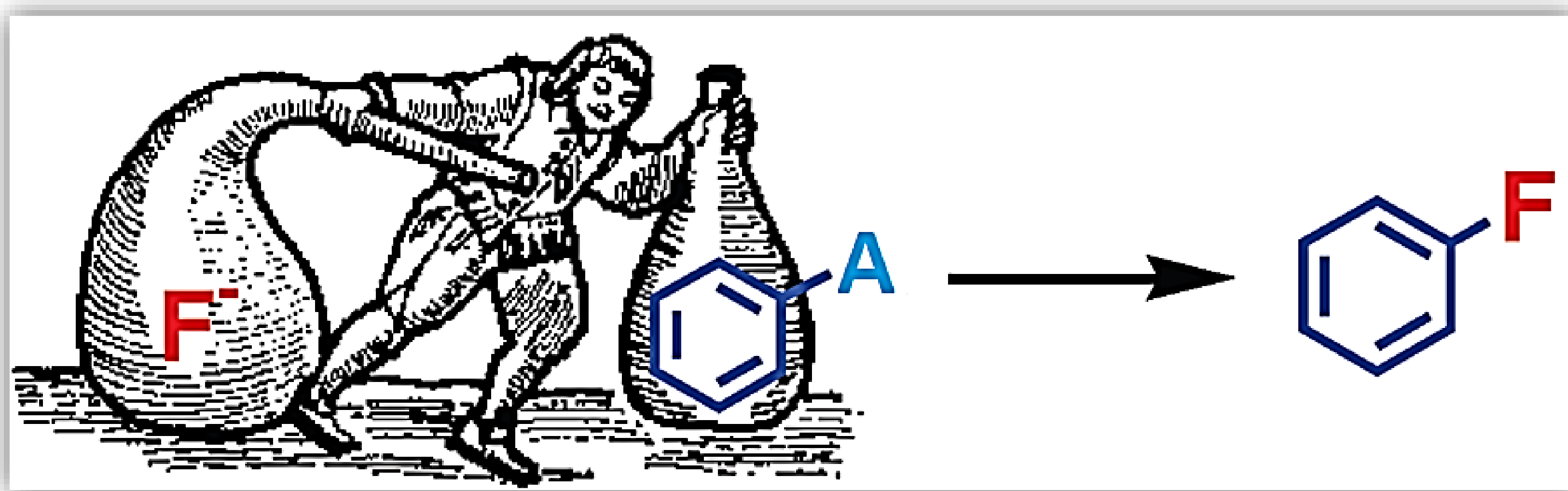
Modern C(sp^2)-F bond forming reactions:

From C–A to C–F (A = H, X, M)



YAN XU

JUN. 17, 2015

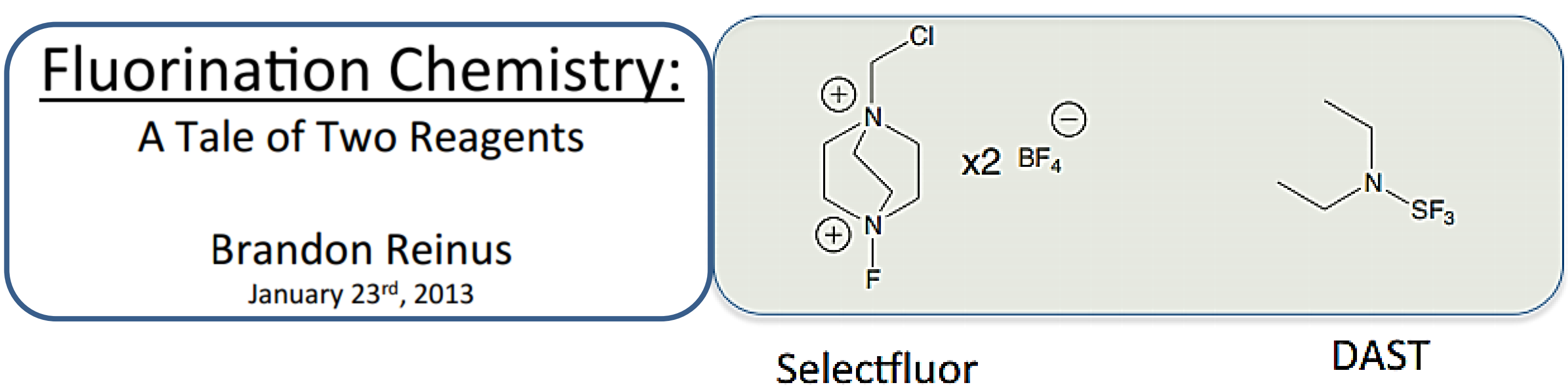
Reference

T. Ritter, ”Modern Carbon–Fluorine Bond Forming Reactions for Aryl Fluoride Synthesis”
Chem. Rev. **2015**, *115*, 612–633

V. V. Grushin, “The Organometallic Fluorine Chemistry of Palladium and Rhodium: Studies toward Aromatic Fluorination”
Acc. Chem. Res., **2010**, *43*, 160–171

T. Ritter, “Introduction of Fluorine and Fluorine-Containing Functional Groups”
Angewandte Chemie International Edition, **2013**, *52*, 8214-8264

J. Yang “Recent Advance in C-H fluorination”
Org. Chem. Front., **2014**, *1* , 434-438

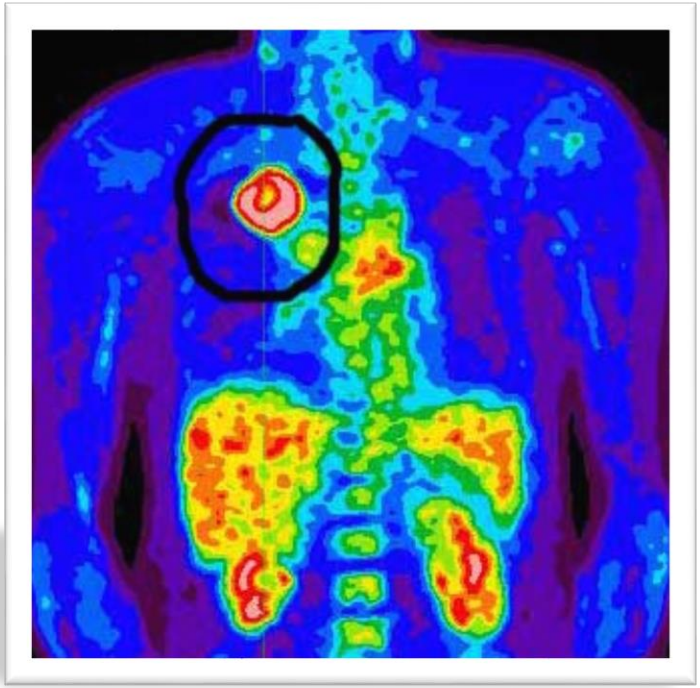


Fluorination chemistry

- *more than 100 years*
- *first examples: second half of the 19th century*

Ann. Chem. Pharm. **1863**, *126*, 58-62

fluorine substitution can impart lots of properties on molecules, such as pharmaceuticals, agrochemicals, materials, and radiotracers for positron emission tomography (PET).



[half-lives]
^{11}C, ^{13}N, ^{15}O: ≤20 min
^{18}F : 110 min

- *Hydrophobic/hydrophilic properties*
- *membrane penetration at physiological pH*
- *strategically used as transition state inhibitors*
- *increased metabolic stability*
- *Increase binding affinity to proteins (hydrogen bond donors)*

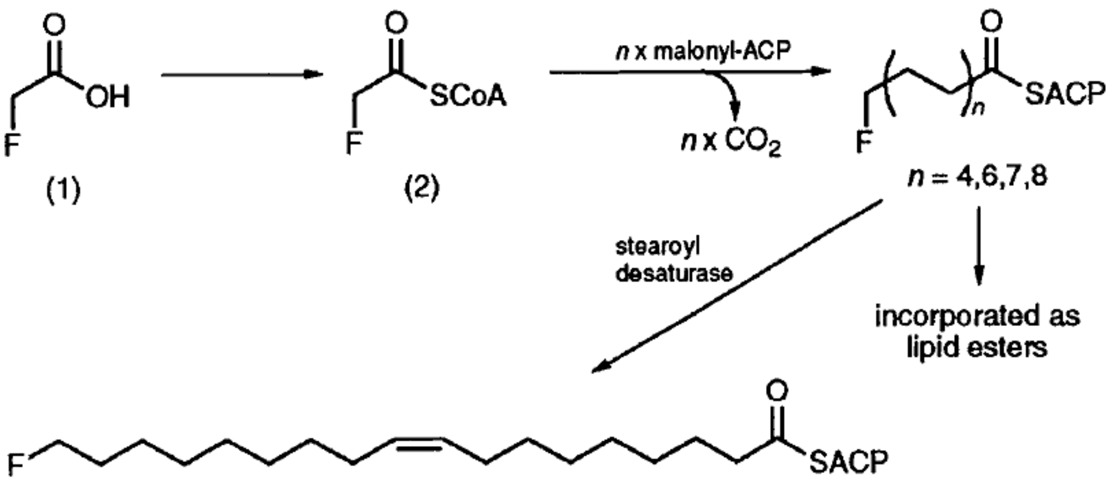
Fundamental challenge of C-F bond forming reaction:

the nature of fluorine itself

High electronegativity

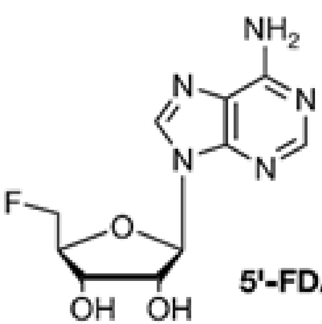
high hydration energy of fluoride anion

- *Weak nucleophile in the presence of hydrogen bond donors*
- *Better nucleophile when hydrogen bond donors are meticulously exclude, but also a strong base*

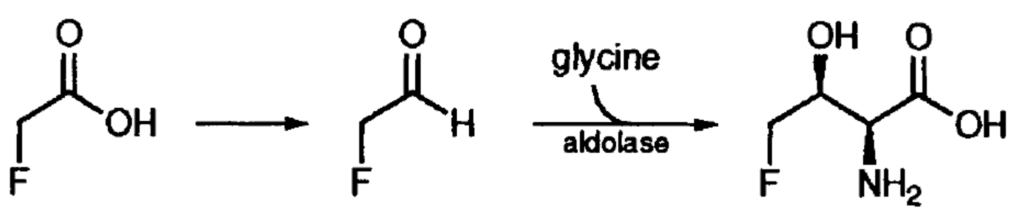


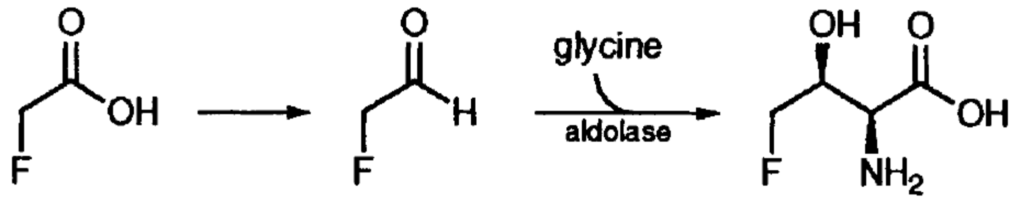
In Nature, haloperoxidase enzymes give rise to thousands of organochlorides and organobromides but no fluoroperoxidase enzyme has been identified

Despite fluorine being the 13th most abundant element in the Earth crust, only a handful of natural organofluorides are known

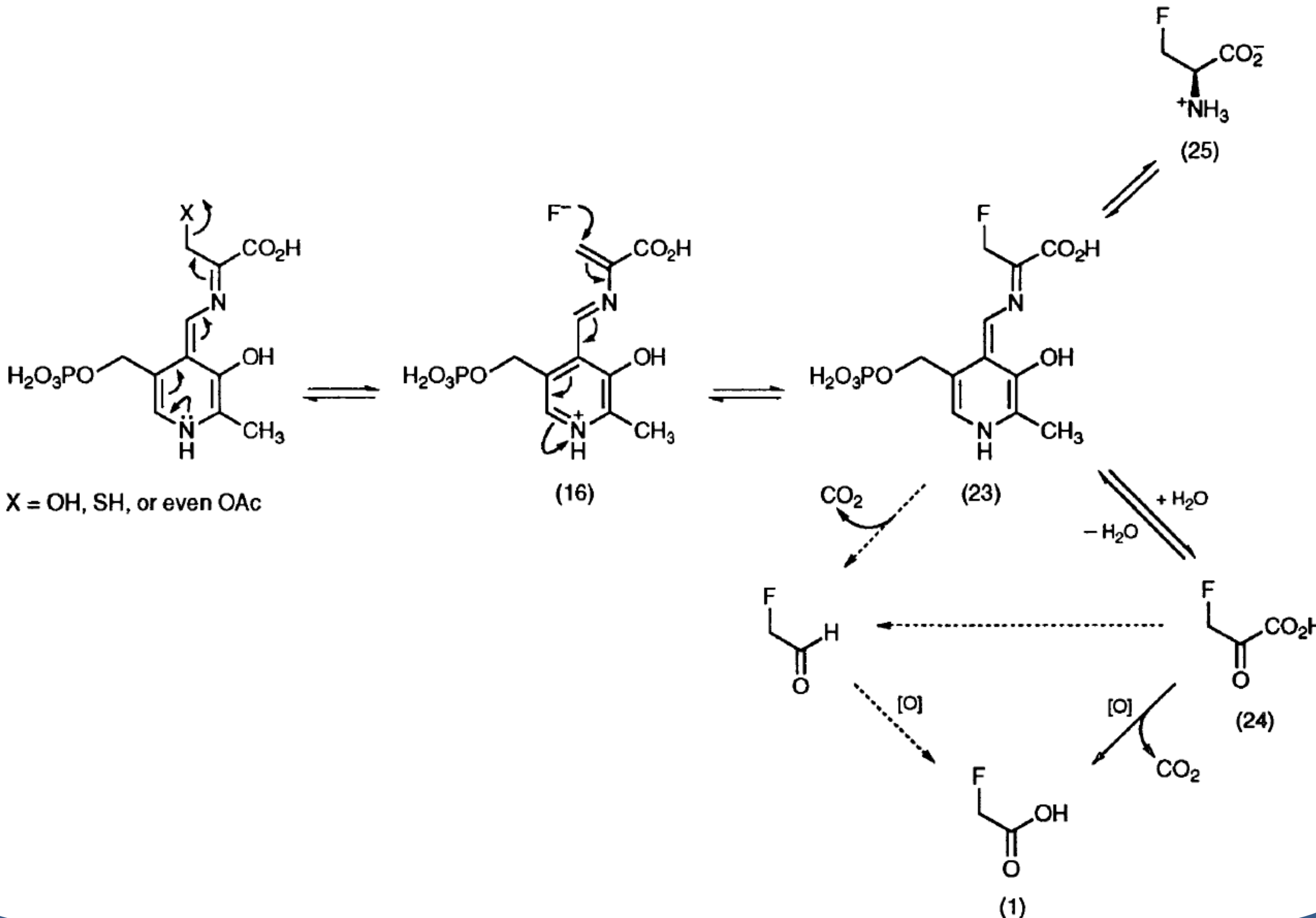


5'-FDA

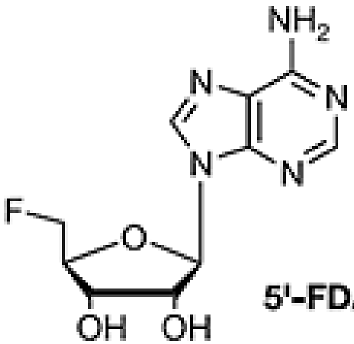




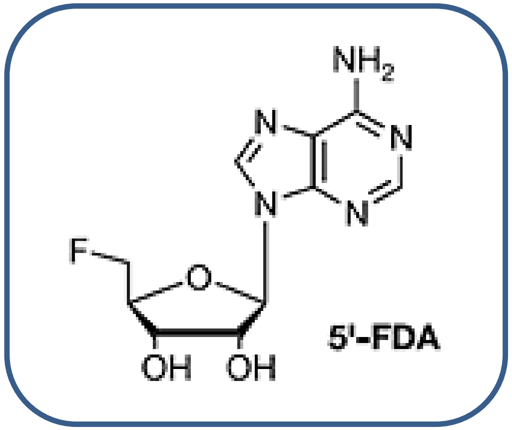
glycine
aldolase

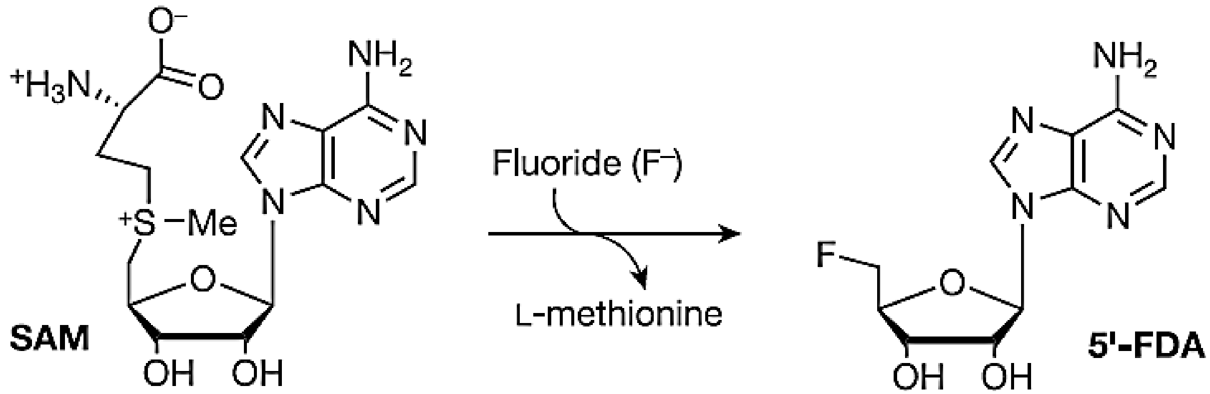


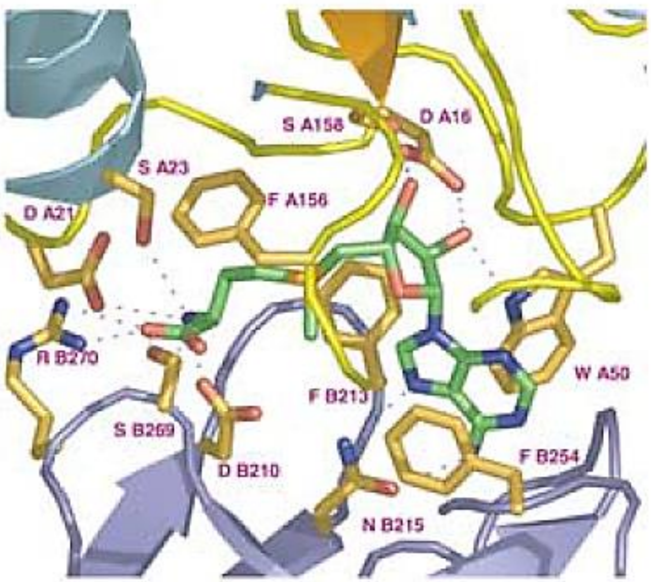
X = OH, SH, or even OAc
(16)
(23)
(24)
(25)
(1)
CO_2
+ H_2O
− H_2O
[O]



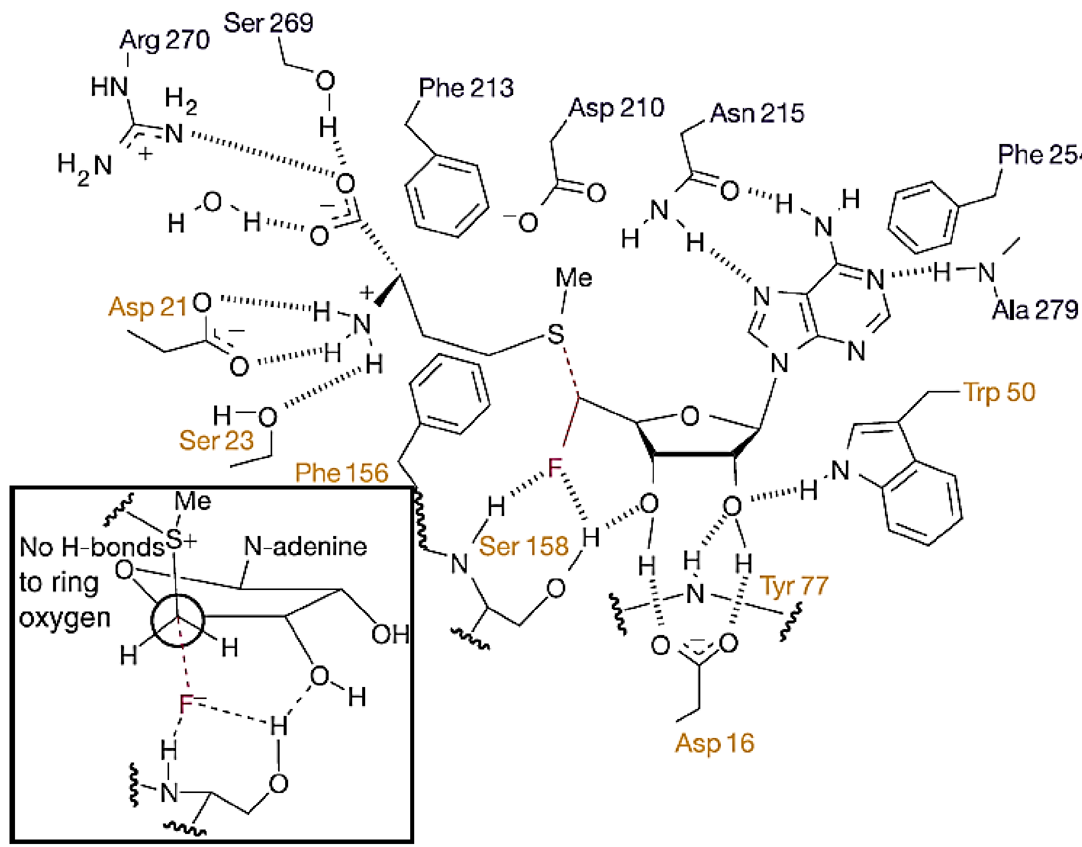
5'-FDA







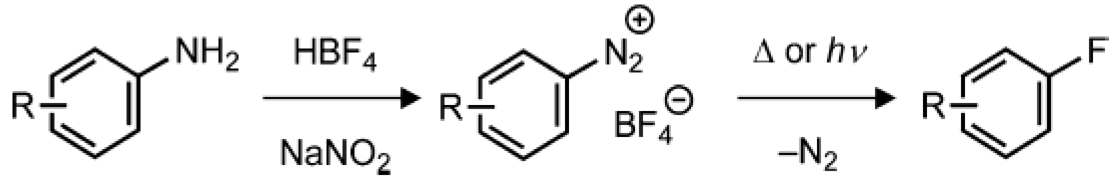
dehydrates solvated fluoride
In the active site



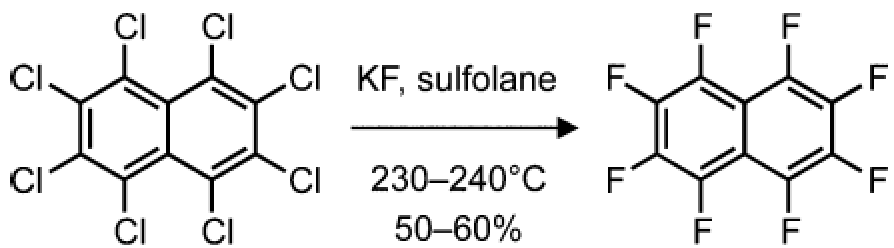
Nature **2004**, *427*, 561.

Nucleophilic C(sp^2)-Fluorination *From C−X to C−F*

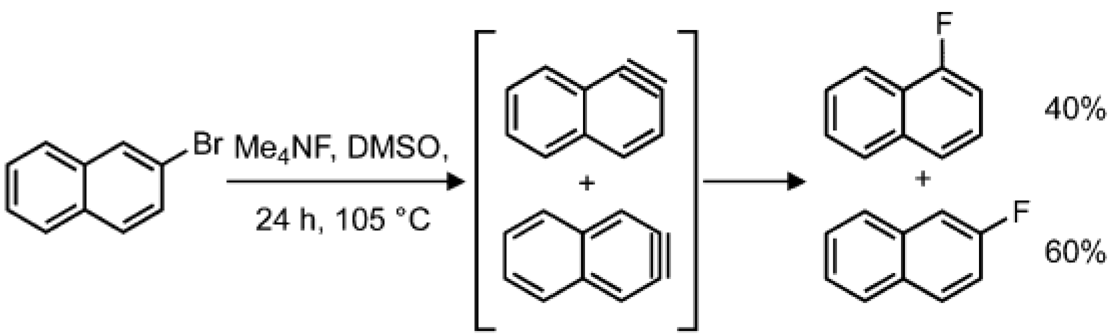
- *Traditional sp^2 C-F bond formation*



Nucleophilic fluorination of aryl diazonium salts (the Balz−Schiemann reaction)

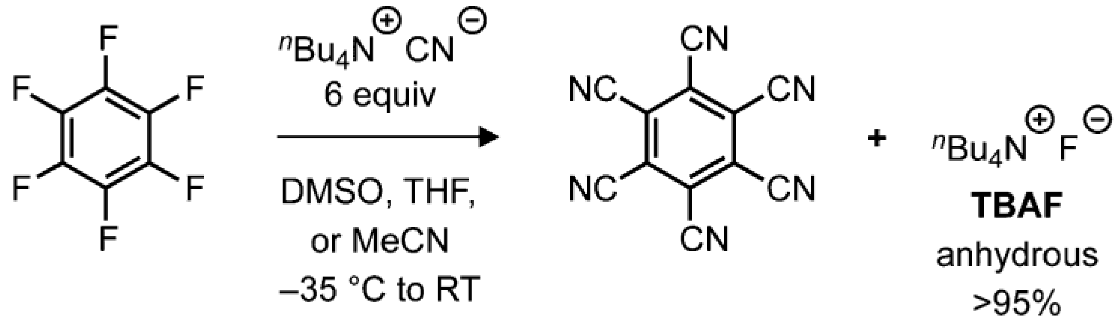


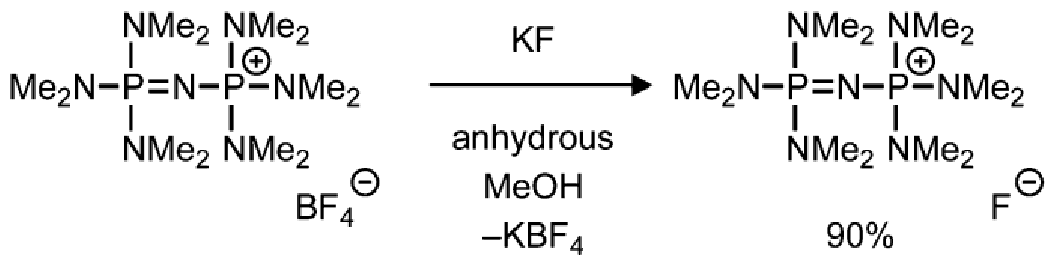
Nucleophlic aromatic substitution of electron-poor arenes (the Halex process).



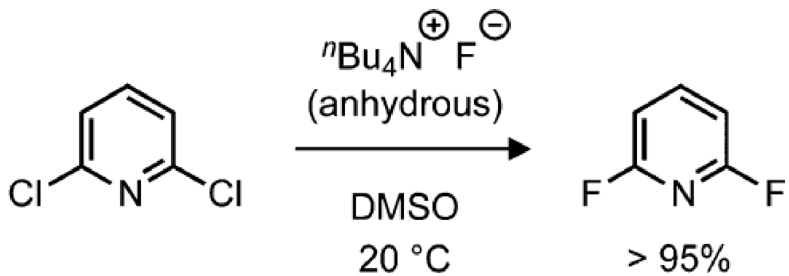
Fluorination of aryl bromides via aryne intermediates.

