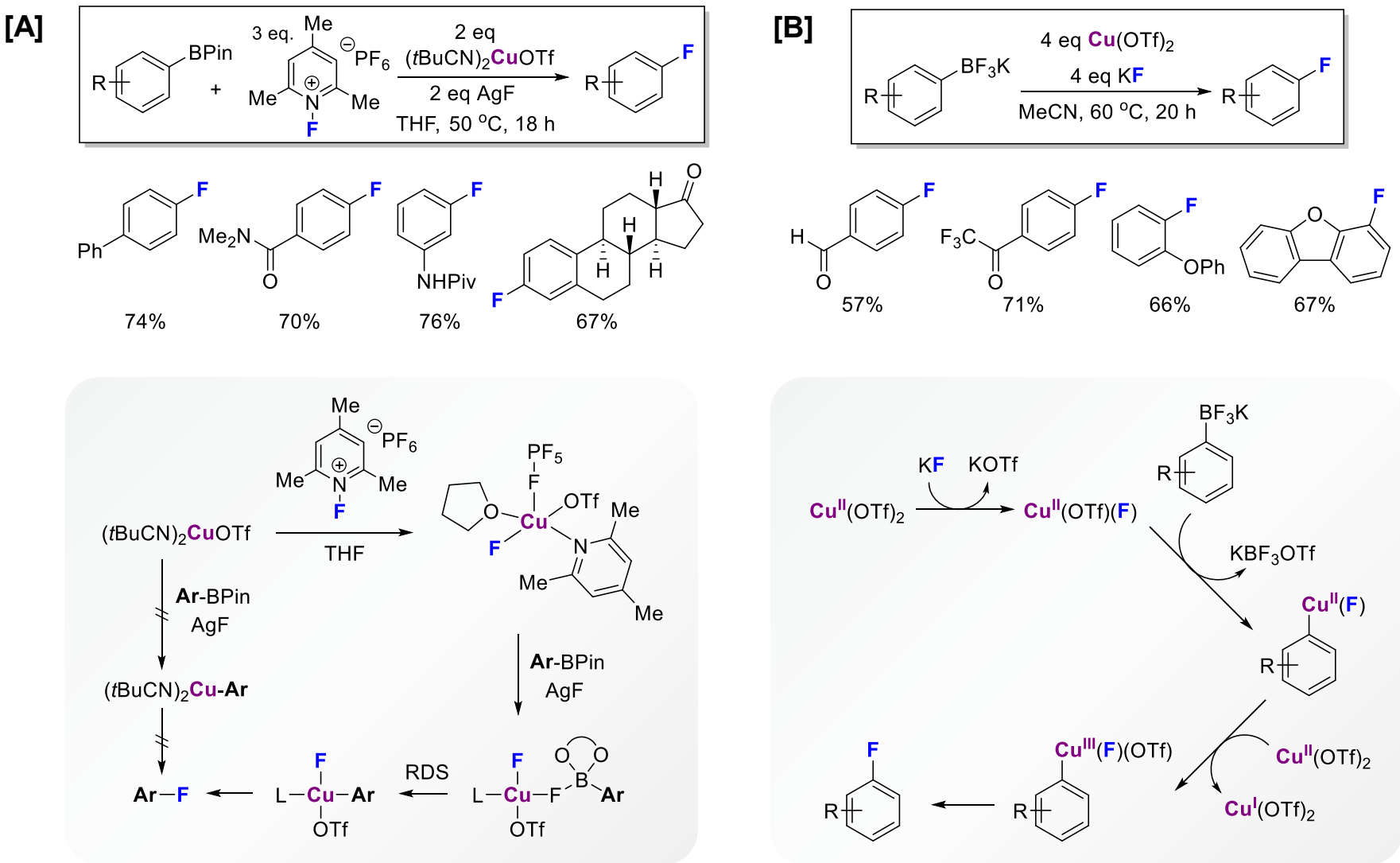






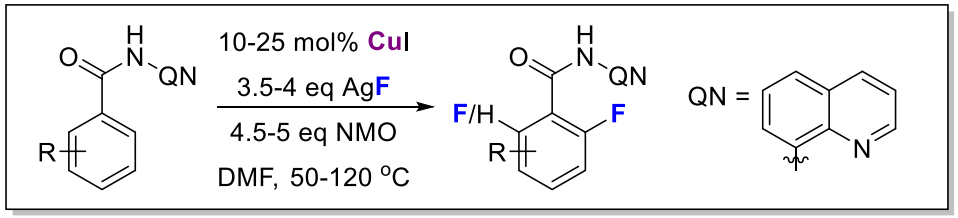
[A] Hartwig *J. Am. Chem. Soc.* **2012**, *134*, 10795; **[B] Liu** *Chem. Sci.* **2014**, *5*, 275.

Copper for Fluorination of Aryl Boronic Esters

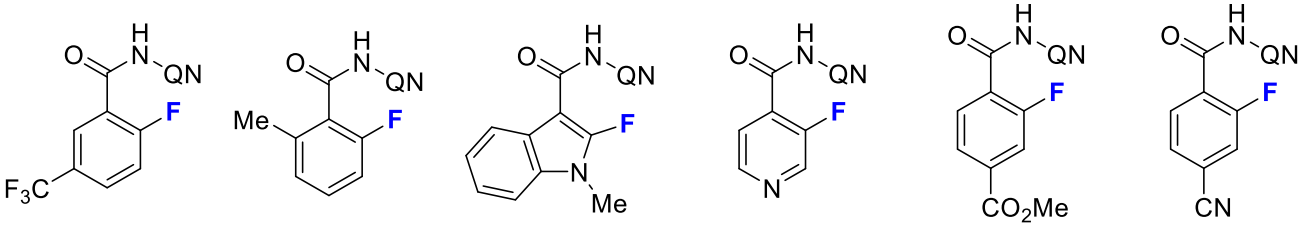


[A] Hartwig *J. Am. Chem. Soc.* **2013**, *135*, 2552; **[B] Sanford** *J. Am. Chem. Soc.* **2013**, *135*, 16292; *J. Am. Chem. Soc.* **2013**, *135*, 4648.

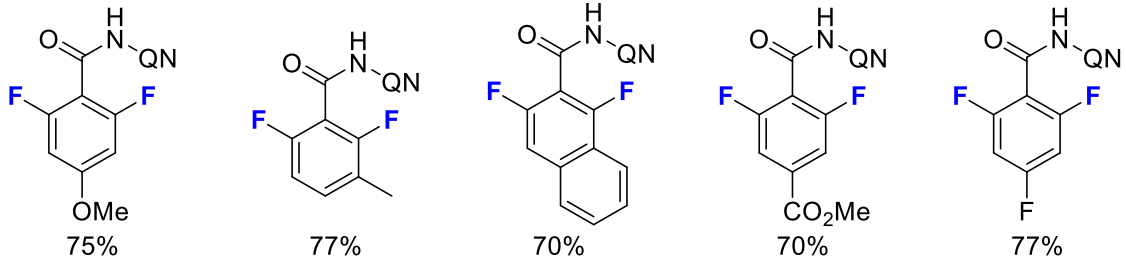
Copper Catalysed Fluorination *via* C-H activation



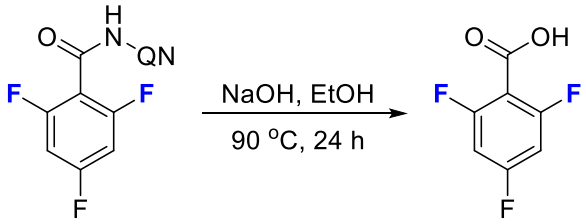
Without pyridine



With 2 eq. pyridine



Auxiliary Cleavage



Industrial Synthesis of Silver Fluoride

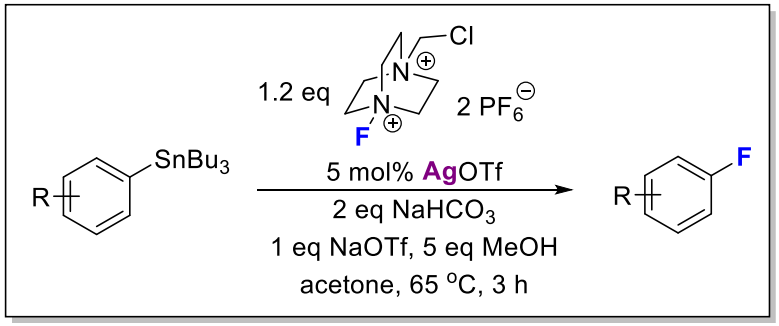
$Ag_2CO_3 + HF \xrightarrow{310\ ^oC} AgF + H_2O + CO_2$

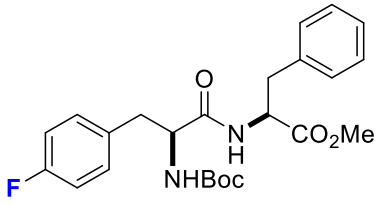
Aldrich : £1200 per mol

Daugulis *J. Am. Chem. Soc.* **2013**, *135*, 9342.

Silver for Fluorination

[A]





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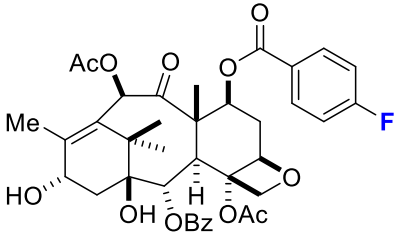

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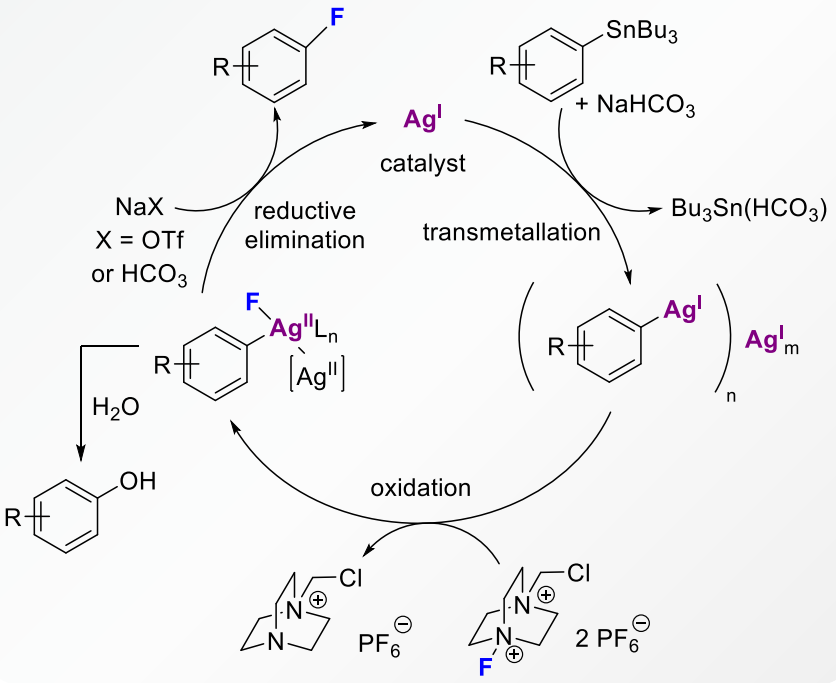
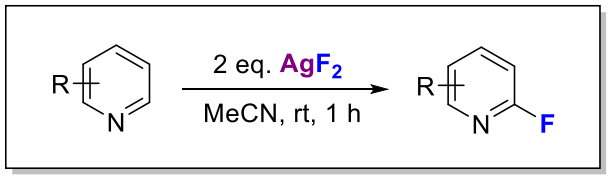
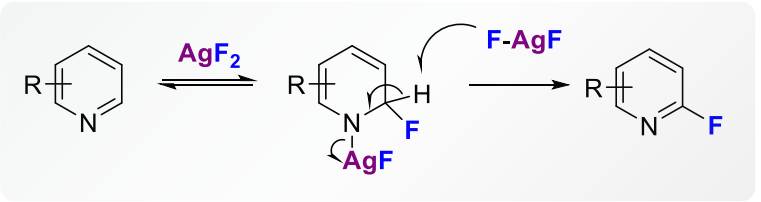
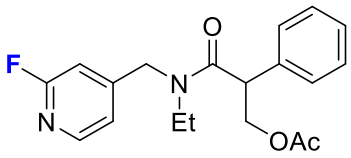


[B]







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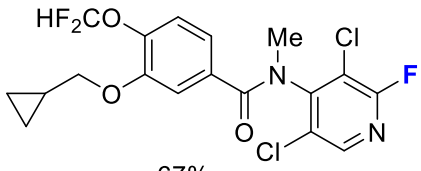

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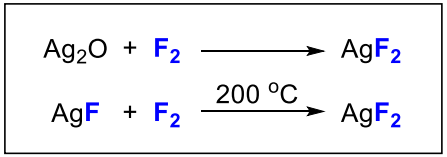
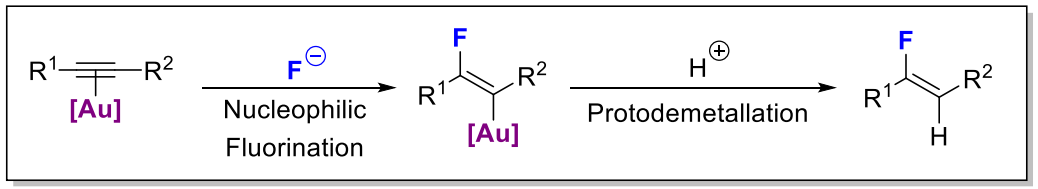
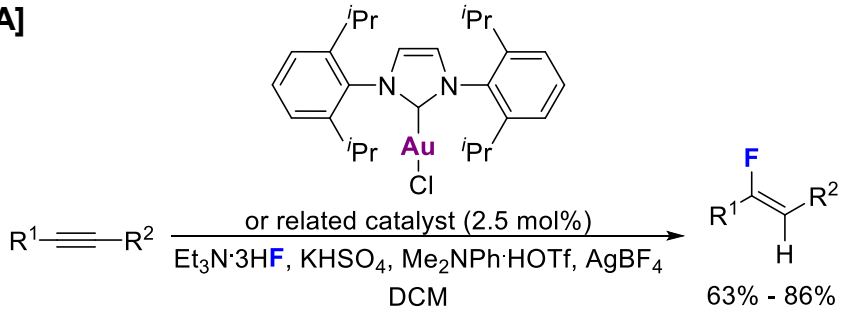


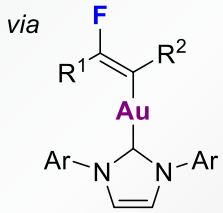
[A] Ritter *J. Am. Chem. Soc*. **2009**, *131*, 1662; *J. Am. Chem. Soc*. **2010**, *132*, 12150; *Org. Lett.* **2009**, *11*, 2860; **[B] Hartwig** *Science* **2013**, *342*, 956

Gold for Catalytic Fluorination



[A]





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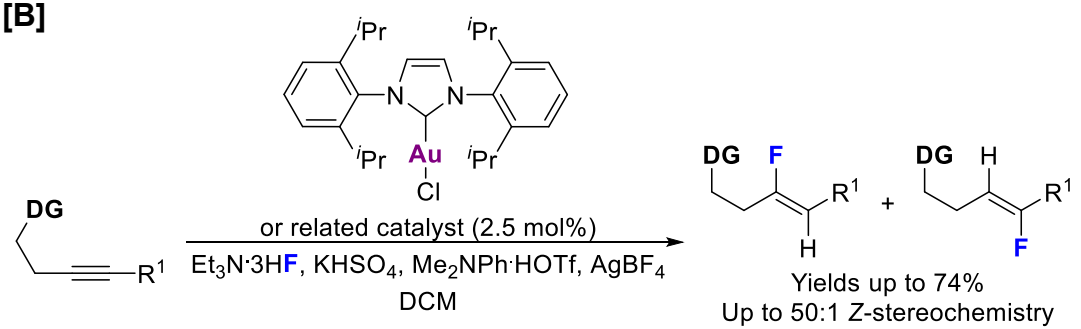
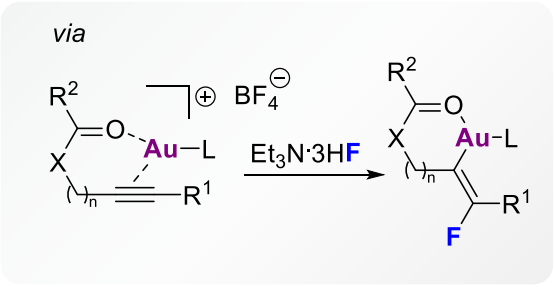
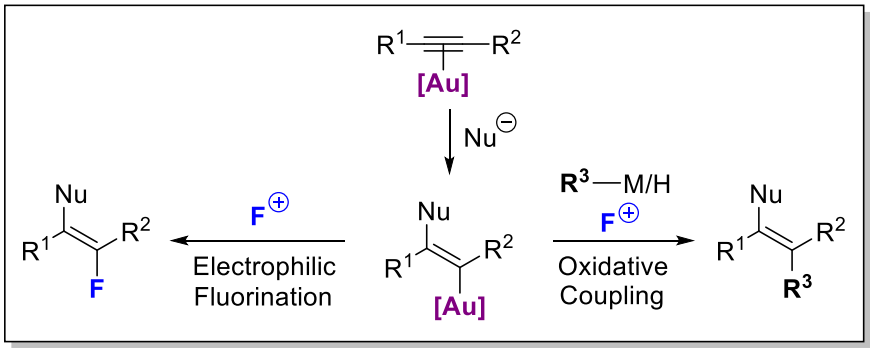


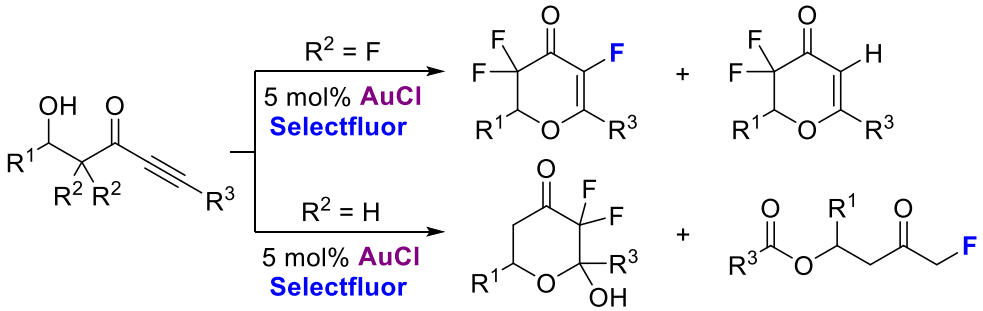


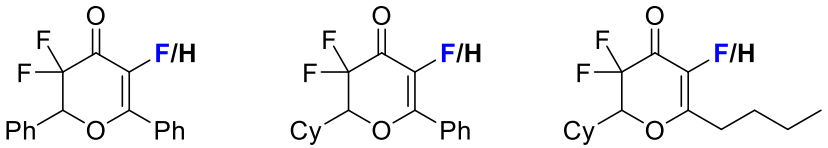
DG = Directing Group

Review : Gouverneur *Isr. J. Chem.* **2010**, *50*, 675; **[A] Sadighi** *J. Am. Chem. Soc.* **2007**, *129*, 7736; **[B] Miller** *Org. Lett.* **2009**, *11*, 4318.

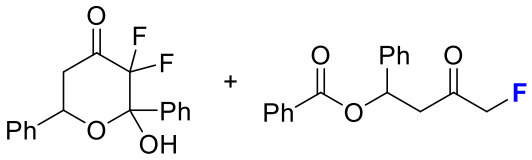
Gold for Catalytic Fluorination



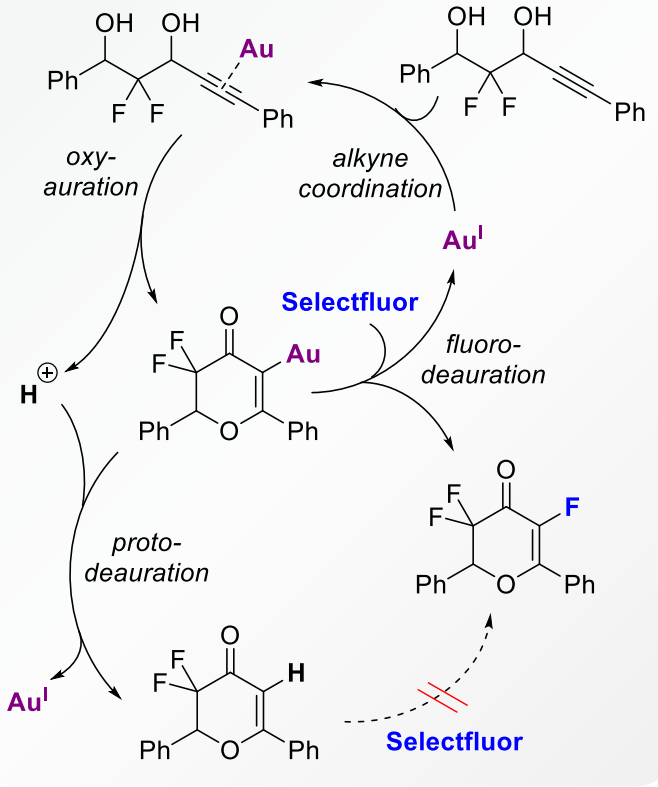




20%/33% (F/H) 20%/15% (F/H) 27%/37% (F/H)

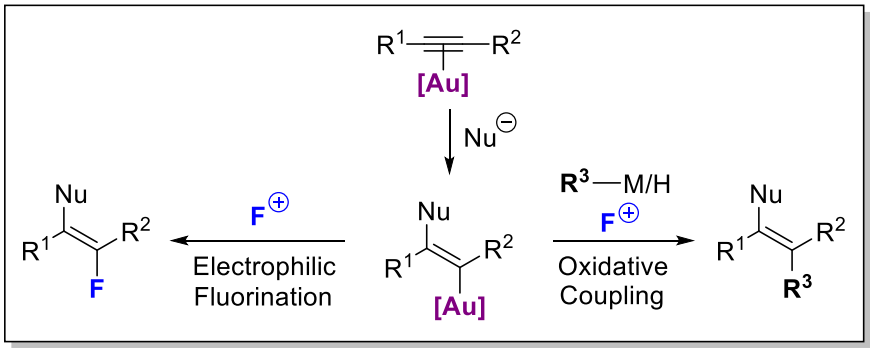


50% : 13%

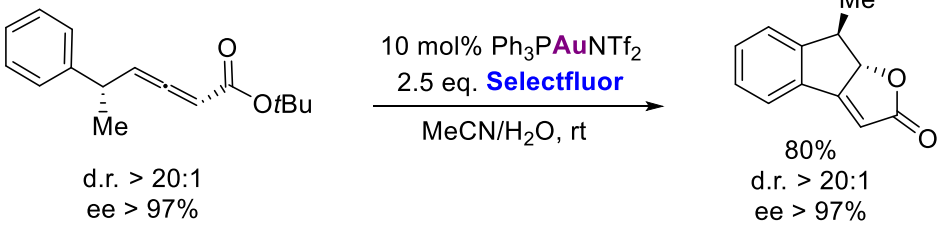


Gouverneur *Angew. Chem. Int. Ed.* **2008**, *47*, 7927; *Chem. Eur. J.* **2011**, *17*, 8248.

Gold for Catalytic Fluorination

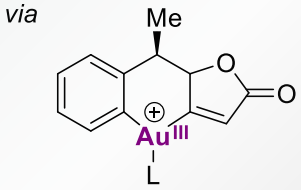


[A]

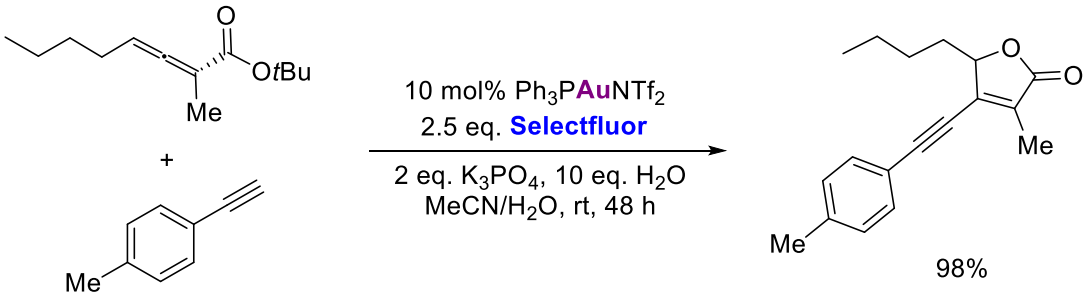


d.r. > 20:1
ee > 97%

80%
d.r. > 20:1
ee > 97%



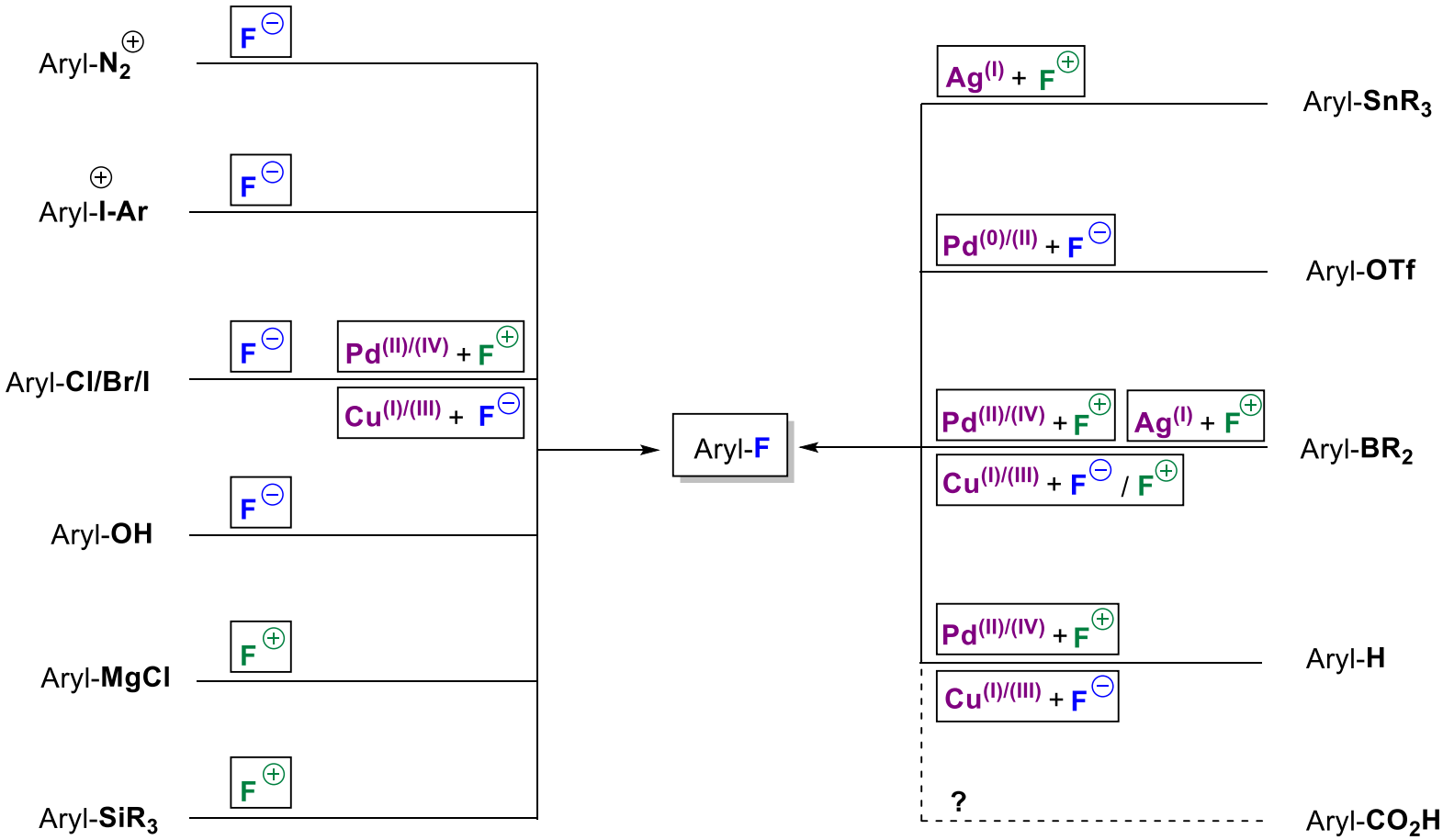
[B]



98%

Review: Gouverneur *Chem. Eur. J.* **2011**, *17*, 8248; *Isr. J. Chem.* **2010**, *50*, 675; **[A] Gouverneur** *Chem. Eur. J.* **2010**, *16*, 4739; **[B] Gouverneur** *Org. Lett.* **2010**, *12*, 4904.

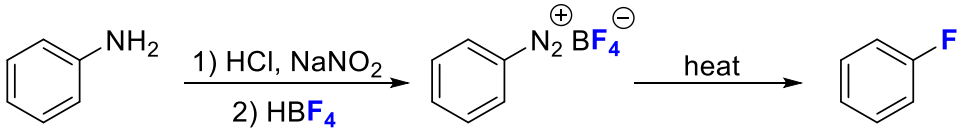
Aromatic Fluorination – the State of Play



Gouverneur *Angew. Chem. Int. Ed.* **2009**, *48*, 8610; *Chem. Commun.* **2012**, 48, 2929; **Ritter** *Angew. Chem. Int. Ed.* **2013**, *52*, 8214; *Chem. Rev.* **2015**, *115*, 612.

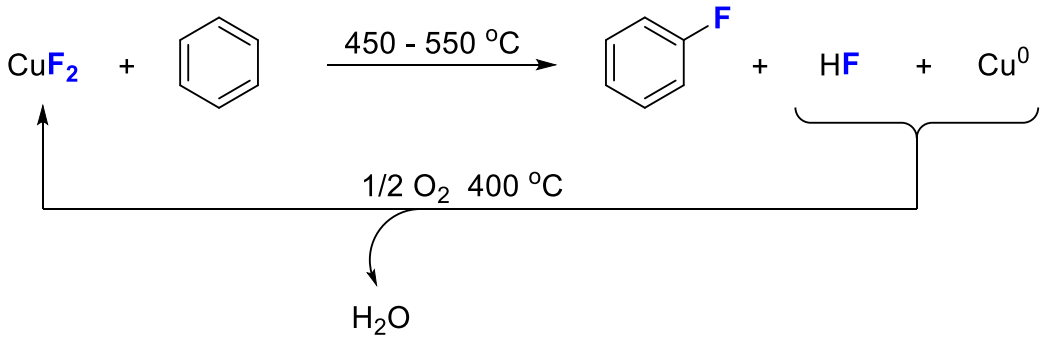
Copper for Fluorination

[A] Typical synthetic route in industrial-scale manufacture of fluorobenzene



produces large quantities of waste ($NaBF_4$ and NaCl)

[B] "Greener" Method



[A] Balz & **Schiemann** *Chem. Ber.* **1927**, *60*, 1186; **[B] Subramanian** *Science* **2002**, *297*, 1665**.**

Csp^3 - F Bond Construction: Challenges and Solutions

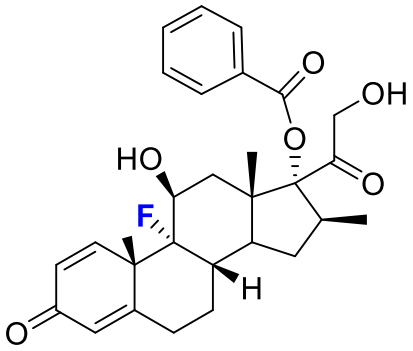
Véronique Gouverneur
University of Oxford
Chemistry Research Laboratory

BOSS XV
Tetrahedron Chair - Lecture 2
July 2016

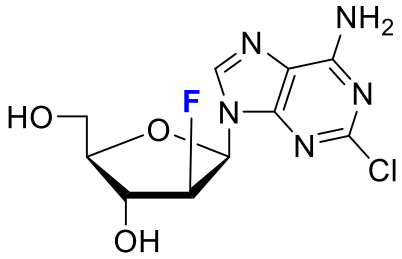
Contents

- Fluorination α to Carbonyl Groups
- Fluorination of Alkenes
- Fluorination of Alkyl Precursors
- Hydrogen Bonded Homoleptic Fluoride-Alcohol and Fluoride-Urea Complexes

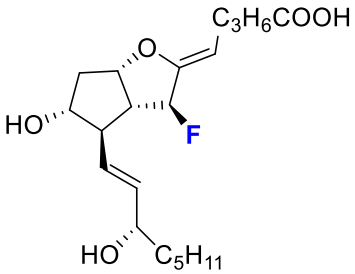
Fluorination in Drug Development



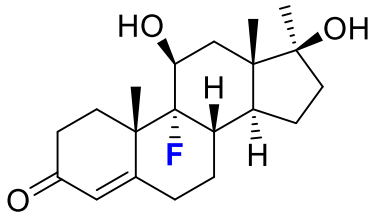
Betamethasone Benzoate
Glucocorticoid



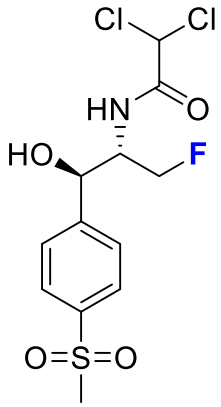
Clofarabine
Anti-metabolite



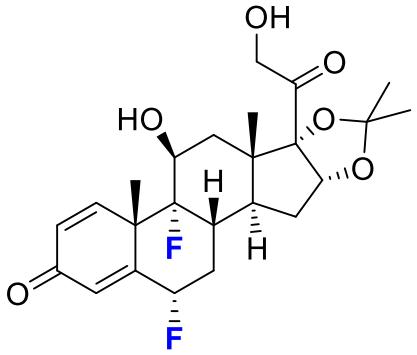
7-F-PGI2
Prostacyclin Receptor



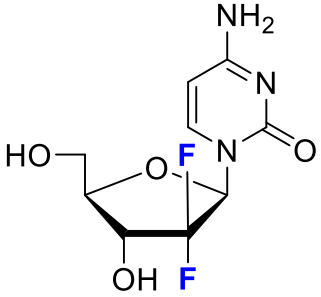
Fluoxymesterone
Anabolic agent



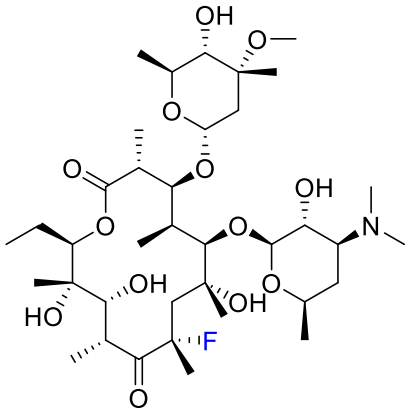
Florfenicol
Antibacterial agent



Fluocinolone Acetonide
Anti-inflammatory



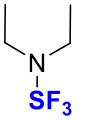
Gemcitabin
Antineoplastic agent
Antiviral agent

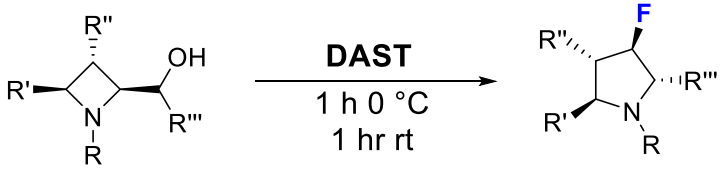


Fluorithromycin (Ritro)
Macrolide Antibiotic

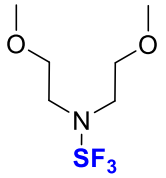
Nucleophilic Fluorination of Alkyl Groups

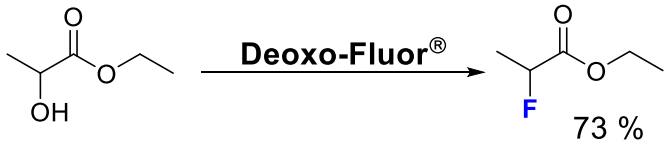
[A] DAST



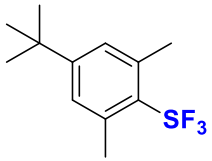


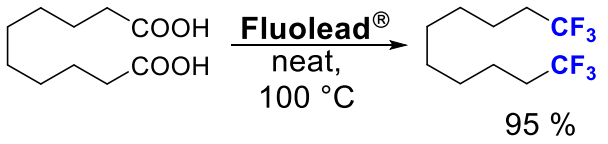
[B] DeoxoFluor®



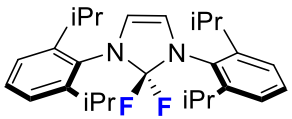


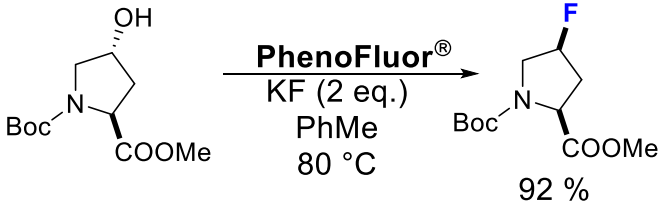
[C] Fluolead®



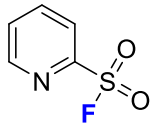


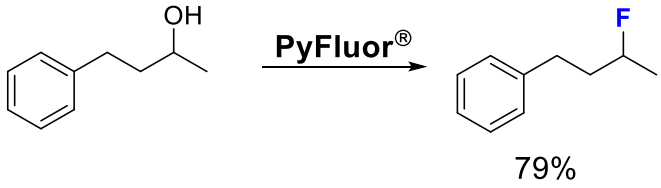
[D] PhenoFluor®



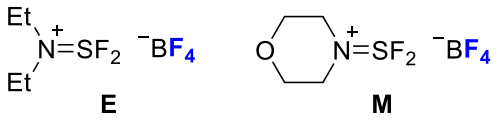


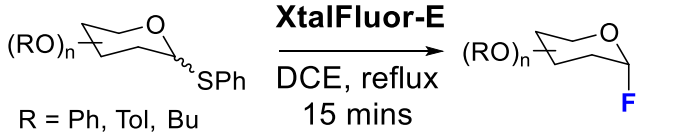
[E] PyFluor®





[F] XtalFluor-E/ XtalFluor-M

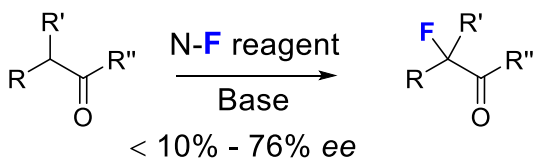


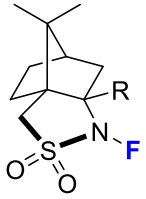


[A] Cossy *Synlett.* **2007**, *2,* 263*; Synlett.* **2008**, *9,* 1345; **[B] Lal** *J. Org. Chem*. **1999,** *64*, 7048; **[C] Umemoto** *J. Am. Chem. Soc.* **2010**, *132,* 18119; **[D] Ritter** *J. Am. Chem. Soc.* **2011**, *133,* 11482; **[E] Doyle** *J. Am. Chem. Soc.* **2015**, *133*, 11482; **[F] Davies** *Chem. Rev.* **2015**, *115,* 566*;* See Also **Fujimoto** *Angew. Chem. Int. Ed*. **2016 DOI**: 10.1002/anie.201603426.

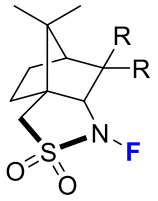
Chiral N-F Reagents

[A] Differding, Lang, Davis, [B] Shibata, [C] Takeuchi

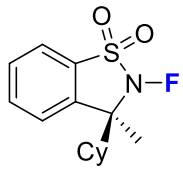




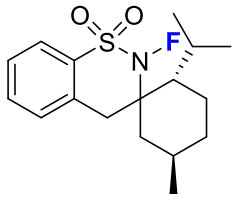
R = H, Me



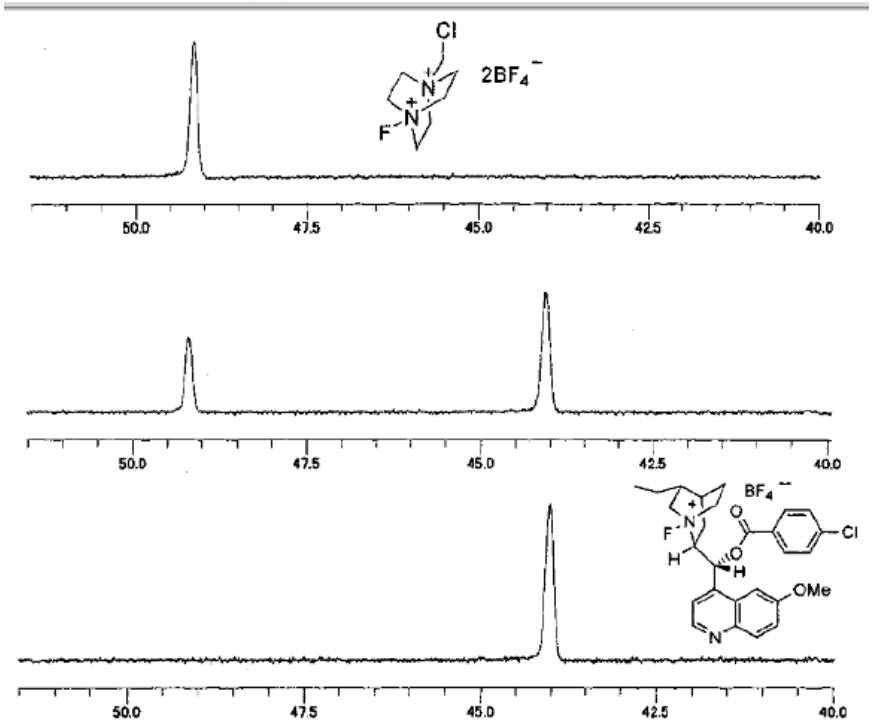
R = H, Cl, OMe

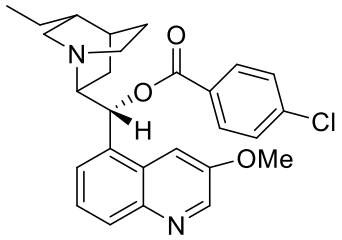


CMIT-F

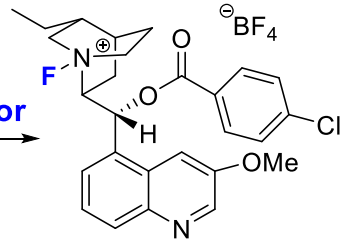


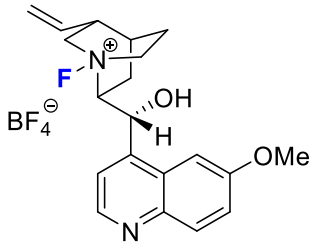
[D] Shibata &Takeuchi, Cahard



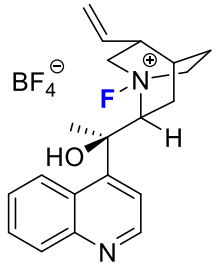


SelectFluor





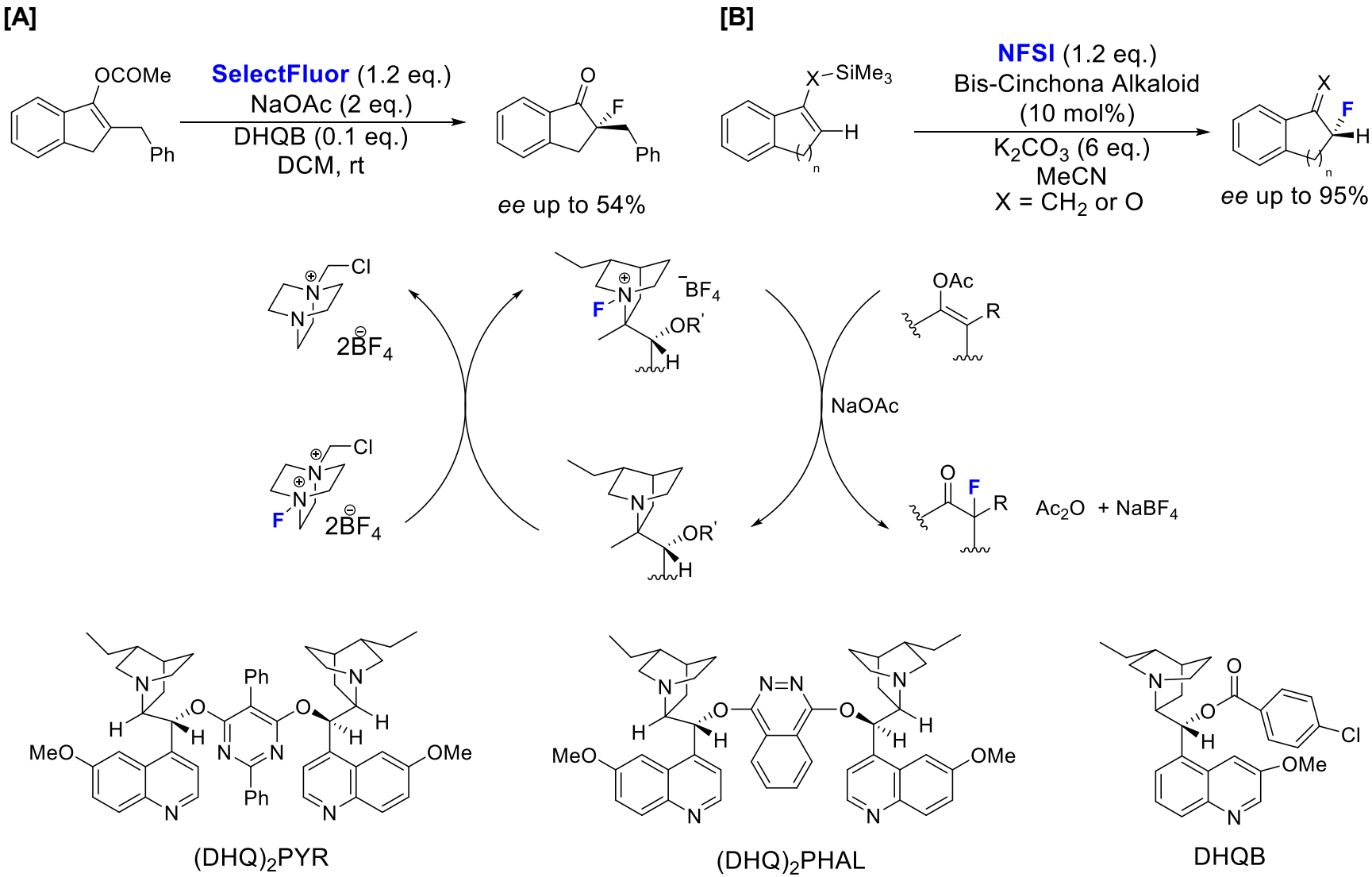
NF-Q-BF_4



F-CD-BF_4

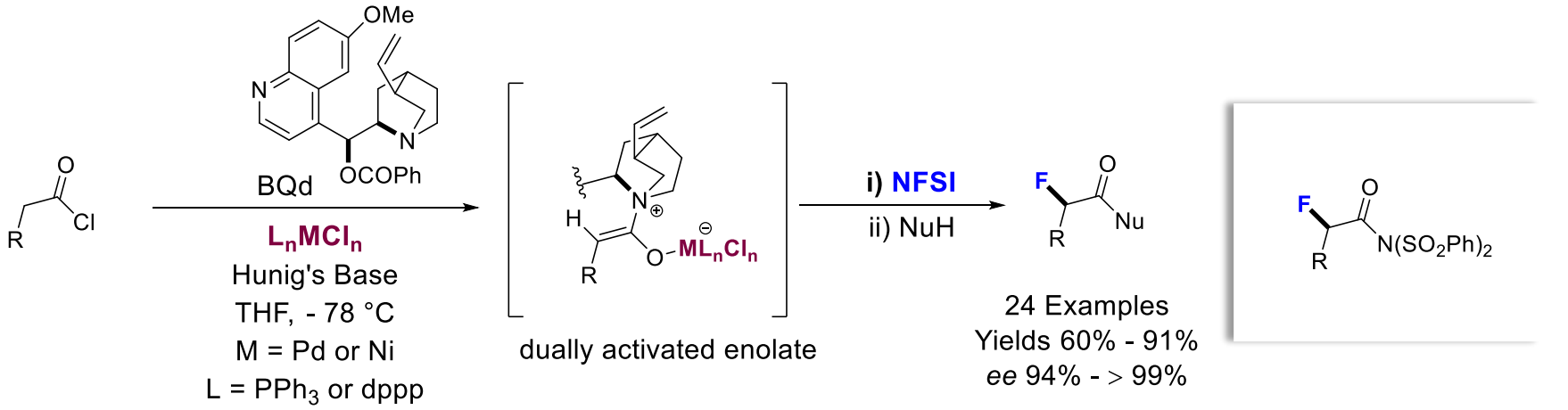
[A] Differding & Lang *Tetrahedron Lett*. **1988**, *29*, 6087; **Davis** *Tetrahedron Lett*. **1993**, *34*, 3971; **[B] Shibata** *J. Org. Chem*. **1999**, *64*, 5708; *Chem. Pharm. Bull*. **2000**, *48*, 1954; **[C] Takeuchi** *J. Org. Chem*. **2000**, *65*, 7583; **[D] Takeuchi** *J. Am. Chem. Soc*. **2000**, *122*, 10728**; Shibata** *J. Am. Chem. Soc*. **2001**, *123*, 7001; **Cahard** *Org. Lett*. **2000**, *2*, 3699.

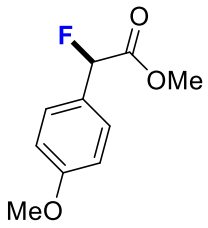
Discovery of Organocatalysed Fluorination



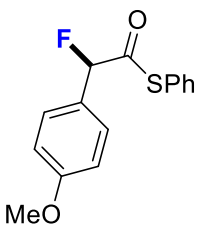
[A] Shibata *J. Fluorine Chem*. **2006**, *127*, 548; **[B] Shibata** *J. Am. Chem. Soc*. **2001**, *123*, 7001; *Angew. Chem. Int. Ed*. **2008**, *47*, 4157.

Fluorination α- to Carbonyl Groups Involving Multiple Catalysts

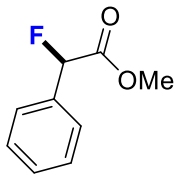




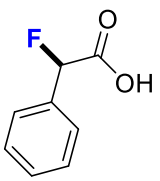
83%, *ee* 99%



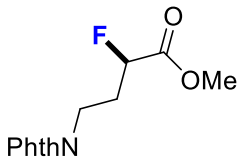
67%, *ee* 98%



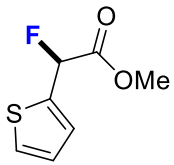
61%, *ee* 99%



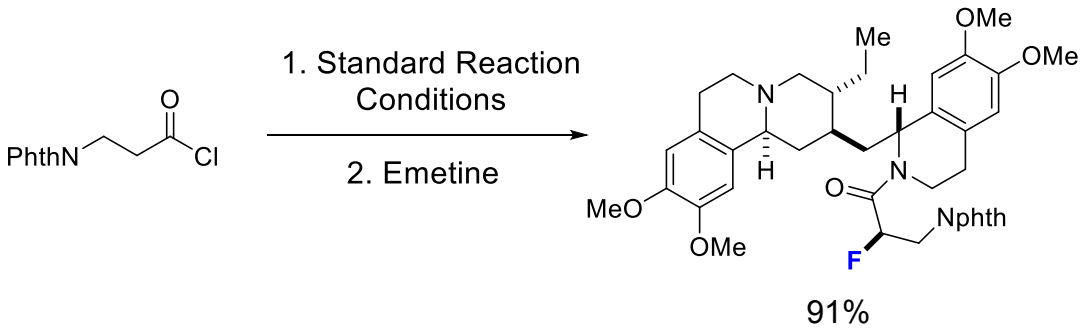
60%, *ee* 99%



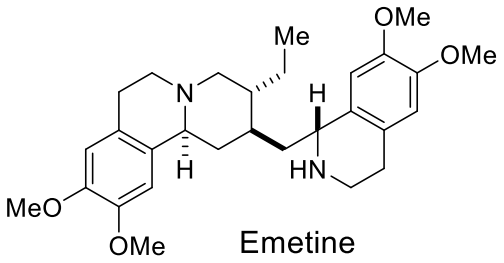
74%, *ee* 99%



69%, *ee* 99%



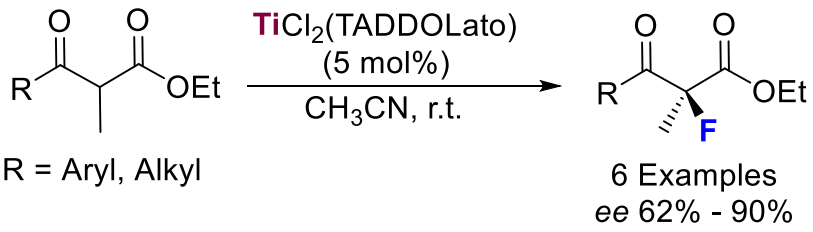
91%

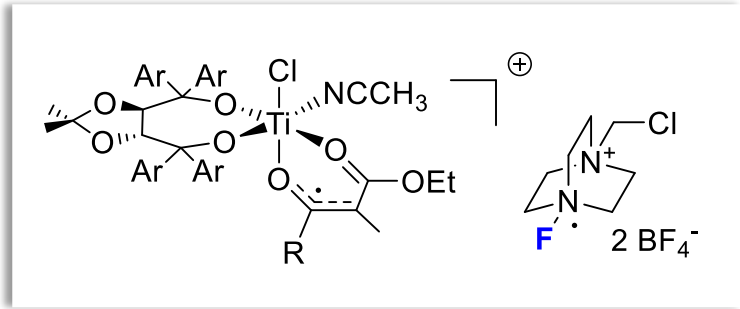


Lectka *J. Am. Chem. Soc.* **2008**, *130*, 17260.

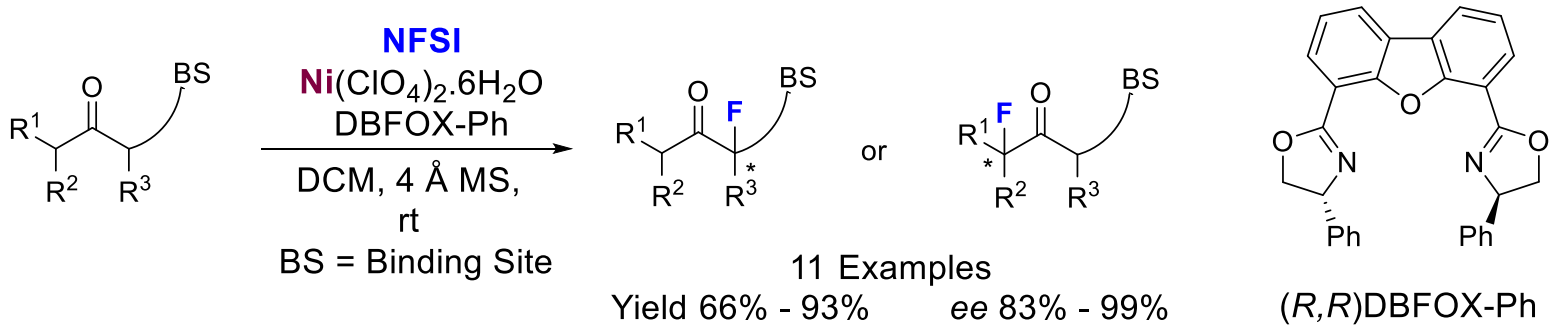
Metal Catalysed Electrophilic Fluorination α- to Carbonyl Groups

[A]

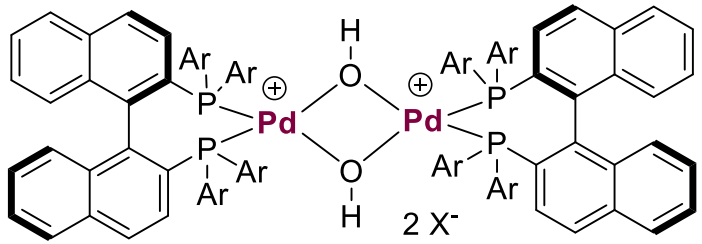




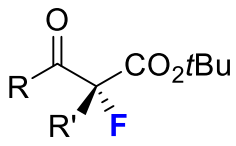
[B]

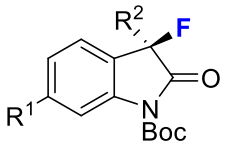


[C]



Ar = Phenyl **(*R*)-BINAP**
Ar = 3,5-dimethylphenyl **(*R*)-DM-BINAP**
X = BF_4 or OTf

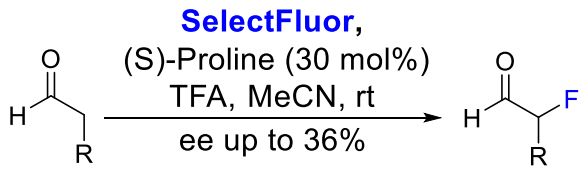


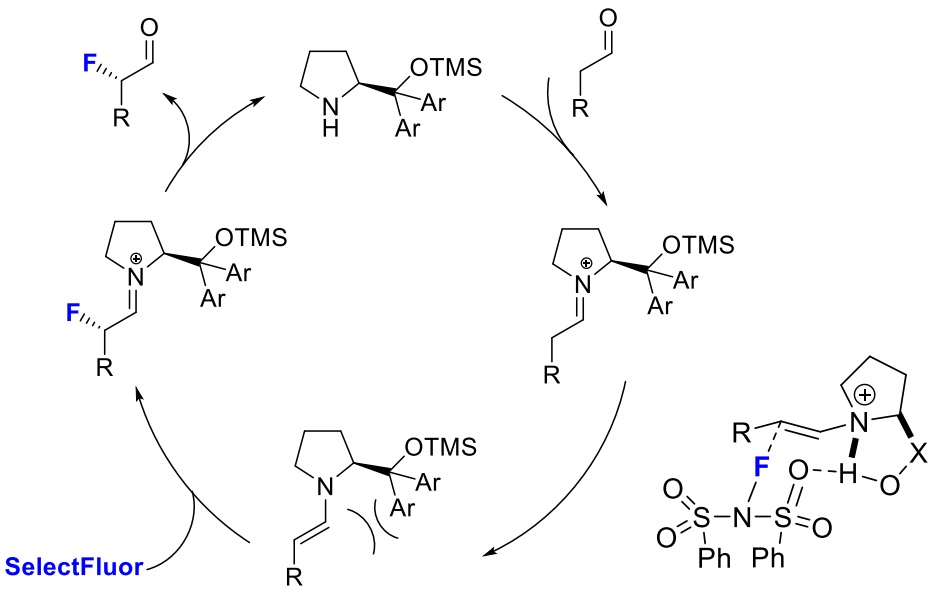


[A] Togni *Angew. Chem. Int. Ed.* **2000**, *39* ,4359; *Tetrahedron*, **2005**, *62*, 7180; **[B] Shibata** *Angew. Chem. Int. Ed.* **2005**, *44*, 4204; **[C] Sodeoka** *J. Am. Chem. Soc.* **2002**, *124*, 14530; **Sodeoka** *J. Am. Chem. Soc.* **2005**, *127,* 10164; **Kim** *Tetrahedron. Lett.* **2005**, *46*, 3115; **Kim** *Org. Lett.* **2005**, *7*, 2309; See Also; **Cahard** *Tetrahedron: Asymmetry.* **2004**, *15*, 1007; **Togni** *Organometallics* **2007**, *26*, 5902.

Organocatalysed Electrophilic Fluorination - Enamines

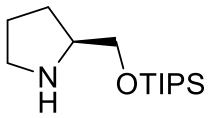
[A]





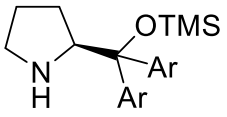
Transition State

[B]



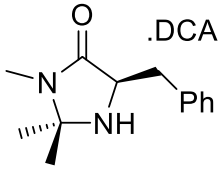
ee up to 66%

[C]



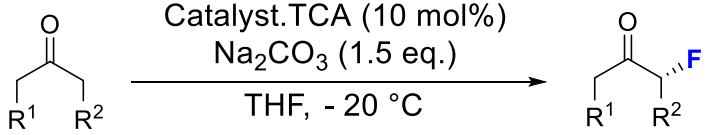
Ar = Ph-3,5-$(CF_3)_2$
ee up to 97%

[D]

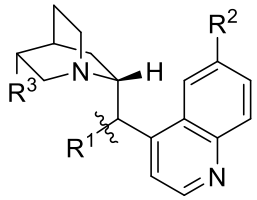


ee up to 99%

[E]



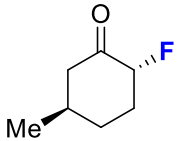
ee up to 99%



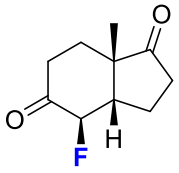
Catalyst. TCA

R^1 = NH$_2$, R^2 = OMe, R^3 = CH_2CH_3

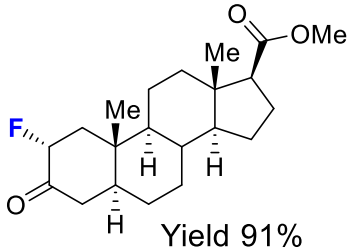
R^1 = NH$_2$, R^2 = H, R^3 = $CHCH_3$



Yield 69%
99:1 dr



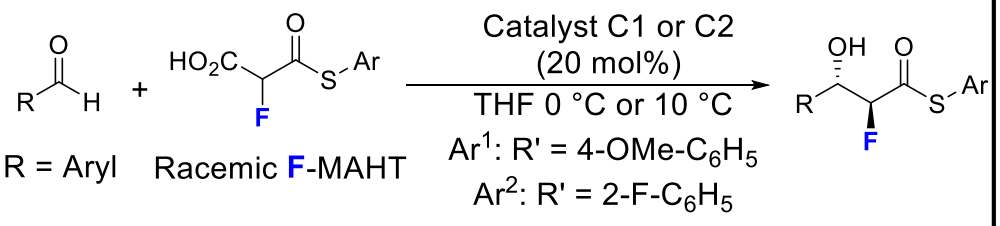
Yield 74%
98 : 2 dr



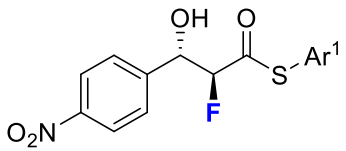
Yield 91%
95 : 5 dr

[A] Enders *Synlett* **2005**, *6*, 991; **[B] Barbas III** *Angew. Chem. Int. Ed*. **2005**, *44*, 3706; **[C] Jorgensen** *Angew. Chem. Int. Ed*. **2005**, *44*, 3703; **[D] MacMillan** *J. Am. Chem. Soc*. **2005**, *127*, 8826; **[E] MacMillan** *J. Am. Chem. Soc*. **2011**, *133*, 1738; **Houk** *J. Am. Chem. Soc.* **2014**, *136*, 9556.

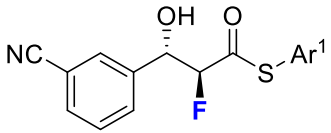
Enantioselective Aldol reactions



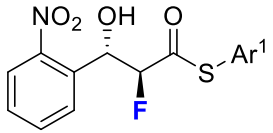
R = Aryl Racemic **F**-MAHT



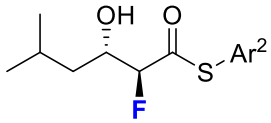
81%, d.r 5:1, *ee* 99%



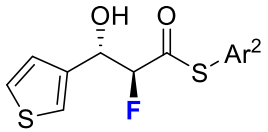
99%, d.r 6:1, *ee* 94%



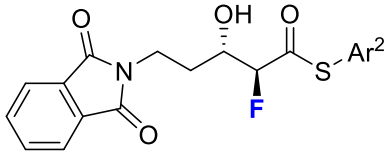
85%, d.r 4:1, *ee* 95%



45%, d.r 12:1, *ee* 62%

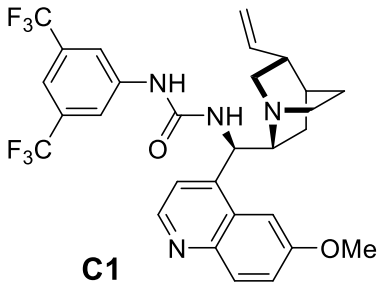


59%, d.r 10:1, *ee* 83%

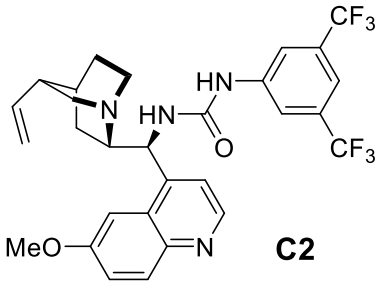


82%, d.r 8:1, *ee* 85%

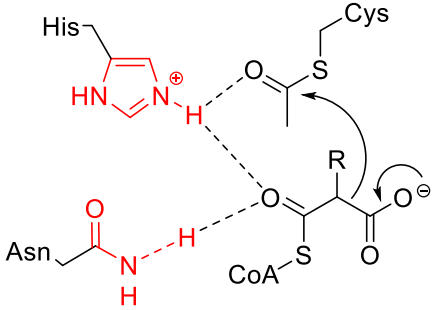
Wennemers *Nat. Chem.* **2016**, *8*, 276.



