CATALYTIC FLUORINATION & TRIFLUOROMETHYLATION

Speaker: Tao Xu

Wednesday seminar

March 6th, 2013

contoso

Outlines

Introduction

- Importance of F & CF_3 compounds
- Traditional ways to introduce F & CF_3
- How nature introduce F & CF_3

TM-Med./Cat. Fluorination

- Cu-mediated C-F formation
- Pd-catalyzed C-F formation
- Ag-catalyzed C-F formation

TM-Med./Cat. CF_3lation

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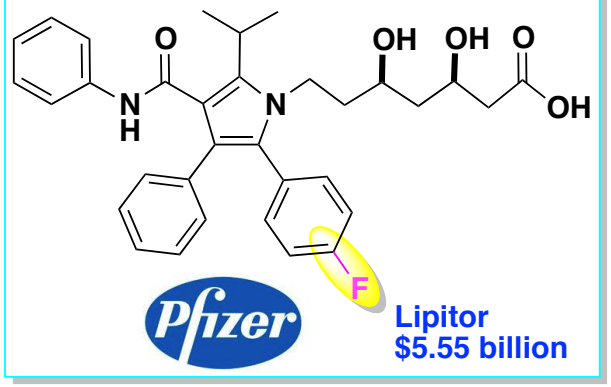
Ref: [1] Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature*, **2011**, *473*, 470.
[2] Qing, F. L. *Chin. J. Org. Chem.* **2012**, *32*, 815.
[3] Tomashenko, O. A.; Grushin, V. V. *Chem. Rev.* **2011**, *111*, 4475.
[4] Grushin, V. V. *Acc. Chem. Res.* **2010**, *43*, 160.
[5] Furuya, T.; Kuttruff, C. A.; Ritter, T. *Curr. Opin. Drug Discov. Dev.* **2008**, *11*, 803.

Why are fluorination & trifluoromethylation important

2011 top prescription drugs

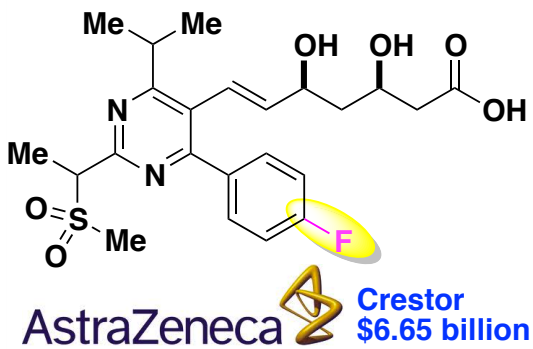
 # 5



Lipitor
$5.55 billion

blood cholesterol lowering

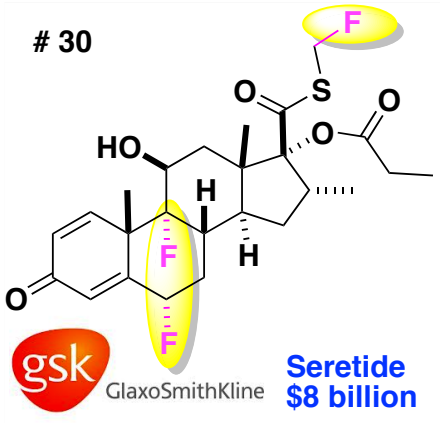
 # 10



Crestor
$6.65 billion

high cholesterol & cardiovascular disease

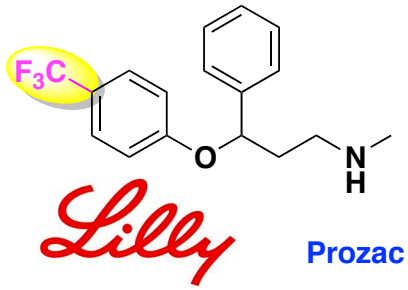
 # 30



Seretide
$8 billion

asthma & chronic obstructive pulmonary disease

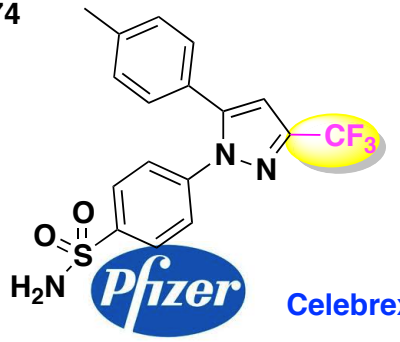
 # 65



Prozac

depressant

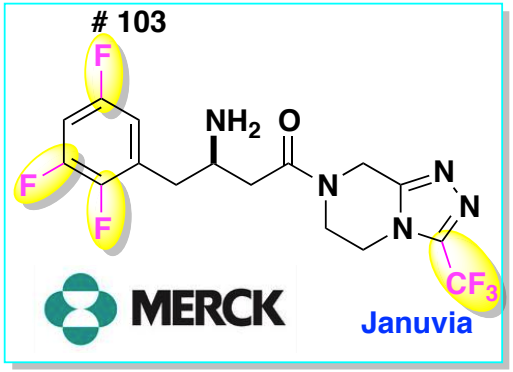
 # 74



Celebrex

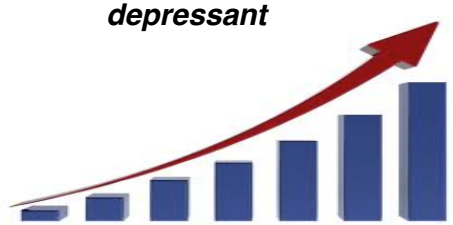
anti-inflammatory & joint pain

 # 103



Januvia

type II diabete inhibitor



Increased i) Lipophilicity ii) Metabolically stablity iii) Bioavailablity iv) Low friction coefficiency v) H-bonding vi) Interaction with target protein

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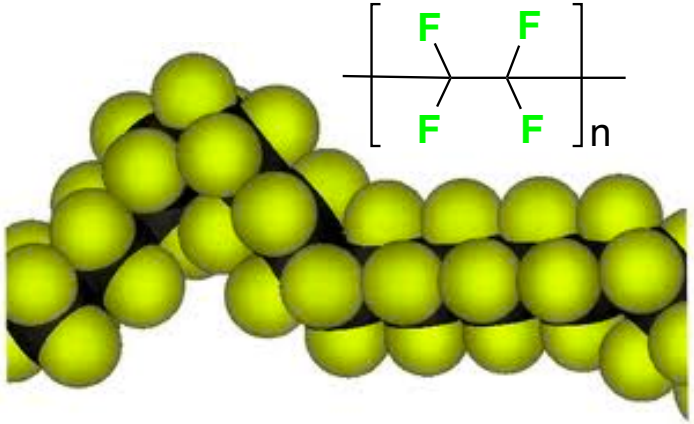
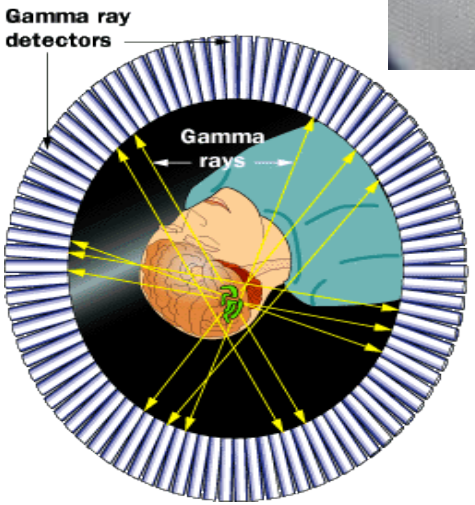
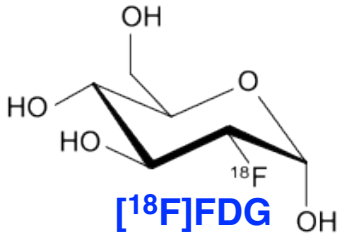
Application of F-containing in material and bio-imaging



MOD防御大师

Positron
Emission
Tomography





[^{18}F]FDG

Millions of PET scans
Half Life of F^{18}=109.771 mins/1.8 hrs

Patterson, J. C. II; Mosley, M. L. *Mol. Imaging Biol.* **2005**, *7*, 197.

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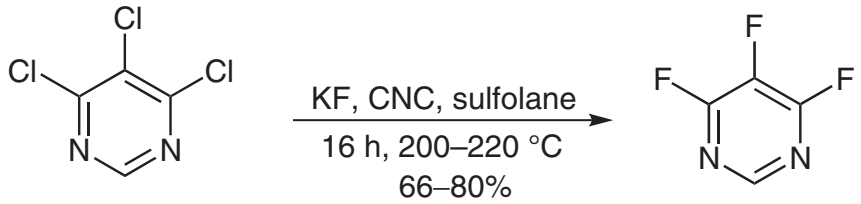
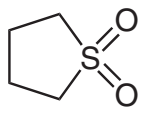
Taditional ways to form C-F bond

Nucleophilic Fluorination----Halex process



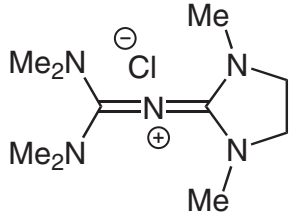
(a) Adams, D. J.; Clark, J. H. *Chem. Soc. Rev.* **1999**, *28*, 225. (b) Horwitz, J. P.; Tomson, A. J. *J. Org. Chem.* **1961**, *26*, 3392.

sulfolane:



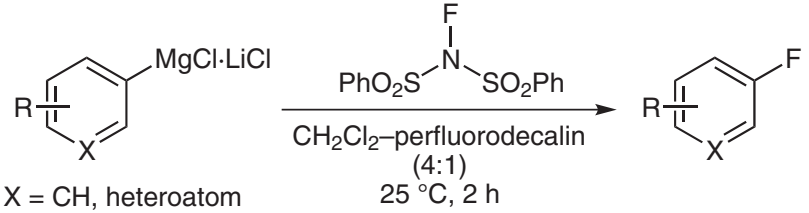
(high-boiling solvent)

CNC:



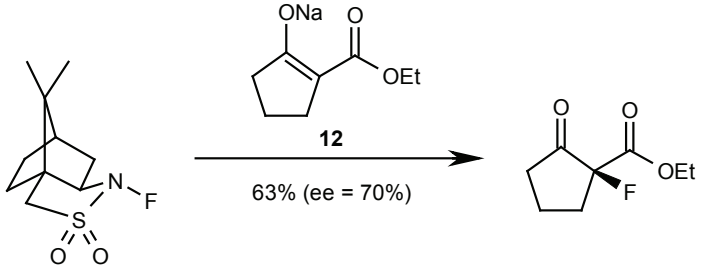
(phase-transfer catalyst)

Electrophilic Fluorination



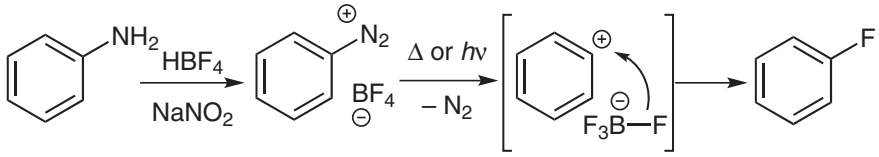
X = CH, heteroatom

Yamada, S.; Gavryushin, A.; Knochel, P. *Angew. Chem. Int. Ed.* **2010**, *49*, 2215.



Davis, F. A.; Zhou, P. *etc J. Org. Chem.* **1998,** *63*, 2273.

Balz-Schiemann reaction



Balz, G.; Schiemann, G. *Ber. Dtsch. Chem. Ges.* **1927**, *60*, 1186.

Summary

i) still important for industry
ii) harsh conditions (pyrolysis)
iii) limited substrates
iv) early stage introduction

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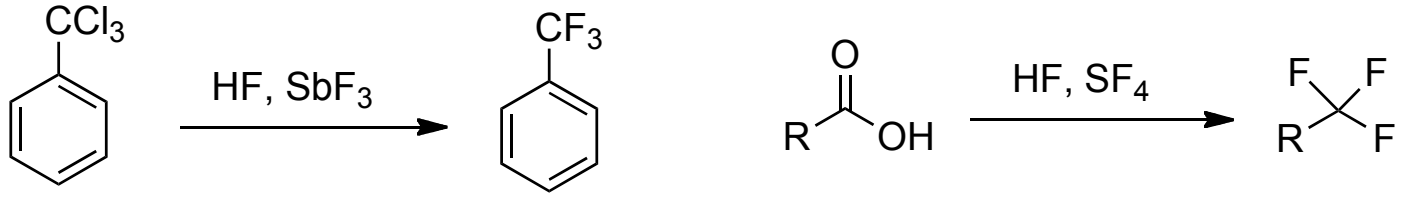
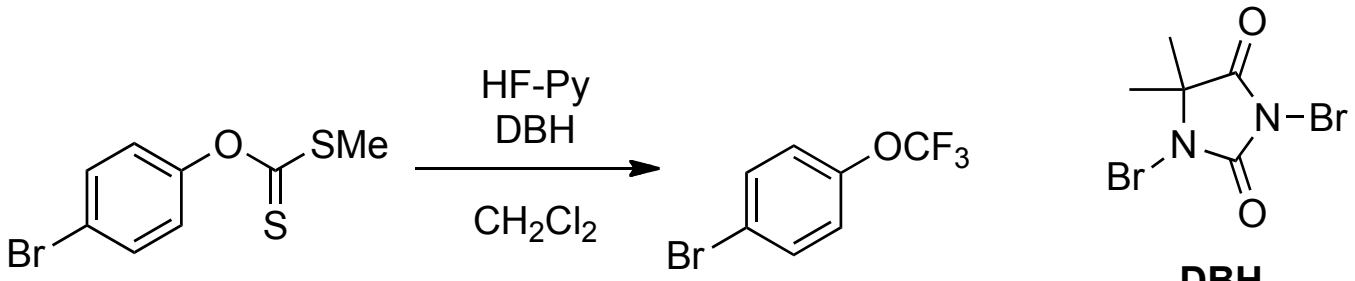
Taditional ways to form C-CF_3 bond

Swarts reaction (1892)