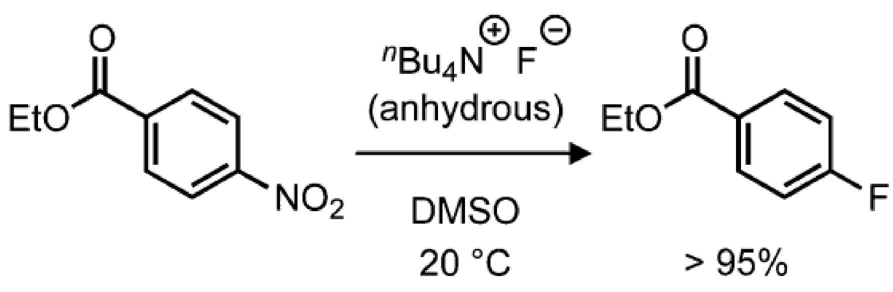
■ *Synthesis of anhydrous "naked" fluoride sources*





■ *Room temperature nucleophilic arene fluorination using anhydrous TBAF*





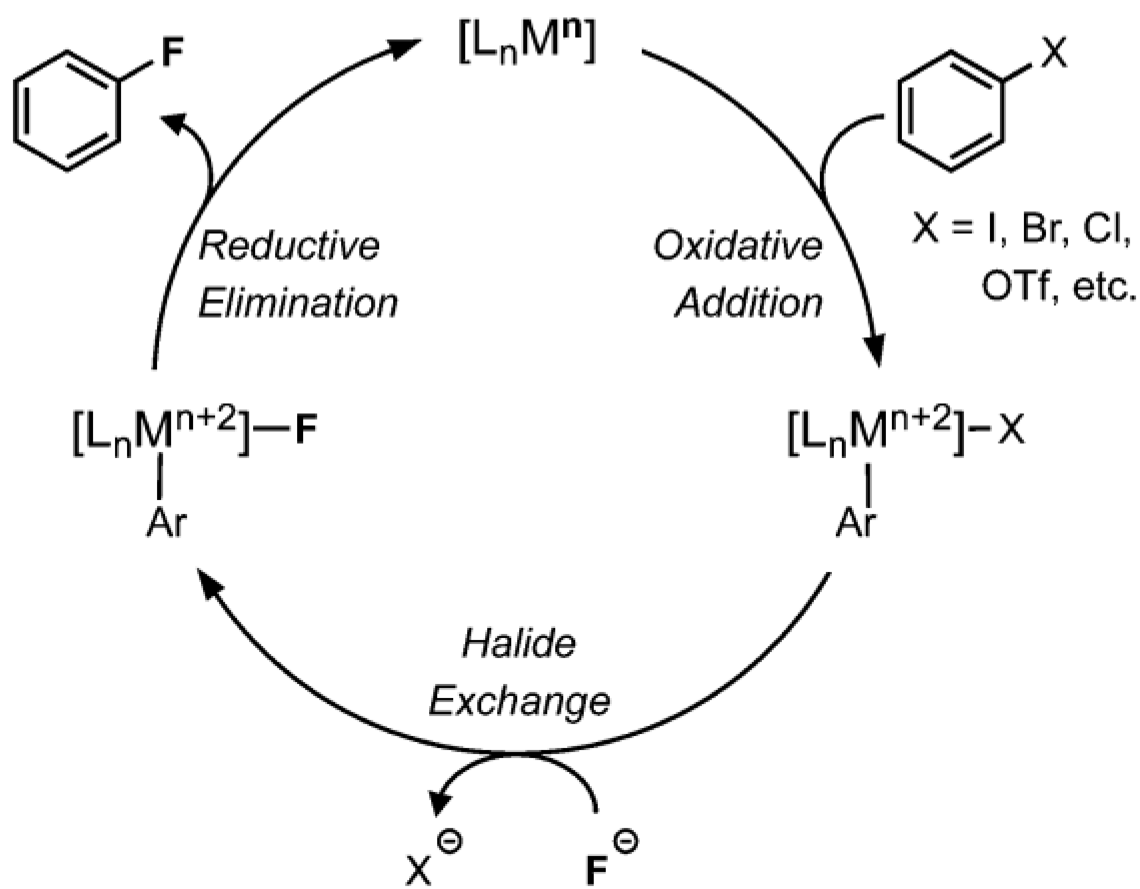
Sun, H.; DiMagno, S. G. *J. Am. Chem. Soc*. **2005**, *127*, 2050.
Sun, H.; DiMagno, S. G. *Angew. Chem., Int. Ed*. **2006**, *45*, 2720.
Sun, H.; DiMagno, S. G. *Chem. Commun*. **2007**, 528.
Schwesinger, R.; Link, R.; Thiele, G.; Rotter, H.; Honert, D.; Limbach, H.-H.; Männle, F. *Angew. Chem., Int. Ed. Engl*. **1991**, *30*, 1372.

Nucleophilic C(sp^2)-Fluorination

Large kinetic barrier to C−F bond formation
Thermodynamically favorable process
(the C−F bond is the strongest of all C−X single bonds)

Therefore, improving nucleophilic arene fluorination can ideally be approached by catalysis

- *General catalysis cycle for metal-catalyzed nucleophilic fluorination.*



Challenges of metal mediated C-F bond formation

Overcoming the activation barrier to C–F bond formation from aryl–metal fluoride complexes is also very challenging!

Grushin, V. V. *Acc. Chem. Res*. **2010**, *43*, 160.

- *Challenges of metal mediated C-F bond formation*

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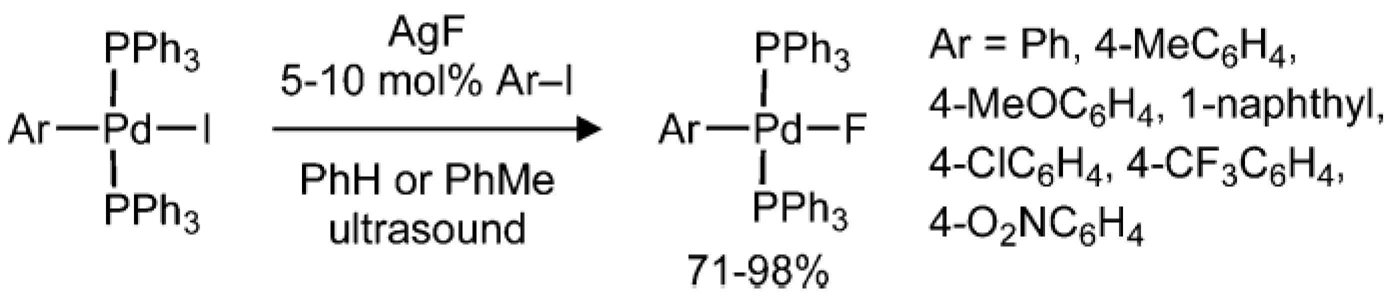
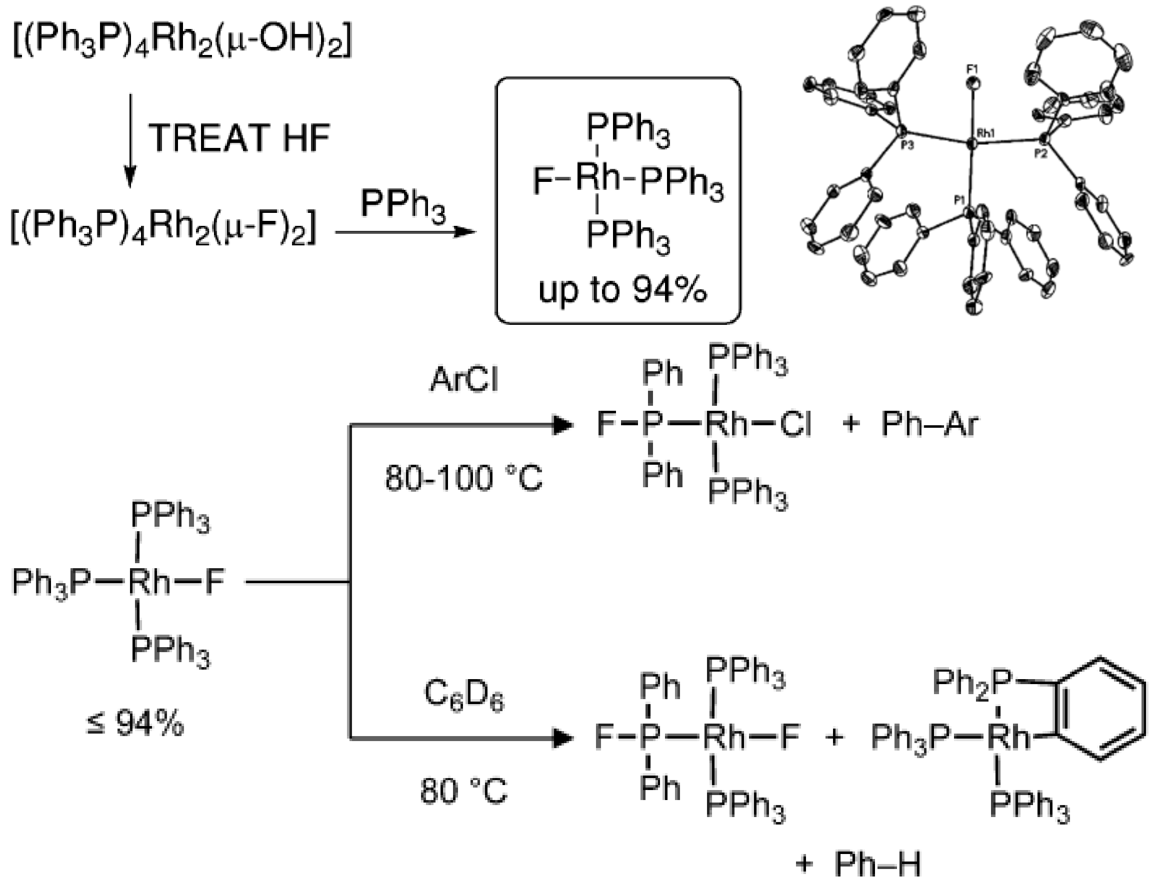
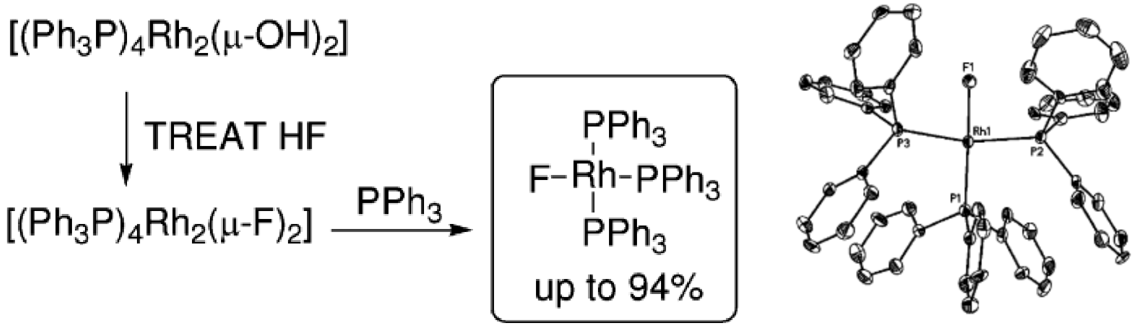


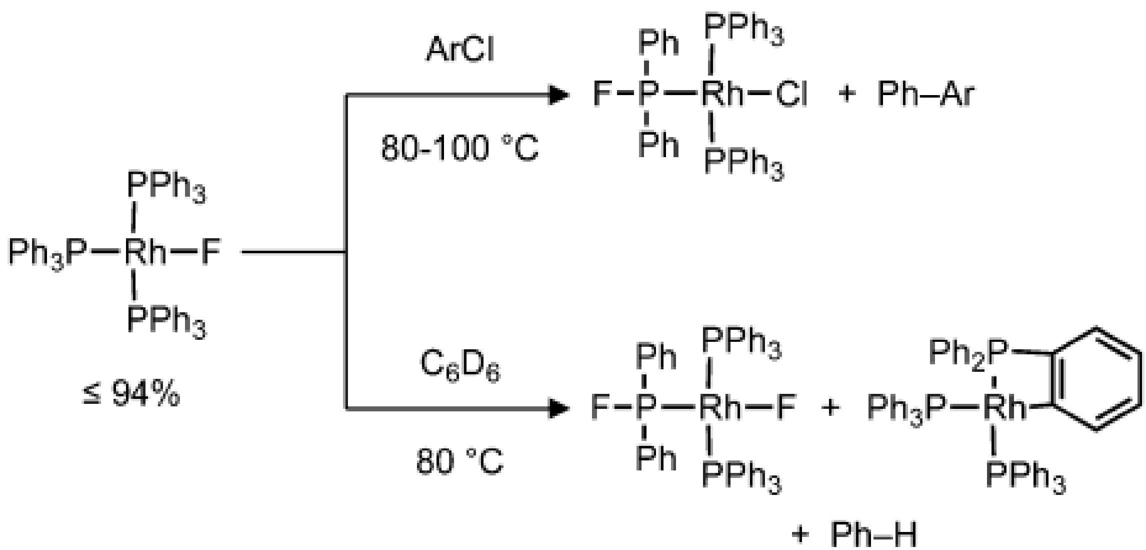
$$[(Ph_3P)_2Pd(Ph)F] \xrightarrow[110-120^{\circ}C]{\text{toluene, } N_2} [(Ph_3P)_3Pd] + Pd + Ph_2 + Ph_3PF_2 + Ph_2PPPh_2$$

Fraser, S. L.; Antipin, M. Y.; Khroustalyov, V. N.; Grushin, V. V. *J. Am. Chem. Soc*. **1997**, *119*, 4769



Pilon, M. C.; Grushin, V. V. *Organometallics* **1998**, *17*, 1774.
Marshall, W. J.; Thorn, D. L.; Grushin, V. V. *Organometallics* **1998**, *17*, 5427.
Grushin, V. V. *Chem. Eur. J.* **2002**, *8*, 1006.



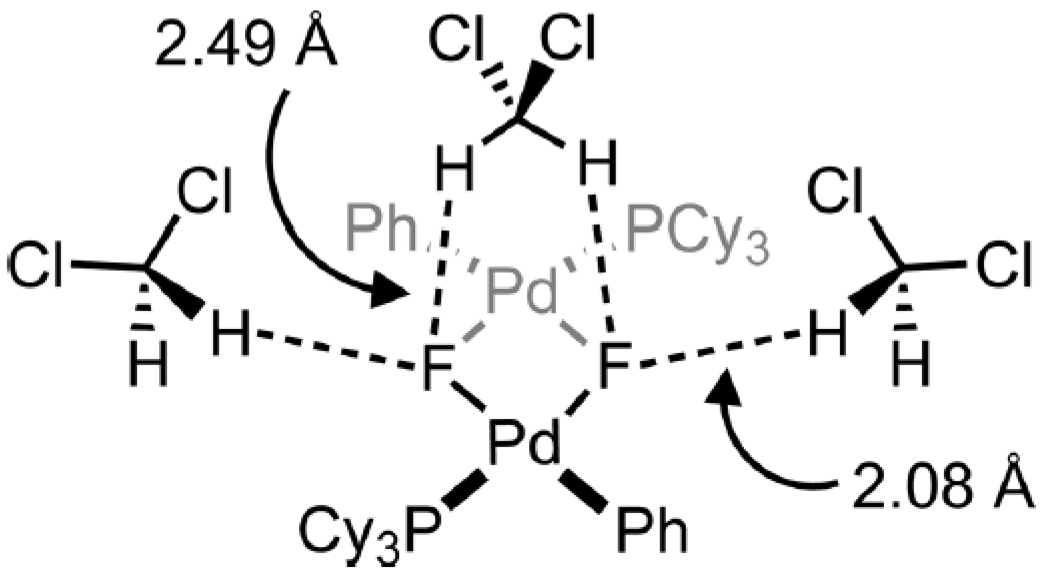


metal–fluorine bonds are significantly polarized toward fluorine.

For reductive elimination to occur, there must be sufficient orbital overlap between the metal–carbon and the metal–fluorine σ-bonds; however, electron is lacking in the region where it is required for C–F

The high polarization of the metal–fluorine bond results in a significant ionic contribution to the bond which strengthens it and increases the energy barrier to C–F reductive elimination

Pilon, M. C.; Grushin, V. V. *Organometallics* **1998**, *17*, 1774.
Marshall, W. J.; Thorn, D. L.; Grushin, V. V. *Organometallics* **1998**, *17*, 5427.
Grushin, V. V. *Chem. Eur. J.* **2002**, *8*, 1006.



An additional challenge:

palladium(II) fluoride complexes have been observed to be strongly basic

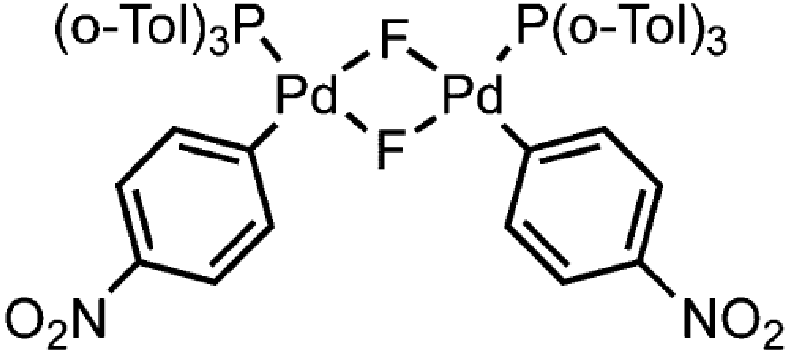
Marshall, W. J.; Thorn, D. L.; Grushin, V. V. *Organometallics* **1998**, *17*, 5427

A promising "early" result, reported by Yandulov

Three-coordinate T-shaped geometry of $Pd^{II}Ar(F)L$ (L = NHC, PR3) was shown to offer kinetics and thermodynamics of Ar-F elimination

Coordination of strong fourth ligands to Pd or *association of hydrogen bond donors* with F each caused stabilization of Pd(II) and increased barrier

Decreasing donor ability of L promotes elimination



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

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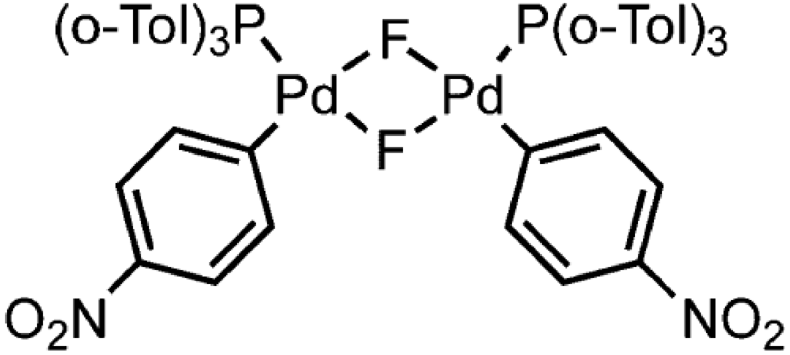
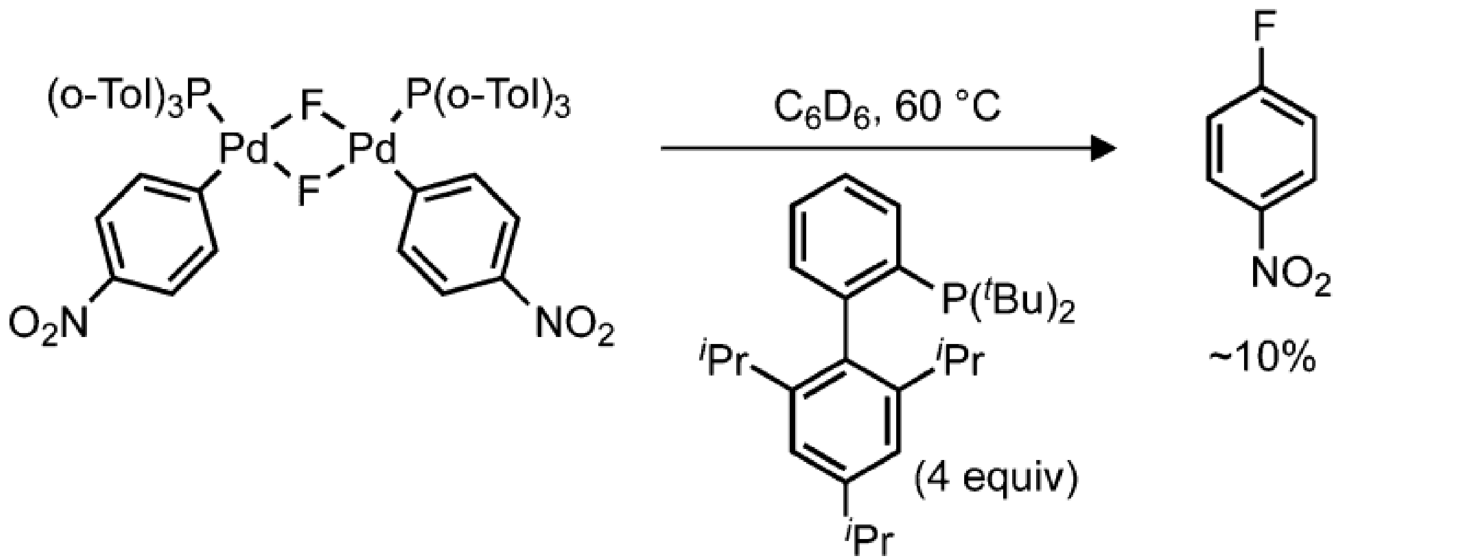


Steric repulsion with $P(t\text{-}Bu)_3$ destabilize dimer by 20 kcal/mol
However, still cannot provide over trace amount of Ar-F product

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

- *First reported aryl C–F bond formation from an arylpalladium(II) fluoride complex*



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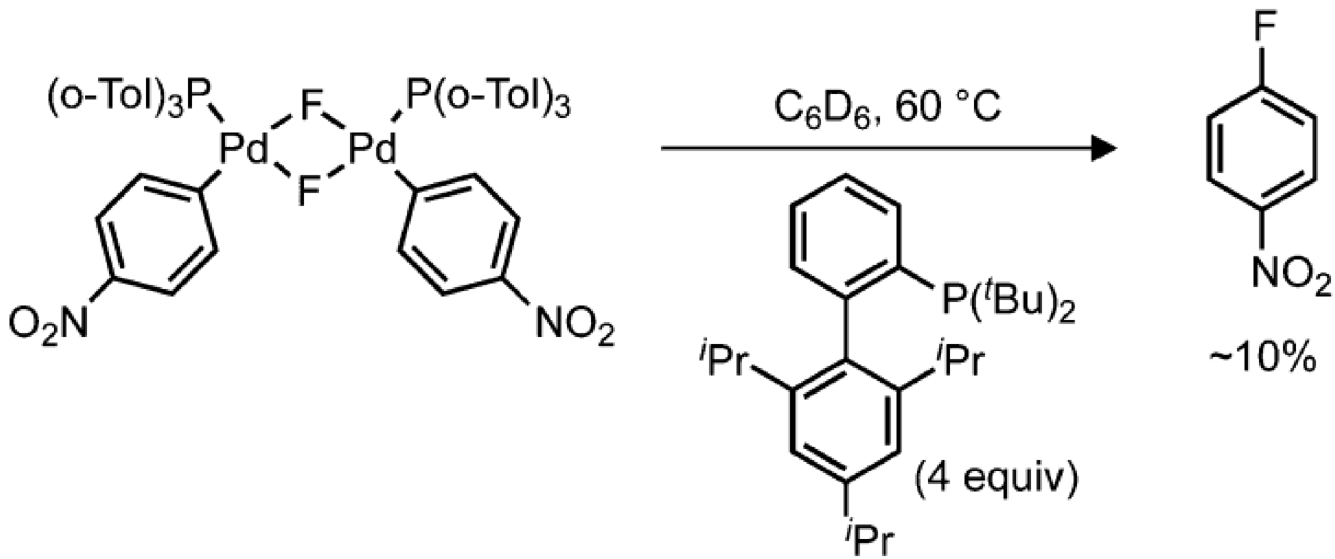
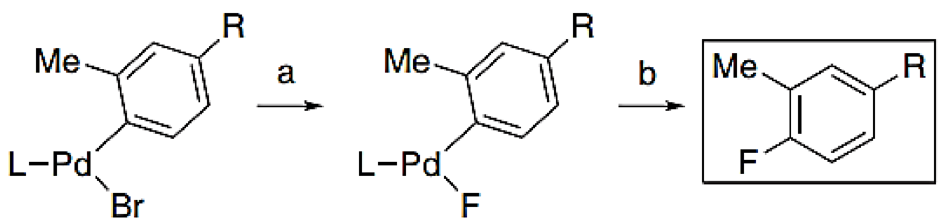


Yandulov, D. V.; Tran, N. T. *J. Am. Chem. Soc*. **2007**, *129*, 1342.

"Reductive elimination mechanism for aryl fluoride formation was not rigorously established, and an S_NAr pathway is also feasible"

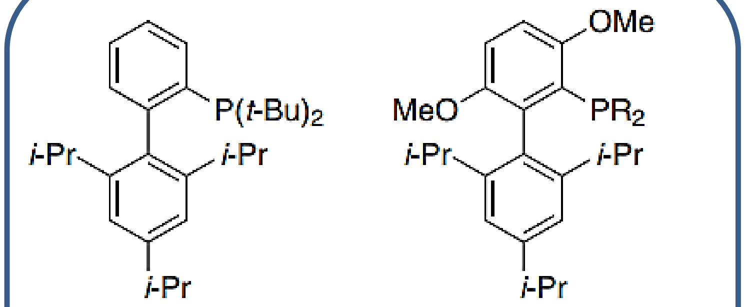
Grushin, V. V.; Marshall, W. J. *Organometallics* **2007**, *26*, 4997.

The breakthrough

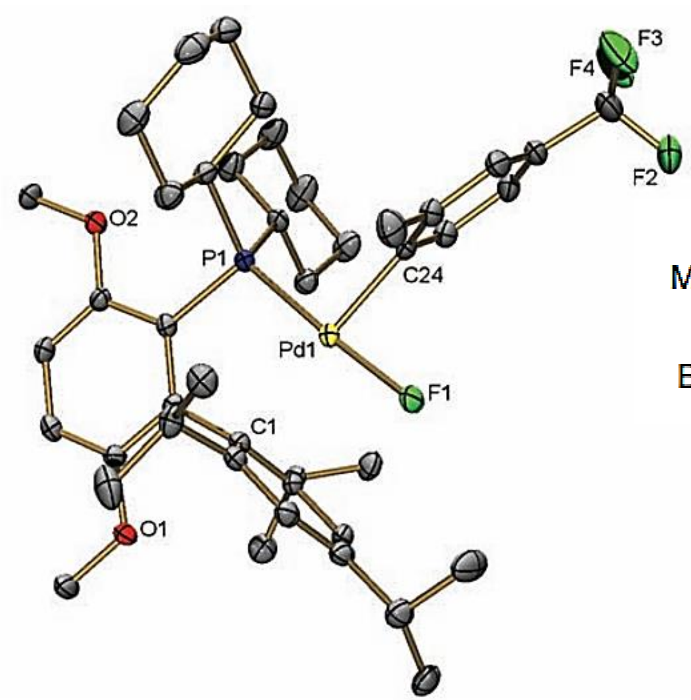


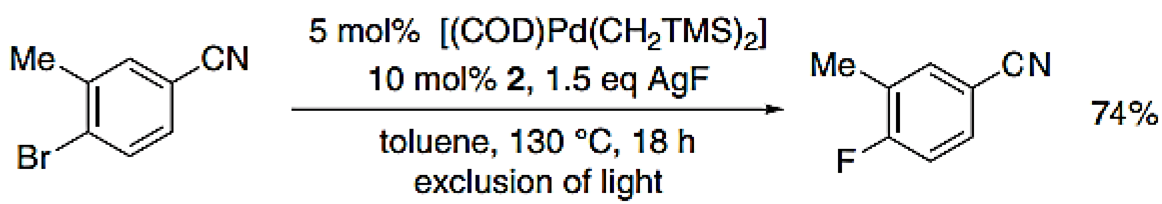
4 R = CF_3 74% **6** 15%
5 R = CN 70% **7** 25%

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.



