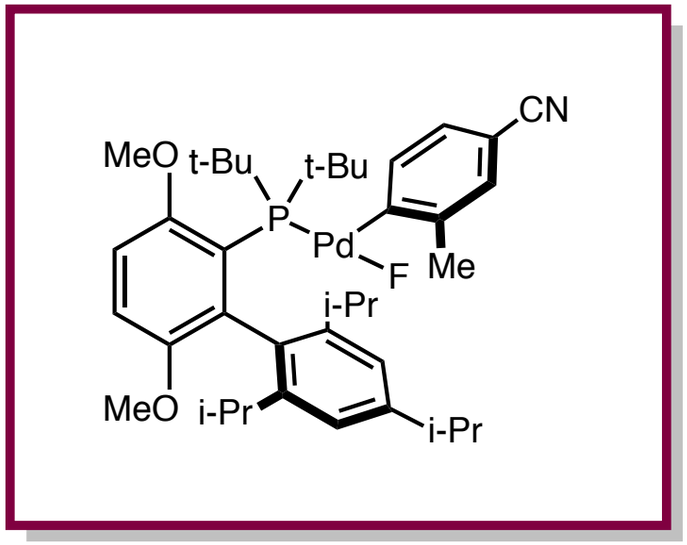
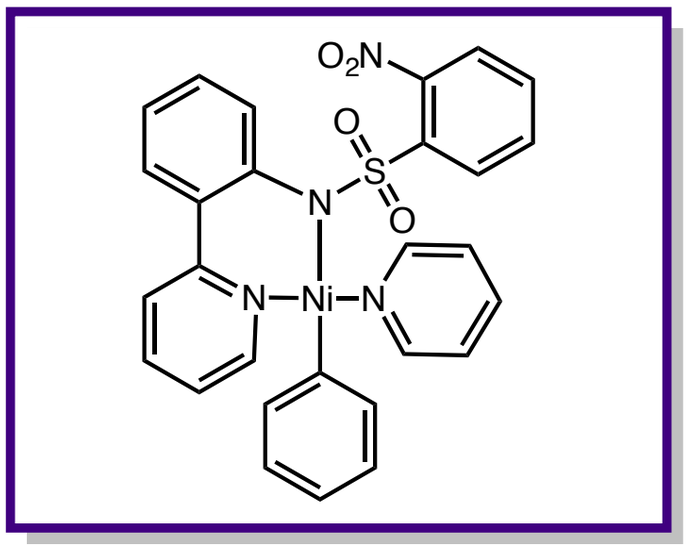
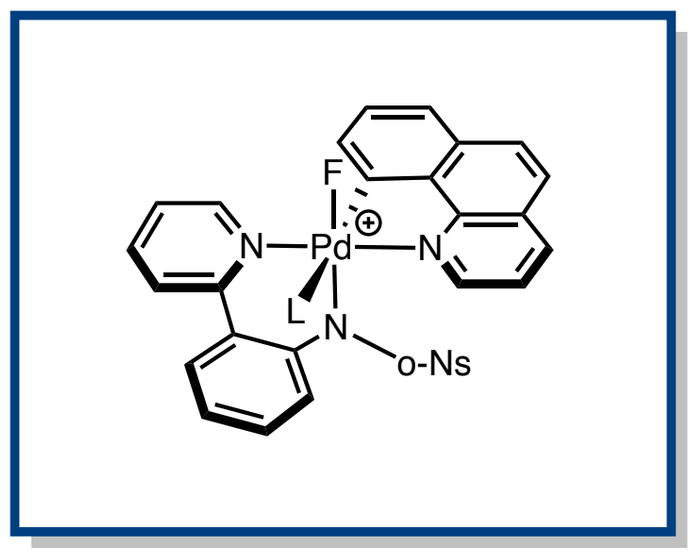
Transition Metals Mediated Fluorination of Arenes and Heteroarenes

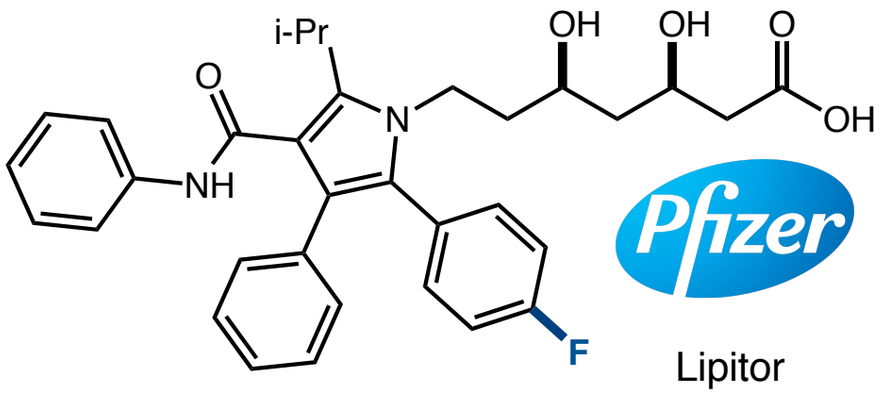






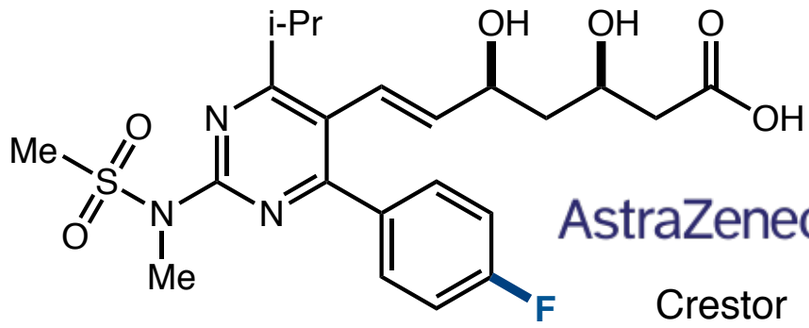
Why Would You Want to Fluorinate an Arene?