Electrophilic Fluorination

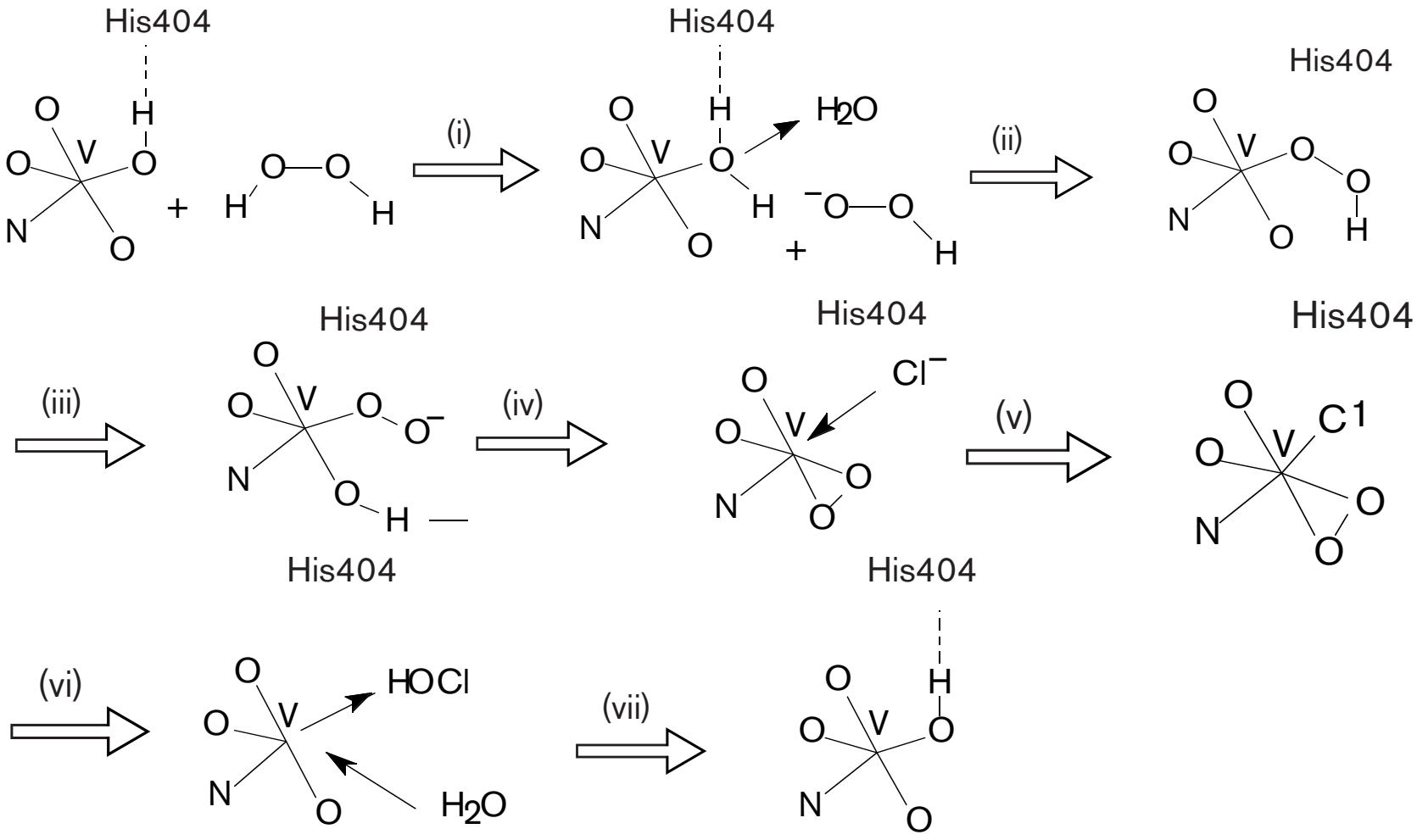


DBH

P. Kirsch, *Modern Fluoroorganic Applications*, Wiley-VCH, Weinheim **2004**.

Nature's way to introduce Cl vs. F

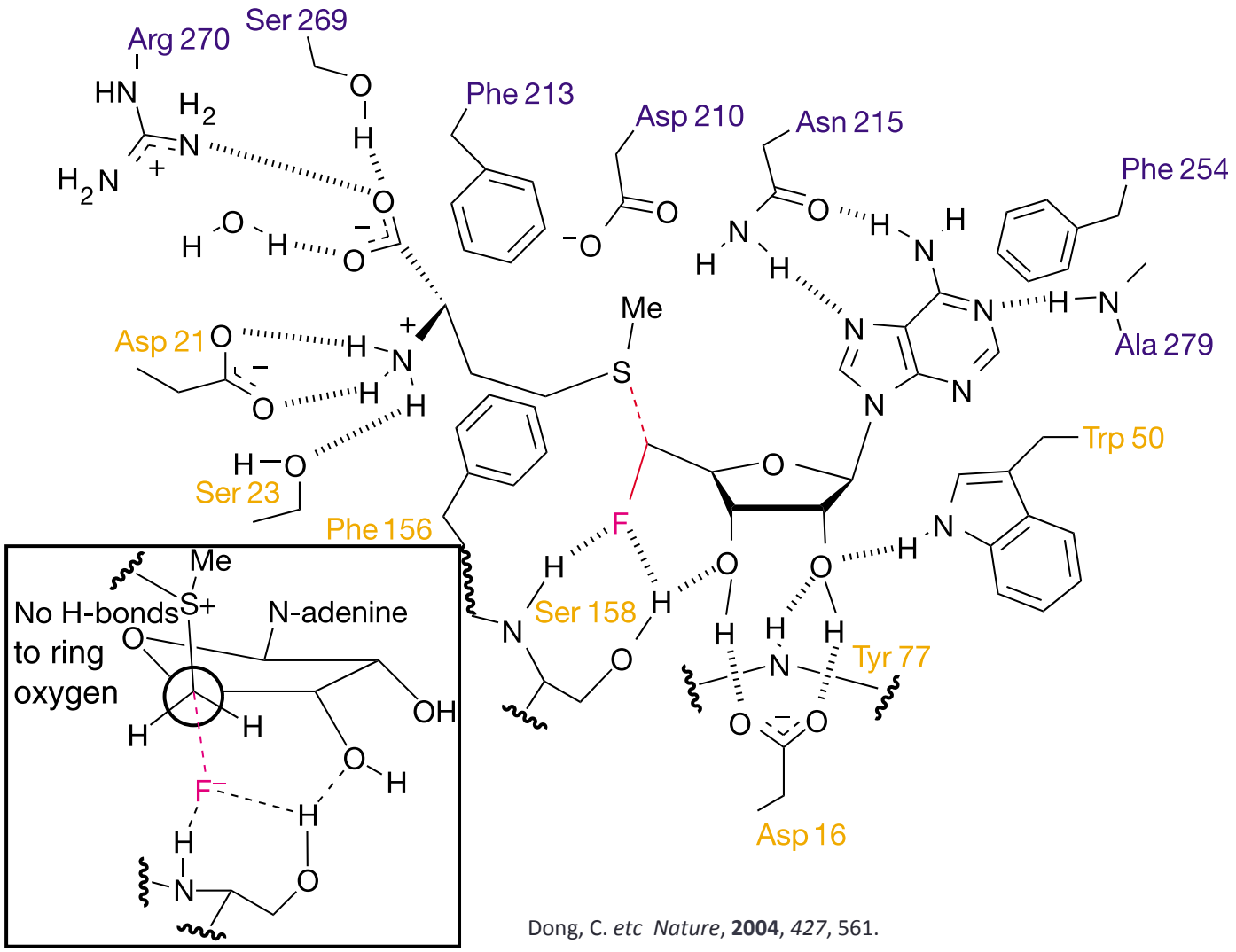
How haloperoxidase function



Littlechild, J. *Curr. Opin. Drug Discov. Dev.* **1999**, *3*, 28.

Nature's way to introduce F

How fluoperoxidase function



Dong, C. *etc* *Nature*, **2004**, *427*, 561.

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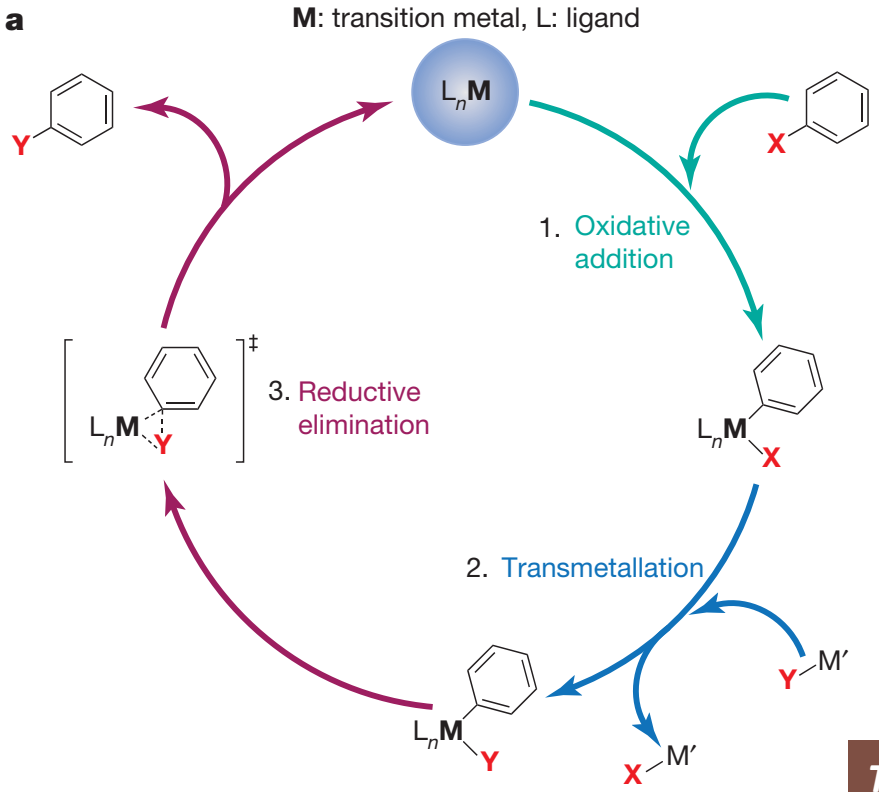
[5] Furuya, T.; Kuttruff, C. A.; Ritter, T. *Curr. Opin. Drug Discov. Dev.* **2008**, *11*, 803.

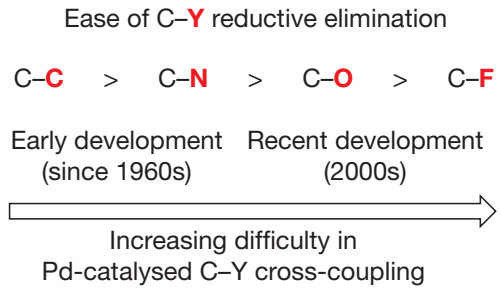
Challenges for Metal catalyzed C-F bond formation

Challenges of TM-cat. C-F bond formtion

a



b



Summary

i) C-F bond is the strongest single bond.
ii) F is the most electron nagetive.
iii) M-F bond is highly polarised & strong.
iv) F forms H-bonding with OH, NH & amide.

The strongest single C-F bond is thermo-dynamically favored, while reductive elimination is kinetically slow. A thermo-dynamically feasible but kinetically challenging reaction can be addressed ideally by catalysis.

First catalytic C-F bond formation (2002)

Hypothesis

$$M{-}F_x + C{-}H \longrightarrow M{-}F_{x-2} + C{-}F + HF \qquad \text{Eq. 1}$$

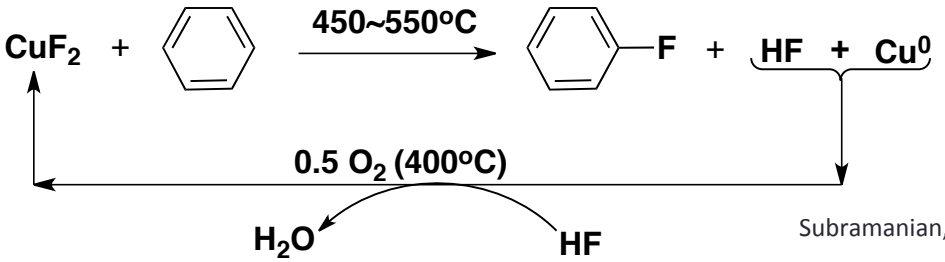
$$M{-}F_{x-2} + 0.5\ O_2 + 2HF \longrightarrow M{-}F_x + H_2O \qquad \text{Eq. 2}$$

Which metal fluoride salts

Table 1. Oxidation-reduction potential for metals in various oxidation states. In the group with reduction potential $E^0 > 1$, the fluorides are strong oxidants and can be recycled with elemental fluorine. For the group with E^0 in the range $1 > E^0 > 0$, the fluorides are moderate oxidants and can be recycled with HF and O_2. For the group with $E^0 < 0$, the fluorides are inert toward C−H bonds. (E^0, reduction potential = 0.0 for $2H^+ + 2e^- \Leftrightarrow H_2$)

$E^0 > 1$	$1 > E^0 > 0$	$E^0 < 0$
$Co^{3+} + e^- \Leftrightarrow Co^{2+}$	$Cu^{2+} + 2e^- \Leftrightarrow Cu^0$	$Zn^{2+} + 2e^- \Leftrightarrow Zn^0$
$Ag^{2+} + e^- \Leftrightarrow Ag^{1+}$	$Ag^{1+} + e^- \Leftrightarrow Ag^0$	$Mg^{2+} + 2e^- \Leftrightarrow Mg^0$
$Pb^{4+} + 2e^- \Leftrightarrow Pb^{2+}$	$Te^{4+} + 4e^- \Leftrightarrow Te^0$	$Al^{3+} + 3e^- \Leftrightarrow Al^0$
$Ce^{4+} + e^- \Leftrightarrow Ce^{2+}$	$Hg^{2+} + 2e^- \Leftrightarrow Hg^0$	$Co^{2+} + 2e^- \Leftrightarrow Co^0$

Catalytic process



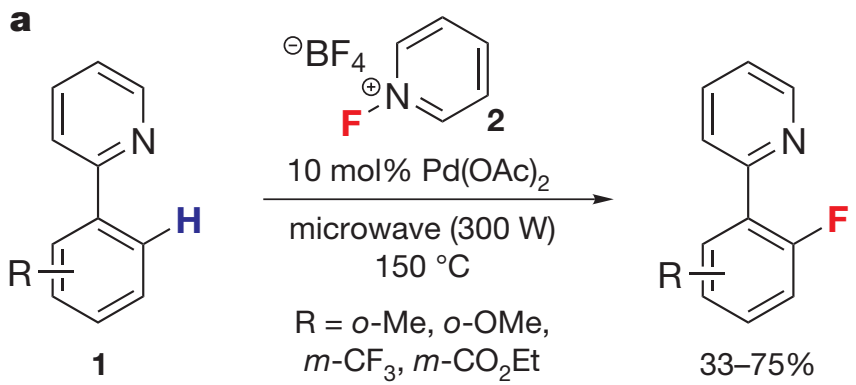
Summary

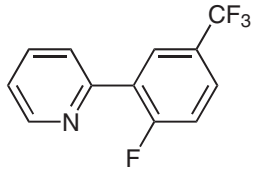
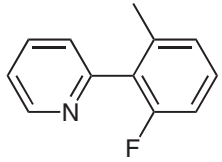
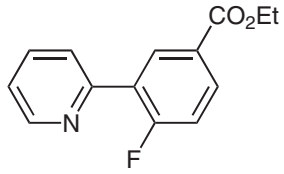
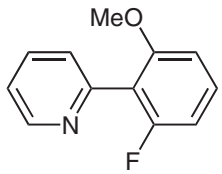
i) Limited substrate scope: PhF, TolF.
ii) Low regioselectivity.
iii) High temperature.

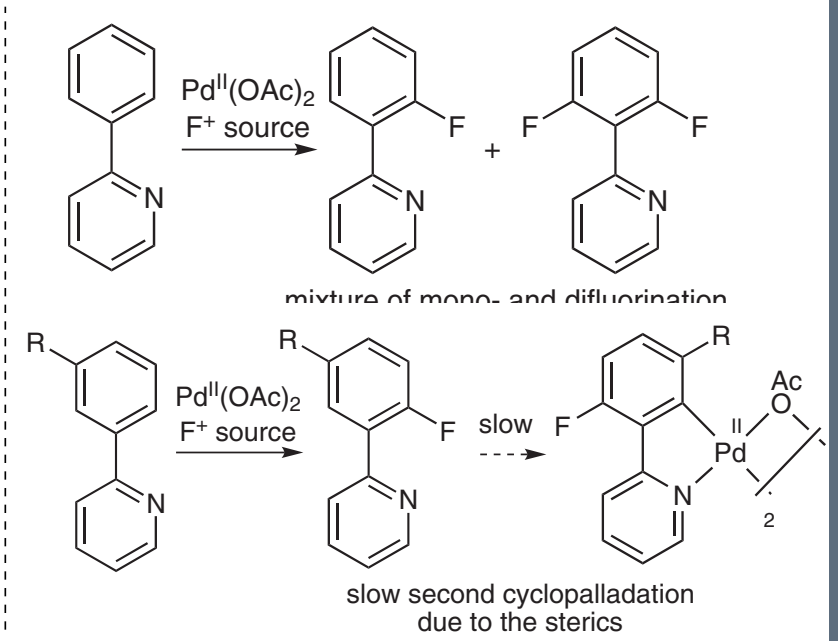
Subramanian, M. A.; Manzer, L. E. *Science*, **2002**, *297*, 1665.

contoso

First Pd catalyzed C-F bond formation (Sanford, 2006)