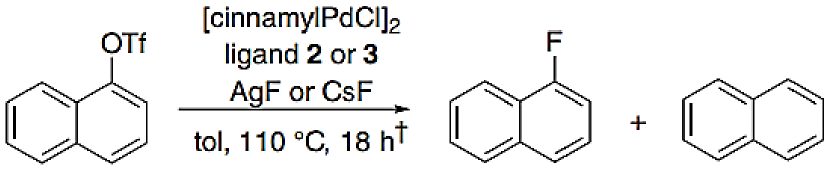
*t*BuXPhos (**1**) BrettPhos (**2**, R = Cyclohexyl)
*t*BuBrettPhos (**3**, R = *t*-Bu)





Three-coordinate T-shaped geometry

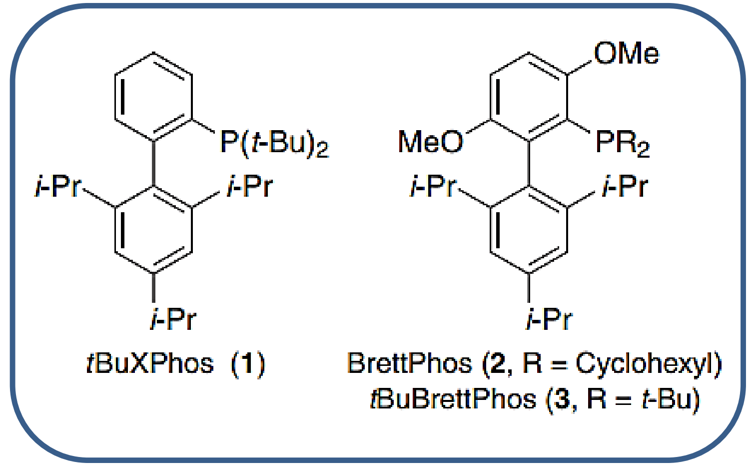
Buchwald, S. L. et al. *Science* **2009**, *325*, 1661.
Noël, T.; Maimone, T. J.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 8900.

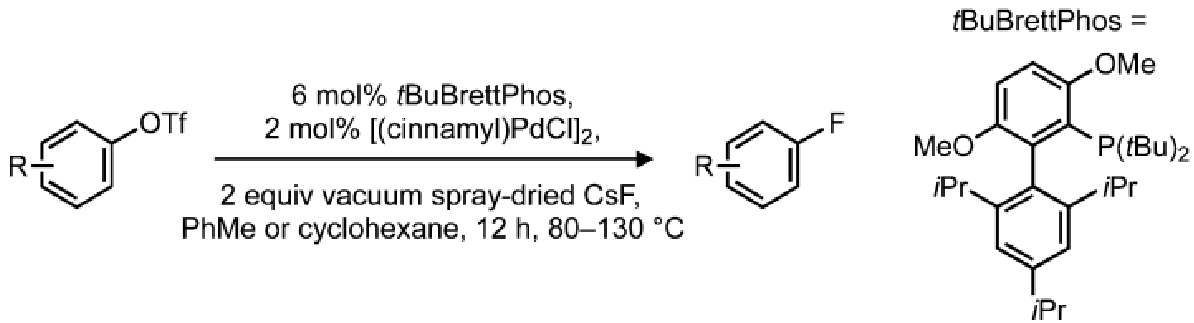


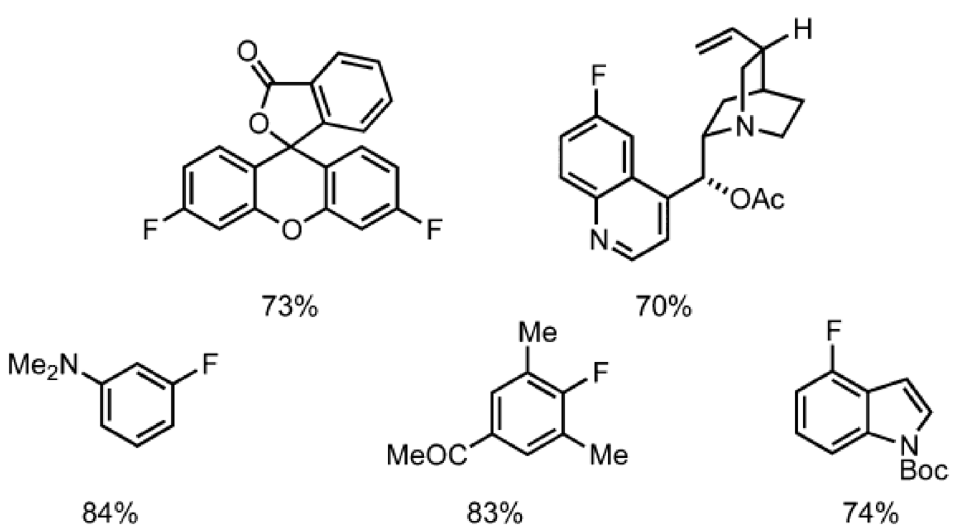
9 **10** **11**

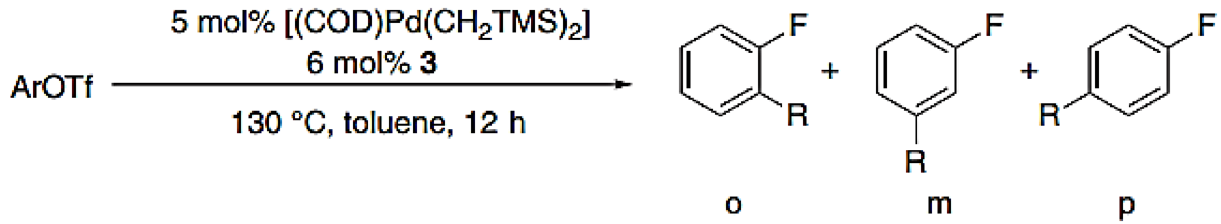
Pd (mol%)*	Ligand (mol%)	F⁻ source (eq)	Conversion	**10**	**11**
10	**2** (10)	AgF (1.5)	‡	trace	‡
10	**2** (10)	CsF (1.5)	90%	30%	5%
10	**3** (10)	CsF (1.5)	100%	71%	1%
2	**3** (3)	CsF (2.0)	100%	79%	1%

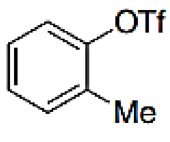
* mol% of palladium equivalents ("Pd"), † time not optimized, ‡ not determined



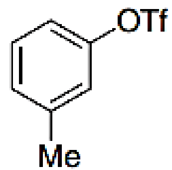




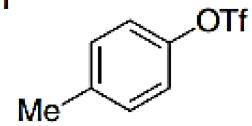




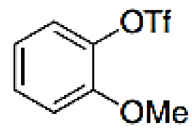
26, 42%
o/m=
>99:1*



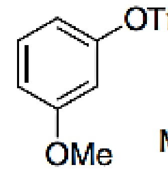
27, 63%
o/m/p=
0:95:5†



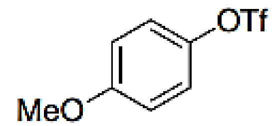
28, 48%
m/p=
36:64†



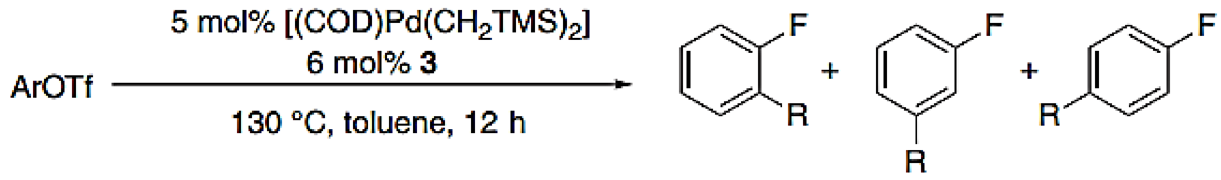
29, 49%
o/m=
98:2*



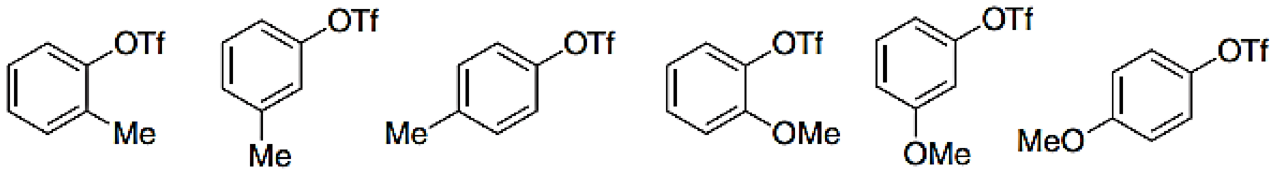
30, 65%
m/p=
98:2*



31, 25%
m/p=
70:30*



o m p



26, 42% o/m= >99:1*

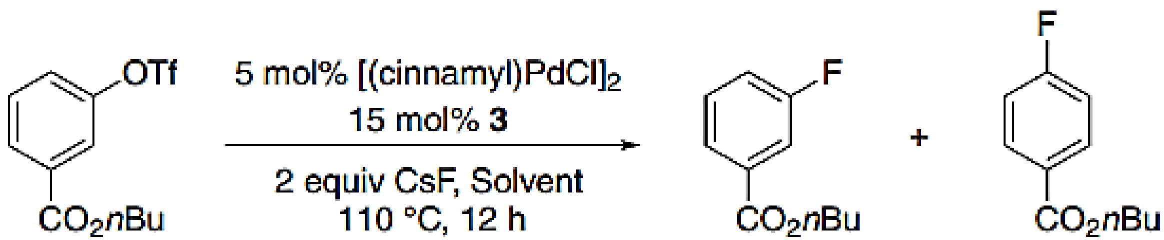
27, 63% o/m/p= 0:95:5†

28, 48% m/p= 36:64†

29, 49% o/m= 98:2*

30, 65% m/p= 98:2*

31, 25% m/p= 70:30*

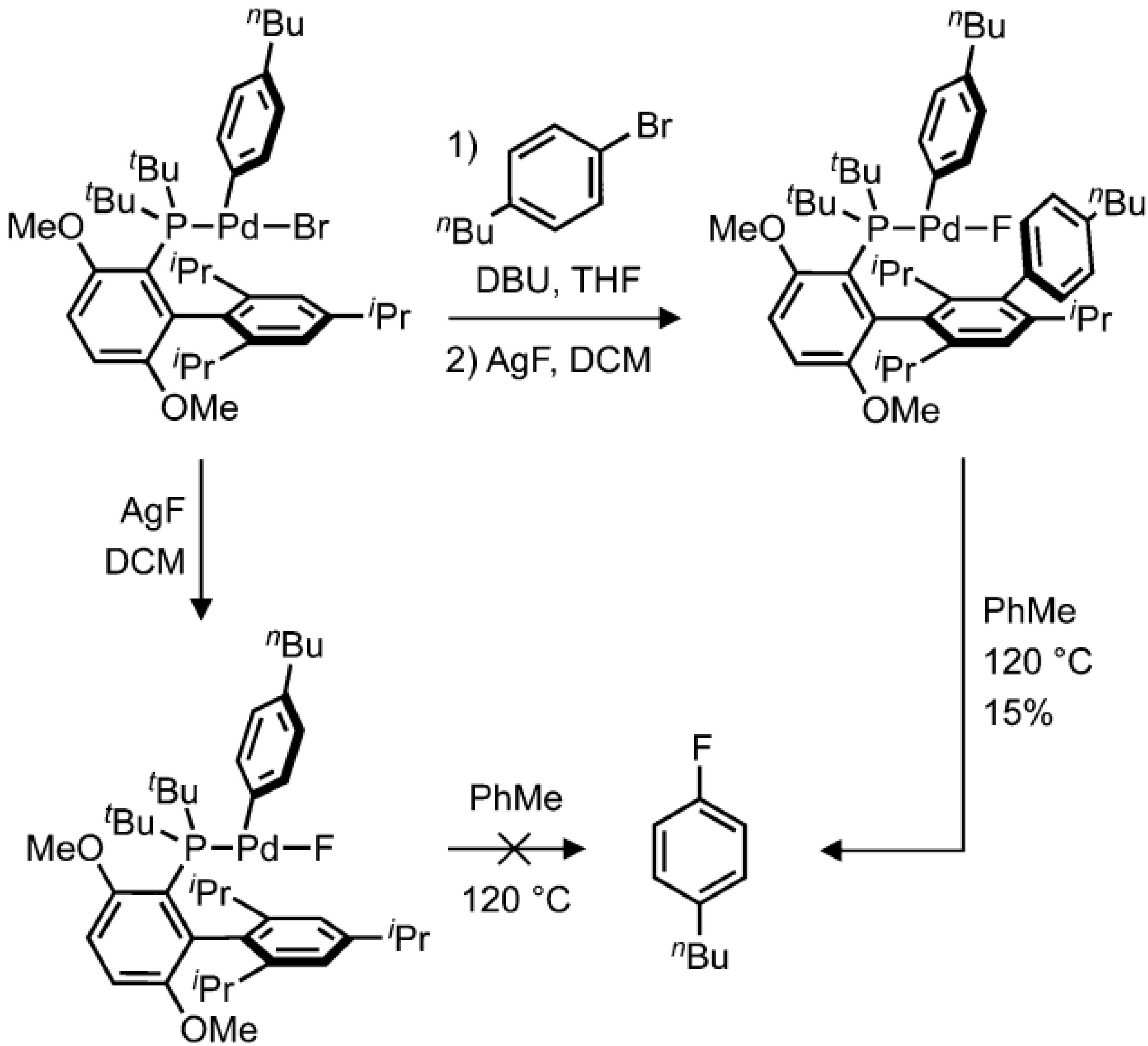


32 **33** **14**

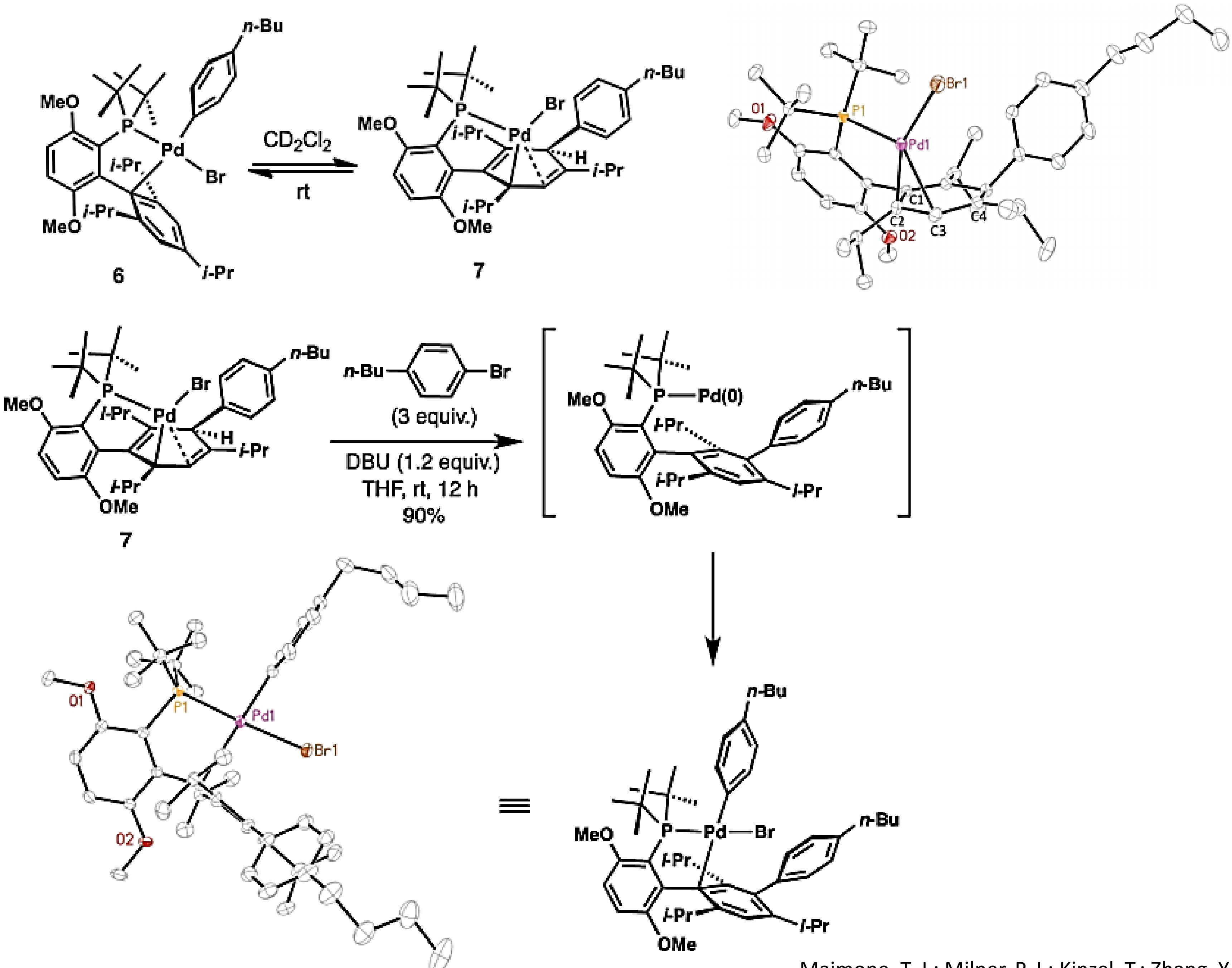
Solvent	conversion	combined yield	ratio **33/14**	ArH
Toluene	100	71%	78:22	2%
Benzene	100	69%	90:10	*
THF	95	18%	78:22	*
Cyclohexane	100	60%	>98:2	1%
n-Heptane	100	39%	85:15	*
Cyclohexane†	100	80%	99:1	1%

* Yield not determined. † Optimized condition 100 °C, isolated yield.

- *ligand modification in 2011*



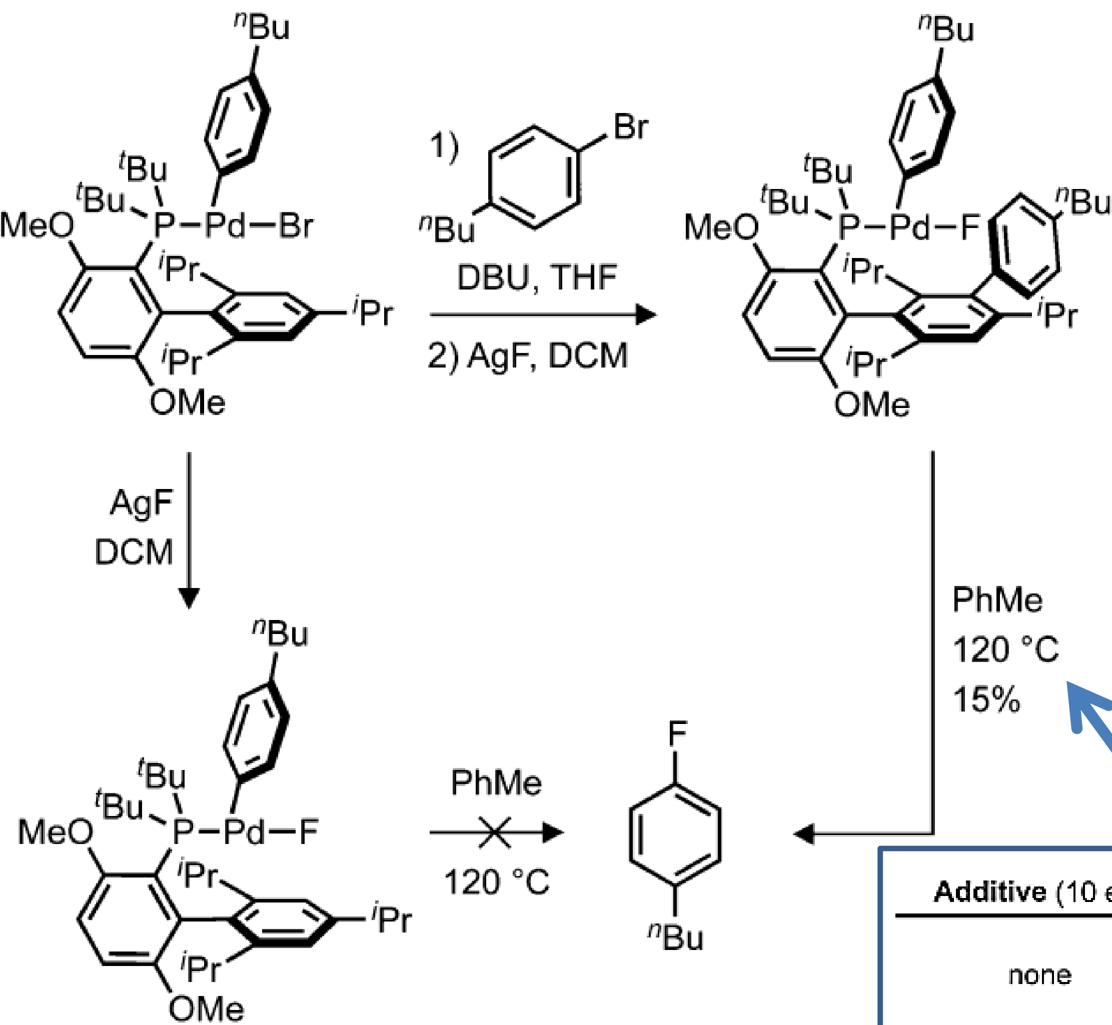
Maimone, T. J.; Milner, P. J.; Kinzel, T.; Zhang, Y.; Takase, M. K.; Buchwald, S. L. *J. Am. Chem. Soc.* **2011**, *133*, 18106.

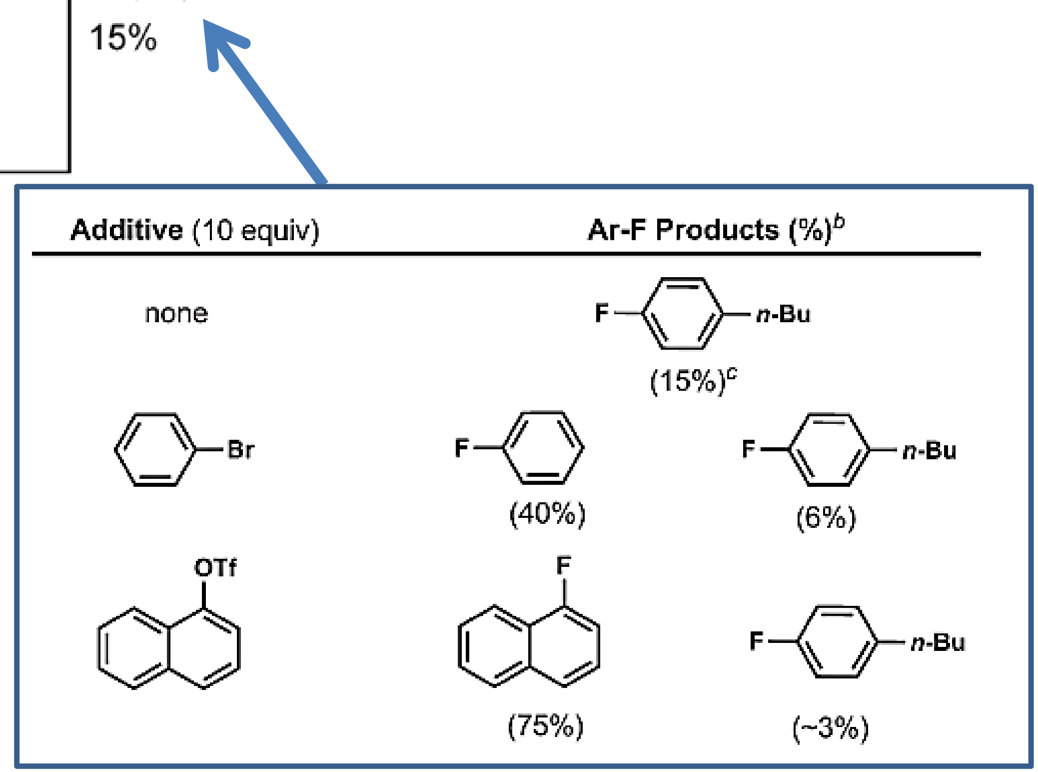


8 (X-ray)

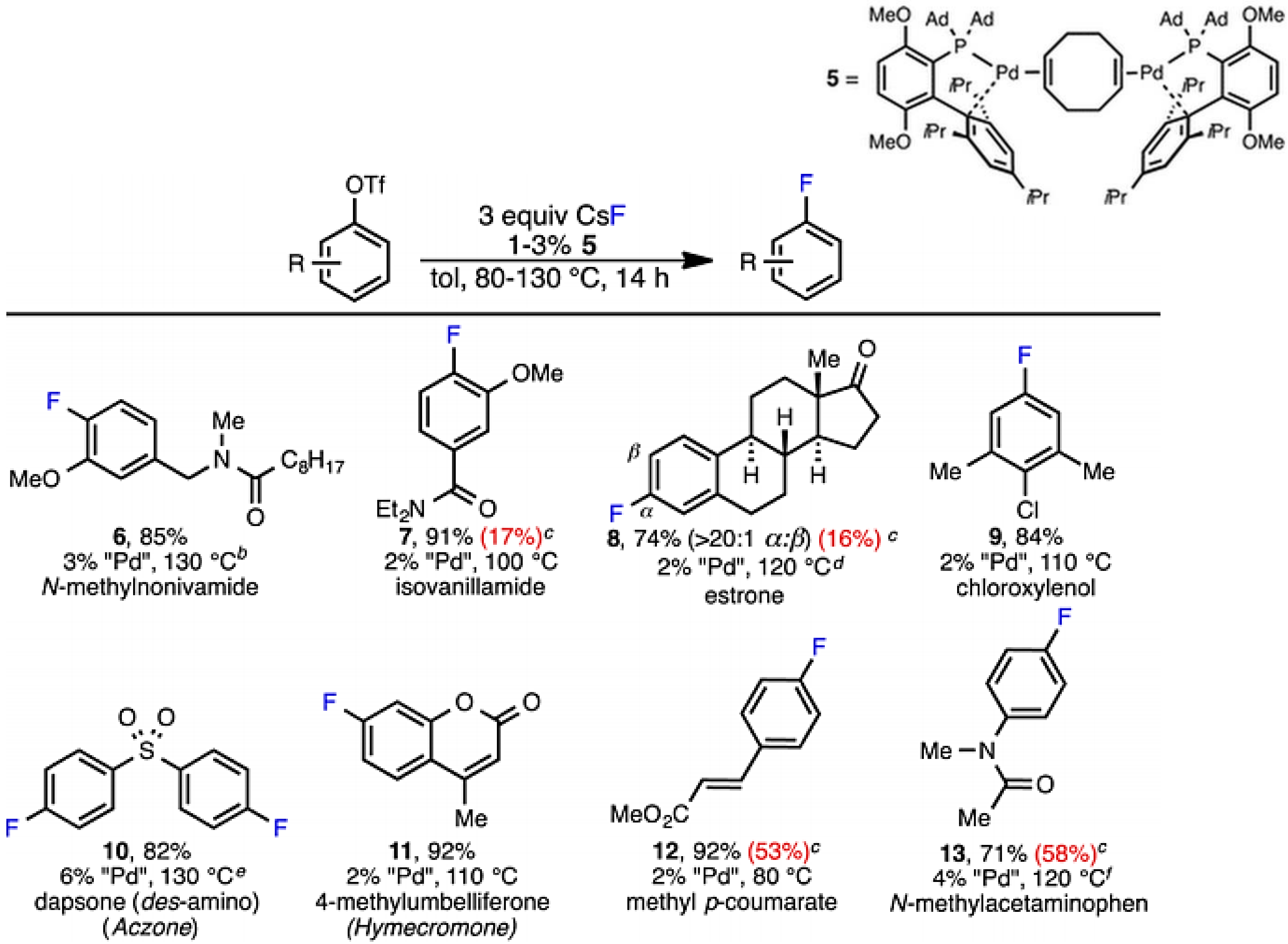
8

Maimone, T. J.; Milner, P. J.; Kinzel, T.; Zhang, Y.; Takase, M. K.; Buchwald, S. L. *J. Am. Chem. Soc.* **2011**, *133*, 18106.