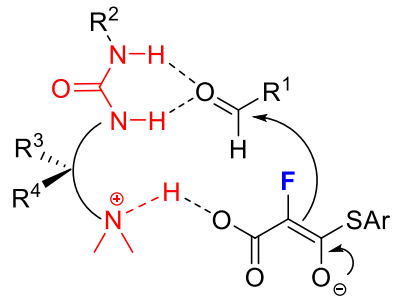
C1



C2



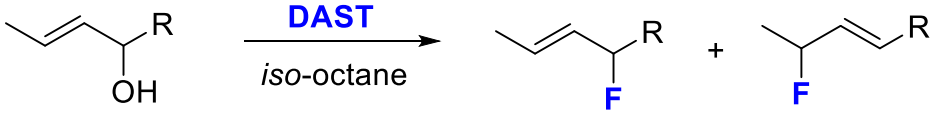
Polyketide synthase
R = H or CH_3



Synthetic Catalyst

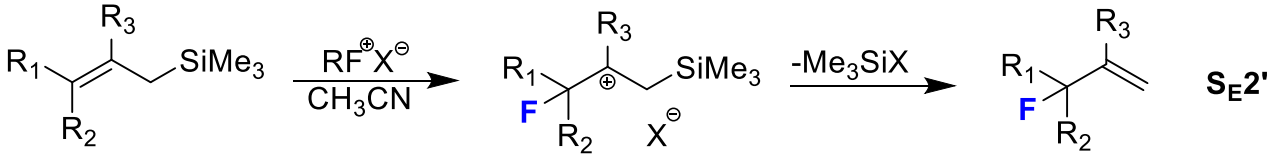
Electrophilic Fluorodesilylation of Allylsilanes

Nucleophilic Fluorination

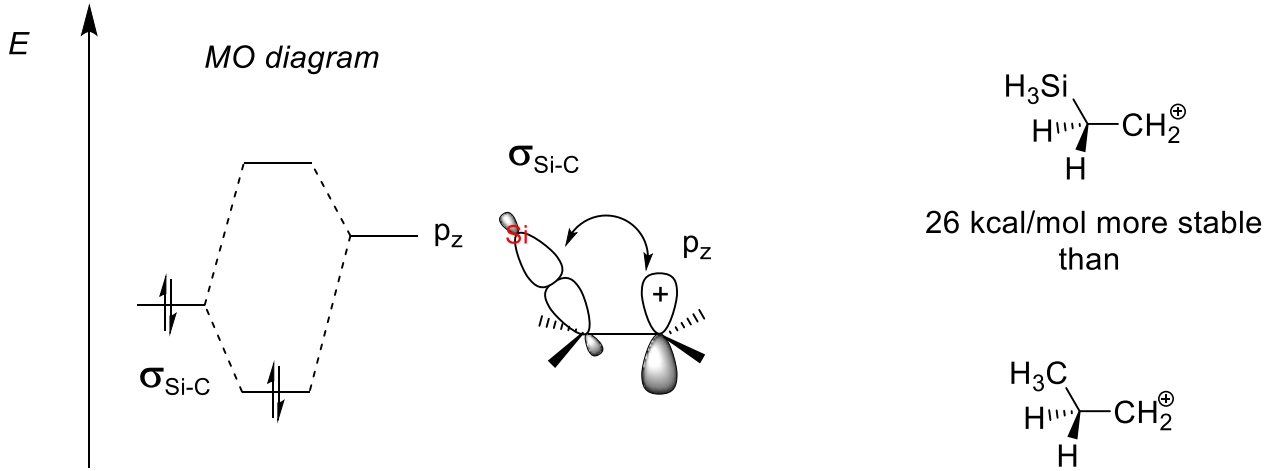


R = H Ratio 2:3
R = *i*-Pr Ratio 5:6

Electrophilic Fluorination



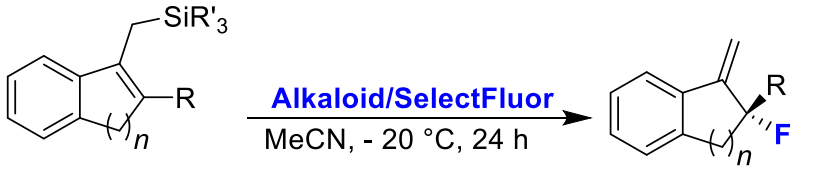
Fluorination: **SelectFluor** (1.2 eq.), $NaHCO_3$ (1.2 eq.)



Middelton *J. Org. Chem.* **1975**, *40*, 574; **Grée** *Tetrahedron. Lett.* **2007**, *48*, 5435; **Fleming** *Chem. Rev.* **1997**, *97*, 2063; **Jorgensen** *J. Am. Chem. Soc.* **1985**, *107*, 1496; **Gouverneur** *Chem. Rev.* **2008**, *108*, 1943; **Gouverneur** *Org. Lett.* **2003**, *5*, 4891; **Gouverneur** *Org. & Biomol. Chem.* **2004**, *2*, 1110; **Gouverneur** *Angew. Chem. Int. Ed.* **2003**, *42,* 3291.

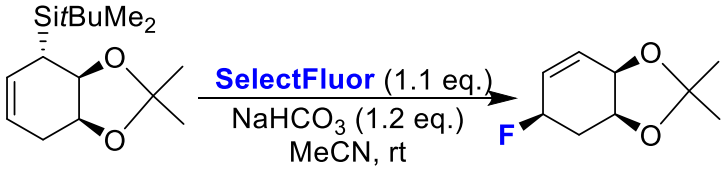
Fluorodesilylation of Allylsilanes

[A/B]



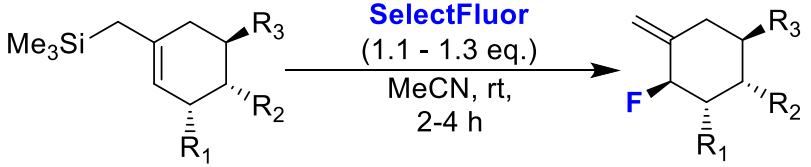
conversion > 95%
ee up to 96%

[C]



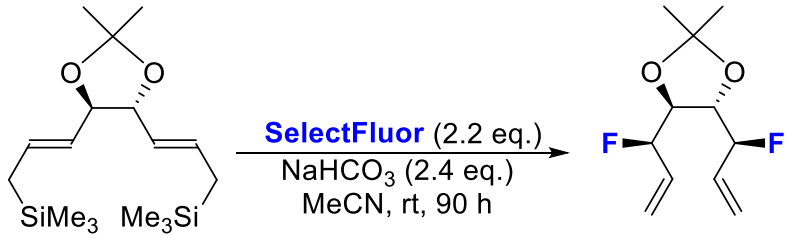
Yield 61 %
d.r. up to 69 : 31

[D]



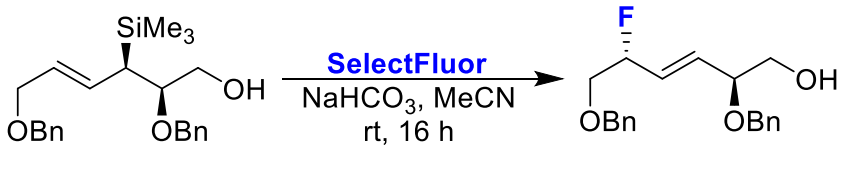
Yield 60% - 91 %
d.r. up to 20:1

[E]



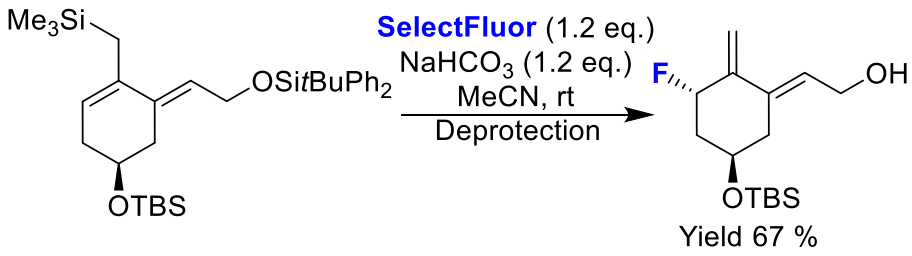
Yield 54%
d.r. 3:2.3:1

[F]



Yield 90 %
ee 93 %, d.r. > 20:1

[G]

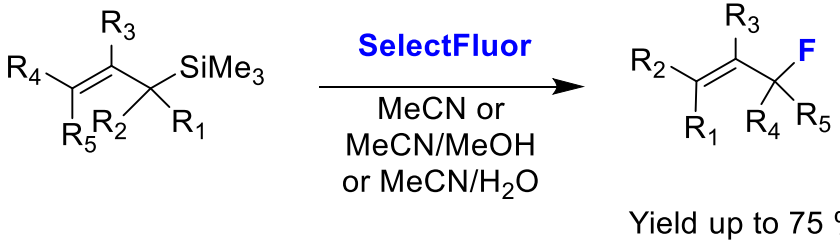


Yield 67 %

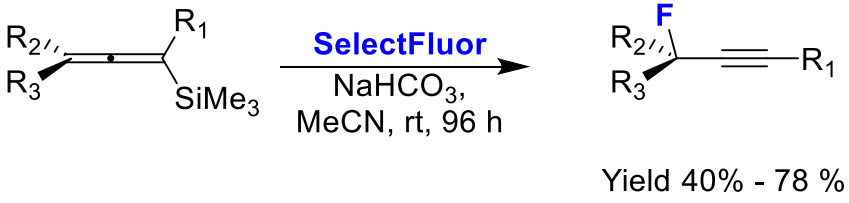
[A] Gouverneur *Angew. Chem. Int. Ed.* **2003**,42, 3291; **[B] Shibata** *Angew. Chem. Int. Ed*. **2008**, *47,* 4157; **[C] Gouverneur** *Chem. Eur. J*, **2006**, *12*, 9176; *Synlett*. **2007**, *7,* 1166; **[D] Gouverneur** *Angew. Chem. Int. Ed*. **2007**, *46*, 5106; *J. Am. Chem. Soc*. **2009**, *131*, 1947; **[E] Gouverneur** *Org. Lett*, **2008**, 4263; **[F] Gouveneur** *Tetrahedron: Asymmetry*, **2009**, *20*, 910; **[G] Gouverneur** *J. Org. Chem.* **2006**, *71*, 5361.

Electrophilic Fluorodesilylation of Organosilanes

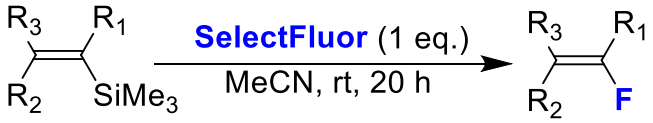
[A]



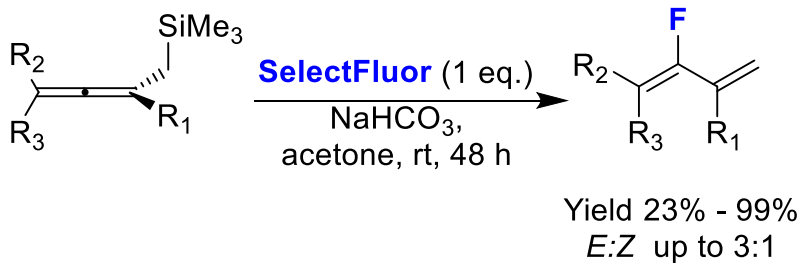
[B]

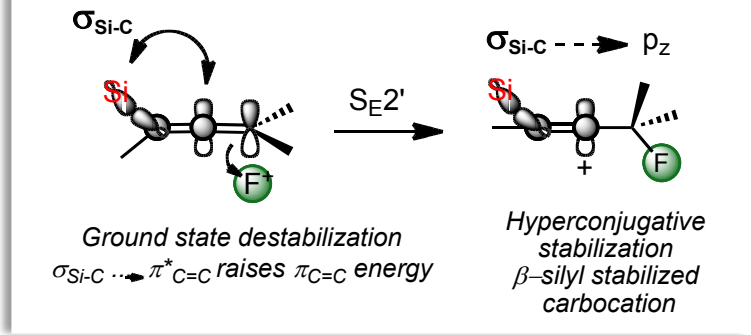


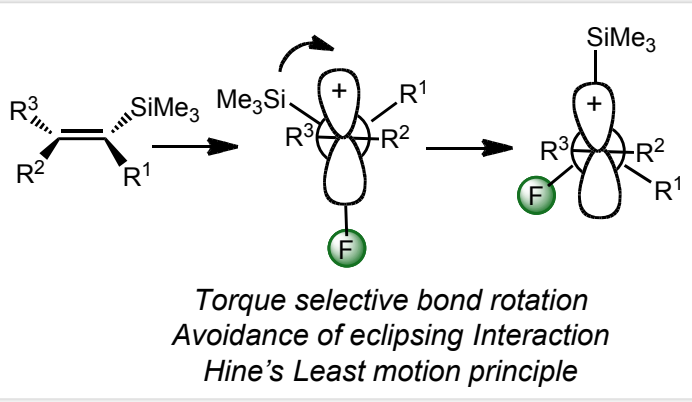
[C]



[D]



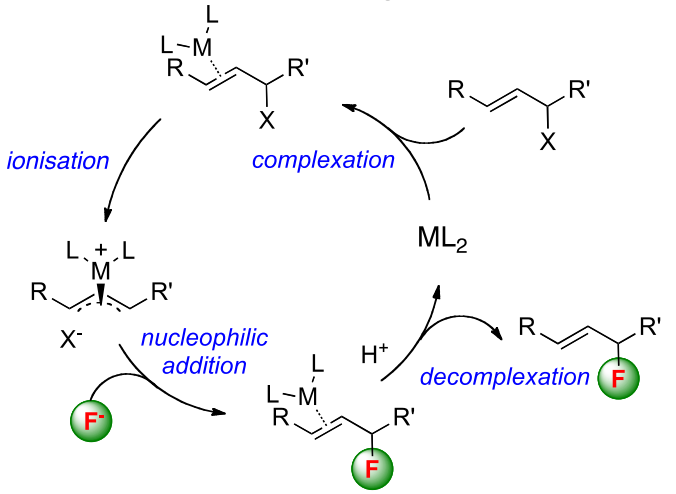




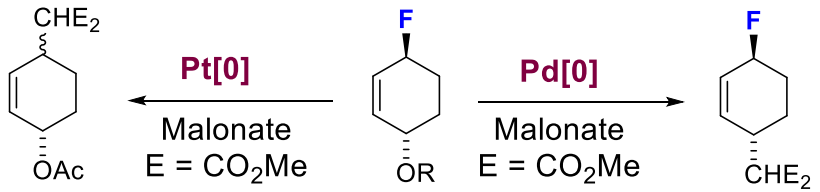
[A] Gouverneur *Chem. Eur. J*. **2002**, *7*, 766; **[B] Gouverneur** *Chem. Commun*. **2006**, 4113; *Org. Biomol. Chem*. **2008**, *6*, 1731;
[C] Gouverneur *Chem. Commun*. **2001**, 233; **[D] Gouverneur** *Org Lett*. **2005**, *7*, 1267.

Catalytic Nucleophilic Allylic Fluorination

[A]



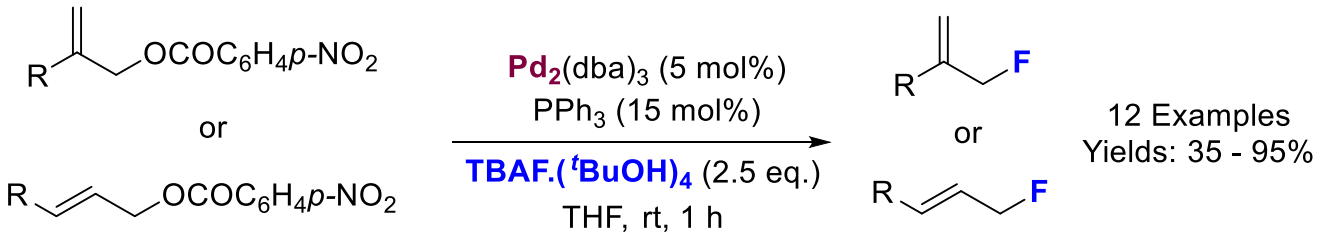
[B]



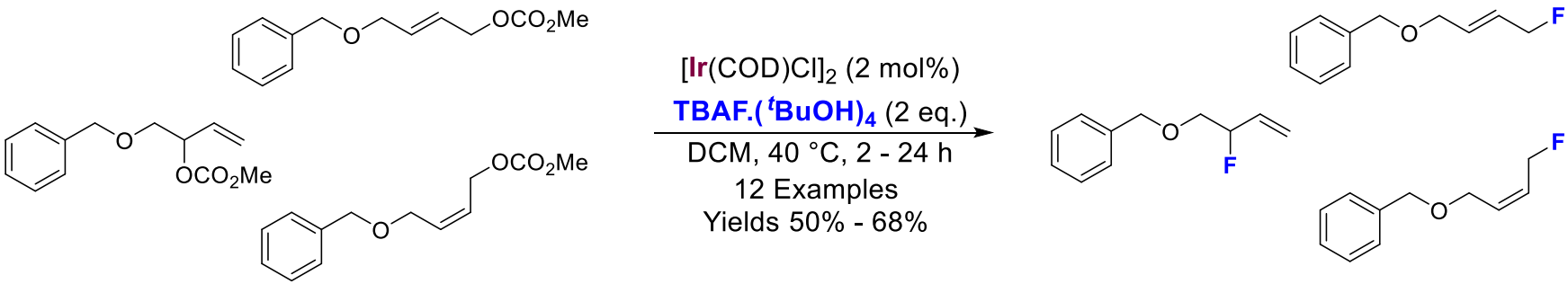
Pd(PPh$_3$)$_4$ OCO_2Me ~ $OCOC_6H_4NO_2$ > OBz ≅ F >> OAc

Pt(PPh$_3$)$_4$ F ≥ OCO_2Me >> OBz ≥ OAc

[C]



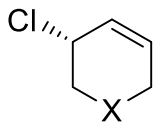
[D]



[A] Gouverneur *Angew. Chem. Int. Ed.* **2009**, *48*, 1296; **[B] Gouverneur & Brown** *Organometallics*, **2012**, *31*, 1408; **[C] Gouverneur** *Angew. Chem. Int. Ed.* **2011**, *50*, 2613; **[D] Gouverneur** *Chem. Sci.* **2013**, *4*, 89; See Also; **Gouverneur** *Angew. Chem. Int. Ed.* **2011**, *50*, 2613.

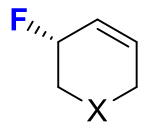
Catalytic Nucleophilic Allylic Fluorination

[A]

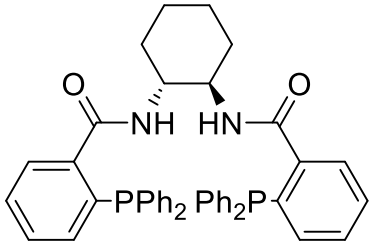


X = CH_2, CHR, NTs, O

$Pd_2(dba)_3$ (5 mol%)
Ligand (10 mol%)
AgF (1.1 eq.)
THF, rt, 24 h

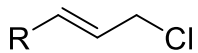


Yields 59% - 85%
ee up to 96%

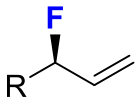


DACH-Phenyl

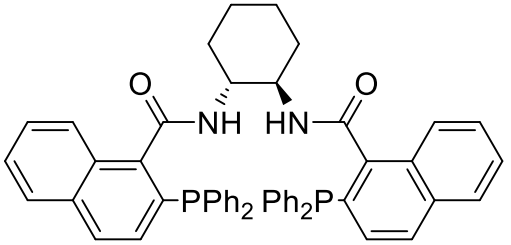
[B]



$Pd_2(dba)_3$ (5 mol%)
Ligand (10 mol%)
AgF (3 eq.)
PhMe, rt, 48 h

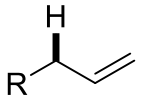


Yields 62% - 88%
ee up to 97%
> 20:1 d.r.

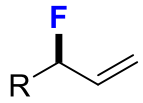


DACH-Naphtyl

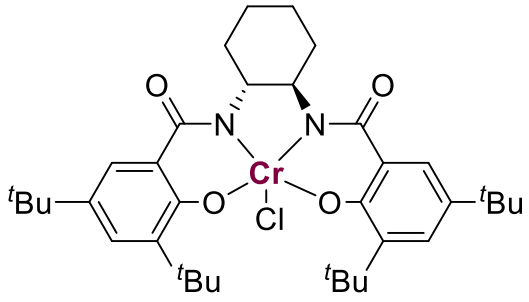
[C]



$Pd_2(TFA)_2$ (15 mol%)
(*R,R*)-(Salen)CrCl (10 mol%)
$Et_3N.3HF$ (6 eq.), BQ (2 eq.)
DCE, 23 °C, 72 h



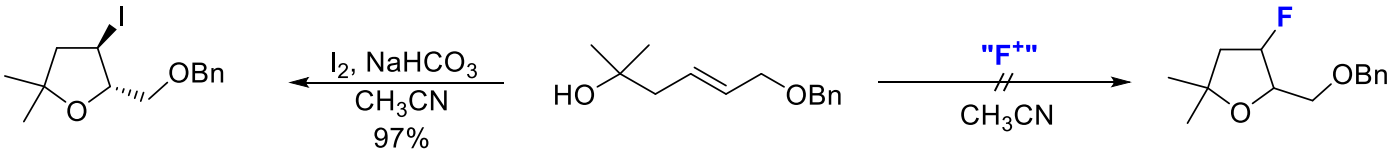
Yields 16% - 68%
Branched: Linear
7.8:1 to 1:20



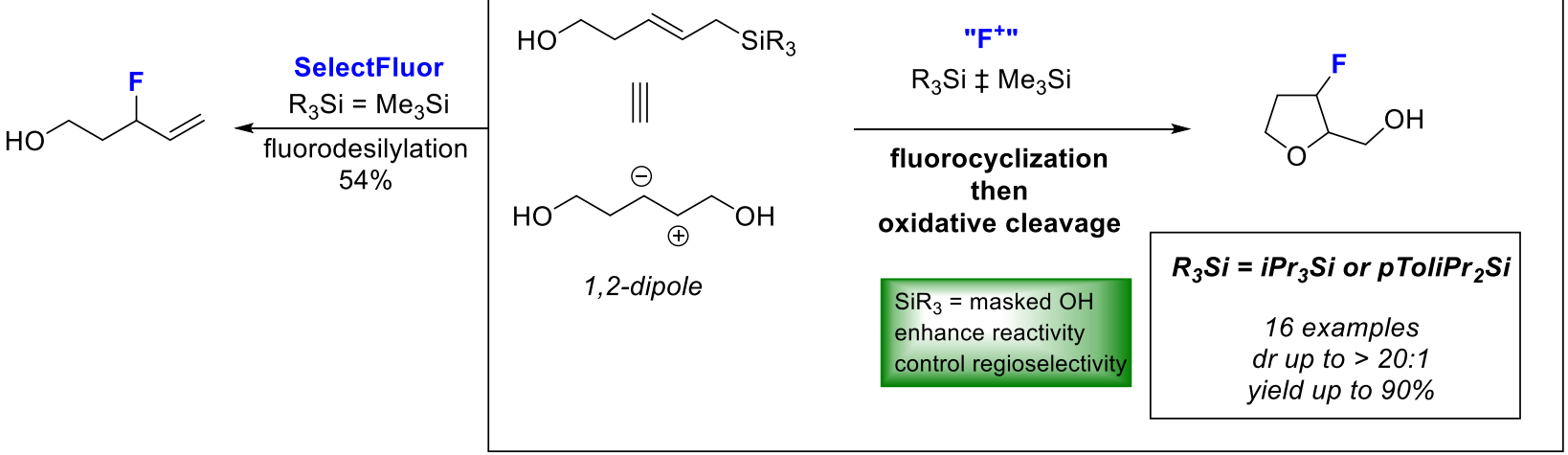
(*R,R*)-(Salen)CrCl

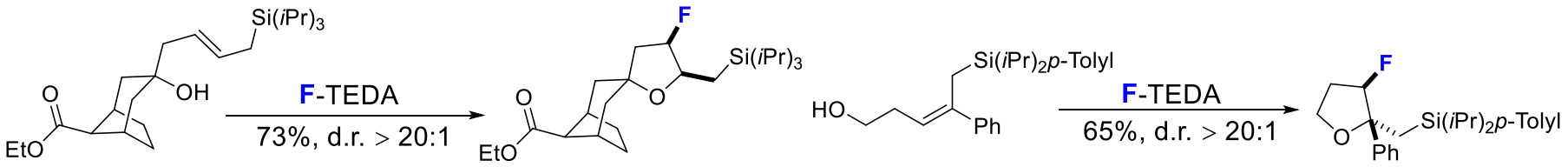
[A] Doyle *J. Am. Chem. Soc.* **2010**, *132*, 17402; **[B] Doyle** *J. Am. Chem. Soc.* **2011**, *133*, 15902; **[C] Doyle** *J. Am. Chem. Soc.* **2013**, *135*, 12990.

Fluorocyclisation



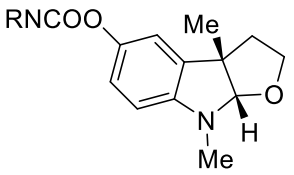
Novel Approach Fluorination-Cyclisation



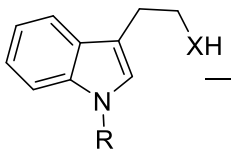


Gouverneur *Acc. Chem. Res.* **2014**, *47*, 3560; **Gouverneur** *Angew. Chem. Int. Ed.* **2003**, *42,* 3291; **Gouverneur** *Angew. Chem. Int. Ed.* **2009**, *48,* 7083; For Iodolactonisation of allylic fluorides see: **Gouverneur** *Angew. Chem. Int. Ed*. **2008**, *47*, 357.
For an isolated example of the fluoronium ion see; **Lectka** *Science* **2013**, *340, 57.*

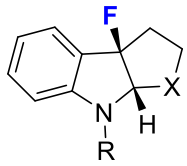
Enantioselective Organocatalytic Fluorocyclisation

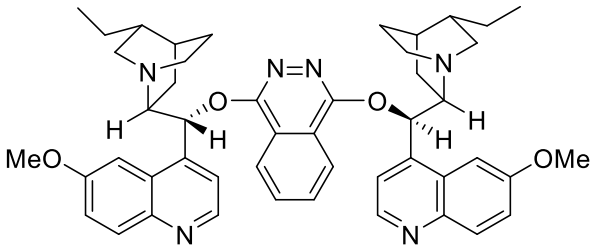


R = alkyl, aryl
(-)-Physovenine
(-)-Cymyl Carbamate
of Physovenol

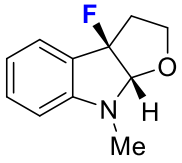


NFSI (1.2 eq.)
$(DHQ)_2PHAL$ (10 mol%)
K_2CO_3 (6 eq.)
acetone, - 78 °C

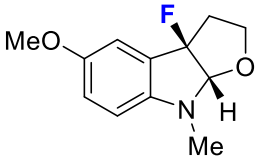




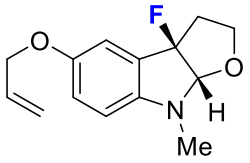
$(DHQ)_2PHAL$



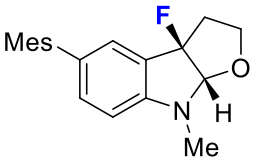
90%, 86% *ee*



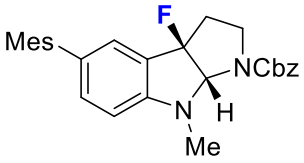
90%, 86% *ee*



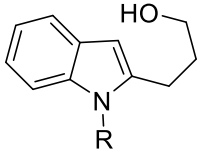
53%, 86% *ee*



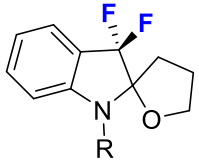
57%, 90% *ee*

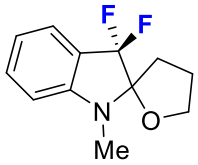


60%, 92% *ee*

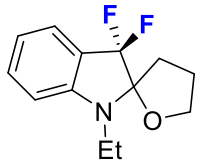


NFSI (1.2 eq.)
$(DHQ)_2PHAL$ (10 mol%)
K_2CO_3 (6 eq.)
acetone, - 78°C

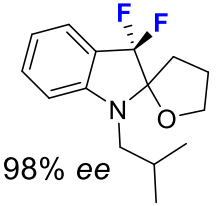




96% *ee*



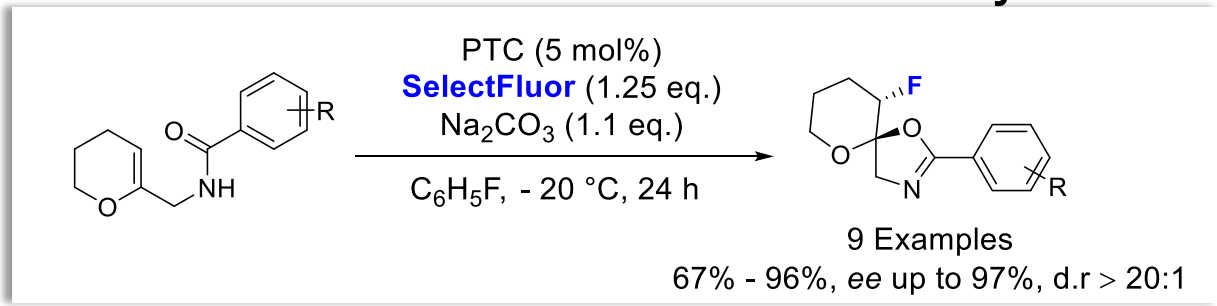
94% *ee*

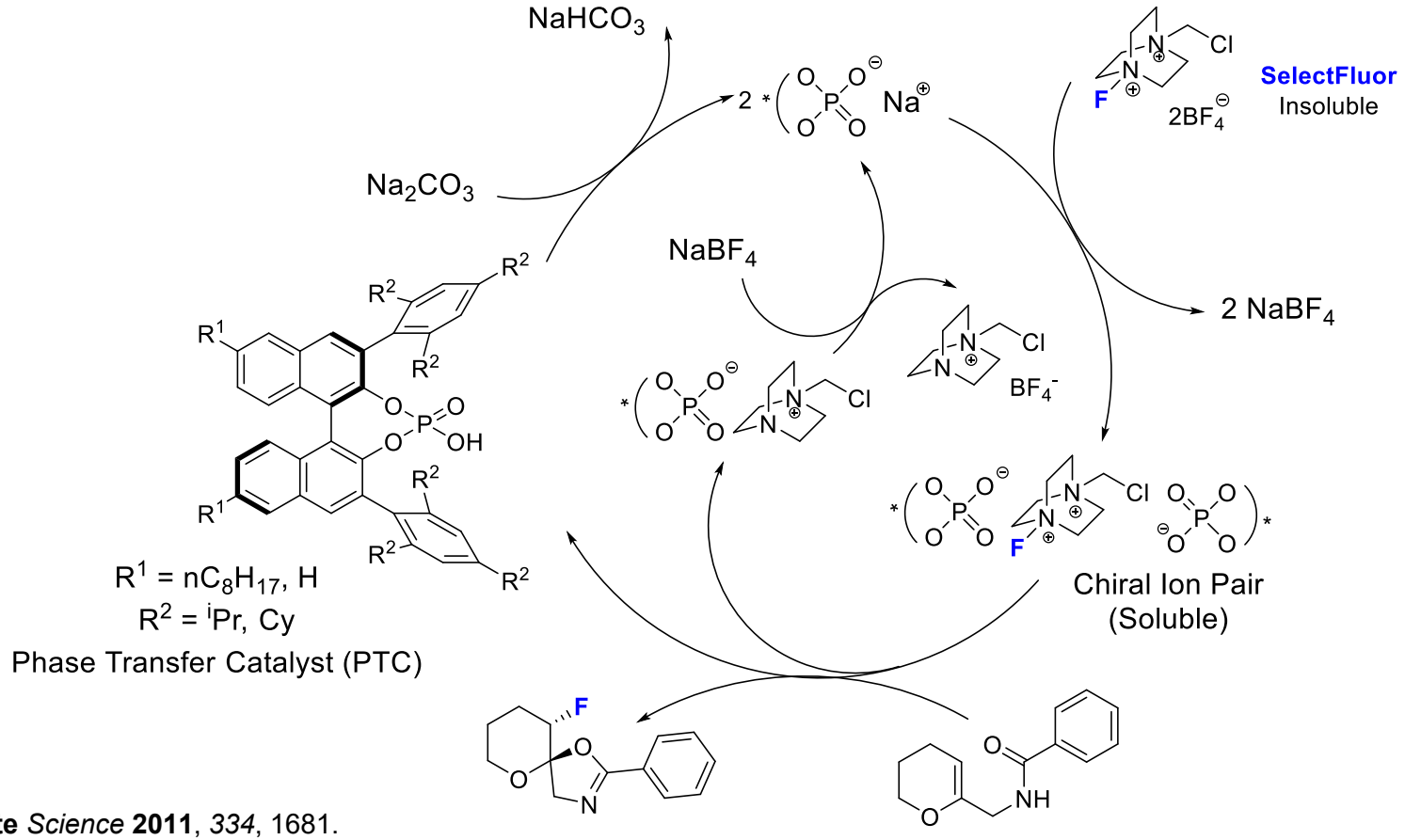


98% *ee*

Gouverneur *Angew. Chem. Int. Ed.* **2011**, *50*, 8105.

Anionic Phase Transfer Catalysis

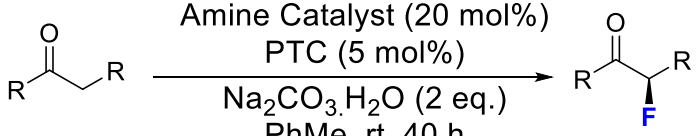




Toste *Science* **2011**, *334*, 1681.
For Examples of Cationic Phase Transfer See; **Kim** *J. Org. Lett*. **2002**, *4*, 545; **Maruoka** *Chem. Commun*. **2010**, *46*, 321; **Cahard** *J. Fluorine. Chem*. **2013**, *150*, 60; **Lu** *Tetrahedron Lett*. **2013**, *54*, 2623.

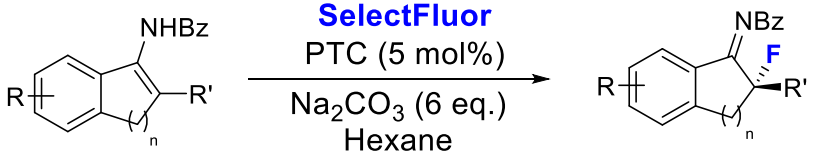
Anionic Phase Transfer Catalysis

[A]



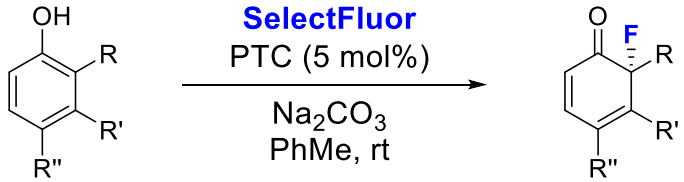
21 Examples, Yields 24% - 36%
ee up to 94%

[B]



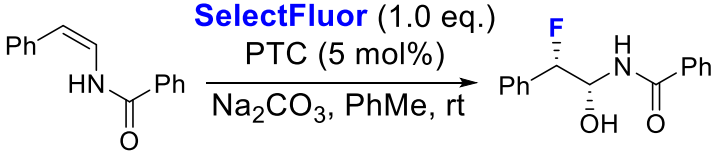
18 Examples
Yields 58% - 94%, *ee* up to 99%

[C]



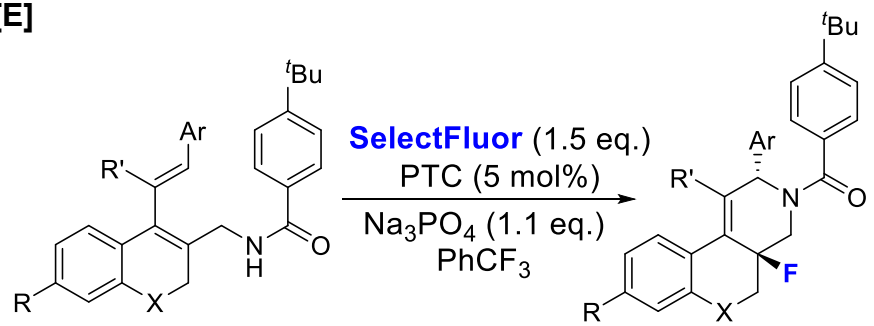
22 Examples
Yields 28% - 97%, *ee* up to 97%

[D]



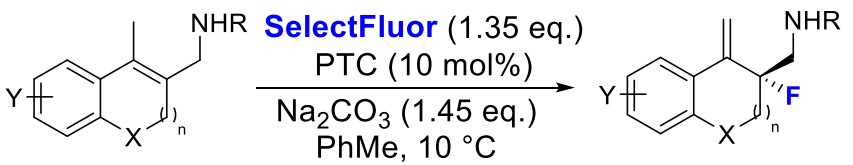
15 Examples, Yields 52% - 86%
up to 98% *ee*, d.r. > 20 : 1

[E]



13 Examples, Yields 85% - 92%,
ee up to 96%, d.r. up to > 20 : 1

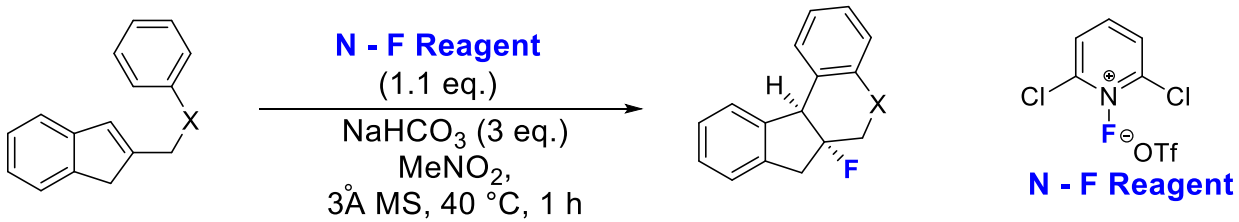
[F]

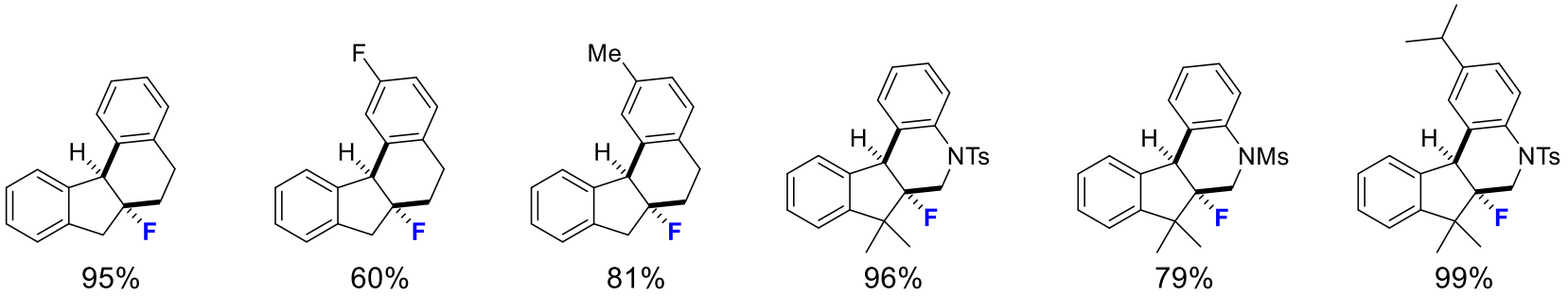


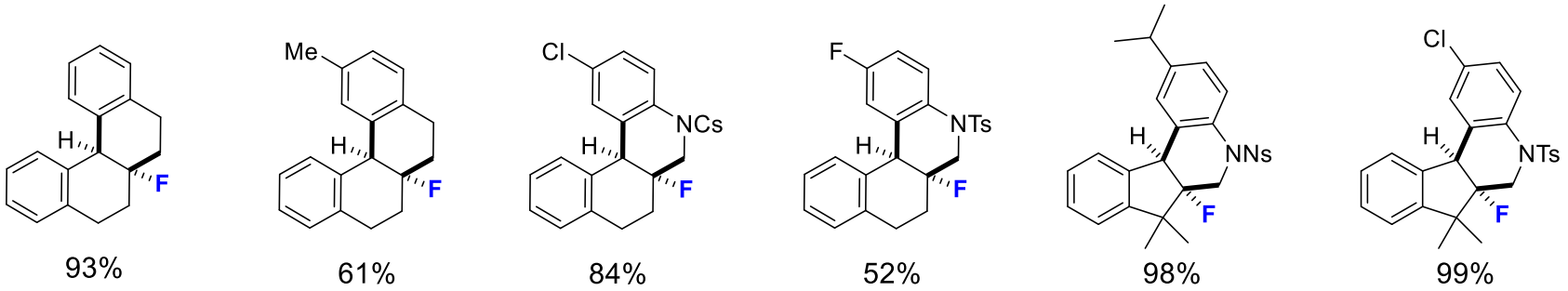
12 Examples
Yields 57% - 88%, *ee* up to 97%

[A] Toste *J. Am. Chem. Soc.* **2014**, *136*, 5225; **[B] Toste** *J. Am. Chem. Soc.* **2012,***134*, 8376; **[C] Toste** *J. Am. Chem. Soc.* **2013**, *135*, 1268; **[D] Toste** *Angew. Chem. Int. Ed.* **2012**, *51*, 9684 ; **[E] Toste** *Angew. Chem. Int. Ed.* **2013**, *52*, 7724; **[F] Toste** *Proc. Nat. Acad. Sci. U.S.A.* **2013**, *110*, 13729.

Fluorocarbocyclisations with N-F Reagents

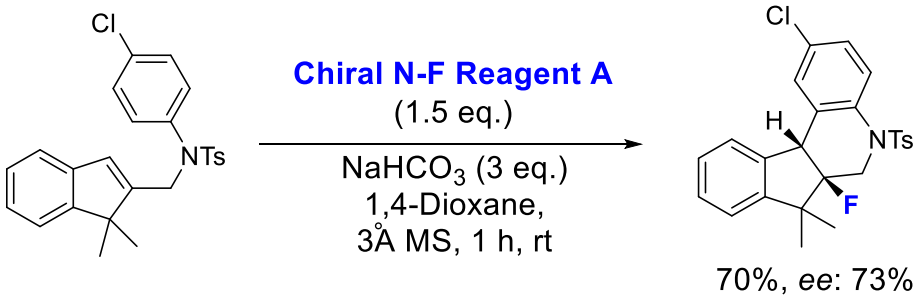




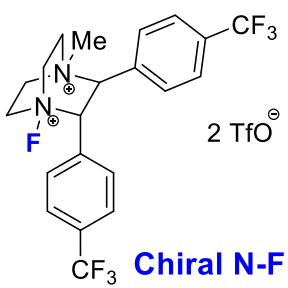


Gouverneur *Angew. Chem. Int. Ed*. **2013**, *52*, 9796; **Gouverneur** *Acc. Chem. Res.* **2014**, *47*, 3560.

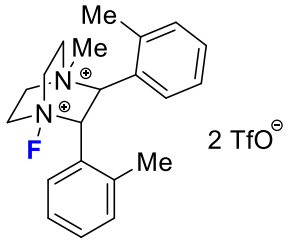
Asymmetric Fluorocarbocyclisations



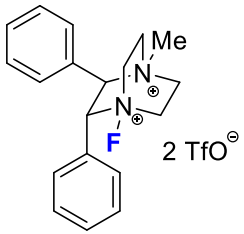
70%, *ee*: 73%



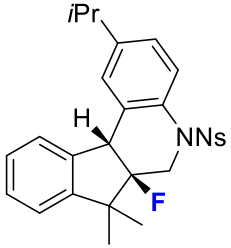
Chiral N-F Reagent A



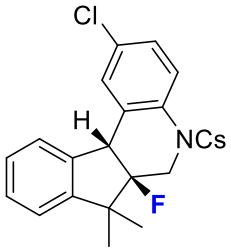
Chiral N-F Reagent B



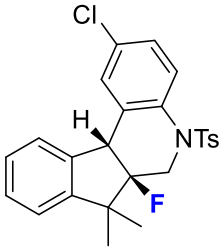
Chiral N-F Reagent C



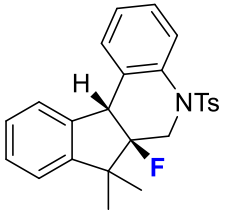
99%, *ee*: 70%



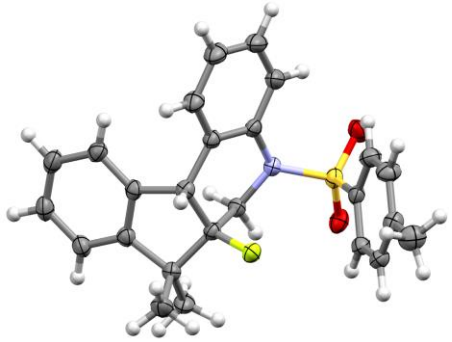
68%, *ee*: 71%



70%, *ee*: 73%



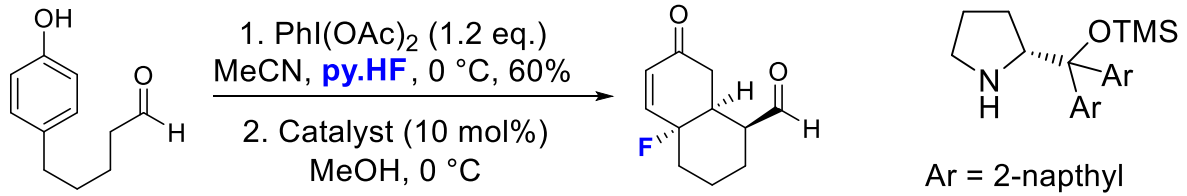
75%, *ee*: 71%



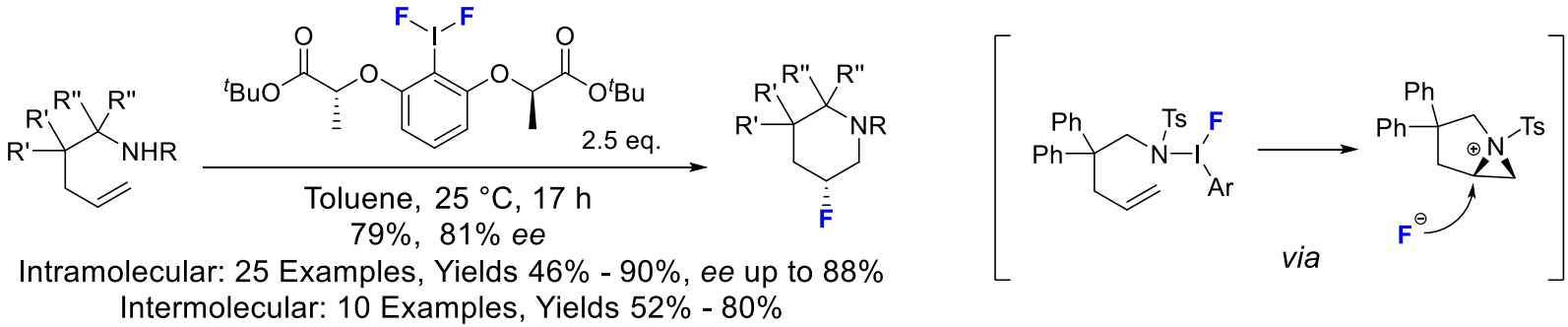
Gouverneur *Angew. Chem. Int. Ed*. **2013**, *52*, 9796; **Gouverneur** *Acc. Chem. Res.* **2014**, *47*, 3560.

Metal-Free Intramolecular Cyclisation-Fluorination of Alkenes

[A]

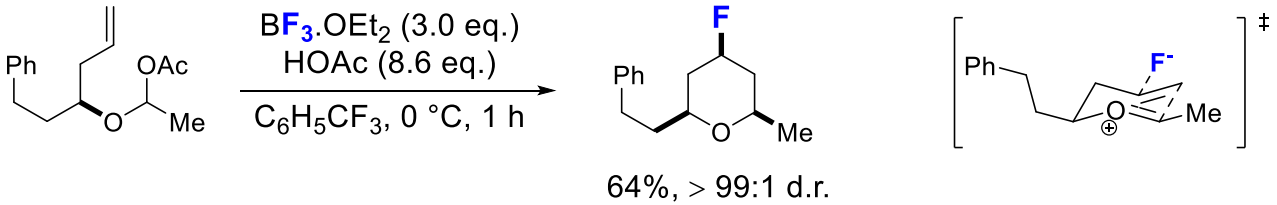


[B]



Intramolecular: 25 Examples, Yields 46% - 90%, *ee* up to 88%
Intermolecular: 10 Examples, Yields 52% - 80%

[C]

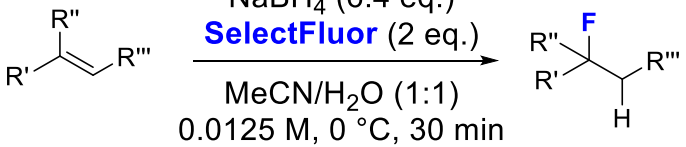


64%, > 99:1 d.r.

[A] Gaunt *J. Am. Chem. Soc.* **2008**, *130*, 404; **[B] Nevado** *Angew. Chem. Int. Ed*, **2013**, *52*, 2469; **[C] Rychnovsky** *J. Org. Chem.* **2001**, *66*, 4679.

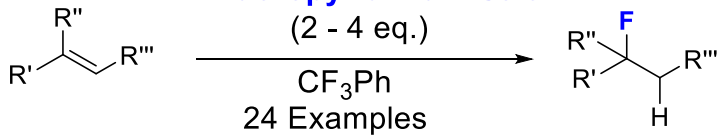
Metal Catalysed Intermolecular 'Radical' Fluorination of Alkenes

[A]

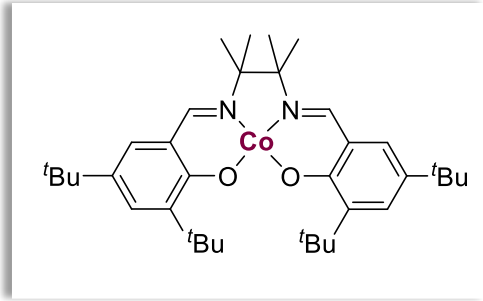


23 Examples
Yields 41% - 79%
ox = oxalate

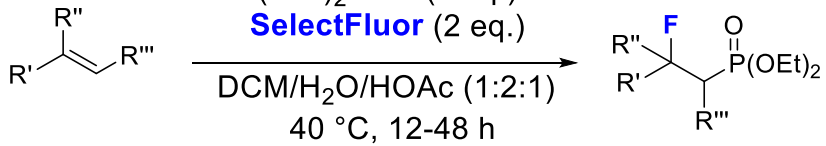
[B]



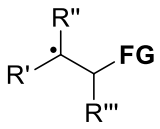
24 Examples
Yields 41% - 82%



[C]



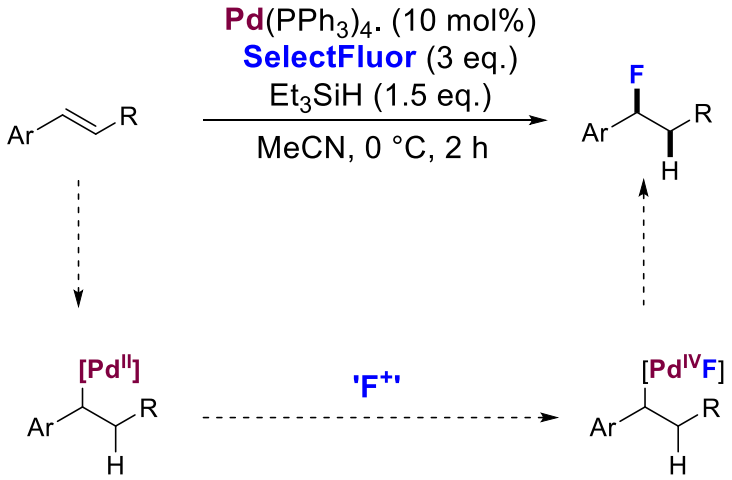
40 °C, 12-48 h
32 Examples
Yields 44% - 93%

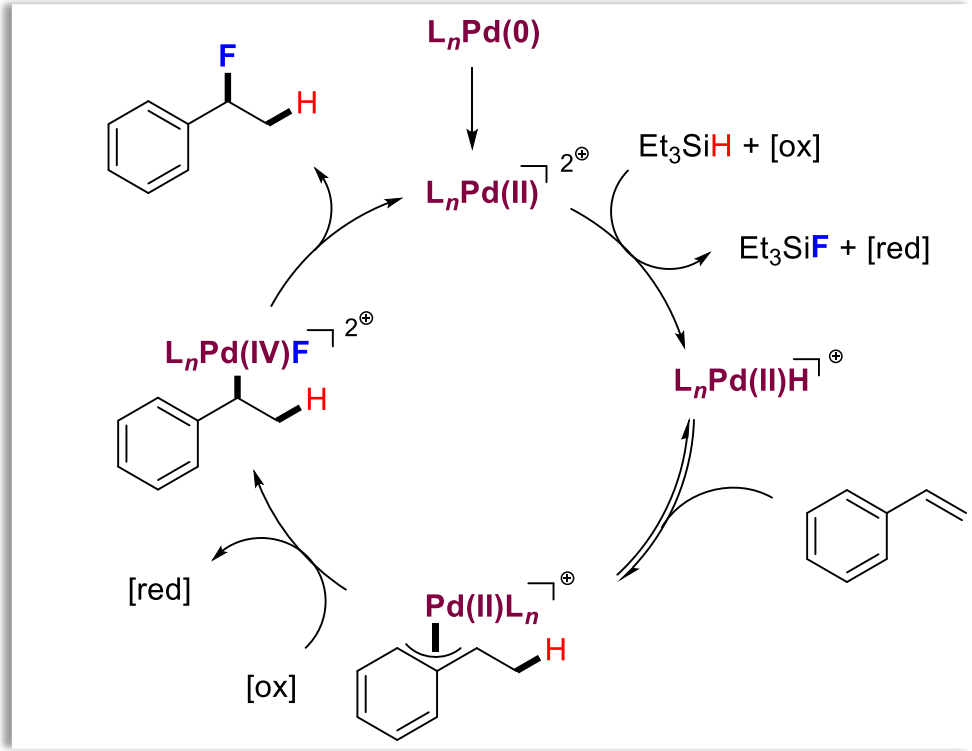


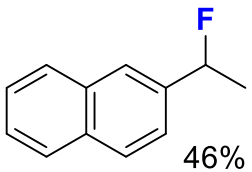
Radical Intermediate
Poor Diastereoselectivity

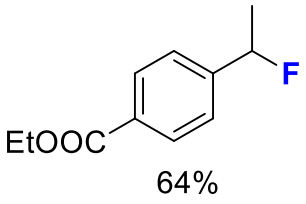
[A] Boger *J. Am. Chem. Soc.* **2012**, *134*, 13588; **[B] Hiroya & Shigehisa** *Org. Lett.* **2013**, *15*, 5158; **[C] Li** *J. Am. Chem. Soc.* **2013**, *135*, 14082.

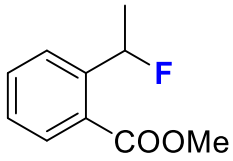
Metal Catalysed *cis*-Specific Hydrofluorination of Alkenes

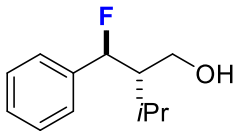


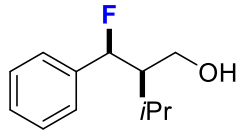








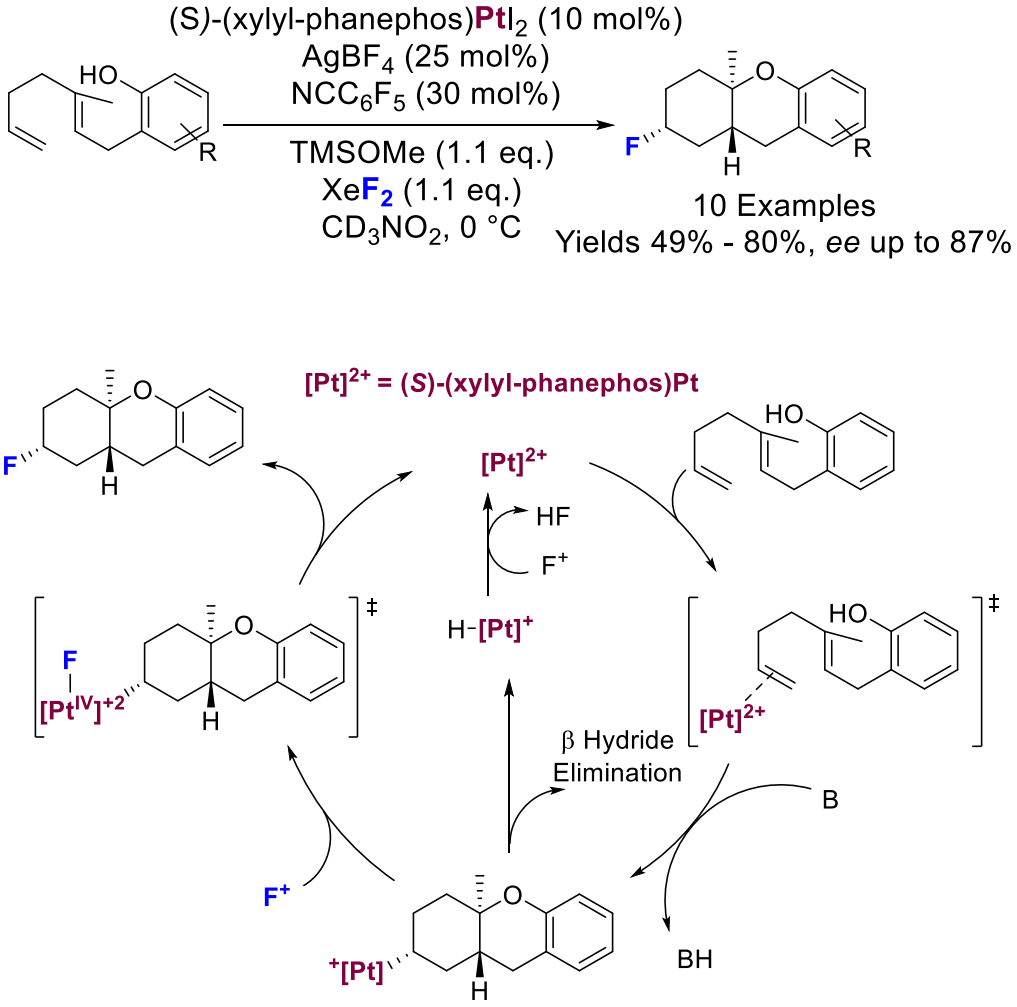




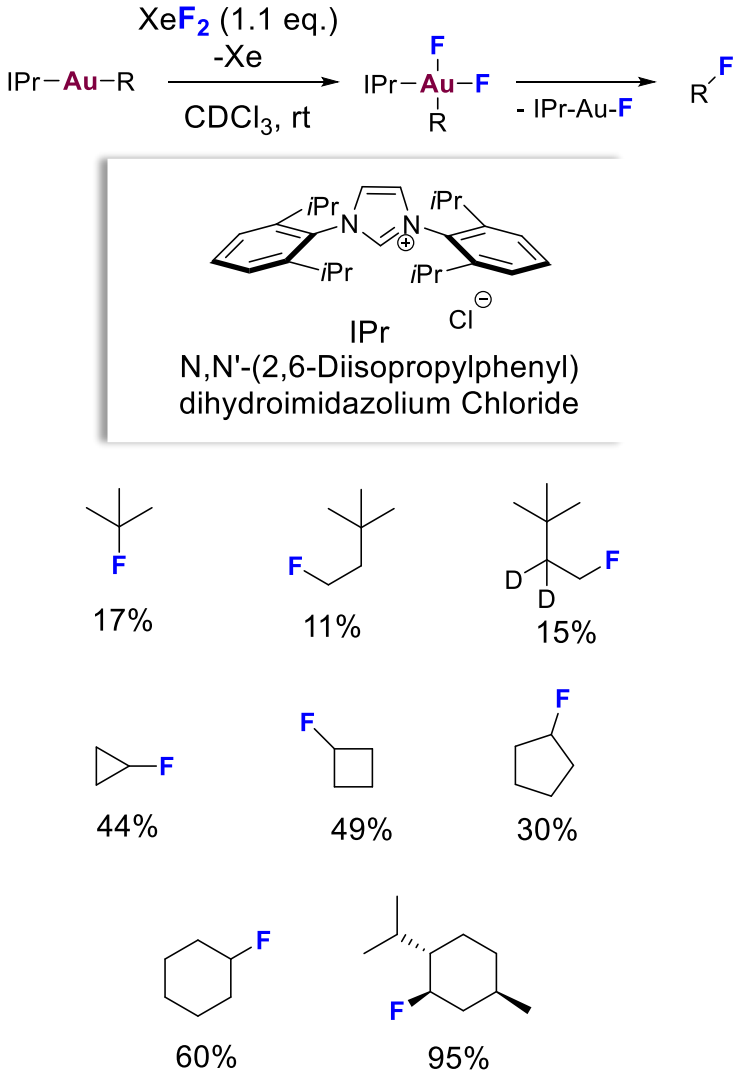
Gouverneur *Angew. Chem. Int. Ed.* **2014**, *53*, 4181.

Use of Metals in Csp^3 - F Bond Formation

[A]



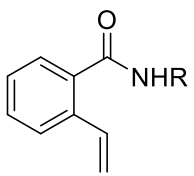
[B]



[A] Gagné *J. Am. Chem. Soc.* **2013**, *135*, 628; **[B] Toste** *Chem. Sci.* **2012**, *3*, 72.

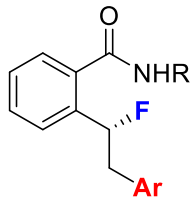
Metal Catalysed Fluoroarylation of Alkenes

[A]

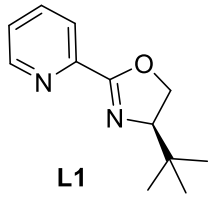


R = Aryl

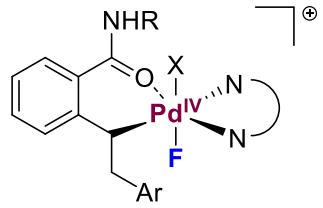
Pd$(OAc)_2$/L1 (15 mol%)
SelectFluor (2 eq.)
ArB(OH)$_2$ (1.2 eq.)
(2-ethylhexylO)$_2$PO$_2$H (30 mol%)
*t*Bu-Catechol
DCM/H_2O (5:1) (0.1 M)
rt, 15 h



27 Examples
Yields 15% - 83%, *ee* up to 96%

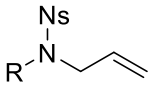


L1

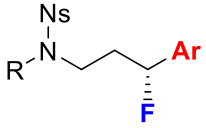


Proposed Key Intermediate
- Regiochemistry influenced by the use of the Directing Group

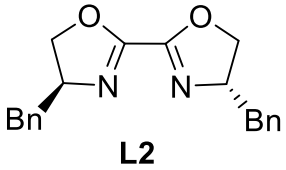
[B]



Pd$(MeCN)_2Cl_2$ (10 mol%)
L2 (13 mol%)
SelectFluor (3 eq.)
ArB(OH)$_2$ (2 eq.)
Benzene/H_2O/BnCN (8:8:1) (0.1 M)
4 °C, 18 h

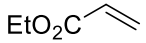


15 Examples
Yields 35% - 80%, *ee* up to 91%

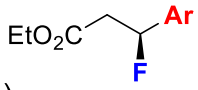


L2

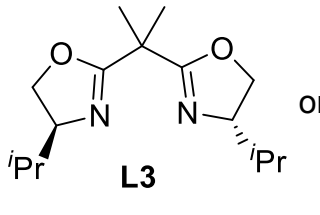
[C]



Pd$(OAc)_2$ (15 mol%)
L3 or L4 (15 mol%)
NFSI (2 - 4 eq.)
ArB(OH)$_2$ (2 eq.)
4-*t*Bu-Catechol (4 mol%)
Acetone/H_2O or *i*PrOH/H_2O (10:1)
20-25 °C, 20 h

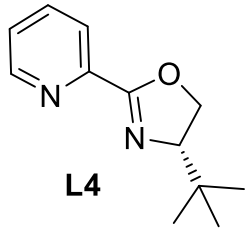


28 Examples
Yields 32% - 98%, *er* up to 97:3
d.r. up to 20:1



L3

or

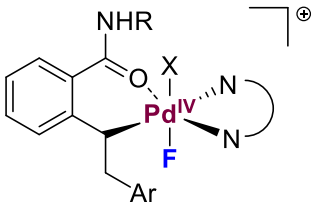


L4

[A] Toste *J. Am. Chem. Soc.* **2014**, *136,* 4101; **[B] Toste** *J. Am. Chem. Soc.* **2015**, *137*, 12207; **[C] Fustero, Toste & Pozo** *Angew. Chem. Int. Ed*. **2016**, **DOI:**10.1002/anie.201603046.