Aryl fluorides are present in a wide range of pharmaceuticals



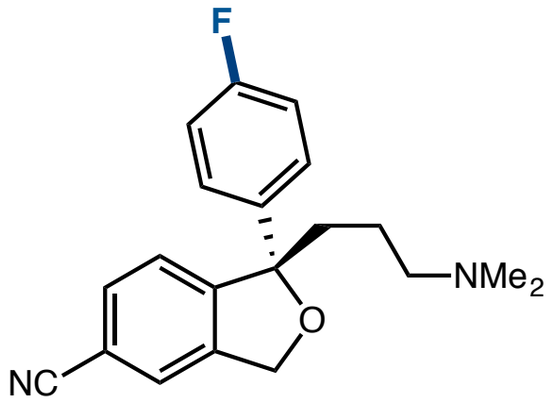
Pfizer

Lipitor



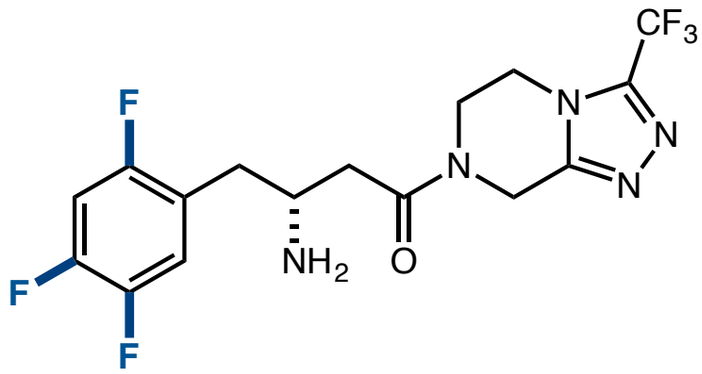
AstraZeneca

Crestor



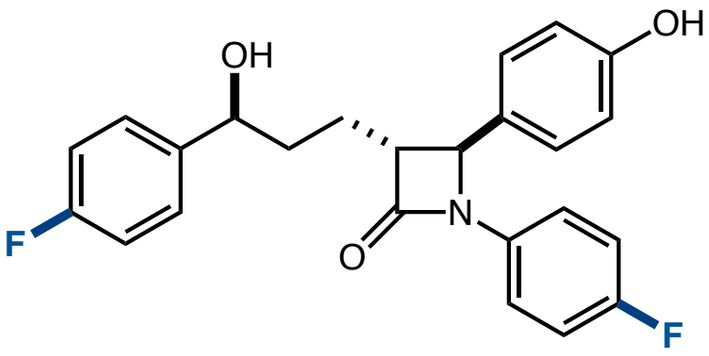
Lundbeck

Lexapro



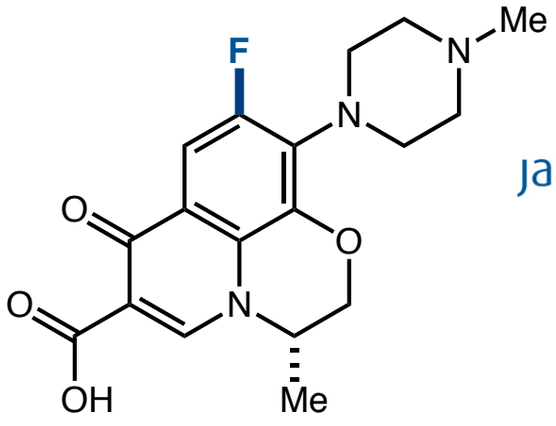
MERCK

Junuvia



MERCK

Zetia



janssen | PHARMACEUTICAL COMPANIES OF Johnson&Johnson

Levaquin

40 fluroine containing drugs introduced to market between 2001 and 2011

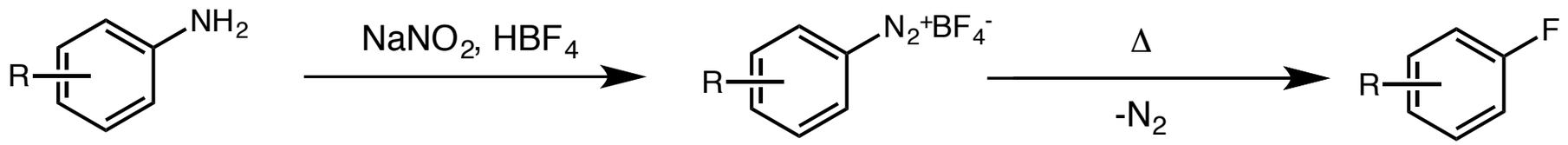
~30% of pharamaceuticals contain at least one fluorine atom

Fustero, S.; Soloshonok, V. A.; Liu, H. et al. *Chem. Rev.* **2014**, *114*, 2432.

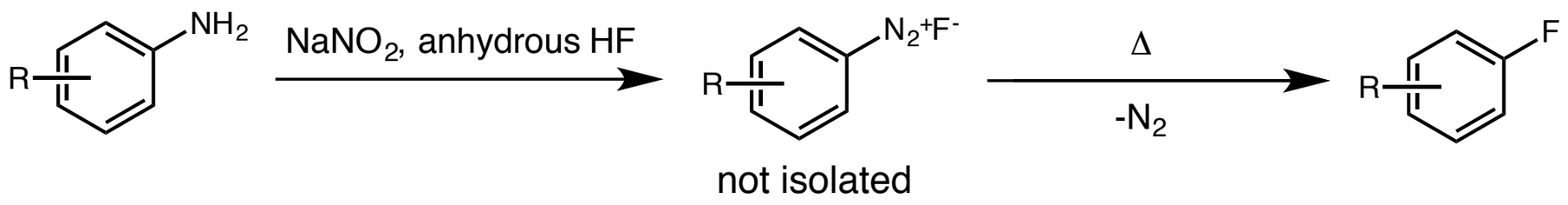
Why Would You Want to Fluorinate an Arene?

Tradition methods are not compatible with complex functionality

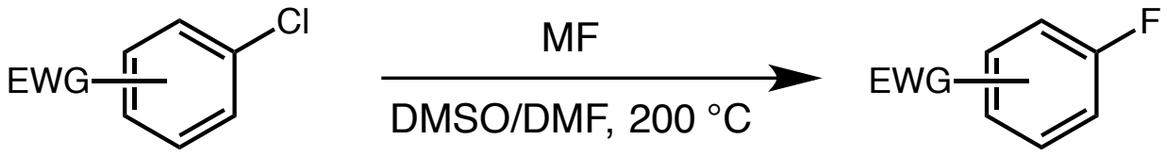
Balz-Schiemann



Lenz-Wallach



S_NAr



Mild methods for the selective introduction of fluorine to complex molecules remains challenging

Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881.
Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320.