Product	Yield (%)	Product	Yield (%)
	75		52
	67		33

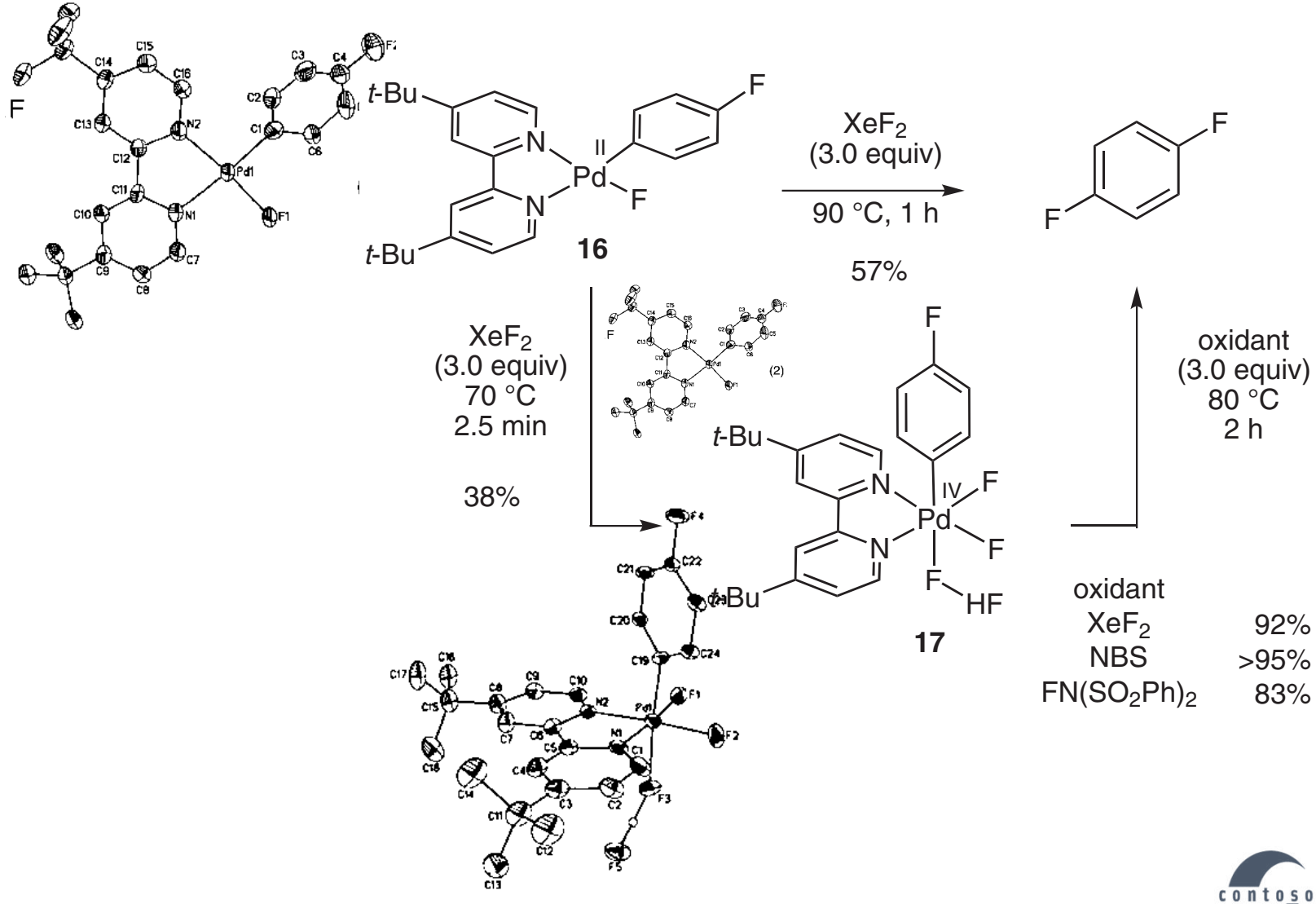


Summary

i) the first Pd-catalyzed C-F bond formation.
ii) harsh conditions still needed. (Microwave)
iii) blocking groups to avoid difluorination.

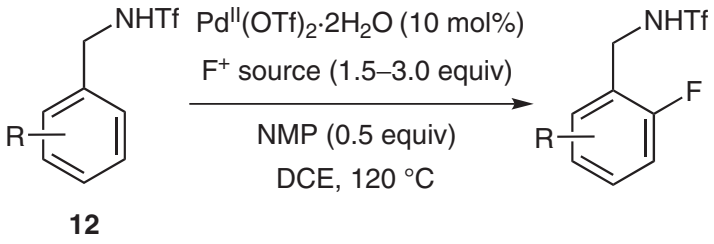
Hull, K. L.; Anani, W. Q.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 7134.

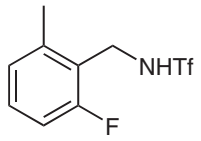
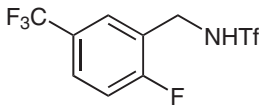
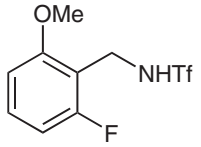
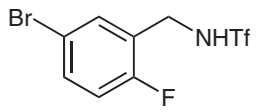
Attempted mechanism study, but not conclusive

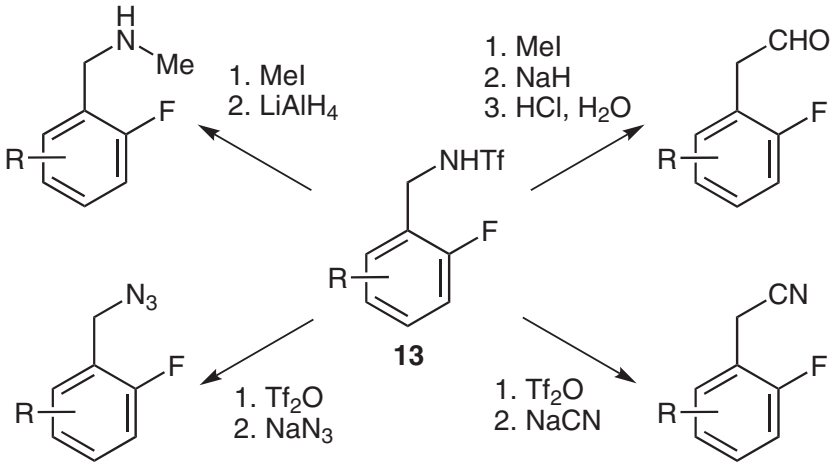


Ball, N. D.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 3796.

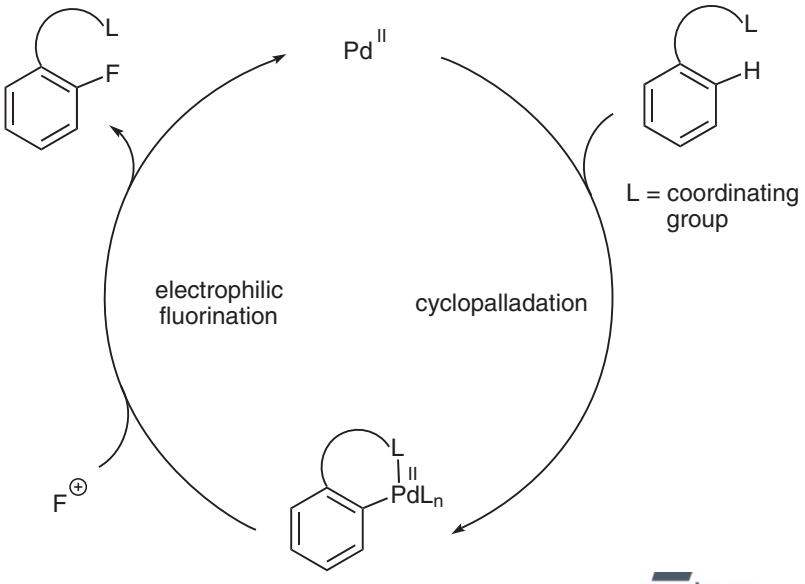
Follow up work by Yu group (2009)



Product	Yield (%)	Product	Yield (%)
	82		81
	60		70



Nucleophilic fluorination



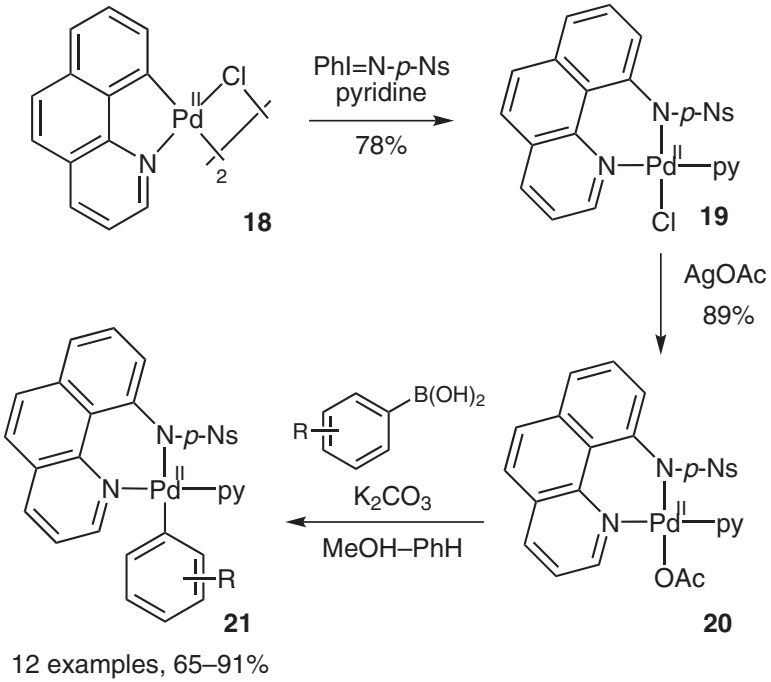
Summary

i) NMP is essential for the fluorination.
ii) blocking groups still remained.
iii) derivatization of DG is versatile.

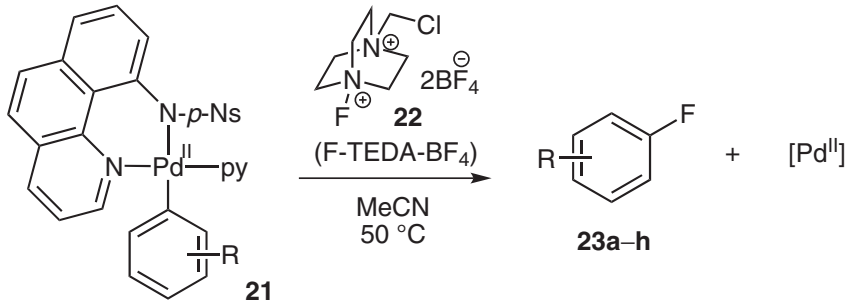
Wang, X.; Mei, T.-S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 7520.

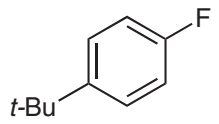
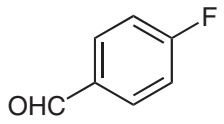
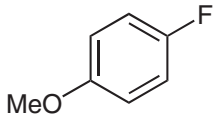
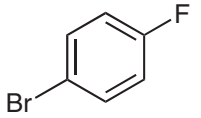
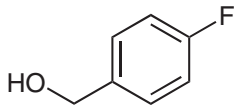
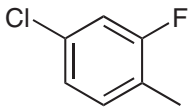
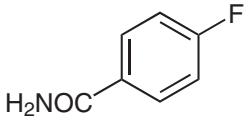
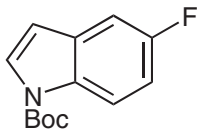
contoso

Pd-catalyzed fluorination of $ArB(OH)_2$ by Ritter (2008)



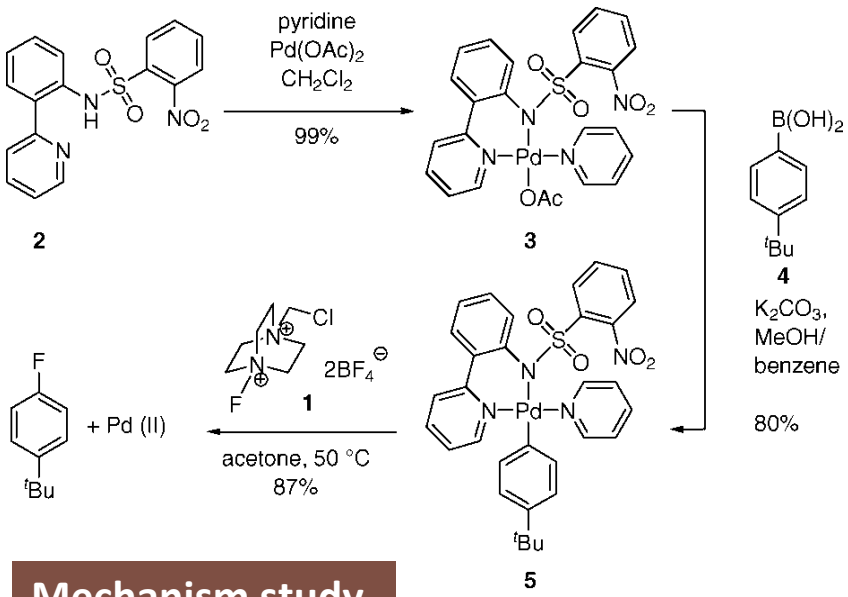
12 examples, 65–91%



Product	Yield (%)	Product	Yield (%)
 **23a**	79	 **23e**	61
 **23b**	46	 **23f**	73
 **23c**	70	 **23g**	82
 **23d**	74	 **23h**	60

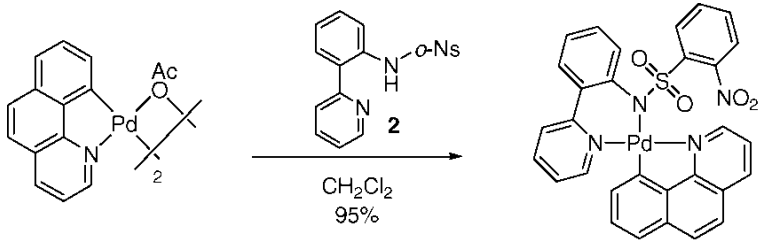
Furuya, T.; Kaiser, H. M.; Ritter, T. *Angew. Chem. Int. Ed.* **2008**, *47*, 5993.

Pd-catalyzed fluorination of $ArB(OH)_2$ by Ritter (2008)



Summary

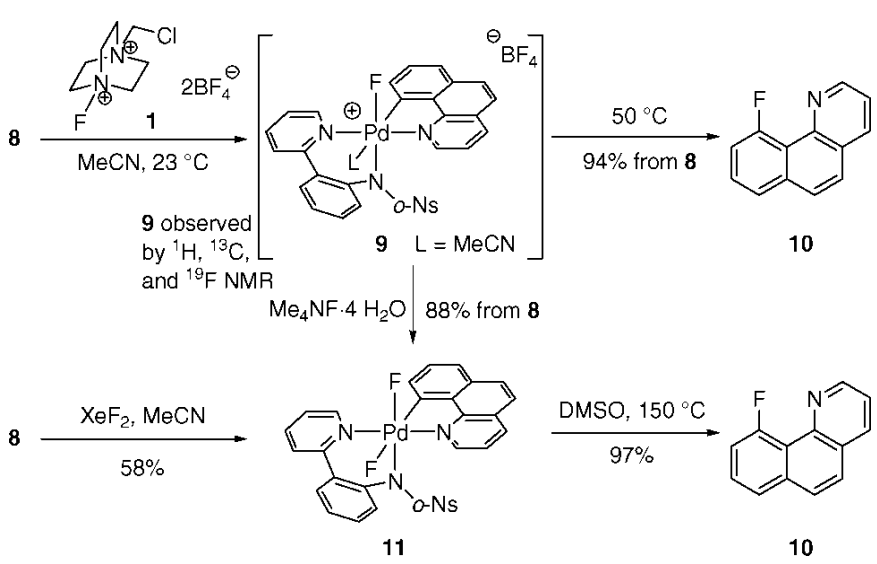
i) A Pd(IV) might be involved.
ii) couldn't observed by NMR.
iii) reversible color change--yellow to orange.

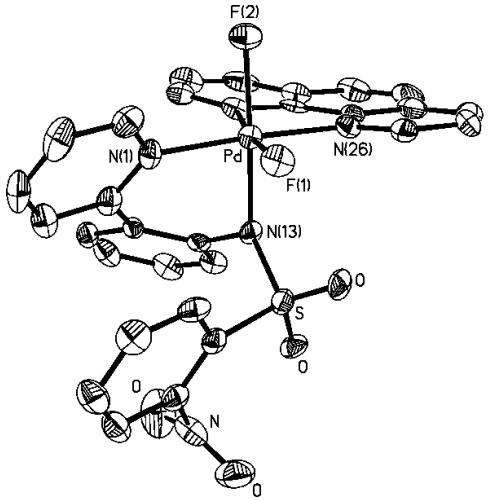


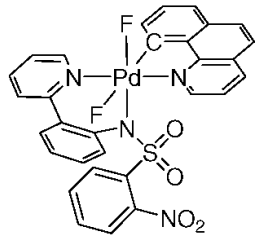
Furuya, T.; Ritter, T. *J. Am. Chem. Soc.* **2008**, *130*, 10060.