Metal Catalysed Fluoroarylation of Alkenes – 1,2 vs 1,1

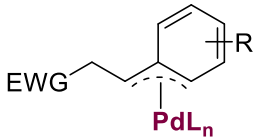
[A,B] 1,2-Fluoroarylation

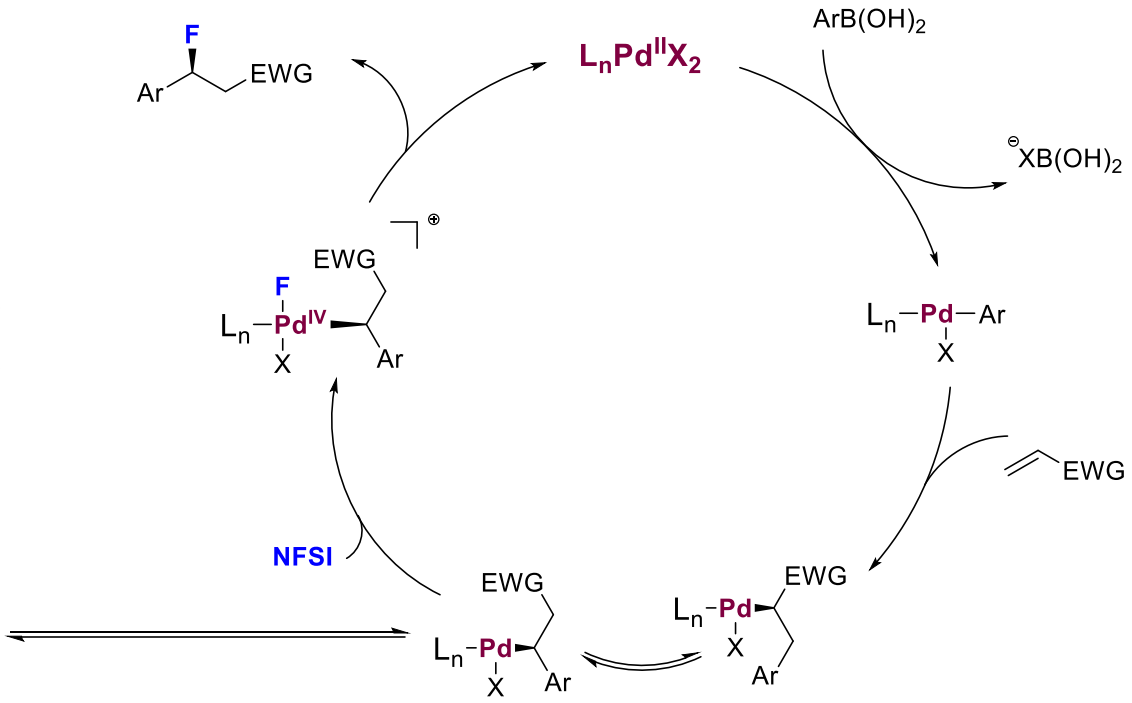


Proposed Key Intermediate
- Regiochemistry influenced by the use of the Directing Group

[C] 1,1-Fluoroarylation

Stabilised π-benzyl palladium species

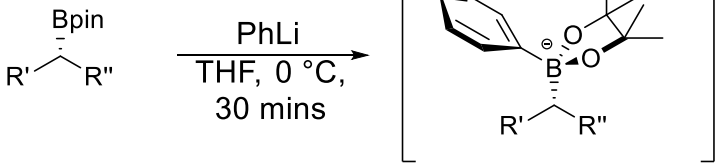


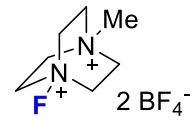


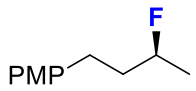
[A] Toste *J. Am. Chem. Soc.* **2014**, *136,* 4101; **[B] Toste** *J. Am. Chem. Soc.* **2015**, *137*, 12207; **[C] Fustero, Toste & Pozo** *Angew. Chem. Int. Ed*. **2016**, **DOI:**10.1002/anie.201603046.

Electrophilic Fluorination of Alkyl Boronic Esters

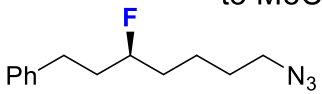
[A]



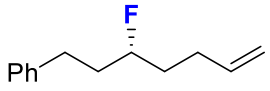




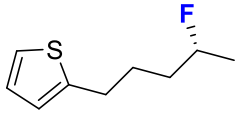
A: 83%, *es* 100%



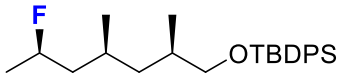
A: 68%, *es* 84%
B: 54%, *es* 98%



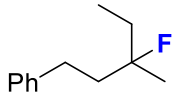
A: 80%, *es* 93%
B: 73%, *es* 99%



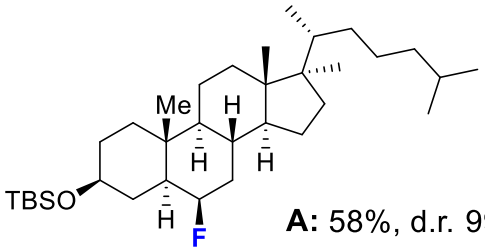
A: 90%, *es* 85%
B: 71%, *es* 92%



A: 61%, d.r. 90:10
B: 51%, d.r. 97:3

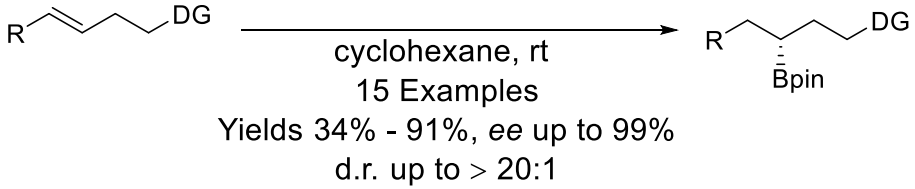


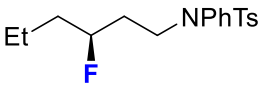
A: 44%, *es* 0%



A: 58%, d.r. 99:1

[B]





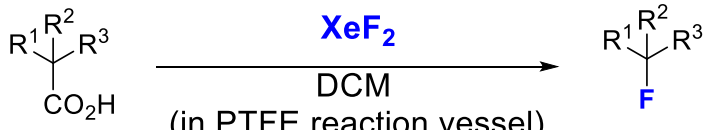
68%, *ee* 70%

F^+ Source: Selectfluor

[A] Aggarwal *J. Am. Chem. Soc.* **2015**, *137*, 10100; **[B] Hartwig** *J. Am. Chem. Soc.* **2016**, *138*, 6703; See Also; **Li** *J. Am. Chem. Soc.* **2014**, *136*, 16439.

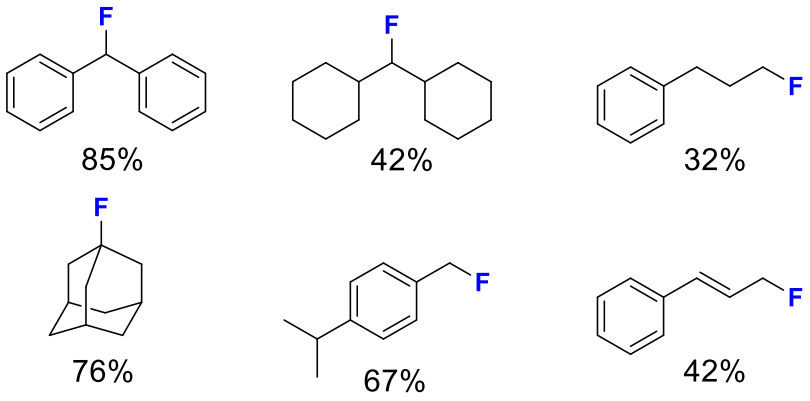
Decarboxylative Fluorination *via* Alkyl Radicals

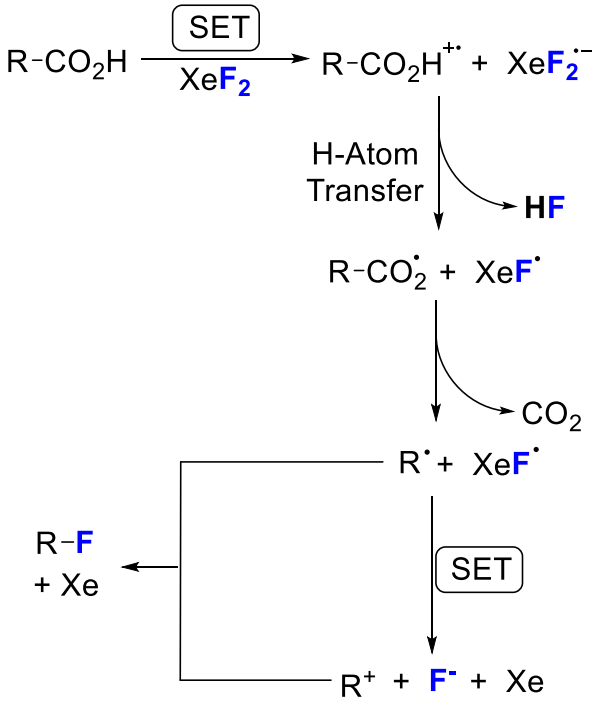
[A]



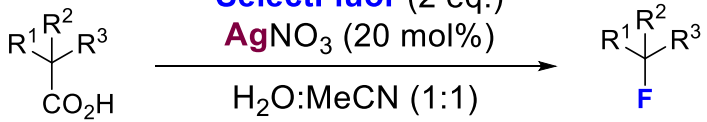
R^1, R^2, R^3 = alkyl, aryl, vinyl

6 Examples
Yields 32% - 85%



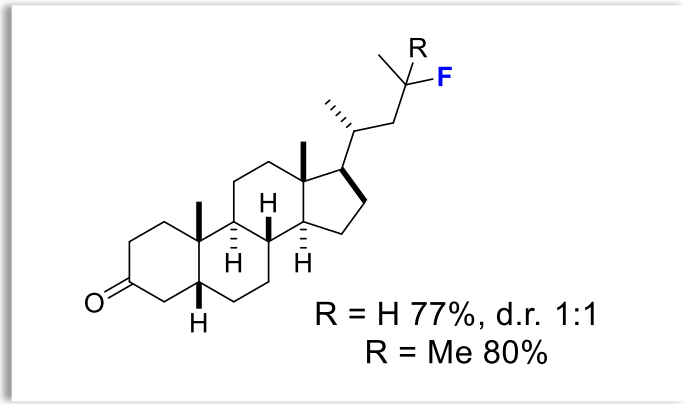


[B]



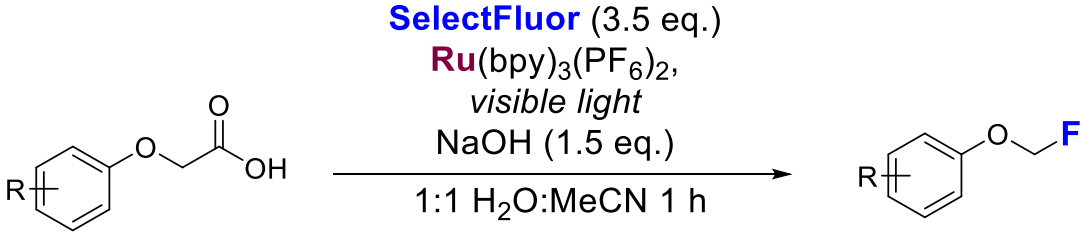
R^1, R^2, R^3 = alkyl, OR, NR_2

28 Examples
Yields 40% - 95%

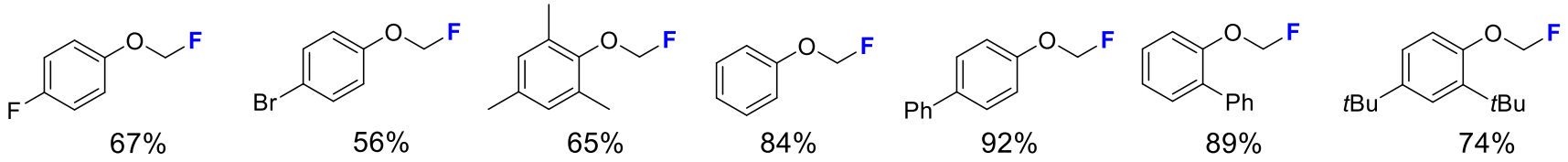


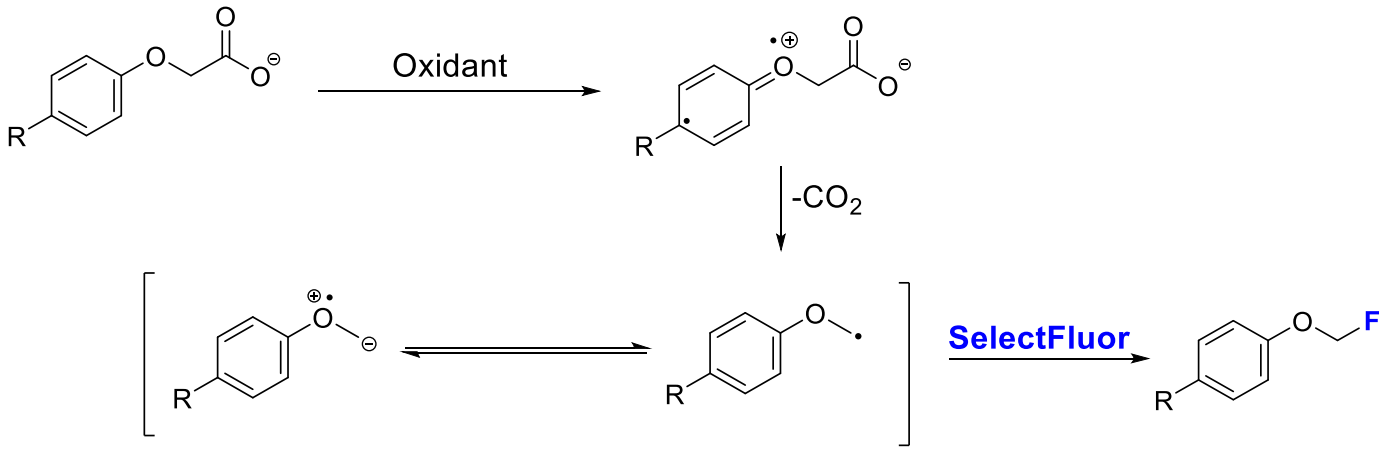
[A] Shaw *Tetrahedron Lett.* **2009**, *50*, 3321; **[B] Li** *J. Am. Chem. Soc.* **2012**, *134*, 10401.

Decarboxylative Fluorination *via* Alkyl Radicals



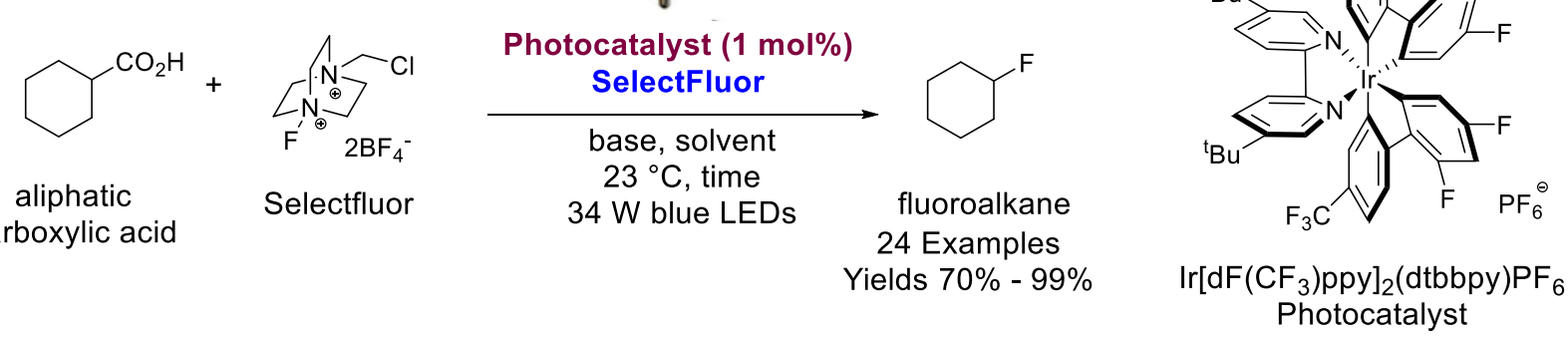
11 Examples
Yields 51% - 92%

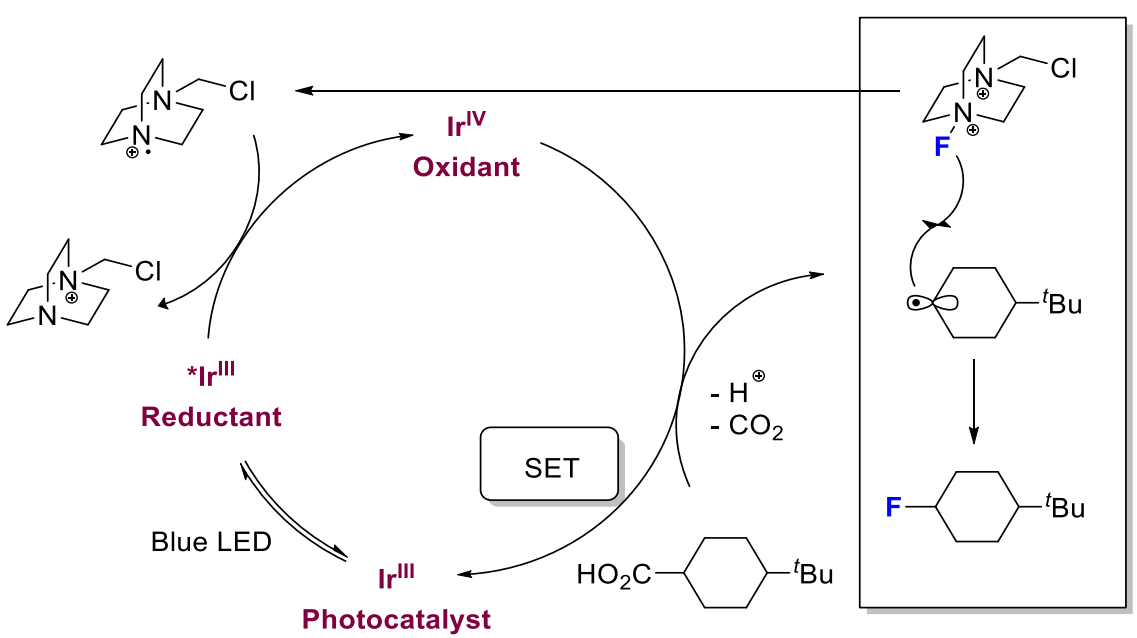


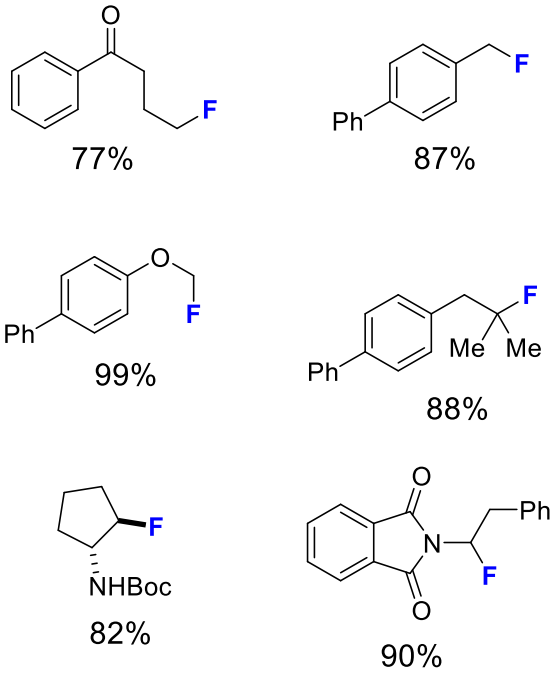


Paquin *J. Am. Chem. Soc*. **2014**, *136*, 2637; See Also; **Sammis** *J. Am. Chem. Soc*. **2012**, *134*, 4026.

Decarboxylative Fluorination *via* Alkyl Radicals



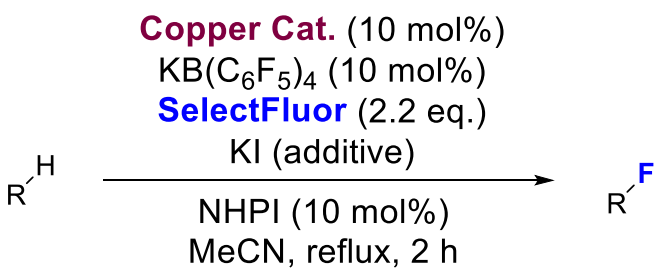




MacMillan *J. Am. Chem. Soc.* **2015**, *137*, 5654.

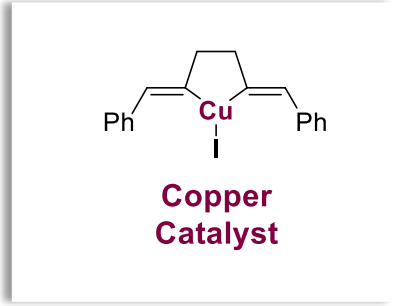
Metal Catalysed Fluorination *via* Alkyl Radicals

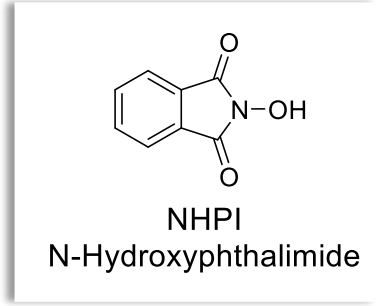
[A]

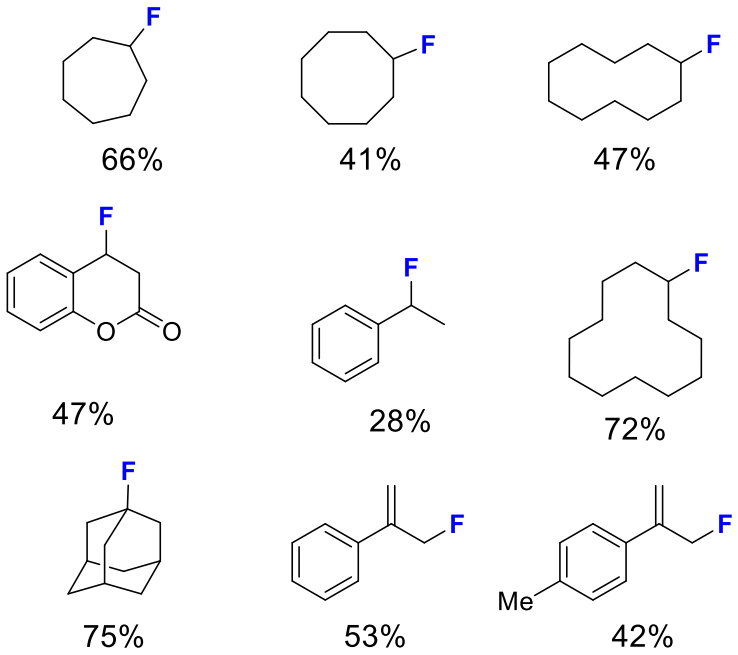


Secondary, Tertiary, Allylic
Benzylic Position

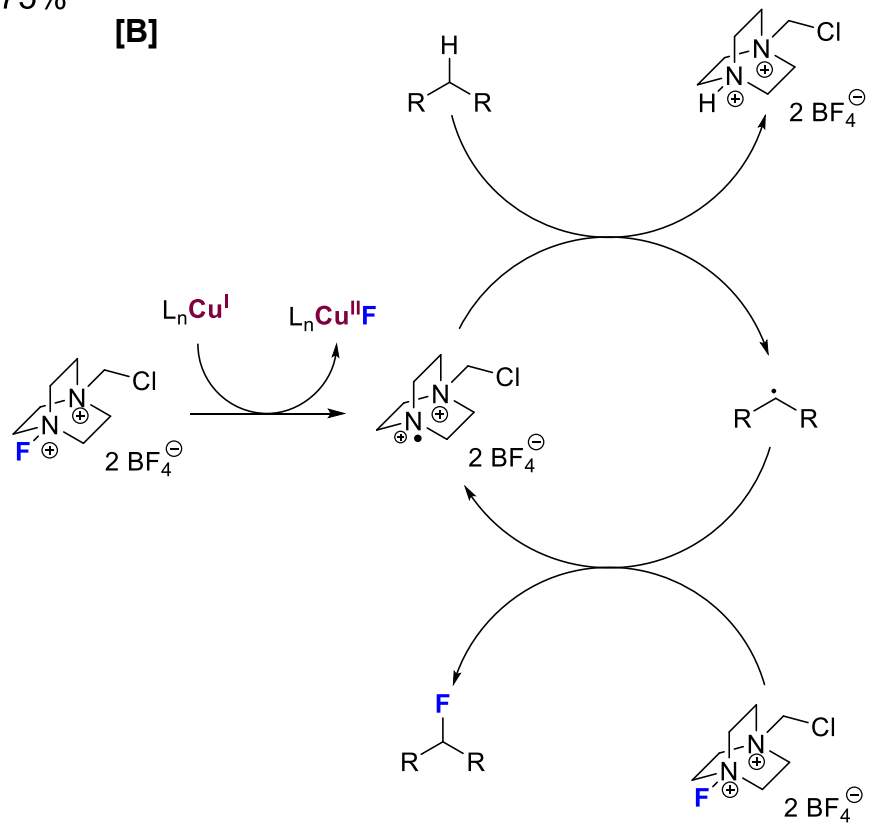
16 Examples
Yields 33% - 75%





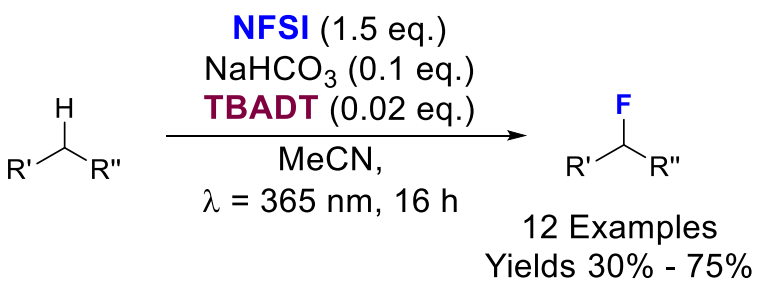


[B]



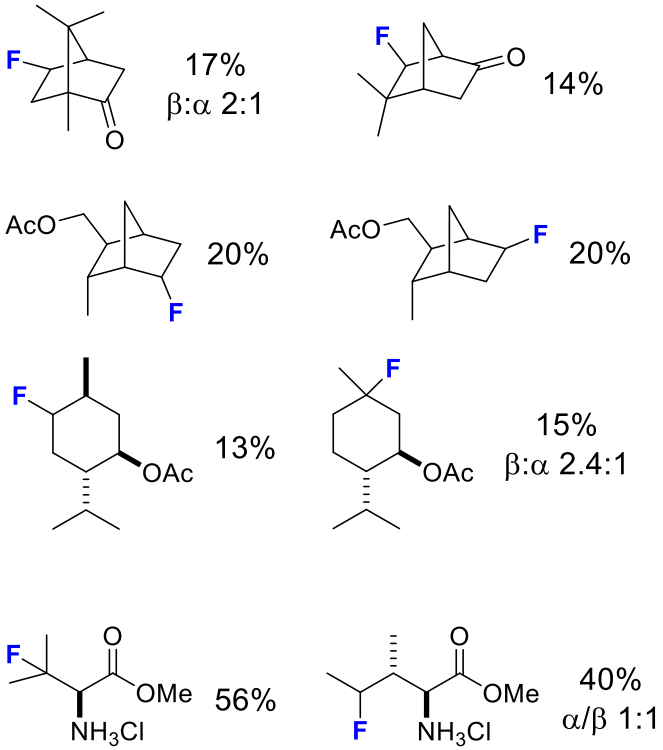
[A] Lectka *Angew. Chem. Int. Ed.* **2012**, *51*, 10580; **[B] Lectka** *J. Am. Chem. Soc.* **2014**, *136*, 9780.

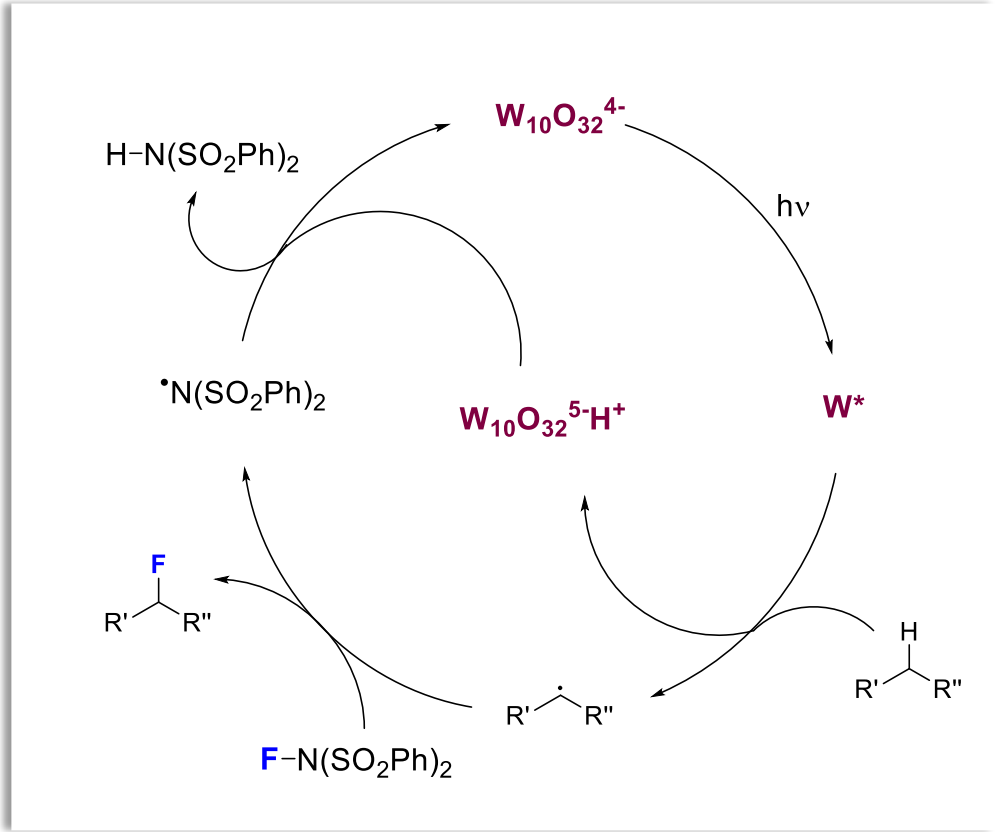
Metal Catalysed Fluorination *via* Alkyl Radicals



$[^nBu_4N]_4W_{10}O_{32}$

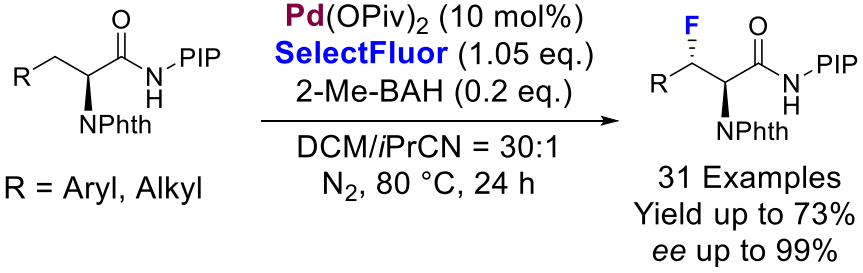
TBADT

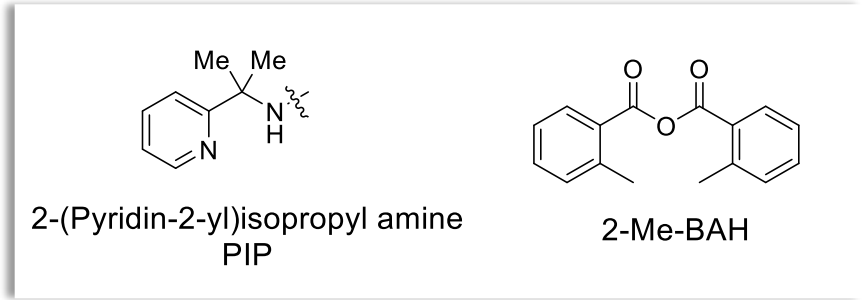


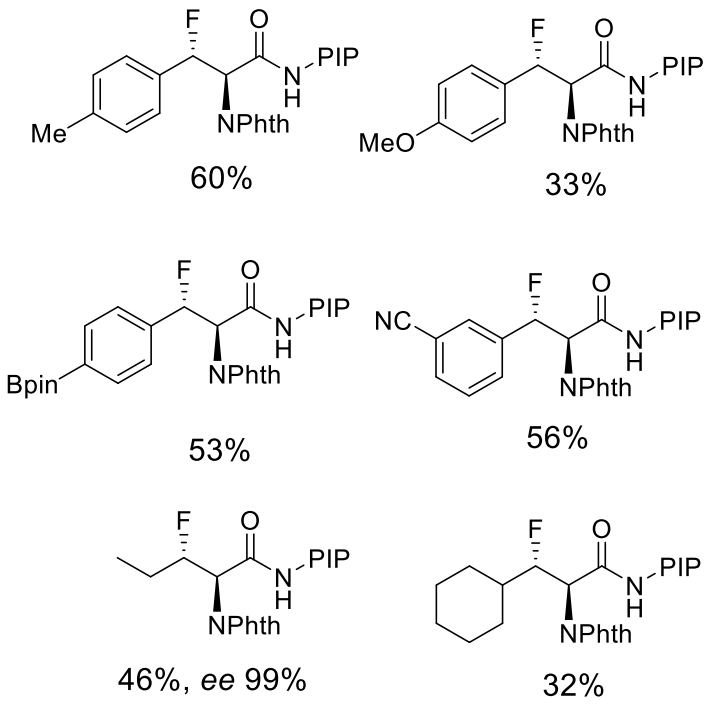


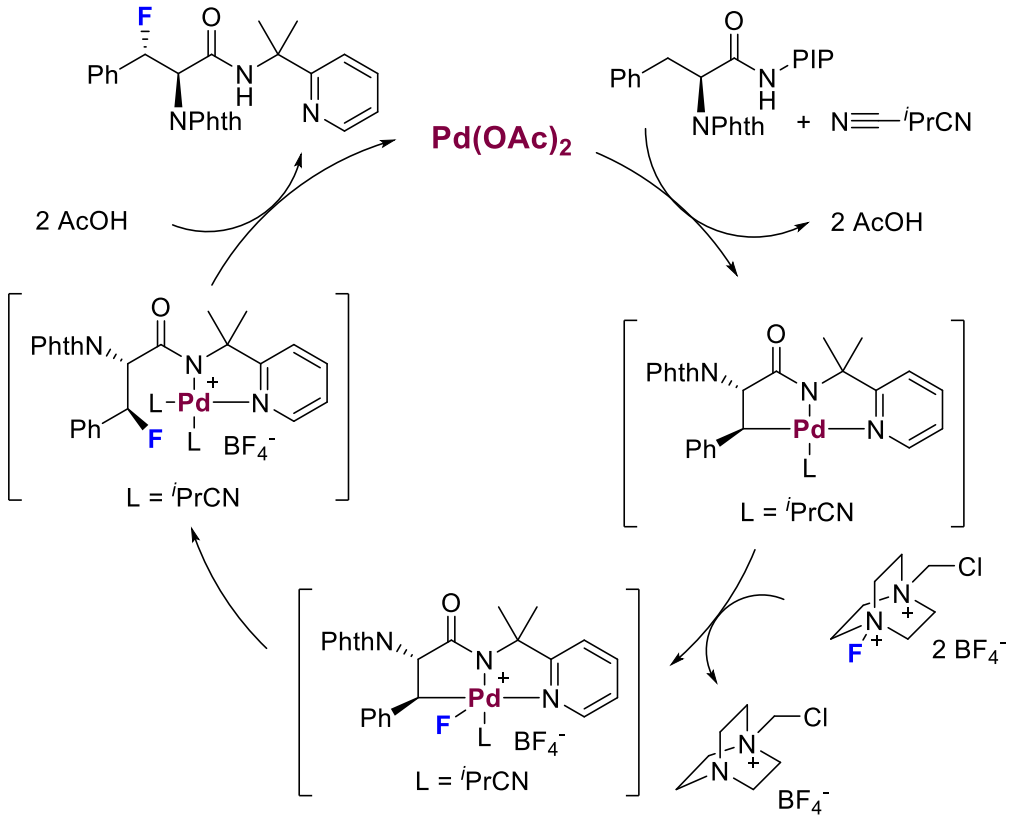
Britton *Angew. Chem. Int. Ed*. **2014,** *53*, 4690; **Britton** *Org. Lett*. **2015**, 17, 5200; **Britton** *Chem. Commun*. **2015**, *51*, 11783.

Metal Catalysed C-H Fluorination



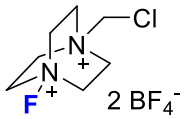




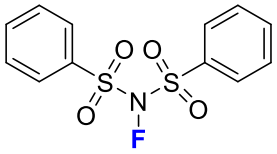


Shi *J. Am. Chem. Soc.* **2015**, *137*, 8219.

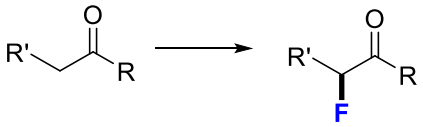
Electrophilic Fluorination



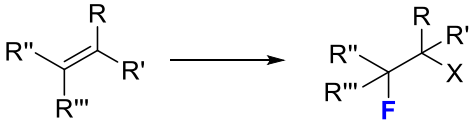
SelectFluor



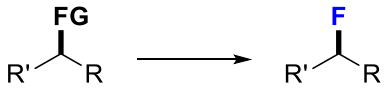
NFSI



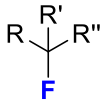
CARBONYLS



ALKENES



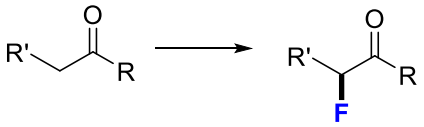
ALKYL PRECURSOR



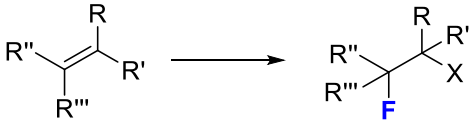
Csp^3 - F
Bond Formation

Nucleophilic Fluorination

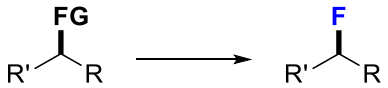
AgF, TBAF, HF.py,
DAST, RCOF



CARBONYLS



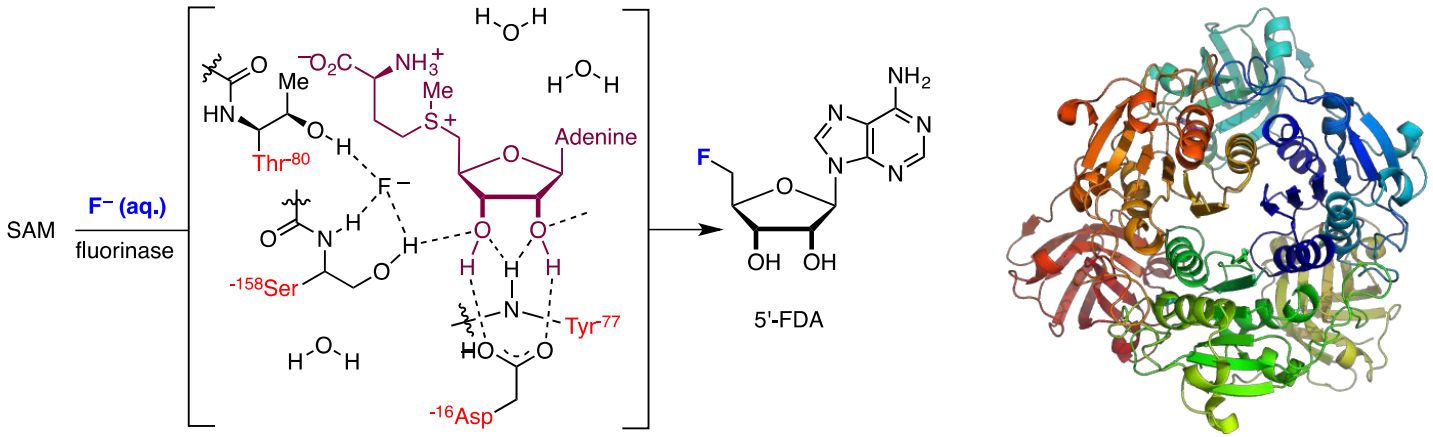
ALKENES



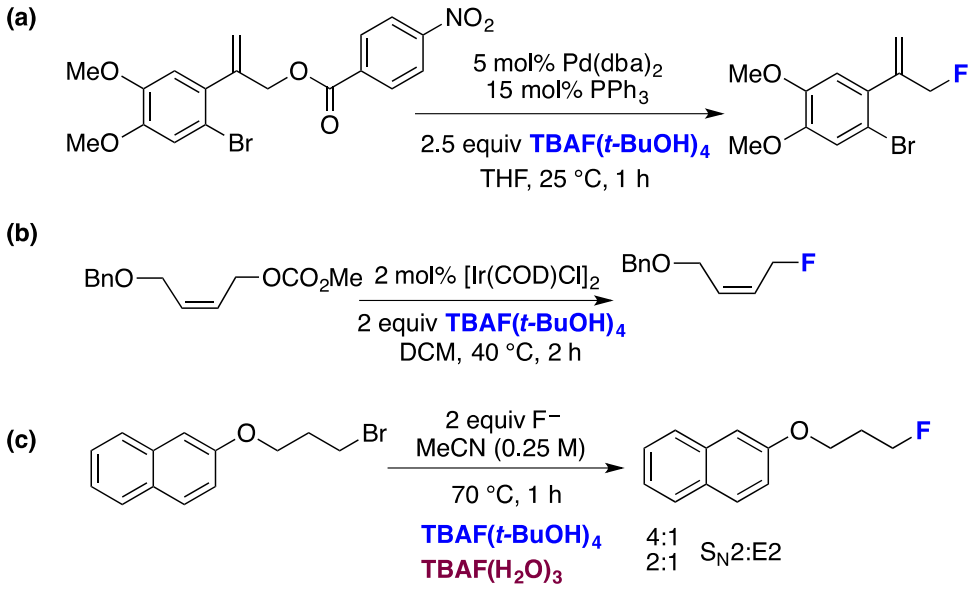
ALKYL PRECURSOR

Importance of the Fluoride Source on Reactivity

[A]

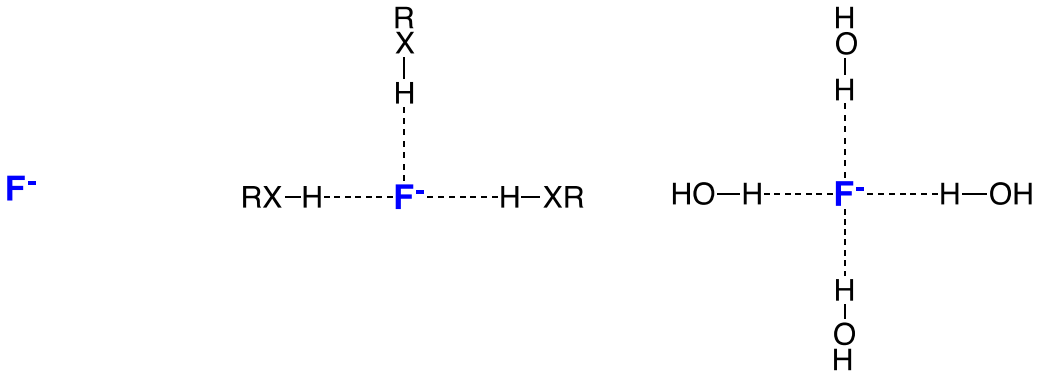


[B]

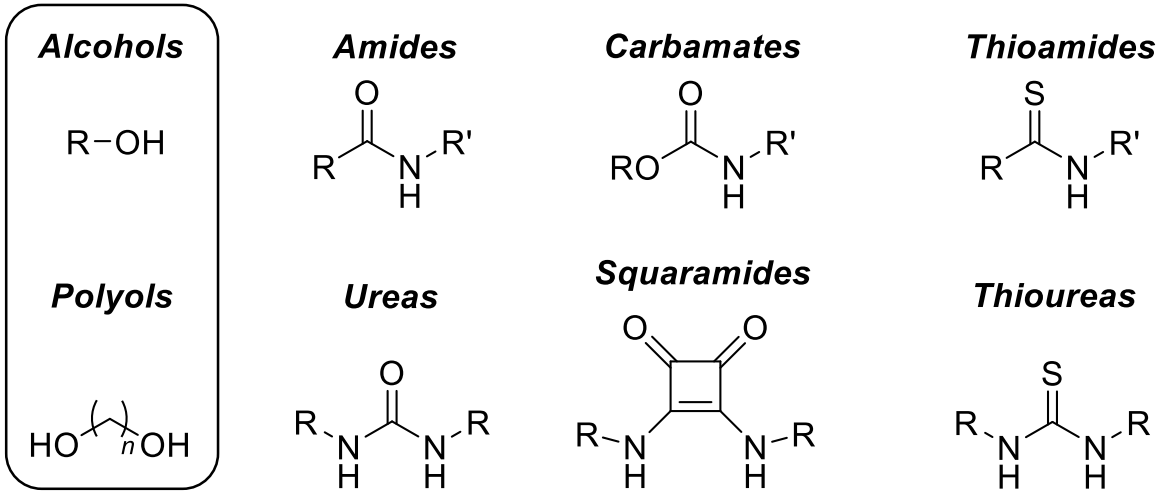


[A] O'Hagan *Nature* **2002**, *416*, 279; **[B] Gouverneur** *Angew. Chem. Int. Ed*. **2011**, *50*, 2613; **Gouverneur** *Chem. Sci*. **2013**, *4*, 89.
See Also: **Kim** *Angew. Chem., Int. Ed*., **2008**, *47*, 8404; **Kim** *Chem Soc Rev*, **2016 DOI:** 10.1039/C6CS00286B

Importance of F^- Source on Reactivity

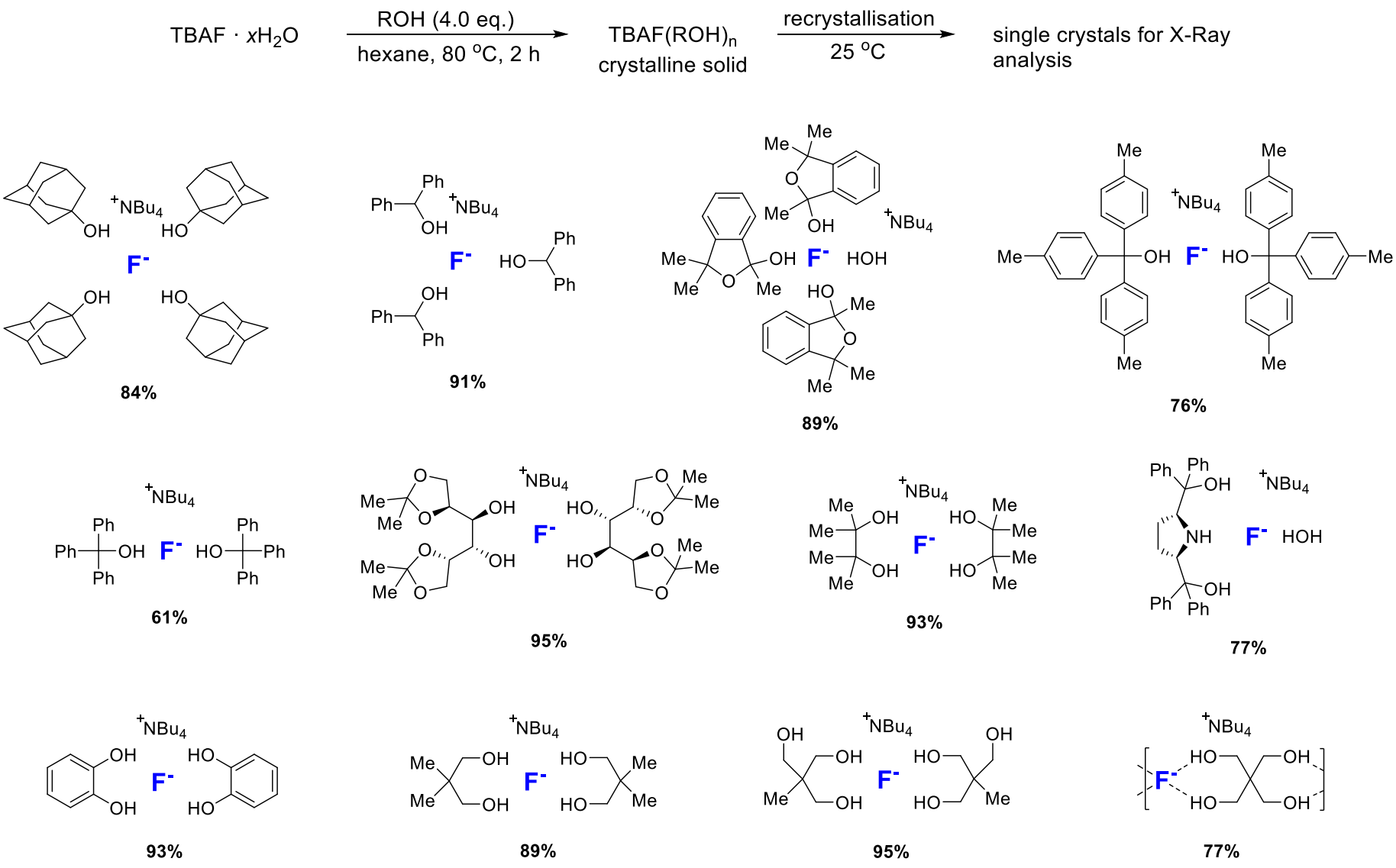


“naked” fluoride	ideal fluoride?	fluoride hydrate
high nucleophilicity *high basicity*	*high nucleophilicity* *low basicity* *low RX^- nucleophilicity*	*low nucleophilicity* *low basicity* *low OH^- nucleophilicity*



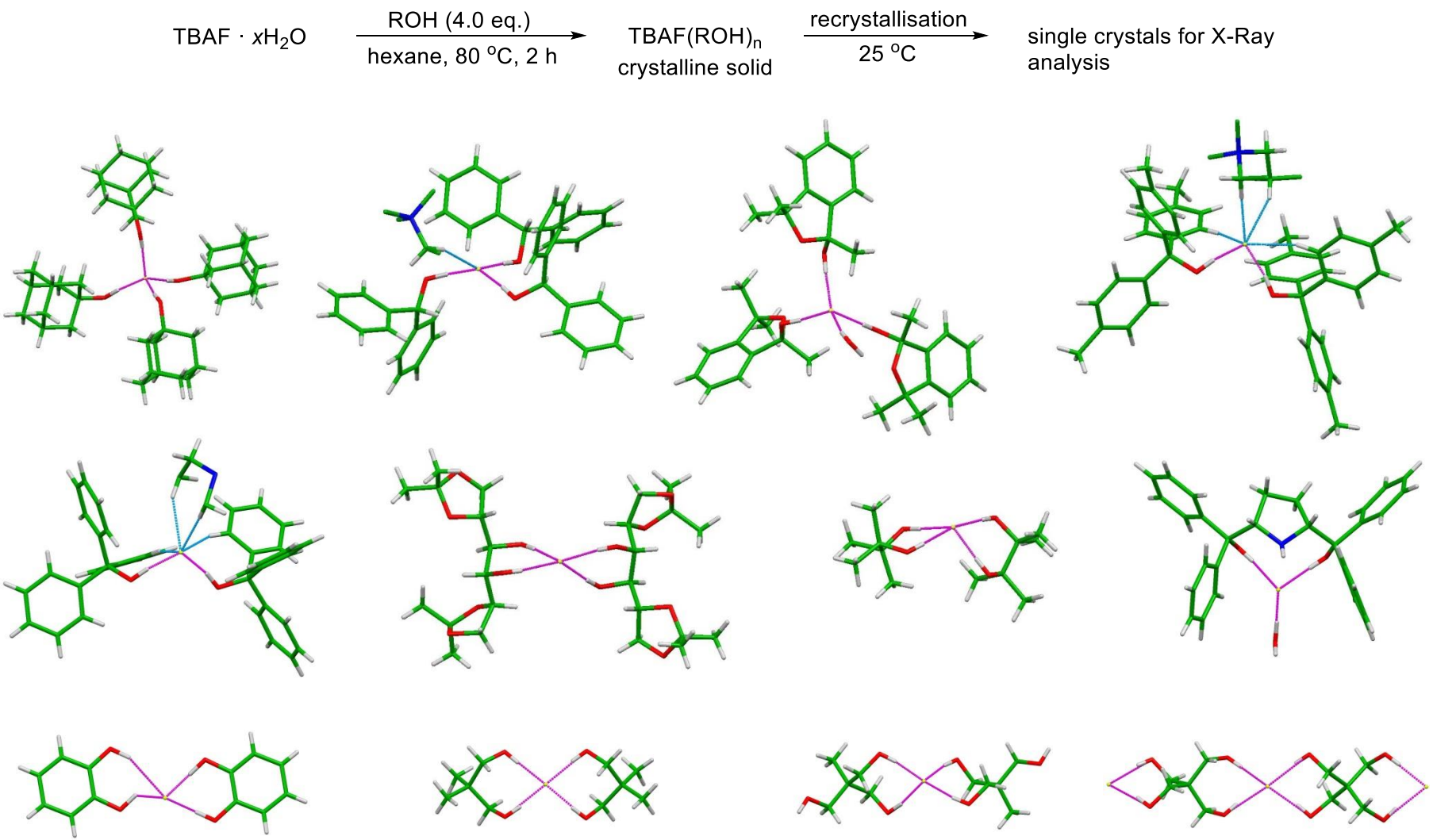
Gouverneur *Chem. Sci*. **2015**, *6*, 5293.

Coordination diversity in hydrogen-bonded homoleptic fluoride-alcohol complexes



Gouverneur *Chem. Sci.* **2015**, *6*, 5293.

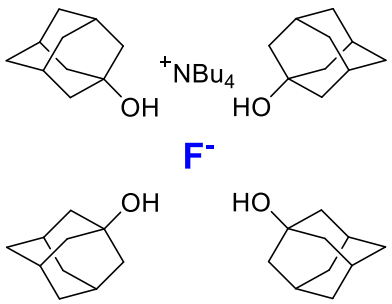
Coordination diversity in hydrogen-bonded homoleptic fluoride-alcohol complexes

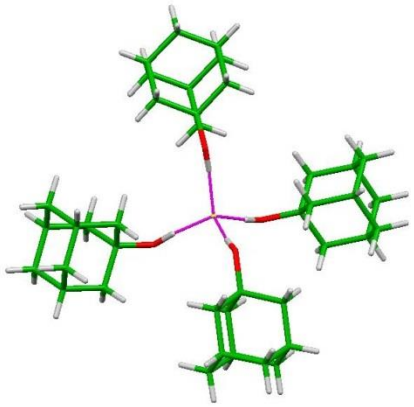


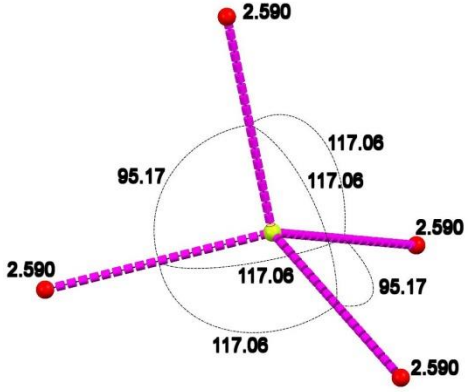
Gouverneur *Chem. Sci*. **2015**, *6*, 5293.

Coordination diversity in hydrogen-bonded homoleptic fluoride-alcohol complexes

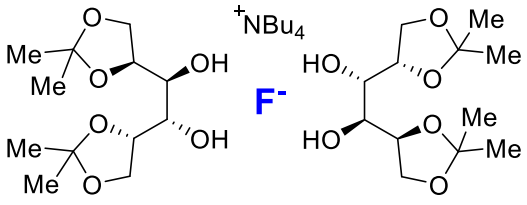
Adamantan-1-ol

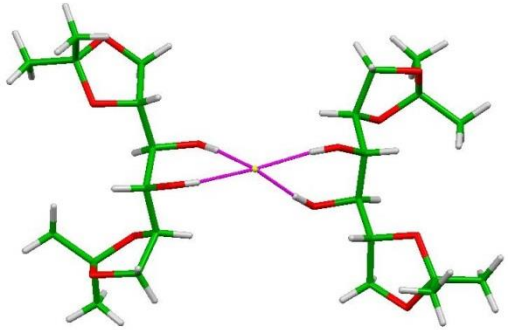


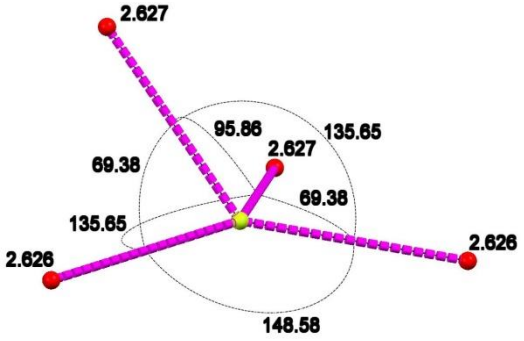




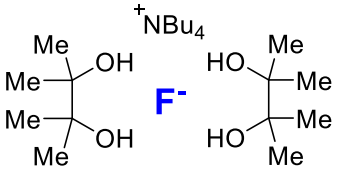
D-Mannitol Diacetonide

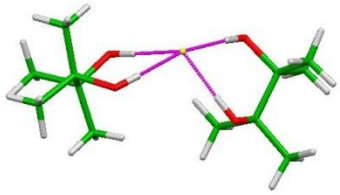


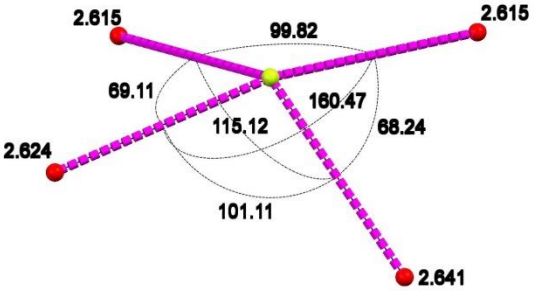




Pinacol



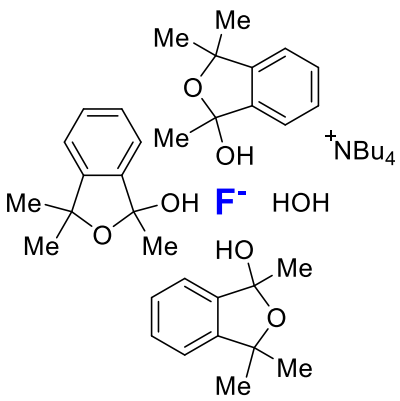


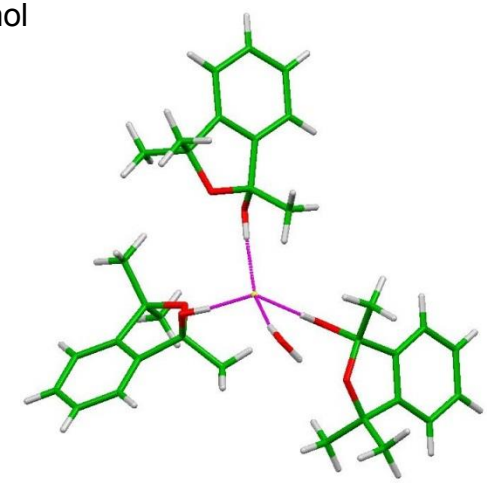


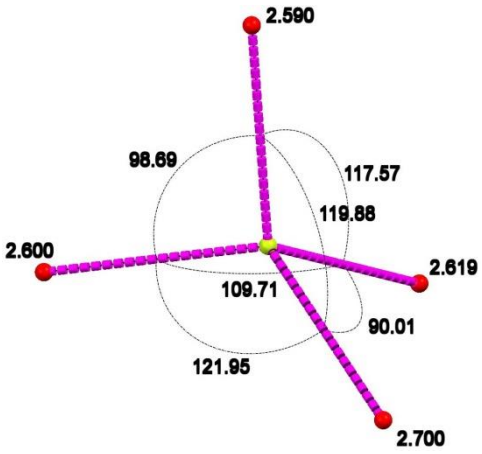
Gouverneur *Chem. Sci*. **2015**, *6*, 5293.

Coordination diversity in hydrogen-bonded homoleptic fluoride-alcohol complexes

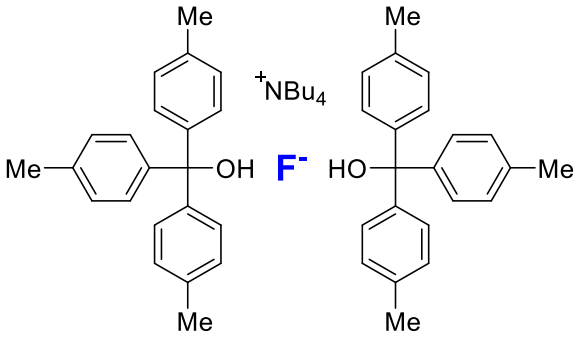
1,3,3-Trimethyl-1,3-dihydro-1-isobenzofuranol

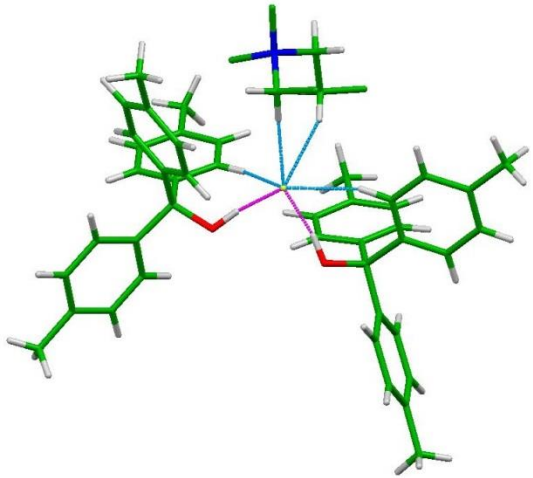


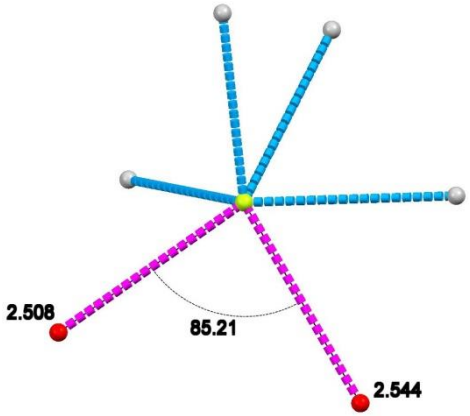




Tri-(*p*-tolyl)-methanol

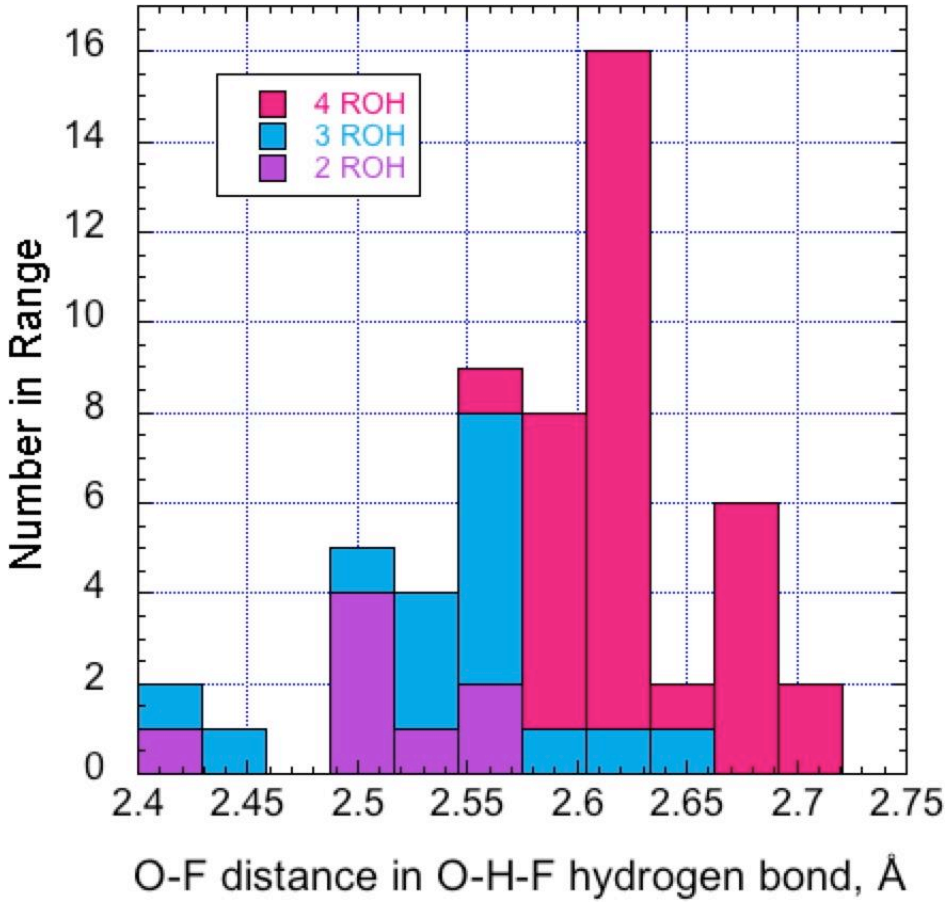






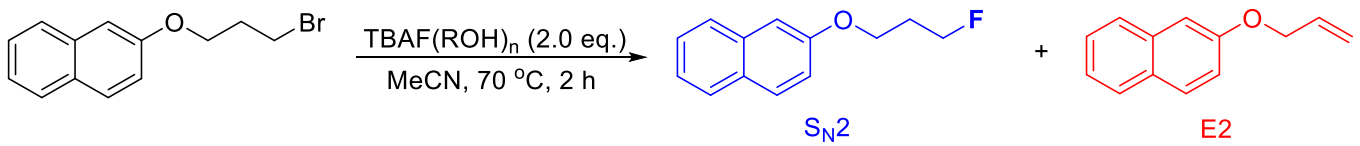
Gouverneur *Chem. Sci*. **2015**, *6*, 5293.