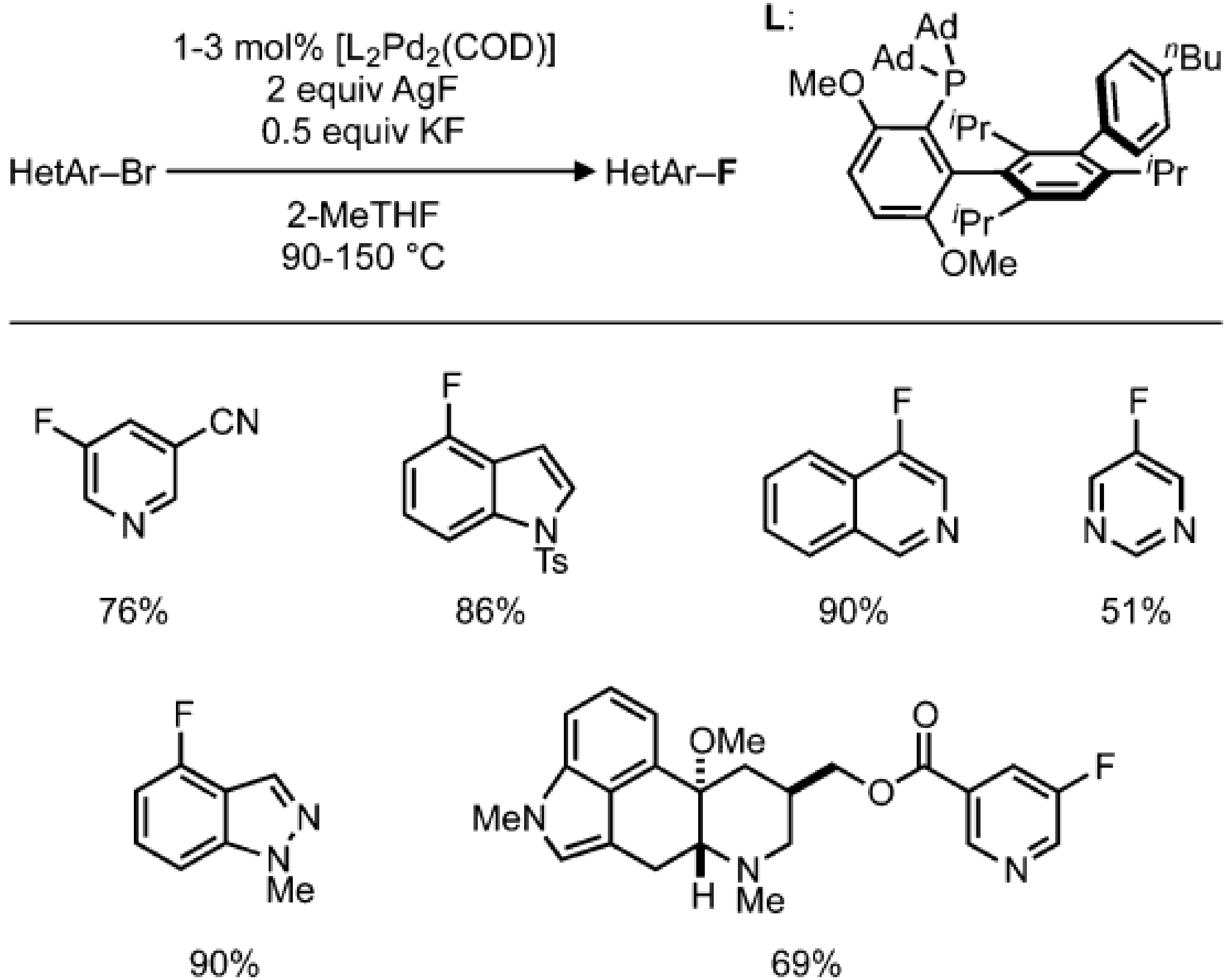




Maimone, T. J.; Milner, P. J.; Kinzel, T.; Zhang, Y.; Takase, M. K.; Buchwald, S. L. *J. Am. Chem. Soc.* **2011**, *133*, 18106.

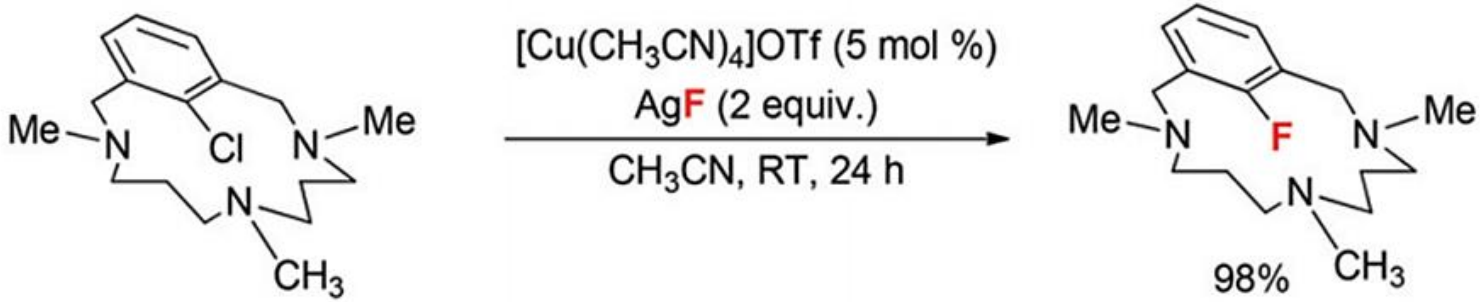


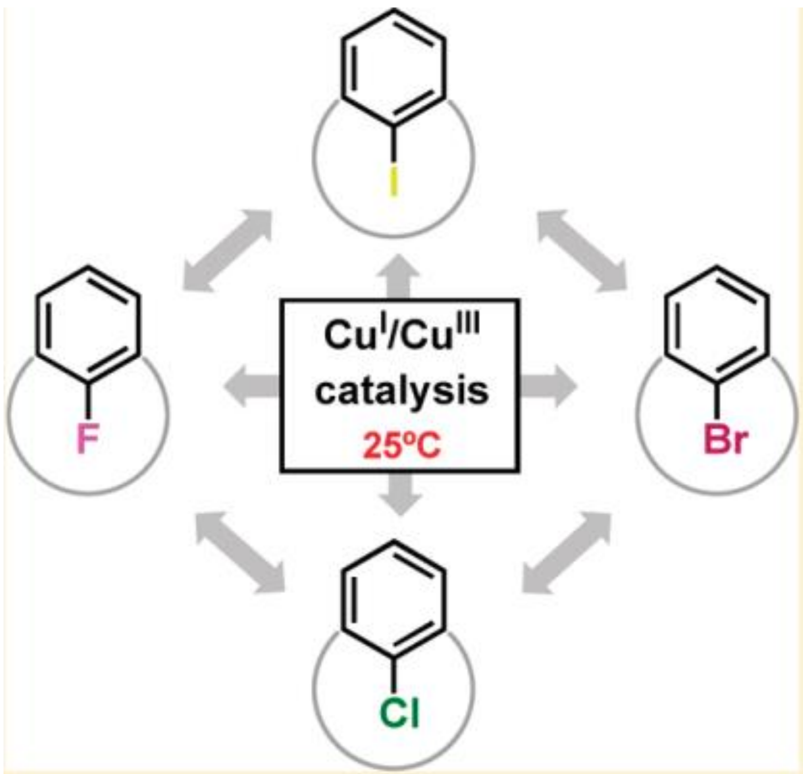
Lee, H. G.; Milner, P. J.; Buchwald, S. L. *Org. Lett*. **2013**, *15*, 5602.

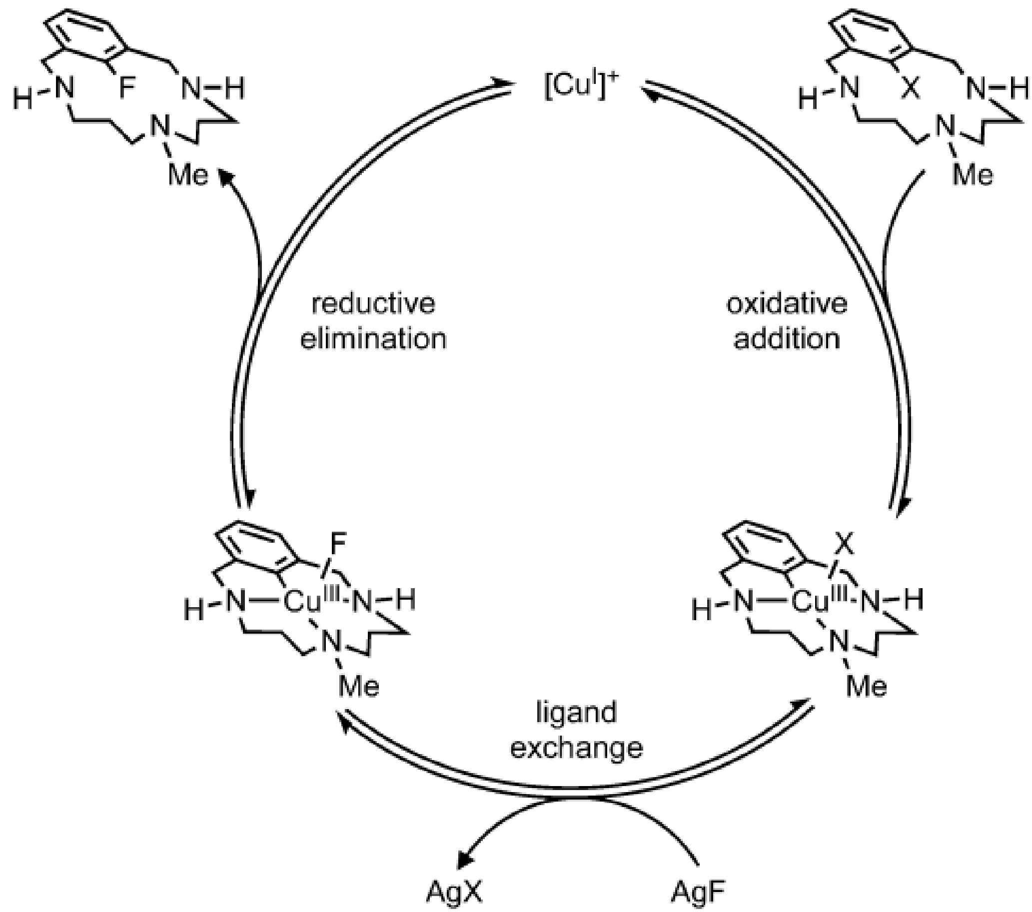


Lee, H. G.; Milner, P. J.; Buchwald, S. L. *J. Am. Chem. Soc*. **2014**, *136*, 3792.

■ *First Cu-catalyzed nucleophilic C-F bond formation*

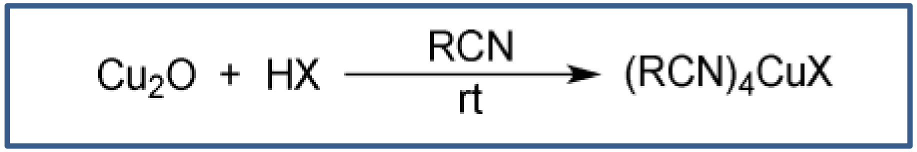


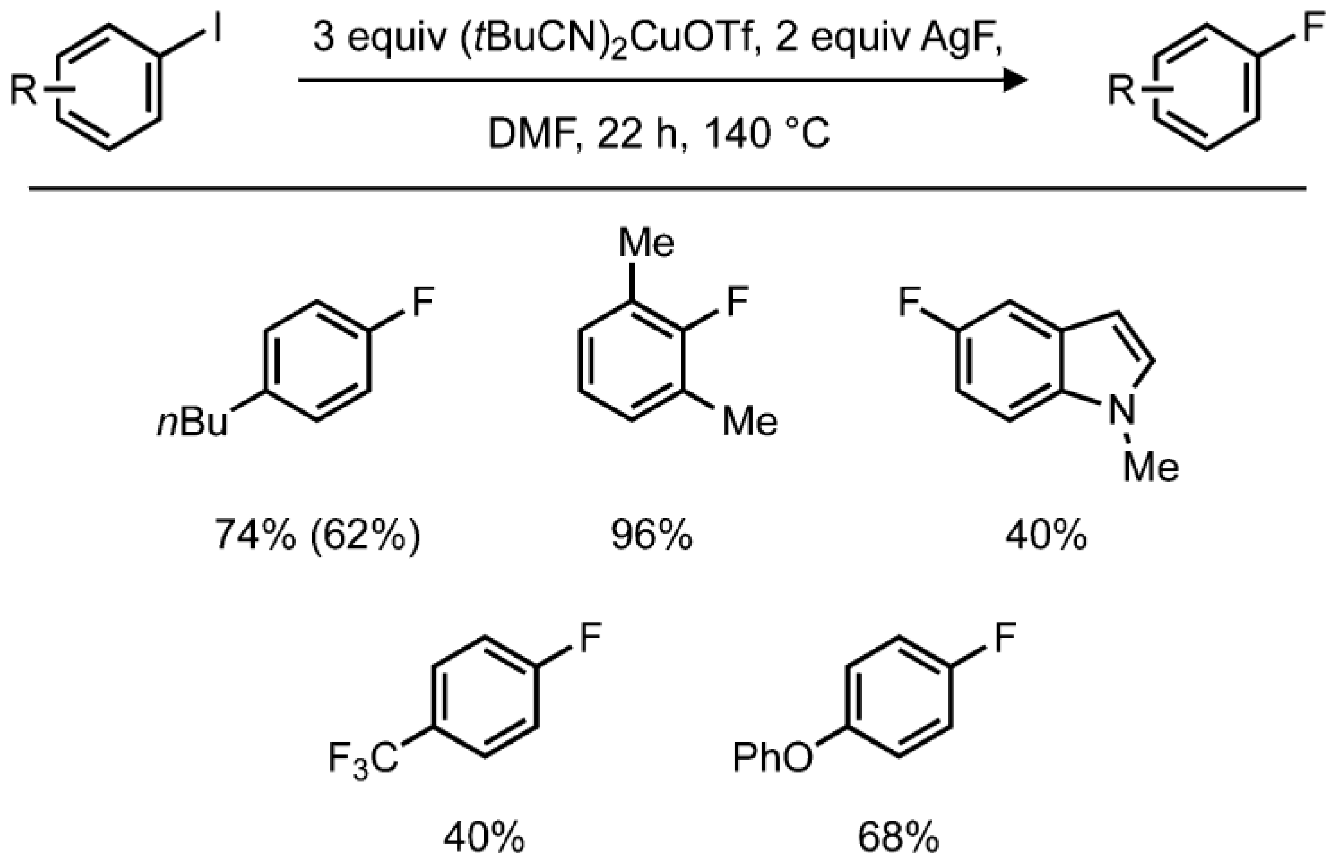




Casitas, A.; Canta, M.; Solà, M.; Costas, M.; Ribas, X. *J. Am. Chem. Soc*. **2011**, *133*, 19386.

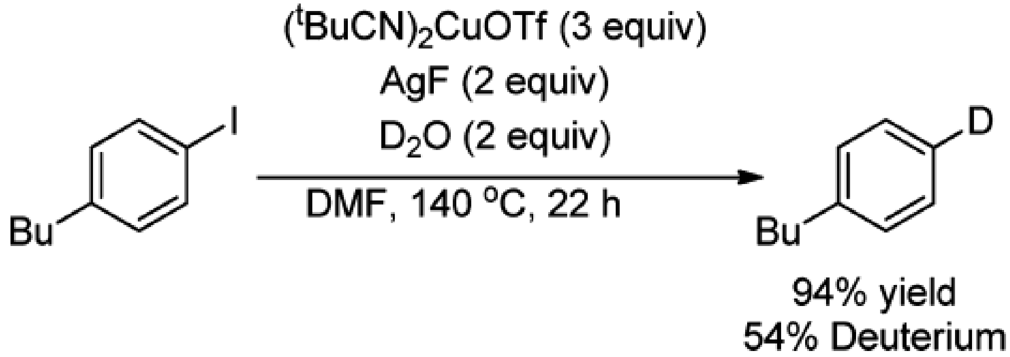
■ *more general copper-mediated fluorination*

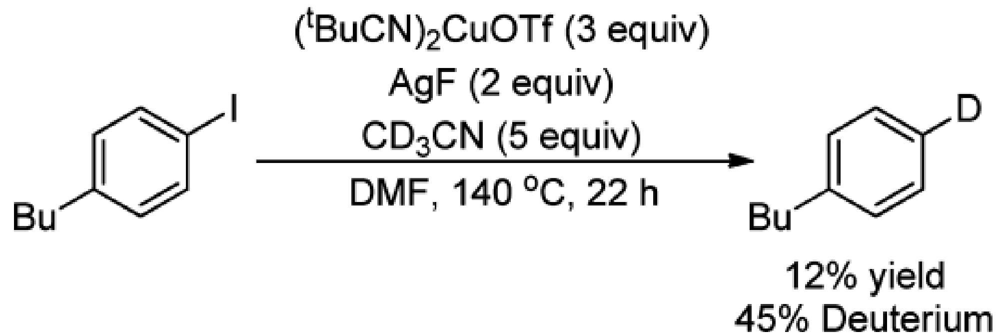




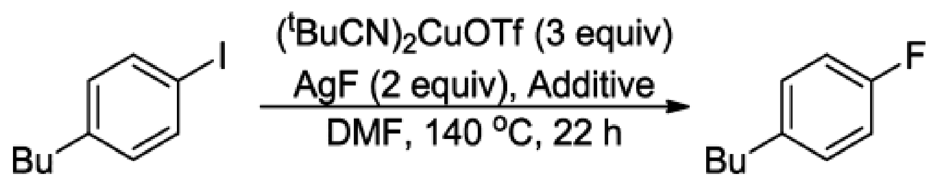
Fier, P. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2012**, *134*, 10795.

- *Sensitive to proton source*



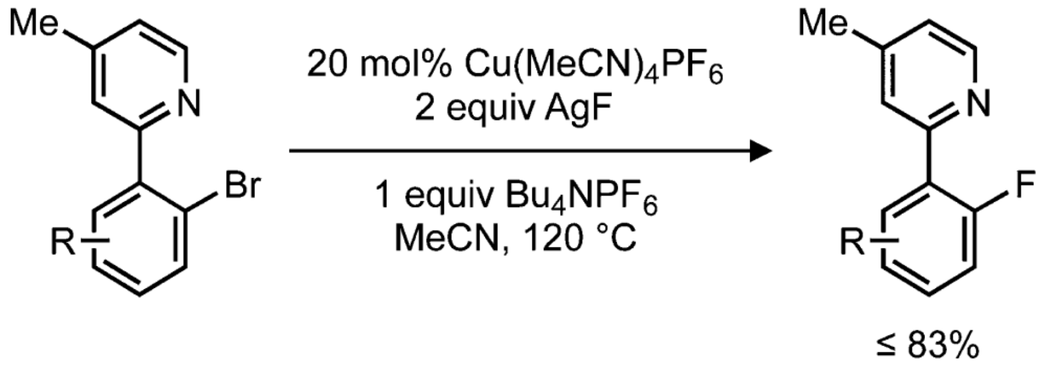


- *Too much AgF is bad. Why?*

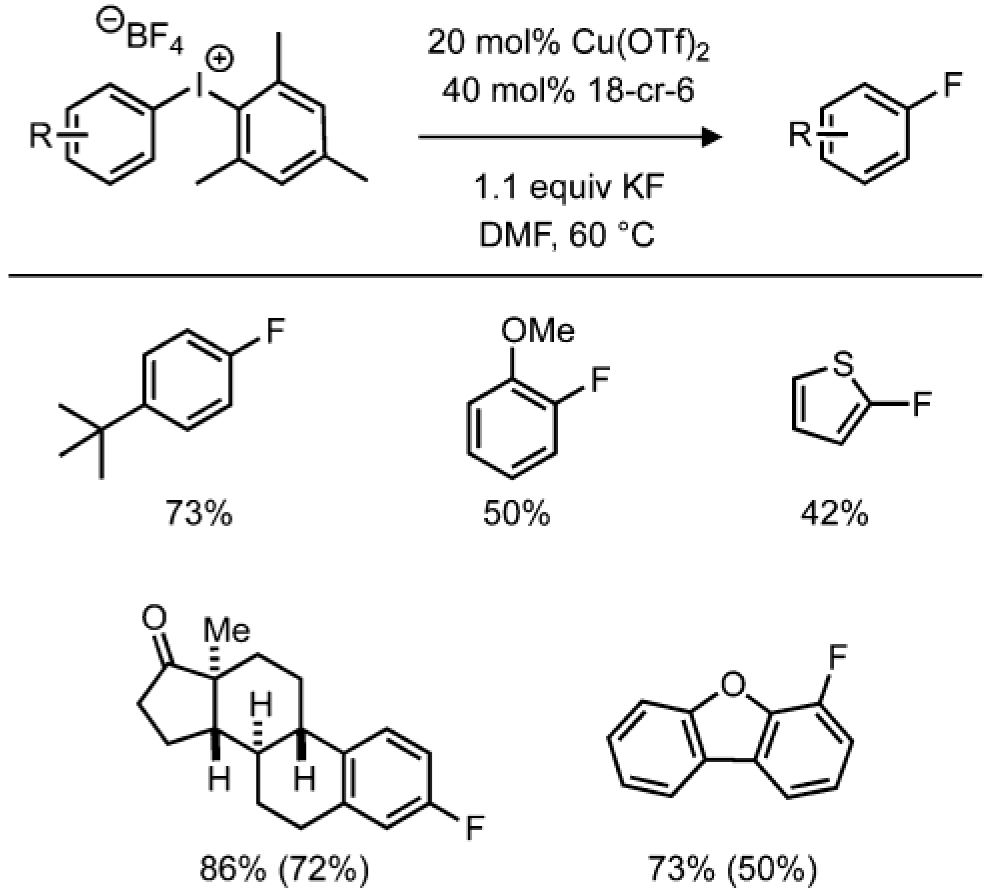


entry	additive	ArF (%)	ArH (%)	conversion (%)
1	AgOTf (1 equiv)	18	13	60
2	AgOTf (2 equiv)	5	22	51
3	CsF (1 equiv)	71	23	100

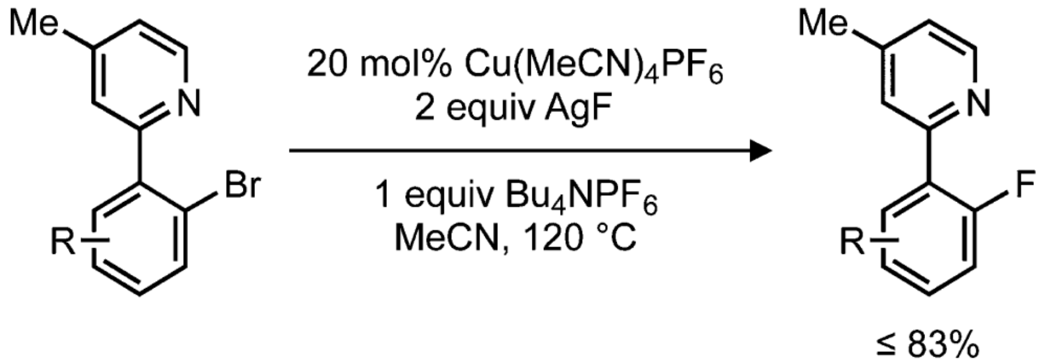
Fier, P. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2012**, *134*, 10795.



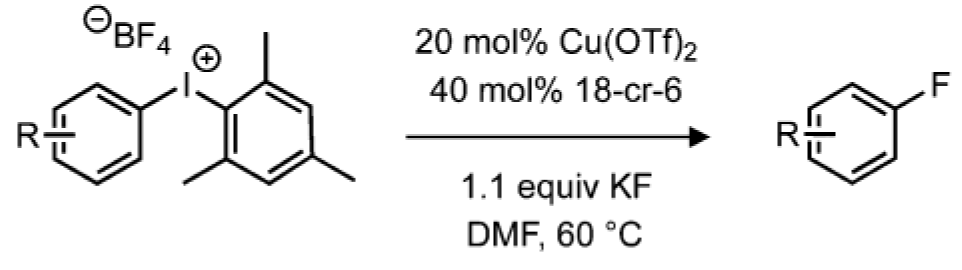
Mu, X.; Zhang, H.; Chen, P.; Liu, G. *Chem. Sci*. **2014**, *5*, 275.

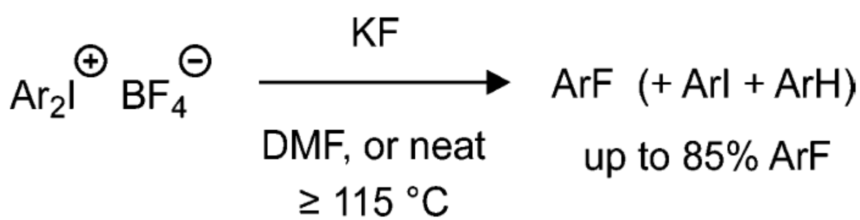


Ichiishi, N.; Canty, A. J.; Yates, B. F.; Sanford, M. S. *Org. Lett*. **2013**, *15*, 5134.

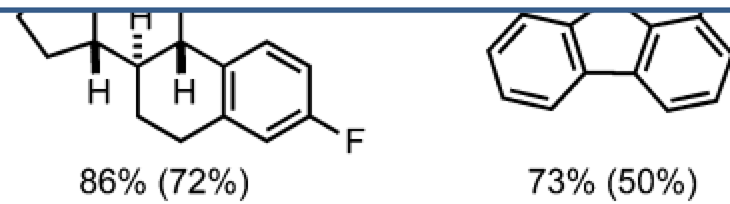


Mu, X.; Zhang, H.; Chen, P.; Liu, G. *Chem. Sci*. **2014**, *5*, 275.