Anayltic pure yellow solid

Mechanism study





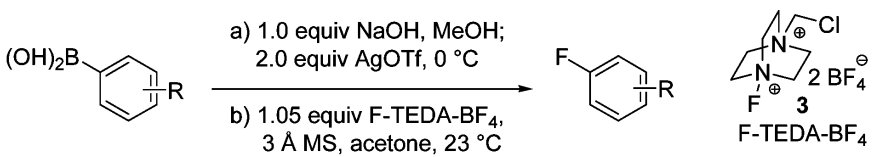


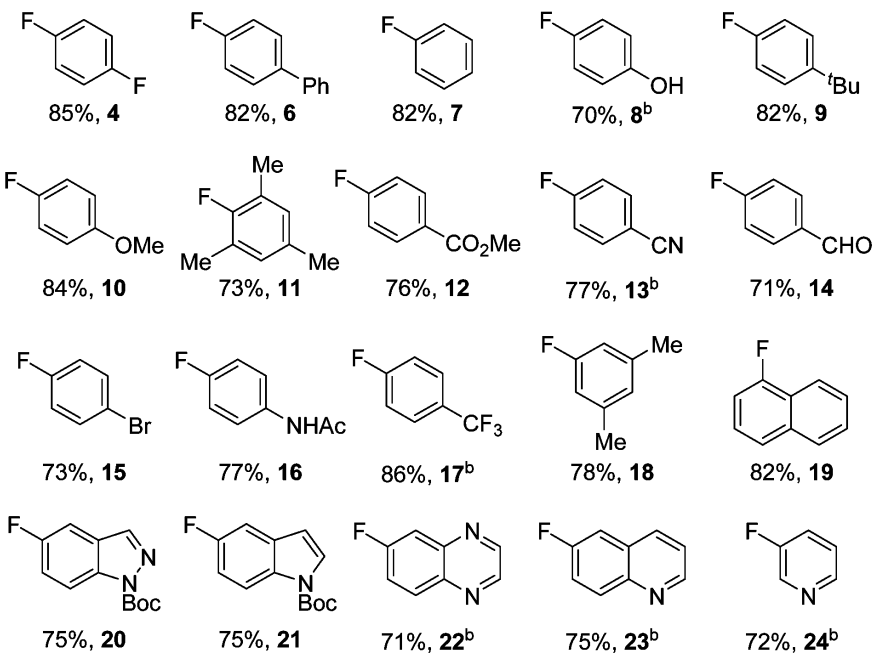
11

^{19}F NMR[14]: –169, –278 ppm; $^{2}J_{F-F}$ = 113 Hz; $^{2}J_{C-F}$ = 63 Hz

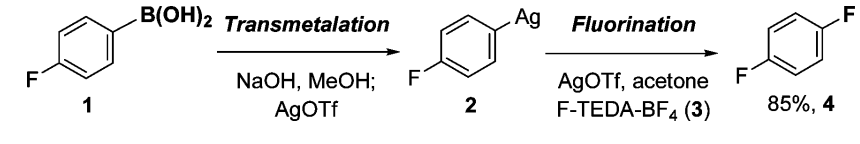
Furuya, T.; Benitez, D.; Tkatchouk, E.; Strom, A. E.; Tang, P.; Goddard, W. A. III.; Ritter, T. *J. Am. Chem. Soc.* **2010**, *132*, 3793.

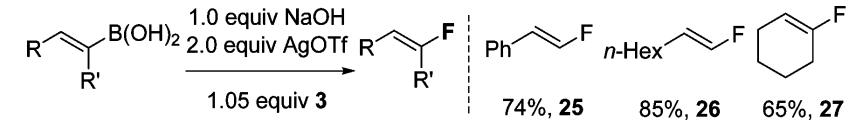
Ag-catalyzed C-F bond formation of $ArB(OH)_2$ (Ritter 2009)

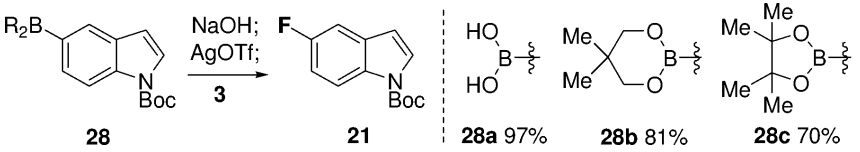




[a] Yields are given for isolated and purified compounds. If boiling points were too low to report accurate yields, the yield was determined by ^{19}F NMR (internal standard, see Supporting Information). Isolated yields and yields determined by ^{19}F NMR differed by less than 5%. [b] 1.2 equiv of NaOH and 3.0 equiv of AgOTf were used.

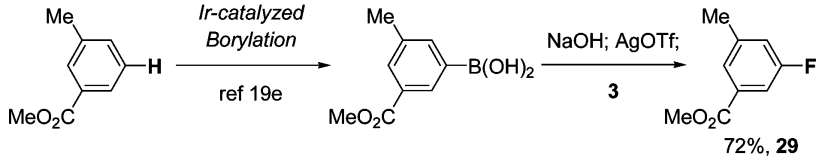




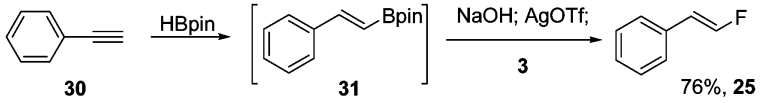


Application

C–H to C–F Transformation



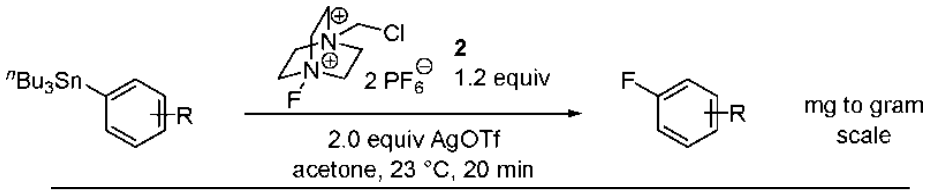
One-pot Alkyne Hydrofluorination

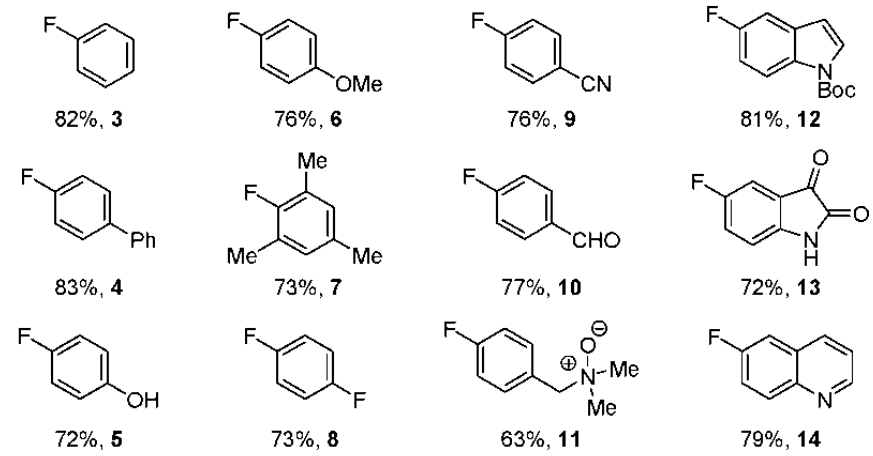


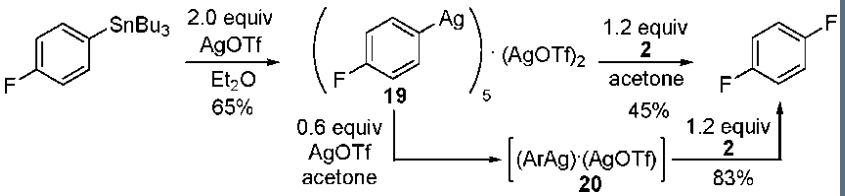
Furuya, T.; Ritter, T. *Org. Lett.* **2009**, *11*, 2860.

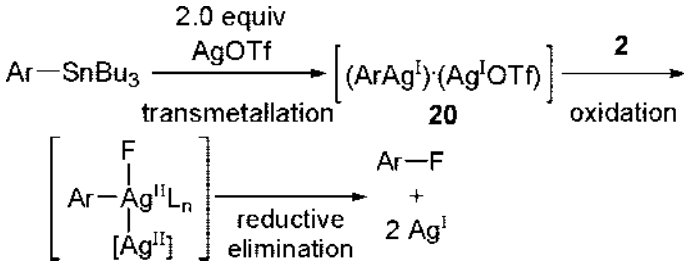
contoso

Ag-catalyzed C-F bond formation of Aryl Stannanes (Ritter 2009)

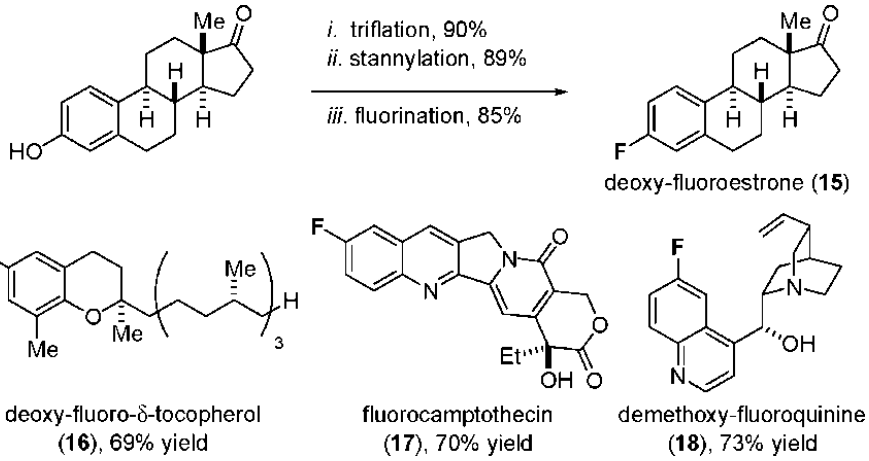


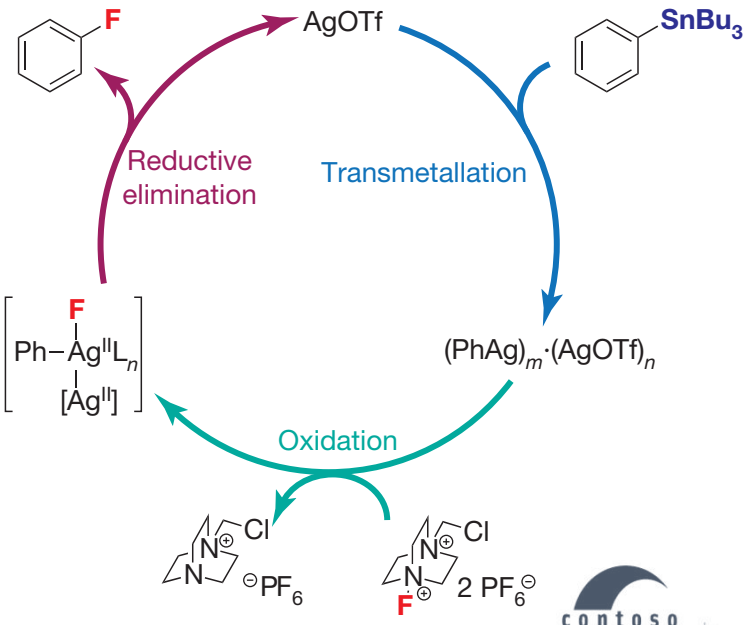






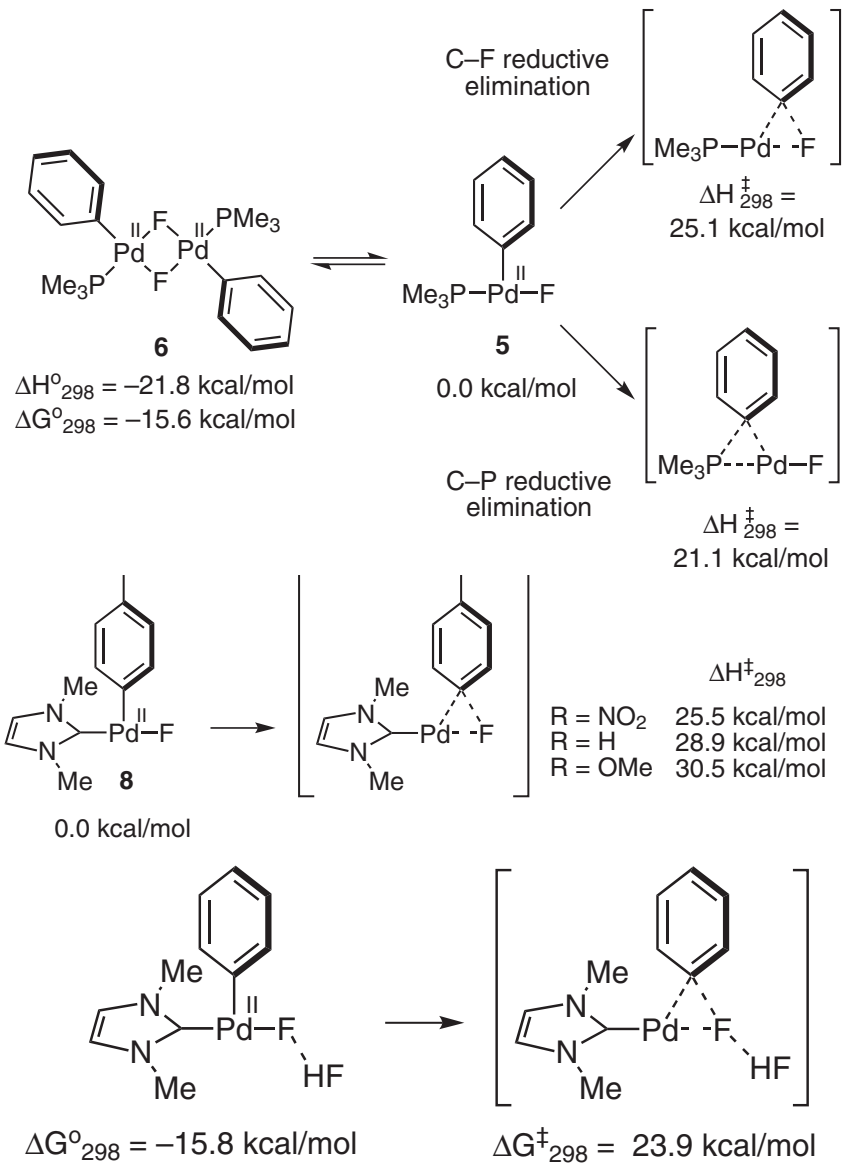
Application in NP substrate

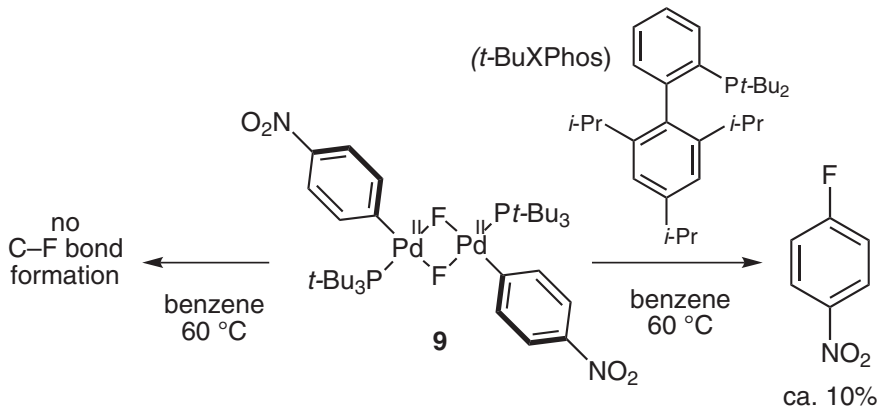




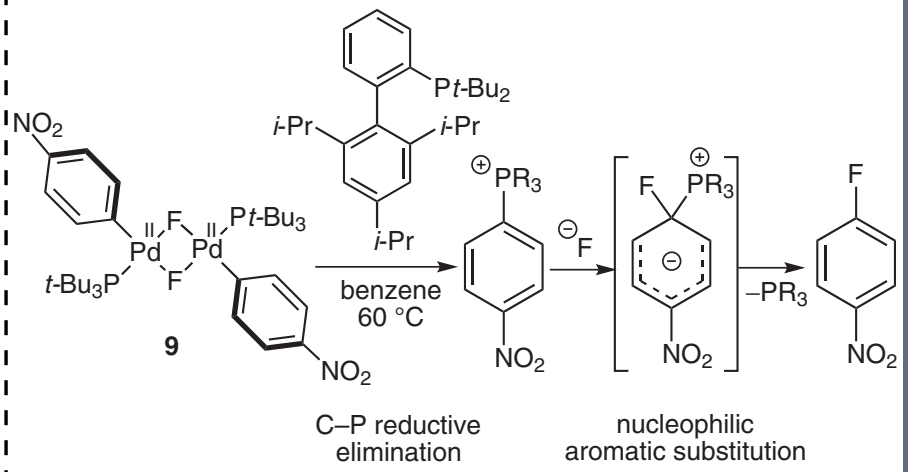
Furuya, T.; Strom, A. E.; Ritter, T. *J. Am. Chem. Soc.* **2009**, *131*, 1662.