Transition Metals Mediated Fluorination of Arenes and Heteroarenes

1. Palladium Catalyzed Processes

- The challenges facing transition metal catalyzed fluorination
- First example of C–F bond formation by reductive elimination
- Buchwalds catalytic fluorination using nucleophilic fluoride

2. Copper Catalyzed and Mediated Processes

- Copper mediated halogen exchange
- Sanford's catalytic fluorination of aryl iodoniums
- Sanford's Chan-Evans-Lam

3. Silver Catalyzed and Mediated Processes

- Oxidative fluorination of aryl nucleophiles
- Hartwig's Chichibabin inspired fluorination of heteroarenes

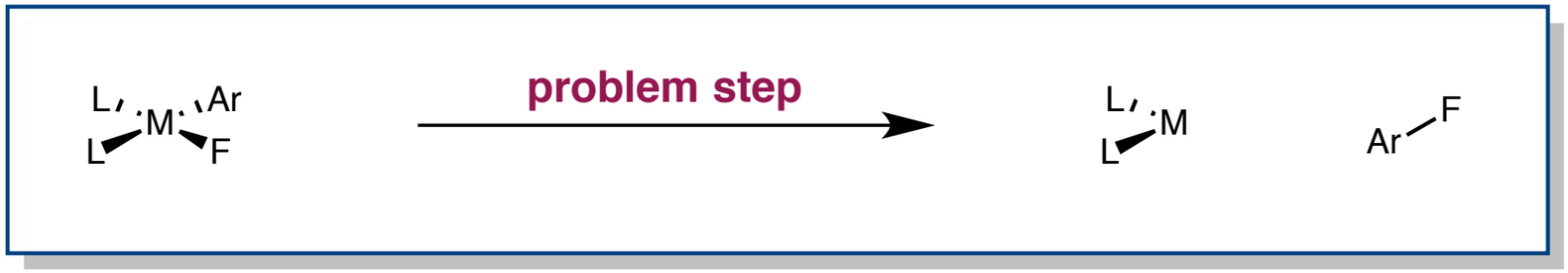
4. Ritter's oxidative fluorination of aryl nickel complexes

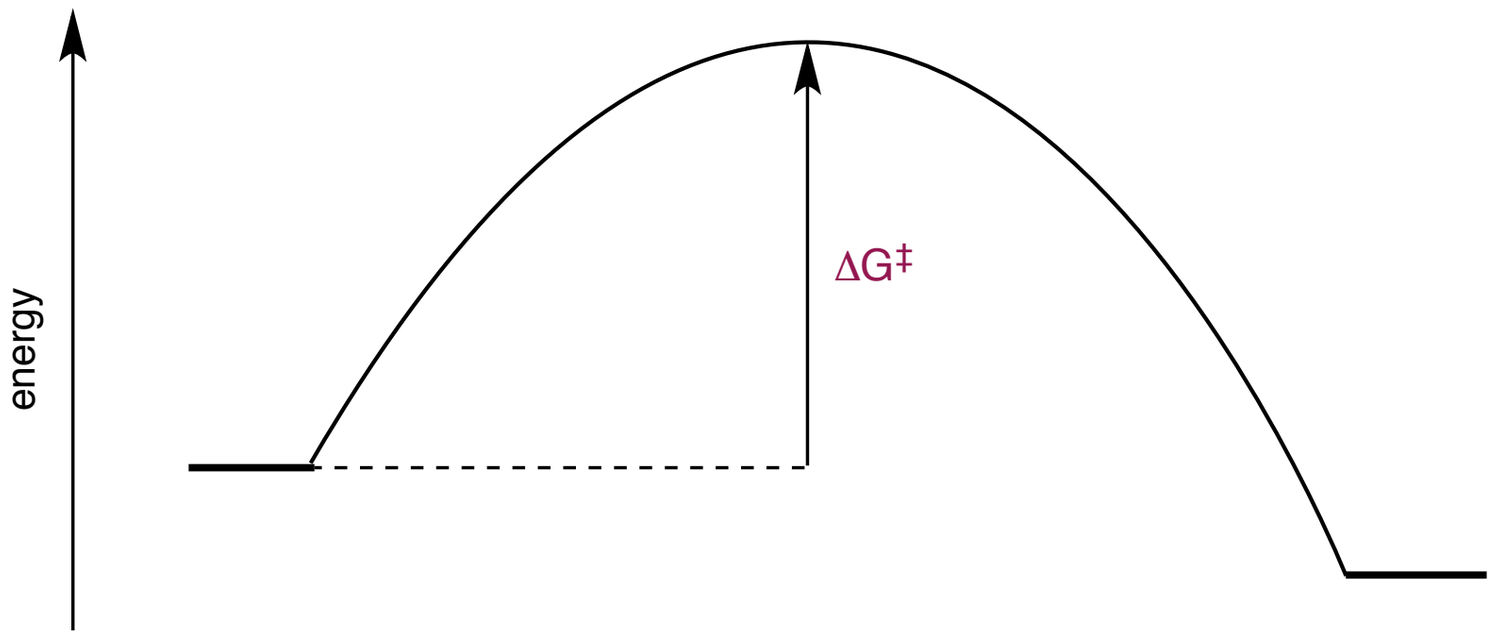
5. Ritter's radical fluorination of aryl potassium trifluoroborates

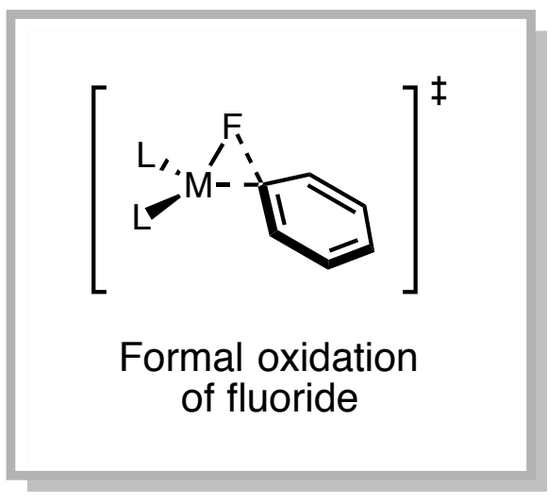
Paquin, J-R. et al. *Chem. Rev.* **2015**, *115*, 9073.
Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2015**, *54*, 2.