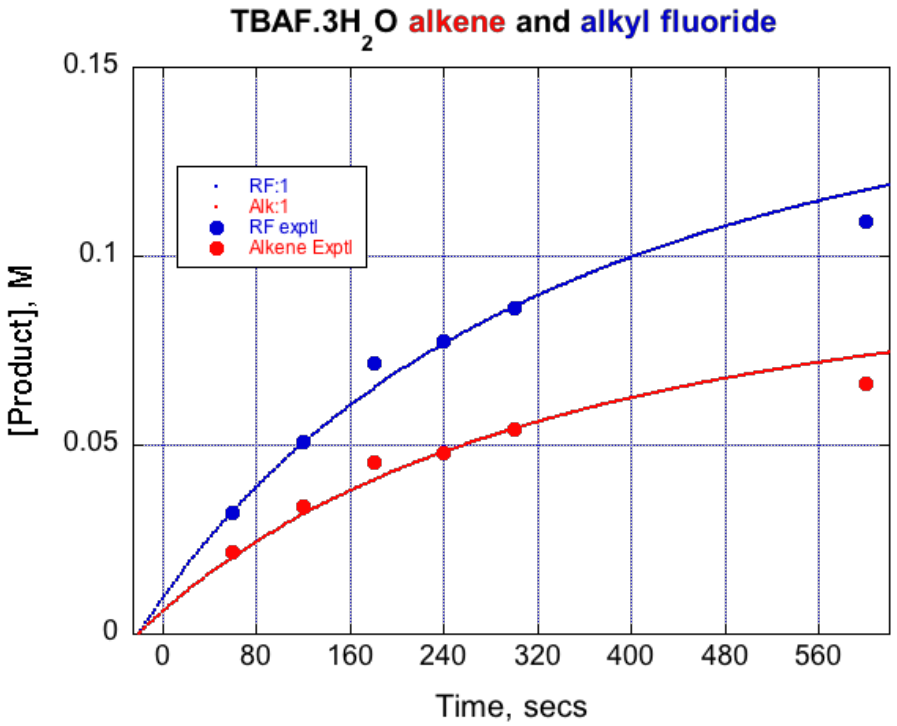
Coordination diversity in hydrogen-bonded homoleptic fluoride-alcohol complexes

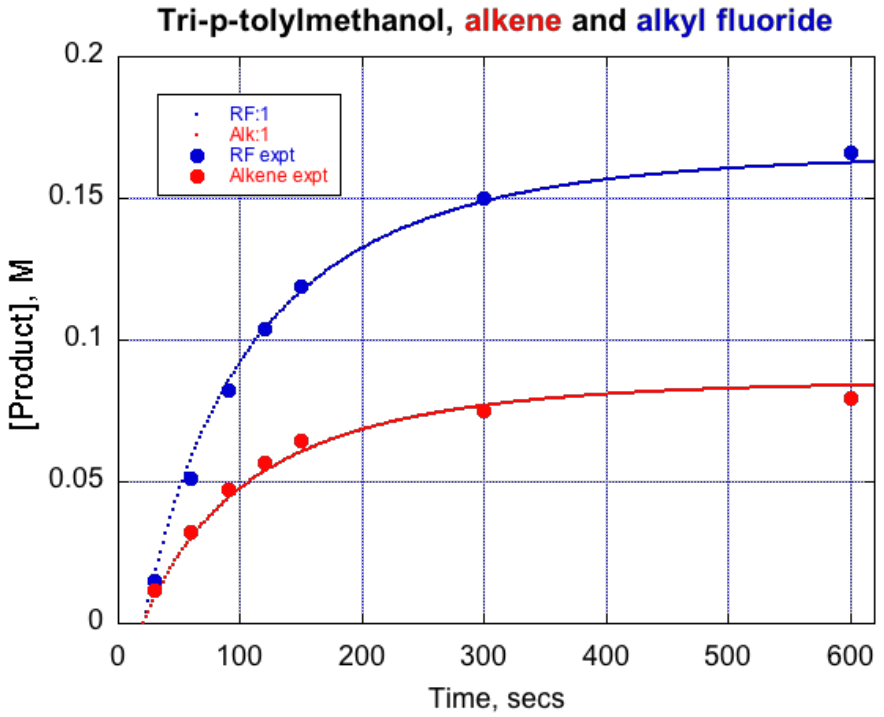


Gouverneur *Chem. Sci*. **2015**, *6*, 5293.

Coordination diversity modulates reactivity and selectivity

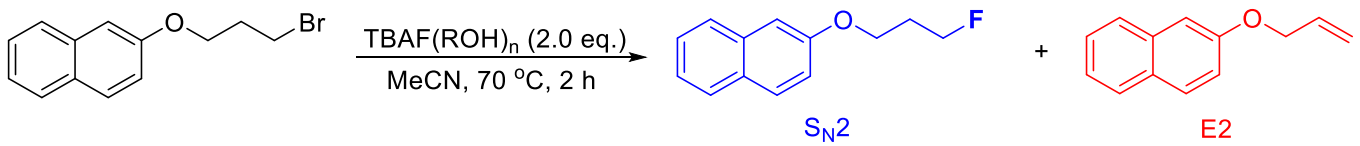


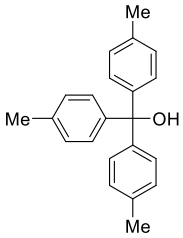
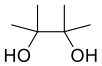
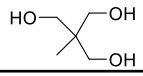




Gouverneur *Chem. Sci.* **2015**, *6*, 5293.

Coordination diversity modulates reactivity and selectivity

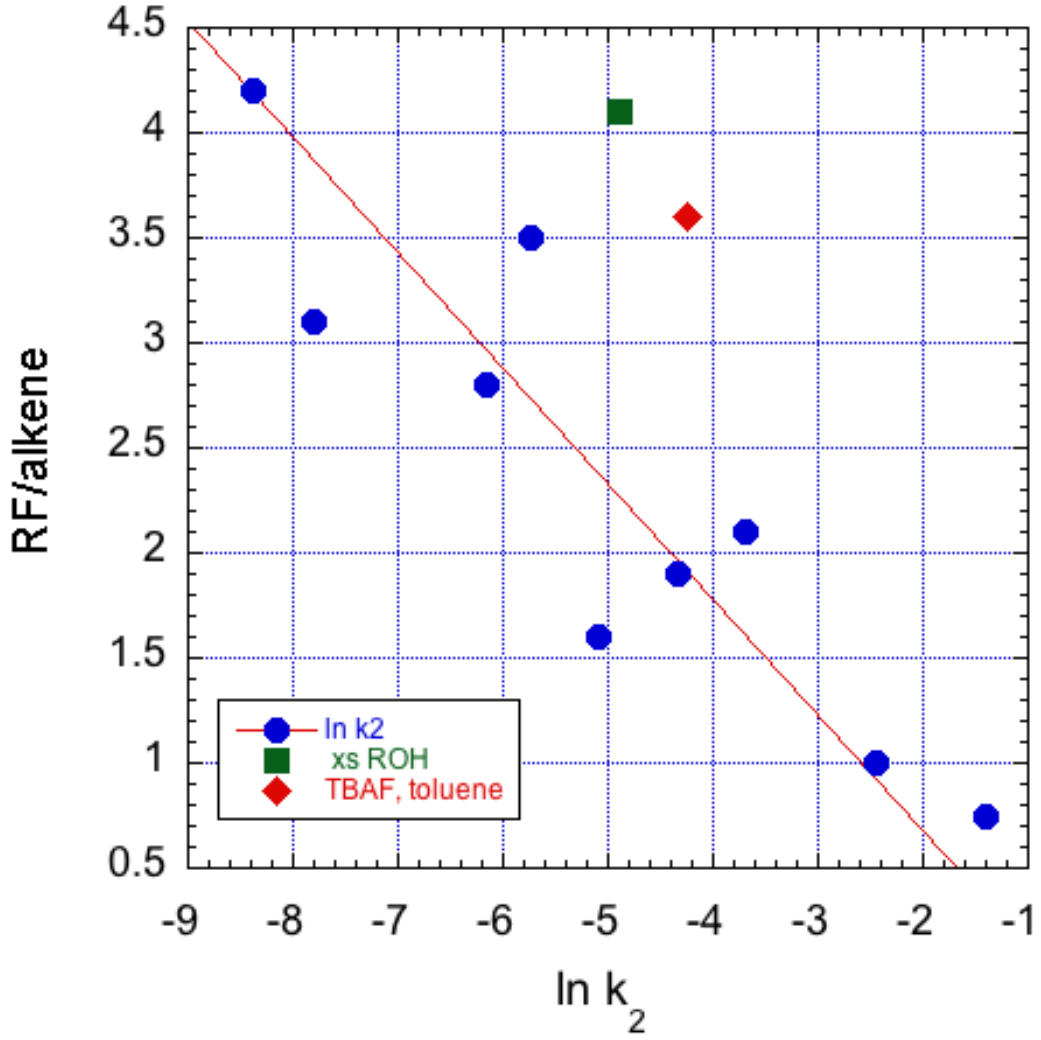


ROH	Coordination	Molarity [M]	k_2 [$M^{-1}s^{-1}$] ·10^{-3}	k_2 (rel)	RF/alkene
	3	0.50	6.16	1.0	1.6
	2	0.50	25.1	4.1	2.1
	2	0.13	87.0	14	1.0
	2	0.050	123	20	0.74
	2	0.50[a]	12.4	2.3	3.6
	4	0.50	13.0	2.1	1.9
	4	0.50	2.14	0.35	2.8
	4	0.50	0.409	0.066	3.1
	4	0.50	0.230	0.0037	4.2

[a] An additional 0.50 M excess of alcohol was present in the reaction mixture.

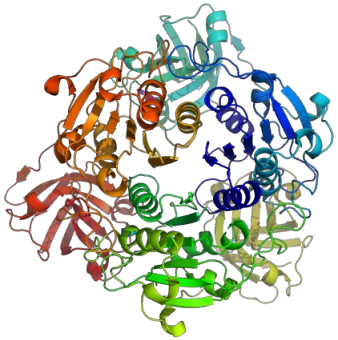
Gouverneur *Chem. Sci.* **2015**, *6*, 5293.

Coordination diversity modulates reactivity and selectivity



Gouverneur *Chem. Sci*. **2015**, *6*, 5293.

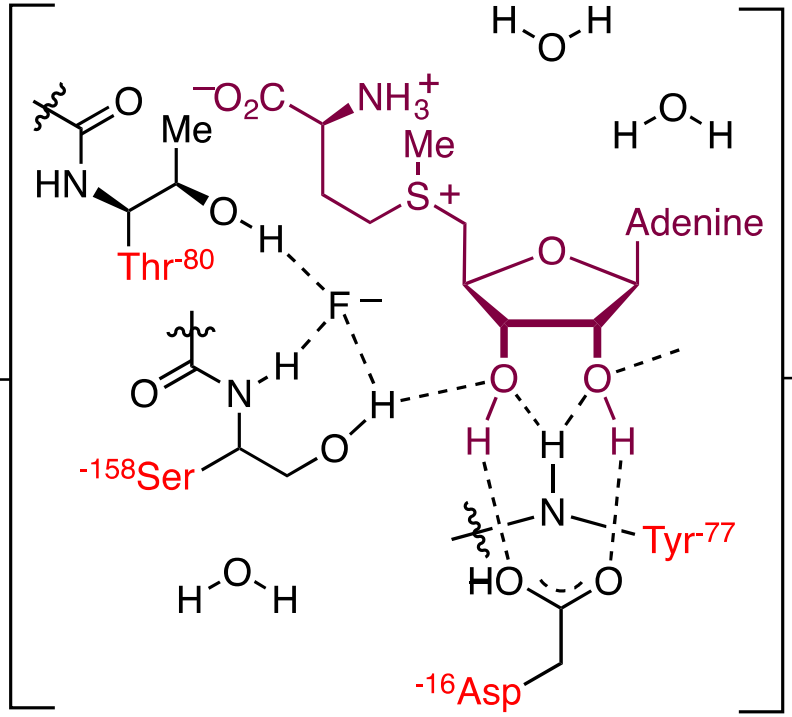
Importance of the Fluoride Source on Reactivity

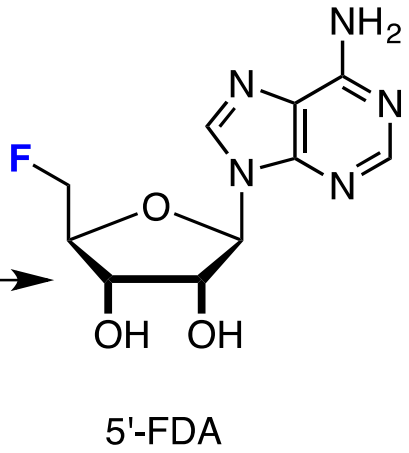


SAM

F^- (aq.)

fluorinase





5'-FDA

O'Hagan *Nature* **2002**, *416*, 279.

Catalytic Reactions for Tri- and Difluoromethylation: The State of Play

Véronique Gouverneur
University of Oxford
Chemistry Research Laboratory

BOSS XV
Tetrahedron Chair - Lecture 3
July 2016

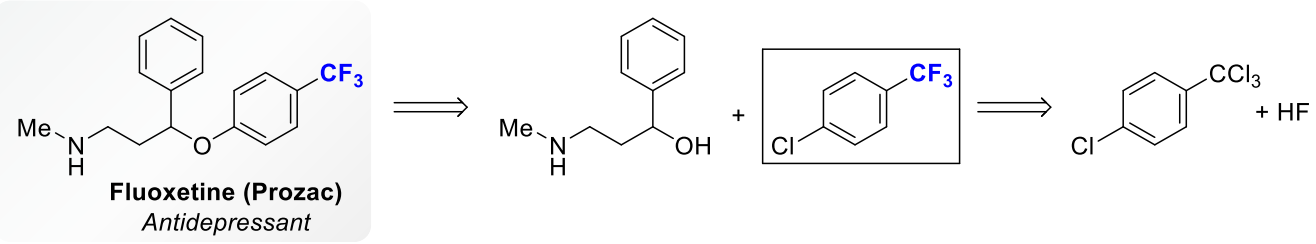
UNIVERSITY OF OXFORD

Contents

- Tri- and Difluoromethylating Reagents
- Tri- and Difluoromethylation of (Hetero)arenes
- $Csp^3 – CF_3$ Bond Construction
- Large Scale Applications

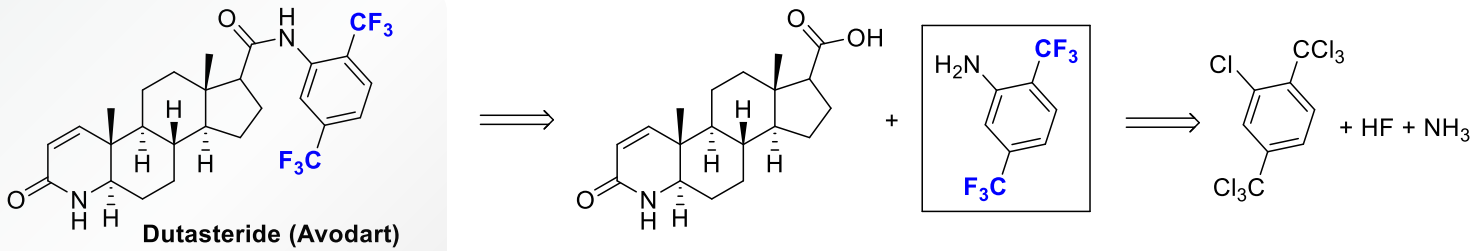
Top-Selling Drugs Containing CF_3

[A]



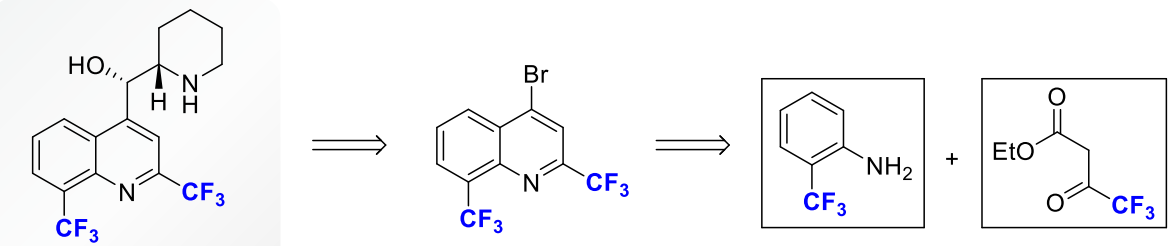
Fluoxetine (Prozac)
Antidepressant

[B]



Dutasteride (Avodart)
Benign prostatic hyperplasia treatment

[C]

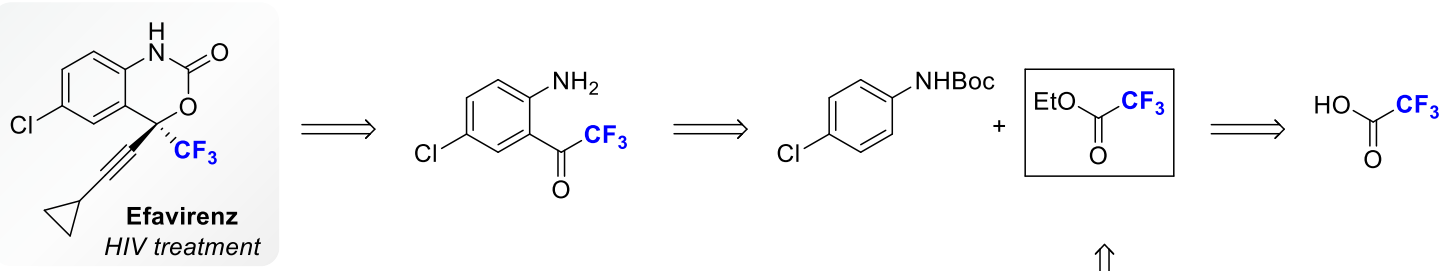


Mefloquine
Antimalarial drug

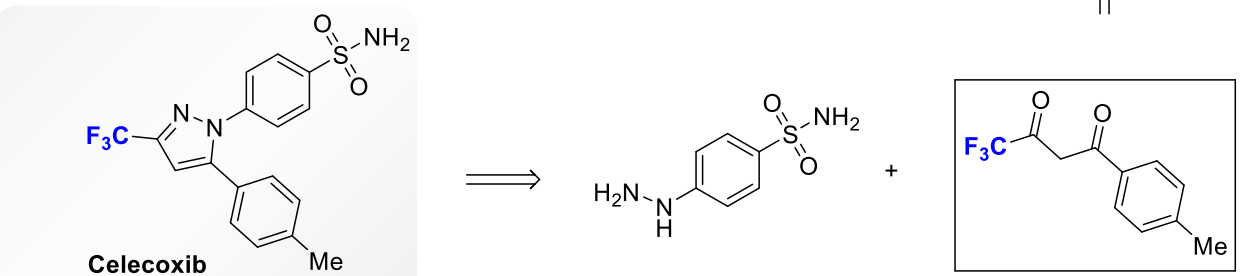
[A] US2004/102651 A1, **2004**; **[B] Reddy** *Org. Process Res. Dev.* **2007**, *11*, 842**; [C] Lutz** *J. Med. Chem.* **1971**, *14*, 926.

Top-Selling Drugs Containing CF_3

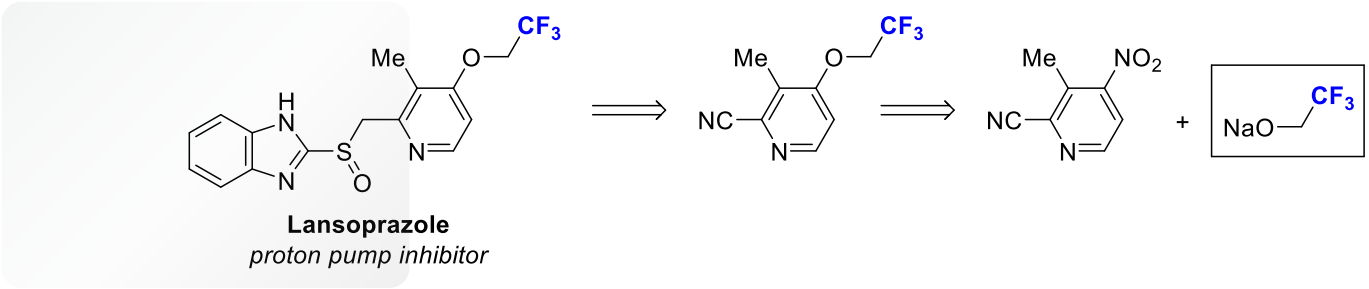
[A]



[B]



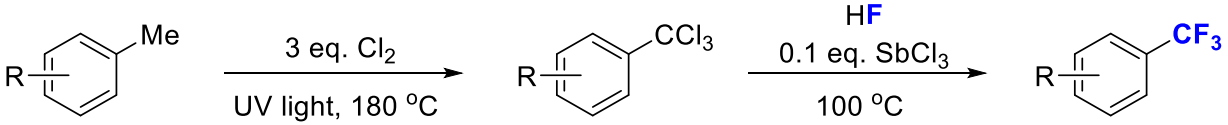
[C]



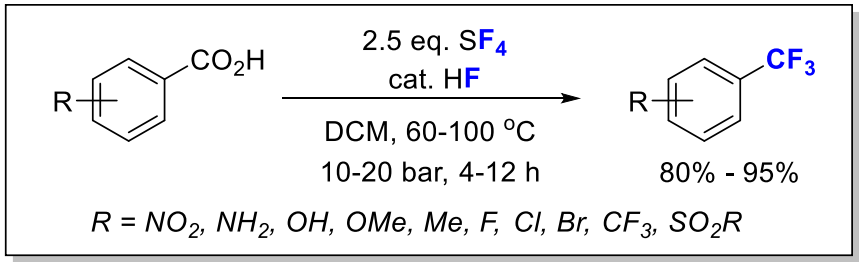
[A] Pierce *J. Org. Chem.* **1998**, *63*, 8536; **[B] Oh** *Tetrahedron Lett.* **2006**, *47*, 7943; **[C] Ahn** *Bull. Korean Chem. Soc.* **2002**, *23*, 626.

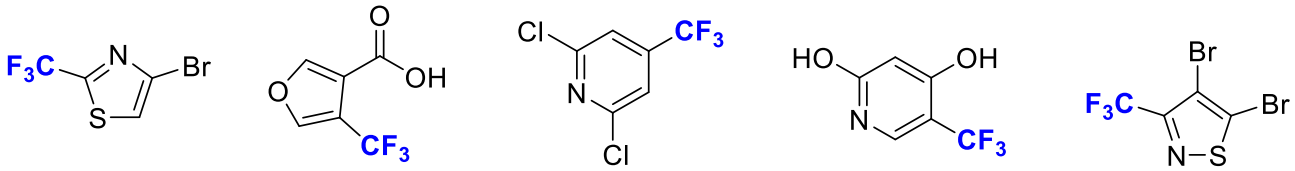
Industrial Preparation of Ar-CF_3

[A] Chlorination of toluene followed by Cl/F exchange



[B] Deoxyfluorination of aromatic carboxylic acids





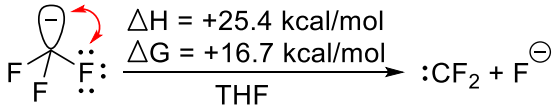
76% 79% 81% 86% 93%

[A] Swarts *Bull. Acad. R. Belg.* **1892**, *24*, 309; **Osswald**, **Müller**, **Steinhäuser** *German Patent*, 575593 (**1933**); **Filler** *Adv. Fluorine Chem.* **1970**, *6*, 1; **[B] Nickson** *J. Fluorine Chem.* **1991**, *55*, 173; **Hasek**, **Smith**, **Engelhardt** *J. Am. Chem. Soc.* **1960**, *82*, 543.

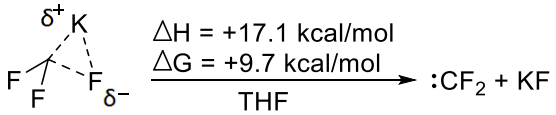
Trifluoromethyl Anion

[A] Calculated C-F bond dissociation enthalpy

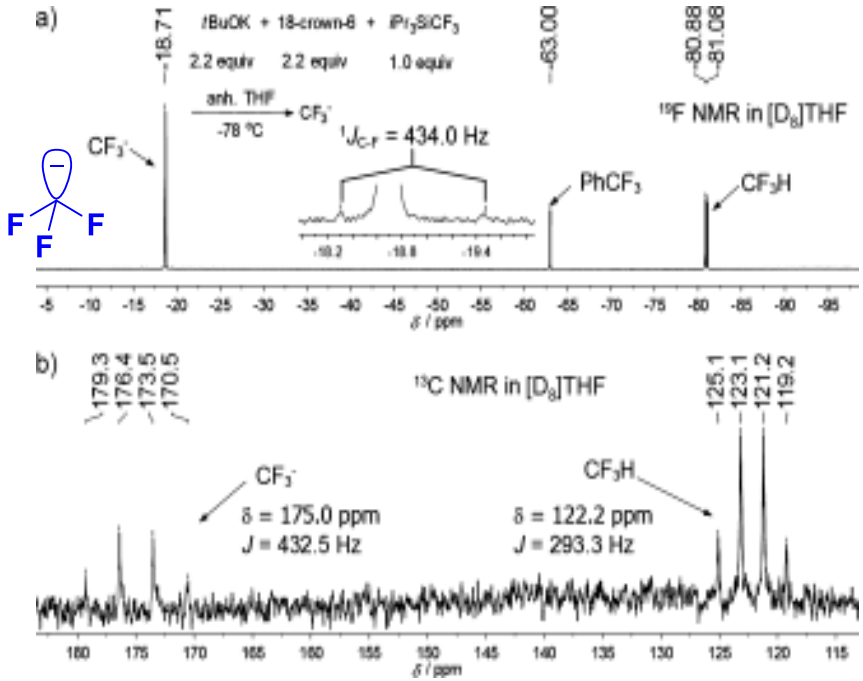
negative charge-lone pair repulsion



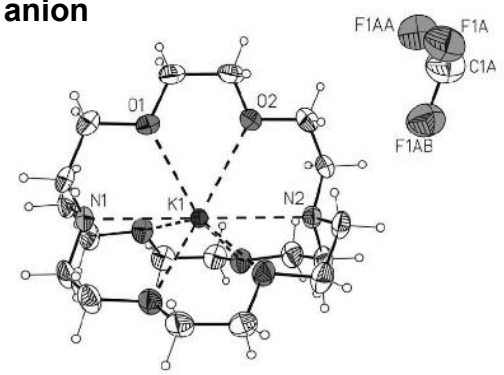
metal-fluorine interactions

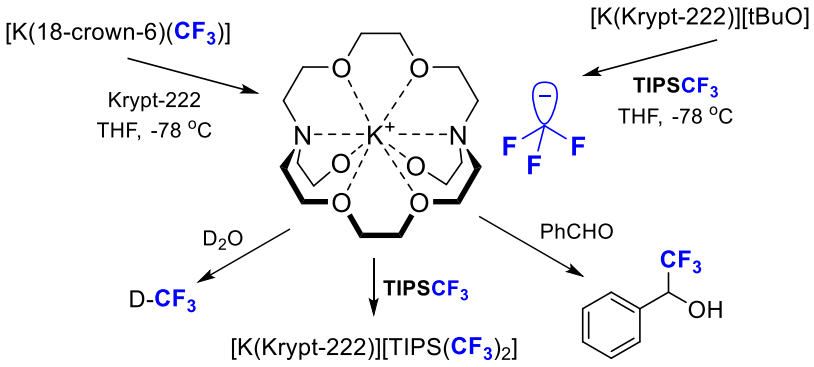


^{19}F and ^{13}C NMR spectra of CF_3 anion



[B] "Free" CF_3 anion





[A] Prakash *Angew. Chem. Int. Ed.* **2014**, *53*, 11575; **[B] Grushin** *Angew. Chem. Int. Ed.* **2015**, *54*, 15289.

Nucleophilic CF_3 Reagents

R = Me: Aldrich, £2400 per mol
R = Et: Aldrich, £17700 per mol

R_3SiCF_3
Prakash
Tet. Lett. **1984**, *25*, 2195

CF_3H
Kashimura
J. Org. Chem. **1991**, *56*, 2

CF_3I
Kobayashi
Tet. Lett. **1969**, *47*, 4095

CF_3Br
Paratian
J. Chem. Soc., Chem. Commun. **1992**, 53

(Phen)$CuCF_3$: Aldrich, £28000 per mol

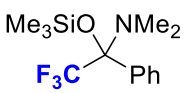
CF_3Cu
Burton
J. Am. Chem. Soc. **1986**, *108*, 832

CF_3Ag
Feng , Weng, Huang
Organomet. **2011**, *30*, 3229

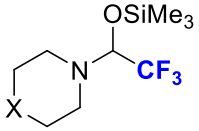
$Cd(CF_3)_2$
$Zn(CF_3)_2$
Burton
J. Am. Chem. Soc. **1985**, *107*, 5014

R_3SnCF_3
Willis
J. Am. Chem. Soc. **1960**, *82*, 1888

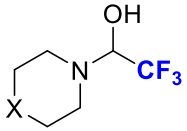
$Hg(CF_3)_2$
Kondratenko
Synthesis **1980**, 932



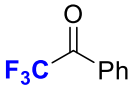
Motherwell
Synlett **2002**, 646



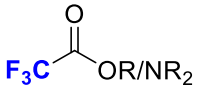
Langlois
Org. Lett. **2000**, *2*, 2101



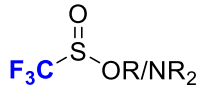
Langlois
Eur. J. Org. Chem. **2001**, 1467



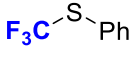
Langlois
Tet. Lett. **2003**, *44*, 1055



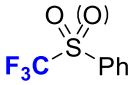
Langlois
Synlett **2000**, 230



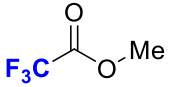
Langlois
Synlett **2000**, 233



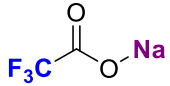
Yokoyama
Synlett **1996**, 1191



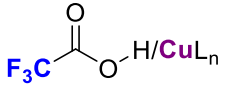
Prakash
Org. Lett. **2003**, *5*, 3253



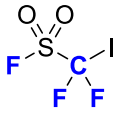
Langlois
J. Fluorine Chem. **2007**, *128*, 1318



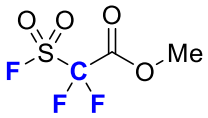
Matsui
Chem. Lett. **1981**, 1719



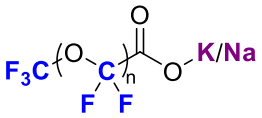
Vicic *J. Fluorine Chem.* **2010**, *131*, 1108
Weng *Chem. Eur. J.* **2016**, *22*, 2075



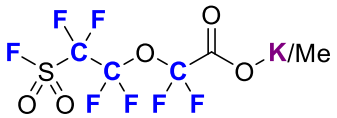
Chen
J. Chem. Soc., Perkin Trans. I **1989**, 2385



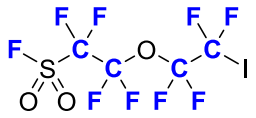
Chen
J. Chem. Soc. Chem. Commun. **1989**, 705



Palmer
US5475165 **1995**



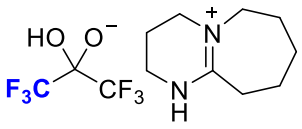
Chen *J. Fluorine Chem.* **1996**, *78*, 177
Chen *J. Chem. Soc., Chem. Commun.* **1993** 1389



Chen
Chin. J. Chem. **1994**, 464

R = Me: TCI, £2100 per mol

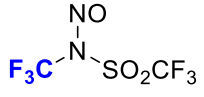
$K[F_3CB(OR)_3]$
Gooβen
Chem. Eur. J. **2011**, *17*, 2689



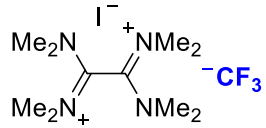
Colby
Org. Lett. **2013**, *15*, 1208

$:CF_2$ reagent + F^-
or DMF
or DBU

Burton *J. Am. Chem. Soc.* **1985**, *107*, 5014
Xiao *Org. Lett.* **2015**, *17*, 532



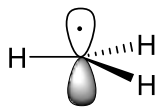
Umemoto
Bull. Chem. Soc. Jpn. **1986**, *59*, 447



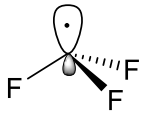
Dolbier
Org. Lett. **2001**, *3*, 4271

Properties of "$CF_3^{\cdot}$" and "CF_3^{+}"

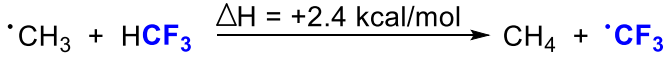
[A] CH_3 radical vs CF_3 radical



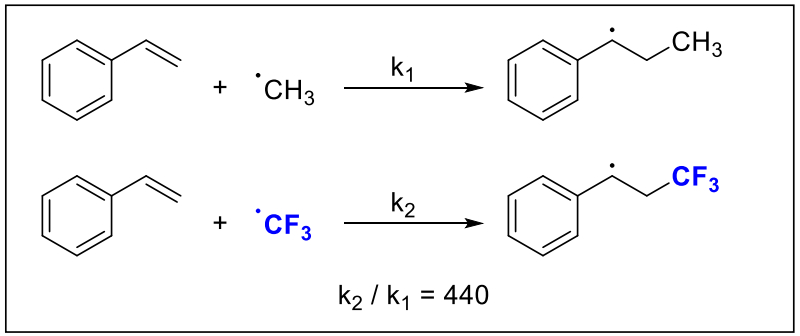
CH_3 radical
planar
"Nucleophilic"



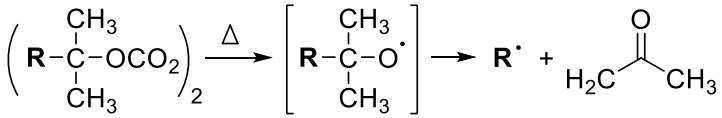
CF_3 radical
trigonal
"Electrophilic"



[A] Relative rate of reaction with styrene



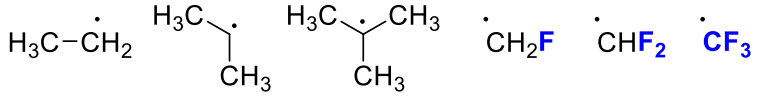
[B] Order of Stability of Fluorinated Radicals



R = CF_3 < CH_3 < CHF_2 ~ CH_2F

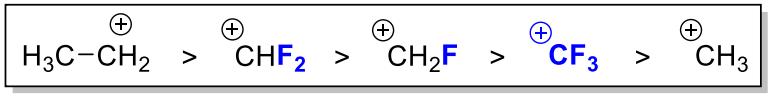
k_{rel} = 0.08 : 1 : 10.2 : 9.0

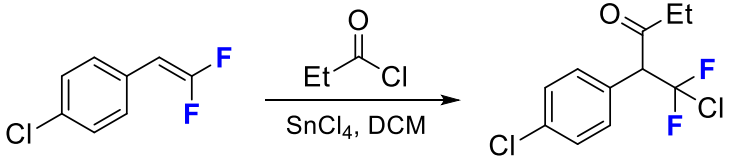
Calculated Stabilisation Energies (eV)

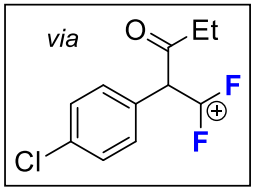


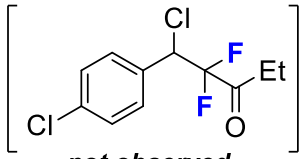
3.3	5.8	8.0	1.6	0.6	- 4.2

[D] Order of Stability of Fluorinated Cations





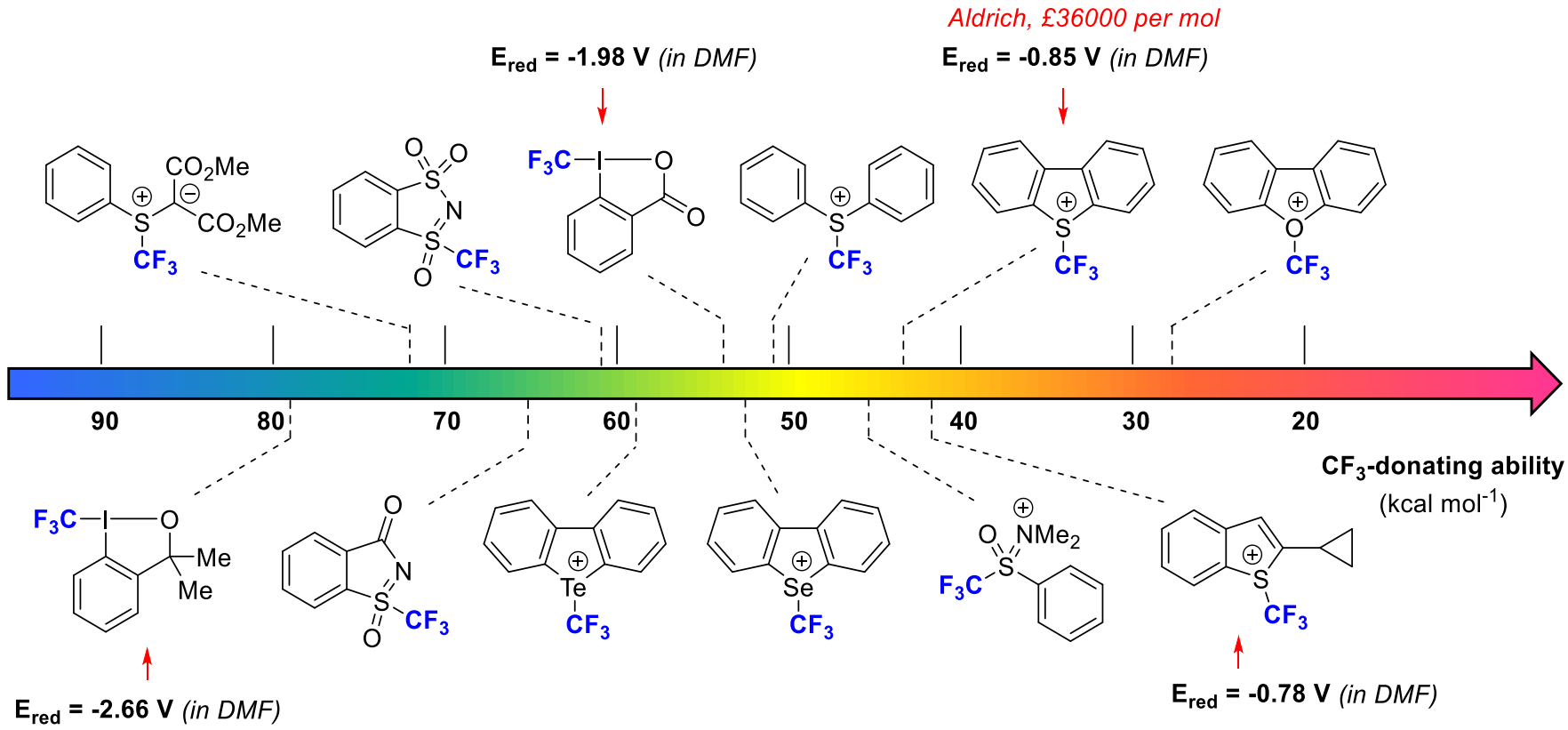




not observed

[A] Studer *Angew. Chem. Int. Ed.* **2012**, *51*, 8950; **Dolbier** *Chem. Rev.* **1996**, *96*, 1557; **[B] Jiang** *J. Org. Chem.* **1989**, *54*, 5648; **Pasto** *J. Org. Chem.* **1987**, *52*, 3062; **[C] Beauchamp** *J. Am. Chem. Soc.* **1974**, *96*, 1269; **Viehe** *Tetrahedron* **1987**, *43*, 4309; **Suda** *Tetrahedron Lett.* **1980**, *21*, 2555.

Electrophilic CF_3 Reagents



Cheng *J. Org. Chem.* **2016**, *81*, 3119; **Médebielle** *J. Fluorine Chem.* **2013**, *155*, 124.

Sources of CF_3 Radical

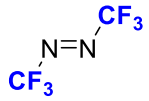
Aldrich, £1200 per mol

CF_3I

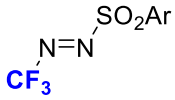
Hazeldine
Chem. Commun. **1949**, *47*, 6632

CF_3Br

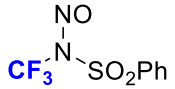
Akiyama
Bull. Chem. Soc. Jpn. **1988**, *61*, 3531



Szwarc
J. Am. Chem. Soc. **1961**, *83*, 4732



Umemoto
Chem. Lett. **1982**, 1519



Umemoto
Tet. Lett. **1982**, *23*, 3929

$Hg(CF_3)_2$

Naumann
J. Fluorine Chem. **1985**, *30*, 73

$Te(CF_3)_2$

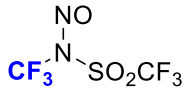
Naumann
J. Fluorine Chem. **1990**, *47*, 283

$Cd(CF_3)_2$
$Sb(CF_3)_3$

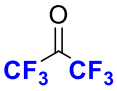
Naumann
J. Fluorine Chem. **1990**, *46* 265

$Bi(CF_3)_3$

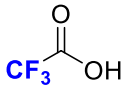
Naumann
J. Fluorine Chem. **2000**, *106*, 217



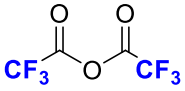
Umemoto
Bull. Chem. Soc. Jpn. **1986**, *59*, 447



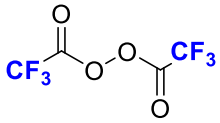
Charles
Trans. Faraday Soc. **1960**, *56*, 794



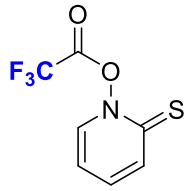
Muller
J. Org. Chem. **1983**, *48*, 1370



Yoshida
J. Chem. Soc. Perkin Trans. I **1989**, 909

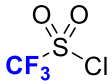


Sawada
J. Fluorine Chem. **1990**, *46*, 423

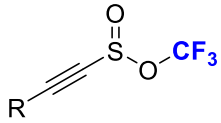


Barton
Tet. **1986**, *42*, 2325

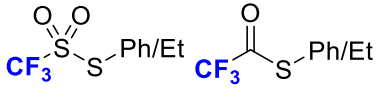
Aldrich, £1000 per mol



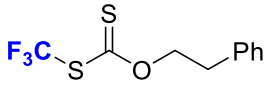
Kamigata
J. Chem. Soc. Perkin Trans. I **1991**, 627



Fuchs
J. Am. Chem. Soc. **1996**, *118*, 4486

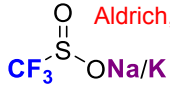


Langlois
Tet. Lett. **2000**, *41*, 3069

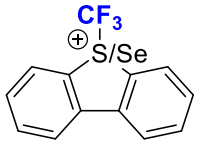


Zard
Org. Lett. **2001**, *3*, 1069

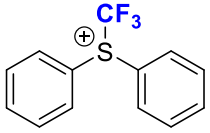
Aldrich, £1200 per mol



Langlois
Phosphorus, Sulfur Silicon Relat. Elem. **1991**, *59*, 169
Langlois *Synlett* **2002**, 1697



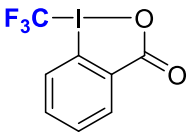
Umemoto
Tet. Lett. **1990**, *31*, 3579



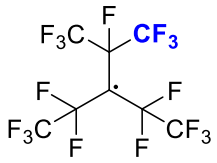
Xiao
Chem. Commun. **2011**, *47*, 6632

$Me_3Si\text{-}CF_3$

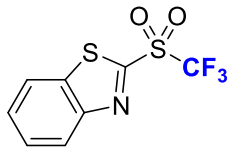
Sanford
Org. Lett. **2011**, *13*, 5464



Togni
ACS Catal. **2012**, *2*, 521

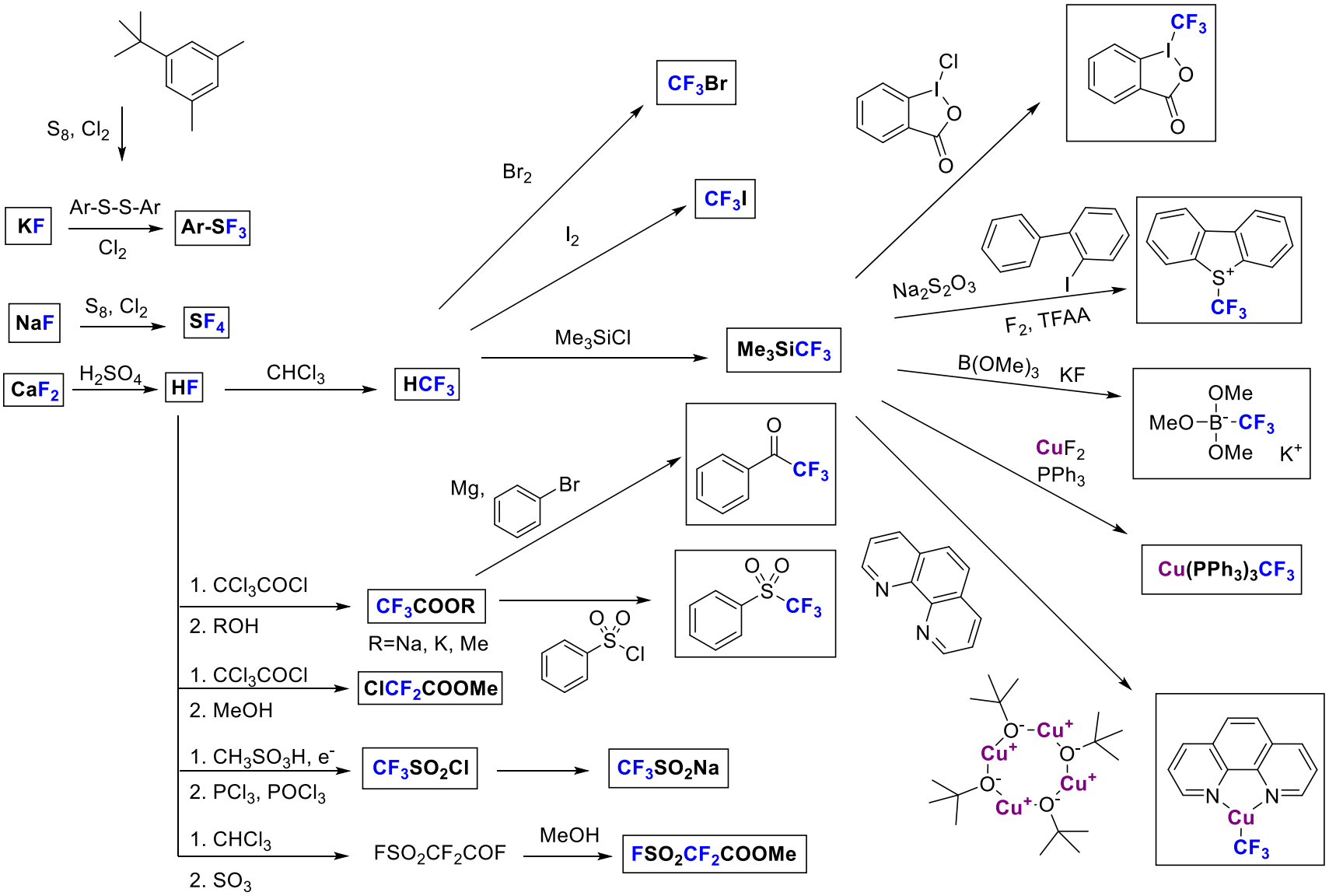


Soloshonok
Chem. Commun. **2015**, *51*, 5967



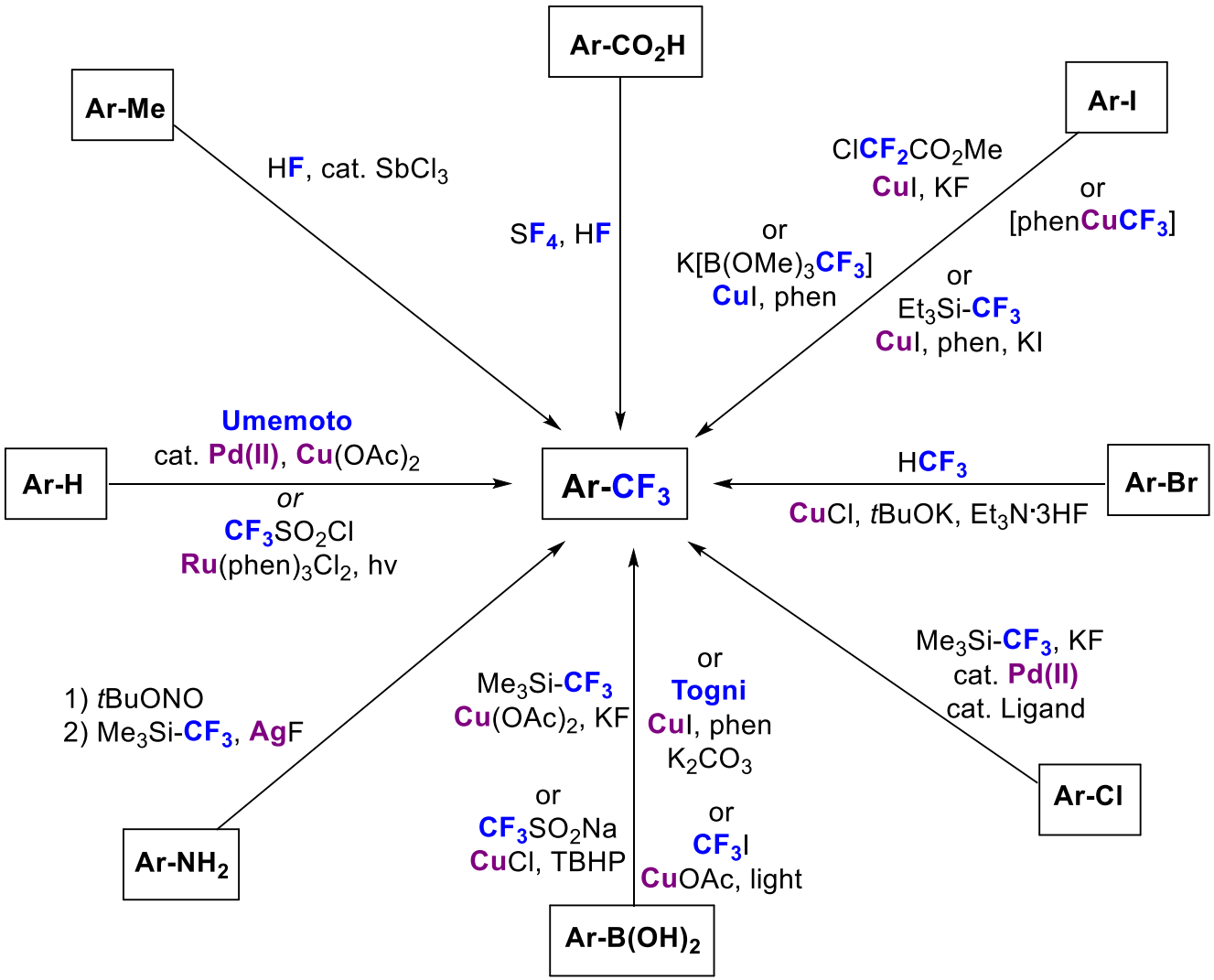
Hu
Angew. Chem. Int. Ed. **2016**, *55*, 2743

Routes to CF_3 Reagents



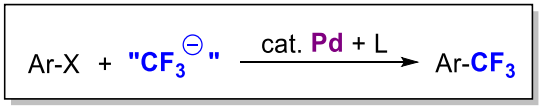
Adapted from Steiner *Chim. Oggi Chem. Today* **2015**, *33*, 26.

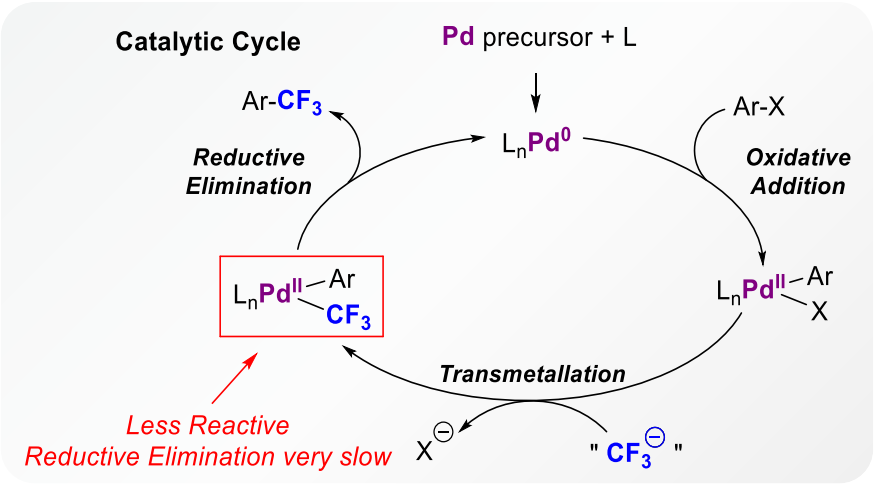
Trifluoromethylation of (Hetero)arenes

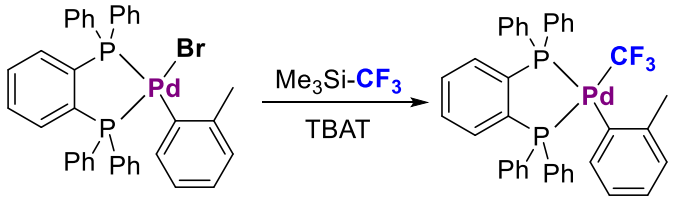


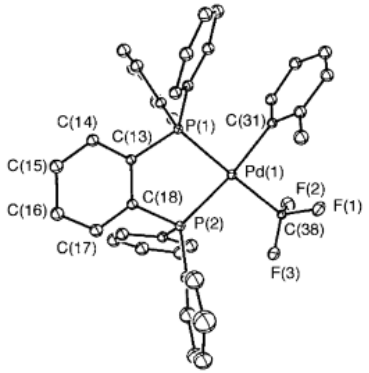
Soloshonok *J. Fluorine Chem.* **2014**, *167*, 37; **Steiner** *Chim. Oggi Chem. Today* **2015**, *33*, 26.

Palladium Mediated Trifluoromethylation of Aryl Halides

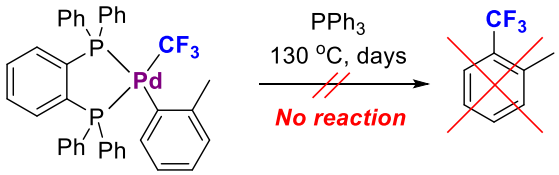


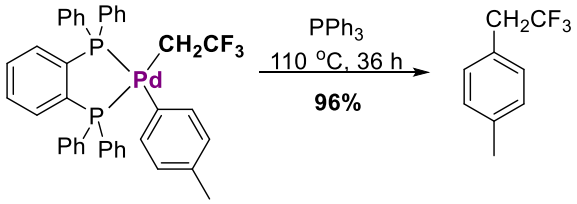


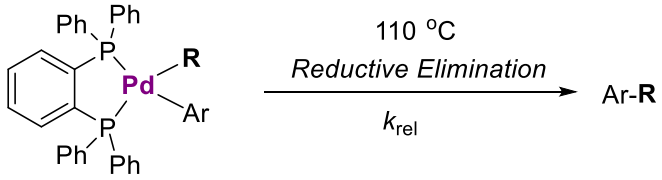




Electronic Effects on Reductive Elimination







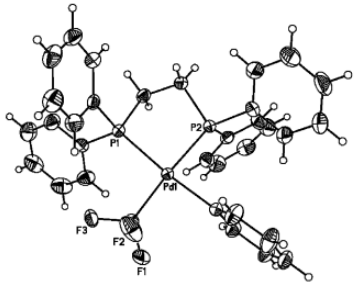
Taft Substituent Constants →	σ*	k_{rel} (110 °C)
R = **CH_3**	0.00	>600
R = **CH_2Ph**	0.22	>250
R = **$CH_2C(O)Ar$**	0.60	31
R = **CH_2CF_3**	0.92	1.7
R = **CH_2CN**	1.30	1
R = **CF_3**	2.60	no reaction

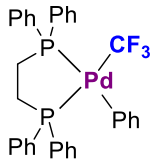
Hartwig *Organometallics* **2004**, *23*, 3398.

Palladium Mediated Trifluoromethylation of Aryl Halides

Effect of Ligands on Reductive Elimination

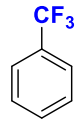
dppe





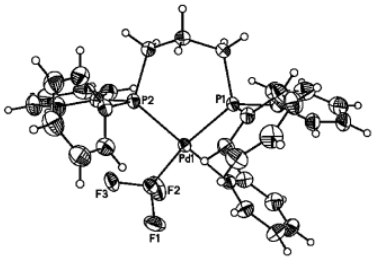
Xylene, 145 °C, 64 h

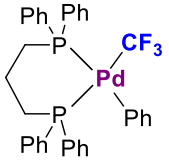
poor selectivity



ca. 10%

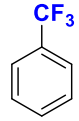
dppp



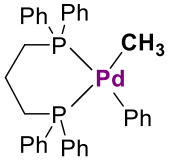


Xylene, 145 °C, 6 h

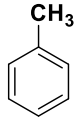
ca. 60% selectivity



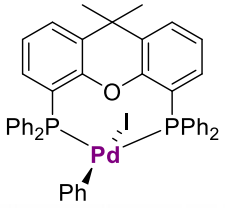
ca. 30%



15 - 40 °C

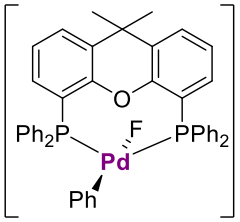


Xantphos

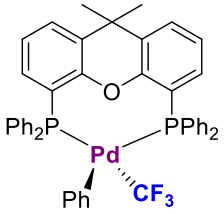


AgF, Benzene

rt, ultrasound

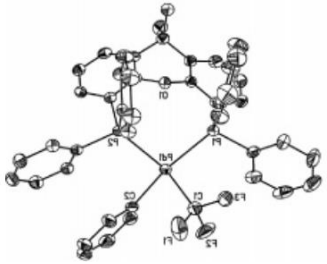


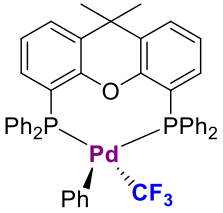
Me_3Si-CF_3



88%

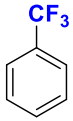
(10:1, *cis*:*trans*)





Benzene

80 °C, 3 h

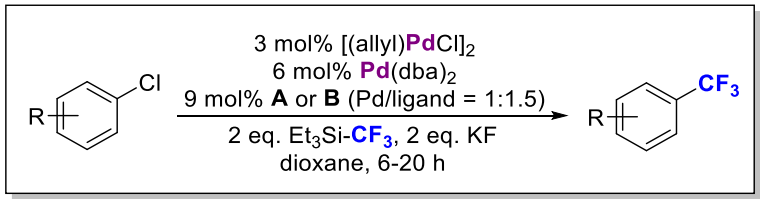


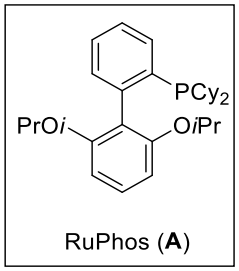
100%

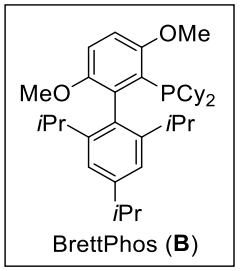
\+ **Pd**(Xantphos)$_2$

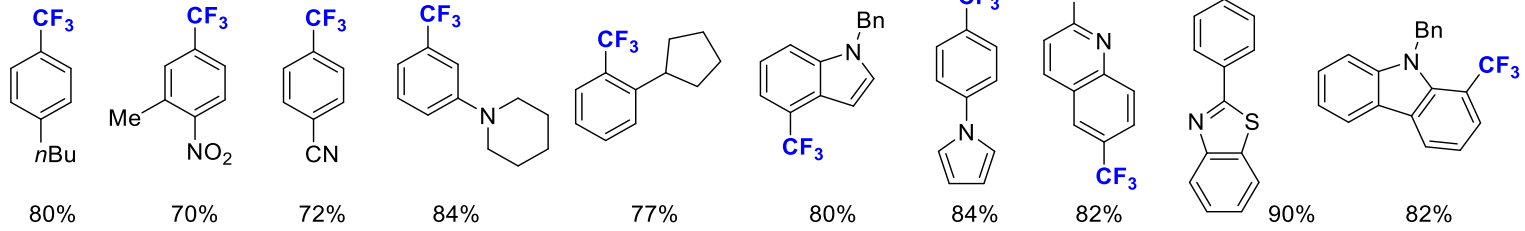
Grushin *J. Am. Chem. Soc.* **2006**, *128*, 4632; *J. Am. Chem. Soc.* **2006**, *128*, 12644; **Ozawa** *Organometallics* **1989**, *8*, 180.

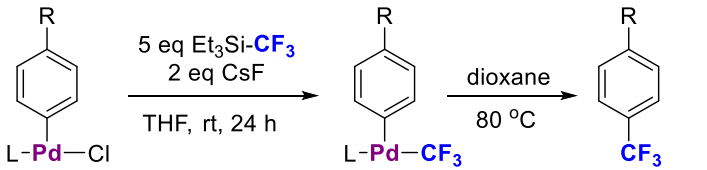
Palladium Catalysed Trifluoromethylation of Aryl Halides

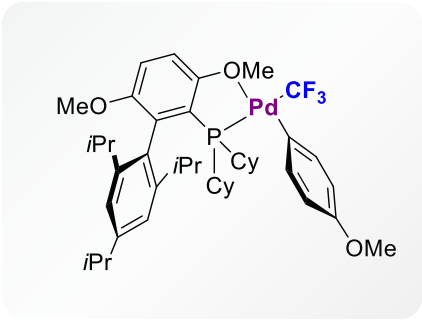






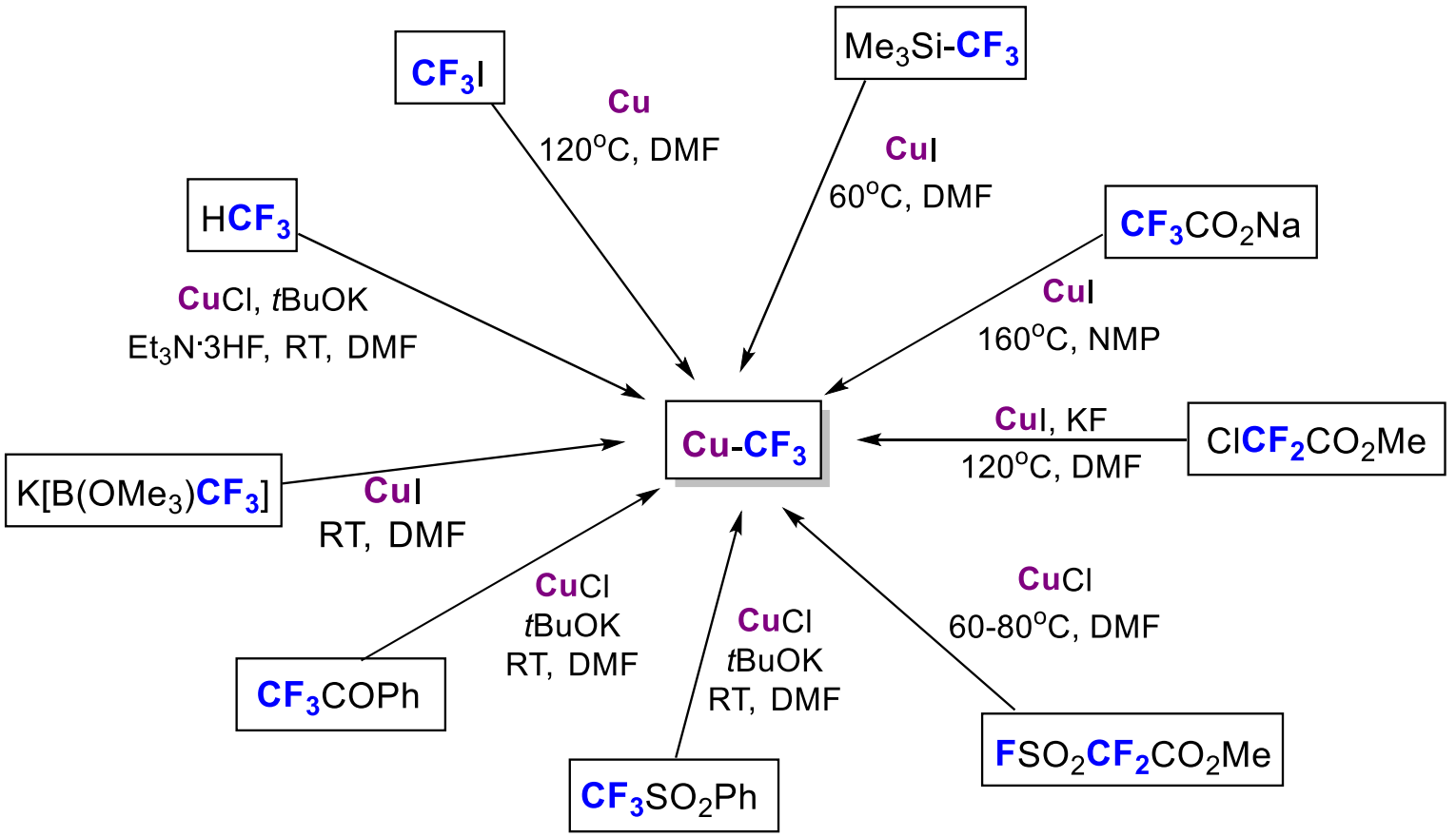






Buchwald *Science* **2010**, *328*, 1679.

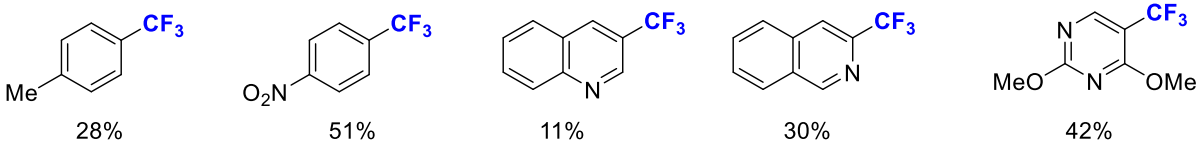
Routes to Cu-CF_3



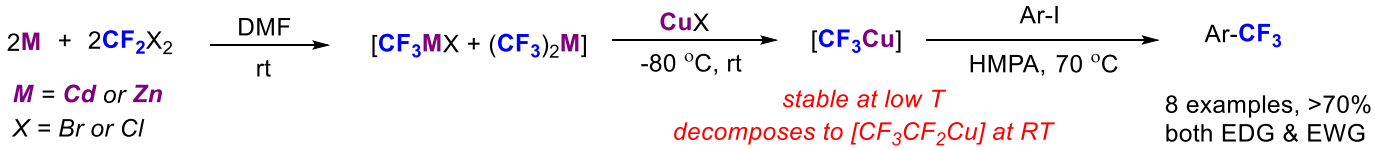
Steiner *Chim. Oggi Chem. Today* **2015**, *33*, 26; **Normant** *Tetrahedron* **2000**, *56*, 275.