First Pd-catalyzed C-F formation back in 2007 (Yandulov)





Proposed mechanism (Grushin 2007)

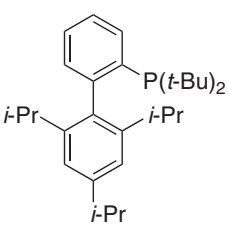


Grushin, V. V.; Marshall, W. J. *Organometallics* **2007**, *26*, 4997.

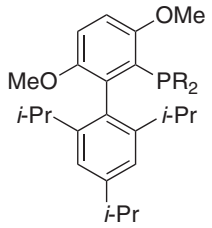
Yandulov, D. V.; Tran, N. T. *J. Am. Chem. Soc.* **2007**, *129*, 1342.

contoso

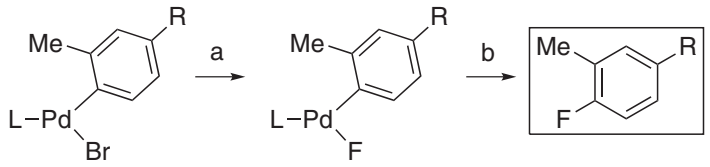
First Pd-catalyzed C-F formation from ArOTf (Buckwald 2009)



*t*BuXPhos (**1**)



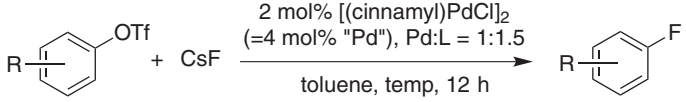
BrettPhos (**2**, R = Cyclohexyl)
*t*BuBrettPhos (**3**, R = *t*-Bu)

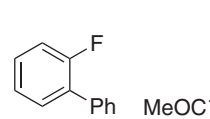


4 R = CF_3 74%
5 R = CN 70%

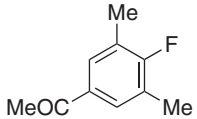
6 15%
7 25%

L = **2**. [a] 5 equiv. AgF, CH_2Cl_2, 25 °C, exclusion of light, 12 to 24 h. [b] toluene, 100 °C, 2 h, yields determined by ^{19}F NMR spectroscopy.

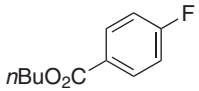




12
82% (2%)
110 °C

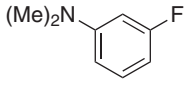


13
83% (2%)
110 °C

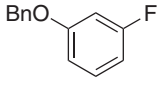


14
77% (1%)
2 mol% "Pd"
80 °C

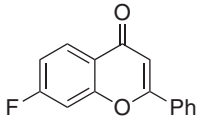
10 mmol scale
85% (n/o)
2 mol% "Pd"
80 °C, 24 h



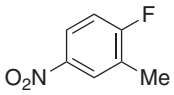
15
84% (1%)%*
C_6H_{12}, 130 °C



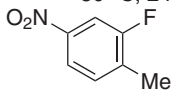
16
57% (2%)*
10 mol% "Pd"
C_6H_{12}, 130 °C



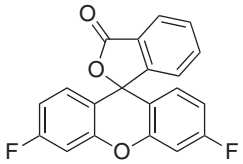
17
63% (2%)
80 °C



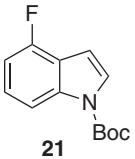
18
80% (<1%)
2 mol% "Pd"
110 °C



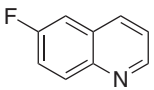
19
83% (2%)
2 mol% "Pd"
110 °C



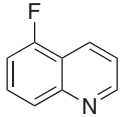
20
73% (n/o)
8 mol% "Pd"
110 °C



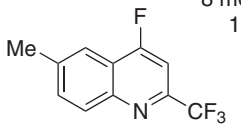
21
73% (4%)
110 °C



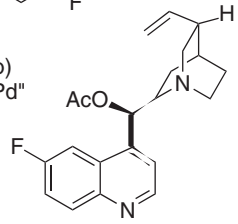
22
78% (2%)
2 mol% "Pd"
120 °C



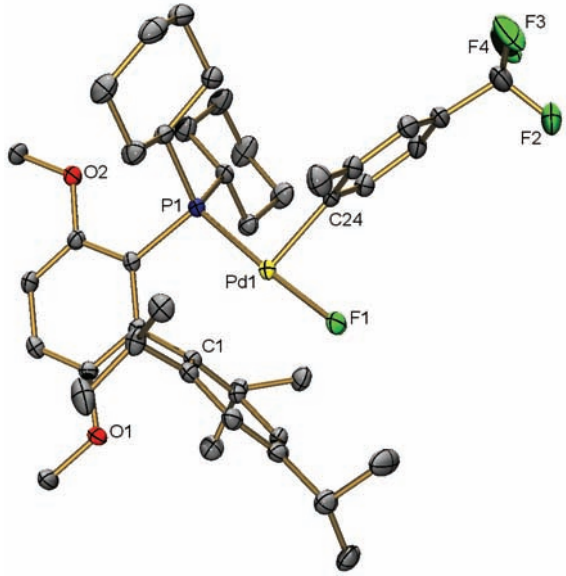
23
75% (1%)
110 °C



24
83% (<1%)
80 °C

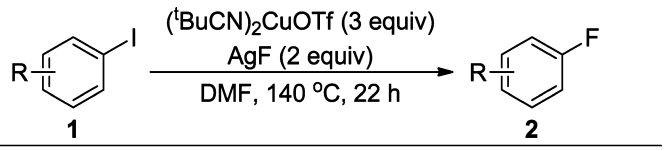


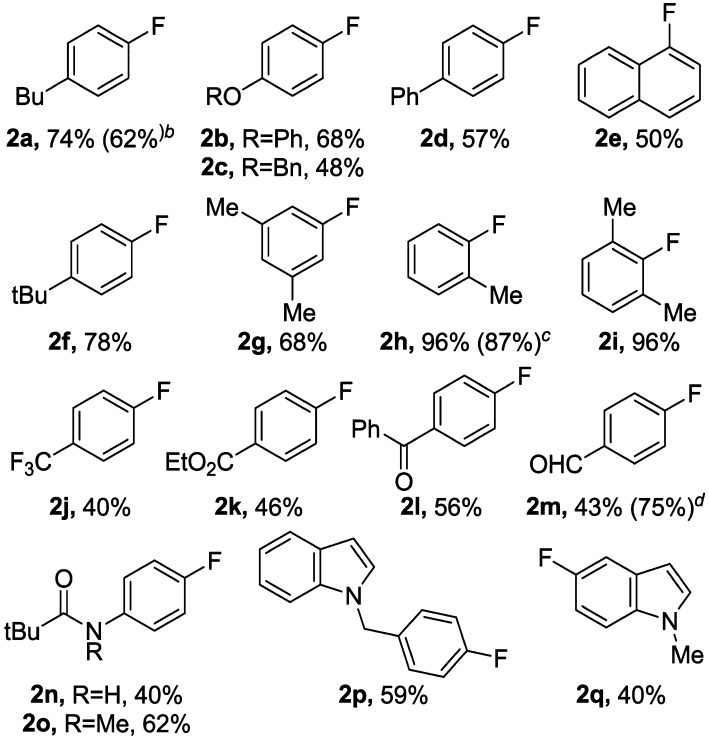
25
70% (n/o)
10 mol% "Pd"
110 °C



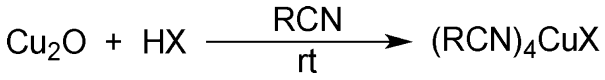
CFluorination & Trifluoromethylation

CuI-mediated fluorination of Aryl iodide & Aryl boron ester (Hartwig 2012)

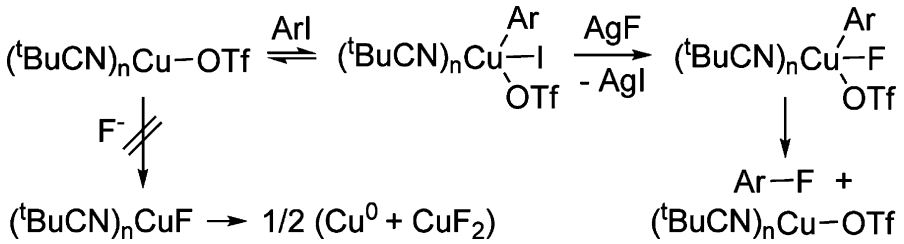




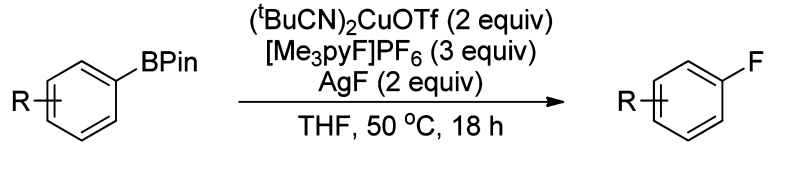
Catalyst preparation

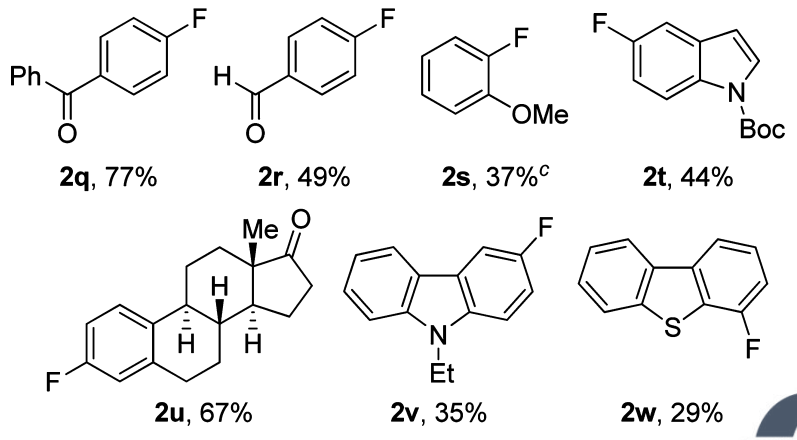


Proposed mechanism



Boron ester substrate





[a] Fier, P. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2012**, *134*, 10795. [b]Fier, P. S.; Luo, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2013**, *135*, 2552.

Outlines

Introduction

- Importance of F-containing compounds
- Traditional ways to introduce F & CF_3
- How nature introduce F & CF_3

TM-Med./Cat. Fluorination

- Cu-mediated C-F formation
- Pd-catalyzed C-F formation
- Ag-catalyzed C-F formation

TM-Med./Cat. CF_3lation

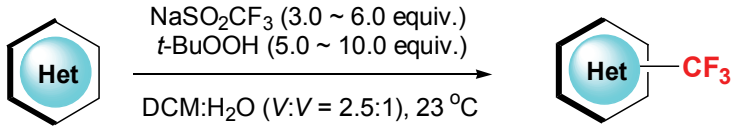
- Pd-catalyzed C-CF_3 formation
- Cu-catalyzed C-CF_3 formation

Ref: [1] Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature*, **2011**, *473*, 470.
[2] Qing, F. L. *Chin. J. Org. Chem.* **2012**, *32*, 815.
[3] Tomashenko, O. A.; Grushin, V. V. *Chem. Rev.* **2011**, *111*, 4475.
[4] Grushin, V. V. *Acc. Chem. Res.* **2010**, *43*, 160.
[5] Furuya, T.; Kuttruff, C. A.; Ritter, T. *Curr. Opin. Drug Discov. Dev.* **2008**, *11*, 803.

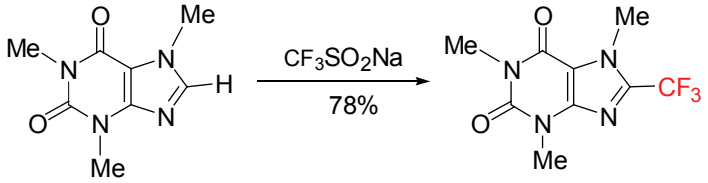
Pd-mediated/catalyzed trifluoromethylation

CF_3 source

a) polyfluorinated methanes (CF_3I, CF_3Br, CF_2Br_2, CF_3H)
b) derivatives of CF_3CO_2H & $FSO_2CF_2CO_2H$.
c) *in situ* generated CF_3Cu from transmetallation.
d) $TMSCF_3$, $TESCF_3$



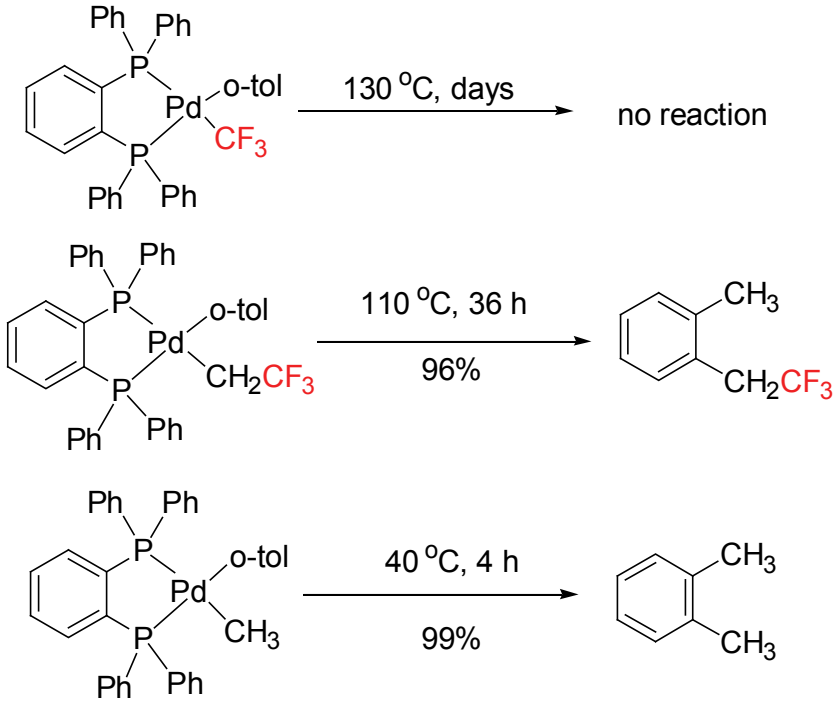
25 examples
33% ~ 96% yields



Caffeine

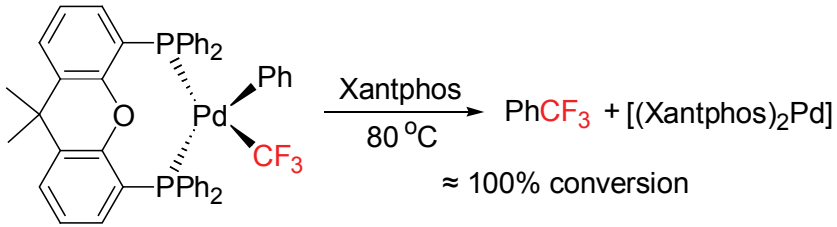
Baran, P. S. *etc. Proc. Natl Acad Sci* USA, **2011**, *108*, 14411.