Challenges Facing Transition Metal Catalysis

Reductive elimination to from the C–F bond is kinetically difficult





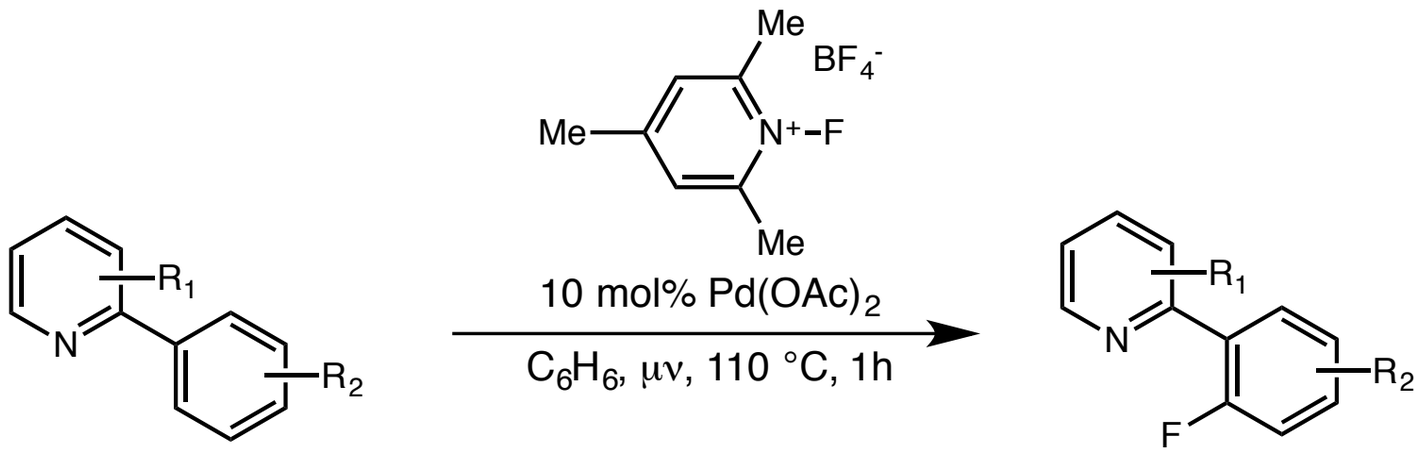


Competing reductive elimination involving the ligand had been a long standing problem

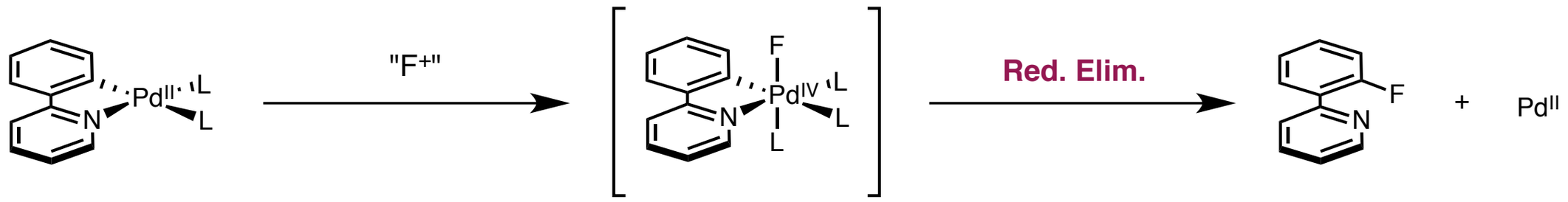
Grushing, V. V. *Chem. Eur. J.* **2002**, *45*, 2720.
Grushin, V. V.; Marshall, W. J. *Organometallics*. **2007**, *26*, 4997.

Palladium Mediated Aryl–F Bond Formation

Reductive elimination from a highly oxidising metal center proved to be fruitful



Key Mechanistic Hypothesis



Hull, K. L.; Anani, W. Q.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 7134.
Furuya, T.; Kaiser, H. M.; Ritter, T. *Angew. Chem. Int. Ed.* **2008**, *47*, 5993.
Furuya, T.; Ritter, T. *J. Am. Chem. Soc.* **2008**, *130*, 10060.

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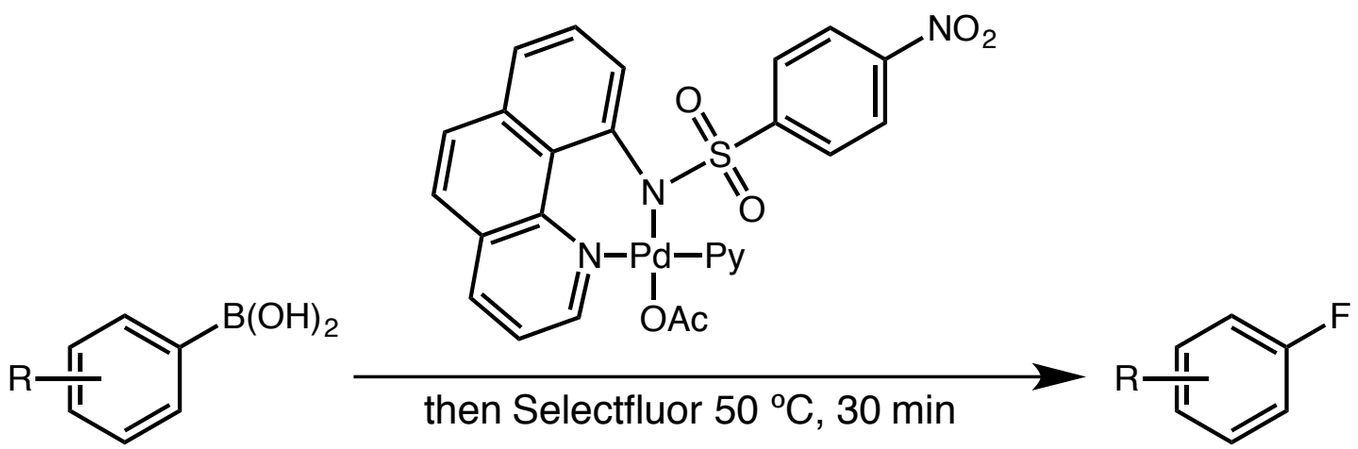
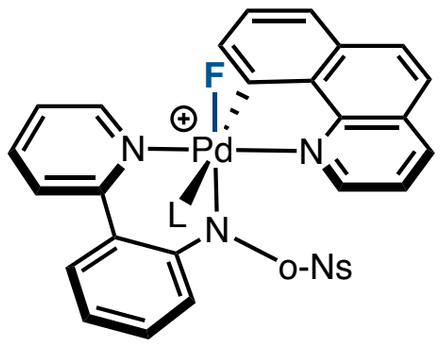
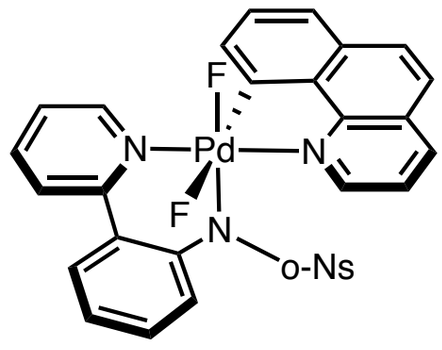