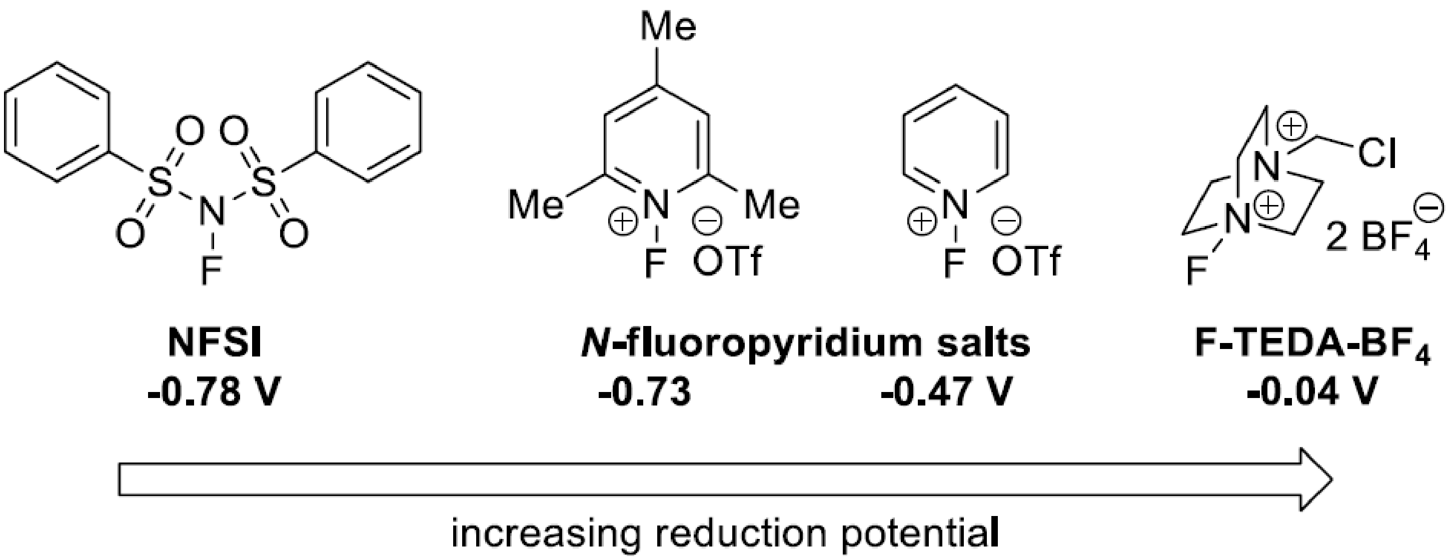
Van Der Puy, M. *J. Fluorine Chem*. **1982**, *21*, 385.



Ichiishi, N.; Canty, A. J.; Yates, B. F.; Sanford, M. S. *Org. Lett*. **2013**, *15*, 5134.

Electrophilic C(sp^2)-Fluorination *From C–M to C–F*

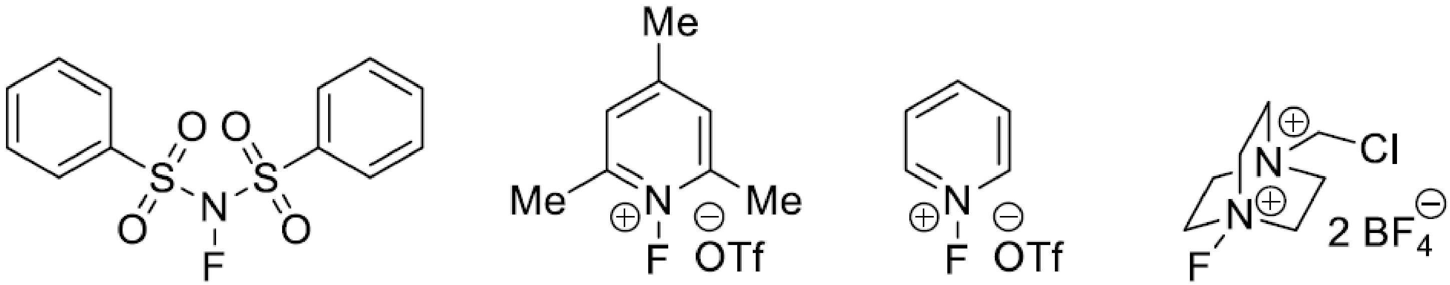
- *Comparison of the redox potential of bench-top stable fluorinating reagents (versus SCE)*



P. T. Nyffeler, S. G. Duron, M. D. Burkart, S. P. Vincent, C. H. Wong, *Angew. Chem. Int. Ed.* **2005**, *44*, 192-212;
G. S. Lal, G. P. Pez, R. G. Syvret, *Chem. Rev.* **1996**, *96*, 1737-1755.

For arylmetal nucleophiles react with ***F_2****,* ***XeF_2*** *or* ***F-OSO_3R*** *, see:*

Diorazio, L. J.; Widdowson, D. A.; Clough, J. M. *Tetrahedron* **1992**, *48*, 8073.
Cazorla, C.; Métay, E.; Andrioletti, B.; Lemaire, M. *Tetrahedron Lett*. **2009**, *50*, 3936.
Vints, I.; Gatenyo, J.; Rozen, S. *J. Org. Chem*. **2013**, *78*, 11794.



NFSI | ***N*-fluoropyridium salts** | | **F-TEDA-BF$_4$**
-0.78 V | **-0.73** | **-0.47 V** | **-0.04 V**

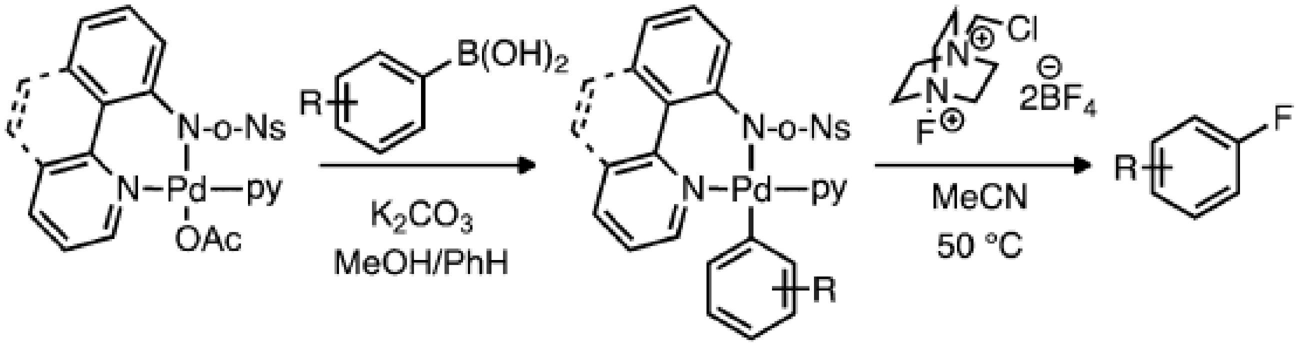
increasing reduction potential

Formally: as source of fluoronium cation ("F+")
Actually: the N–F bonds are polarized toward fluorine, with a partial negative charge on fluorine.

S_N2 displacement?
*the σ*N–F orbitals are sterically inaccessible on **N***
*the σ*N–F orbitals are too small on **F***

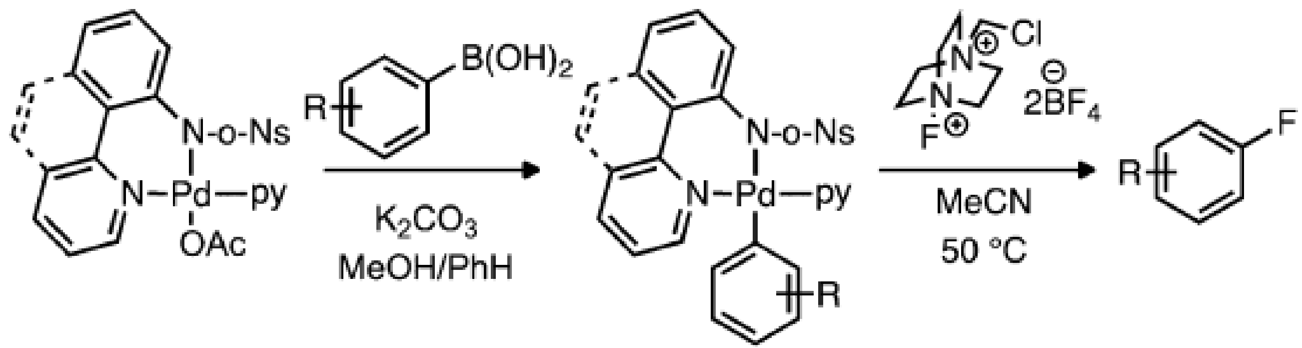
two-electron oxidation
single-electron transfer

C–F Reductive Elimination from Pd(IV).

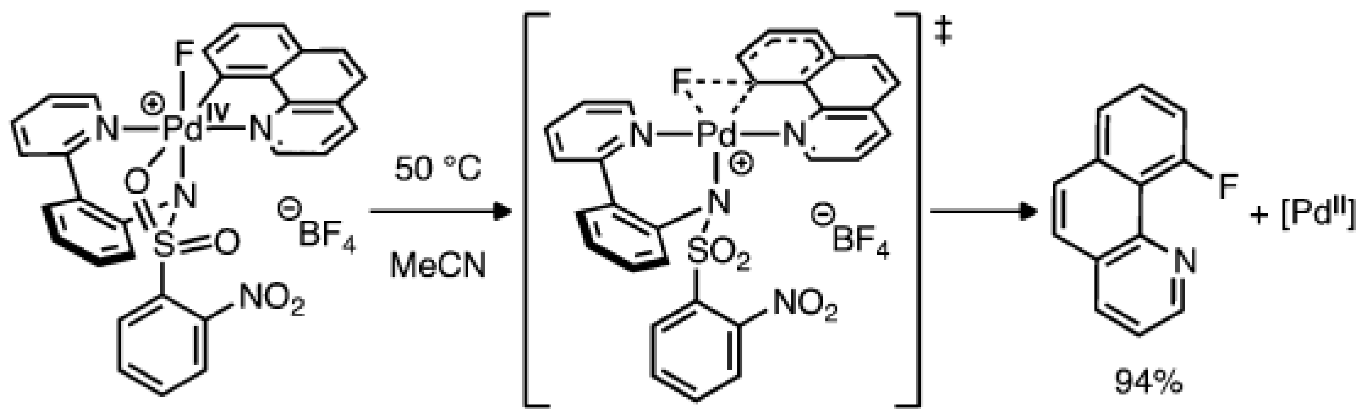


Furuya, T.; Kaiser, H. M.; Ritter, T. *Angew. Chem., Int. Ed*. **2008**, *47*, 5993.

C–F Reductive Elimination from Pd(IV).



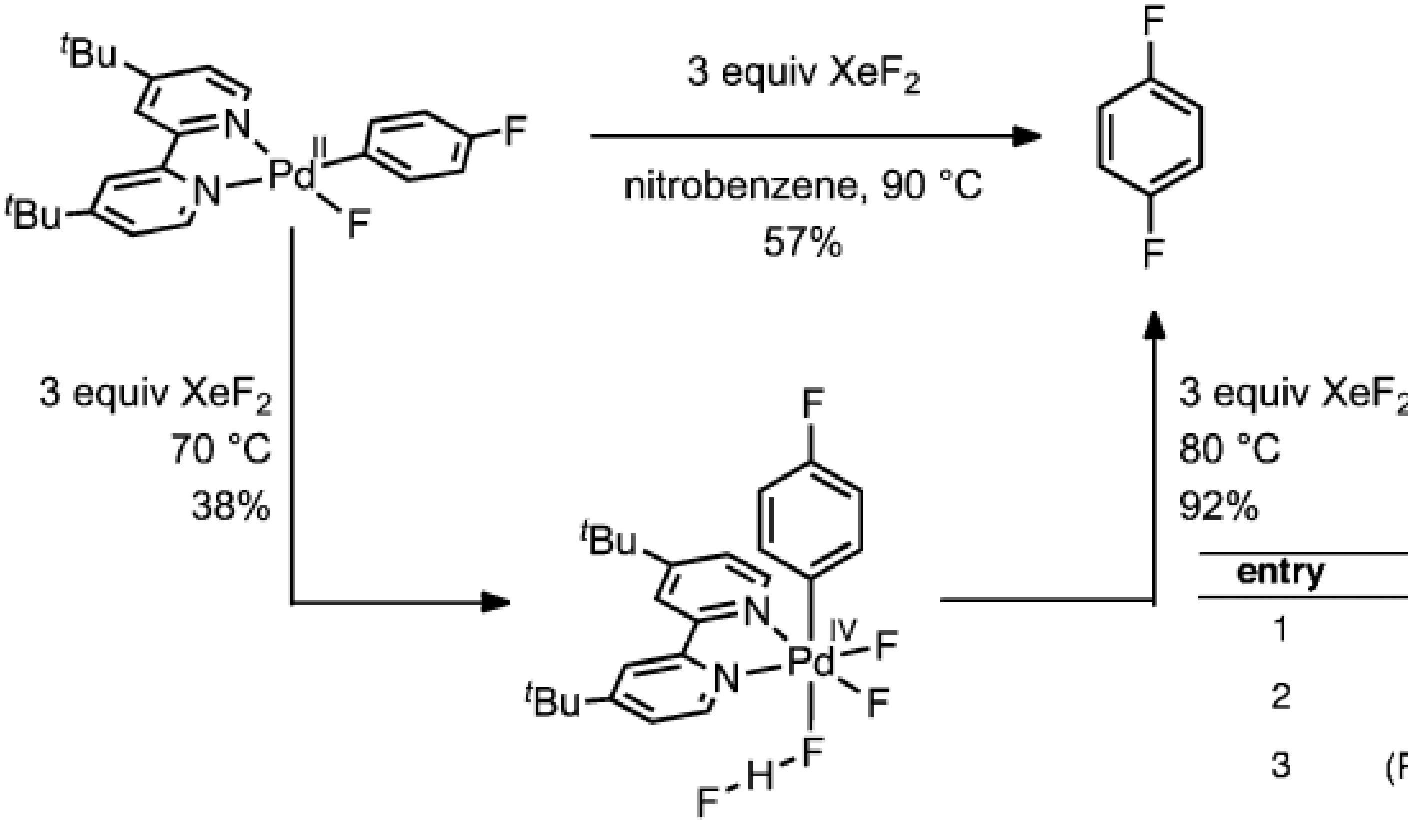
Furuya, T.; Kaiser, H. M.; Ritter, T. *Angew. Chem., Int. Ed*. **2008**, *47*, 5993.

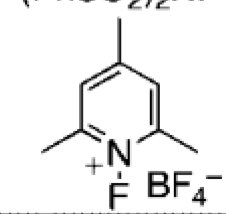


- *Dissociation of one oxygen ligand*

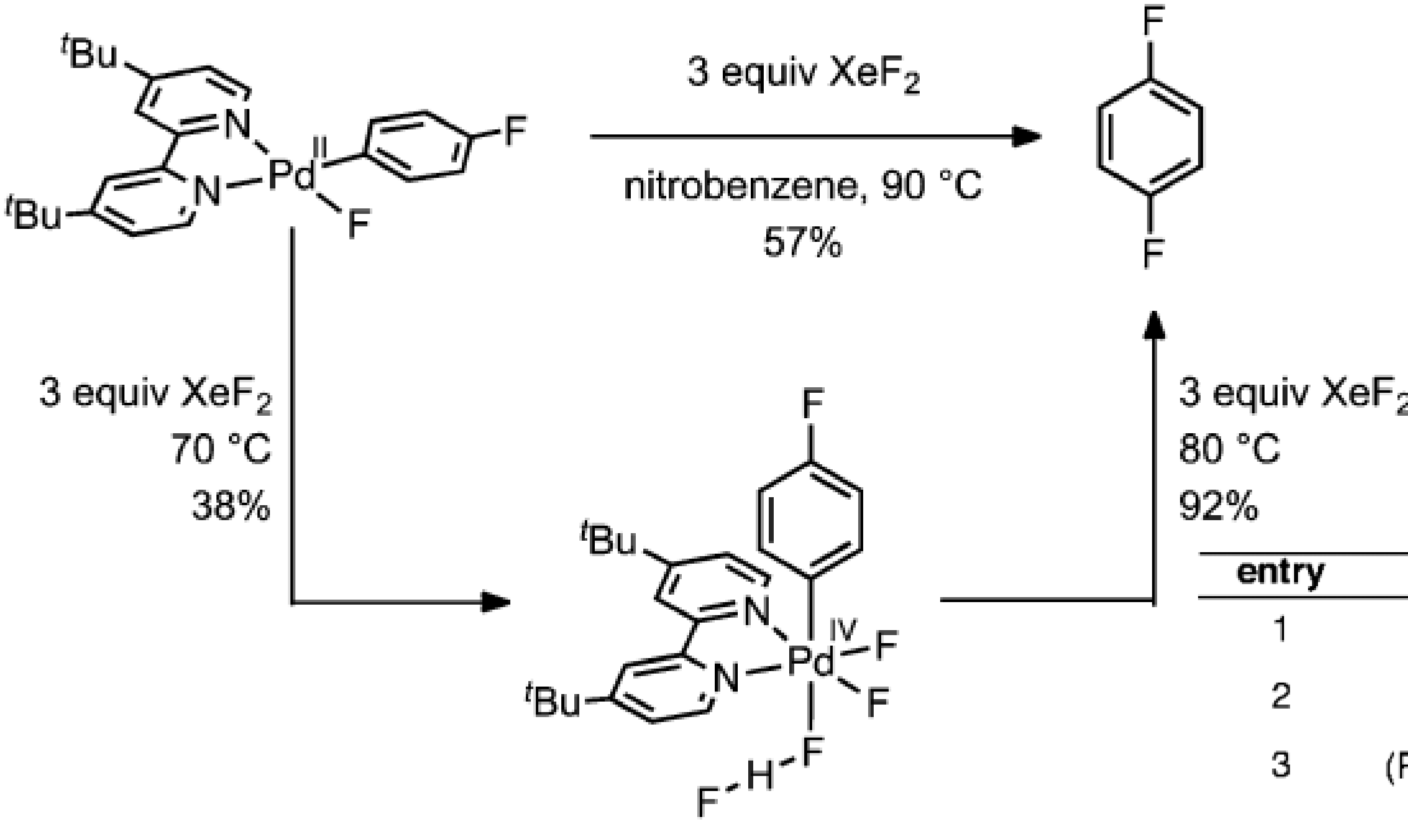
- *five-coordinate Pd(IV) cationic complex*
- *concerted reductive elimination*

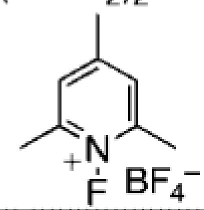
Furuya, T.; Ritter, T. *J. Am. Chem. Soc*. **2008**, *130*, 10060.
Ritter, T. et al *J. Am. Chem. Soc*. **2010**, *132*, 3793



entry	"F+"	3a
1	none	trace
2	XeF_2	92%
3	$(PhSO_2)_2NF$	83%
4		50%

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

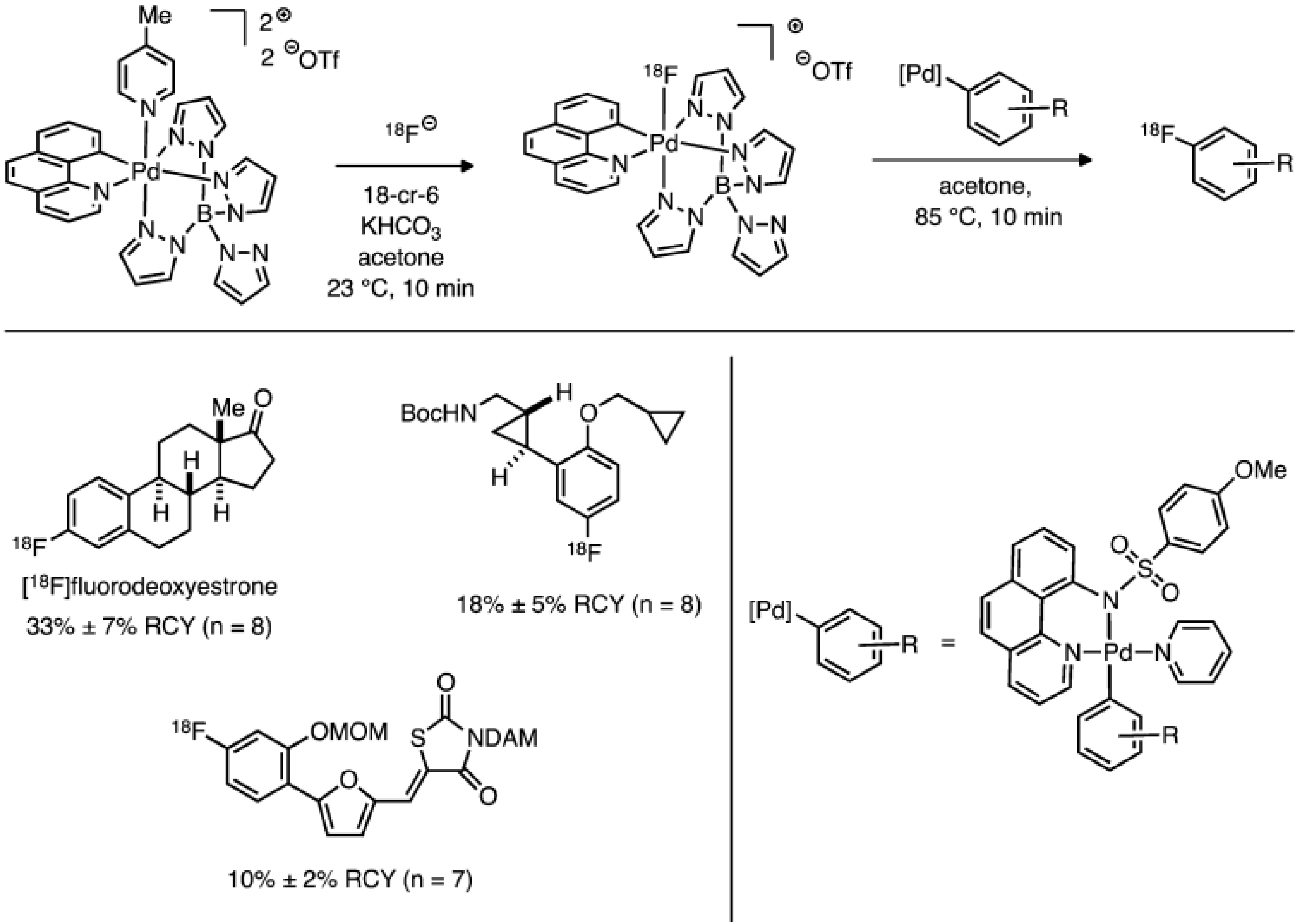


entry	"F+"	3a
1	none	trace
2	XeF_2	92%
3	$(PhSO_2)_2NF$	83%
4		50%

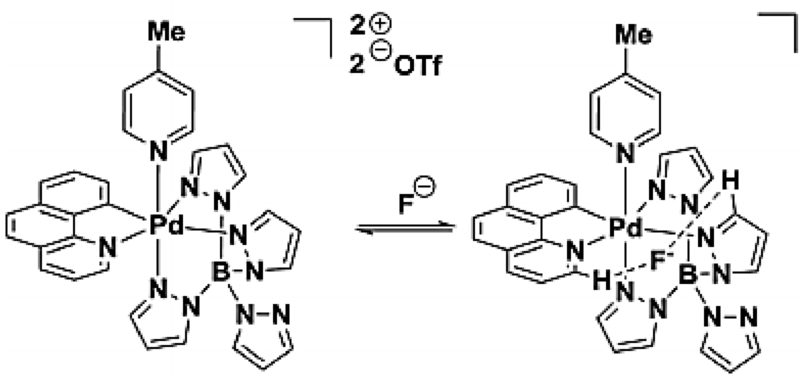
"NBS also reacted to afford 3a in >95% yield, suggesting that the oxidant does not serve as the source of fluorine." ***--Sanford--***

"the mechanism of C−F bond formation in this case is unclear, and both electrophilic C−Pd bond cleavage and C−F reductive elimination are feasible."
--Ritter--

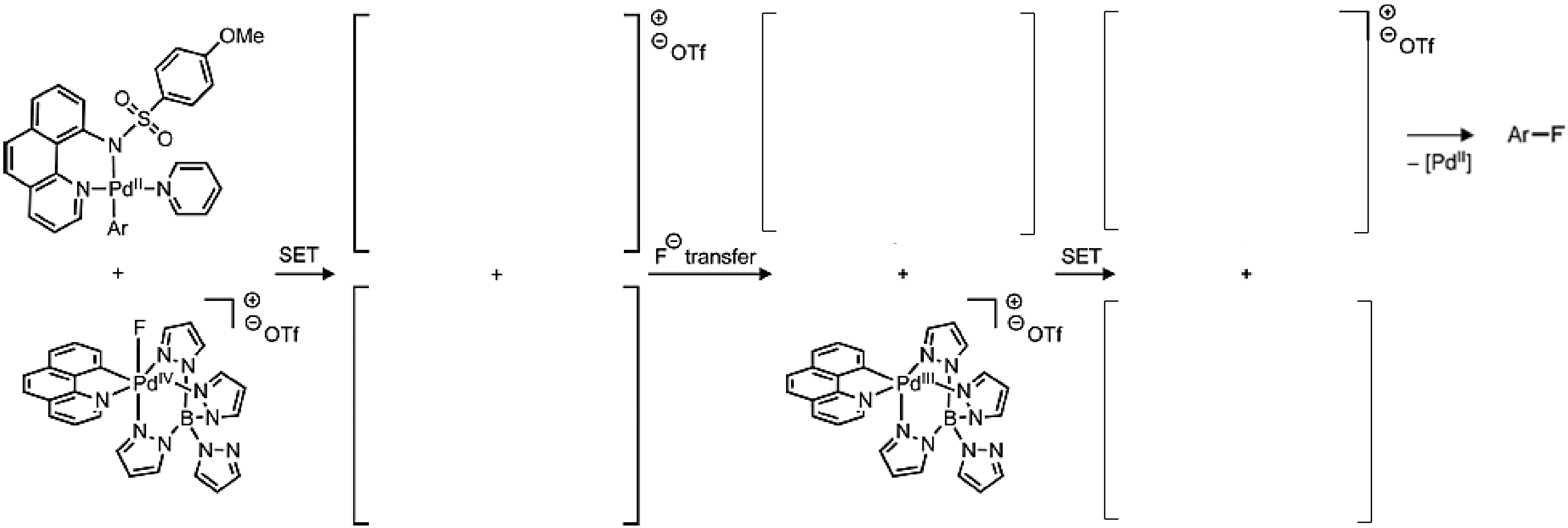
Ball, N. D.; Sanford, M. S. *J. Am. Chem. Soc*. **2009**, *131*, 3796.