Difficulty of reductive elimination



Culkin, D. A.; Hartwig, J. F. *Organometallics* **2004**, *23*, 3398.

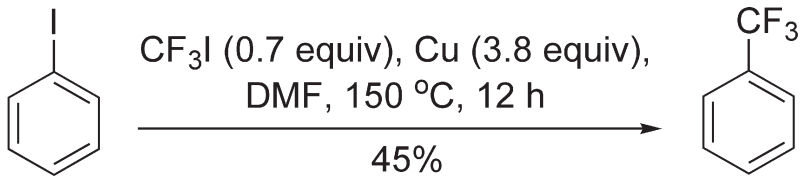
Large bite angle



Grushin, V. V.; Marshall, W. J. *J. Am. Chem. Soc.* **2006**, *128*, 12644.

First example CF_3 RE on Pd(II) center

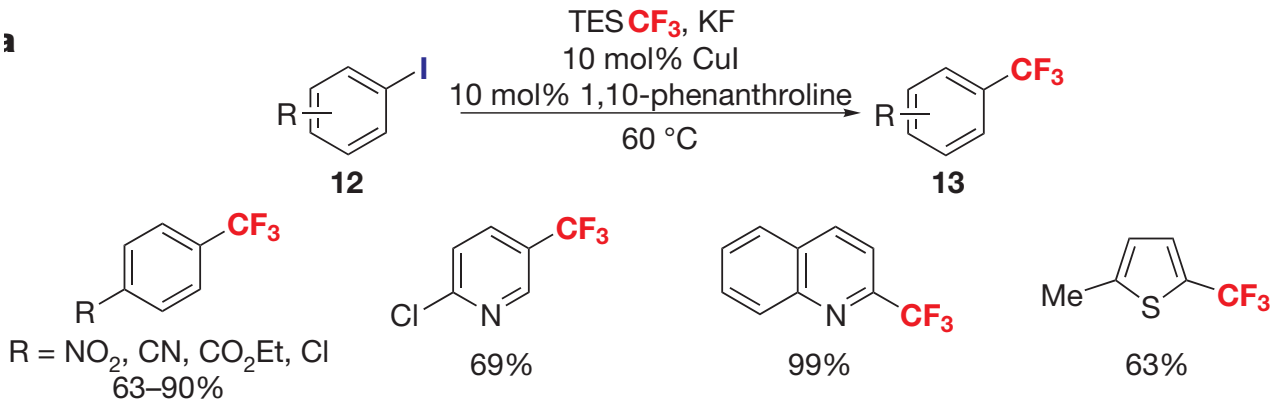
Cu-mediated Ar-CF_3 bond forming reaction



The first Ar-CF_3 forming cross-coupling reaction

Mcloughlin, V. C. R.; Thrower, J. *Tetrahedron* **1969**, *25*, 5921.

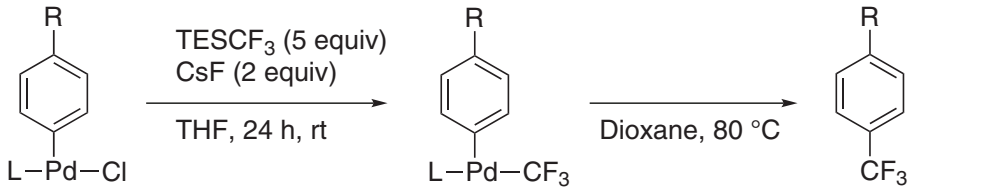
First Cu-catalyzed reaction (2009)



Oishi, M.; Kondo, H.; Amii, H. *Chem. Commun.* **2009**, 1909.

Pd-mediated/catalyzed trifluoromethylation

A



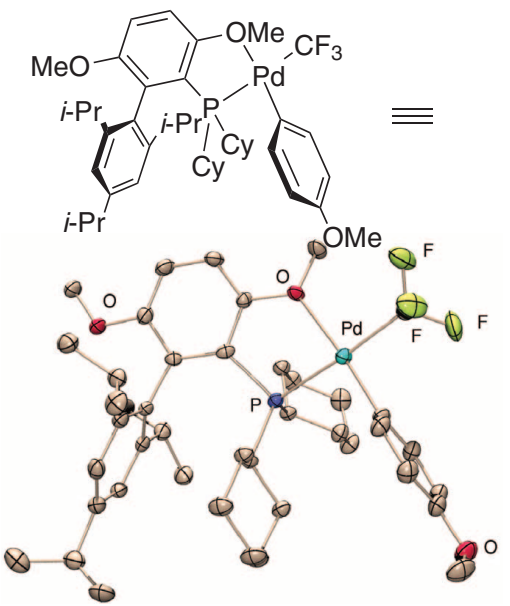
12a: R=CO_2Me
12b: R=OMe

(L = **6**)

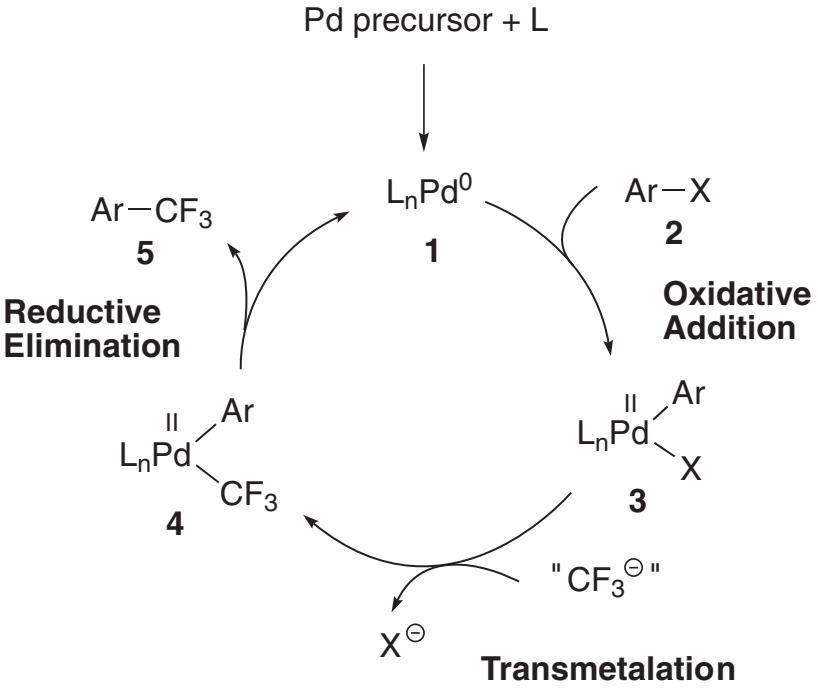
13a: 38%
13b: 37%

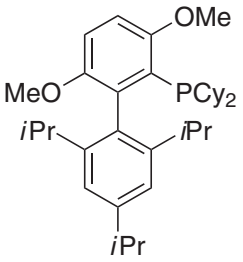
14a: $t_{1/2}$ = 22 min
14b: $t_{1/2}$ = 24 min

B



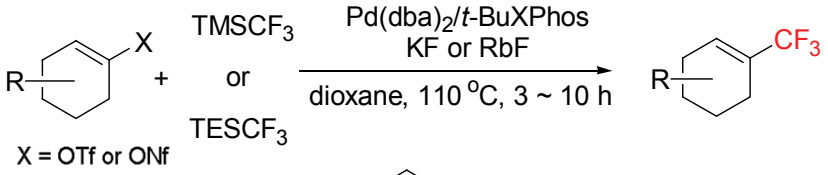
Difficulty of reductive elimination



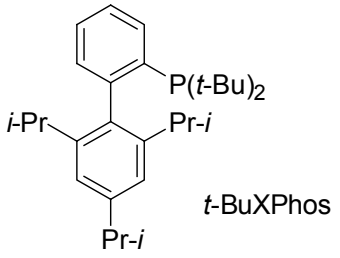


BrettPhos (**6**)

Recent results



X = OTf or ONf

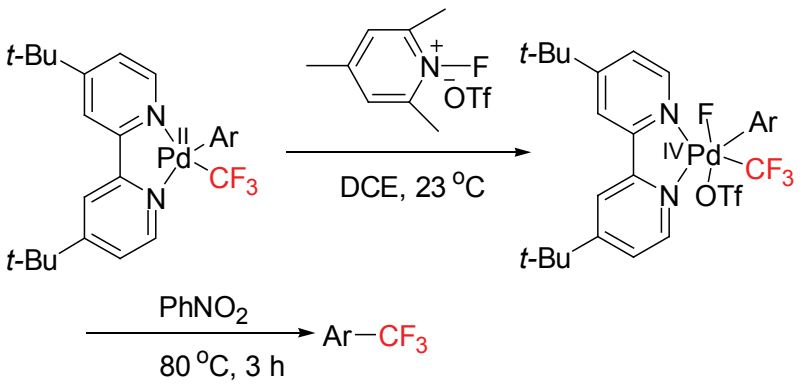


t-BuXPhos

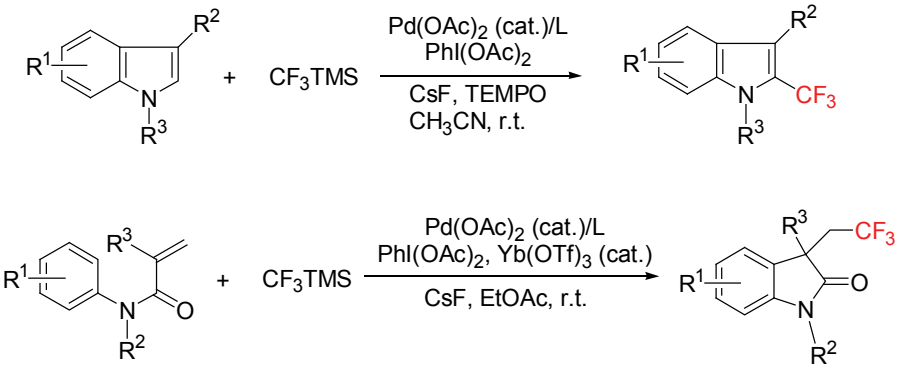
Cho, E. J.; Senecal, T. D.; Kinzel, T.; Zhang, Y.; Watson, D. A.; Buchwald, S. L. *Science* **2010**, *328*, 1679.

Cho, E. J.; Buchwald, S. L. *Org. Lett*, **2011**, *13*, 6552.

Pd-mediated/catalyzed trifluoromethylation (Sanford 2010)

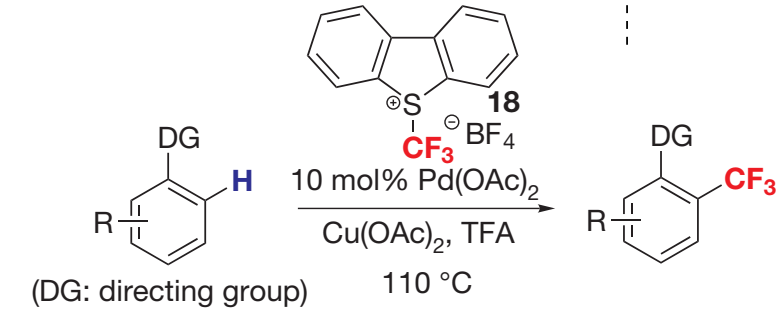


Ball, N. D.; Kampf, J. W.; Sanford, M. S. *J. Am. Chem. Soc.* **2010**, *132*, 2878.

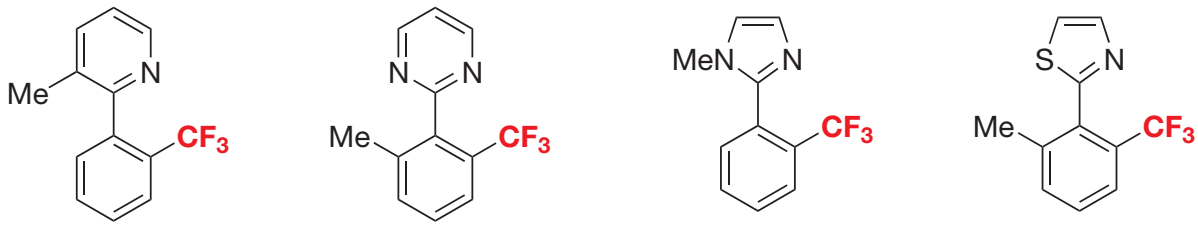


[a] Mu, X.; Chen, S.; Zhen, X.; Liu, G. *Chem. Eur. J.* **2011**, *17*, 6039.
[b] Mu, X.; Wu, T.; Wang, H. Y.; Guo, Y.; Liu, G. *J. Am. Chem. Soc.* **2012**, *134*, 878.

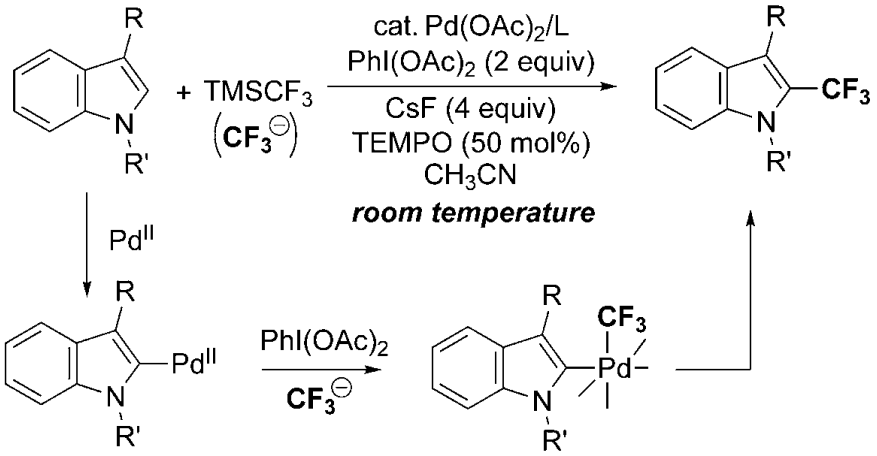
Yu's work



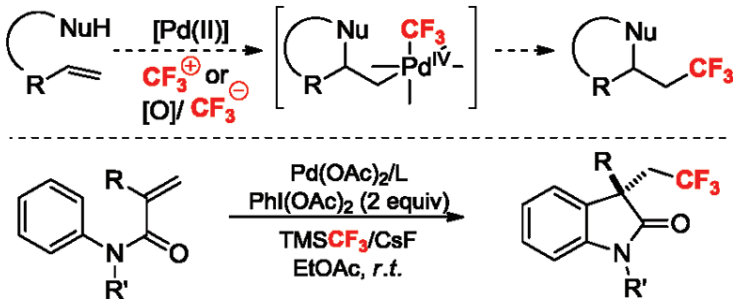
(DG: directing group)



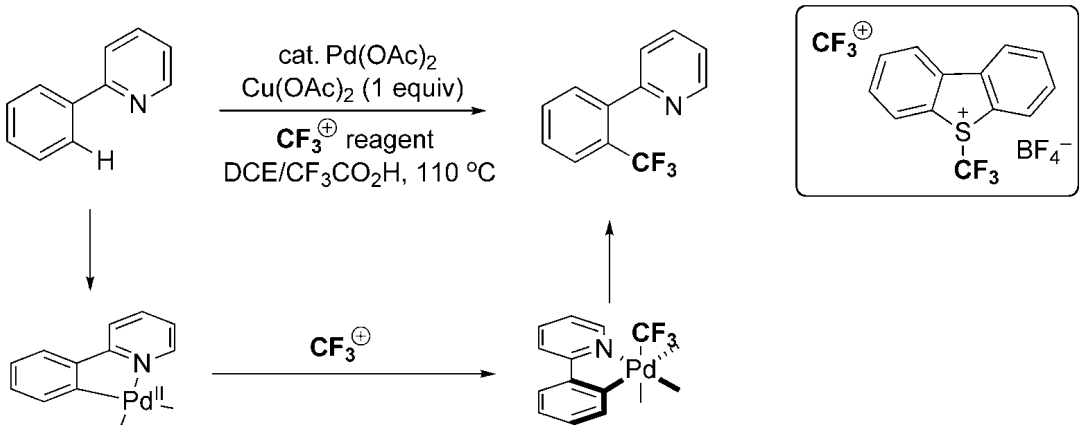
Wang, X.; Truesdale, L.; Yu, J. Q. *J. Am. Chem. Soc.* **2010**, *132*, 3648.