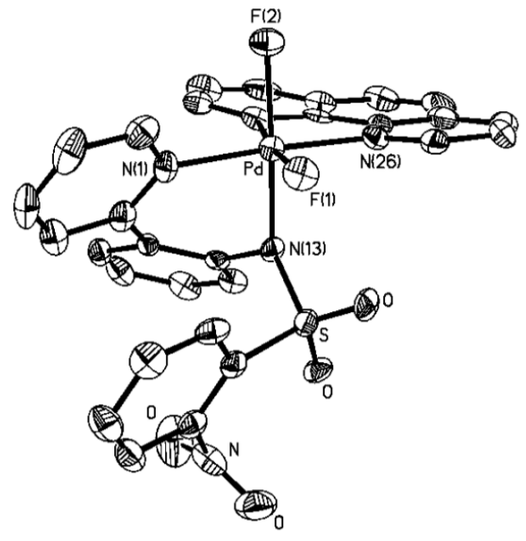
Pd(IV) intermediate observed spectrascopically and isolated



Observed in solution



Air and moisture stable orange solid



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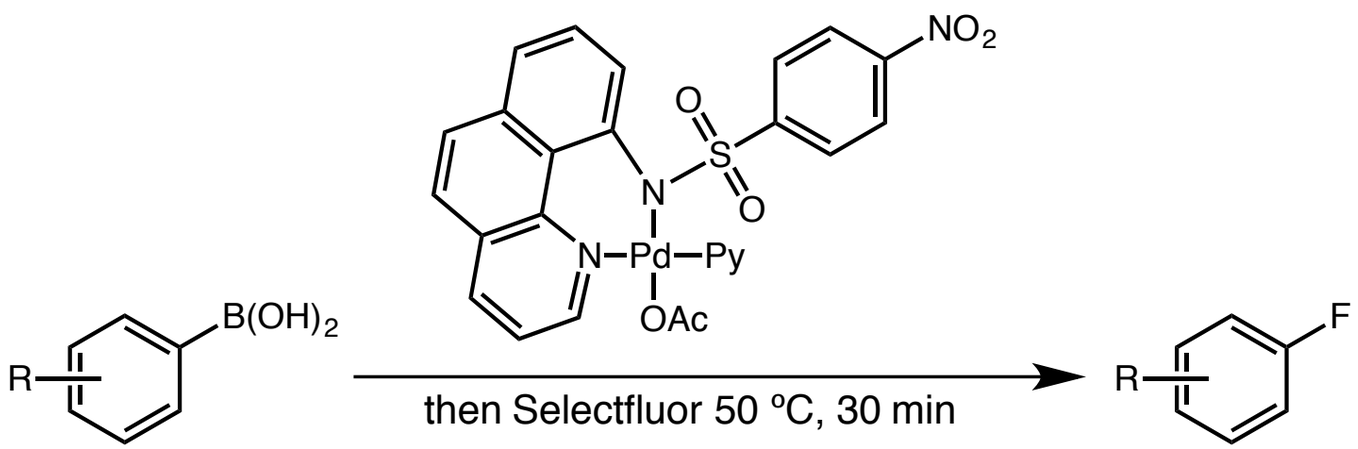

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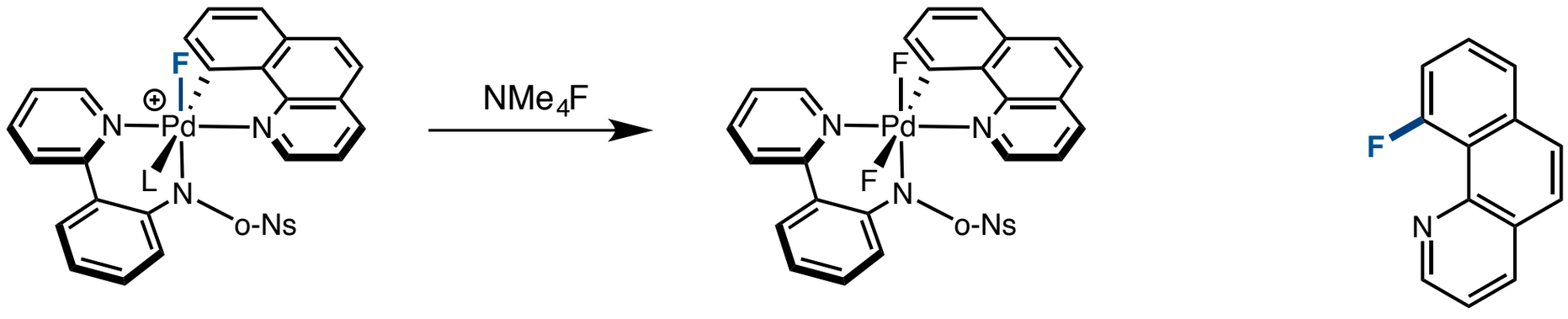

50 °C
94% Yield

150 °C
97% Yield

Hull, K. L.; Anani, W. Q.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 7134.
Furuya, T.; Kaiser, H. M.; Ritter, T. *Angew. Chem. Int. Ed.* **2008**, *47*, 5993.
Furuya, T.; Ritter, T. *J. Am. Chem. Soc.* **2008**, *130*, 10060.

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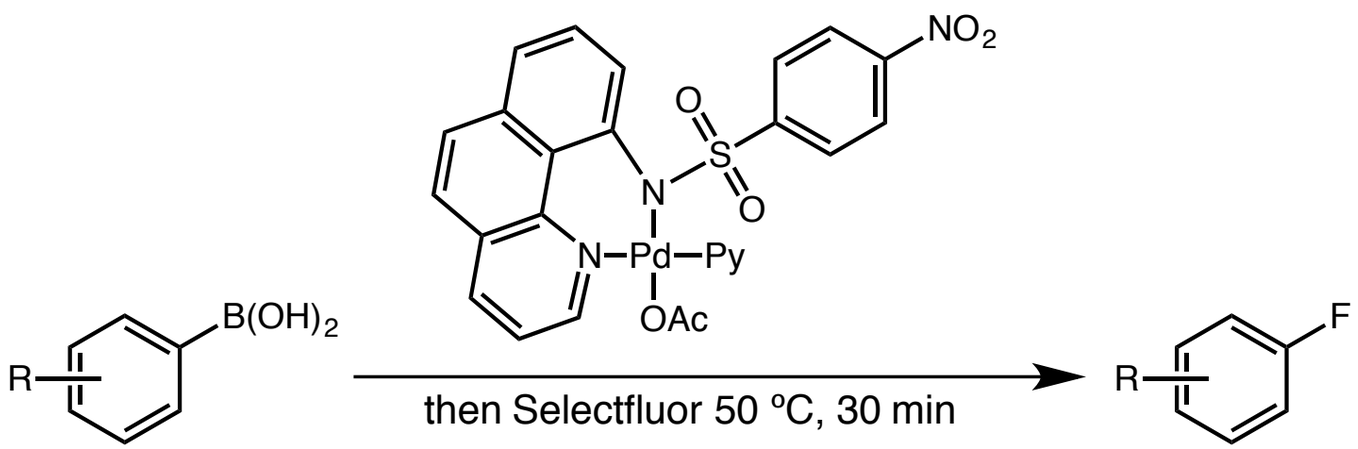