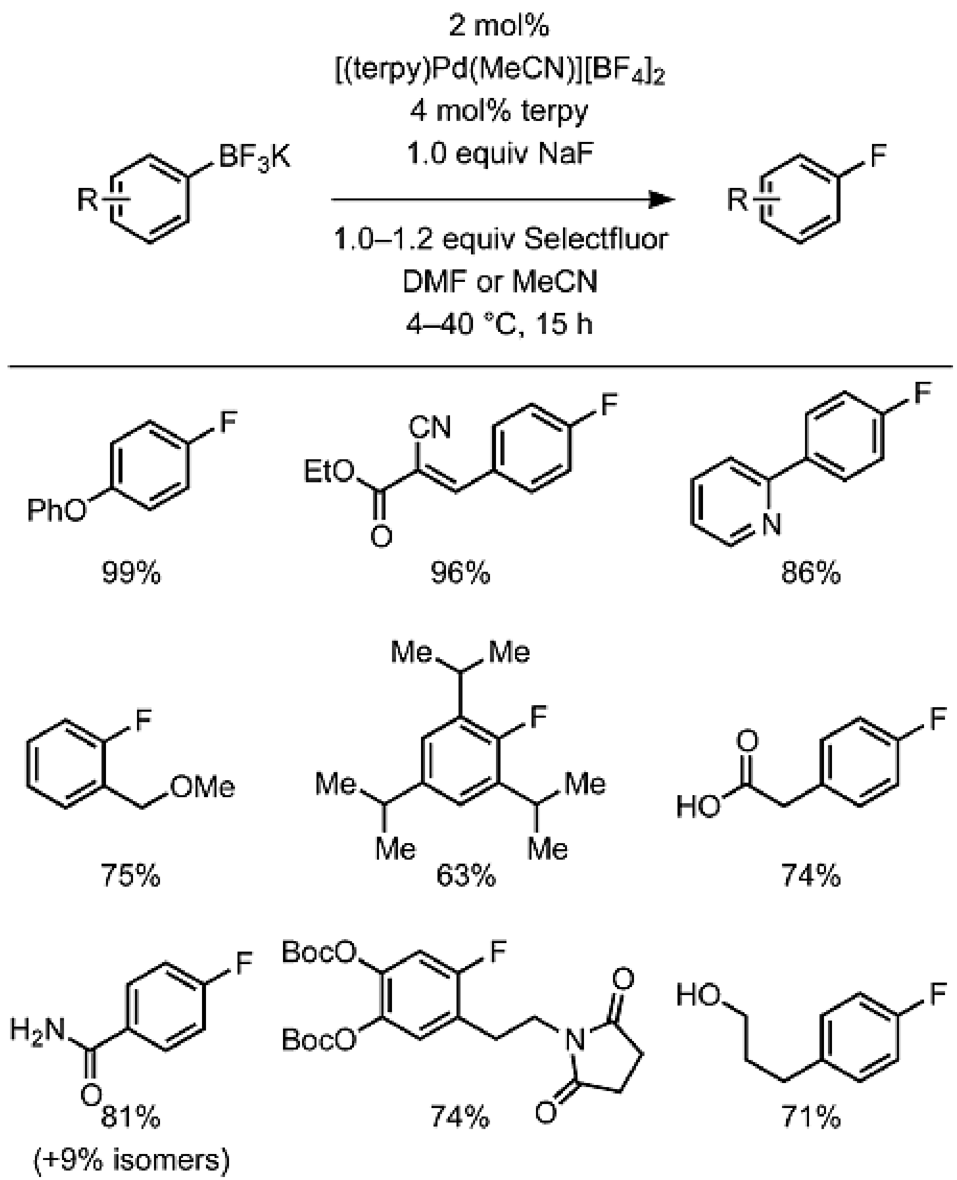
Lee, E.; Kamlet, A. S.; Powers, D. C.; Neumann, C. N.; Boursalian, G. B.; Furuya, T.; Choi, D. C.; Hooker, J. M.; Ritter, T. *Science* **2011**, *334*, 639.



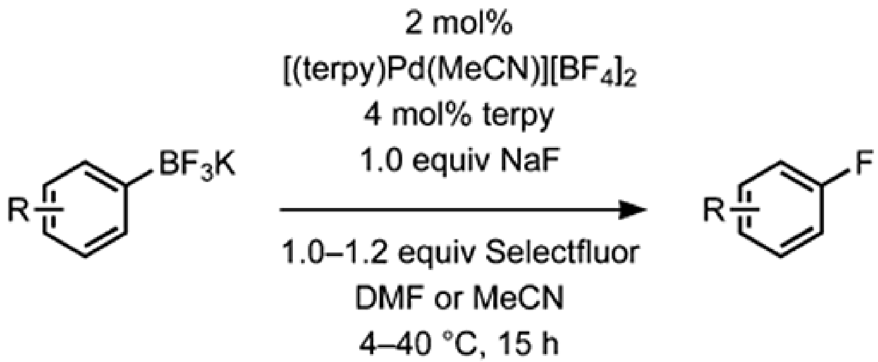
- *super electron-deficient Pd(IV)*
- *very quick transmetallation with F^- (even at 10^{-4} M concentratio*



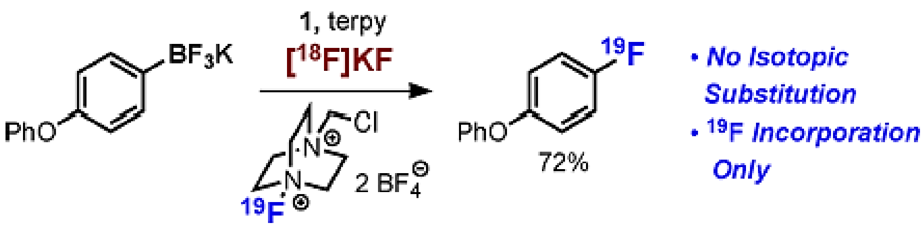
Lee, E.; Kamlet, A. S.; Powers, D. C.; Neumann, C. N.; Boursalian, G. B.; Furuya, T.; Choi, D. C.; Hooker, J. M.; Ritter, T. *Science* **2011**, *334*, 639.
Brandt, J. R.; Lee, E.; Boursalian, G. B.; Ritter, T. *Chem. Sci*. **2014**, *5*, 169.

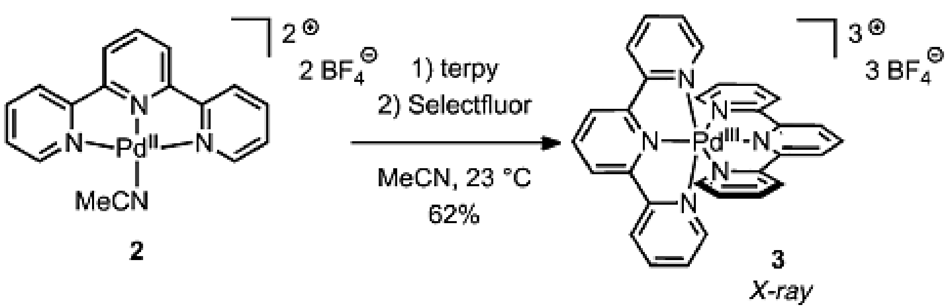


Mazzotti, A. R.; Campbell, M. G.; Tang, P.; Murphy, J. M.; Ritter, T. *J. Am. Chem. Soc.* **2013**, *135*, 14012.

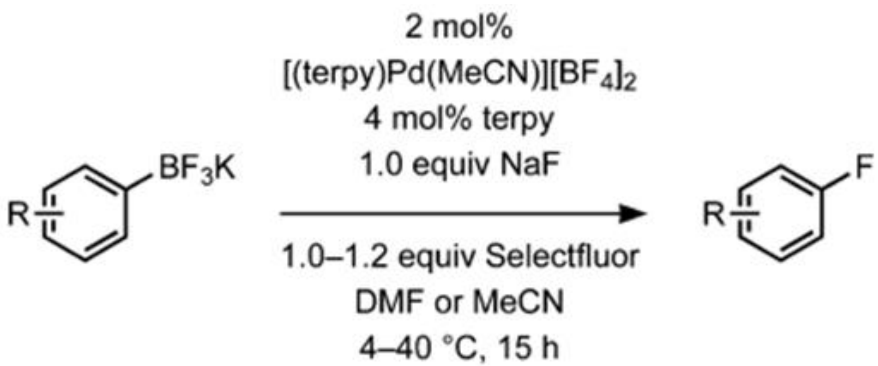


- *first-order kinetic dependence on the Pd catalyst*
- *saturation kinetics with respect to terpyridine*
- *zero-order dependence on aryl trifluoroborate*

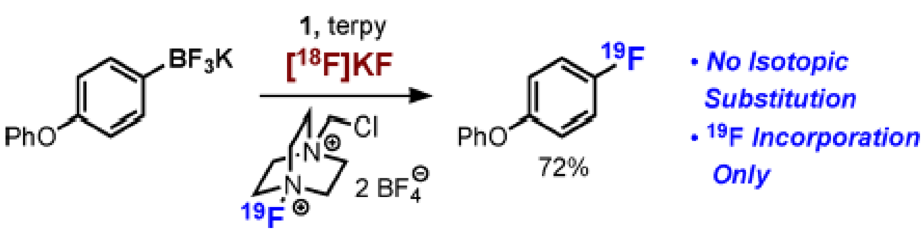


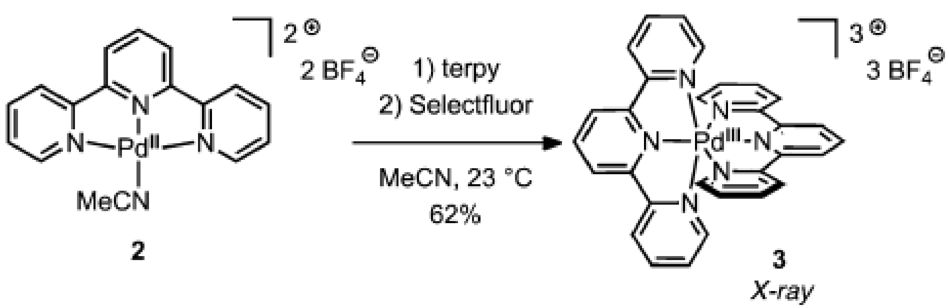


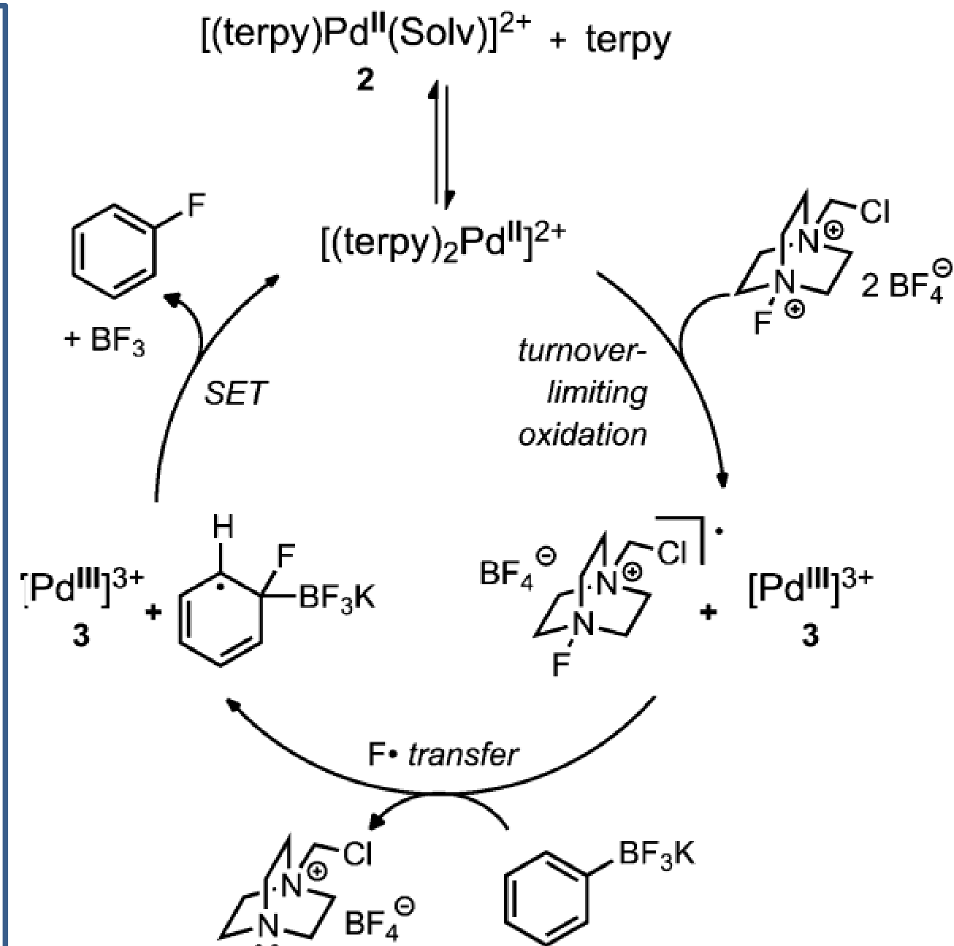
Mazzotti, A. R.; Campbell, M. G.; Tang, P.; Murphy, J. M.; Ritter, T. *J. Am. Chem. Soc.* **2013**, *135*, 14012.



- *first-order kinetic dependence on the Pd catalyst*
- *saturation kinetics with respect to terpyridine*
- *zero-order dependence on aryl trifluoroborate*

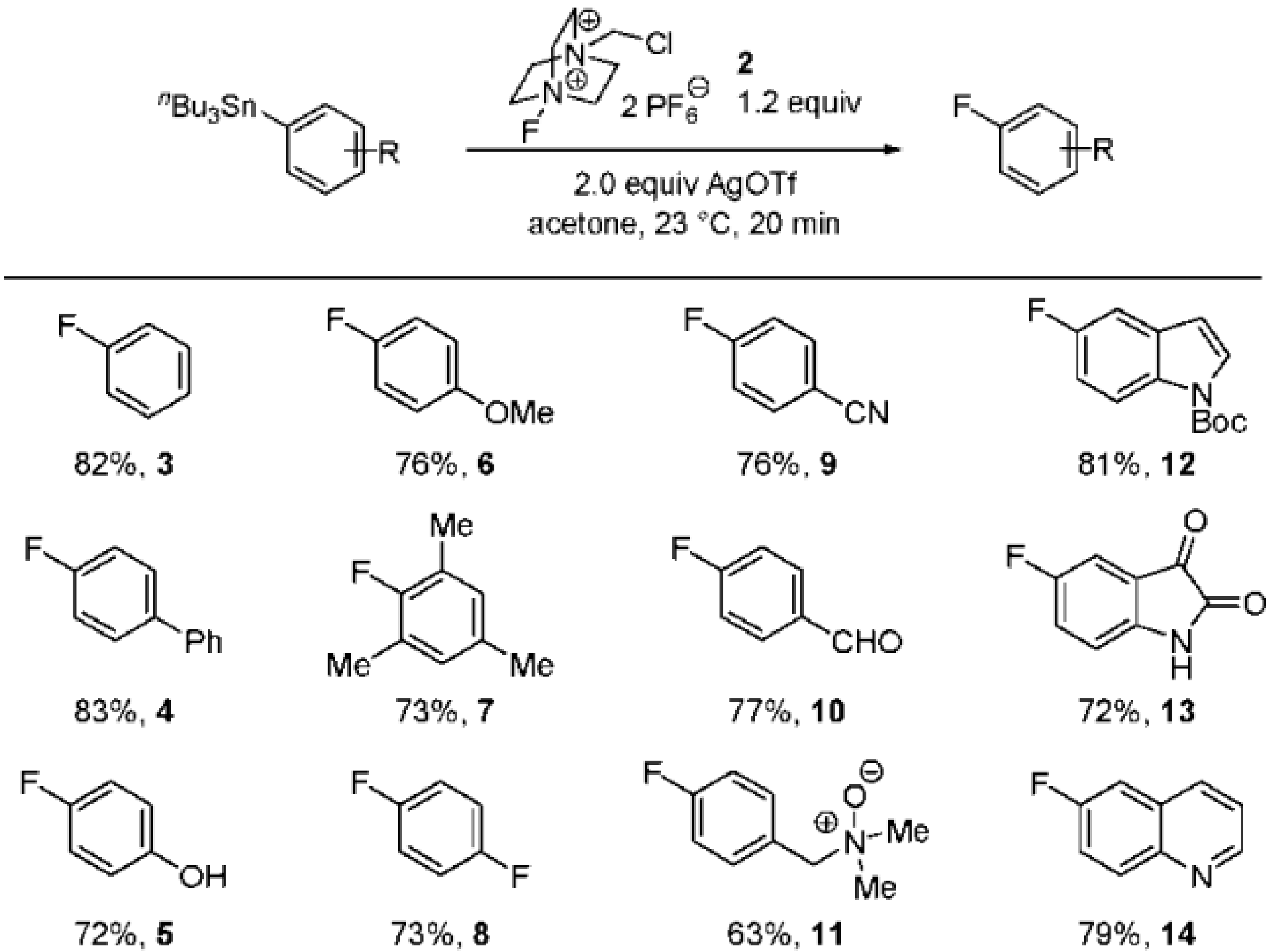






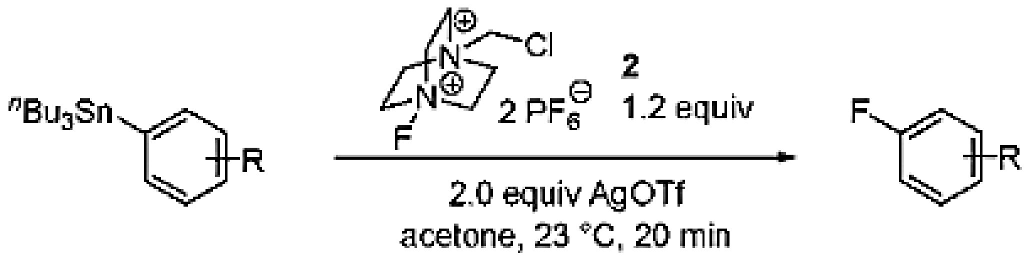
Mazzotti, A. R.; Campbell, M. G.; Tang, P.; Murphy, J. M.; Ritter, T. *J. Am. Chem. Soc.* **2013**, *135*, 14012.

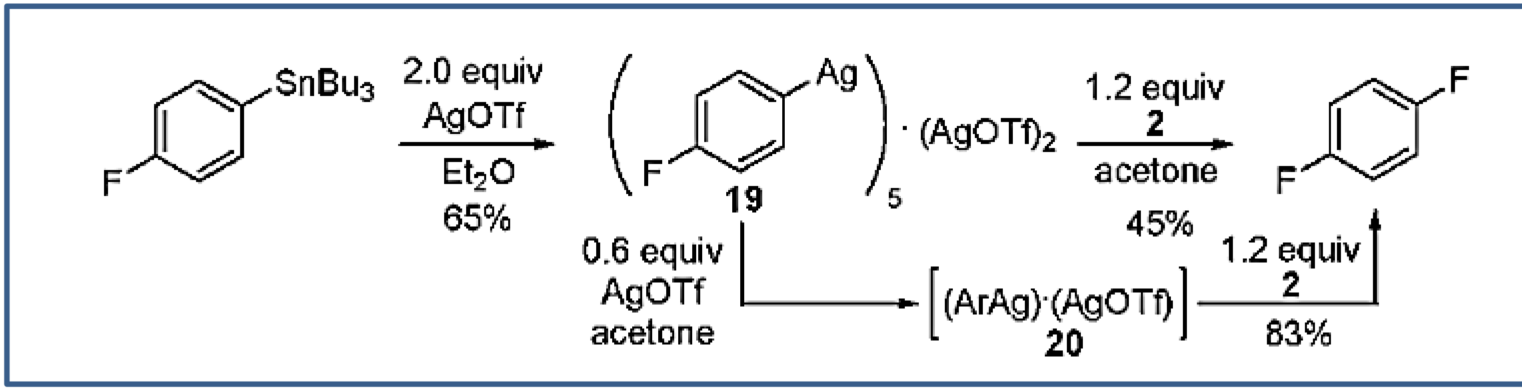
C–F Reductive Elimination from Silver(II).



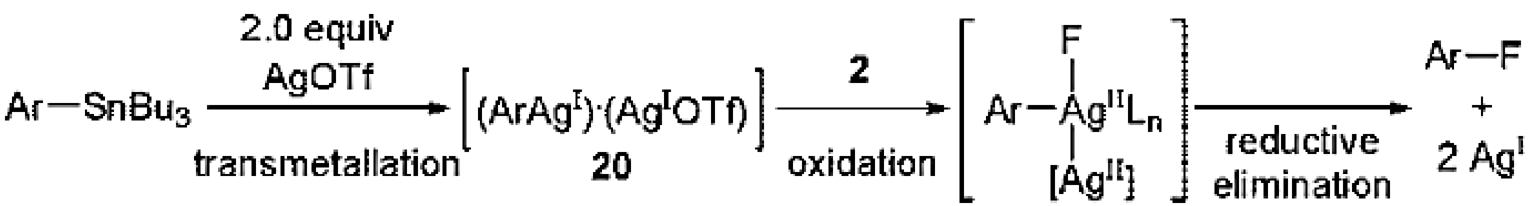
Furuya, T.; Strom, A. E.; Ritter, T. *J. Am. Chem. Soc.* **2009**, *131*, 1662.

C–F Reductive Elimination from Silver(II).



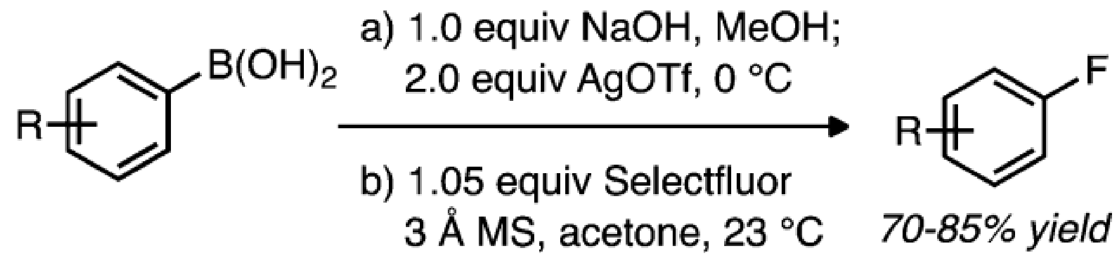


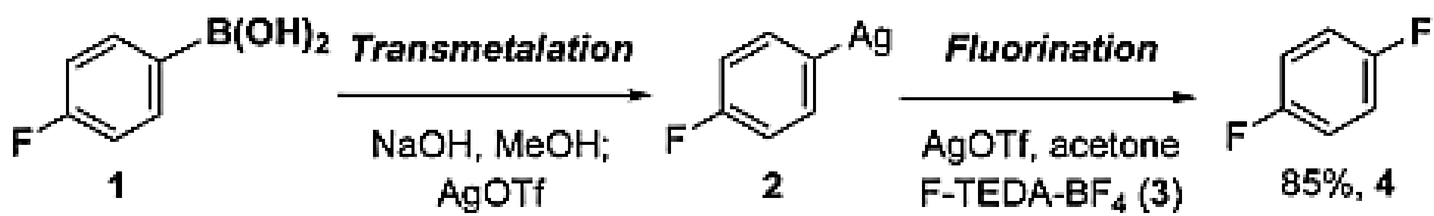
Bimetallic Oxidation-Reductive Elimination mechanism:



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

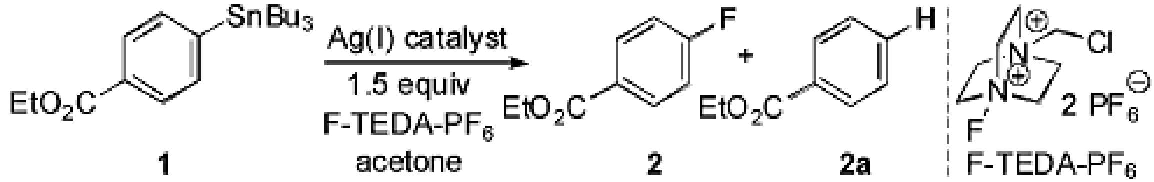
■ *Using arylboronic acid*





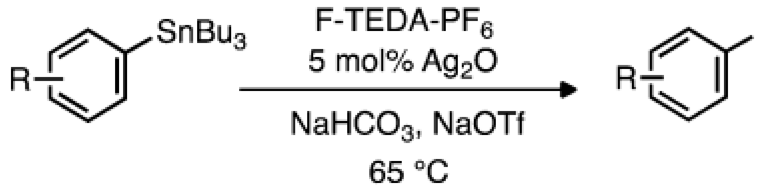
Furuya, T.; Ritter, T. *Org. Lett*. **2009**, *11*, 2860.

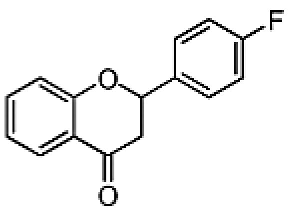
From silver-mediate to silver catalysis



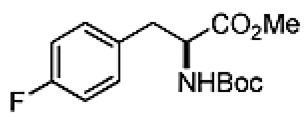
Ag(I) catalyst	Base (2.0 equiv)	Additive	Temp time	Yield[a] **2**	Yield[a] **2a**
10 mol% AgOTf	none	none	65 °C 3 h	30%	(68%)
5 mol% Ag_2O	$NaHCO_3$	none	65 °C 5 h	87%	(9%)
5 mol% Ag_2O	$NaHCO_3$	1.0 equiv NaOTf	65 °C 3 h	90%	(5%)
5 mol% Ag_2O	**$NaHCO_3$**	**1.0 equiv NaOTf 5.0 equiv MeOH**	**65 °C 3 h**	**92%**	**(2%)**
1 mol% Ag_2O	$NaHCO_3$	1.0 equiv NaOTf	90 °C 18 h	92%	(2%)
1 mol% Ag_2O	$NaHCO_3$	1.0 equiv NaOTf 5.0 equiv MeOH	90 °C 18 h	75%	(20%)

Tang, P.; Furuya, T.; Ritter, T. *J. Am. Chem. Soc*. **2010**, *132*, 12150.