Copper Mediated Trifluoromethylation of Aryl Halides

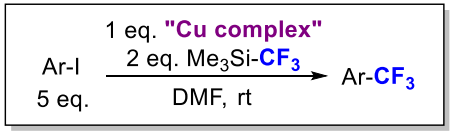
[A] First example

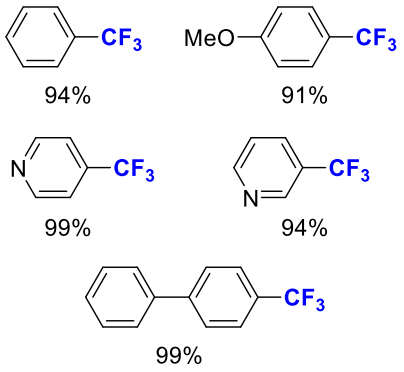


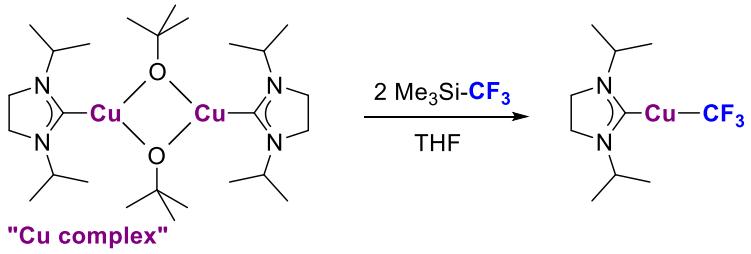
[B] First pregenerative route to $CuCF_3$

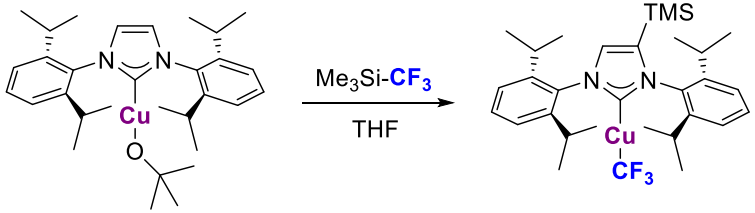


[C] First thermally stable and well-defined $CuCF_3$ complex





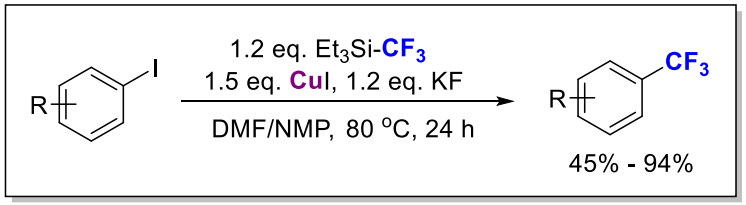




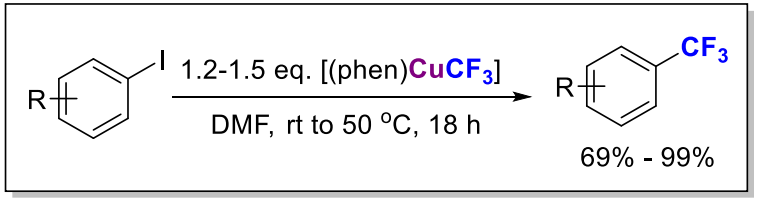
[A] Kobayashi *Tetrahedron Lett.* **1969**, *47*, 4095; *J. Chem. Soc., Perkin Trans. 1* **1980**, 2755; **[B] Burton** *J. Am. Chem. Soc.* **1986**, *108*, 832; **[C] Vicic** *J. Am. Chem. Soc.* **2006**, *130,* 8600.

Copper Mediated Trifluoromethylation of Aryl Halides

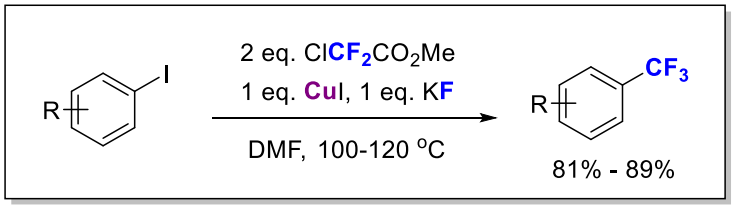
[A]



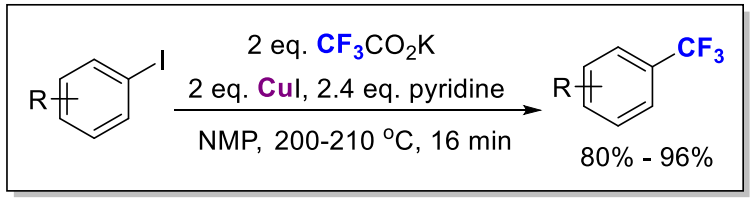
[B]



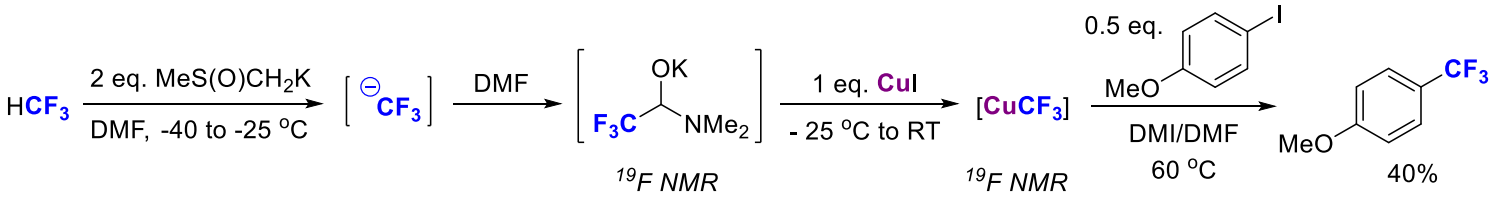
[C]



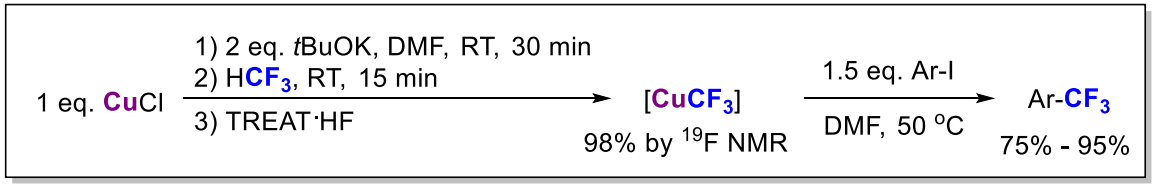
[D]



[E]



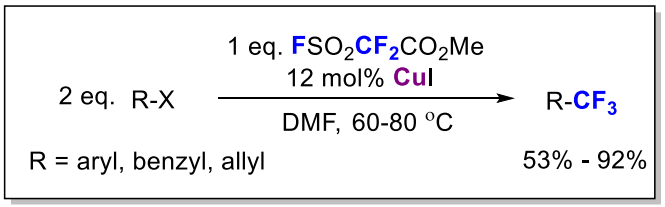
[F]

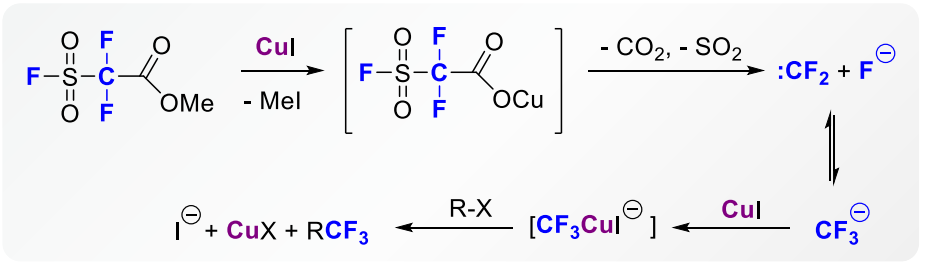


[A] Fuchikami *Tetrahedron Lett.* **1991**, *32*, 91; **[B] Hartwig** *Angew. Chem. Int. Ed.* **2011**, *50*, 3793; **[C] Chen** *Tetrahedron Lett.* **1991**, *32*, 7689; **[D] Buchwald** *Angew. Chem. Int. Ed.* **2013**, *52*, 11628; **[E] Normant** *Tetrahedron* **2000**, *56*, 275; **[F] Grushin** *J. Am. Chem. Soc.* **2011**, *133*, 20901.

Copper Catalysed Trifluoromethylation of Aryl Halides

[A]





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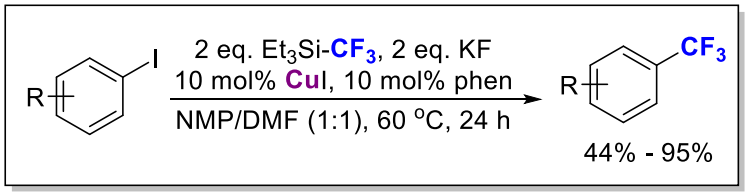
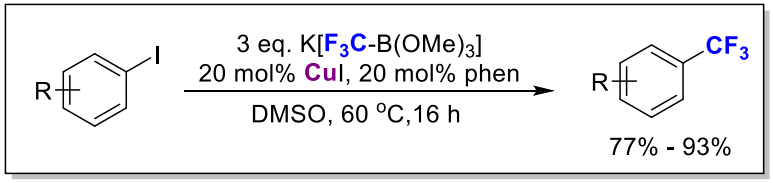
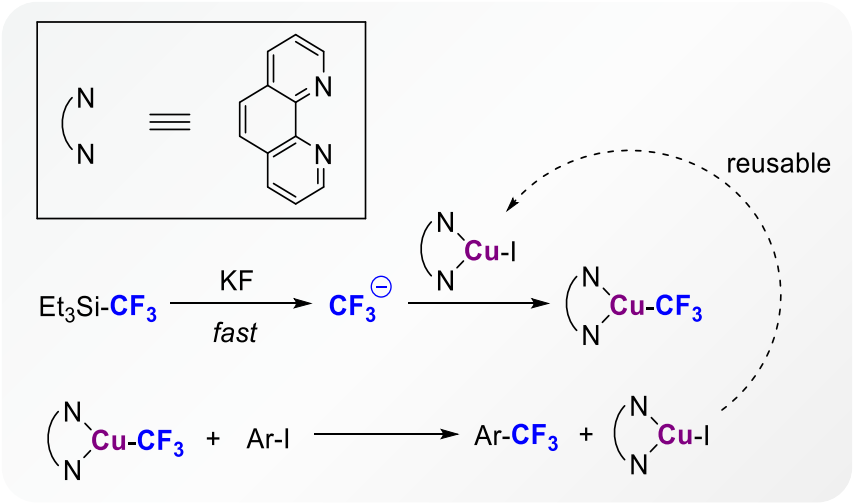
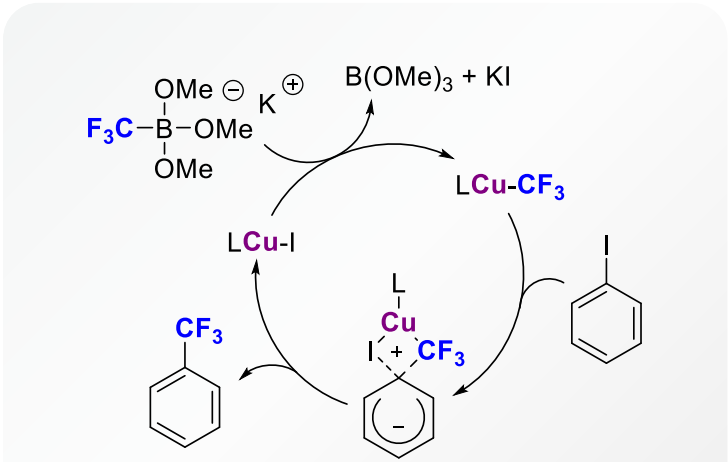


[C]



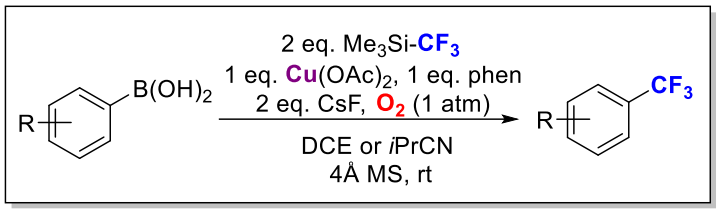


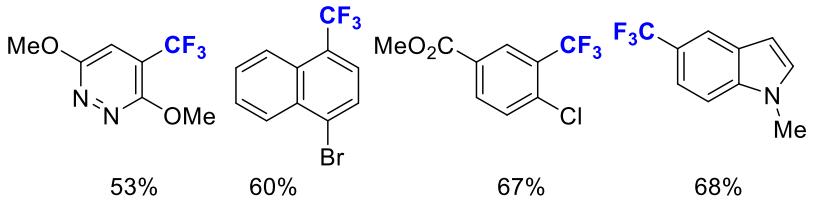


[A] Chen *J. Chem. Soc., Chem. Commun.* **1989**, 705; **[B] Amii** *Chem. Commun.* **2009**, 1909; **[C] Gooßen** *Chem. Eur. J.* **2011**, *17*, 2689; **Novak** *Org. Lett.* **2014**, *16*, 4268.

Copper Mediated Trifluoromethylation of Ar-B(OR)$_2$

[A]





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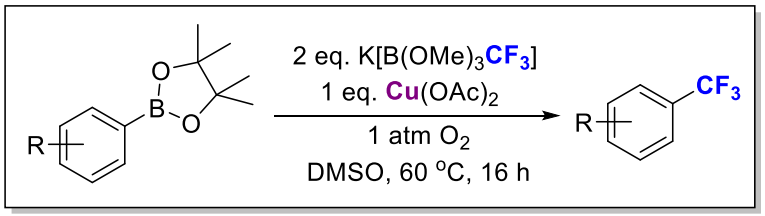
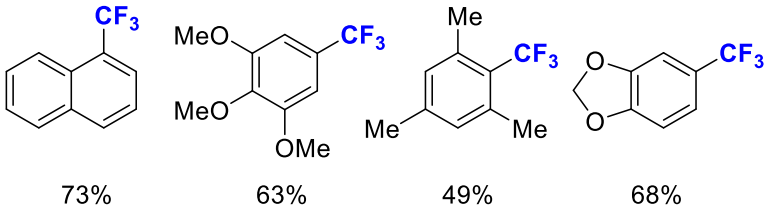
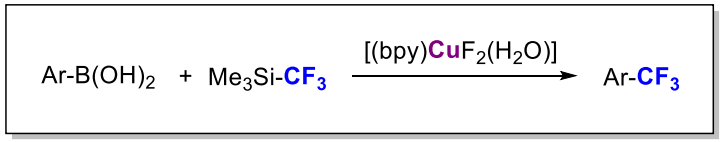
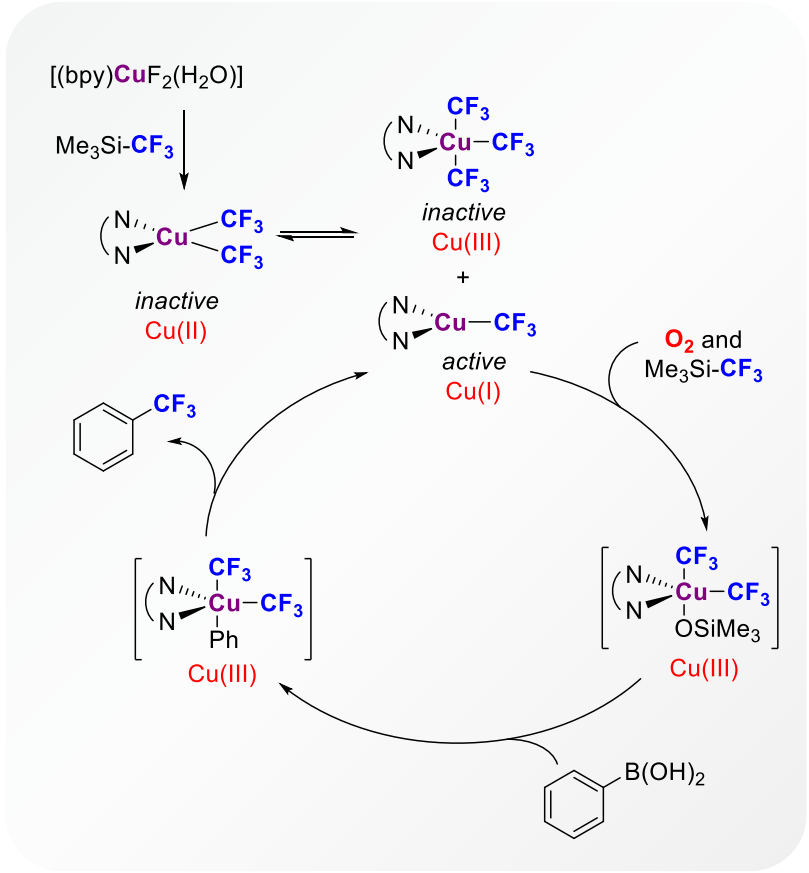




[C]

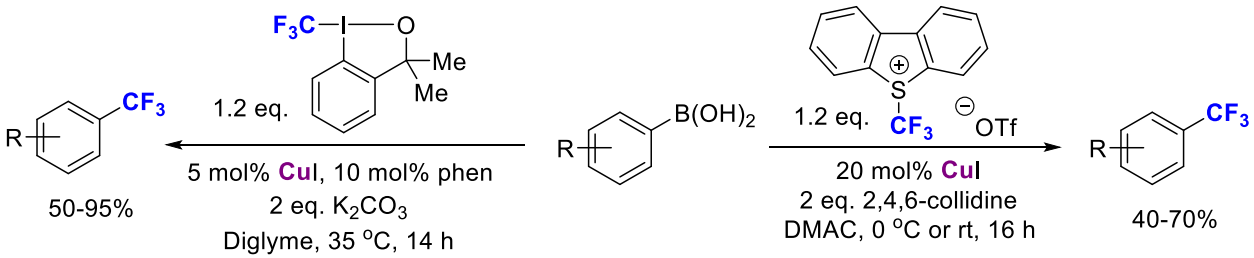




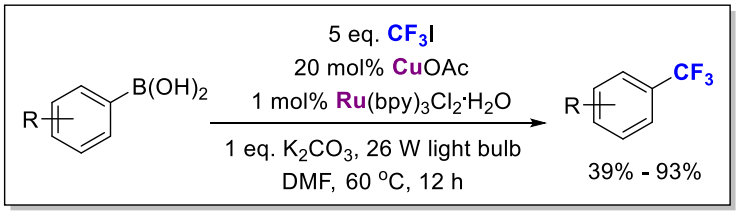
[A] Buchwald *J. Org. Chem.* **2011**, *76*, 1174; **[B] Gooßen** *Chem. Eur. J.* **2012**, *18*, 1577; **[C] Grushin** *J. Am. Chem. Soc.* **2014**, *136*, 16998.

Copper Catalysed Trifluoromethylation of Ar-B(OR)$_2$

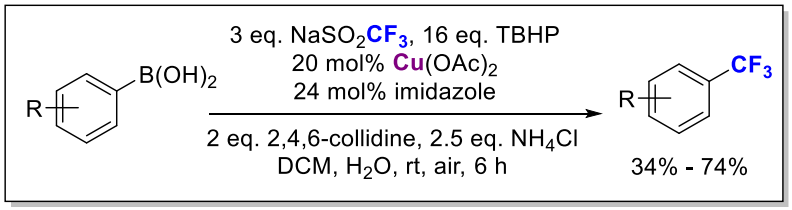
[A]

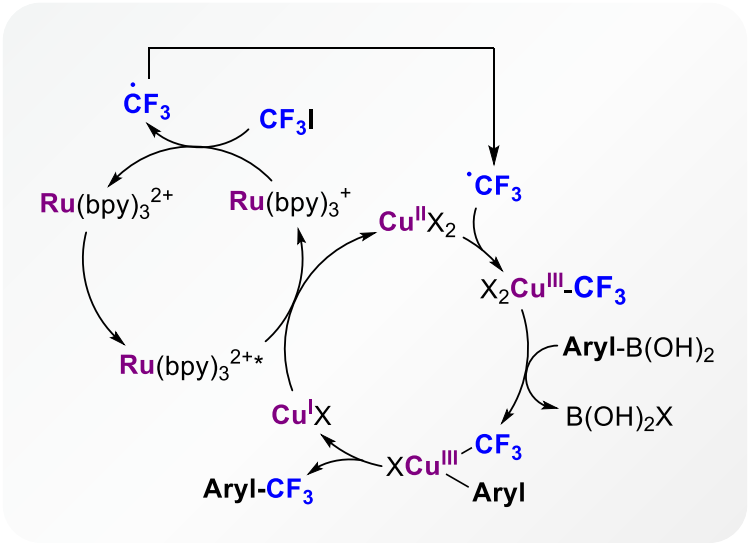


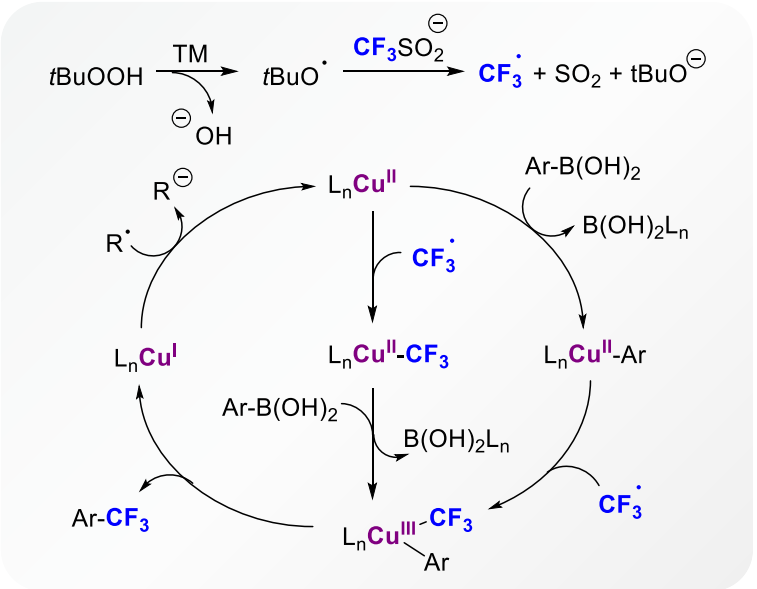
[B]



[C]



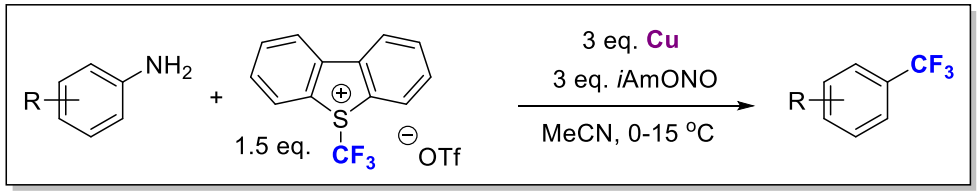


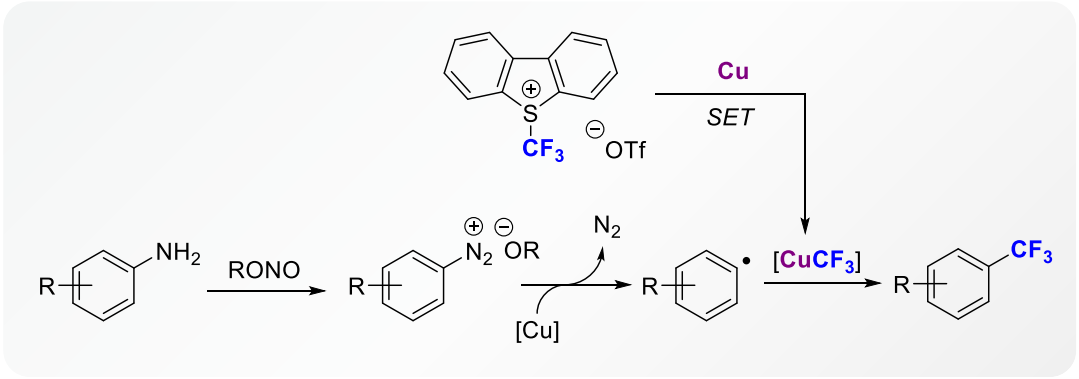


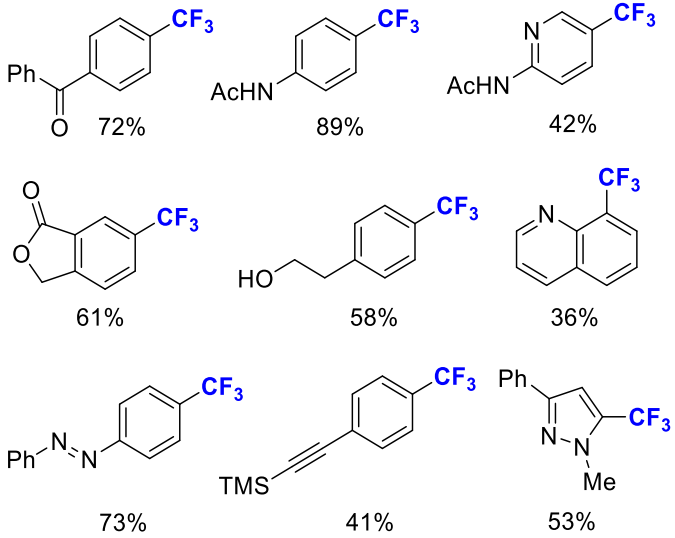
[A] Liu *Chem. Comm.* **2011**, *47*, 4300; **Shen** *Org. Lett.* **2011**, *13*, 2342; **[B] Sanford** *J. Am. Chem. Soc.* **2012**, *134*, 9034; **[C] Qing** *J. Org. Chem.* **2012**, *77*, 1251; **Beller** *Chem. Commun.* **2013**, *49*, 2628.

Copper Mediated Trifluoromethylation of Diazonium Salts

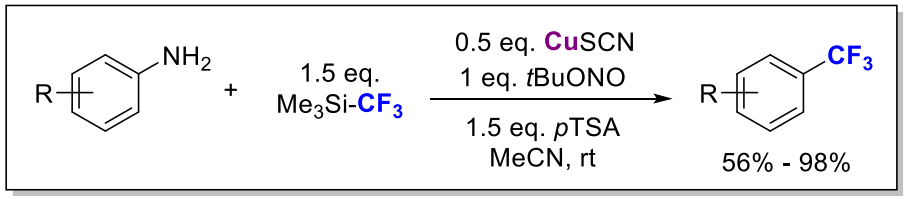
[A]

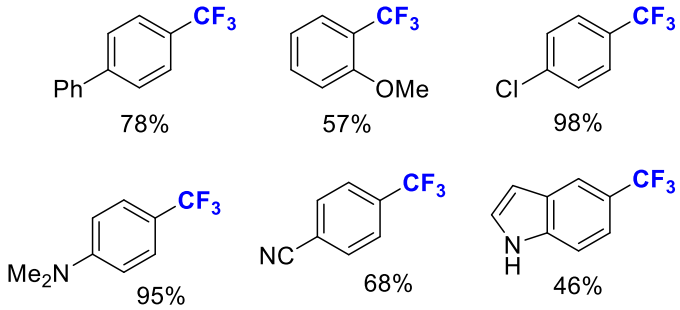






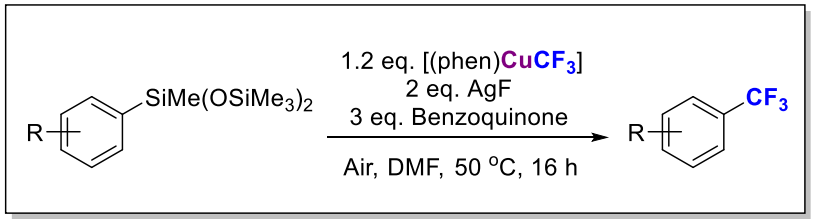
[B]

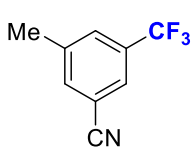




[A] Fu *J. Am. Chem. Soc.* **2013**, *135*, 8436; **[B] Gooßen** *Angew. Chem. Int. Ed.* **2013**, *52*, 7972.

Copper Mediated Trifluoromethylation of Arylsilanes





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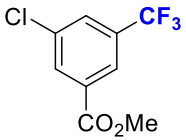

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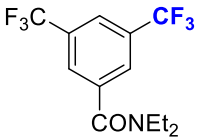

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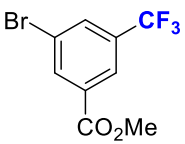

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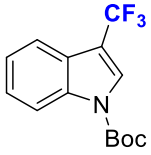

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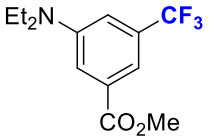

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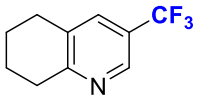

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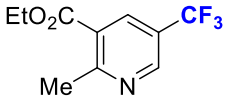

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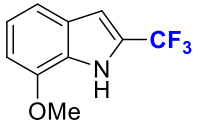

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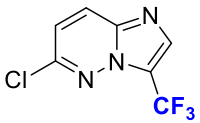

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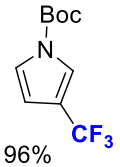

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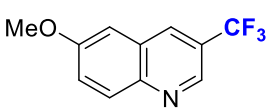

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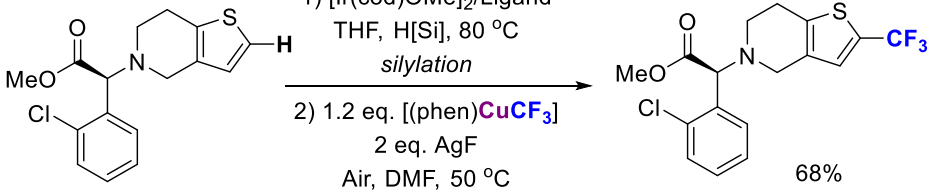

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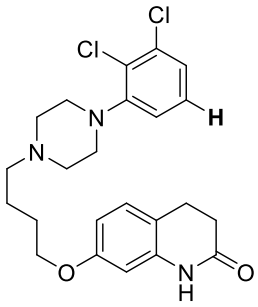
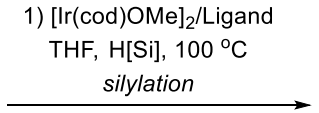
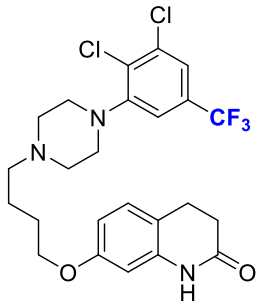




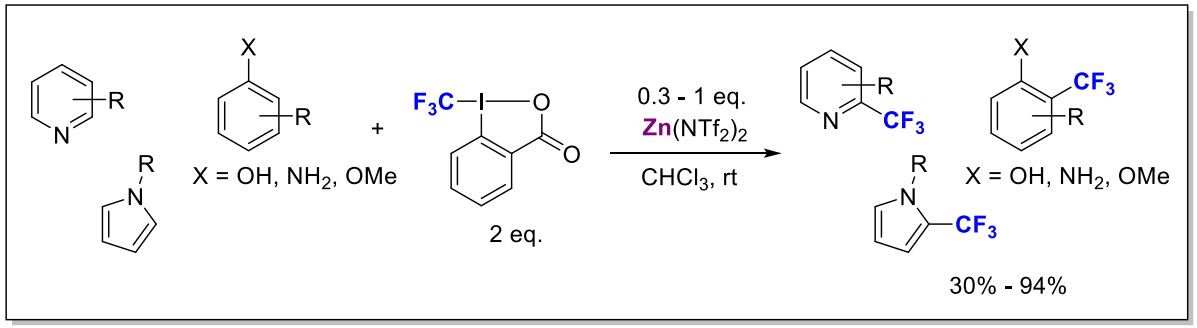


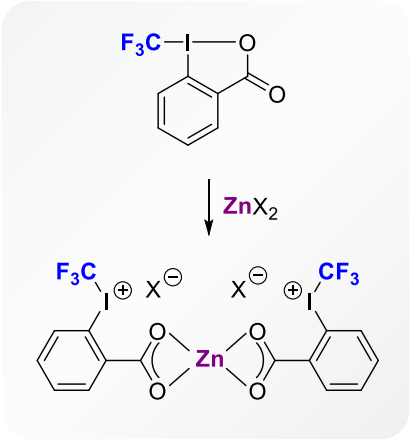
31%

Hartwig *Angew. Chem. Int. Ed.* **2016**, *55*, *DOI: 10.1002/anie.201601163.*

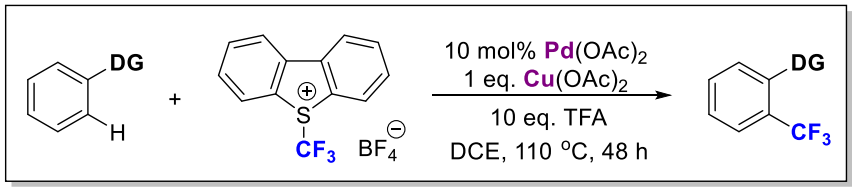
Trifluoromethylation *via* C-H Functionalisation

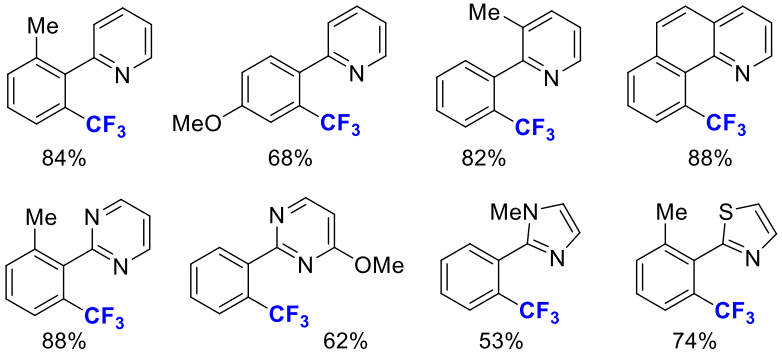
[A] Lewis Acid Activation

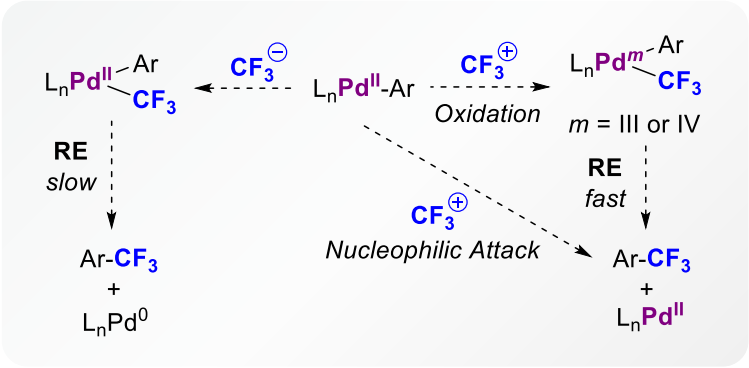


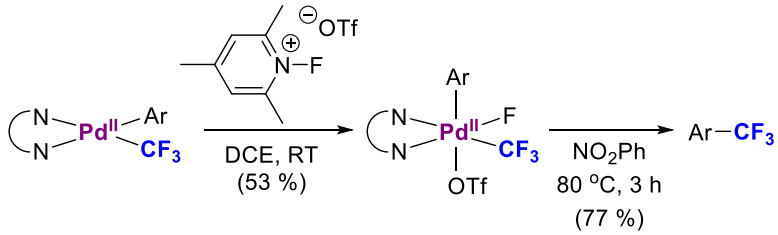


[B] Palladium Catalysed C-H activation





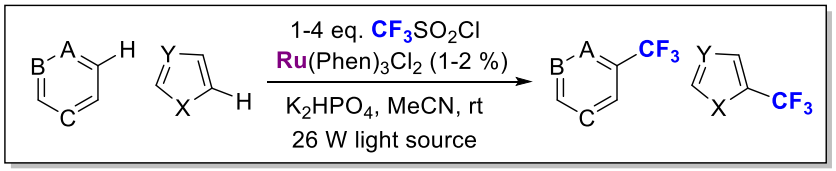


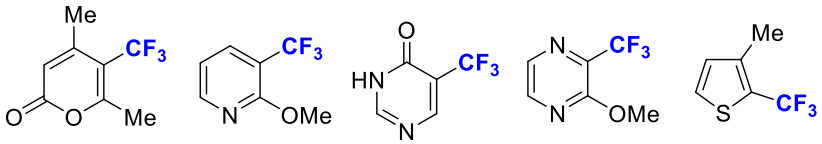


[A] Togni *J. Fluorine Chem.* **2010**, *131*, 951; **[B] Yu** *J. Am. Chem. Soc.* **2010**, *132*, 3648; **Sanford** *J. Am. Chem. Soc.* **2010**, *132*, 2878 for recent example using CF_3Br see: **Beller** *Angew. Chem. Int. Ed.* **2016**, *55*, 2782.

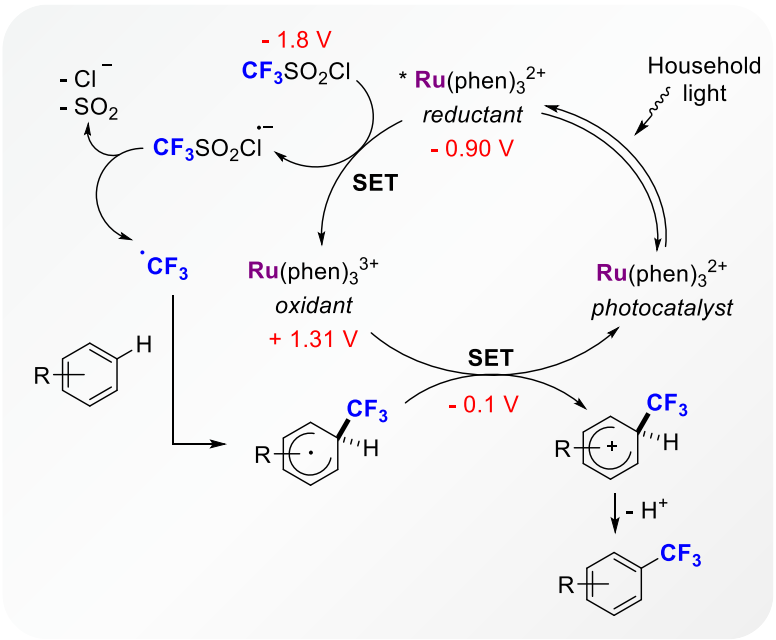
Trifluoromethylation *via* C-H Functionalisation

[A]

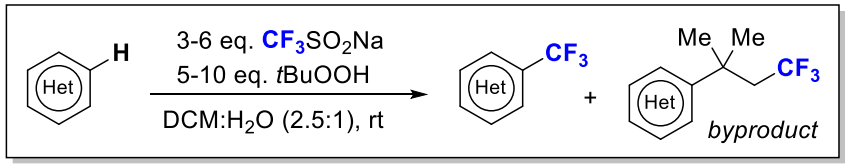


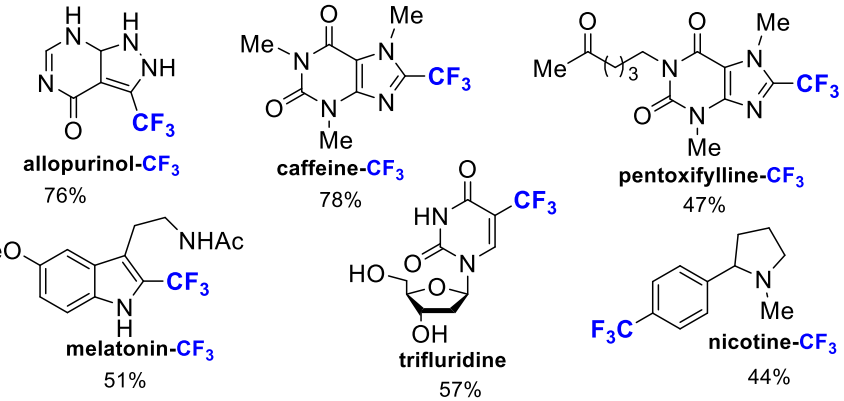


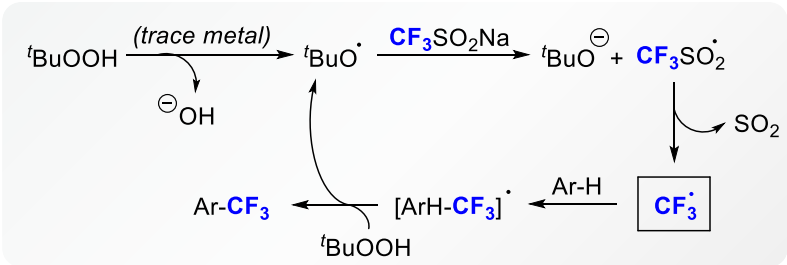
90% 78% (3:1) 74% 82% 76% (3:1)



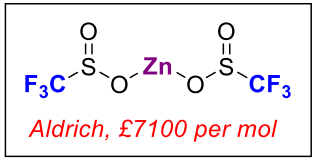
[B]







[C]

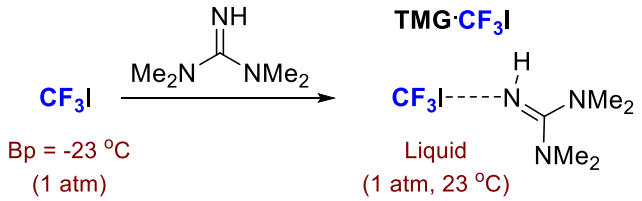


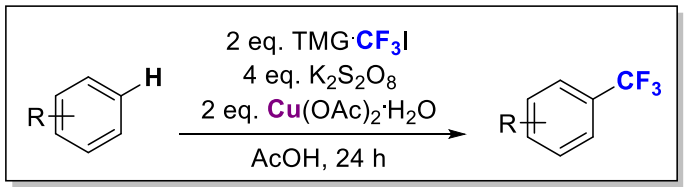
- enhanced reactivity
- easily prepared
- bench-stable
- free-flowing solids

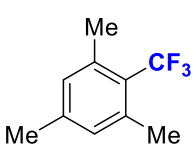
[A] MacMillan *Nature* **2011**, *480*, 224; **[B] Baran** *Proc. Natl. Acad. Sci. U.S.A.* **2011**, *108*, 14411; **[C] Baran** *Nature* **2012**, *492*, 95.

Trifluoromethylation *via* C-H Functionalisation

[A]







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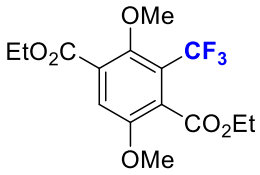

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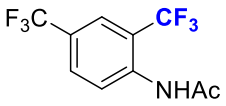

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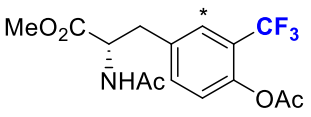
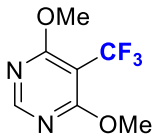
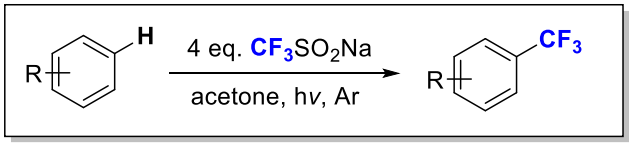


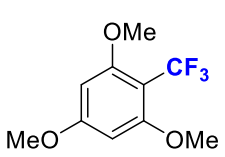
52% (1.7:1)



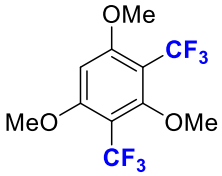
50%

[B]

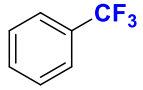




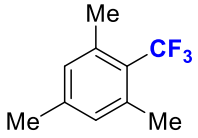
95% (2h)



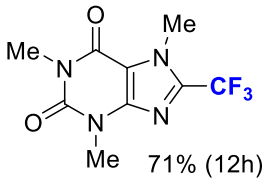
85% (20h)



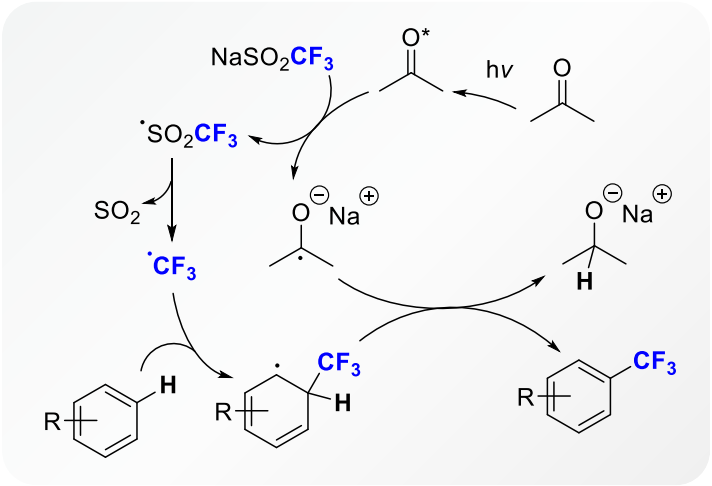
72% (6h)



70% (6h)



71% (12h)



[A] Ritter *Angew. Chem. Int. Ed.* **2015**, *54*, 3712 **[B] Li** *J. Am. Chem. Soc.* **2016**, *138*, 5809.

Difluoromethylating Reagents

$Cd(CF_2H)_2$

Burton *J. Fluorine Chem.* **1988**, *39*, 425

$Zn(CF_2H)_2$

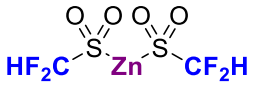
Burton *J. Fluorine Chem.* **2007**, *128*, 1198

nBu_3SnCF_2H

Prakash *Angew. Chem. Int. Ed.* **2012**, *51*, 12090

(NHC)$AgCF_2H$

Shen *Organomet.* **2015**, *34*, 3065

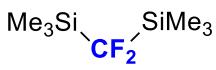


Baran *J. Am. Chem. Soc.* **2012**, *134*, 1494

ICF_2H

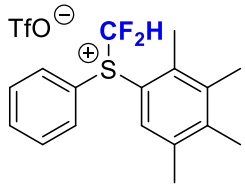
Chen *J. Chem. Soc. Chem. Commun.* **1994**, 737

Aldrich, £9700 per mol

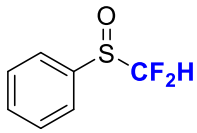


Me_3SiCF_2H

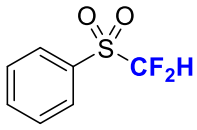
Prakash *J. Am. Chem. Soc.* **1997**, *119*, 1572



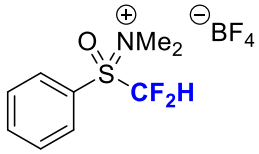
Prakash *Org. Lett.* **2007**, *9*, 1863



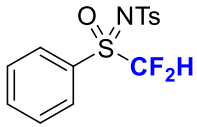
Prakash *Org. Lett.* **2007**, *9*, 1863



Prakash *J. Org. Chem.* **2003**, *68*, 4457



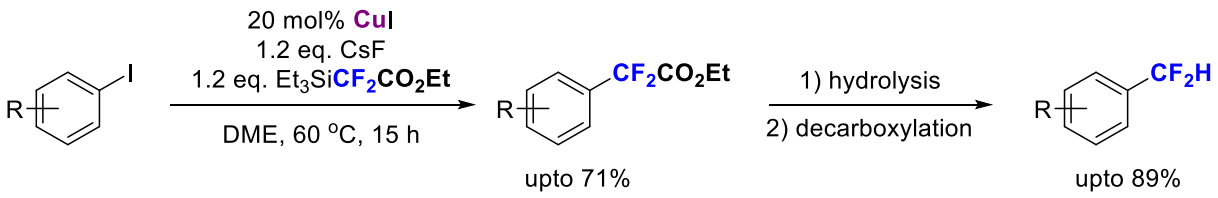
Prakash *J. Fluorine Chem.* **2011**, *132*, 792



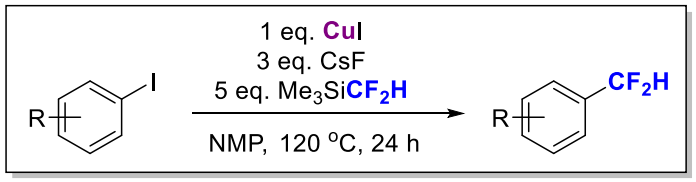
Akita *Chem. Eur. J.* **2016**, *22*, 1262

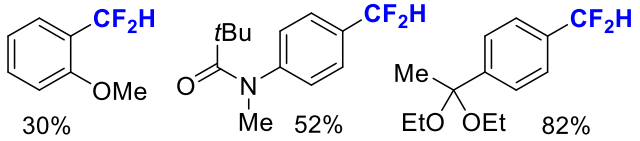
Copper Mediated Aromatic Difluoromethylation of Aryl Halides

[A]



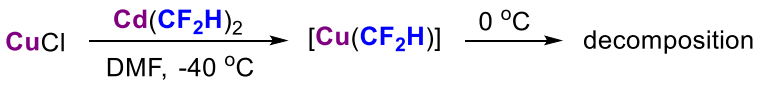
[B]

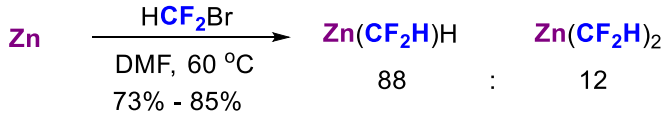


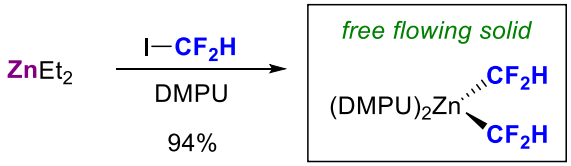


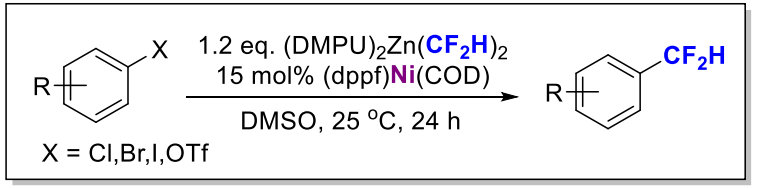
via $Cu(CF_2H)_2^-$?

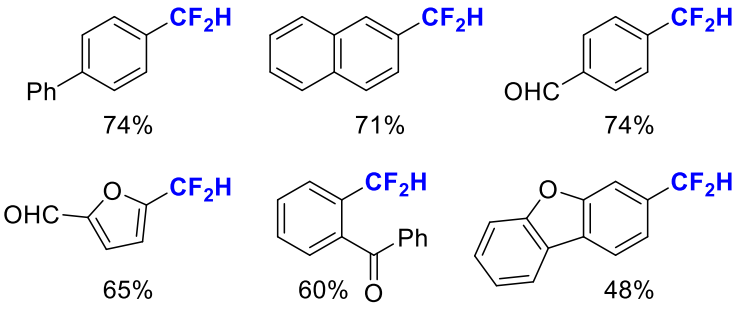
[C]







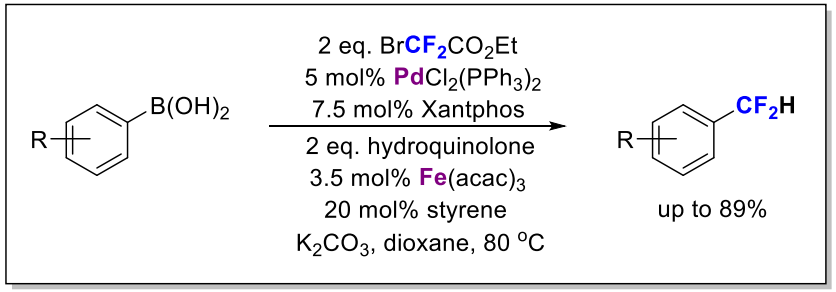


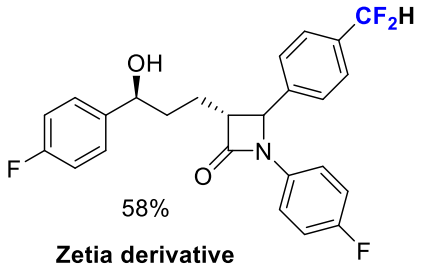


[A] Amii *Org. Lett.* **2011**, *13* , 5560; **[B] Hartwig** *J. Am. Chem. Soc.* **2012**, *134*, 5524; **Prakash** *Angew. Chem. Int. Ed.* **2012**, *51*, 12090; **Qing** *Org. Chem. Front.* **2014**, *1*, 774; **[C] Eujen** *J. Organomet. Chem.* **1996**, *519*, 7; **Burton** *J. Fluorine Chem.* **2007**, *128*, 1198; **Vicic** *J. Am. Chem. Soc.* **2016**, *138*, 2536.

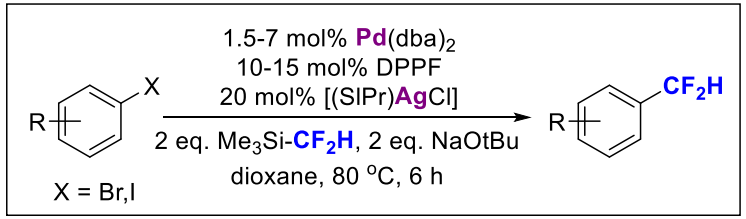
Palladium Catalysed Difluoromethylation of Aryl-X and –$B(OH)_2$

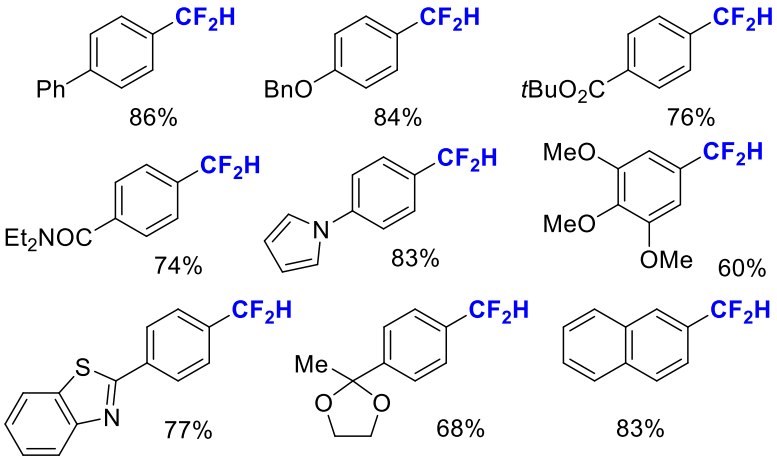
[A]

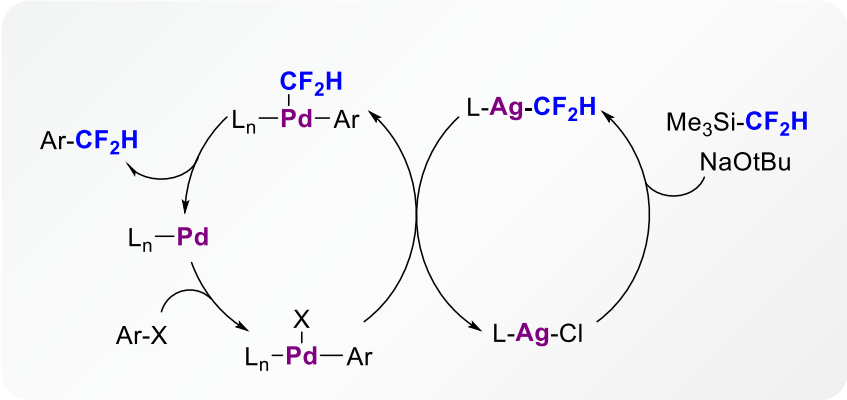




[B]

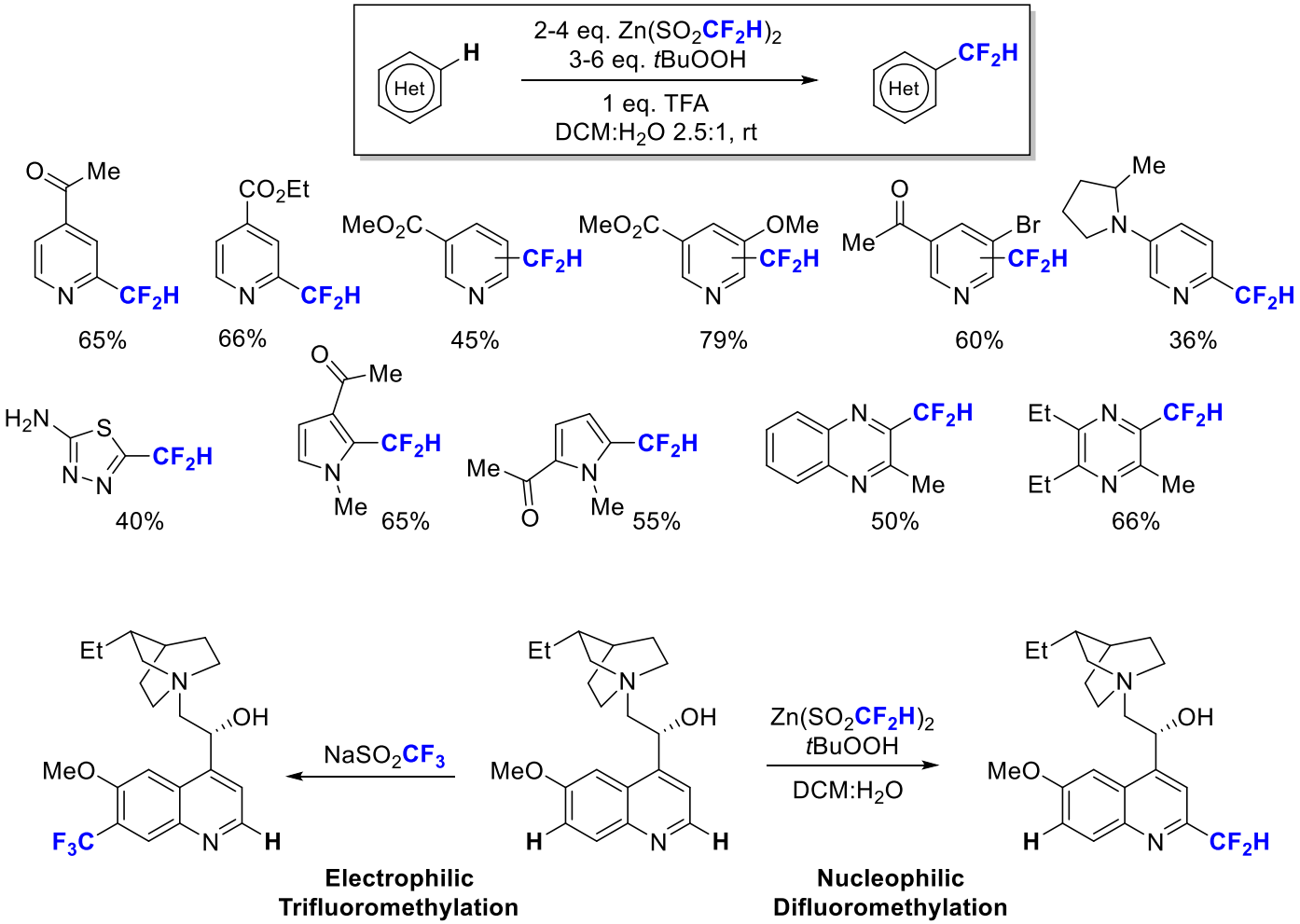






[A] Zhang *Org. Lett.* **2016**, *18*, 44; **[B] Shen** *Nat. Commun.* **2014**, *5*, 5405.

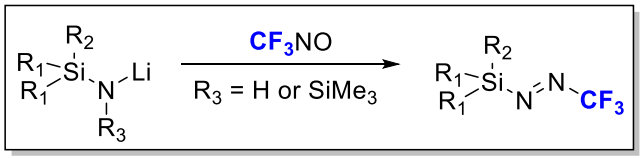
Arene Difluoromethylation *via* C-H Functionalisation

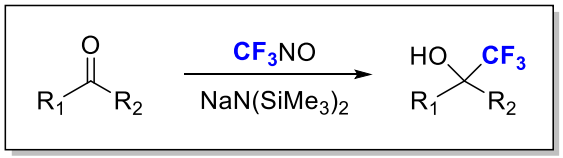


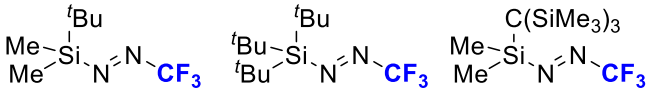
Baran *J. Am. Chem. Soc.* **2012**, *134*, 1494.

Trifluoromethylation – Addition to Carbonyl Groups

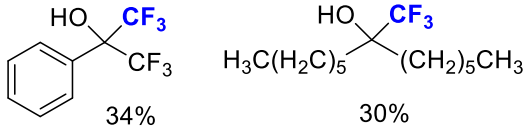
[A] Pioneering Work





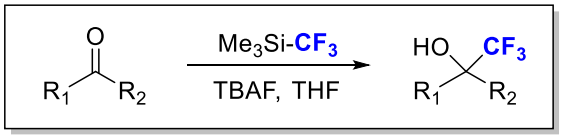


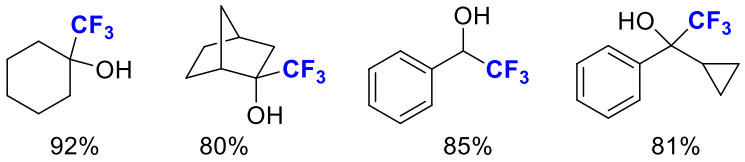
6% 11% 33%



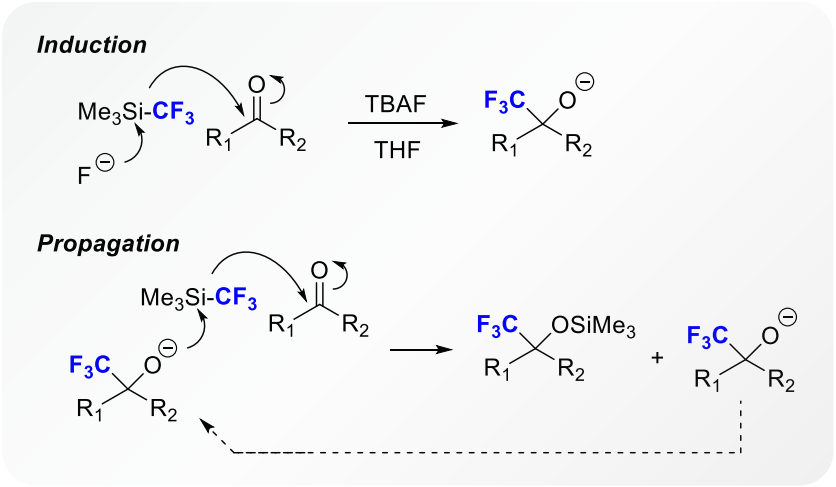
34% 30%

[B] Ruppert-Prakash Reagent





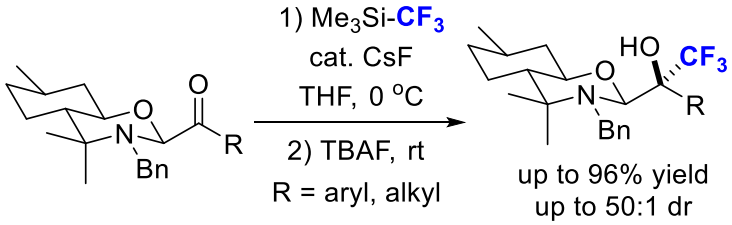
92% 80% 85% 81%



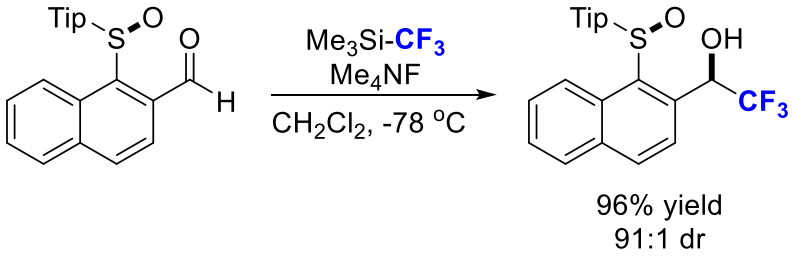
[A] De Meijere *Angew. Chem. Int. Ed.* **1977**, *16*, 854; *Angew. Chem. Int. Ed.* **1982**, *21*, 443; **[B] Ruppert** *Tetrahedron Lett.* **1984**, *25*, 2195; **Prakash** *J. Am. Chem. Soc*. **1989**, *111,* 393.