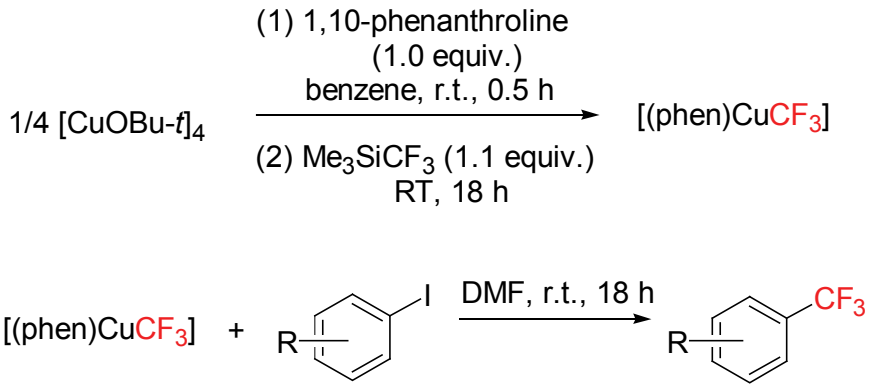
Mu, X.; Chen, S.; Zhen, X.; Liu, G. Chem. Eur. J. 2011, 17, 6039.



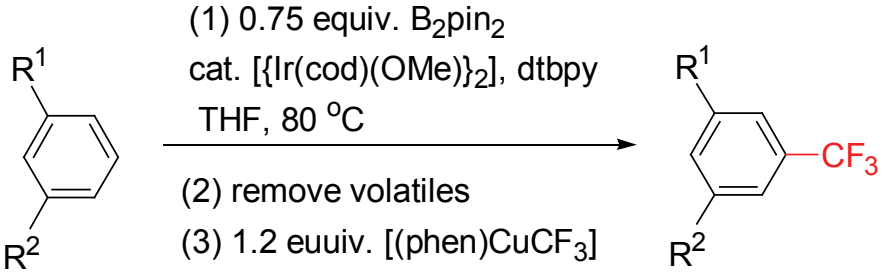
Mu, X.; Wu, T.; Wang, H. Y.; Guo, Y.; Liu, G. *J. Am. Chem. Soc.* **2012**, *134*, 878.



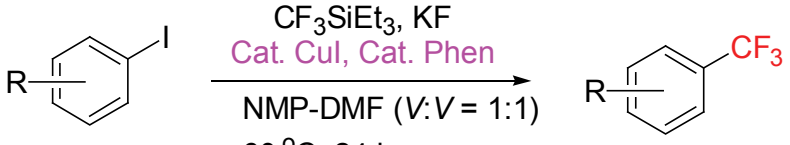
Cu-mediated/catalyzed trifluoromethylation



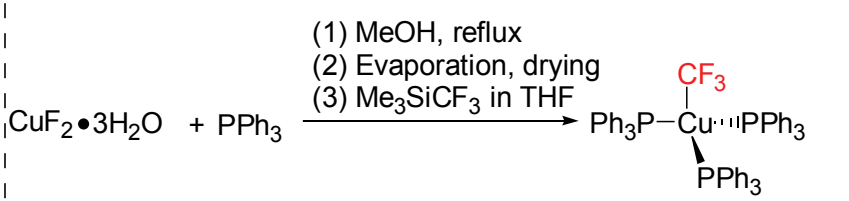
Morimoto, H.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2011**, *50*, 3793.

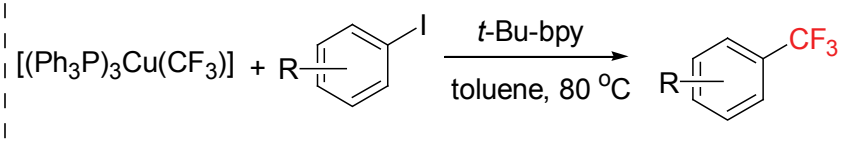


Litvinas, N. D.; Fier, P. S.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2012**, *51*, 536.

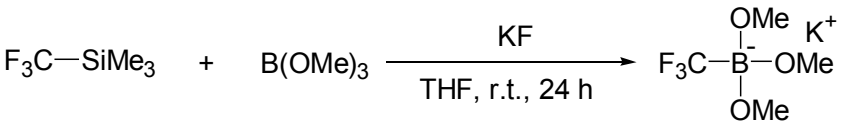


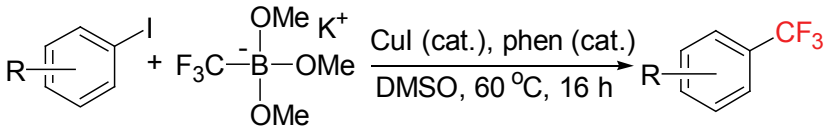
Oishi, M.; Kondo, H.; Amii, H. *Chem. Commun.* **2009**, 1909.

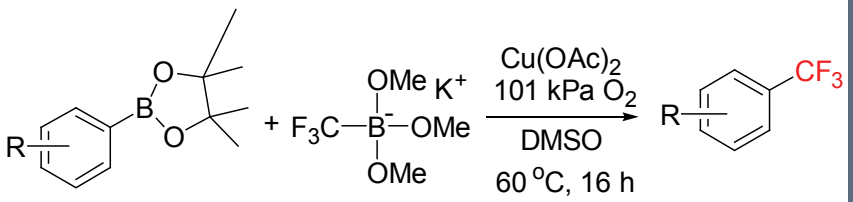




Grushin, V. V. *etc. Angew. Chem., Int. Ed.* **2011**, *50*, 7655.

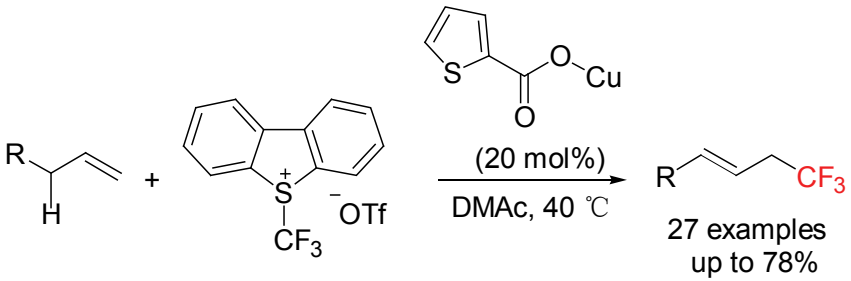


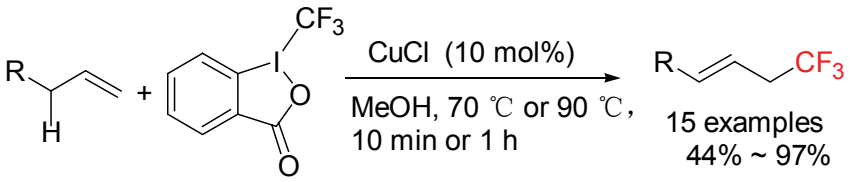




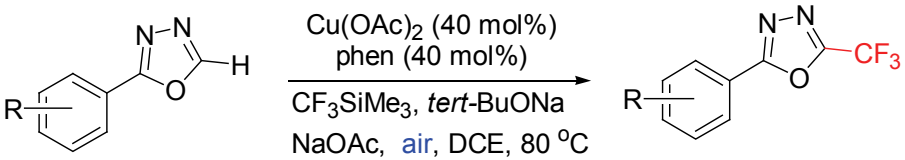
[a] Knauber, T.; Gooben, L. J. *Chem. Eur. J.* **2011**, *17*, 2689.
[b] Khan, B. A.; Gooben, L. J. *Chem. Eur. J.* **2012**, *18*, 1577

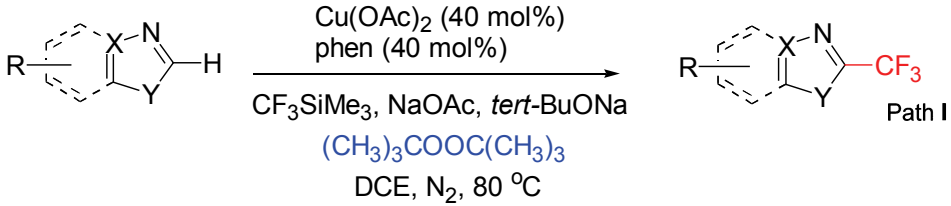
Cu-mediated/catalyzed trifluoromethylation

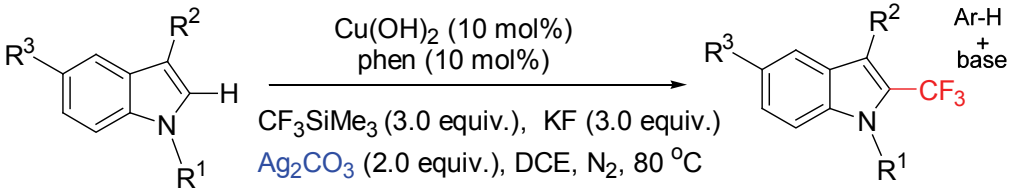


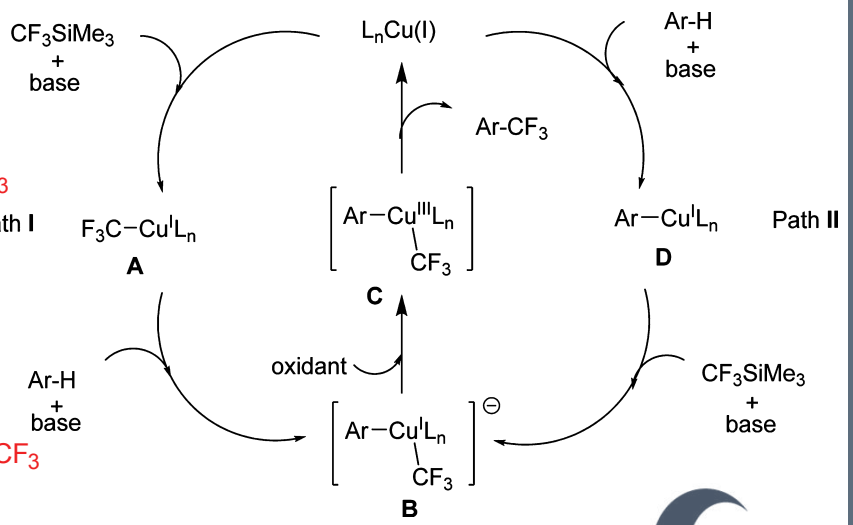


[a] Xu, J.; Liu. L. etc *J. Am. Chem. Soc.* **2011**, *133*, 15300.
[b] Wang, X.; Wang, J. etc. *J. Am. Chem. Soc.* **2011**, *133*, 16410.



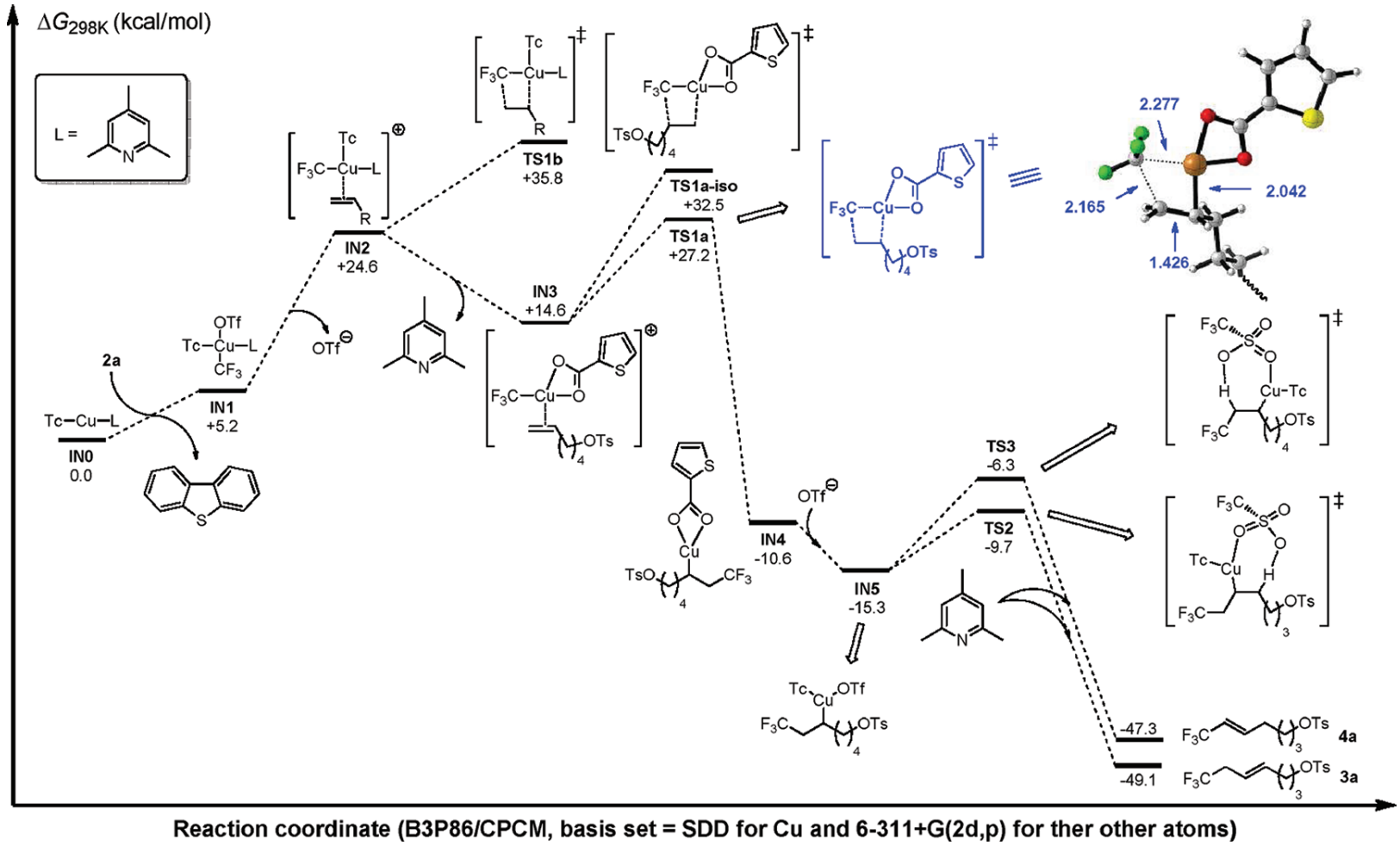






Chu, L.; Qing, F. L. *J. Am. Chem. Soc.* **2012**, *134*, 1298.