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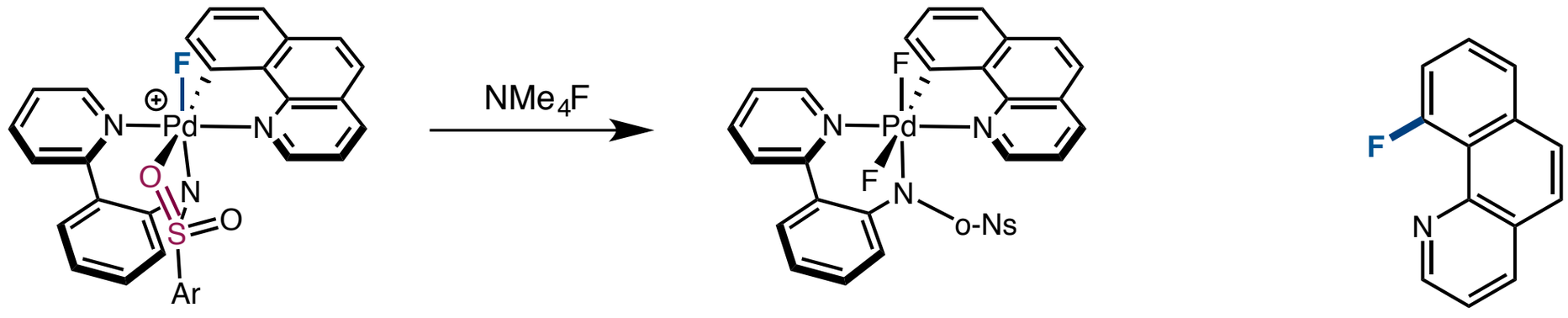

tridentate co-ordination of
the pyridyl-sulfonamide ligand

Hull, K. L.; Anani, W. Q.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 7134.
Furuya, T.; Kaiser, H. M.; Ritter, T. *Angew. Chem. Int. Ed.* **2008**, *47*, 5993.
Furuya, T.; Ritter, T. *J. Am. Chem. Soc.* **2008**, *130*, 10060.

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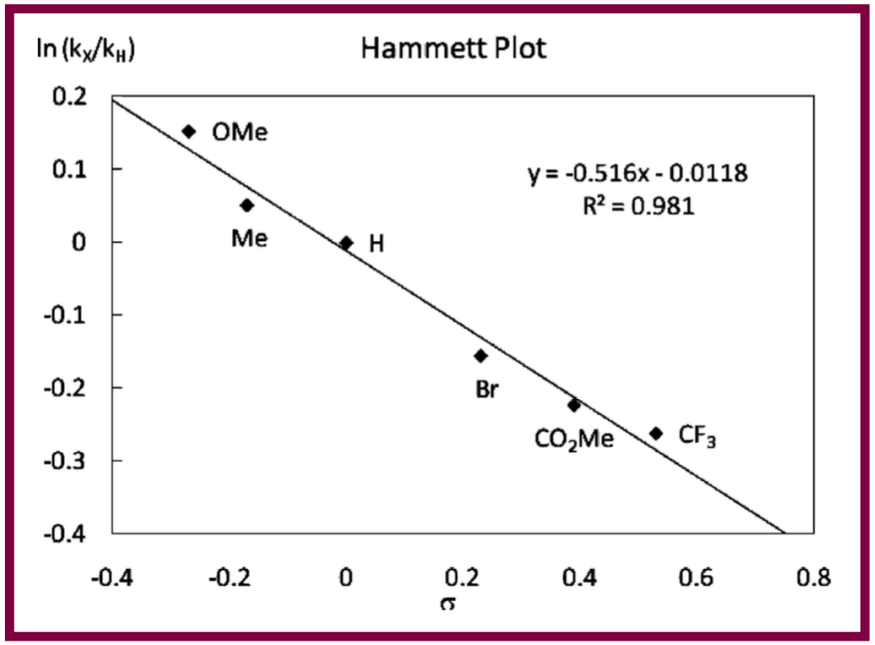
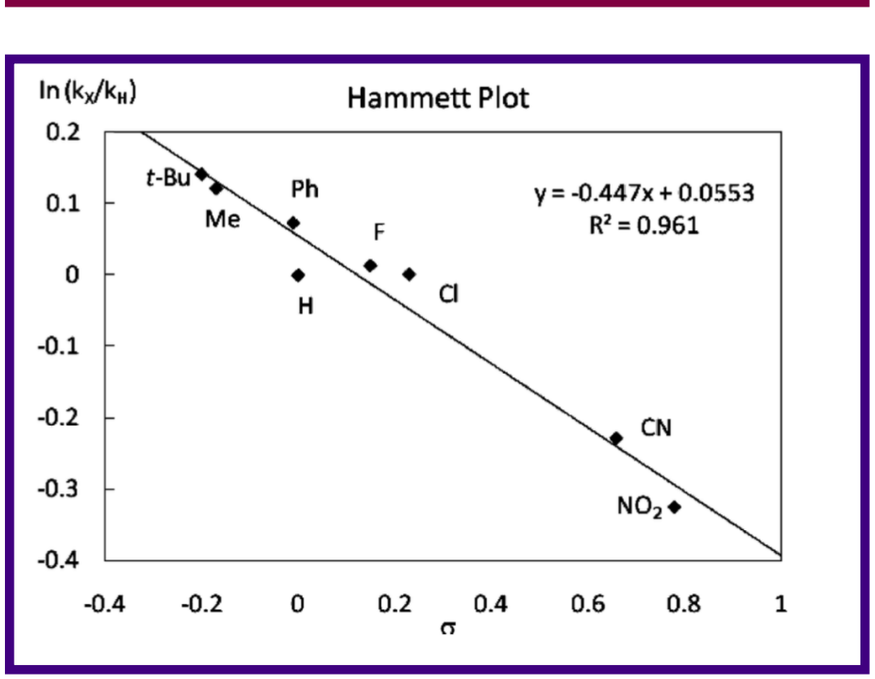
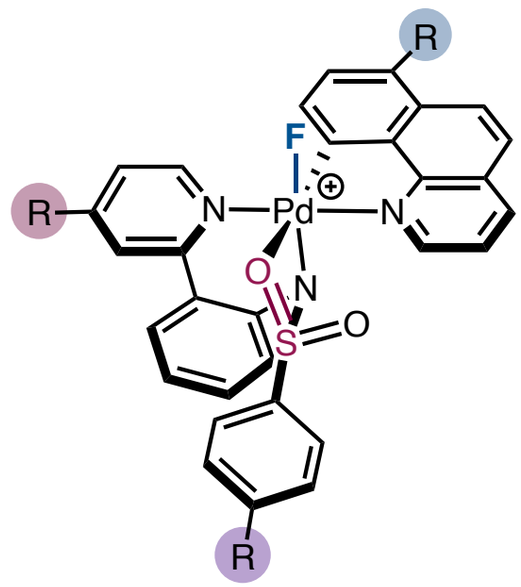
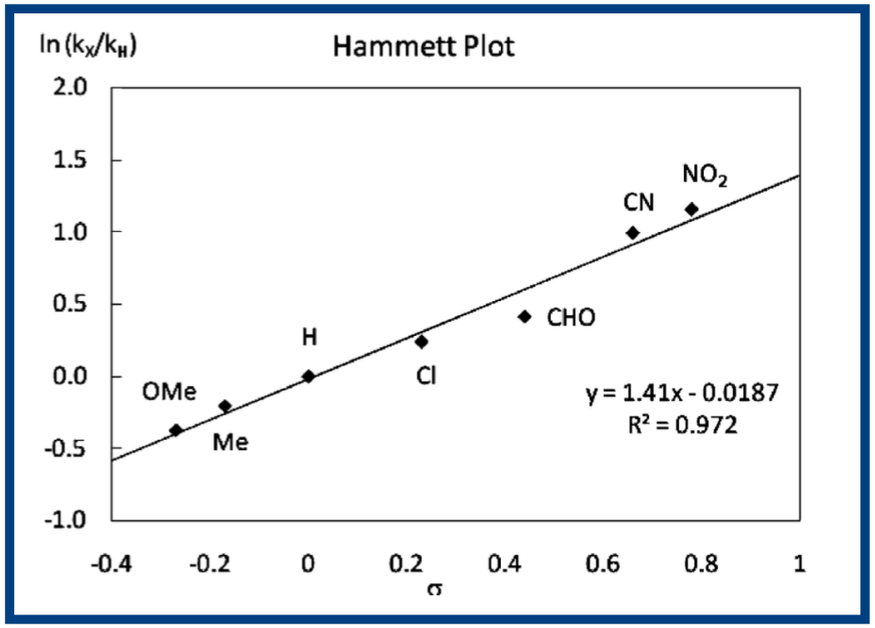
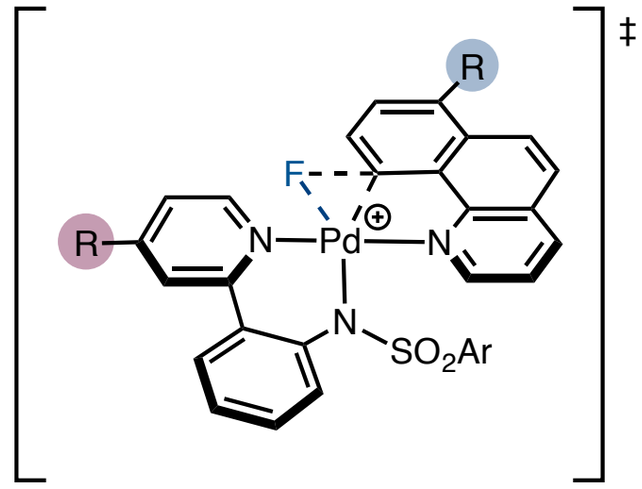