Trifluoromethylation – Addition to Carbonyl Groups

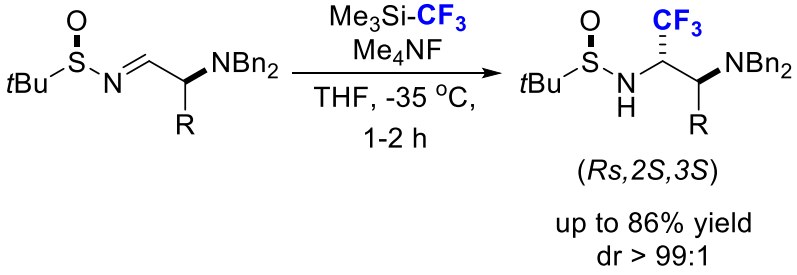
[A] Felkin-Anh



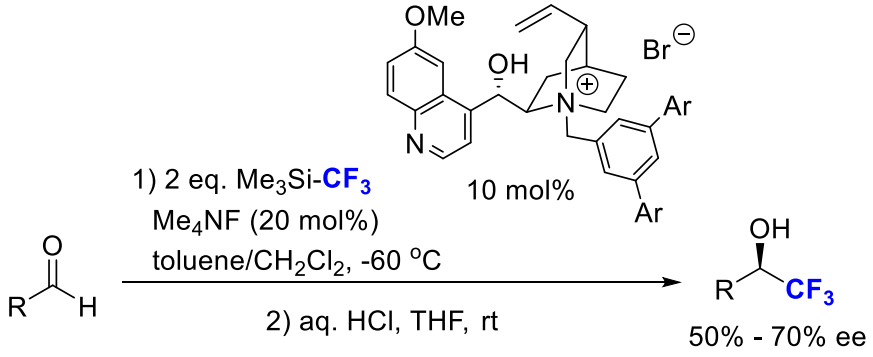
[B] Auxiliary Based Methods



[C] Chiral Auxiliary Approach



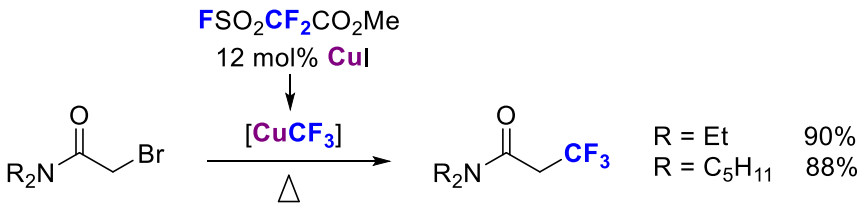
[D] Cinchona Alkaloid



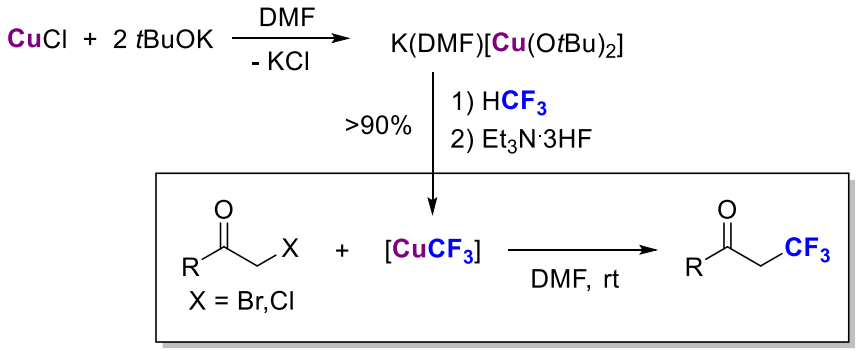
[A] Pedrosa *J. Org. Chem.* **2006**, *71*, 2177; **[B] Toru** *Tetrahedron Lett.* **2006**, *47*, 1337; **[C] Prakash** *Angew. Chem. Int. Ed.* **2001**, *40*, 589; *J. Am. Chem. Soc.* **2002**, *124*, 6538; **Dolbier** *J. Org. Chem.* **2005**, *70*, 4741; **[D] Shibata** *J. Fluorine Chem.* **2013**, *152*, 46; *Angew. Chem. Int. Ed.* **2009**, *48*, 6324; **Feng** *Tetrahedron* **2007**, *63*, 6822.

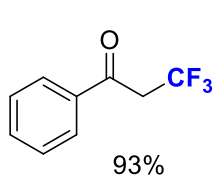
Trifluoromethylation *alpha* to Carbonyl Groups

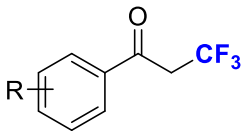
[A]



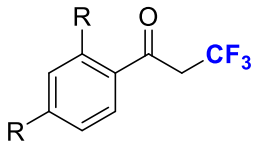
[B]



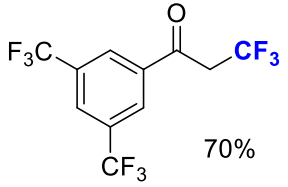


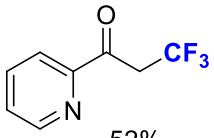


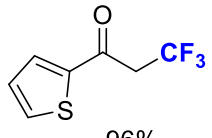
85-95%
R = Me, OMe,
F, Cl, Br, NO_2

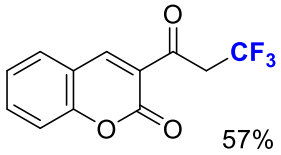


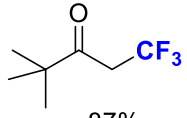
80-93%
R = Me, Cl

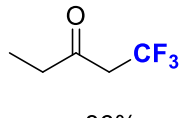


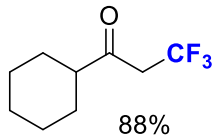








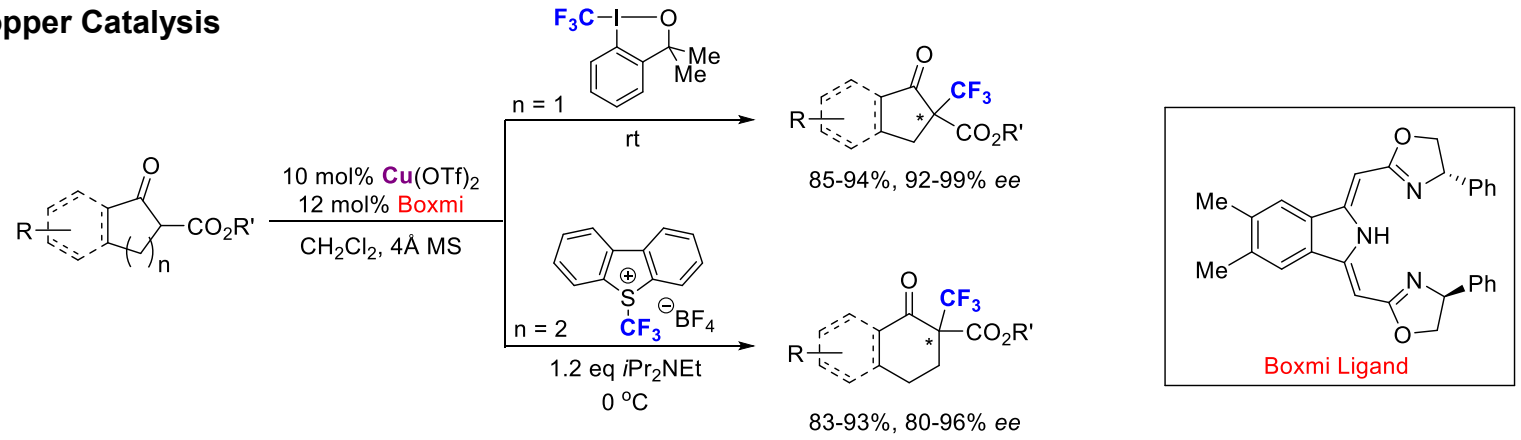




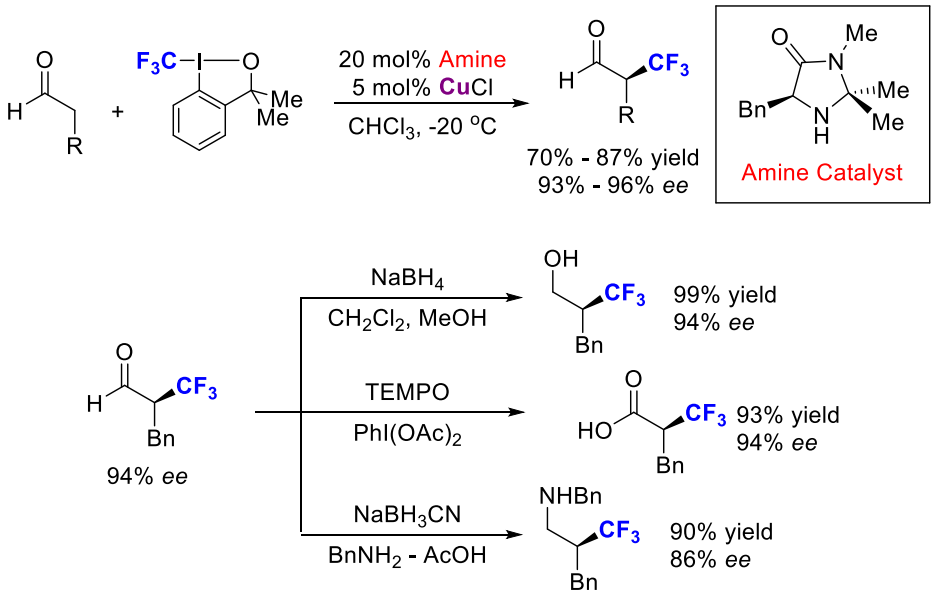
[A] Chen *Chem. Commun.* **1989**, 705; **[B] Grushin** *J. Am. Chem. Soc.* **2012**, *134*, 16167.

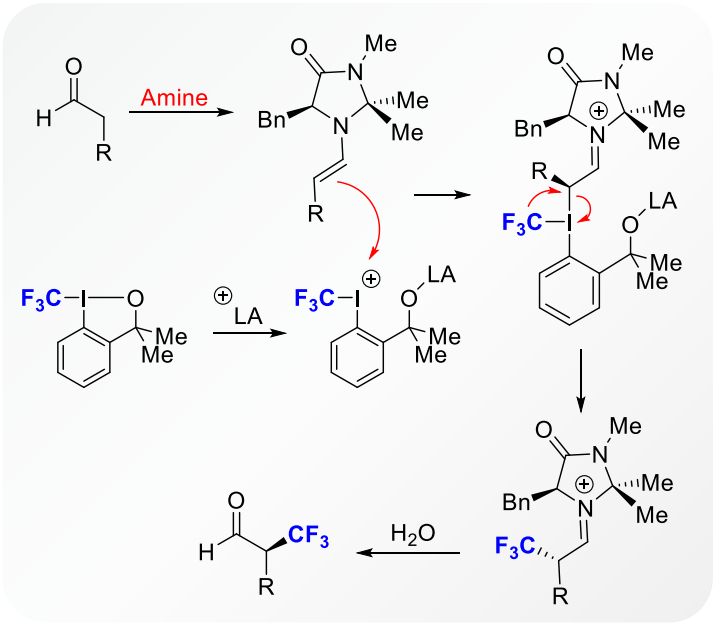
Trifluoromethylation *alpha* to Carbonyl Groups

[A] Copper Catalysis



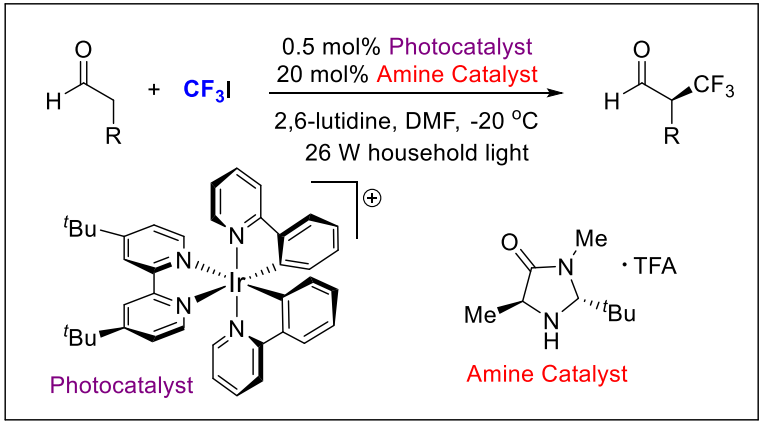
[B] Enamine-Copper Catalysis

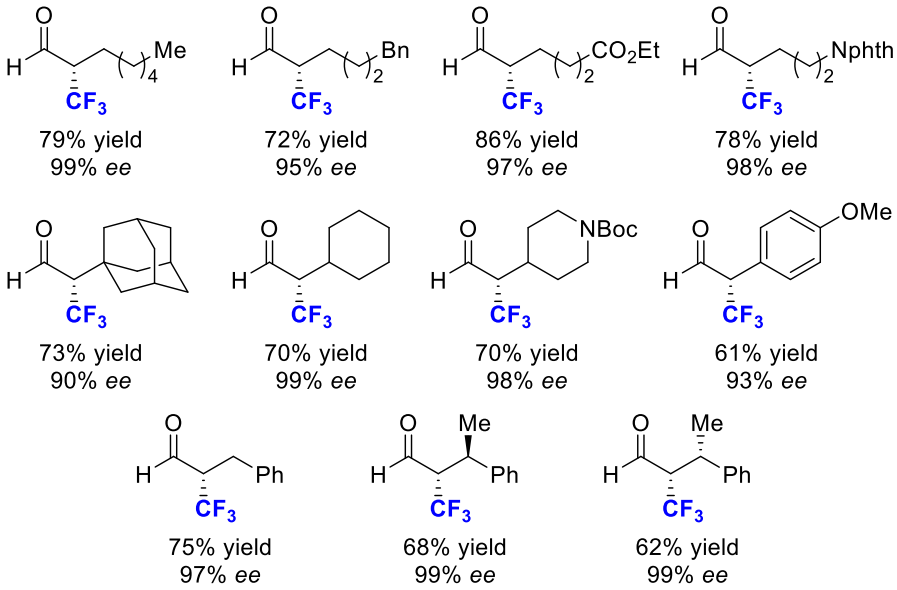


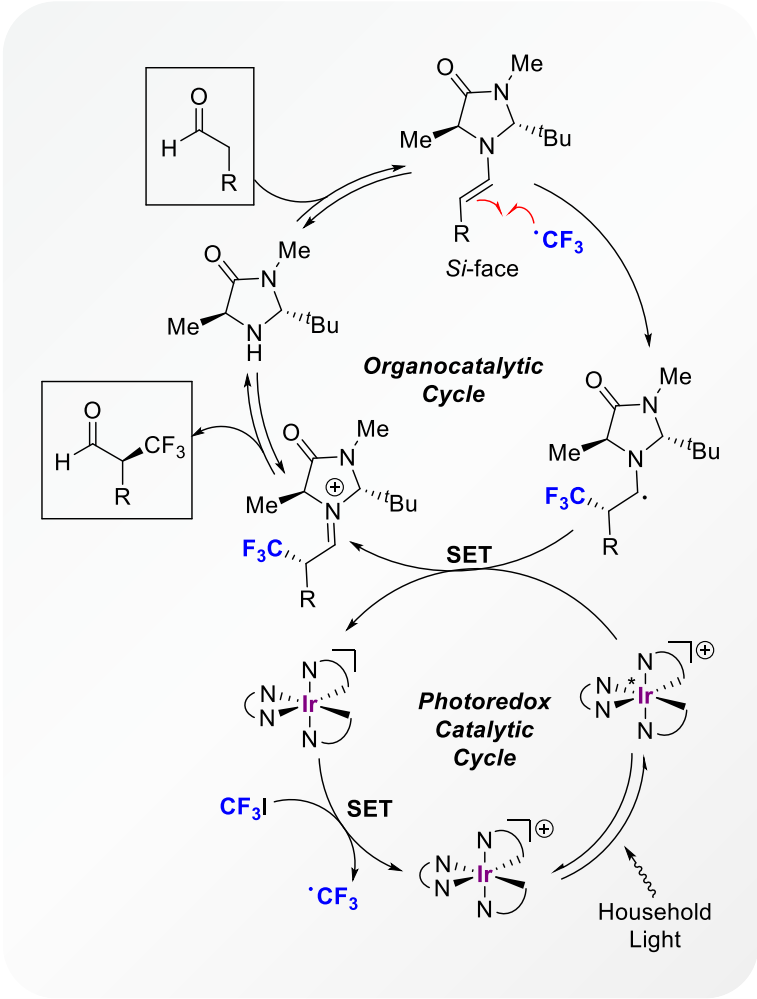


Early works: Umemoto *J. Am. Chem. Soc.* **1993** *115*, 2156; **Cahard** *J. Fluorine Chem.* **2007**, *128*, 975; **Shibata** *Org. Biomol. Chem.* **2009**, *7*, 3599; **[A] Gade** *J. Am. Chem. Soc.* **2012**, *134*, 10769; **[B] MacMillan** *J. Am. Chem. Soc.* **2010**, *132*, 4986.

Trifluoromethylation *alpha* to Carbonyl Groups

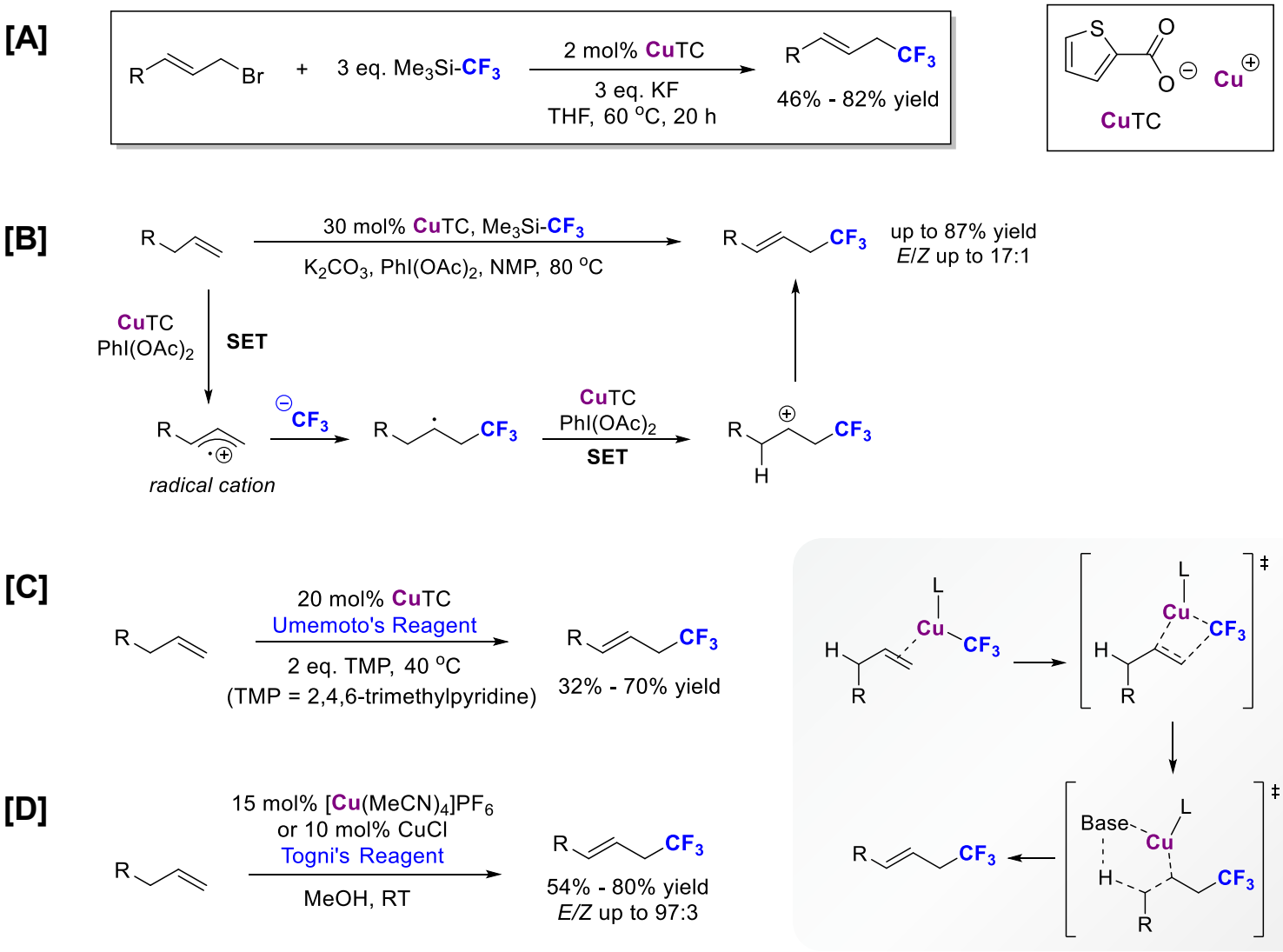






MacMillan *J. Am. Chem. Soc.* **2009**, *131*, 10875.

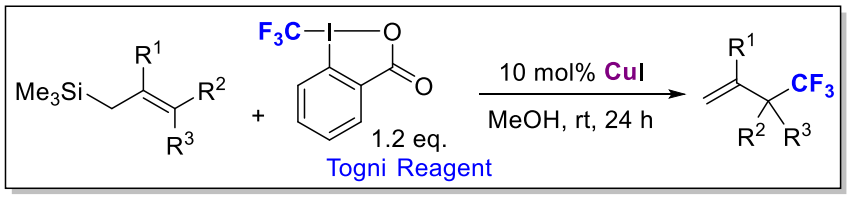
Allylic Trifluoromethylation of Allyl Halides and Alkenes

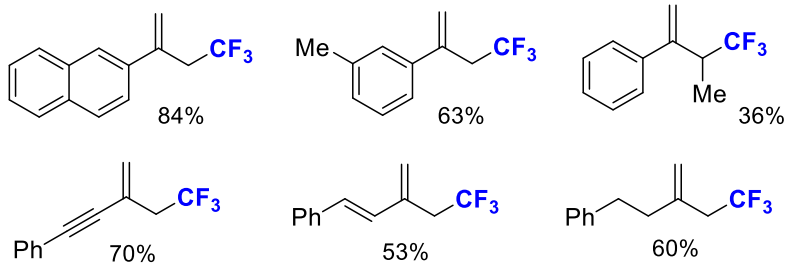


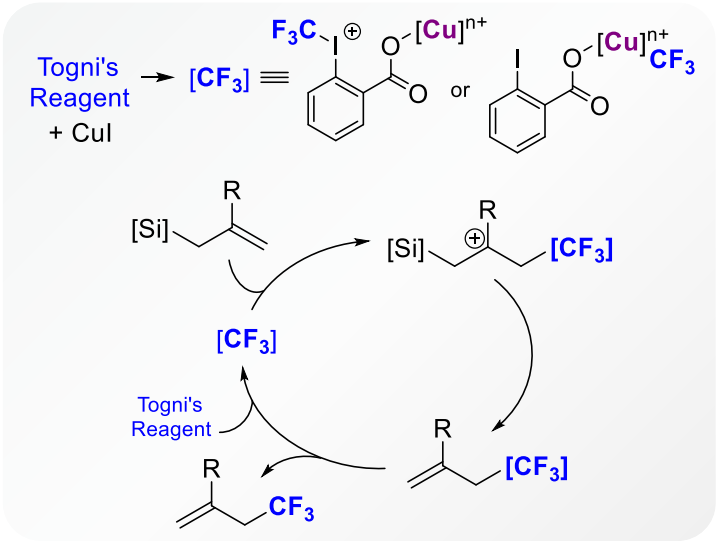
[A] Nishibayashi *Chem. Eur. J.* **2012**, *18*, 13255; **Szabo** *J. Org. Chem.* **2013**, *78*, 7330. **[B] Qing** *Org. Lett.* **2012**, *14*, 2106; **[C] Liu** *J. Am. Chem. Soc.* **2011**, *133*, 15300; **[D] Buchwald** *Angew. Chem. Int. Ed.* **2011**, *50*, 9120; **Wang** *J. Am. Chem. Soc.* **2011**, *133*, 16410.

Trifluoromethylation of Allylsilanes

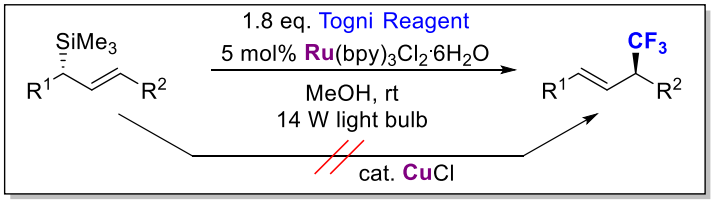
[A] Copper Catalysis

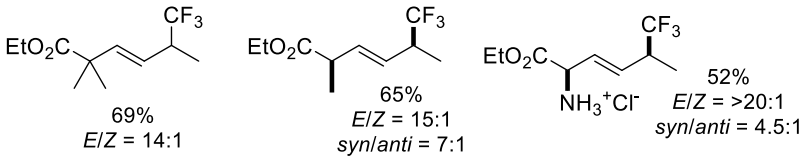


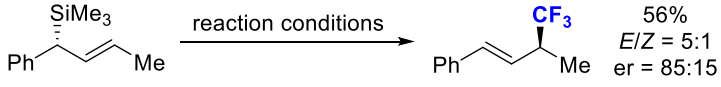


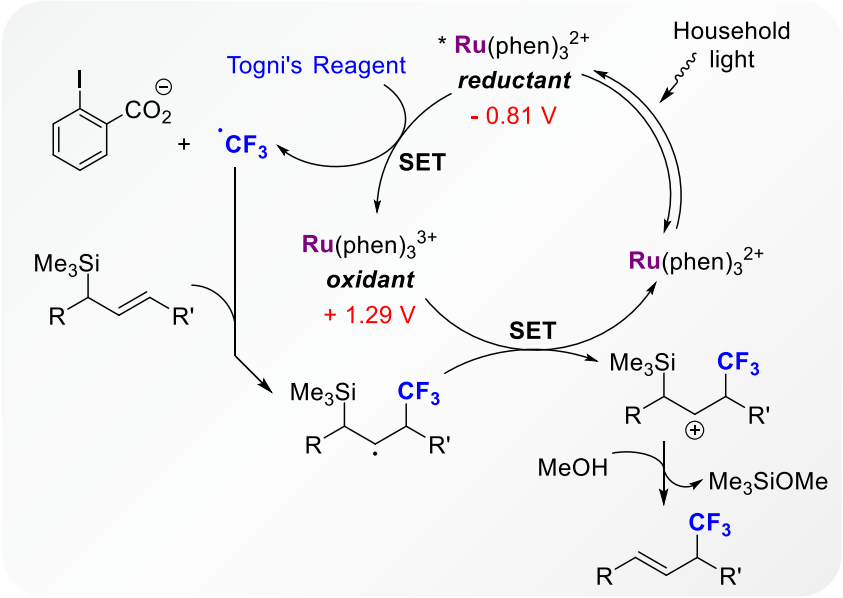


[B] Photoredox Catalysis





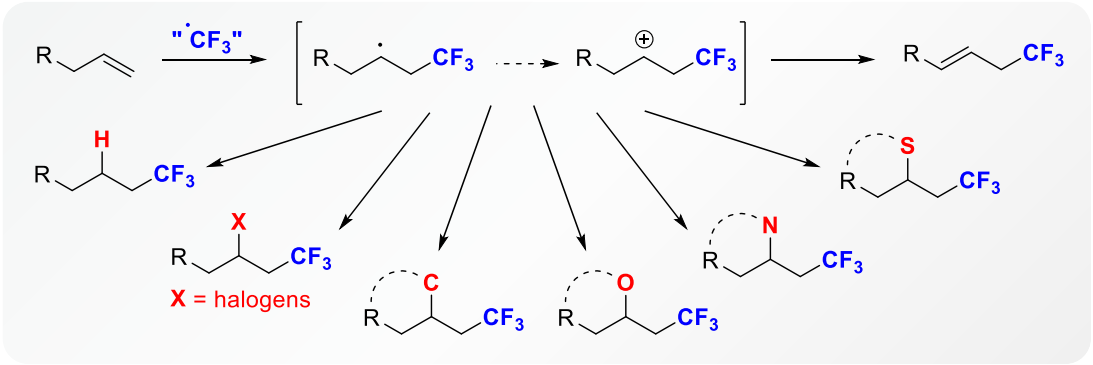




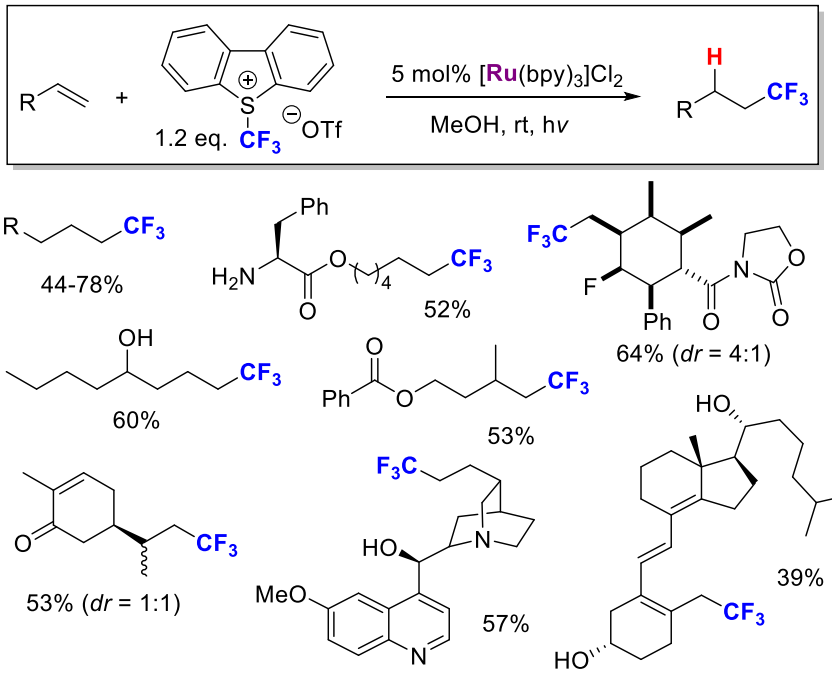
[A] Sodeoka *Angew. Chem. Int. Ed.* **2012**, *51*, 4577; **Gouverneur** *Chem. Eur. J.* **2012**, *18*, 8583; **[B] Gouverneur** *Org. Lett.* **2013**, *15*, 1250.

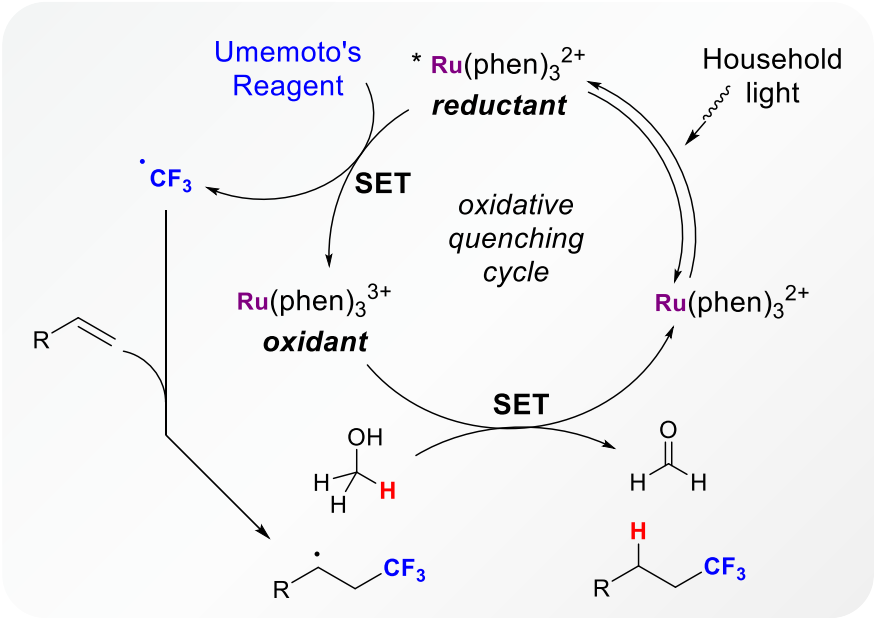
Trifluoromethylation of Alkenes

[A]



[B] Hydrotrifluoromethylation of unactivated alkenes



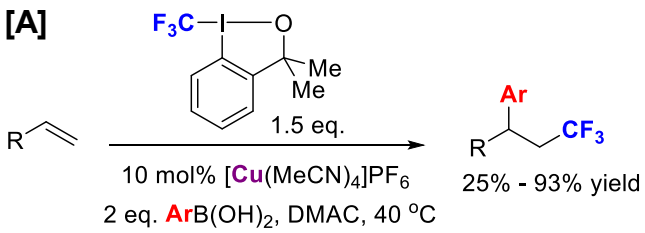


[A] Palacios *Chem. Rev.* **2015**, *115,* 1847; **Nevado** *Chem. Soc. Rev.* **2014**, *43*, 6598; **[B] Gouverneur** *J. Am. Chem. Soc.* **2013**, *135*, 2505; **Nicewicz** *Chem. Sci.* **2013**, *4*, 3160; **Qing** *Angew. Chem. Int. Ed.* **2013**, *52*, 2198.

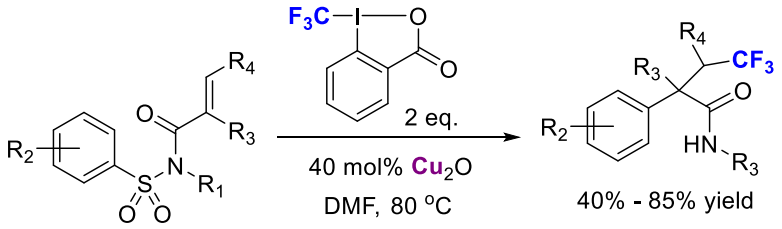
Trifluoromethylation of Alkenes

Carbotrifluoromethylation

[A]

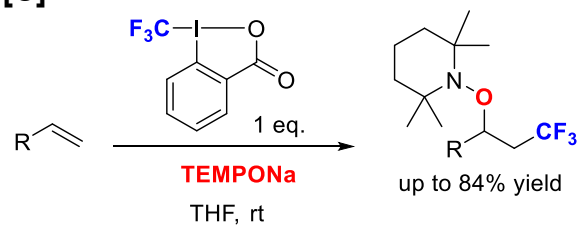


[B]

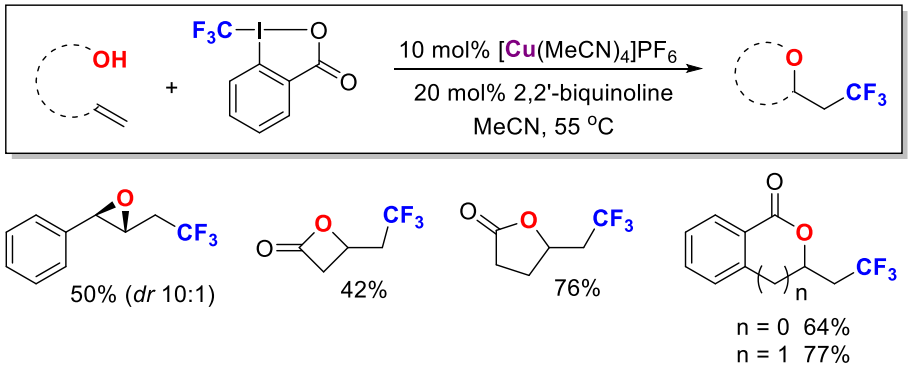


Oxytrifluoromethylation

[C]

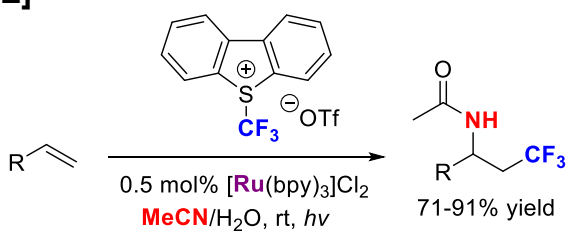


[D]

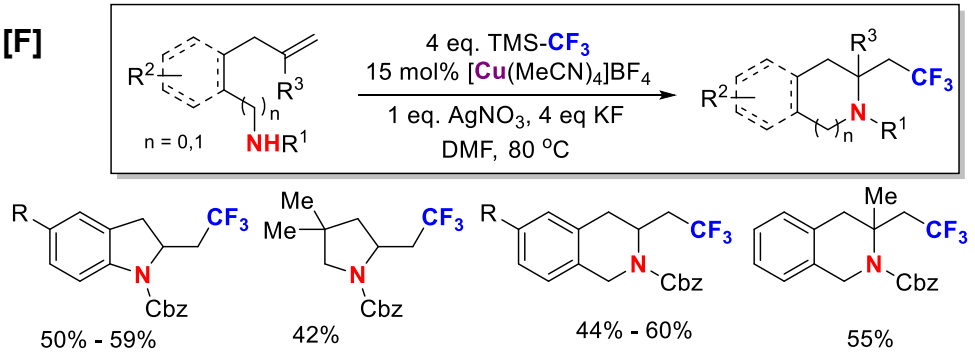


Aminotrifluoromethylation

[E]



[F]



[A] Liu *J. Am. Chem. Soc.* **2014**, *136,* 10202; **[B] Nevado** *J. Am. Chem. Soc.* **2013**, *135*, 14480; **[C] Studer** *Angew. Chem. Int. Ed.* **2012**, *51*, 8221; **[D] Buchwald** *J. Am. Chem. Soc.* **2012**, *134*, 12462; **[E] Akita** *Org. Lett.* **2013**, *15*, 2136; **[F] Liu** *J. Org. Chem.* **2014**, *79*, 7084.

Criteria for Large-Scale Application

Criteria	+	+/-	-
Substrate cost (generic, based on functional group)	Low cost, e.g. Ar-H Ar-Cl Ar-NH_2 Ar-COOH	Medium cost, e.g. Ar-Br Ar-Bpin (Pin = pinacolyl)	High cost, e.g. Ar-I Ar-$B(OH)_2$
Reagent Cost	Low cost reagent, e.g. HF HCF_3 CF_3COONa $CClF_2COOMe$ CF_3SO_2Cl	Medium cost, e.g. SF_4 CF_3I $TMSCF_3$/$TESCF_3$ CF_3SO_2Na/CF_3SO_2K FSO_2CF_2COOMe $PhCOCF_3$ $PhSO_2CF_3$	High cost, e.g. Fluolead Togni Reagent Trifluoromethylator Umemoto Reagent Yagupolskii Reagent $Cu(P(Ph_3)_3)CF_3$
Metal cost	Low cost, e.g. Cu, Fe, Sb: s/c > 1 Re, Ru: s/c > 100 Pd: s/c > 1000	Medium cost, e.g. Cu,Sb: s/c = 1 – 0.1 Re, Ru: s/c = 100 – 10 Pd: s/c = 1000 – 100	High cost, e.g. Re, Ru: s/c < 10 Pd: s/c = < 100
Ligand cost	Low cost, e.g. 1,10-Phenanthroline: s/c > 10 Brettphos: s/c > 1000	Medium cost, e.g. 1,10-Phenanthroline: s/c = 10 – 1 Brettphos: s/c = 1000 – 100	High cost, e.g. 1,10-Phenanthroline: s/c < 1 Brettphos: s/c < 100
Requirement of protocol	No special requirement	Irradiation Strictly inert conditions Strictly dry conditions	Autoclave Secondary containment

s/c = substrate to catalyst ratio; **Steiner** *Chim. Oggi Chem. Today* **2015**, *33*, 26.

Criteria for Large-Scale Application

Criteria	+	+/-	-
Toxicity and eco-toxicity of metals and reagents	Low e.g. Fe, Zn or metal free HCF_3	Medium e.g. Cu, CF_3COOR, CF_3I	High e.g. Pd, Ru, HF, SF_4
Metal removal / waste generation	Little waste: No metals involved Few reagents, little excess Recyclable solvents	Medium waste: Metals (catalytic) Several reagents Recyclable solvents	Much waste: Metal (stoichiometric) Several reagents in excess Non-recyclable solvents (i.e. dipolar aprotic solvents)
Efficiency and yield of the trifluoromethyl-building step	High efficiency, e.g. Equimolar amounts of reagents Yield: 80-100%	Moderate efficiency, e.g. Substantial excess of reagents Yield: 60-80%	Low efficiency e.g. large excess of reagents Yield < 60%
Potential for difficult to remove byproducts (e.g. regioisomers or Ar-H)	Very low	Low	Medium to high
Status quo of the trifluoromethylation / fluorination protocol	> 100 kg to multi-tonne scale	1 kg to 100 kg scale	< 1 kg scale

Steiner *Chim. Oggi Chem. Today* **2015**, *33*, 26.

Potential of Selected Trifluoromethylation Methods

Substrate	Reagent Cost	Metal and Catalyst Cost	Specific Requirements	Waste Load	Toxicity and Eco-toxicity	Status Quo
Ar-CH_3	Cl_2 (3 eq.) HF (3 eq.)	0 – 0.1 eq. Sb	Autoclave	HCl	Cl_2, HF	100 tonnes
Ar-NH_2	Umemoto reagent (1.5 eq.), *t*BuONO	3 eq. Cu	-	Cu	Cu	mmol
Ar-NH_2	*t*BuONO (1 eq.), *p*TSA (1.5 eq.) Me_3SiCF_3 (1.5 eq.)	0.5 eq. CuSCN	-	Cu	Cu	mmol
Ar-COOH	SF_4 (2.5 eq.)	HF	Autoclave	SOF_2	SF_4, HF	100 kg
Ar-COOH	$ArSF_3$ (2.5 eq.)	-	Autoclave	ArSOF	-	mmol
Ar-Cl	$TESCF_3$ (2 eq.)	0.05 eq. Pd, Brettphos	Strictly dry	-	Pd	mmol
Ar-I	$CClF_2COOMe$ (2-4 eq.), KF (1 eq.)	1-1.5 eq. CuI	-	Cu	Cu	5 kg
Ar-I Ar-Br	HCF_3 (1.5 eq.), *t*BuOK, $Et_3N{\cdot}3HF$	1.5 eq. Cu	Strictly inert	Cu	Cu	mmol
Ar-I	$TESCF_3$ (2 eq.)	0.1 eq. Cu	-	Cu	Cu	mmol
Ar-I	Trifluoromethylator (1.2 eq.)	1.2 eq. Cu	-	Cu	Cu	mmol
Ar-$B(OH)_2$	CF_3SO_2Na (3 eq.) (TBHP)	1 eq. Cu	-	Cu CF_3SO_2Na	Cu	mmol
Ar-$B(OH)_2$	CF_3I (5 eq.)	0.2 eq. Cu, 0.01 eq. Ru	Irradiation	Cu, CF_3I	Cu	mmol
Ar-$B(OH)_2$	Togni reagent (1.2 eq.)	0.05 eq. Cu, Phen	-	Cu	Cu	mmol
Ar-Bpin	$K[B(OMe)_3CF_3]$ (2 eq.), O_2	1 eq. Cu(OAc)	-	Cu	Cu	mmol
Het-H	CF_3SO_2Cl (1-4 eq.)	0.02 eq. Ru, Phen	Irradiation		Ru	mmol
Het-H	CF_3I (3 eq.), H_2O_2 (2 eq.)	0.3 eq. $FeSO_4$ or Cp_2Fe	-	CF_3I	CF_3I	40 kg
Het-H	$Zn(CF_3SO_2)_2$ (1-4 eq.) TBHP (3-5 eq.)	Zn	-	Zn	Zn	mmol

Steiner *Chim. Oggi Chem. Today* **2015**, *33*, 26.

The Art of ^{18}F-Labelling for Applications in Positron Emission Tomography

Véronique Gouverneur
University of Oxford
Chemistry Research Laboratory

BOSS XV
Tetrahedron Chair - Lecture 4
July 2016

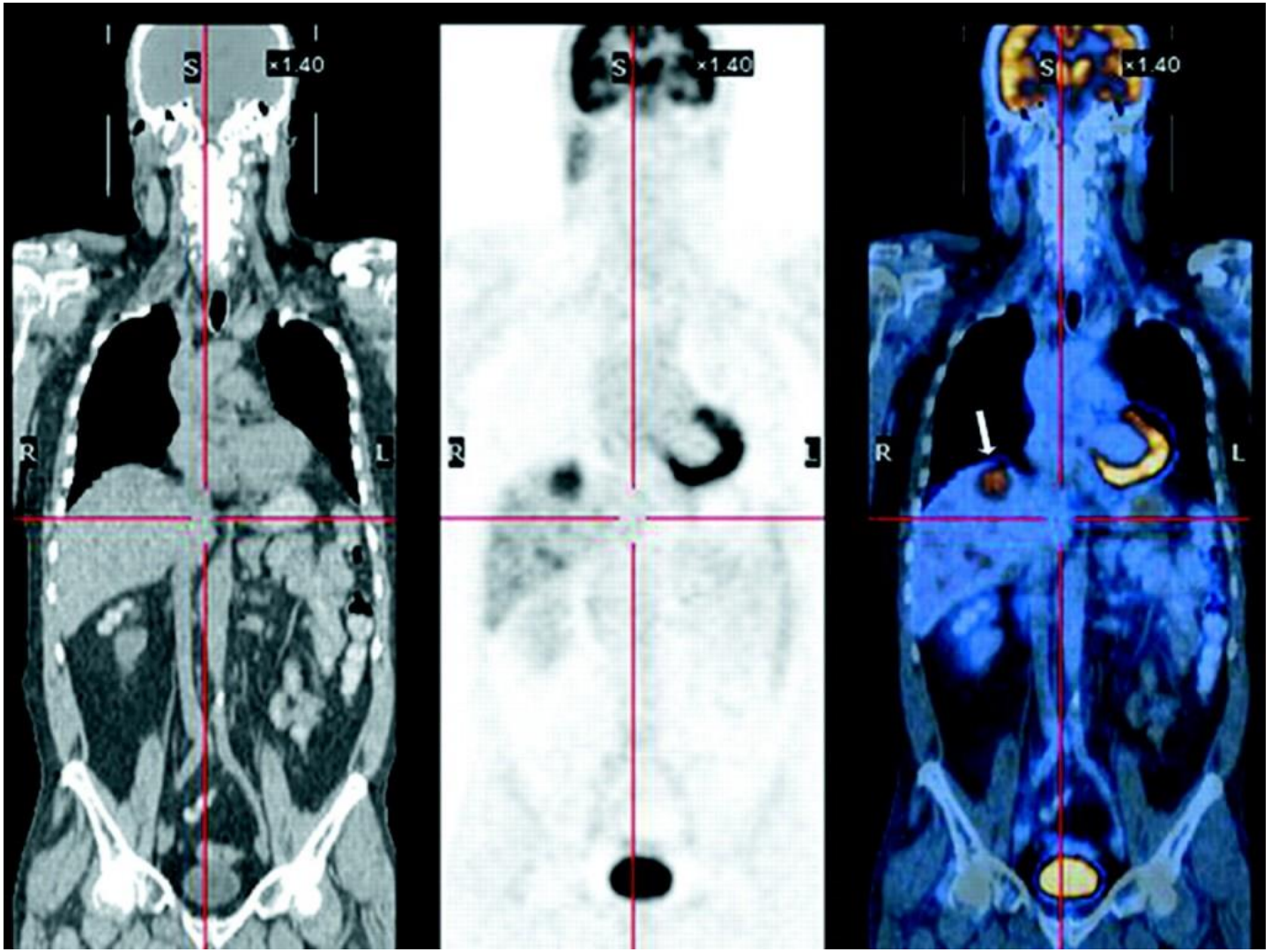
UNIVERSITY OF OXFORD

Contents

- Fundamentals of Radiolabelling
- ^{18}F Fluorination of Sp^3 Carbons
- ^{18}F Fluorination of (Hetero)Arenes
- ^{18}F Trifluoromethylation of (Hetero)Arenes
- ^{18}F Fluorination of Other Motifs

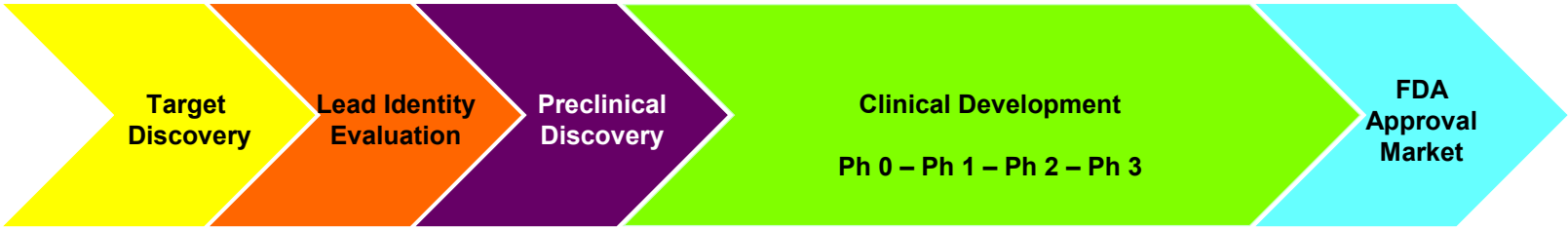
^{18}F Positron Emission Tomography

Synthetic [^{18}F]labelled (bio)molecules, tools to diagnose, monitor and treat diseases.



Matthews *Br. J. Clin. Pharmacol.* **2011**, *175,* 175.

^{18}F-PET and Drug Development



Biodistribution (Drug)

- **>>> Labelled drug candidate**
- Dynamic *in vivo* distribution of drug candidate
- Measurement of human pharmacokinetic parameters
- Assessment of Blood Brain Barrier penetration

Surrogate Marker of Efficacy (Radiotracer)

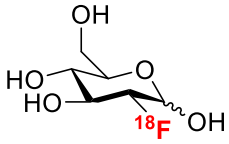
- **>>> Validated (patho)physiology biomarker**
- Diagnosis and follow-up of diseases progression
- Insight into the mechanism of action
- Surrogate of behavioral end-point for proof of concept studies

Occupancy Studies (Radioligand)

- **>>> Validated PET ligand**
- TE (target engagement) from displacement studies
- Relationship between TE and dose
- Information on TE kinetics and dosing regimen

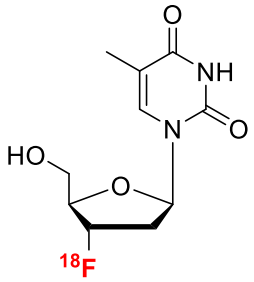
Matthews *Br. J. Clin. Pharmacol.* **2011**, *175,* 175.

Commonly Used Radiotracers



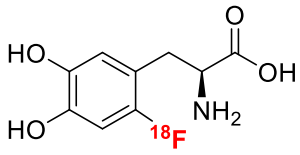
[^{18}F]FDG

Oncology
Metabolism
Clinical
Sokoloff, *J. Nucl. Med.* **1993**



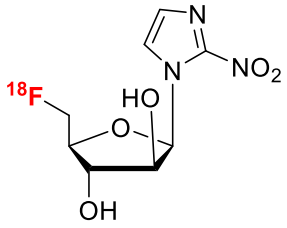
[^{18}F]Fluorothymidine

Oncology
Cellular Profileration
Preclinical
Grierson *Nat. Med.* **1998**



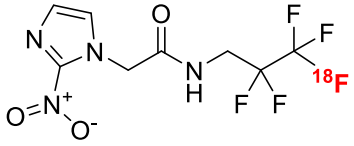
6-[^{18}F]Fluoro-*L*-DOPA

Neurology
Receptor Measurement
Clinical
Elsinga *Appl. Radiat. Isot.* **1999**



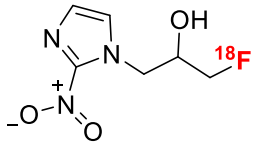
[^{18}F]FAZA

Cardiology/Oncology
Hypoxia
Preclinical
Machualla *Radioanal. Nuc. Chem.* **1999**



[^{18}F]EF5

Cardiology/Oncology
Hypoxia
Preclinical
Solin *J. Nuc. Med.* **2008**

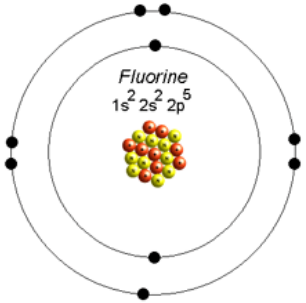


[^{18}F]FMISO

Cardiology/Oncology
Hypoxia
Clinial
Tang *Nuc. Med. Biol.* **2005**

^{19}F and ^{18}F Isotopes

^{19}F



Atomic Number: 9
Atomic Mass: 18.998404 amu
Melting Point: -219.62 ºC(53.530006 K, -363.31598 ºF)
Boiling Point: -188.14 ºC (85.01 K, -306.652 ºF)
Number of Protons: 9
Number of Neutrons: 10

Number of Electrons: 9

^{18}F

Nuclear reaction from

Oxygen-18 ^{18}O

Protons	8
Neutrons	10

natural, stable isotope
Natural abundance 0.2%

+ 1 proton
- 1 neutron

→

Natural abundance:	**Radioisotope**
Half-life:	**109.771 min**
Decay product:	**18-Oxygen**
Isotope mass:	**18.0009380(6)**

Decay Mode	**Decay Energy**
Positron emission	**0.6335 MeV**
Beta emission	**1.6555 MeV**

Number of Protons: 9
Number of Neutrons: 9

Number of Electrons: 9

^{18}F-Production: Nuclear Reaction

Cyclotron

cyclotron beam
(*p* = proton)

radioisotope produced

$^{18}O(p,n)^{18}F$

target nucleus

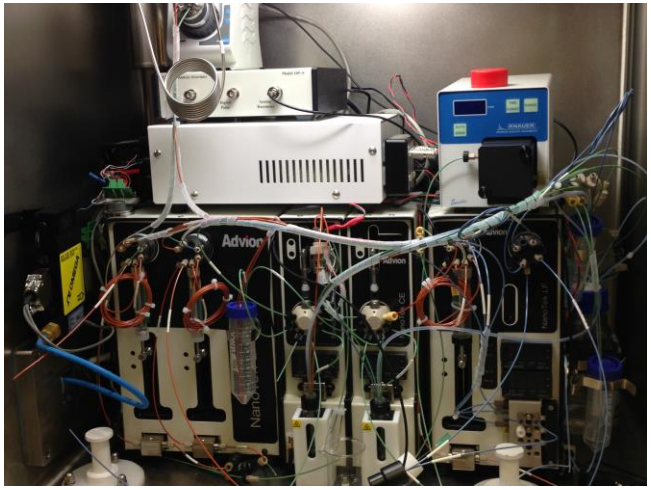
side-product of radioisotope production (n = neutron)

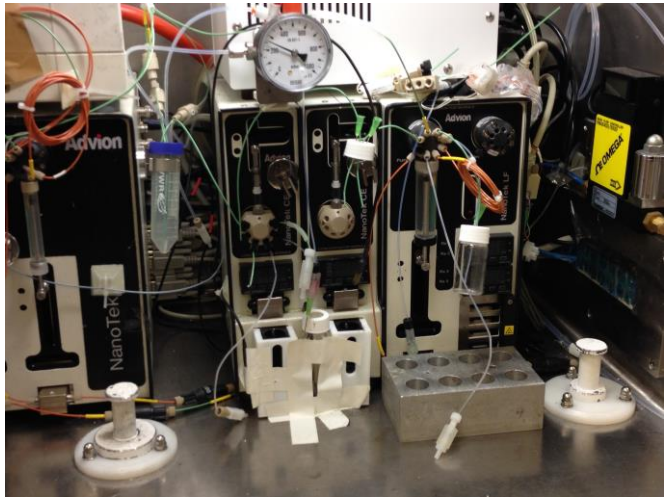
$^{18}O(p,n)^{18}F$ on a $H_2{}^{18}O$ target using 11-18 MeV protons

Matthews *Br. J. Clin. Pharmacol.* **2011**, *175,* 175.

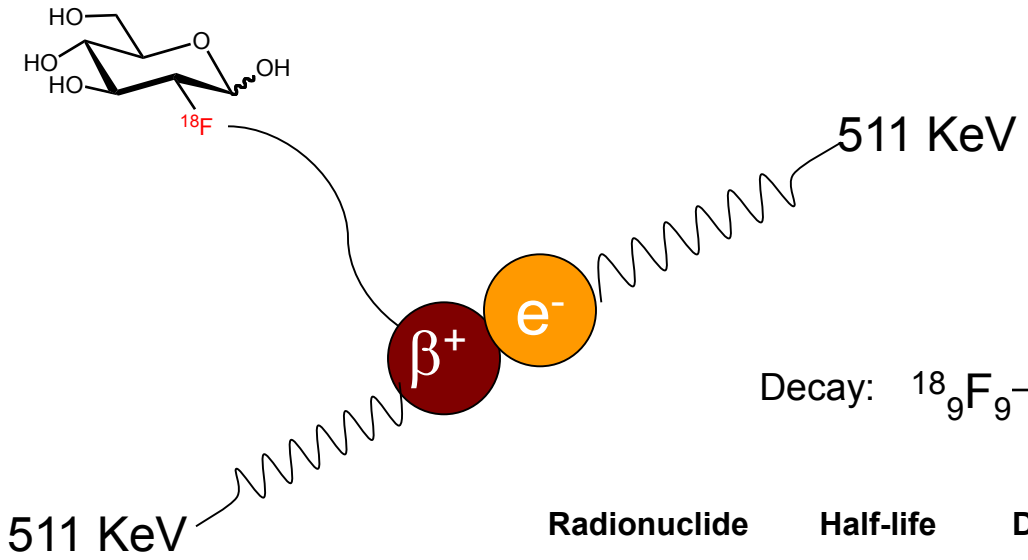
^{18}F-Radiochemistry - Chemistry Department (Oxford)

- Half-life of 109.8 min
- ^{18}F quantities are minuscule compared to precursor 1-10 nmol
- $[^{18}F]F^-/H_2{}^{18}O$ and $[^{18}F]F_2$ ($^{18}F^{19}F/^{19}F_2$)
- Radiolysis for scale up reaction
- Automation radiosynthetic platform





^{18}F versus ^{13}N, ^{15}O, ^{76}Br or ^{124}I



Coincidence detection of the two opposed and externally detectable γ-rays each 511keV photons (emitted at ~ 180°)
Secondary and highly penetrating 511- keV gamma radiation

Decay: $^{18}_{9}F_{9} \longrightarrow {}^{18}_{8}O_{10} + \beta^{+} + \nu$

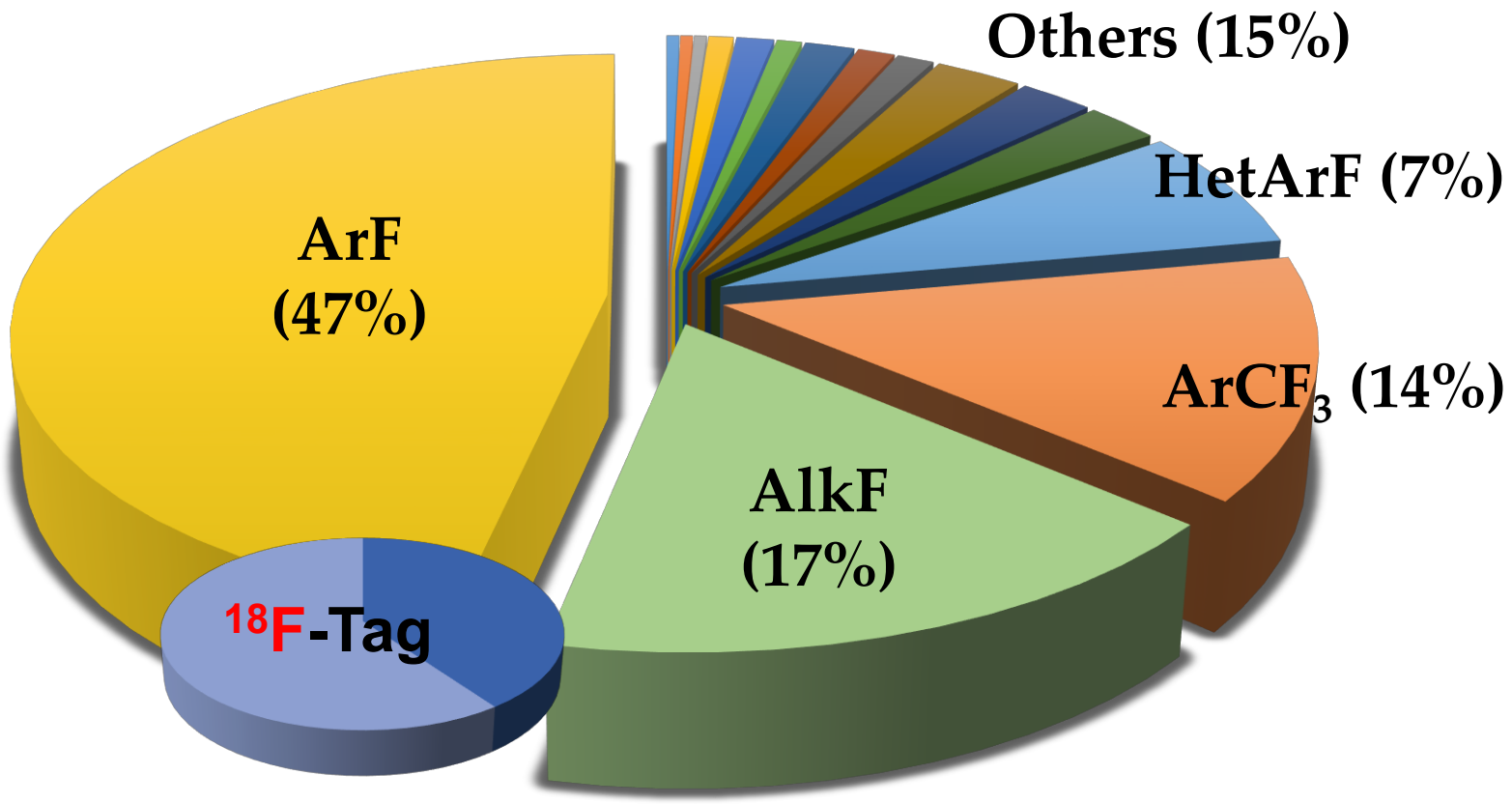
Radionuclide	Half-life	Decay (%)	$E^{+}_{\beta+\,max}$ (MeV)	average β^{+} range (mm)
^{11}C	20.4 min	β^{+} (99)	0.97	0.85
^{13}N	10 min	β^{+} (100)	1.20	1.15
^{15}O	2 min	β^{+} (100)	1.74	1.80
^{18}F	**110 min**	**β^{+} (97)**	**0.64**	**0.46**
^{76}Br	16.1 h	β^{+} (57)	3.98	-
^{124}I	4.18 days	β^{+} (24)	2.13	-

- Versatility and Biogenicity: C, N, O and F
- Short Half-Lives: Rapid synthesis-purification; Repeat study in the same subject within min/hours
- Non-Invasive Detection of Radiotracer: Quantitative *in vivo* autography and regional kinetic study in subject
- True tracer: High specific activity (> 37 GBq/μmol); administered mass: 1–10 nmol per subject

Matthews *Br. J. Clin. Pharmacol.* **2011**, *175,* 175.

Diversity of Fluorine containing Pharmaceuticals

> 20% of marketed drugs contain at least one fluorine



Aiming for functional ^{18}F Labelling

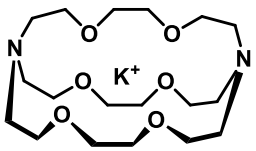
Nucleophilic ^{18}F-Fluorinating Reagents

3 mg K_2CO_3
15 mg $K_{2.2.2}$
CH_3CN/H_2O

$F^-(H_2{}^{18}O)_n$ in $H_2{}^{18}O$

Activity = 4 GBq
^{18}F Half-life = 109 min

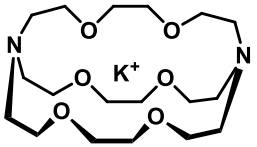
$F^-(H_2O)_n$



In H_2O/CH_3CN

$F^-(H_2O)_n$

Azeotropic ↓ Drying



$F^-(H_2O)_m$

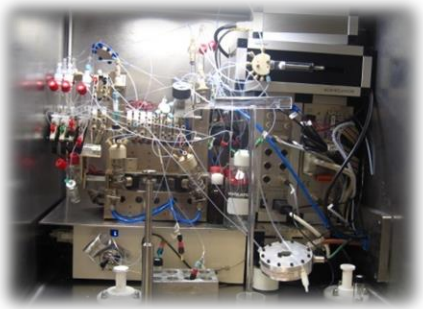
$[^{18}F]KF/K_{2.2.2}$ complex

Activity = 3.0-3.5 GBq

Re-dissolve in CH_3CN → and use aliquots

- ❑ Amount of $[^{18}F]F^-$ available is very low: In the order of nmol ($1.0x10^{-6}$ mmol)
- ❑ Substrate is often in >1000x excess

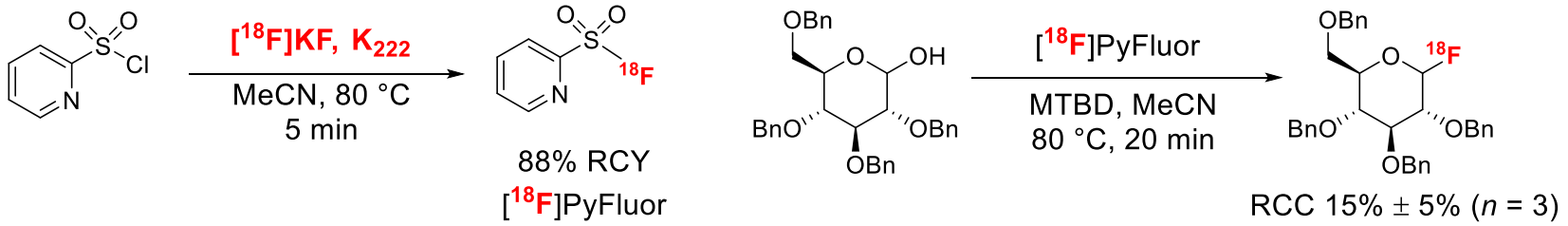
Cyclotron



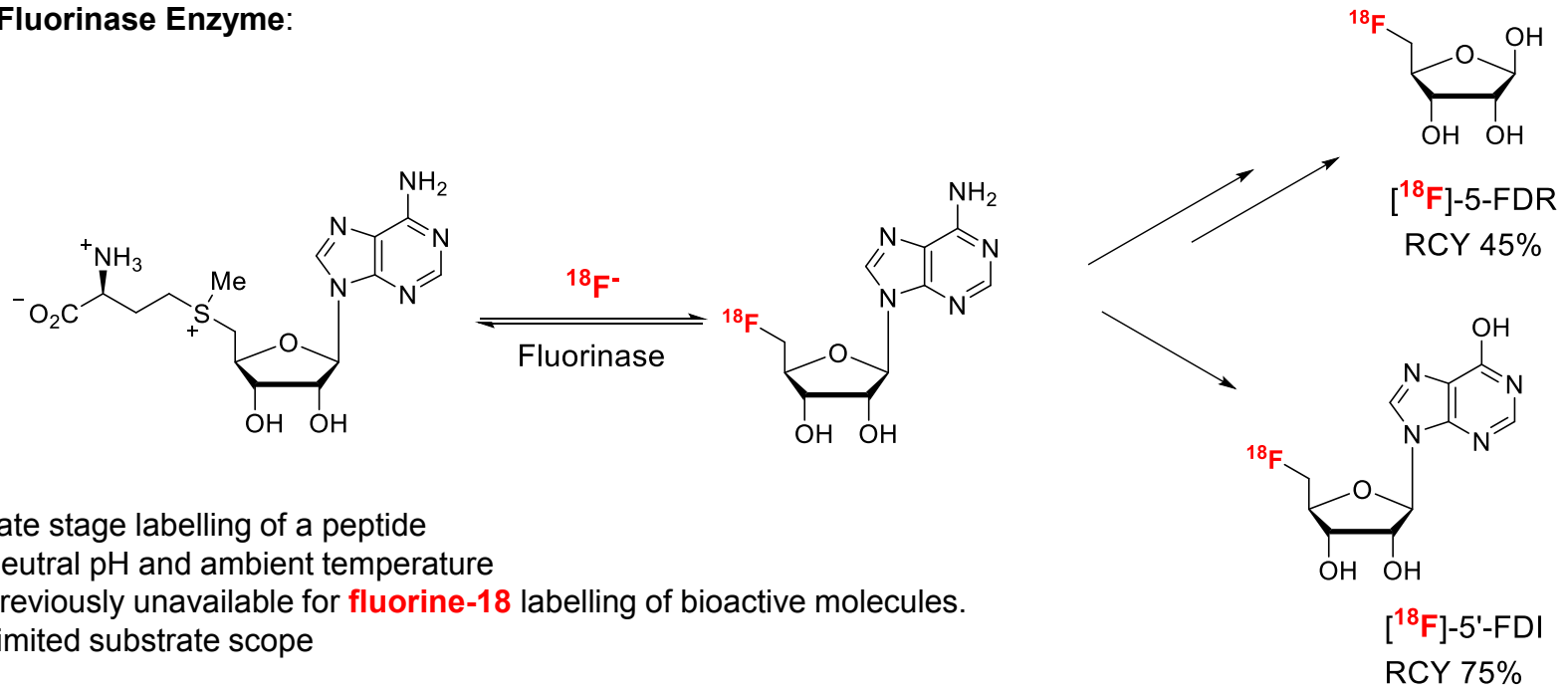
Gouverneur *Chem. Rev.* **2016**, *116*, 719; *Angew. Chem. Int. Ed.* **2012**, *51*, 11426.