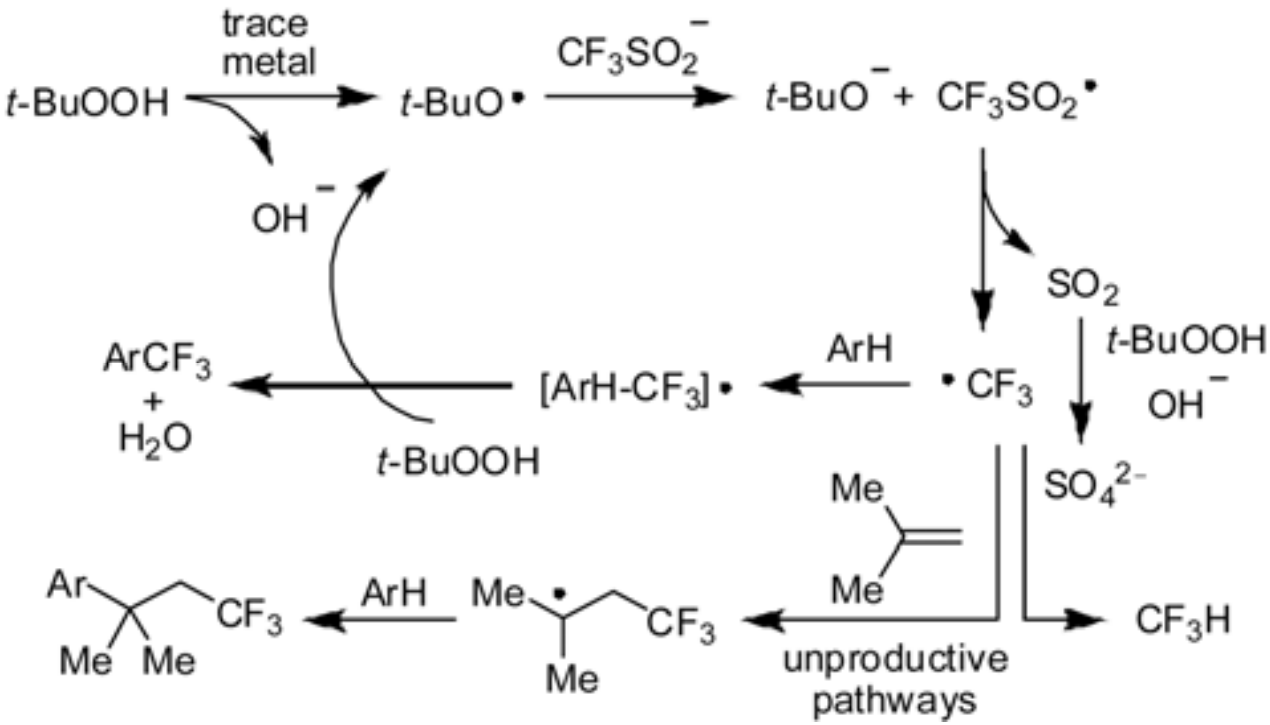
mechanism


ΔG298K (kcal/mol)
L =
IN0
0.0
IN1
+5.2
IN2
+24.6
IN3
+14.6
TS1b
+35.8
TS1a-iso
+32.5
TS1a
+27.2
IN4
-10.6
IN5
-15.3
TS3
-6.3
TS2
-9.7
-47.3
-49.1
4a
3a
2a
2.277
2.042
2.165
1.426
Reaction coordinate (B3P86/CPCM, basis set = SDD for Cu and 6-311+G(2d,p) for ther other atoms)

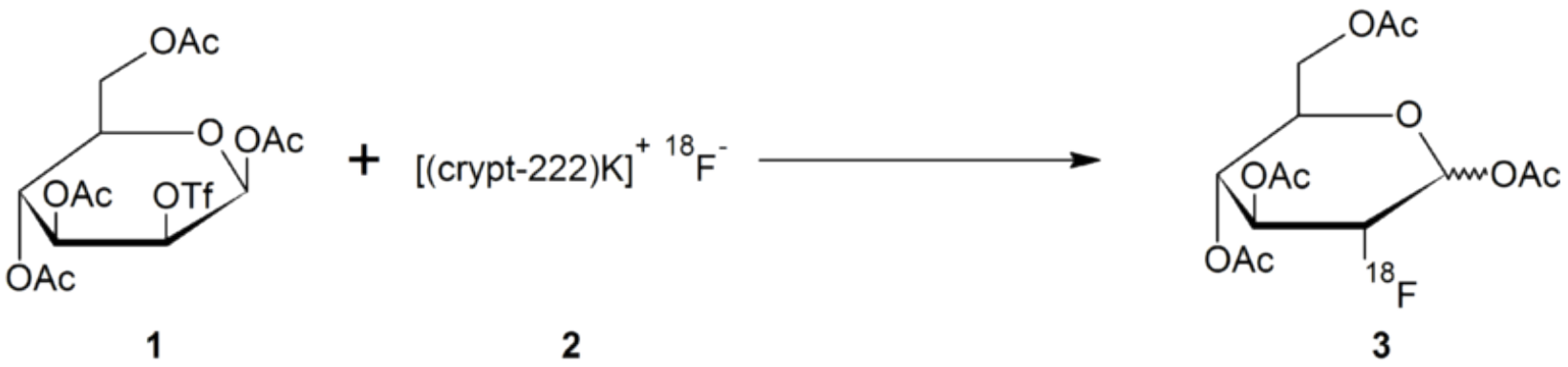
TO BE CONTINUED

Thank you!

contoso


trace
metal
t-BuOOH
t-BuO•
CF3SO2−
t-BuO− + CF3SO2•
OH−
SO2
t-BuOOH
OH−
ArCF3
+
H2O
[ArH-CF3]•
ArH
•CF3
t-BuOOH
SO4 2-
Me
Me
Ar
CF3
Me Me
ArH
Me
CF3
Me
CF3H
unproductive
pathways

^{18}F-FDG synthesis



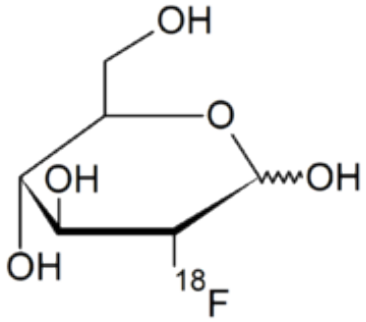
1 **2** **3**

Ac = CH_3CO

Tf = CF_3SO_2

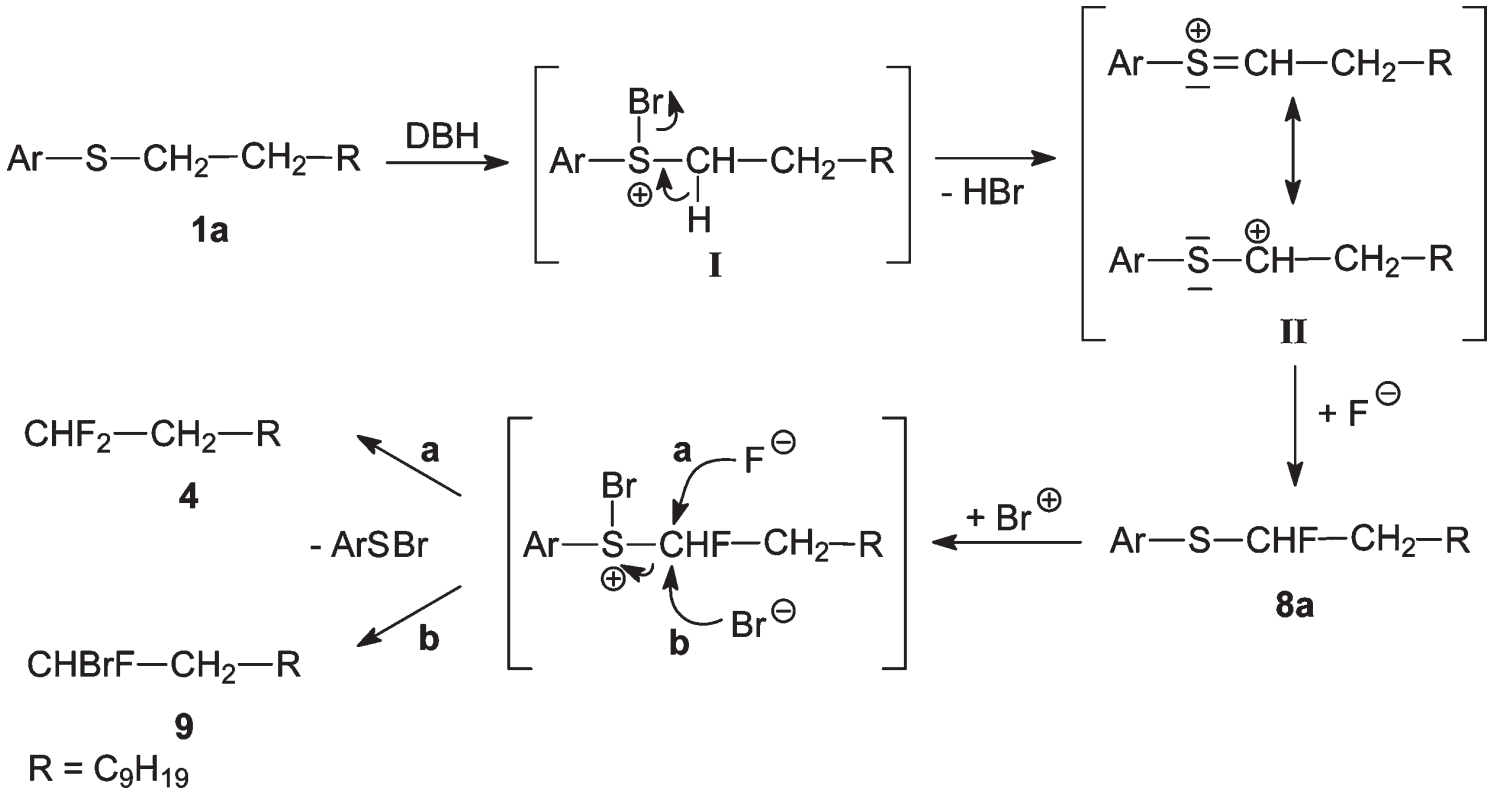
1. NaOH

2. HCl

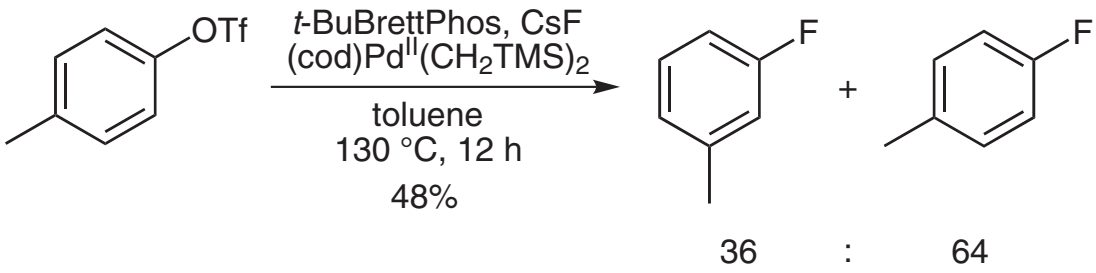


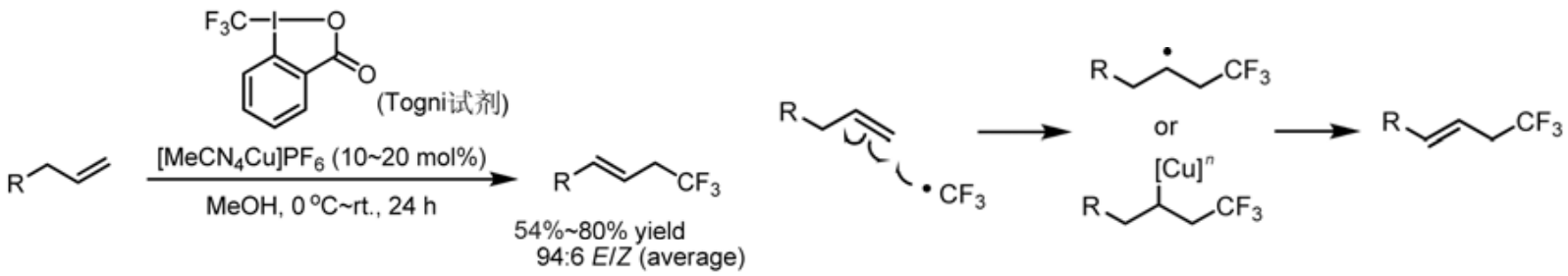
4

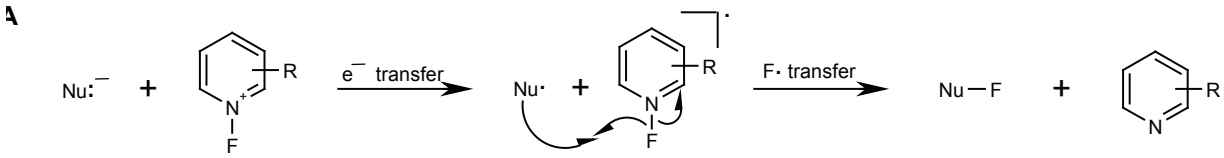
Mechanism of DBH

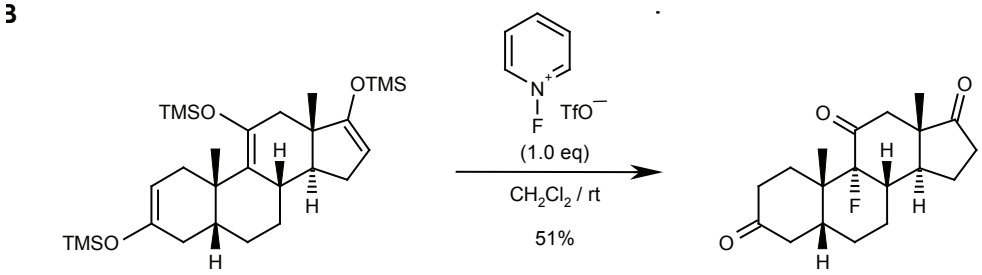


question

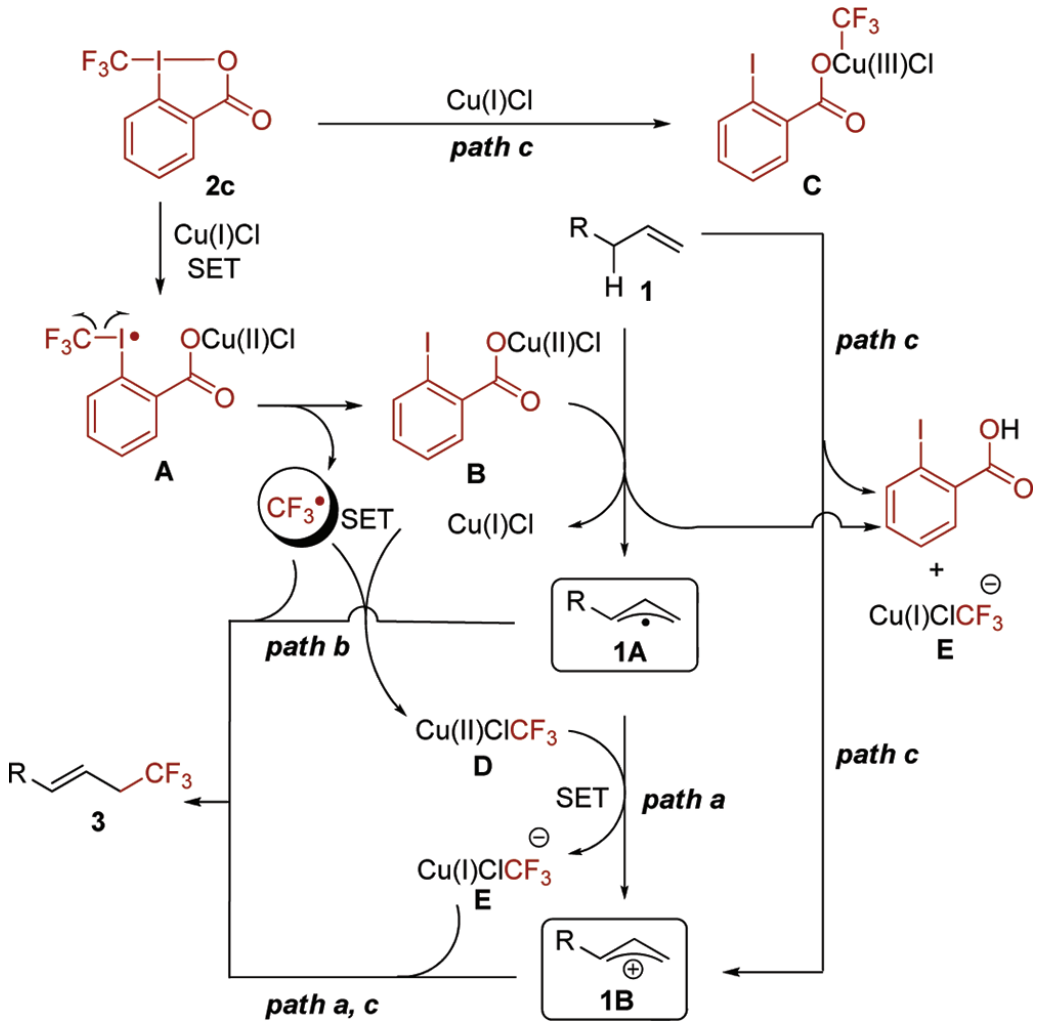








contoso


F3C—I—O
O
2c
Cu(I)Cl
path c
CF3
OCu(III)Cl
I
O
C
Cu(I)Cl
SET
R
H 1
path c
F3C—I•
OCu(II)Cl
O
A
I
OCu(II)Cl
O
B
CF3•
SET
Cu(I)Cl
I
OH
O
+
Cu(I)ClCF3
E
R
1A
path b
Cu(II)ClCF3
D
SET
path a
path c
R
CF3
3
Cu(I)ClCF3
E
R
1B
path a, c