More electron rich Pd(IV) center – Faster RE







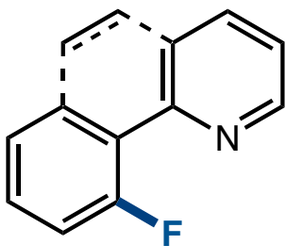
Trigonal prism

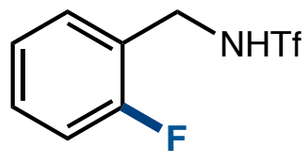
Sulfonamide ligand - basal
Significant +ve charge on Pd center in TS

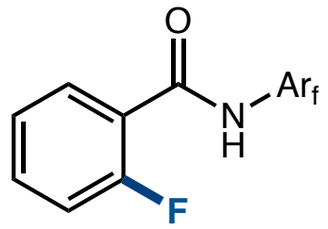
Ritter, T.; Goddard, W. A. III et al. *J. Am. Chem. Soc.* **2010**, *132*, 3793.

Palladium Mediated Aryl–F Bond Formation

C–H activation – Limited Substrate Scope

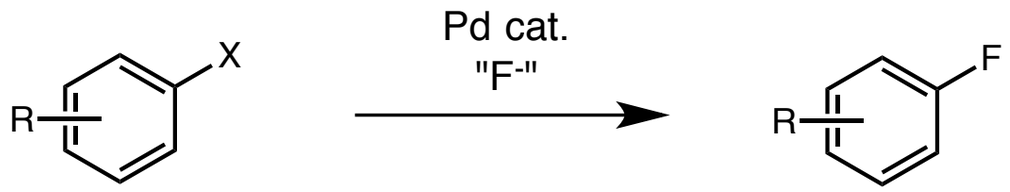






Ritter technology – Controllable regioselectivity but stiochiometric in Palladium