Nucleophilic ^{18}F-Fluorinating Reagents

[A] [^{18}F]PyFluor:



[B] Fluorinase Enzyme:

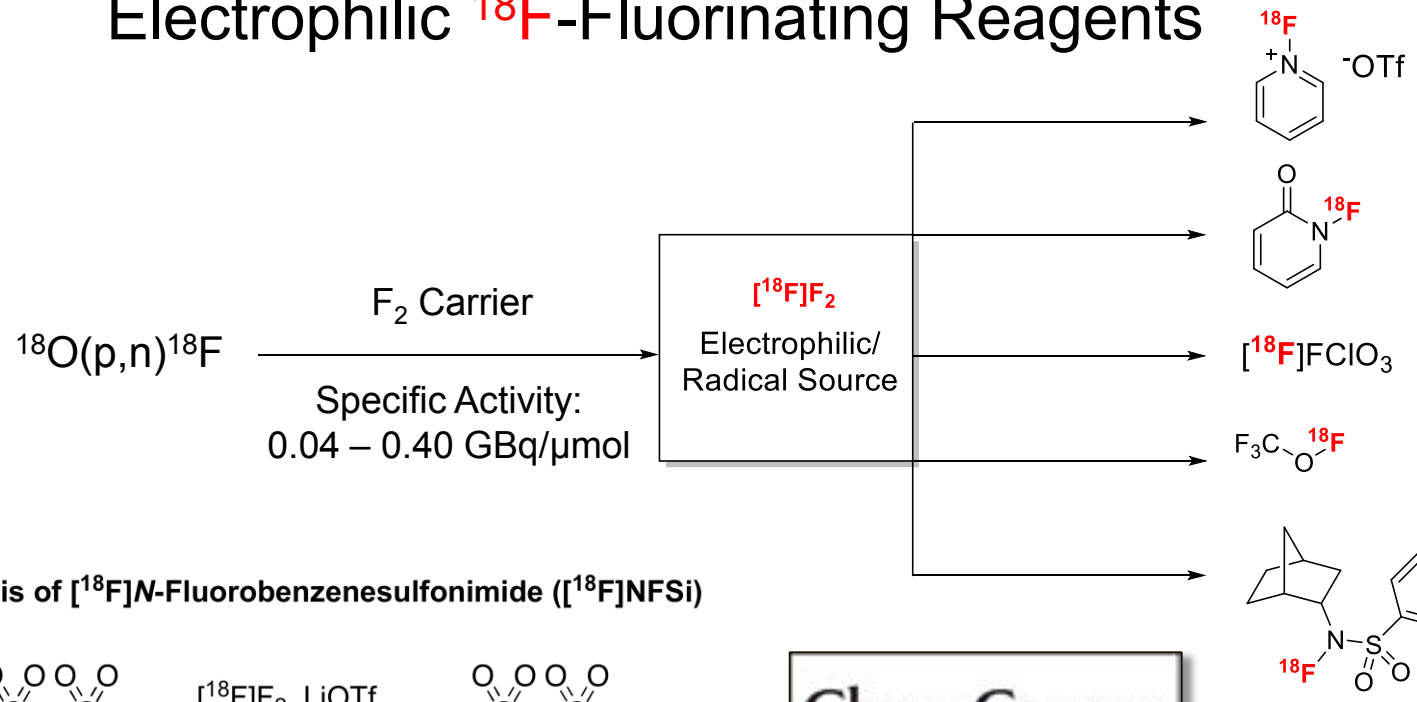


- Late stage labelling of a peptide
- Neutral pH and ambient temperature
- Previously unavailable for **fluorine-18** labelling of bioactive molecules.
- Limited substrate scope

[A] Doyle *J. Am. Chem. Soc.* **2015**, *137,* 9571; **[B] O'Hagan** *Chem. Commun.* **2006**, *6,* 652; *Nature* **2002**, *416*, 279.

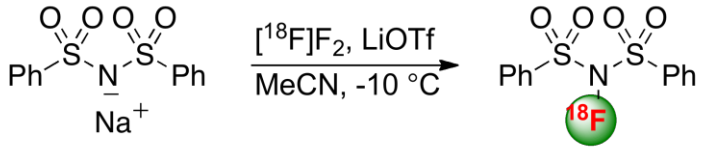
Electrophilic ^{18}F-Fluorinating Reagents

[A]



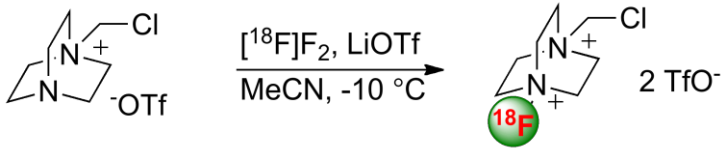
[B]

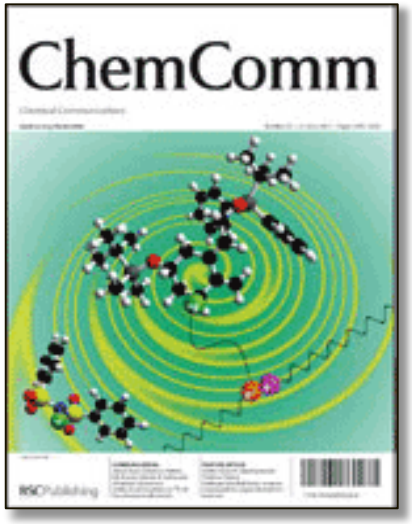
Synthesis of [^{18}F]*N*-Fluorobenzenesulfonimide ([^{18}F]NFSi)



[C]

Synthesis of [^{18}F]Selectfluor bis(triflate)





[A] Gouverneur *Chem. Rev.* **2016**, *116*, 719; *Angew. Chem. Int. Ed.* **2012**, *51*, 11426; **[B] Gouverneur & Solin** *Chem. Commun.* **2007**, 2330; **[C] Gouverneur & Solin** *Angew. Chem. Int. Ed.* **2010**, *49*, 6821.

Specific Activity

$$\text{Specific Activity (SA) [GBq/mmol]} = \frac{\text{Amount of radioactivity [GBq]}}{\text{Mass [mmol]}}$$

1 Bq = 1 s^{-1}

1 Ci = 3.7 x 10^{10} Bq = 37 GBq

1 Bq = 2.70 x 10^{-11} Ci

Specific Activity $(SA)_{max}$ [Bq/mol] = $N_0\lambda$

$\lambda = \ln 2/t_{1/2}$ Decay Constant

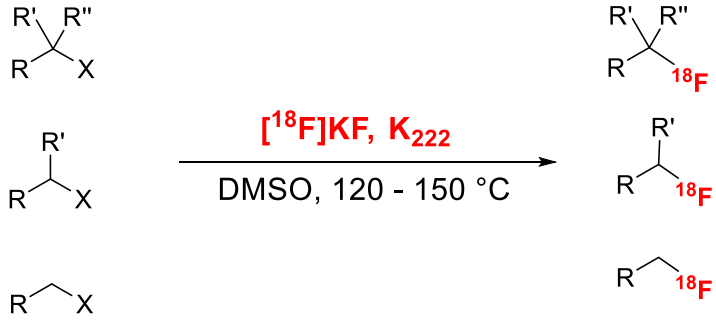
N_0 = 6.022 x 10^{23} mol^{-1} Avogadro Constant

Radionuclide	Half Life /min	Nuclear Reaction	Target	Product	Theoretical SA limit GBq/μmol	Maximum SA reported GBq/μmol	Decay Product
^{18}F	**110**	**^{18}O(p,n)^{18}F**	**[^{18}O]H_2O**	**[^{18}F]F^-**	**6.34 x 10^4**	**4000**	**^{18}O**
		^{20}Ne(d,α)^{18}F	**Ne(+F_2)**	**[^{18}F]F_2**		**55**	
^{11}C	20.4	^{14}N(p,α)^{11}C	N_2(+O_2)	[^{11}C]CO_2	3.4 x 10^5	500-2000	^{11}B
				[^{11}C]CH_4			
^{13}N	9.97	^{16}O(p,α)^{13}N	H_2O	[^{13}N]NO_x	7.0 x 10^5	> 400	^{13}C
			H_2O+EtOH	[^{13}N]NH_3			
^{15}O	2.04	^{14}N(d,n)^{15}O	N_2(+O_2)	[^{15}O]O_2	3.36 x 10^5	4 X 10^{-3}	^{15}N

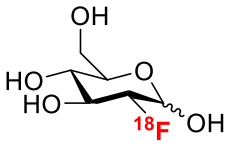
Gee *Angew. Chem. Int. Ed*. **2008**, *47*, 8998.

^{18}F-Fluorination *via* S_N2 Substitution

[A] Nucleophilic Fluorination of [^{18}F]Fluoroalkanes:

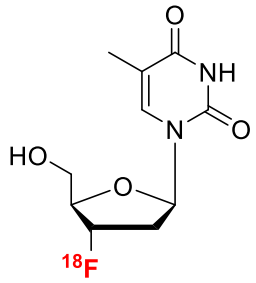


X = Cl, I, OMs, OTs, OTf



[^{18}F]FDG

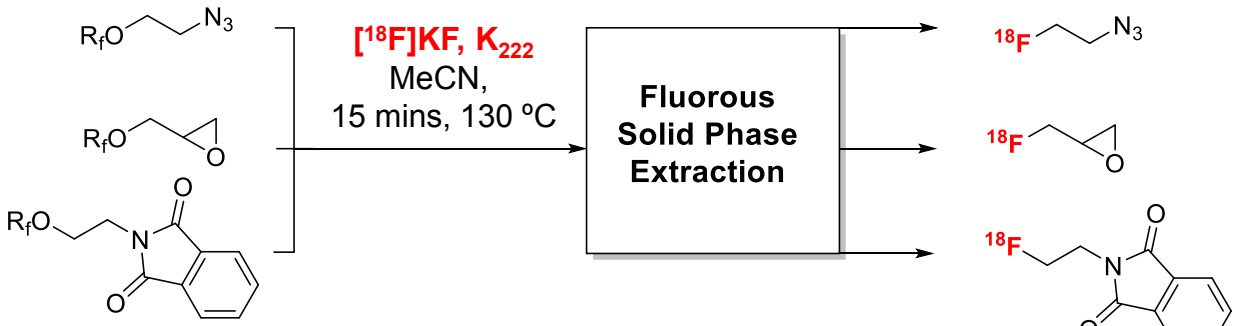
Oncology
Metabolism
Clinical
Sokoloff, *J. Nucl. Med.* **1993**



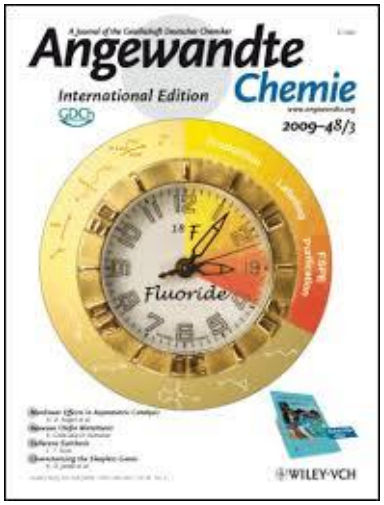
[^{18}F]Fluorothymidine

Oncology
Cellular Proliferation
Preclinical
Grierson, *Nat. Med.* **1998**

[B] Purification: Nucleophilic Fluorination as a Fluorous Detagging Process

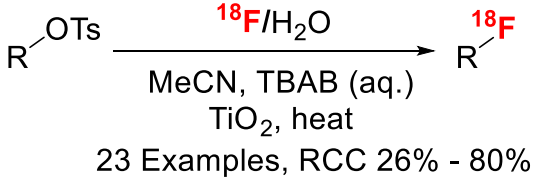


R_f = Fluorous Tag
E.g. $C_8F_{17}(CH_2)_2SO_2$

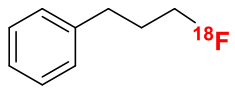


[A] Gee *Angew. Chem. Int. Ed*. **2008**, *47*, 8998; **[B] Gouverneur** *Angew. Chem. Int. Ed*. **2009**, *48*, 586.

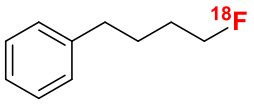
^{18}F-Fluorination *via* S_N2 Substitution



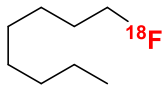
23 Examples, RCC 26% - 80%



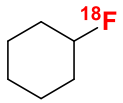
RCC 80% ± 2%



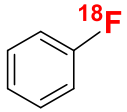
RCC 77% ± 4%



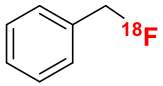
RCC 80% ± 1%



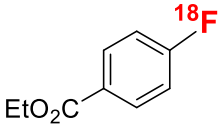
RCC 79% ± 1%



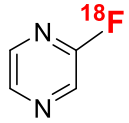
RCC 78% ± 3%



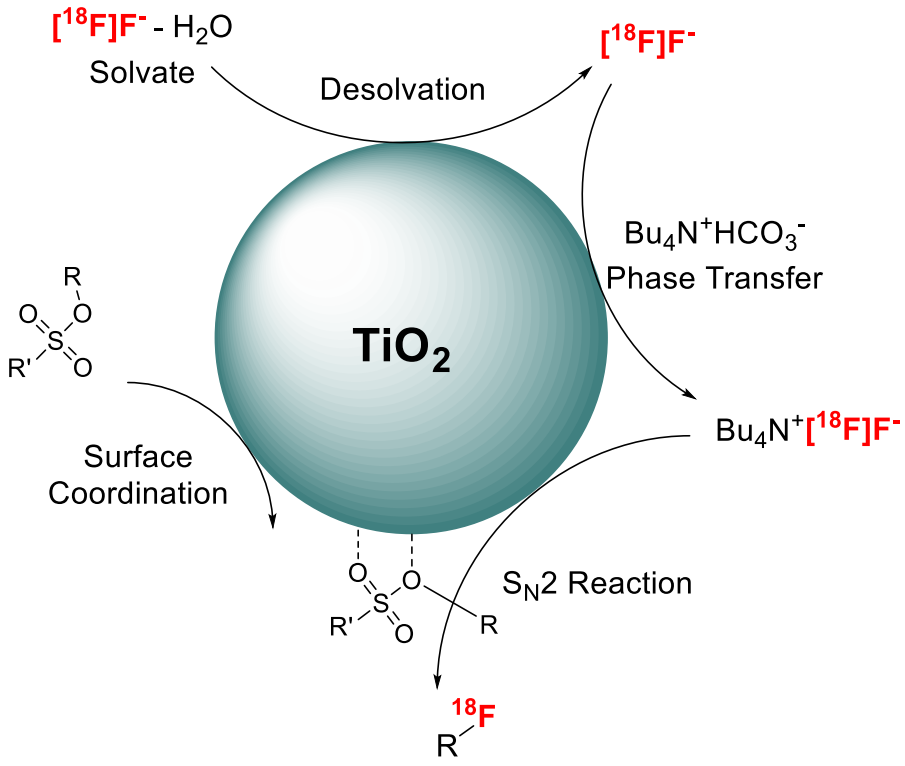
RCC 80% ± 3%



RCC 78% ± 4%



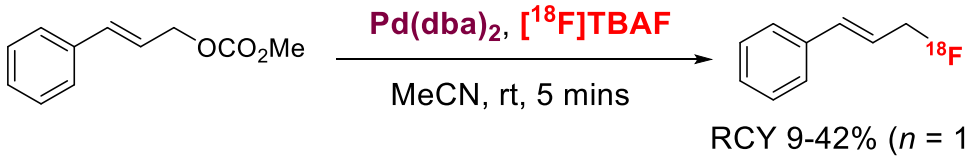
RCC 68% ± 5%



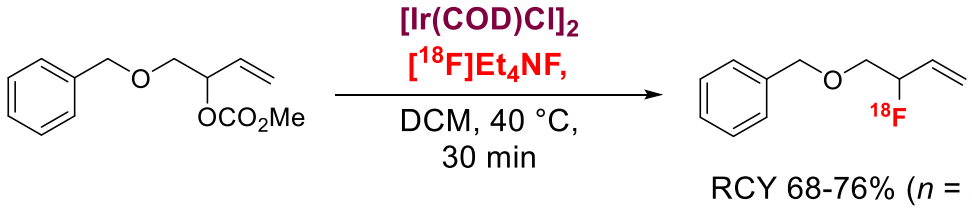
Dam *J. Am. Chem. Soc.* **2015**, *137*, 5686.

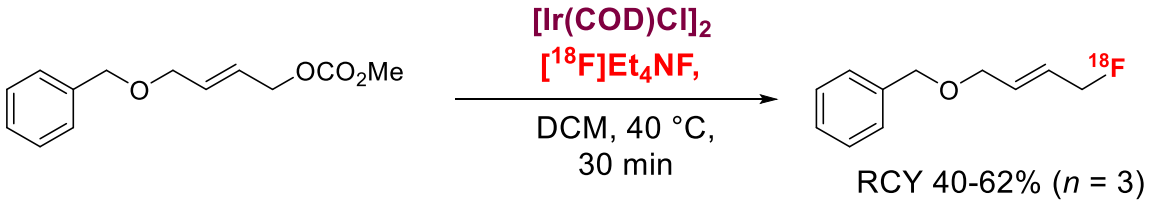
Pd and Ir Catalysed ^{18}F-Csp^3 Formation from $[^{18}F]F^-$

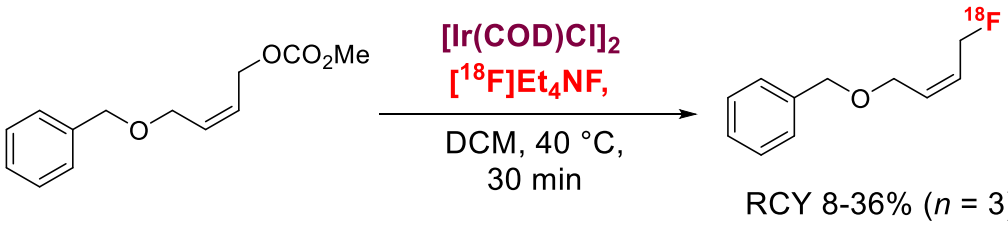
[A]



[B]

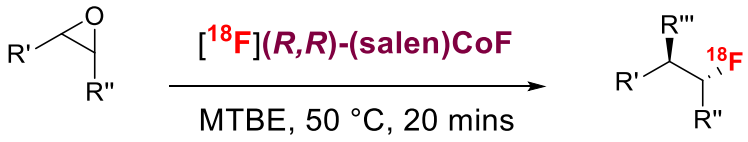




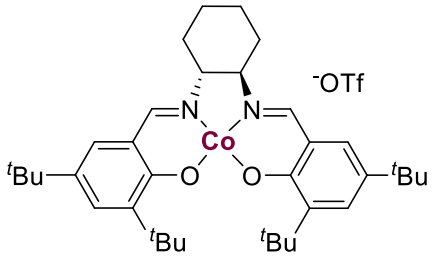


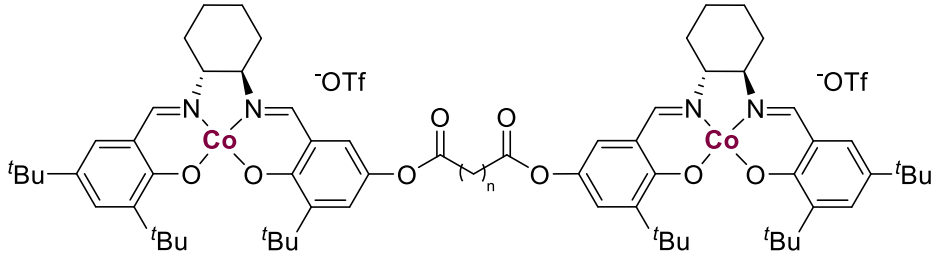
[A] Gouverneur *Angew. Chem. Int. Ed.* **2011**, *50,* 2613; **[B] Gouverneur** *Chem. Commun.* **2012**, *48*, 2929; *Chem. Sci.* **2013**, *4*, 89.

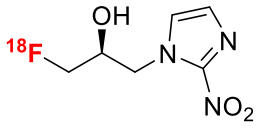
^{18}F-Fluorination of Epoxides



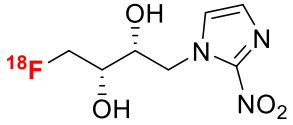
6 Examples
RCY 23% - 68%
ee up up to > 95%



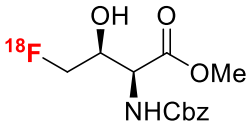




RCY 67% ± 4% (*n* = 3)
ee 90%
[^{18}F]FMISO



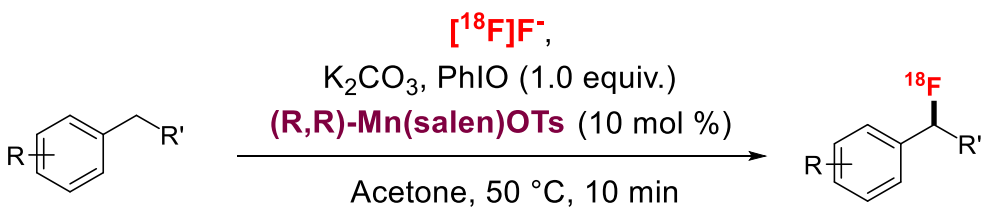
RCY 71% ± 1% (*n* = 3)
d.r 1:1, *ee* > 95%
[^{18}F]FETNIM

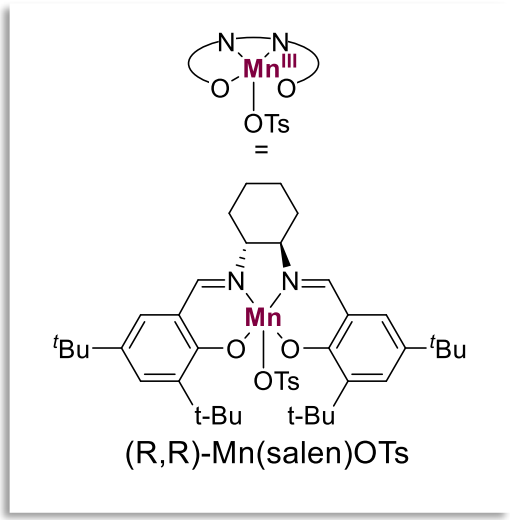


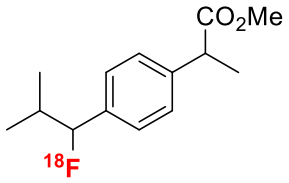
RCY 60% ± 5% (*n* = 3)
d.r > 99:1
[^{18}F]*N*-Cbz-*L*-fluoro-threonine methyl ester

Doyle & Kung *J. Am. Chem. Soc.* **2014**, *136*, 5294.

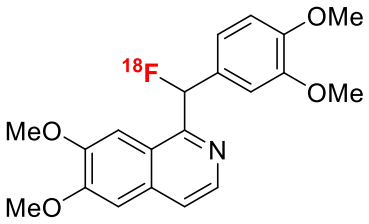
Manganese Catalysed Benzylic ^{18}F-Fluorination



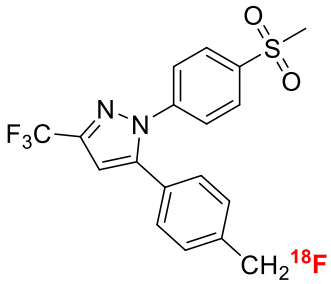




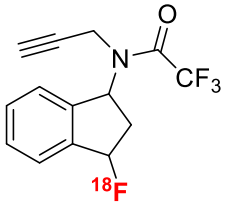
[^{18}F]Ibuprofen ester
COX inhibitor
65% ± 10% (*n* = 6)



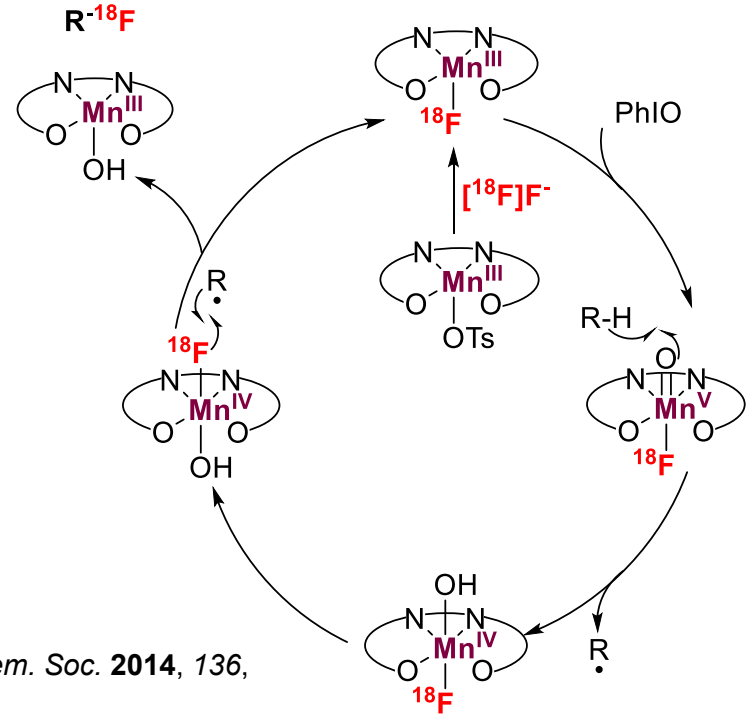
[^{18}F]Papaverine
PDE$_{10A}$ inhibitor
22% ± 5% (*n* = 4)



[^{18}F]celecoxib analog
COX-2 selective inhibitor
23% ± 3% (*n* = 4)

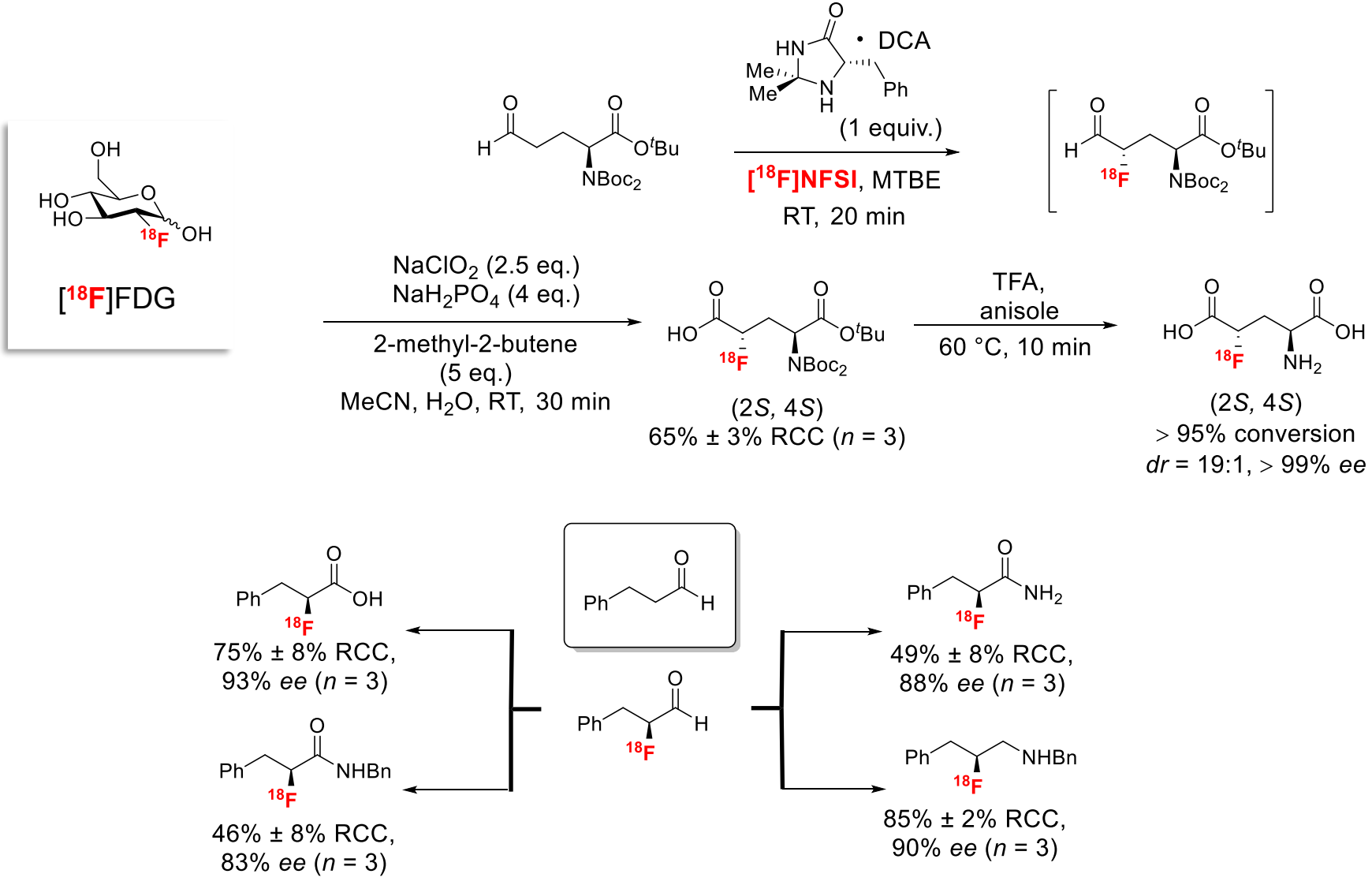


[^{18}F]-*N*-TFA rasagiline
MAO-B inhibitor
72% ± 10% (*n* = 5)



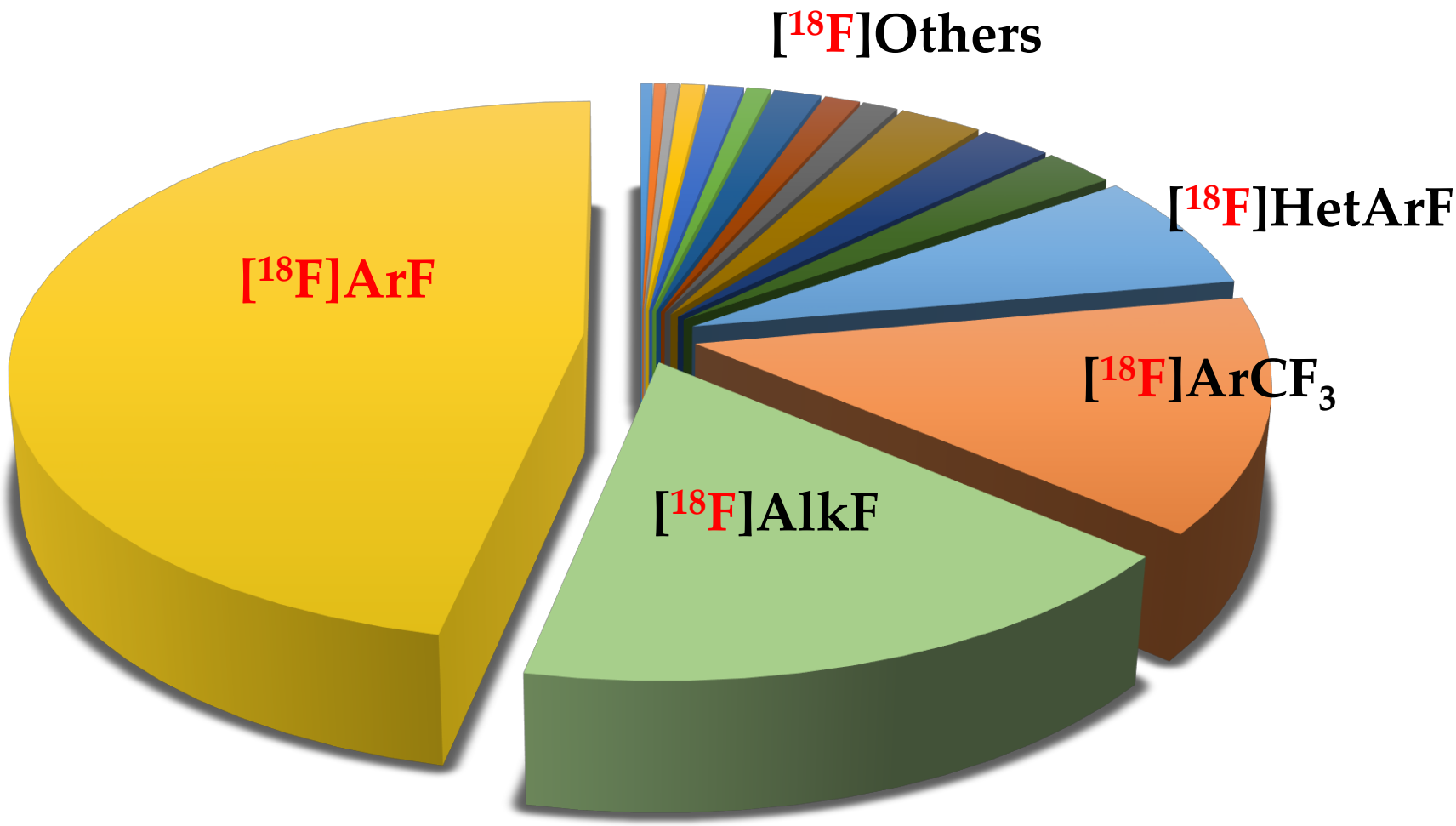
Groves *Angew. Chem. Int. Ed.* **2013**, *52*, 6024; **Groves & Hooker** *J. Am. Chem. Soc.* **2014**, *136*, 6842**;** See Also; **Groves** *Science*, **2012**, *337*, 1322

Merging Organocatalysis with Radiochemistry



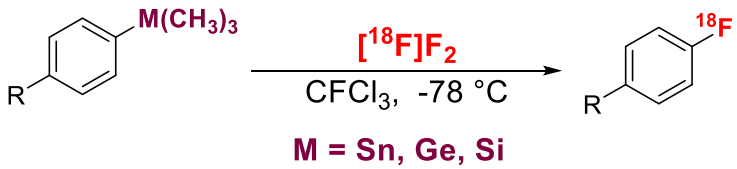
Gouverneur *Angew. Chem. Int. Ed.* **2015**, *54*, 13366; **Gouverneur** *Chem. Sci.* **2016**, *7*, 1645.

^{18}F-Fluorination of Aromatics and Heteroaromatics

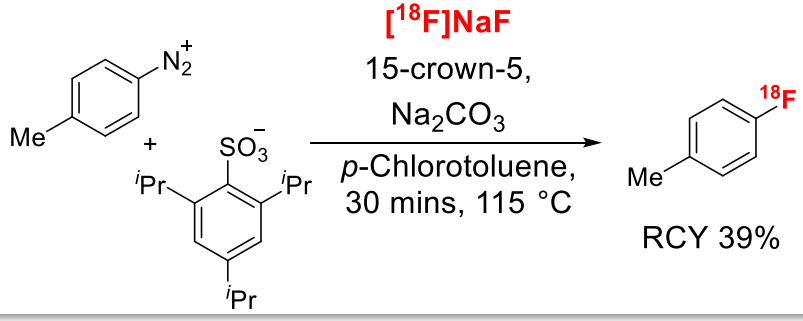


^{18}F-Fluorination of Aromatics

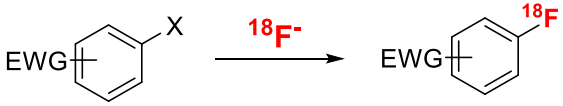
[A] Metal Mediated Reactions: Electrophilic ^{18}F-Fluorination



[A] Balz-Schiemann Reactions: Nucleophilic ^{18}F-Fluorination

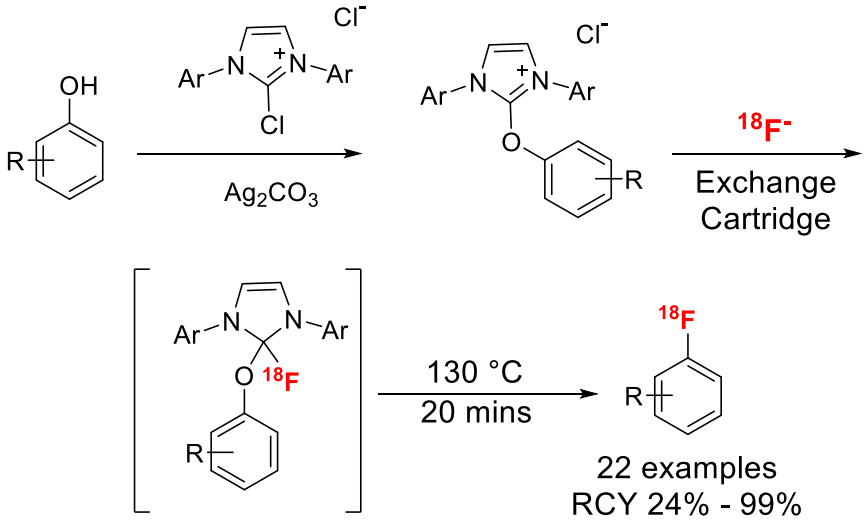


[A] S_NAr: Nucleophilic ^{18}F-Fluorination



X = NO_2, quarternary ammonium salts

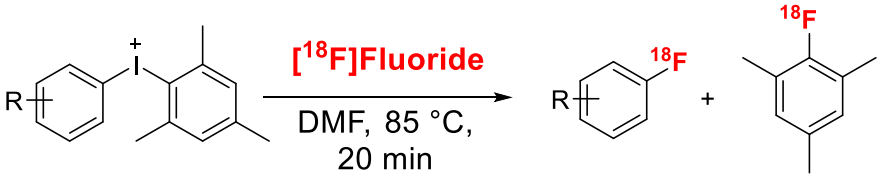
[B] Concerted ^{18}F-Deoxyfluorination



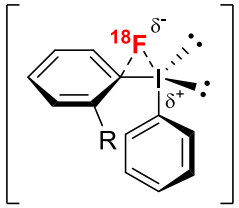
[A] Gouverneur *Chem. Rev.* **2016**, *116*, 719; *Angew. Chem. Int. Ed.* **2012**, *51*, 11426. **[B] Ritter** *Nature* **2016** *ASAP*.

^{18}F-Fluorination of Arenes *via* Iodonium Salts/Ylides

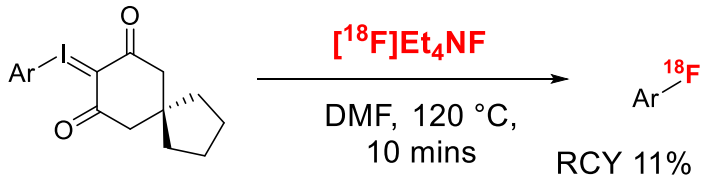
[A] ^{18}F-Fluorination of Arenes *via* Iodonium Salts



Favoured Transition State

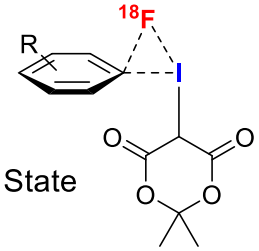


[B] ^{18}F-Fluorination of Arenes *via* Iodonium Ylides

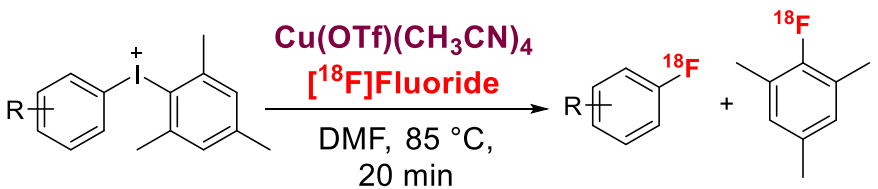


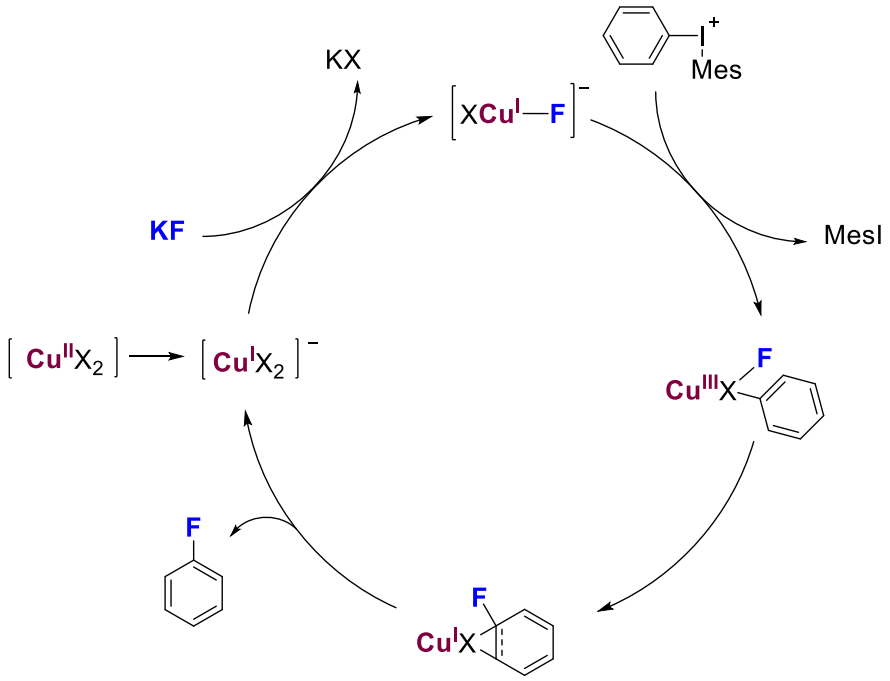
RCY 11% - 65%

Transition State



[C] ^{18}F-Fluorination of Arenes *via* Iodonium Salts

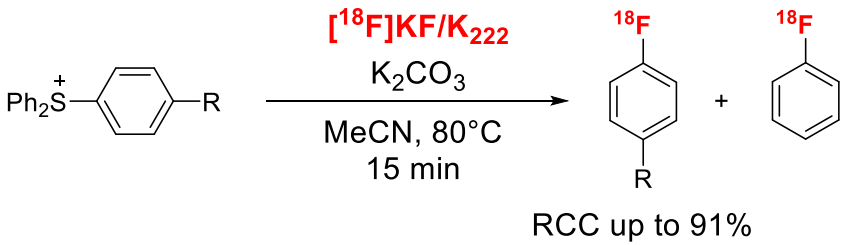


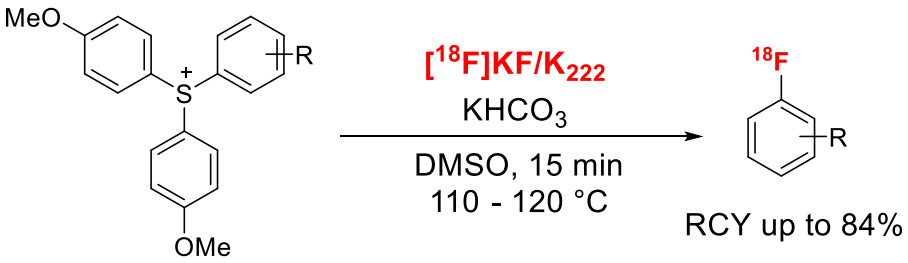


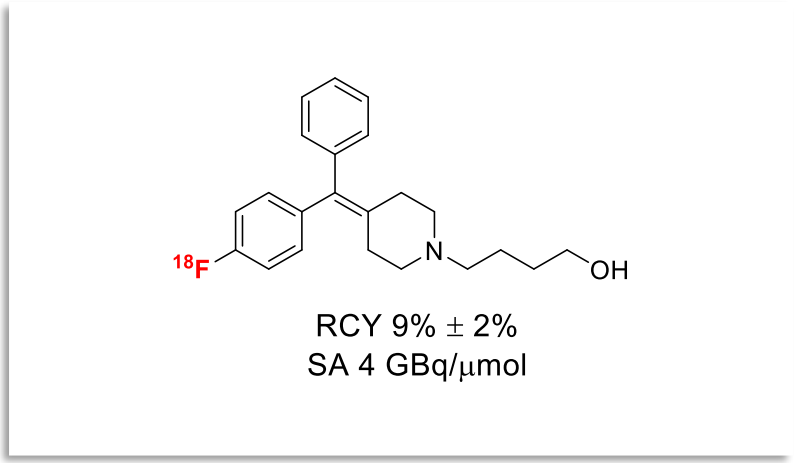
[A] Pike *J. Chem. Soc. Perkin Trans.* **2000**, 2158; *J. Chem. Soc. Perkin Trans.* **1999**, 2707; *Chem. Eur. J.* **2010**, *16*, 10418.
[B] Vasdev *Nature. Commun.* **2014**, *5*, 4365; *J. Fluorine. Chem.* **2015** ,*178*, 249; *Chem. Sci.* **2016 DOI:** 10.1039/C6SC00197A;
[C] Sanford *Org. Lett.* **2013**, *15*, 5134; *Org. Lett.* **2014**, *16*, 3224; *Organometallics.* **2014**, *33*, 5525.

^{18}F-Fluorination *via* Sulfonium and Sulfoxide Precursors

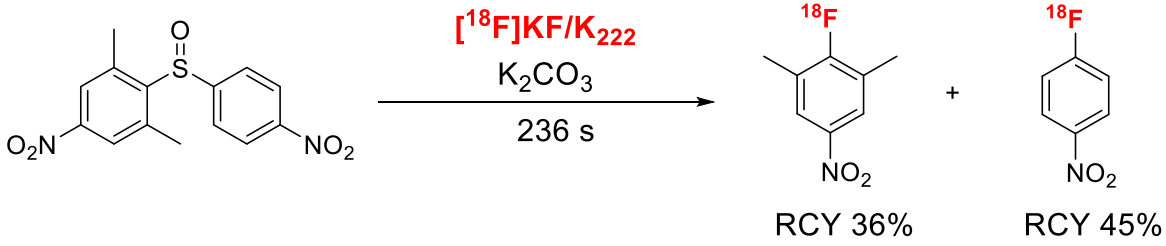
[A] Sulfonium Precursors







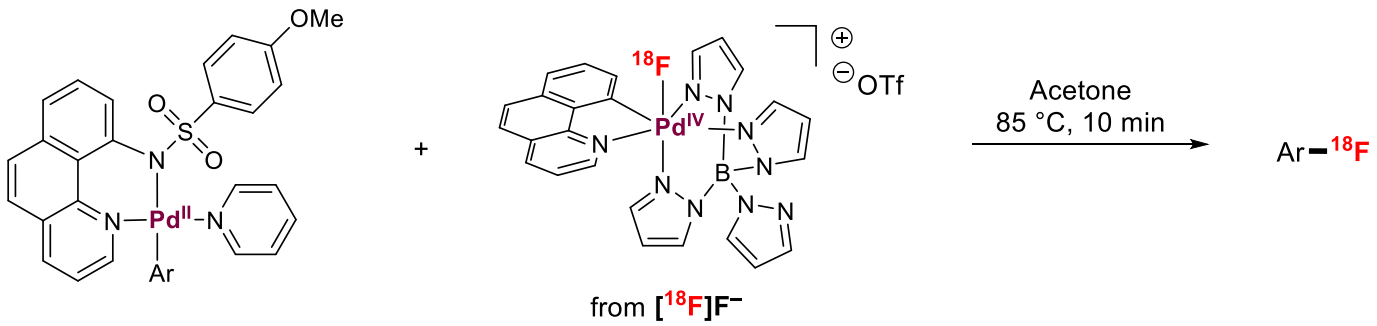
[B] Sulfoxide Precursors



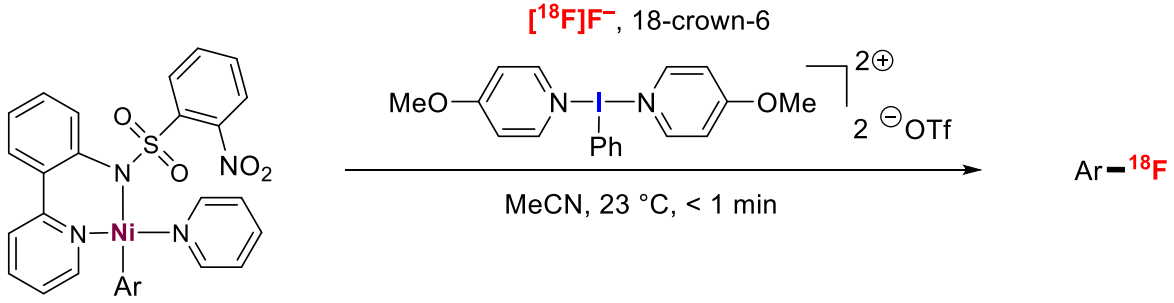
[A] Lehmann *Eur. J. Org. Chem.* **2012**, *2012*, 889; **Årstad** *Sci. Rep*. **2015**, *5*, 9941; **[B] Pike** *Chem. Comm.* **2013**, *49,* 215; *J. Labelled. Compd. Radiopharm.* **2015**, *58,* 5149.

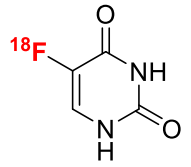
Metal Mediated ^{18}F-Fluorination

[A] [^{18}F]Fluorination *via* Pd^{II} / Pd^{IV}:



[B] [^{18}F]Fluorination *via* Ni^{II}:

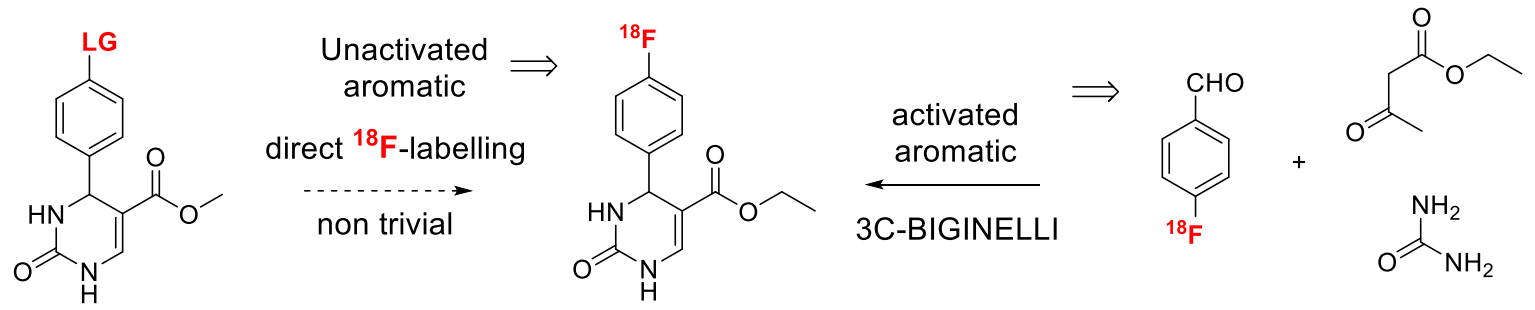


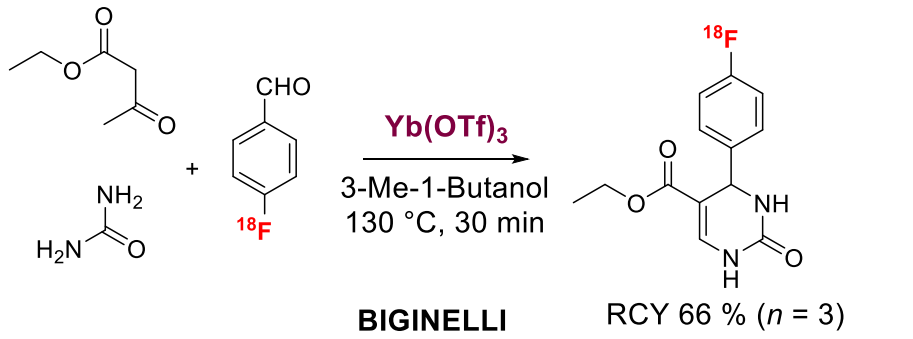


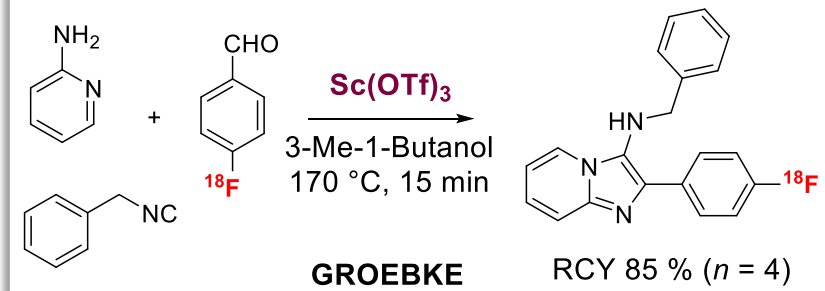
[^{18}F]5-Fluorouracil
0.5 - 0.7 GBq
0.92% ± 0.18 RCY
SA > 370 GBq/μmol (*n* = 3)

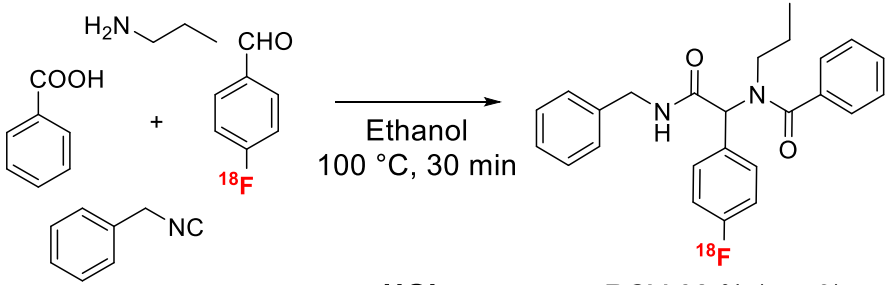
[A] Ritter *Science* **2011**, *334*, 639; **[B]** *J. Am. Chem. Soc.* **2012**, *134*, 17456; *Organometallics*. **2016**, *35*, 1008.

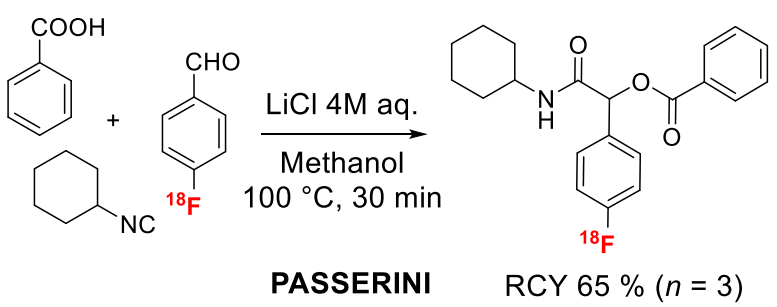
A Convergent Towards ^{18}F-Arenes







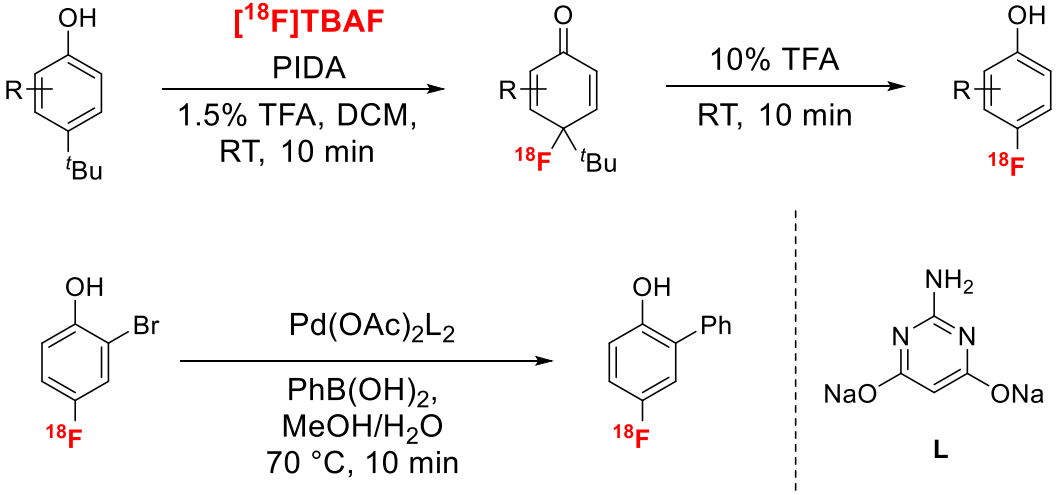


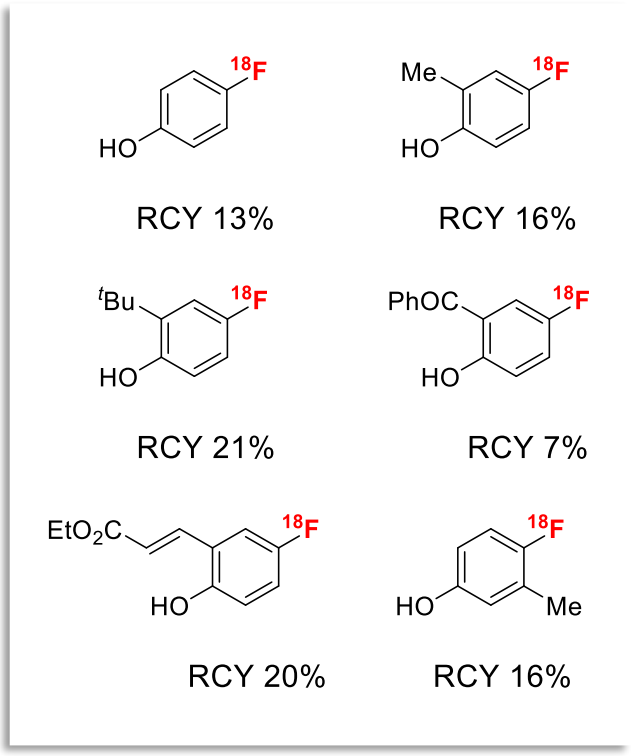


Gouverneur *Chem. Sci.* **2011**, *2*, 123.

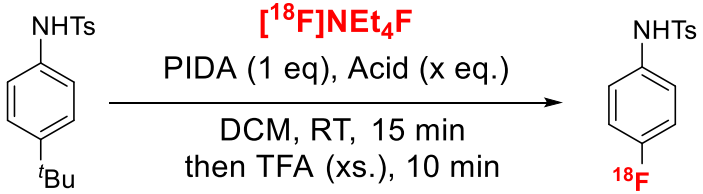
Metal Free Oxidative ^{18}F-Fluorination

[A] ^{18}F-Fluorination of Phenols:





[B] ^{18}F-Fluorination of *N*-Arylsulfonamides:

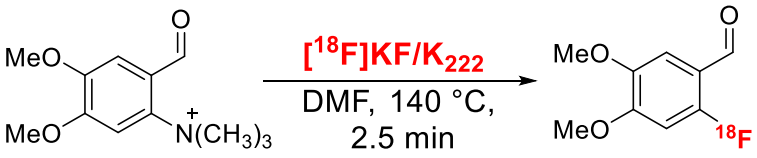


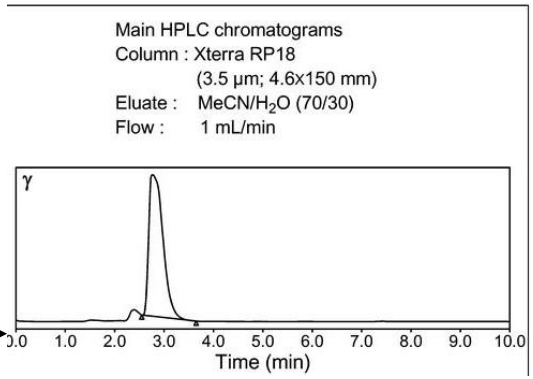
TFA (4 eq.): 2% ± 1% RCY (n = 4)
HF.pyr (1 eq.): 52% ± 6% RCY (n = 4)

[A] Gouverneur *Angew. Chem. Int. Ed.* **2012**, *51*, 6733; **[B] Gouverneur** *J. Fluorine. Chem.* **2015**, *108*, 33.

[^{18}F]F-*L*-DOPA from [^{18}F]Fluoride

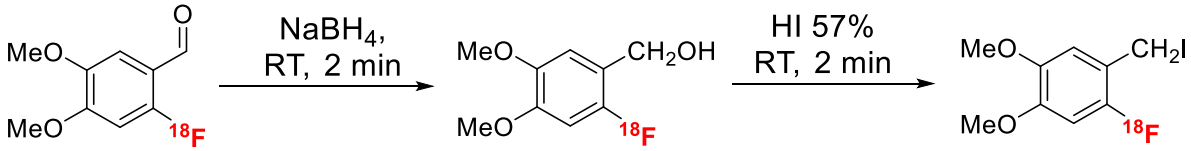
Radiolabelling - Liquid Phase

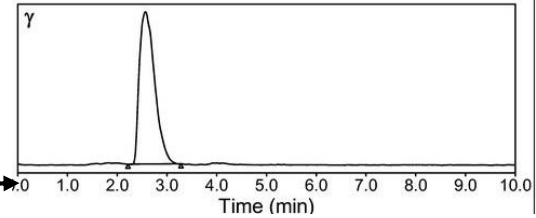




Trapping on Solid Phase Extraction (SPE) Cartridge

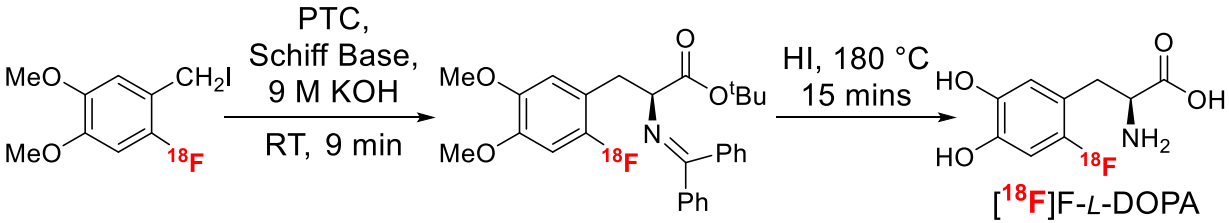
Reaction on the Solid Support





Toluene Elution

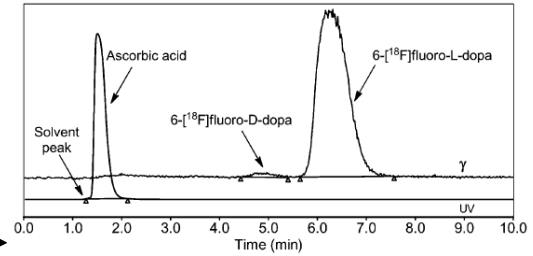
Enantioselective Alkylation



[^{18}F]F-*L*-DOPA

RCY 36% ± 3% (*n* = 8)

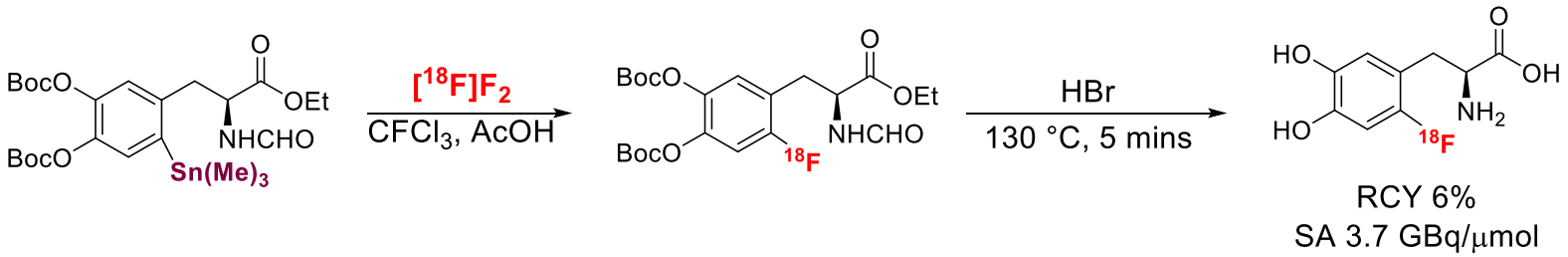
SA ≥ 753 GBq/µmol



Luxen *J. Nucl. Med.* **2013**, *54*, 1154.