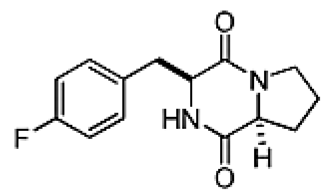




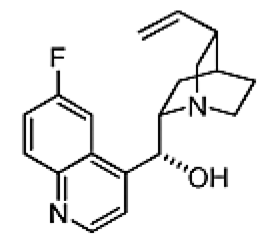
flavanone
90%, **8**



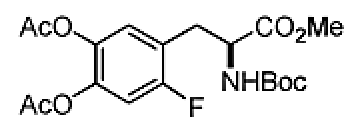
Boc-Tyr-OMe
85%, **9**



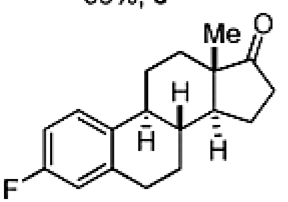
maculosin
78%, **10**



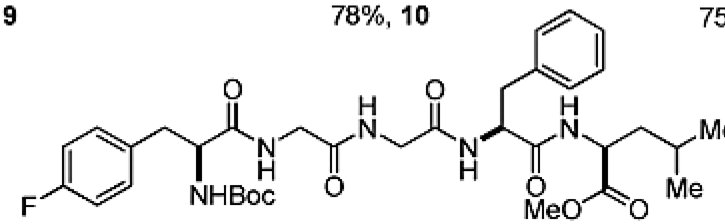
quinine
75%, **11**[a]



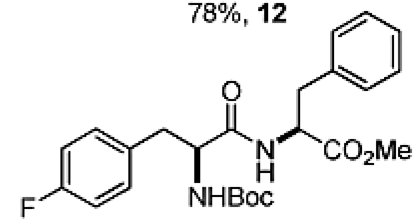
DOPA
78%, **12**



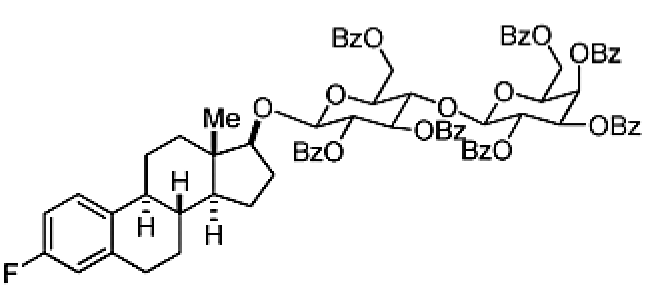
estrone
81%, **13**



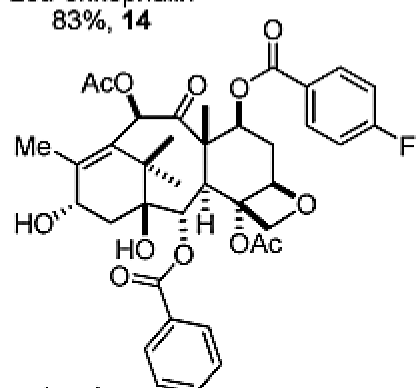
Leu-enkephalin
83%, **14**



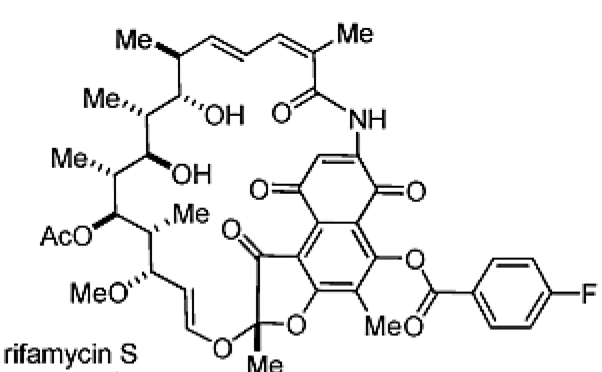
Boc-Tyr-Phe-OMe
92%, **15**



estrol-17-β-D-lactoside heptabenzoate
80%, **16**



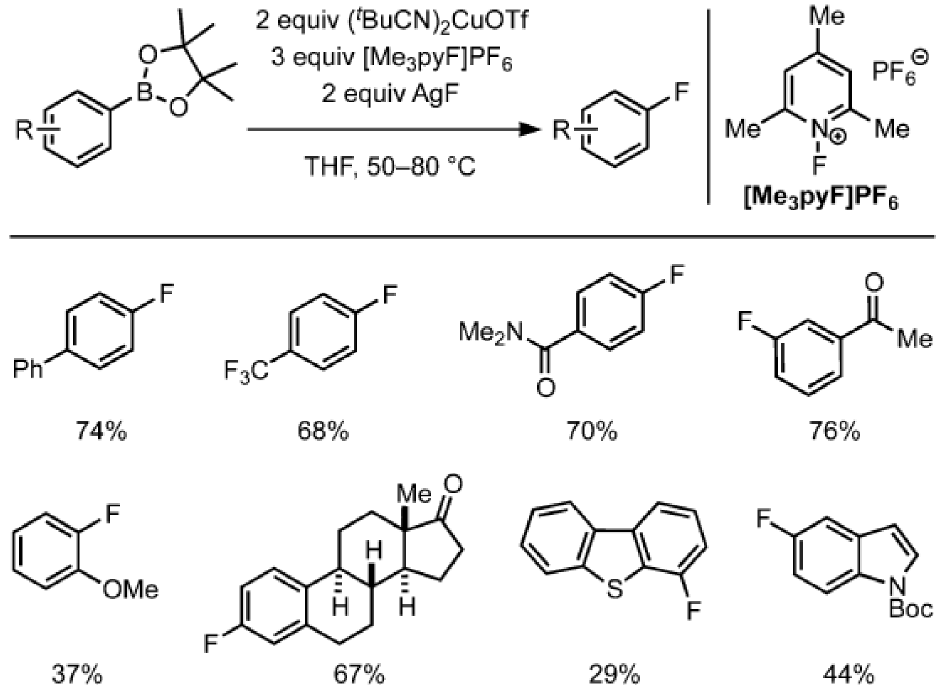
taxol
72%, **17**



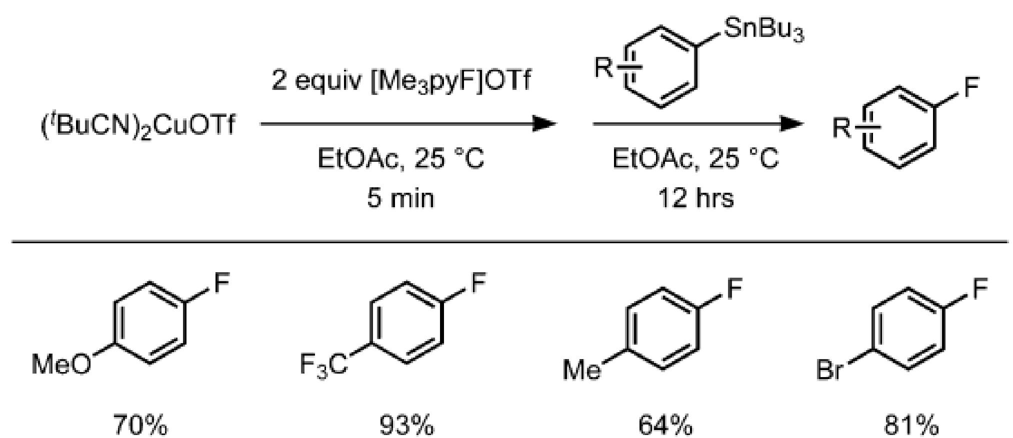
rifamycin S
65%, **18**[b]

Tang, P.; Furuya, T.; Ritter, T. *J. Am. Chem. Soc*. **2010**, *132*, 12150.

C–F Reductive Elimination from Cu(III)

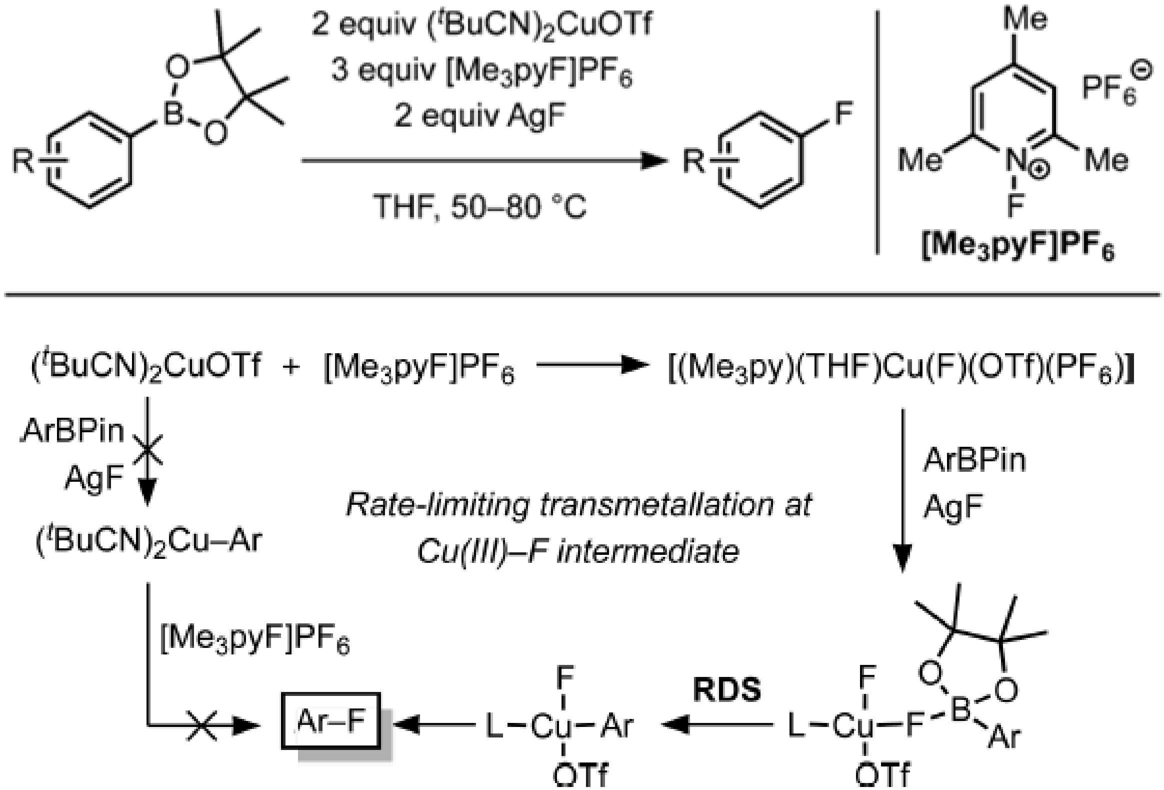


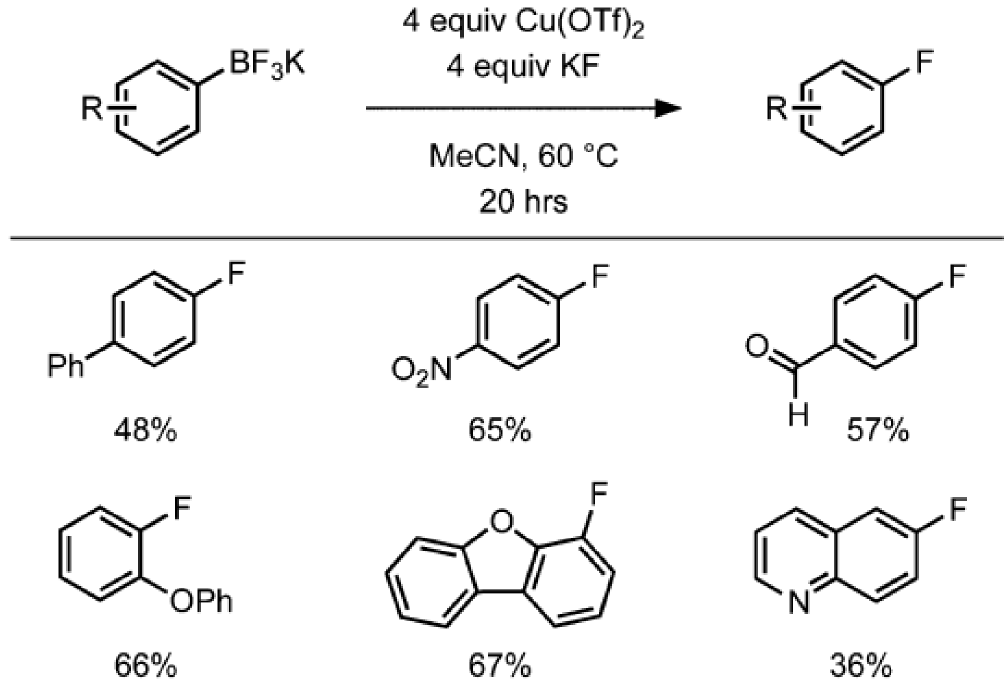
Fier, P. S.; Luo, J.; Hartwig, J. F. *J. Am. Chem. Soc*. **2013**, *135*, 2552



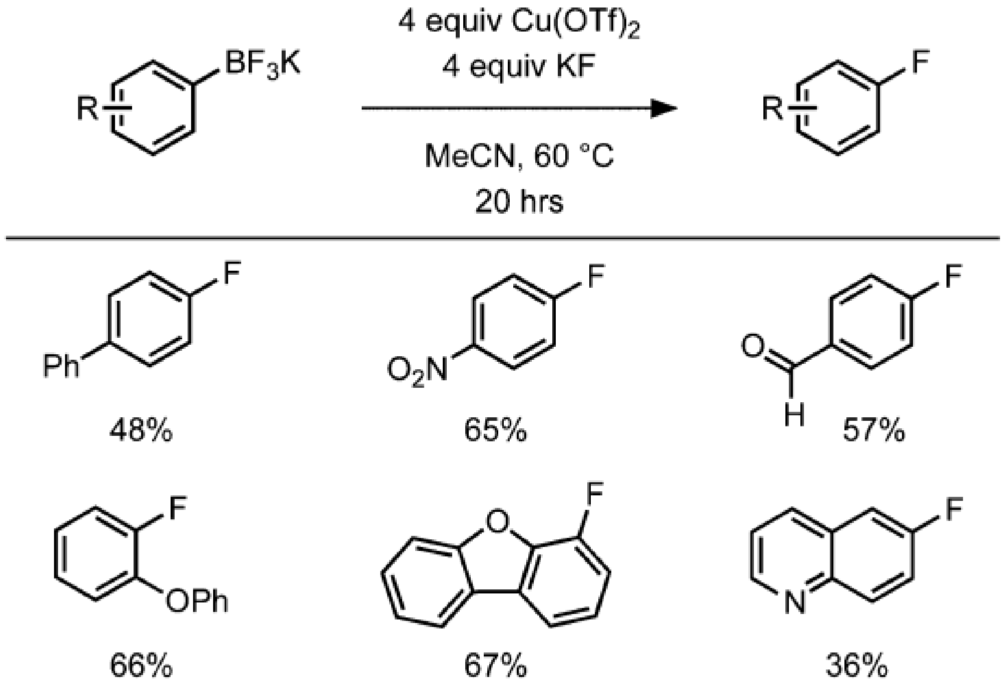
Ye, Y.; Sanford, M. S. *J. Am. Chem. Soc*. **2013**, *135*, 4648

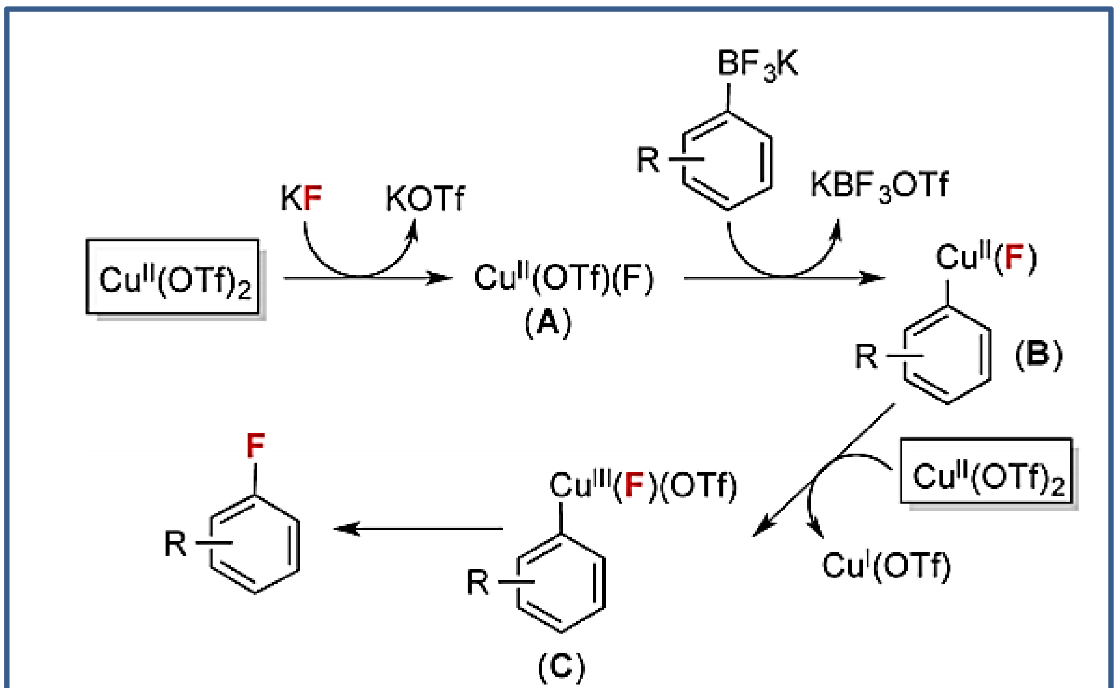
Proposed mechanism





Ye, Y.; Schimler, S. D.; Hanley, P. S.; Sanford, M. S. *J. Am. Chem. Soc*. **2013**, *135*, 16292.





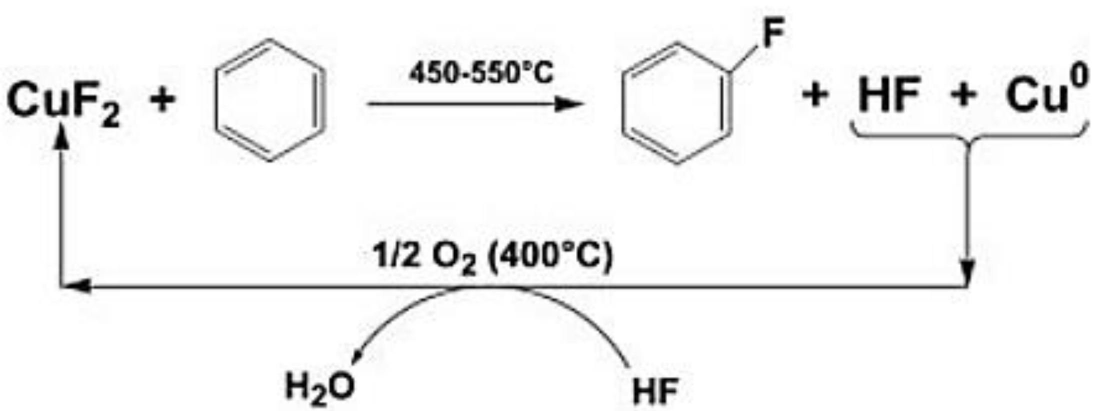
Ye, Y.; Schimler, S. D.; Hanley, P. S.; Sanford, M. S. *J. Am. Chem. Soc*. **2013**, *135*, 16292.

Electrophilic C(sp^2)-Fluorination *From C–H to C–F*

- *An early example*

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

$E^0>1$, the fluorides are strong oxidants and can be recycled with elemental fluorine
$1>E^0>0$, the fluorides are moderate oxidants and can be recycled with HF and O_2
$E^0<0$, the fluorides are inert toward C-H bonds



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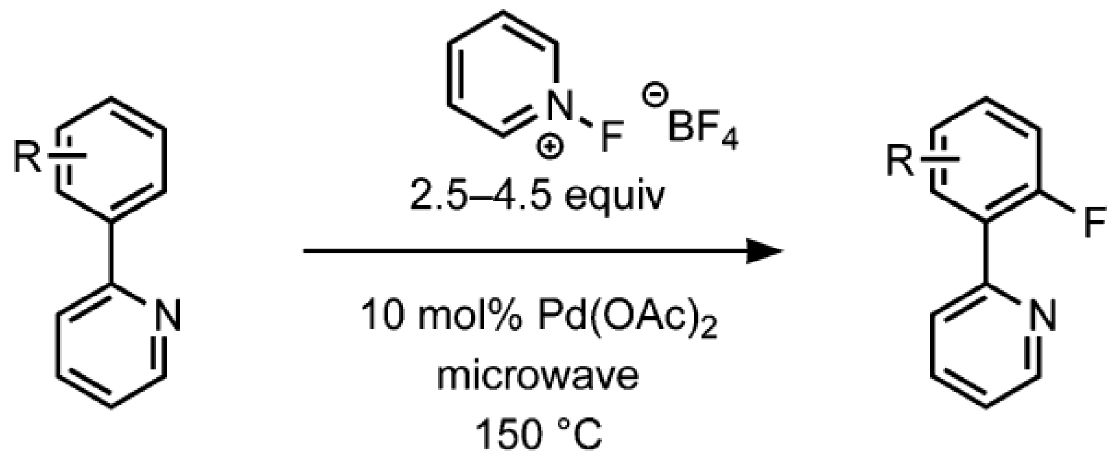
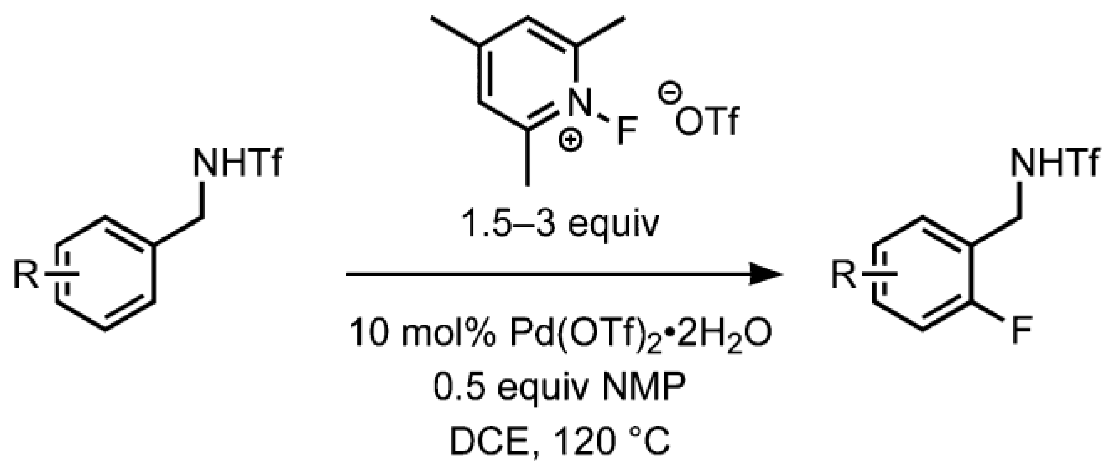


Hull, K. L.; Anani, W. Q.; Sanford, M. S*. J. Am. Chem. Soc*. **2006**, *128*, 7134.



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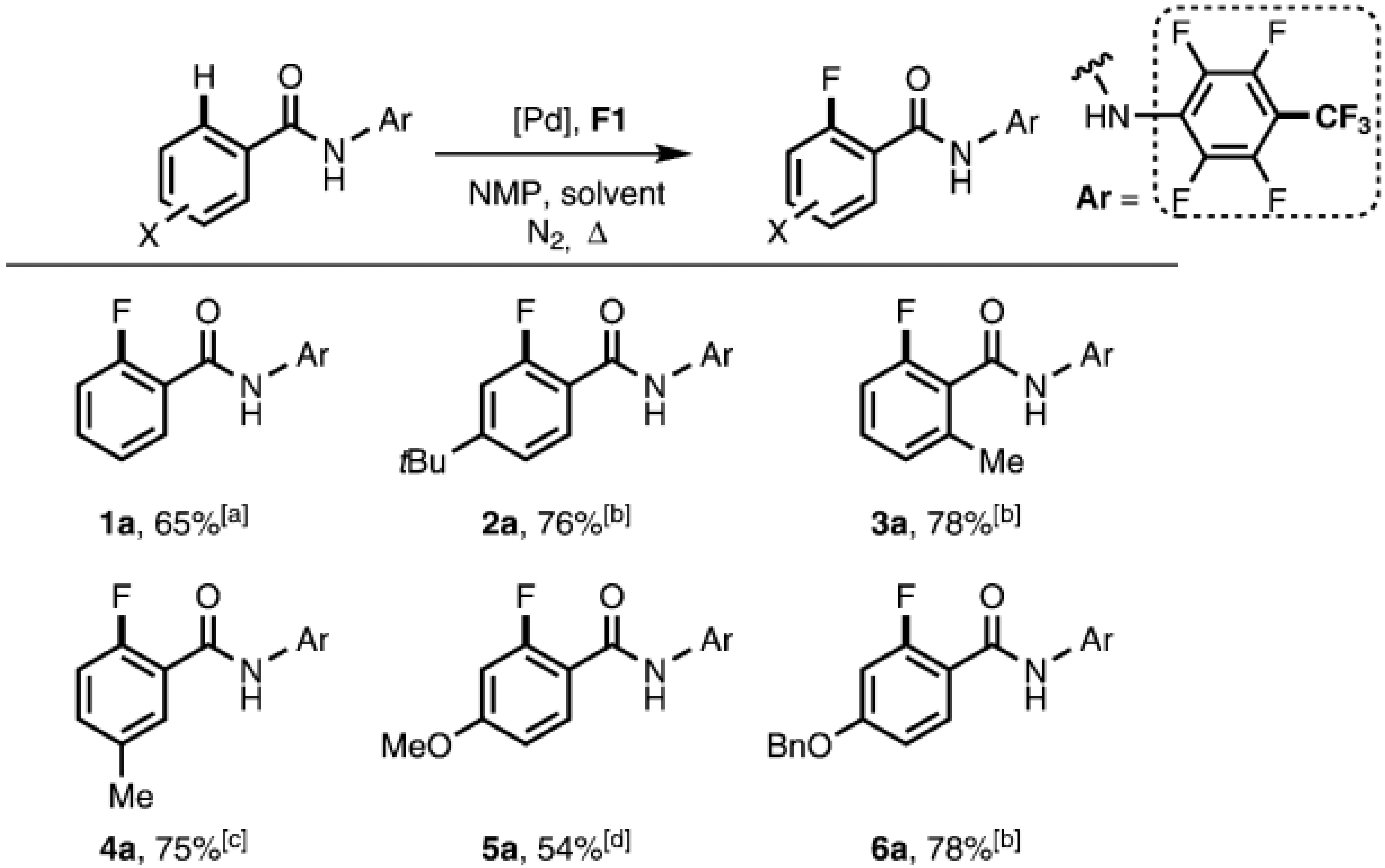
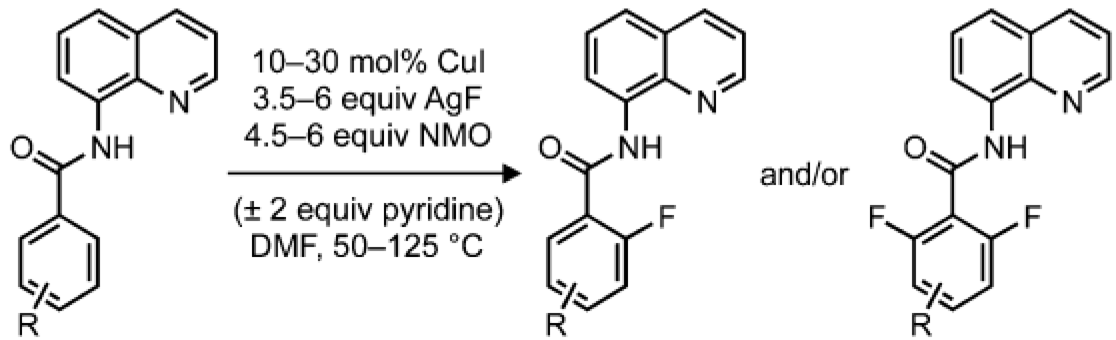


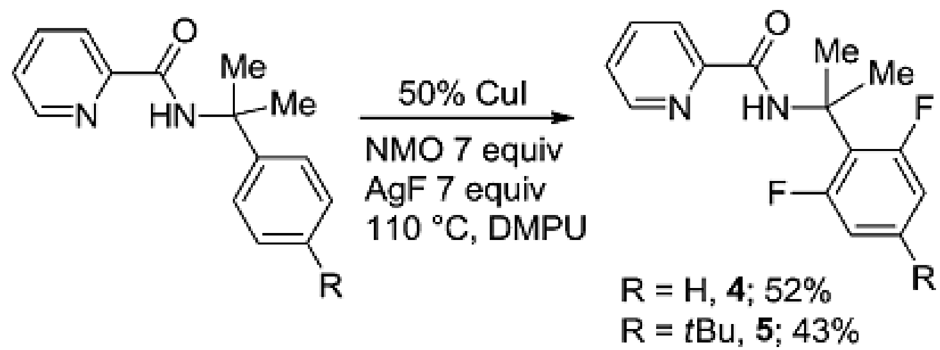
Chan, K. S. L.; Wasa, M.; Wang, X.; Yu, J.-Q. *Angew. Chem., Int. Ed*. **2011**, *50*, 9081

For minor expasion, see:

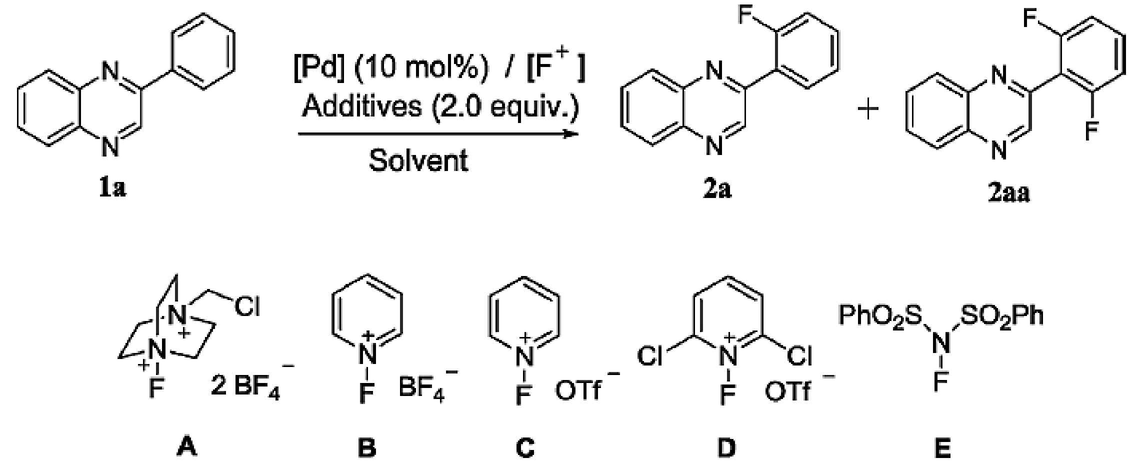
Lou, S.-J.; Xu, D.-Q.; Xia, A.-B.; Wang, Y.-F.; Liu, Y.-K.; Du, X.-H.; Xu, Z.-Y. *Chem. Commun*. **2013**, *49*, 6218.