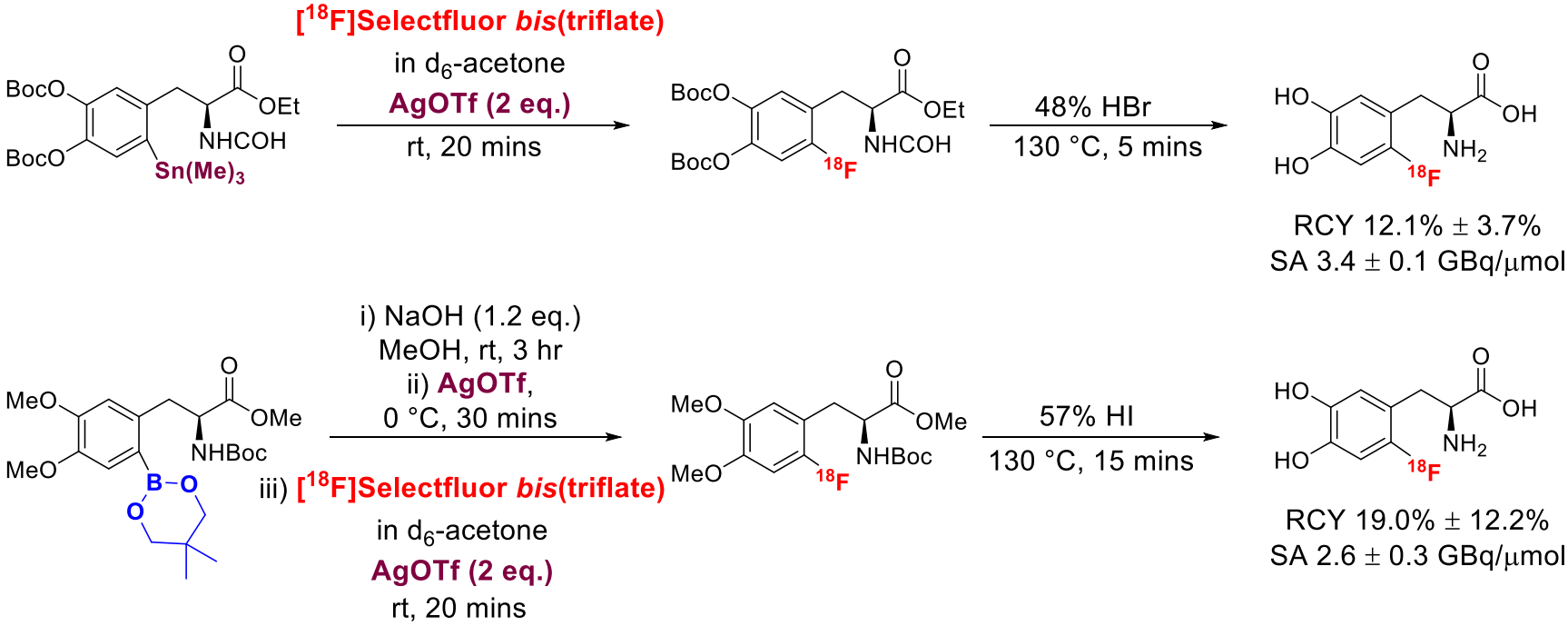
[^{18}F]F-*L*-DOPA Formation from [^{18}F]F^{+}

[A].



RCY 6%
SA 3.7 GBq/μmol

[B,C]

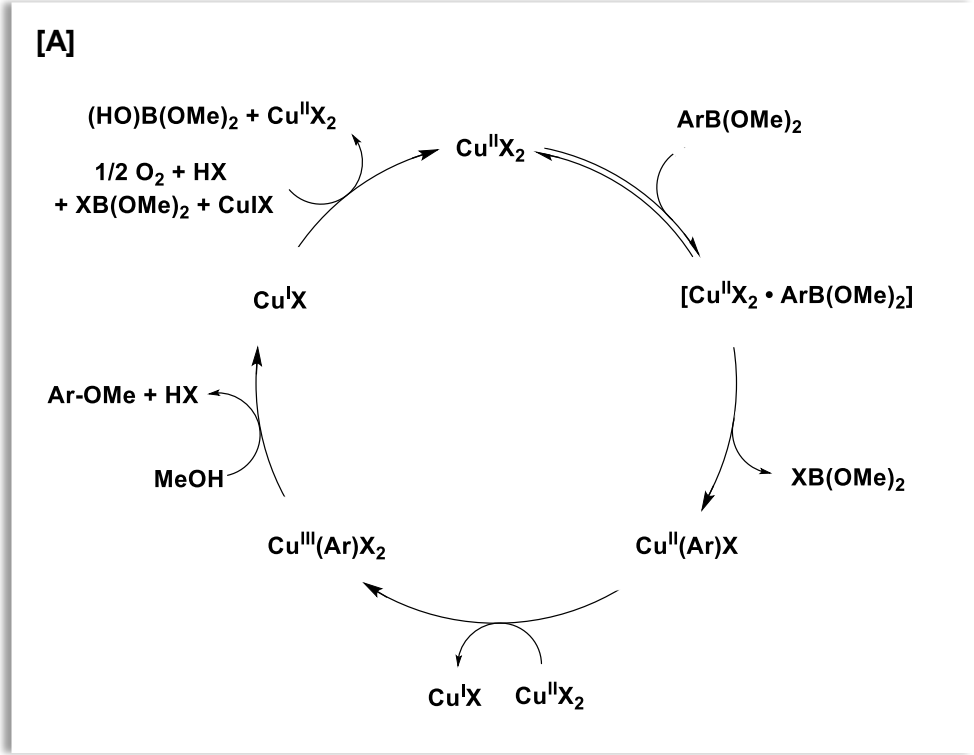


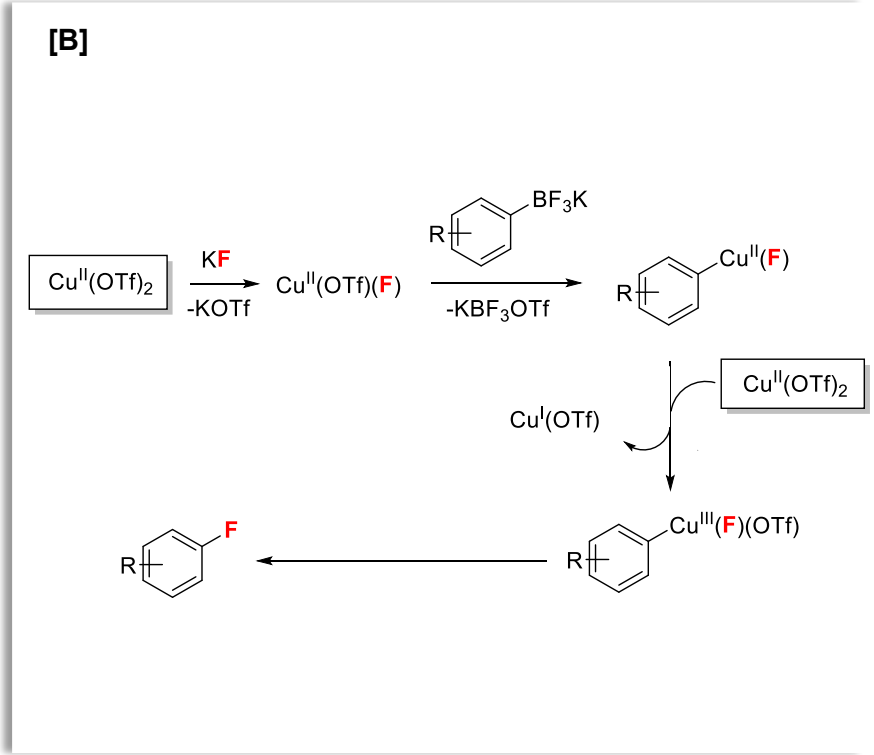
RCY 12.1% ± 3.7%
SA 3.4 ± 0.1 GBq/μmol

RCY 19.0% ± 12.2%
SA 2.6 ± 0.3 GBq/μmol

[A] Solin *Radiochim. Acta.* **2008**, *96*, 845; **[B,C] Gouverneur** *Chem. Commun.* **2007**, *23*, 2330*; Angew. Chem. Int. Ed.* **2010**, *49*, 6821; *Chem. Commun.* **2013**, *14*, 1341.

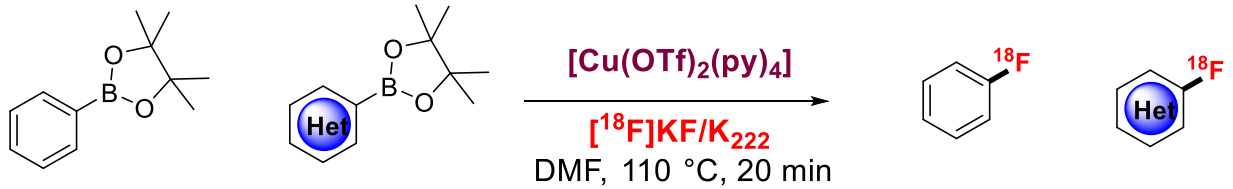
^{18}F-Labelling of Fluoro(Hetero)Arenes with [^{18}F]F^-



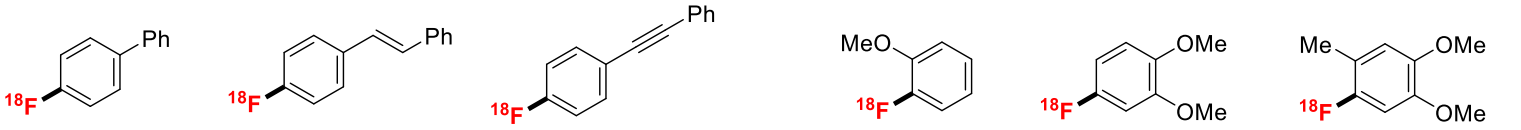


[A] Stahl *J. Am. Chem. Soc.* **2009**, *131*, 5044; **[B] Sanford** *J. Am. Chem. Soc.* **2013**, *135*, 16292;

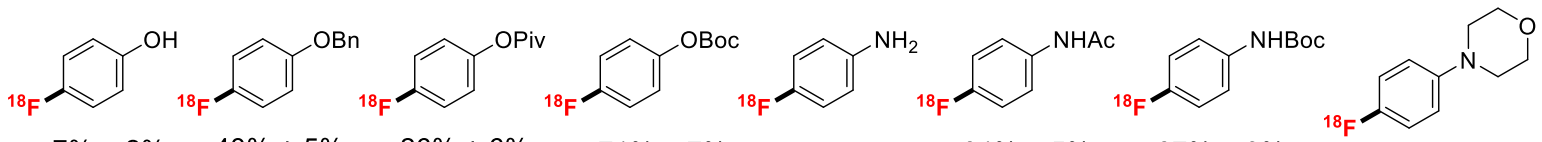
Copper Mediated ^{18}F-Labelling of Fluoro(Hetero)Arenes



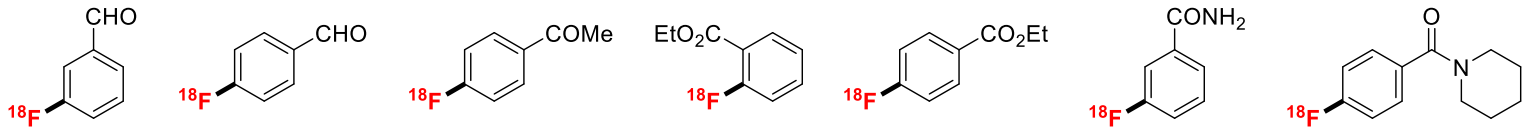
Conditions: Substrate 0.06 mmol, Cu complex 0.0053 mmol i.e. 11:1, in 300 µL DMF. All n = 4.



74% ± 5% 56% ± 5% 68% ± 2% 11% ± 2% 54% ± 3% 62% ± 4%



7% ± 2% 43% ± 5% 26% ± 6% 71% ± 7% 5% ± 1% 64% ± 5% 67% ± 3% 44% ± 6%

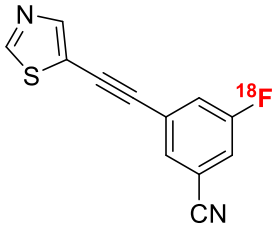


59% ± 8% 47% ± 7% 66% ± 6% 10% ± 1% 57% ± 7% 4% ± 2% 83% ± 2%

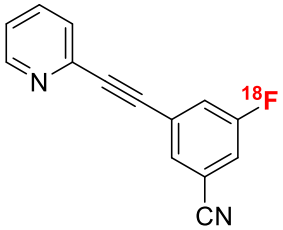
> **Specific activity > 110 GBq.µmol^{-1}**
> **ICP demonstrates that Cu is well removed upon purification (< 2 ppm)**
> **Amenable to automation using commercially available kits**

Gouverneur *Angew. Chem. Int. Ed*. **2014,** *53*, 7678; See also: **Sanford & Scott** *Org. Lett*. **2015**, *17*, 5780 (Boronic Acid).

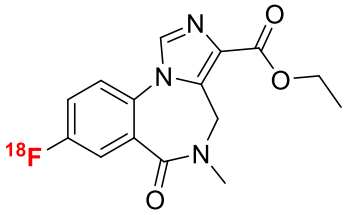
Cu-Mediated Nucleophilic Fluorination of Known Radiotracers and Radiopharmaceuticals



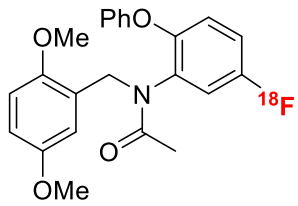
[^{18}F]FMTEB
RCY 29% ± 6% (n = 2)



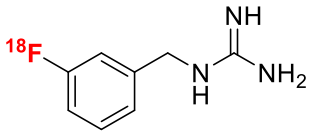
[^{18}F]FPEB
RCY 13% ± 5% (n = 2)



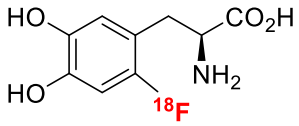
[^{18}F]Flumazenil
RCY 35 ± 7 (n = 3)



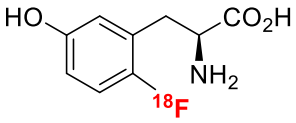
[^{18}F]DAA1106
RCY 39% ± 1% (n = 2)



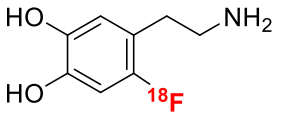
[^{18}F]MFBG
RCY 25% ± 2% (n = 2)



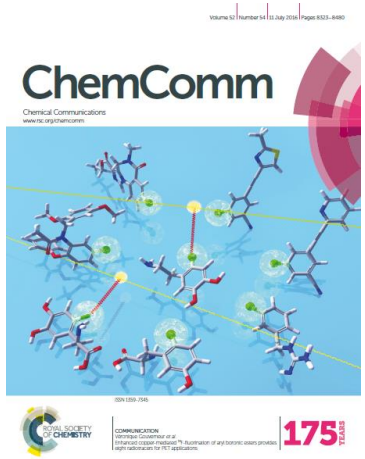
6-[^{18}F]Fluoro-*L*-DOPA
RCY 22% ± 3% (n = 2)



[^{18}F]FMT
RCY 11% ± 3% (n = 2)



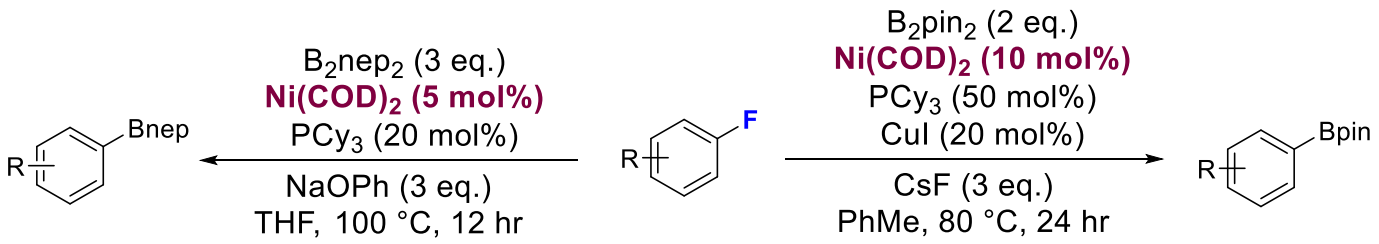
6-[^{18}F]FDA
RCY 29% ± 5% (n = 2)

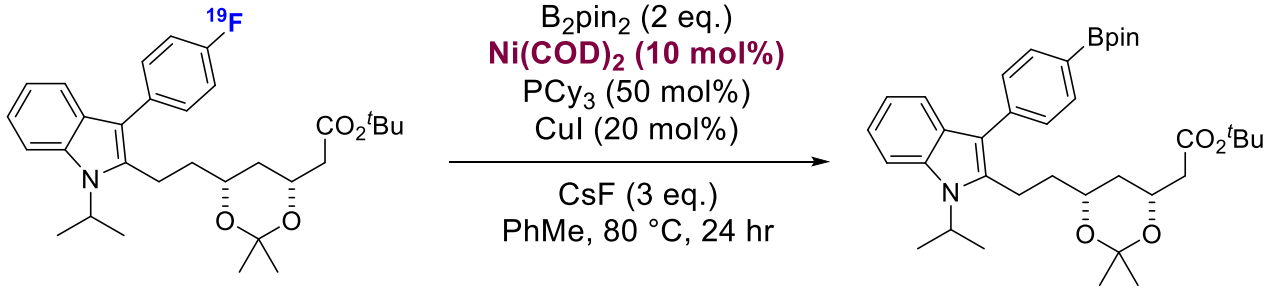


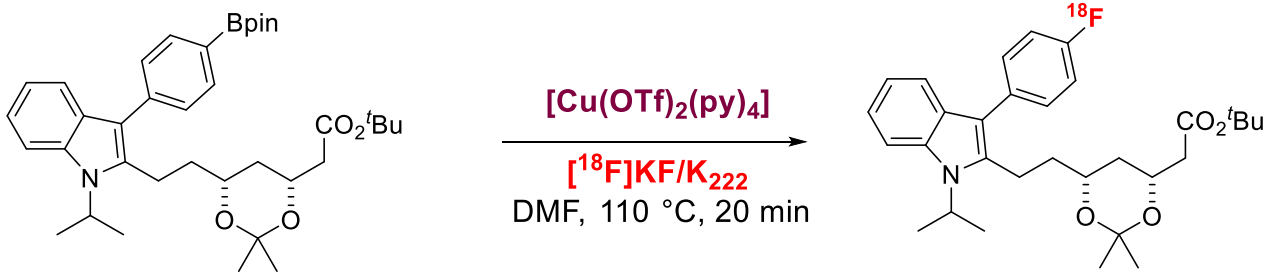
Gouverneur *Chem. Comm.* **2016**, *52*, 8323. (Collaboration J. Passchier, A. Hoepping)

Aryl-^{19}F ⟶ Aryl-Boronics ⟶ Aryl-^{18}F

[A, B]



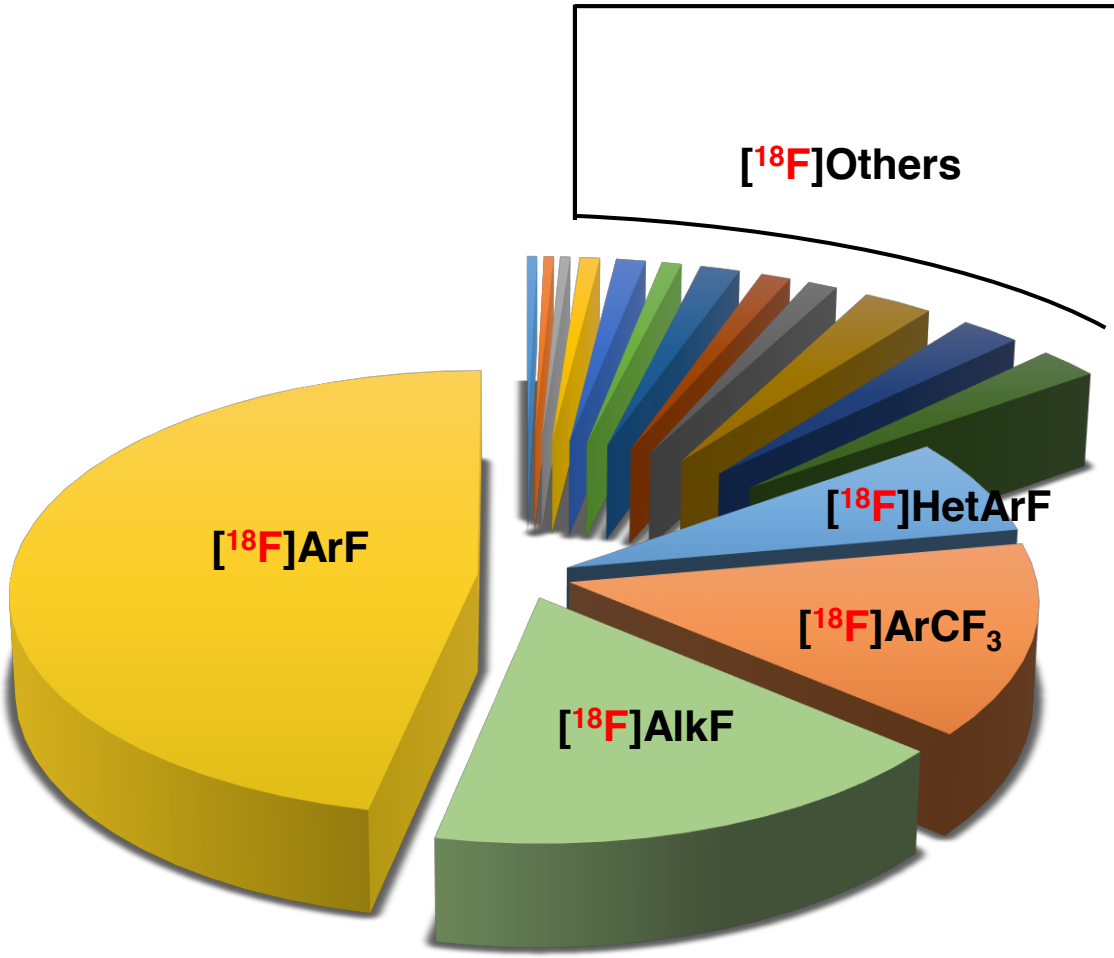




RCY 55%
Dihydrofluvastatin Derivative

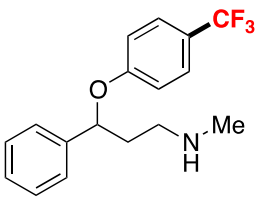
[A] Martin *J. Am. Chem. Soc.* **2015**, *137*, 12407; **[B] Hosoya** *J. Am. Chem. Soc.* **2015**, *137*, 14313.

^{18}F-Fluorination of Other Motifs

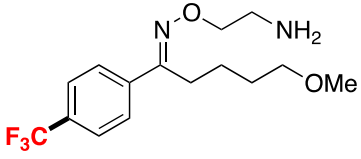


$[^{18}F]OCHF_2$
$[^{18}F]OCF_3$
$[^{18}F]NHCH_2CF_3$
$[^{18}F]SCH_2F$
$[^{18}F]COCF_3$
$[^{18}F]HetArCF_3$
$[^{18}F]SCH_2CF_3$
$[^{18}F]OCH_2CF_3$
$[^{18}F]SCHF_2$
$[^{18}F]AlkCF_3$
$[^{18}F]AlkF_2$
$[^{18}F]Alk/ArylCF_2CF_3$

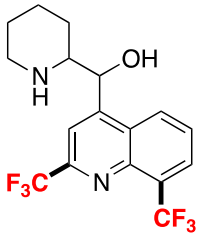
Trifluoromethylated (Hetero)arenes in Drug Discovery



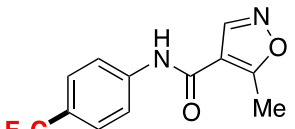
Fluoxetine
antidepressant



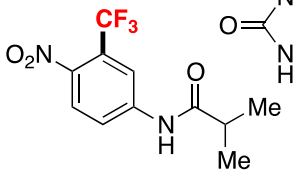
Fluvoxamine
antidepressant



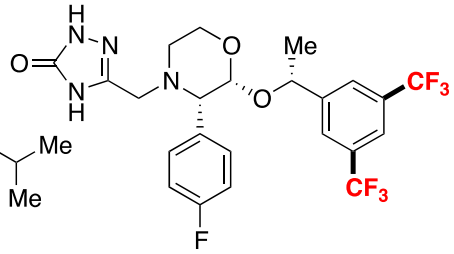
Mefloquine
antimalarial agent



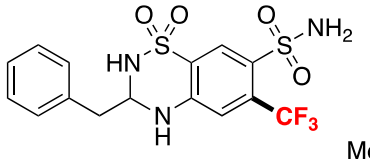
Leflunomide
antirheumatic agent



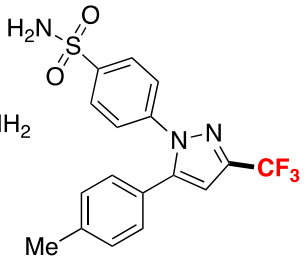
Flutamide
antineoplastic agent



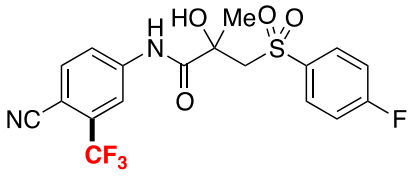
Aprepitant
antiemetic



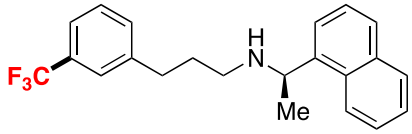
Bendroflumethiazide
diuretic



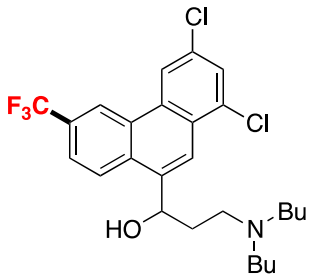
Celecoxib
anti-inflammatory



Bicalutamide
antineoplastic agent

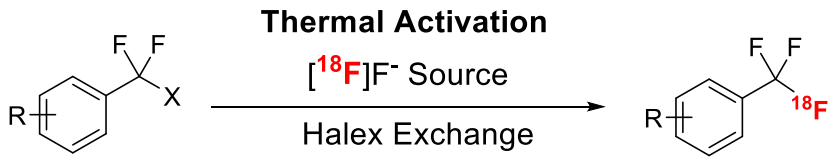


Cinacalcet
calcimimetic agent

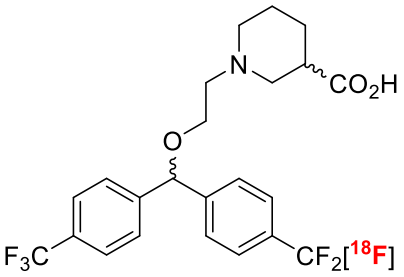


Halofantrine
calcimimetic agent

^{18}F-Labelling of Trifluoromethyl (Hetero)Arenes: Halex Exchange

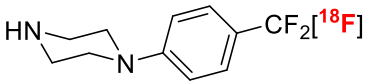


[A]



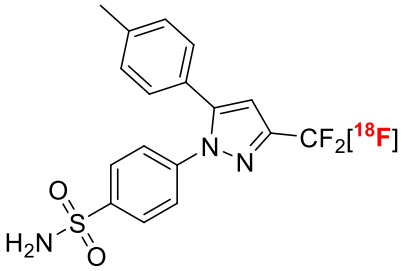
GABA Receptor
RCY 17 - 28%
SA 0.037 GBq/μmol

[B]



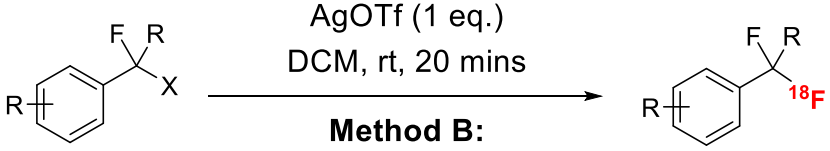
Serotonin Agonist
RCY 27%
SA 0.07 GBq/μmol

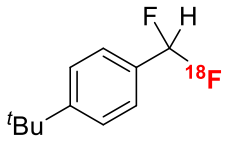
[C]



COX-2 Inhibitor
RCY 10 ± 2%
SA 4.44 ± 1.48 GBq/μmol

[D]

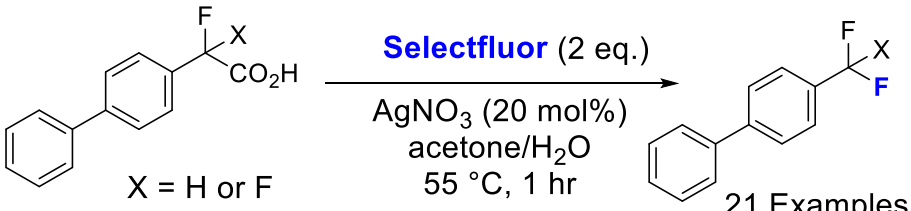


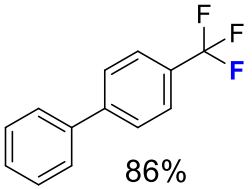


Method A
RCY 10% (363 MBq)
SA 0.03 GBq/μmol

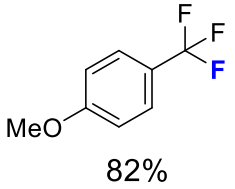
[A] Gregor *Appl. Radiat. Isol.* **1990**, *41*, 823; **[B] Wolf** *J. Label. Compd. Radiopharm.* **1990**, *28*, 1441; **[C] Prabhakaran** *Bioorg. Med. Chem.* **2007**, *15*, 1802; **[D] Gouverneur** *Synlett* **2015**, *27*, 25.

Decarboxylative ^{18}F-Labelling of Trifluoro and Difluoromethyl (Hetero)Arenes

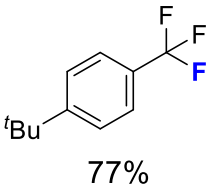




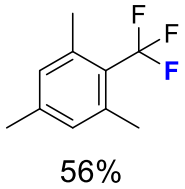
86%



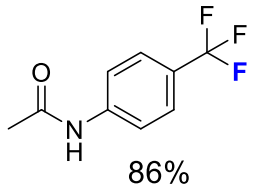
82%



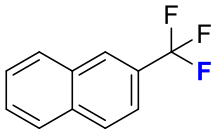
77%



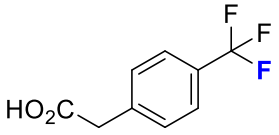
56%



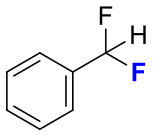
86%



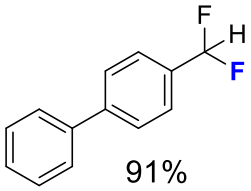
51%



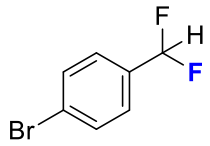
17%



72%

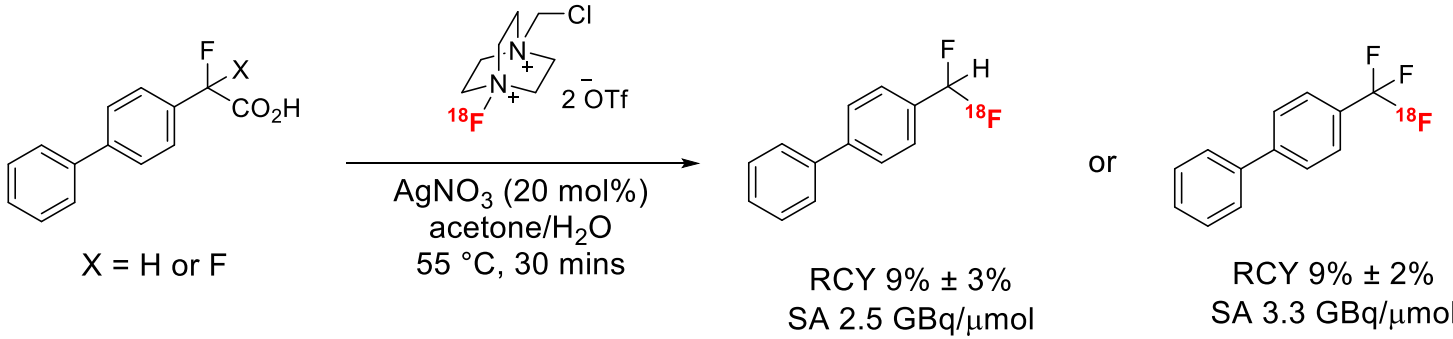


91%



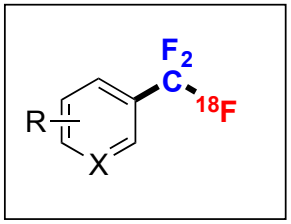
82%

^{18}F-Fluorination Towards [^{18}F]Trifluoromethyl and [^{18}F]Difluoromethyl arenes:



Gouverneur *Org. Lett.* **2013**, *15*, 2648.

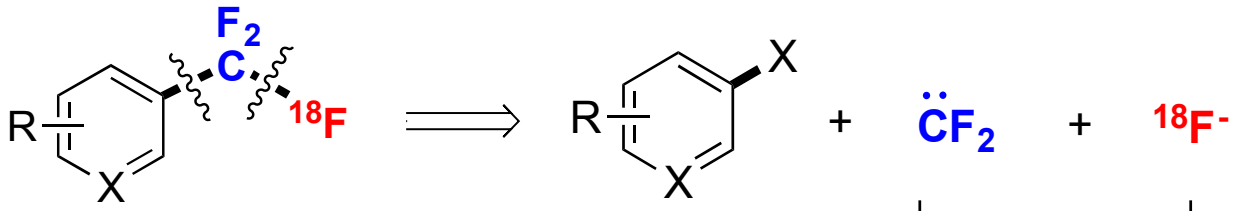
Multicomponent ^{18}F-Labelling of Trifluoromethyl (Hetero)Arenes



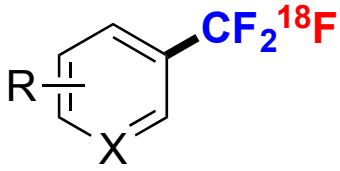
- From [^{18}F]fluoride
- Arenes and heteroarenes
- Readily available precursors
- Logistically and operationally simple

Conceptual Advance

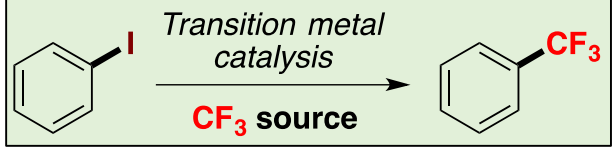
Deconstructing the CF_3 Group
Simultaneous C-C and C-F bond disconnection
Multicomponent approach



cross-coupling

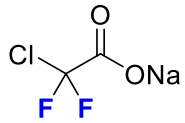


C-C Disconnection

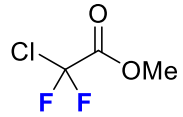


Burton *J. Fluorine Chem.* **1991,** *55*, 225; **Chen** *J. Fluorine Chem.* **1993,** *65*, 11; **Amii** *Chem. Commun.* **2009,** 1909; **Hartwig** *Angew. Chem. Int. Ed.* **2011,** *50*, 3793.

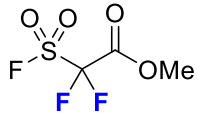
Difluorocarbene



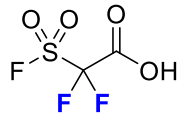
Haszeldine *Proc. Chem. Soc., London* **1960**, 81



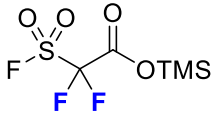
Burton *J. Fluorine Chem.* **1976**, *8*, 97



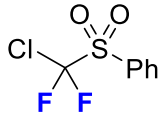
Chen *Sci. Sin., Ser. B (Engl. Ed.)* **1986**, *30*, 561



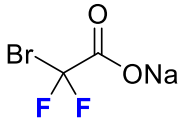
Chen *J. Org. Chem.* **1989**, *54*, 3023



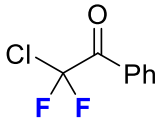
Chen *Org. Lett.* **2000**, *2*, 563



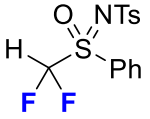
Hu *Chem. Commun.* **2007**, 5149



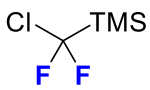
Amii *Synthesis* **2010**, 2080



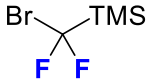
Hu *J. Org. Chem.* **2006**, *71*, 9845



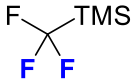
Hu *J. Org. Lett.* **2009**, *11*, 2109



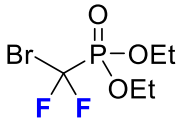
Hu *J. Chem. Commun.* **2011**, *47*, 2411



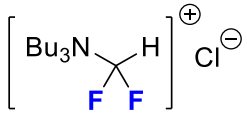
Hu *J. Chem. Commun.* **2011**, *47*, 2411



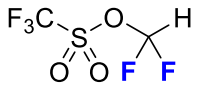
Hu *Angew. Chem. Int. Ed.* **2011**, *50*, 7153



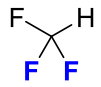
Zafrani & **Segall** *Tetrahedron* **2009**, *65*, 5278



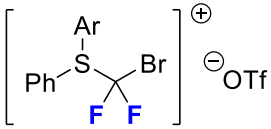
Hu *Chin. J. Chem.* **2011**, *29*, 2717



Hartwig *Angew. Chem. Int. Ed.* **2013**, *52*, 2092

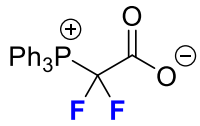


Dolbier *J. Org. Chem.* **2013**, *78*, 8904



Ar = 2,3,4,5-Me_4C_6H

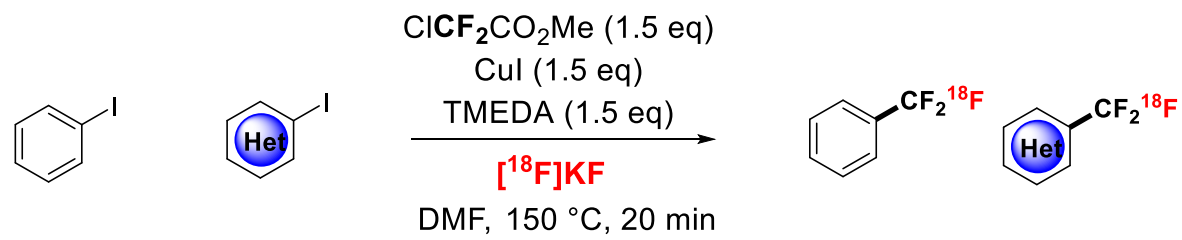
Shibata *ChemistryOpen* **2012**, *1*, 221



Xiao *Chem. Eur. J.* **2013**, *19*, 15261

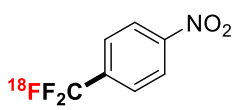
Hu *Synthesis* **2014**, *46*, 842

^{18}F-Labelling of Trifluoromethyl (Hetero)Arenes

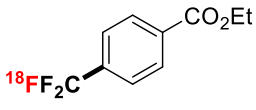


[^{18}F]$CuCF_3$

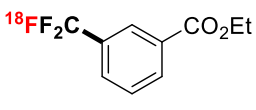
Key Reagent



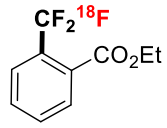
87% ± 3% (*n* = 3)



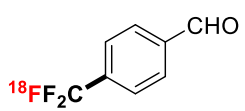
63% ± 5% (*n* = 3)



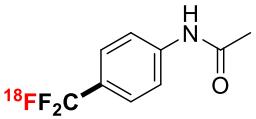
59% ± 9% (*n* = 3)



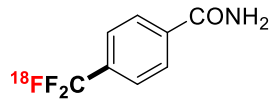
80% ± 2% (*n* = 3)



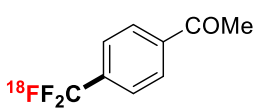
46% ± 3% (*n* = 3)



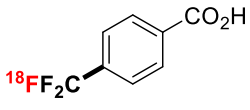
41% ± 18% (*n* = 3)



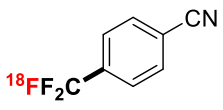
11% ± 7% (*n* = 3)



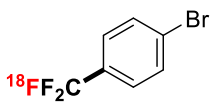
48% ± 4% (*n* = 3)



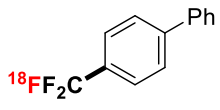
0% (*n* = 3)



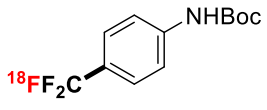
71% ± 4% (*n* = 3)



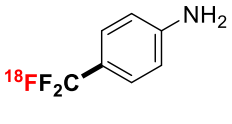
49% ± 4% (*n* = 3)



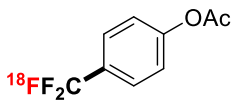
41% ± 13% (*n* = 3)



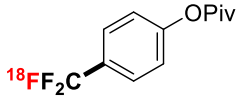
45% ± 9% (*n* = 3)



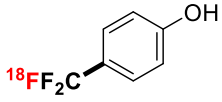
0% (*n* = 3)



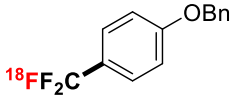
11% ± 2% (*n* = 3)



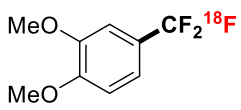
39% ± 9% (*n* = 3)



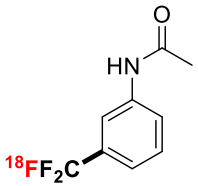
5% ± 4% (*n* = 3)



55% ± 11% (*n* = 3)



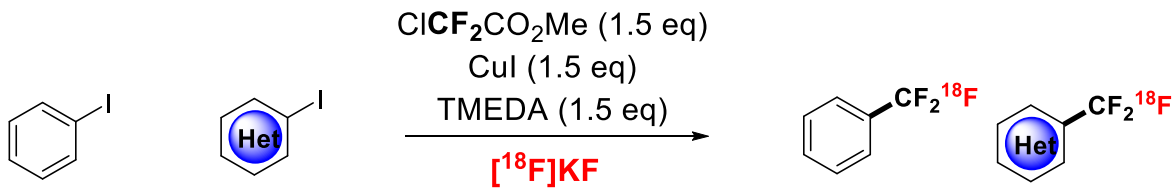
55% ± 3% (*n* = 3)



44% ± 8% (*n* = 3)

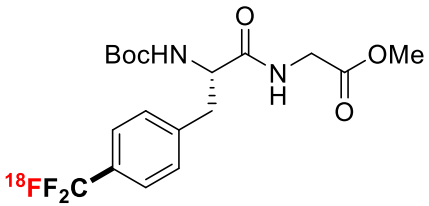
Gouverneur & Passchier *Nat. Chem.* **2013**, *5*, 941.

^{18}F-Labelling of Trifluoromethyl (Hetero)Arenes

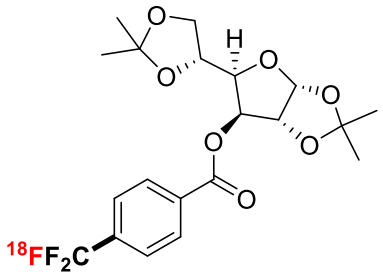


[^{18}F]$CuCF_3$

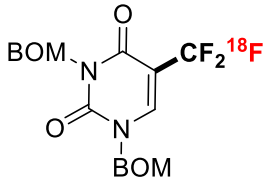
Key Reagent



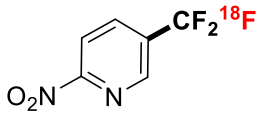
36% ± 2% (*n* = 3)



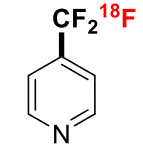
50% ± 8% (*n* = 3)



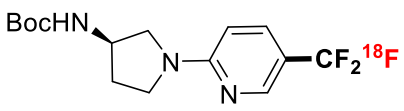
BOM = benzyloxylmethyl acetal
45% ± 7% (*n* = 3)



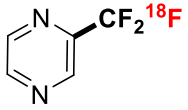
87% ± 3% (*n* = 3)
SA 0.1 GBq/μmol



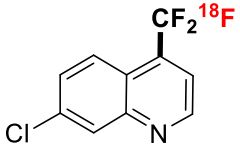
48% ± 5% (*n* = 3)



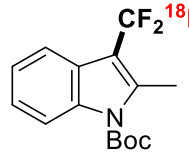
64% ± 12% (*n* = 3)



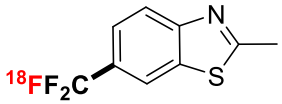
67% ± 8% (*n* = 3)



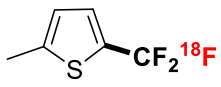
38% ± 10% (*n* = 3)



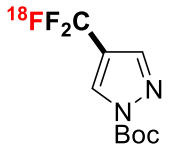
19% ± 3% (*n* = 3)



40% ± 12% (*n* = 3)



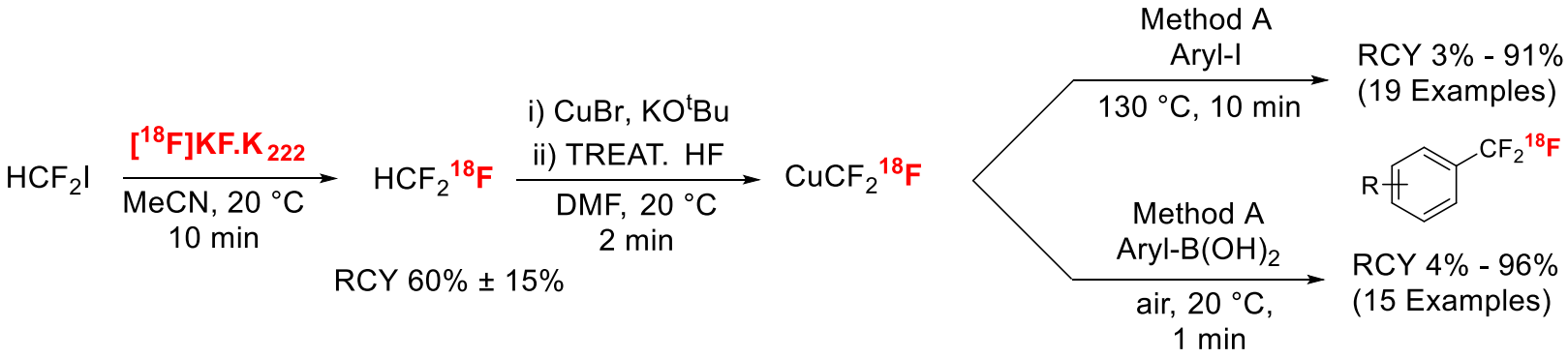
17% ± 5% (*n* = 3)

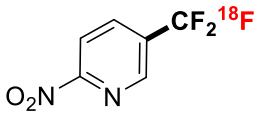


0% (*n* = 3)

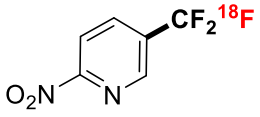
Gouverneur & Paschier *Nat. Chem.* **2013**, *5*, 941.

[^{18}F]CF_3 Trifluoromethylation of Aryl Iodides and Boronic Acids

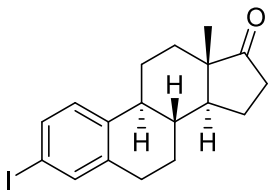


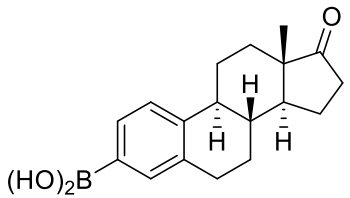


65% ± 7% (*n* = 2)
SA 21.7 ± 1.4 GBq/μmol
From Aryl Iodide



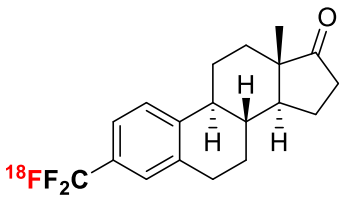
65% ± 3% (*n* = 2)
SA 20.8 ± 1.8 GBq/μmol
From ArylB(OH)$_2$





Method A
[^{18}F]$CuCF_3$, DMF,
130 °C, 10 min

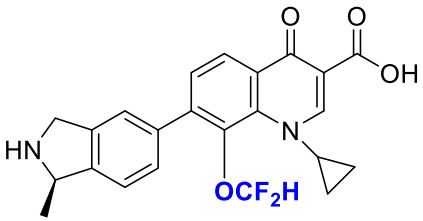
Method B
[^{18}F]$CuCF_3$, DMF,
air 20 °C, 1 min



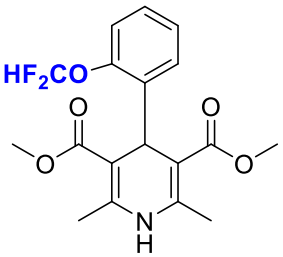
A: 7% ± 4% (*n* = 3)
B: 73% ± 9% (*n* = 3)

Vugts *Angew. Chem. Int. Ed.* **2014**, *53*, 11046.

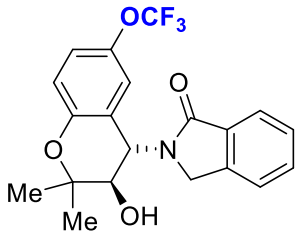
^{18}F-Labelling of Ar-OCF_3, -SCF_3, -$OCHF_2$



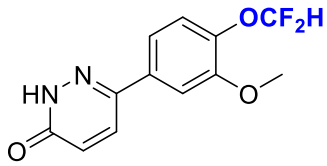
Garenoxacin



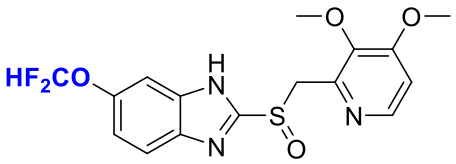
Riodipine



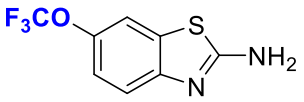
Celikalim



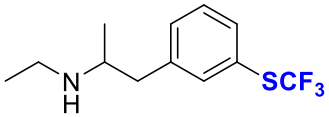
Zardaverine



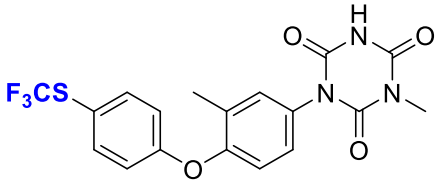
(-)-Pantaprozole



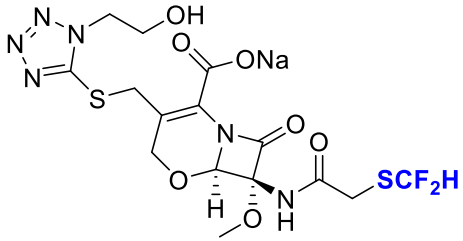
Riluzole



Flutiorex



Toltrazuril
Baycox, Tolcox

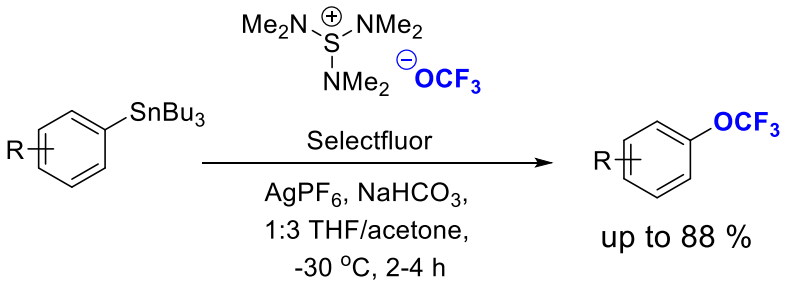


Flomoxef sodium
(Flumarin)

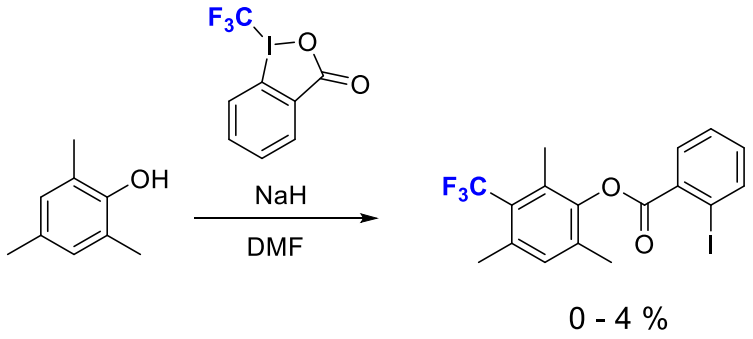
Leroux *Curr. Top. Med. Chem.* **2014**, *14*, 941.

Syntheses of Ar-OCF_3, -SCF_3, -$OCHF_2$

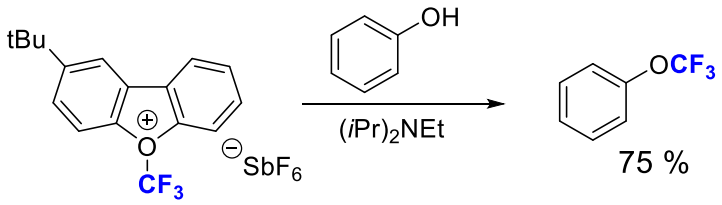
[A]



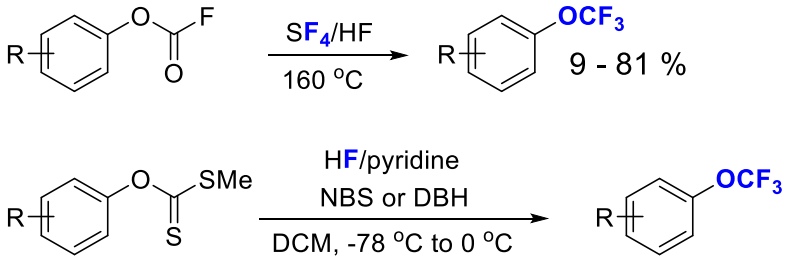
[B]



[C]

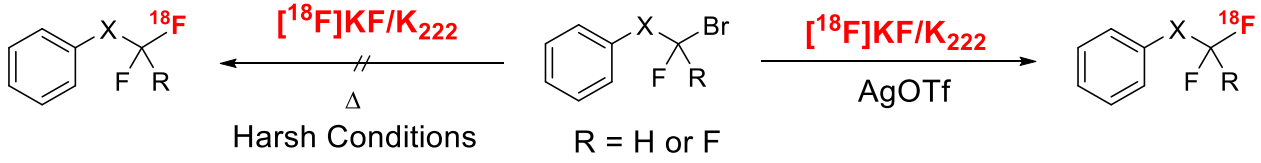


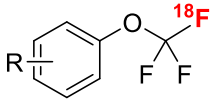
[D, E]



[A] Ritter *J. Am. Chem. Soc.* **2011**, *133*, 13308; **[B] Togni** *J. Org. Chem.* **2008,** *73*, 7678; **[C] Umemoto** *J. Org. Chem.* **2007**, *72*, 6905; **[D] Sheppard** *J. Org. Chem.* **1964**, *29*, 1; **[E] Kanie** *Chem. Soc. Jpn.* **2000**, *73*, 471.

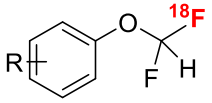
^{18}F-Labelling of Ar-OCF_3, -SCF_3, -$OCHF_2$





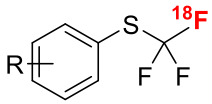
Conditions B :
2 eq. AgOTf, DCE, 60 °C, 20 min

7 examples
RCY 10 - 72 %



Conditions A :
1 eq. AgOTf, DCM, rt, 20 min

9 examples
RCY 66 - 79 %

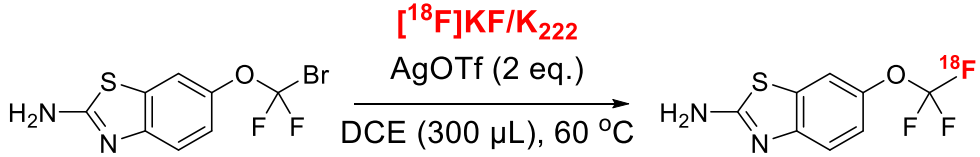


Conditions A :
1 eq. AgOTf, DCM, rt, 20 min

Conditions B :
2 eq. AgOTf, DCE, 60 °C, 20 min

9 examples
A : RCY 1 - 60 %
B : 6 - 92 %

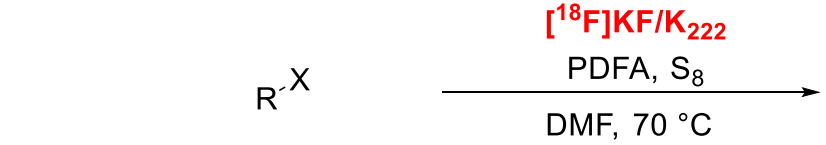
Radiochemical synthesis of Riluzole



RCY = 29 % ± 5 %
(*n* = *4*)

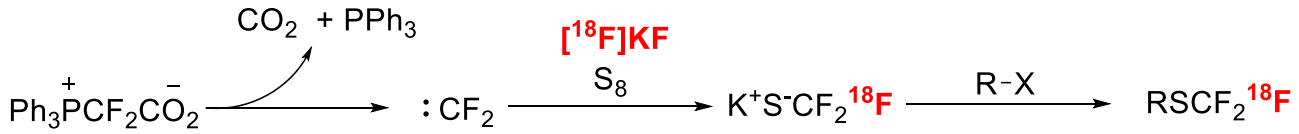
Gouverneur *Angew. Chem. Int. Ed.* **2015**, *54*, 9991.

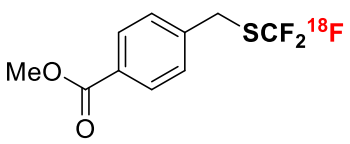
[^{18}F]Trifluoromethylthiolation of Aliphatic Electrophiles



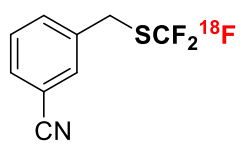
R = Alkyl, Allyl,
Benzyl (Aromatic or Heteroaromatic)

RCY = 22% - 82%

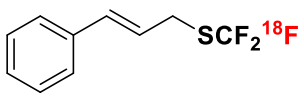




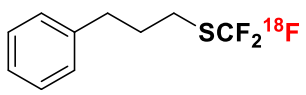
77% ± 3% (*n* = 3)



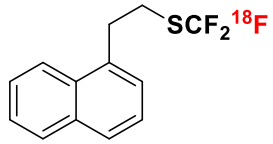
82% ± 4% (*n* = 3)



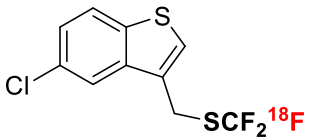
78% ± 4% (*n* = 3)



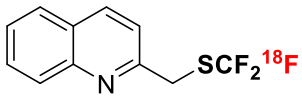
47% ± 3% (*n* = 3)



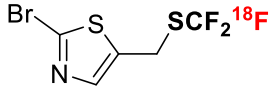
27% ± 3% (*n* = 3)



83% ± 2% (*n* = 3)



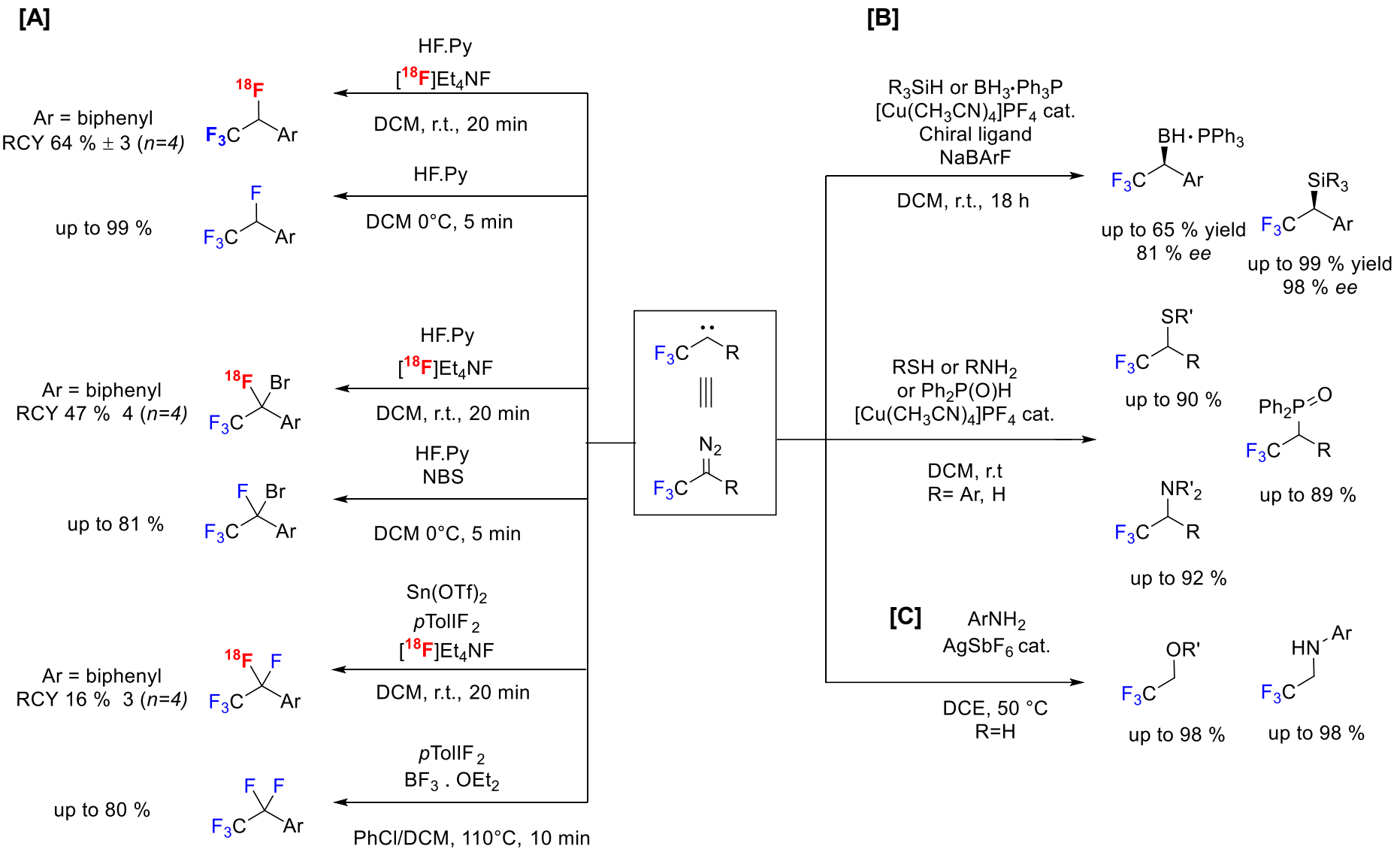
51% ± 7% (*n* = 3)



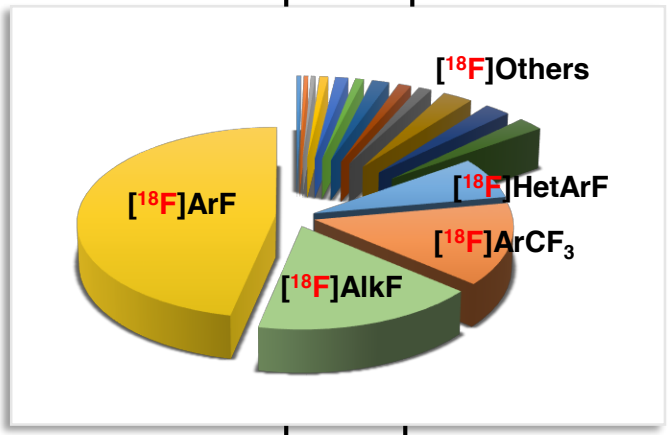
82% ± 2% (*n* = 3)

Liang *Angew. Chem. Int. Ed.* **2015**, *54*, 13236**.**

[^{18}F]Fluorination of Other Motifs



[A] Gouverneur *Org. Lett.* **2014**, *16*, 6004; **[B] Gouverneur** *Angew. Chem. Int. Ed.* **2016**, *55*, 3785; **[C] Wang** *Angew. Chem. Int. Ed.* **2015**, *54*, 14505.



Aryl-**LG**
Aryl-N_2^+
Aryl-I^+-Ar
Aryl-**I=Ar**
Aryl-$S^+(Ar')_2$
Aryl-**SO(Ar')**
Aryl-**OH**

$^{18}F^-$

Aryl[Pd^{II}]
Aryl[Ni^{II}]

$^{18}F^-$

Aryl-**Bpin**
Aryl-**$B(OH)_2$**

$^{18}F^-$ Cu

Aryl-**[Sn]**

$^{18}F^+$ Ag

Aryl-**Bnep**

$^{18}F^+$ Ag

[^{18}F]ArF

AlkylSCF$_2$^{18}F
ArylSCF$_2$^{18}F
ArlyOCF$_2$^{18}F
ArylOCHF^{18}F
ArylCF^{18}FCF$_3$
ArylCH^{18}FCF$_3$

$CuSCF_2{}^{18}F$

S_8:CF_2 $^{18}F^-$

Alkyl-**Cl/Br/I**

Ag $^{18}F^-$

Aryl-**OCF_2LG**
Aryl-**CFHLG**
Aryl-**SCF_2LG**

$^{18}F^-$

$CF_3(R)C{=}N_2$

Akyl-**LG**

$^{18}F^-$

Epoxide

$^{18}F^-$ Co

Allyl-**OCO_2Me**

$^{18}F^-$ Pd/Ir

Benzyl-**H**

$^{18}F^-$ Mn

RCH_2CHO

$^{18}F^+$ Organocat.

[^{18}F]AlkF

[^{18}F]$ArCF_3$
[^{18}F]HetArF

$^{18}F^-$

Aryl-**CF_2LG**

Ag $^{18}F^+$

Aryl-**CF_2CO_2H**

$CuCF_2{}^{18}F$ $^{18}F^-$:CF_2

Aryl-**I**

$CuCF_2{}^{18}F$ $^{18}F^-$ HCF_2I

Aryl-**$B(OH)_2$**

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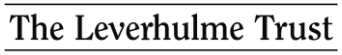

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