Ding, Q.; Ye, C.; Pu, S.; Cao, B. *Tetrahedron* **2014**, *70*, 409





Truong, T.; Klimovica, K.; Daugulis, O. *J. Am. Chem. Soc*. **2013**, *135*, 9342.

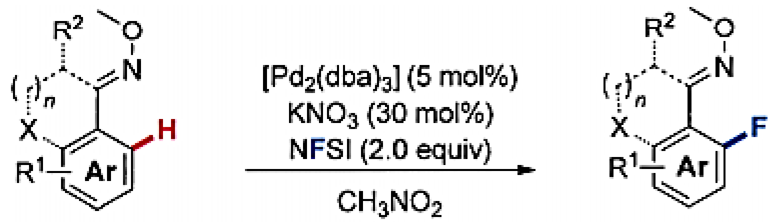


Entry	Cat.	[F+]	Add.	Solvent	Yields of **2a/2aa**[b] (%)
1	$Pd(OAc)_2$	A	TFA	DCE	Trace/0
2	$Pd(OAc)_2$	B	TFA	DCE	5/0
3	$Pd(OAc)_2$	C	TFA	DCE	3/0
4	$Pd(OAc)_2$	D	TFA	DCE	5/trace
5	$Pd(OAc)_2$	E	TFA	DCE	68/24
15	$Pd(OAc)_2$	E	HOAc	MS 1	19/trace
16	$Pd(OAc)_2$	E	PivOH	MS 1	18/trace
17	$Pd(OAc)_2$	E	HOTf	MS 1	48/trace
18	$Pd(OAc)_2$	E	MSA	MS 1	64/15
19	$Pd(OAc)_2$	E	PTSA	MS 1	56/5
20	$Pd(OAc)_2$	E	TFAA	MS 1	70/3
21	$Pd(OAc)_2$	E	NMP	MS 1	7/trace

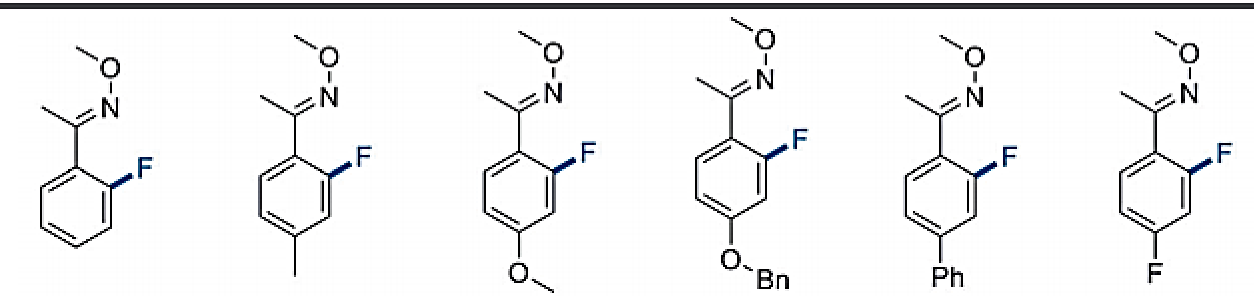
Lou, S.-J.; Xu, D.-Q.; Xia, A.-B.; Wang, Y.-F.; Liu, Y.-K.; Du, X.-H.; Xu, Z.-Y. *Chem. Commun*. **2013**, *49*, 6218.

aromatic C(sp^2)–H bond fluorination

	DG	[F]	Additive	*T* [°C]
Sanford	pyridine	*N*-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate (1.5–2.0 equiv)	–	110 (microwave)
Yu	triflamide or *N*-arylbenzamide	*N*-fluoro-2,4,6-trimethylpyridinium triflate (1.5–3.0 equiv)	NMP (0.5 equiv)	120
Daugulis	8-aminoquinoline benzamide	AgF (3.5–6.0 equiv)	NMO (4.5-8.0 equiv)	50–125

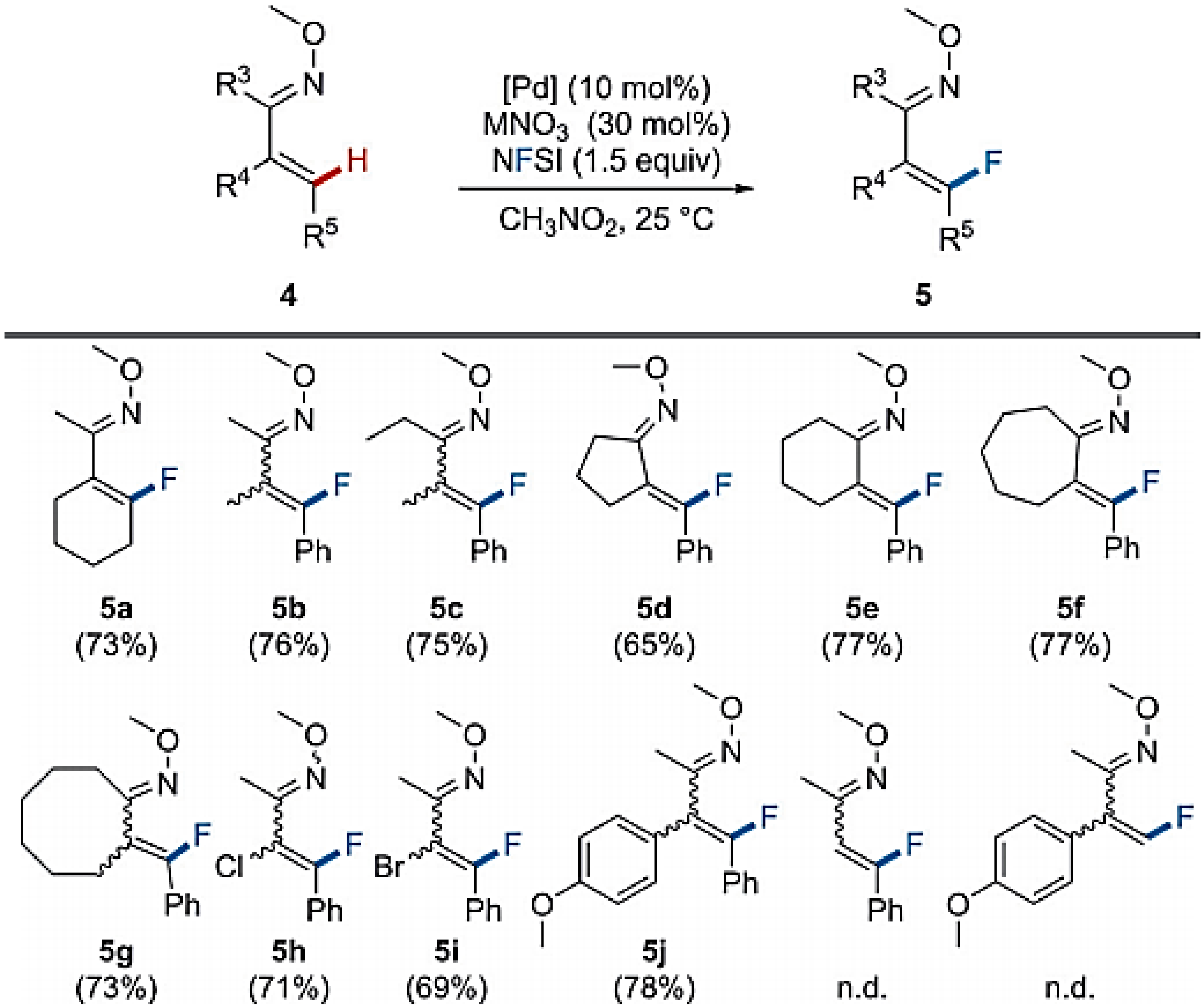


1 → **2 or 3**

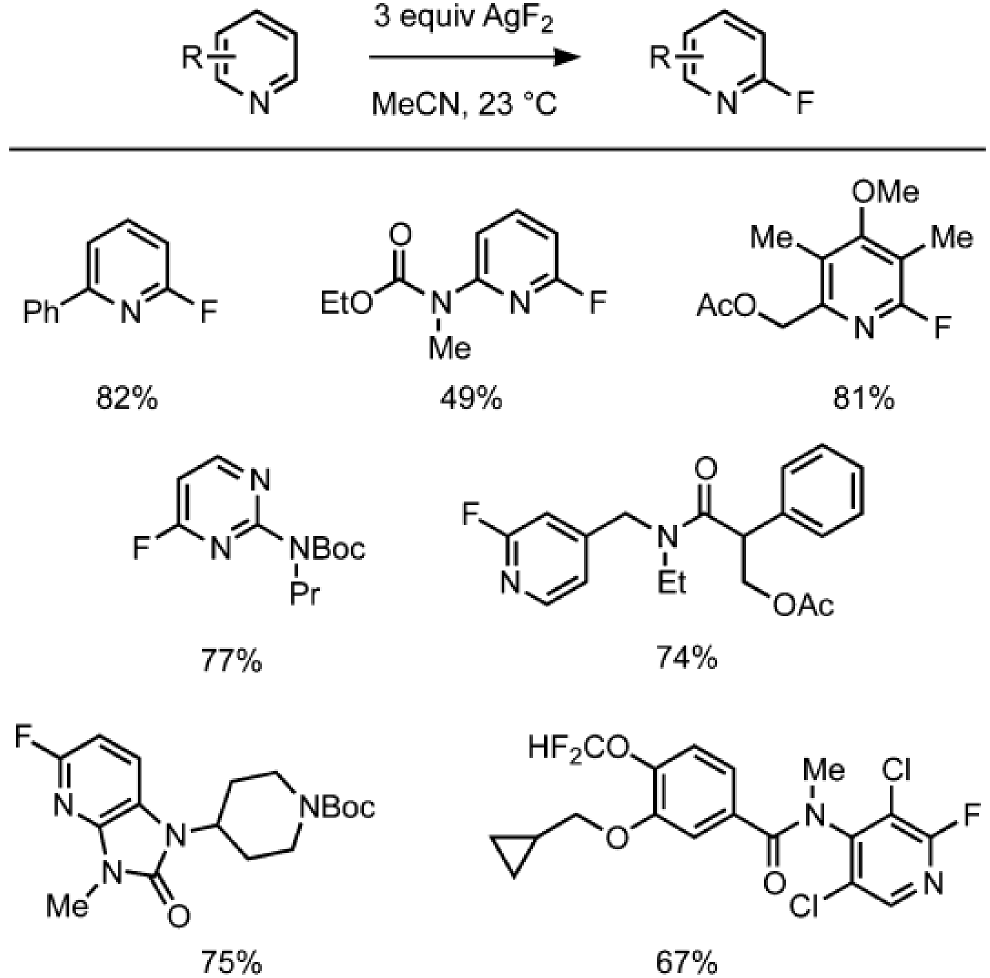


2a (25 °C; 78%)
2b (25 °C; 80%)
2c (25 °C; 86%)
2d (25 °C; 80%)
2e (25 °C; 79%)
2f (40 °C; 83%)

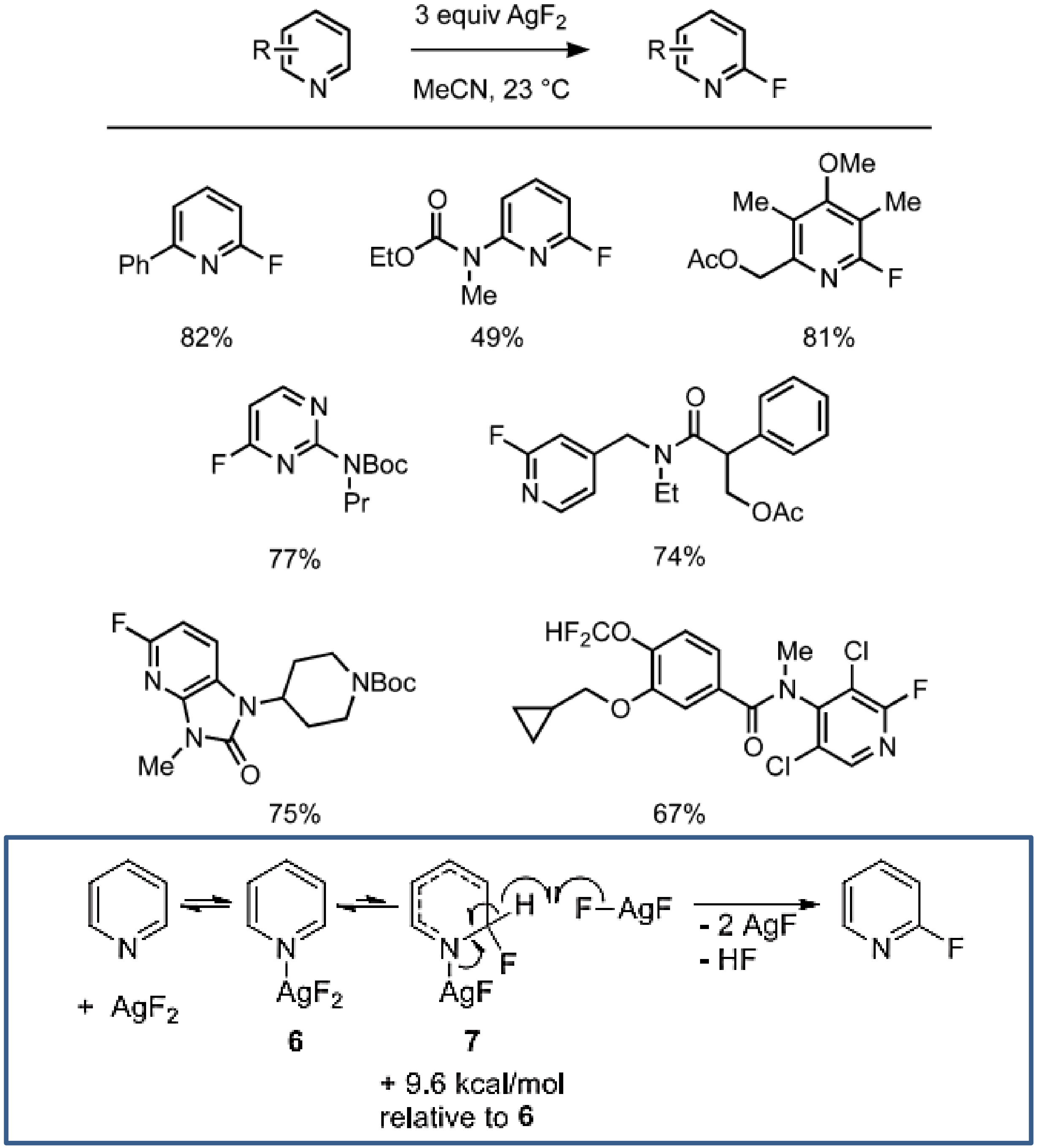
Lou, S.-J.; Xu, D.-Q.; Xu, Z.-Y. Angew. Chem., Int. Ed. **2014**, *53*, 10330



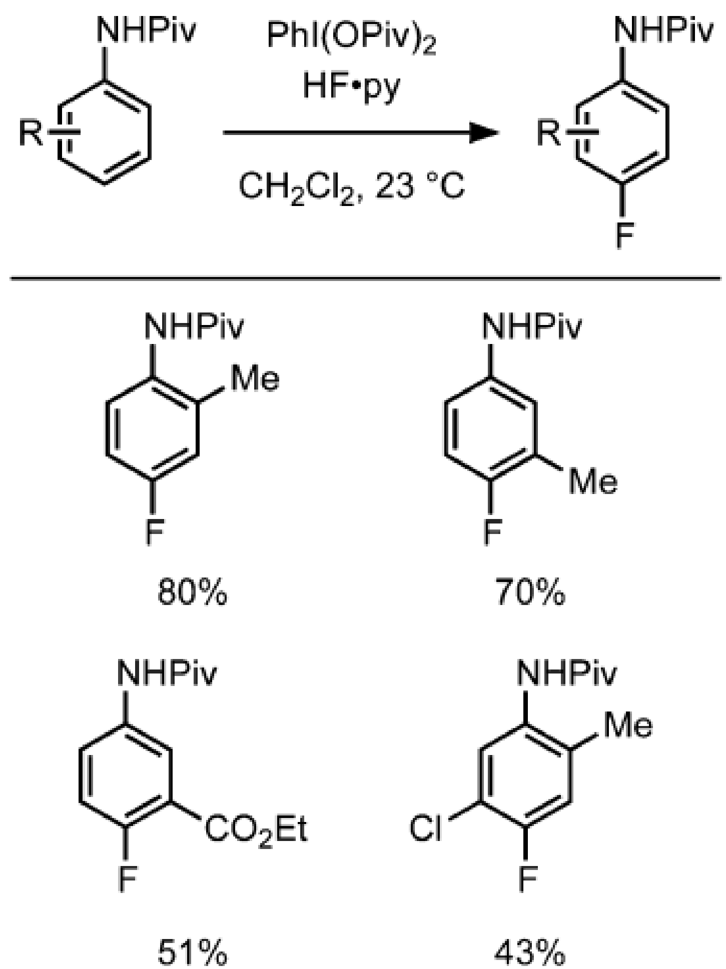
Lou, S.-J.; Xu, D.-Q.; Xu, Z.-Y. Angew. Chem., Int. Ed. **2014**, *53*, 10330



Fier, P. S.; Hartwig, J. F. *Science* **2013**, *342*, 956.



Fier, P. S.; Hartwig, J. F. *Science* **2013**, *342*, 956.



Tian, T.; Zhong, W.-H.; Meng, S.; Meng, X.-B.; Li, Z.-J. *J. Org. Chem*. **2013**, *78*, 728

Summary and outlook

Modern C(sp²)-F bond forming reactions:
Still a challenging and important problem

transition-metal catalysis approach has been the most successful to date

From C–M to C–F

- most effective for highly functionalized substrates
- requires expensive electrophilic fluorinating reagents
- poor atom economy
- arylmetal substrates not always readily available.

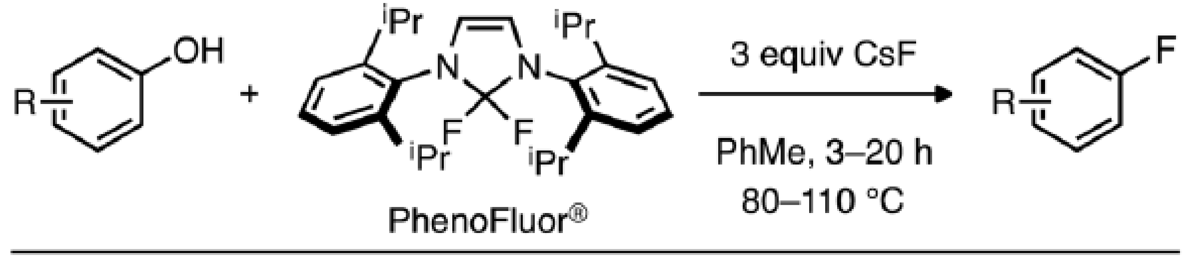
From C–X to C–F

- inexpensive fluoride salts and aryl halides
- basicity of fluoride → undesired reactions

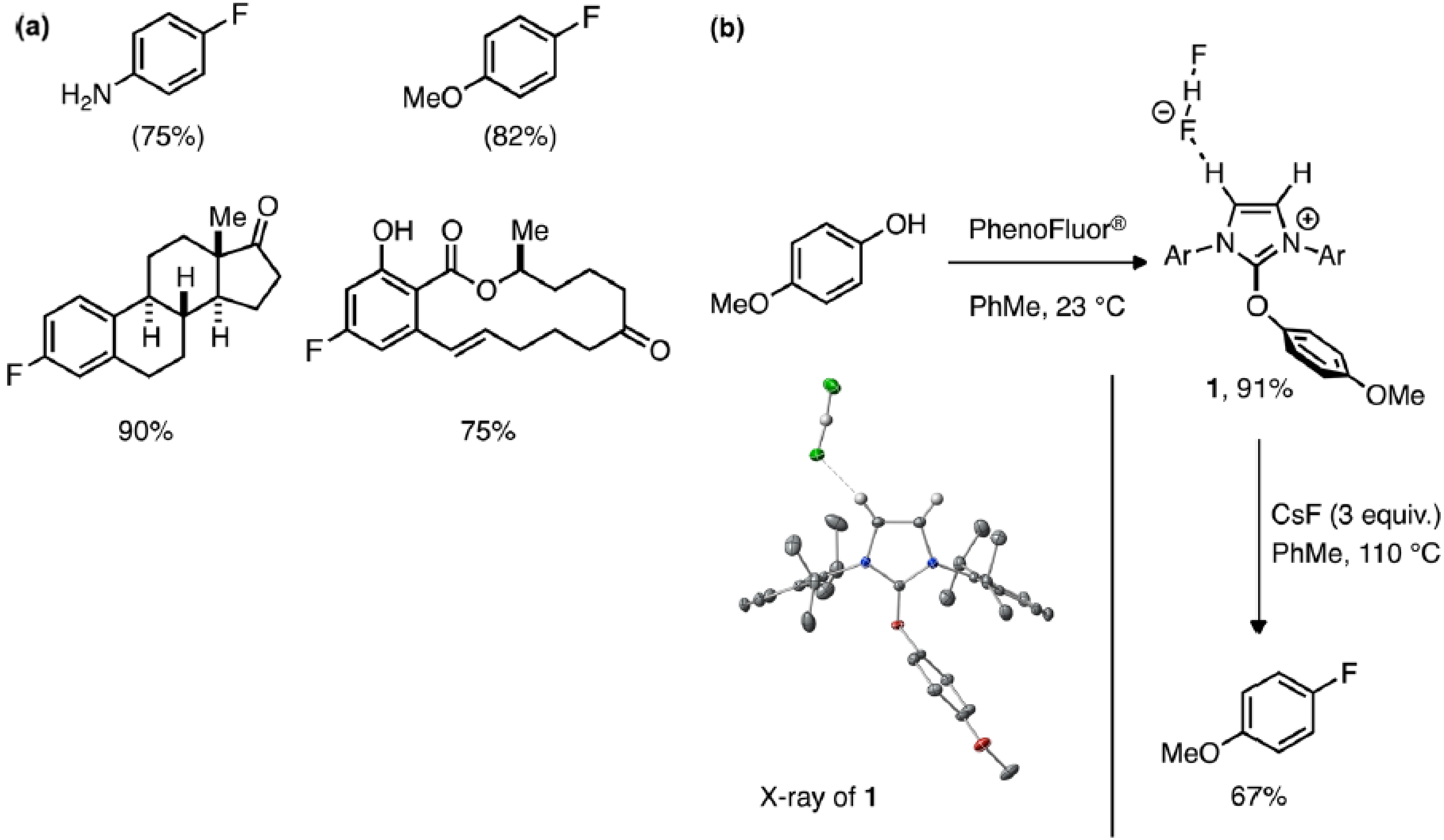
From C–H to C–F

- step and atom economy
- poor FG tolerance
- require directing-group

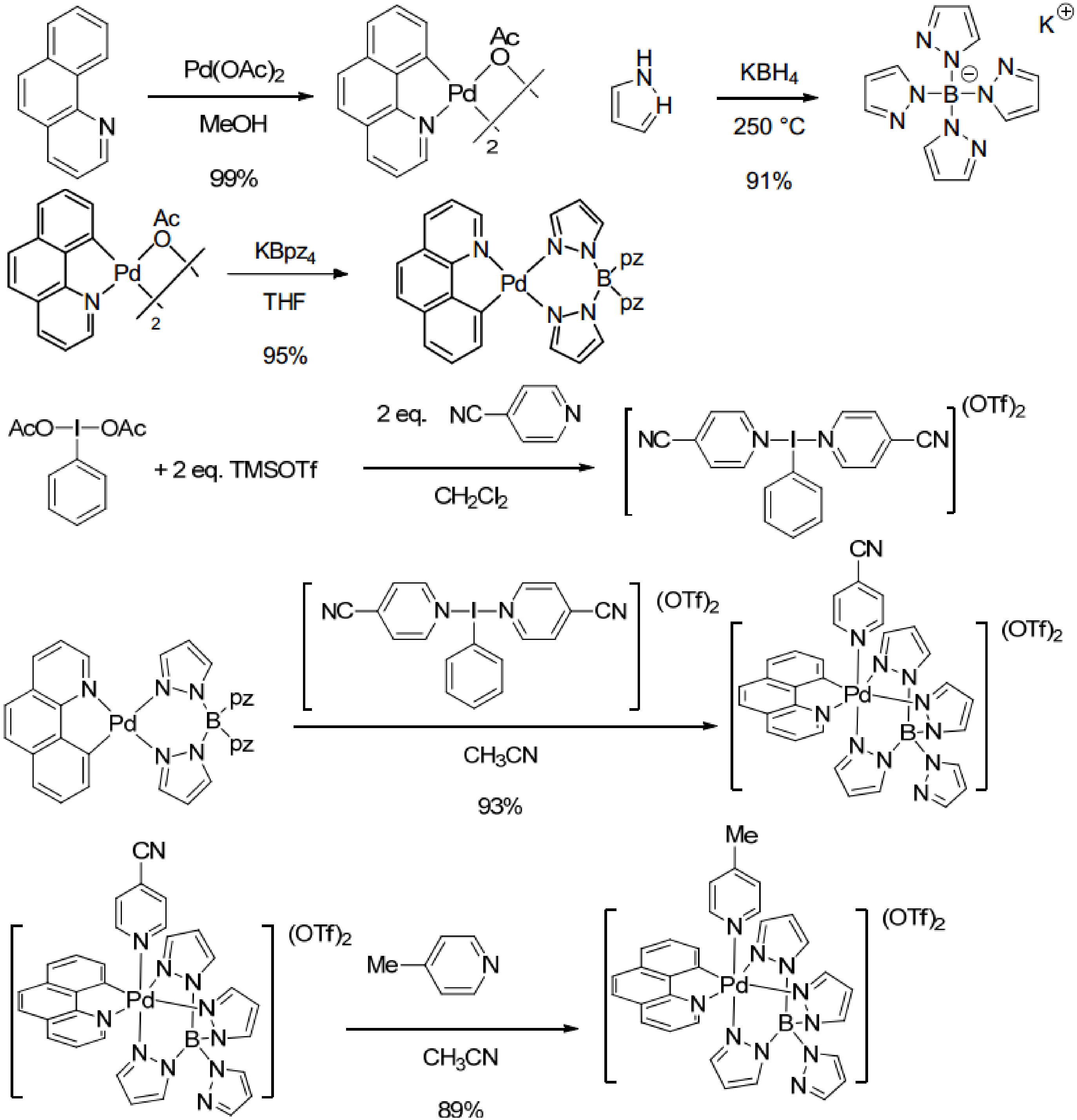

Thanks!
For your Time



Q1



Tang, P.; Wang, W.; Ritter, T. *J. Am. Chem. Soc*. **2011**, *133*, 11482.


Pd(OAc)2
MeOH
99%
KBH4
250 °C
91%
KBpz4
THF
95%
AcO–I–OAc
+ 2 eq. TMSOTf
2 eq.
CH2Cl2
(OTf)2
CH3CN
93%
CH3CN
89%

Q2

Q3