Ideal Reaction – But reductive elimination from Pd(II) is much more challenging



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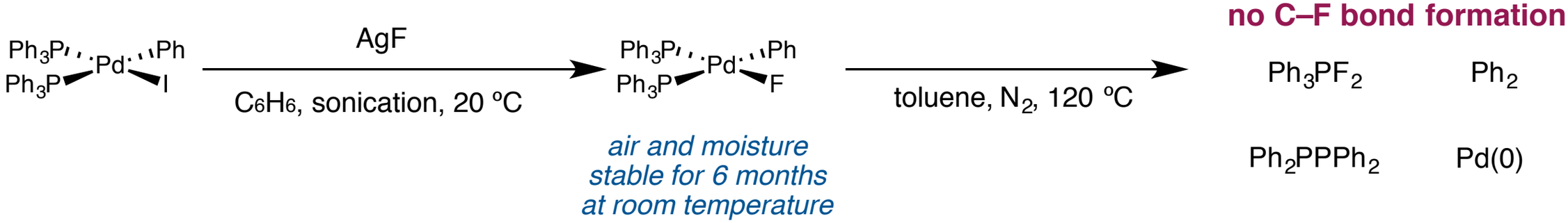
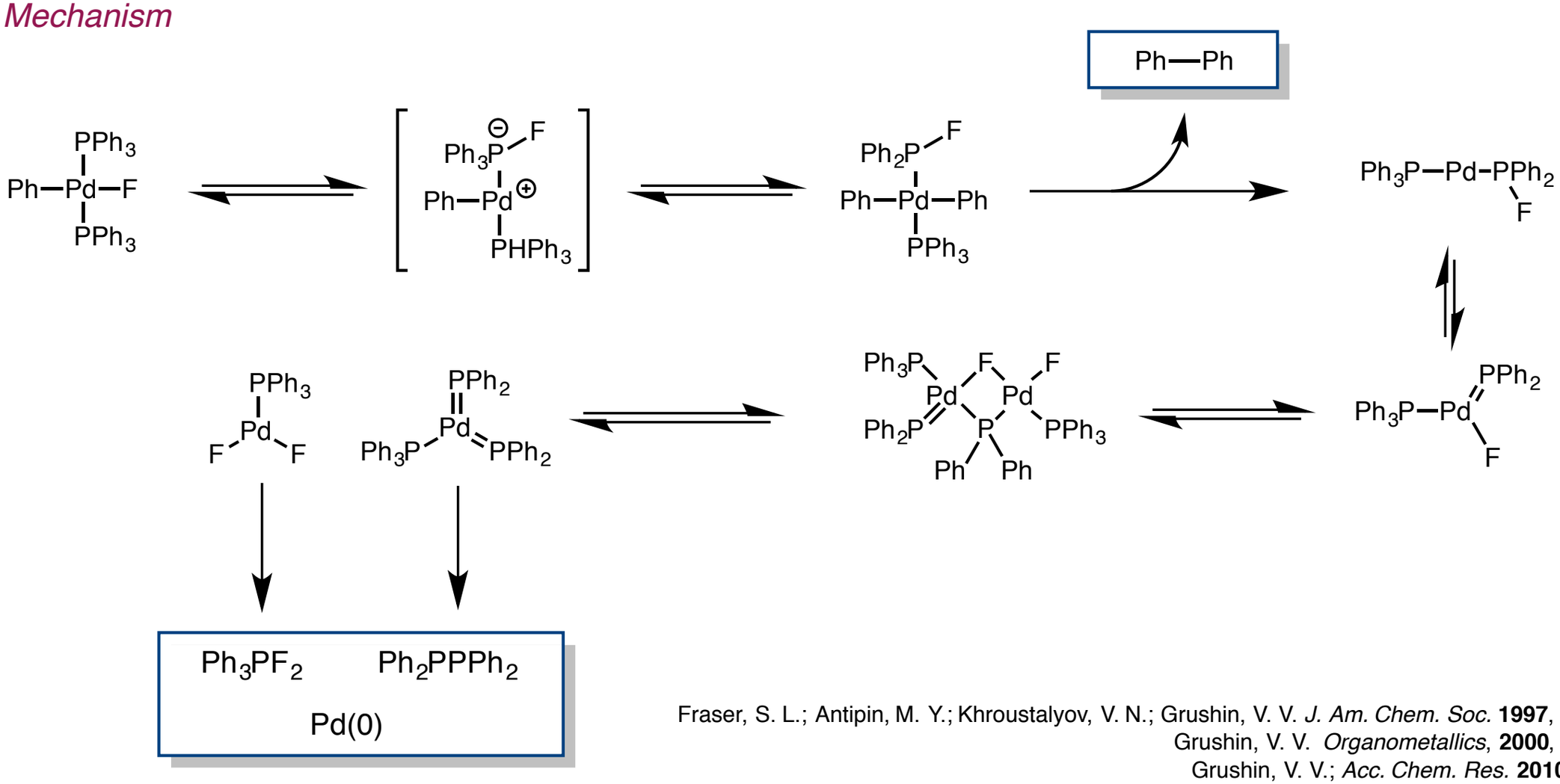
Furuya, T.; Kaiser, H. M.; Ritter, T. *Angew. Chem. Int. Ed.* **2008**, *47*, 5993.
Wang, X.; Mei, T. -S.; Yu, J. –Q. *J. Am. Chem. Soc.* **2009**, *131*, 7520.
Chan, K. S. L.; Wasa, M.; Wang, X.; Yu, J. –Q. *Angew. Chem. Int. Ed.* **2011**, *50*, 9081.

Palladium Mediated Aryl–F Bond Formation

Reductive elimination from Pd(II) is challenging



Mechanism



Fraser, S. L.; Antipin, M. Y.; Khroustalyov, V. N.; Grushin, V. V. *J. Am. Chem. Soc.* **1997**, *119*, 4769.
Grushin, V. V. *Organometallics*, **2000**, *19*, 1888.
Grushin, V. V.; *Acc. Chem. Res.* **2010**, *43*, 160.
Grushin, V. V.; Marshall, W. J. *Organometallics.* **2007**, *26*, 4997.

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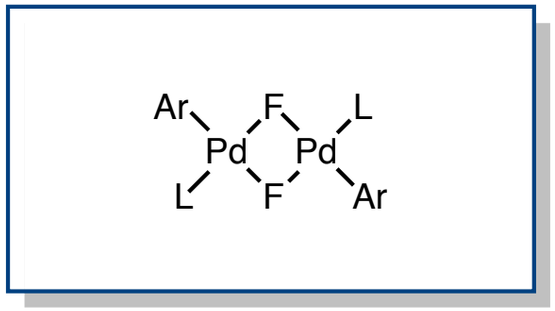
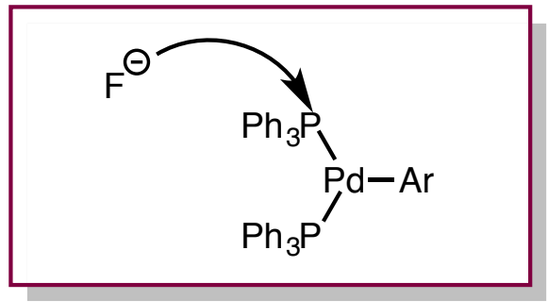
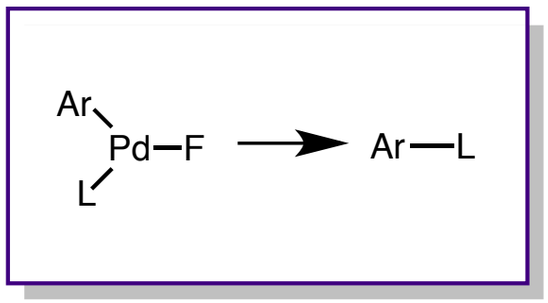




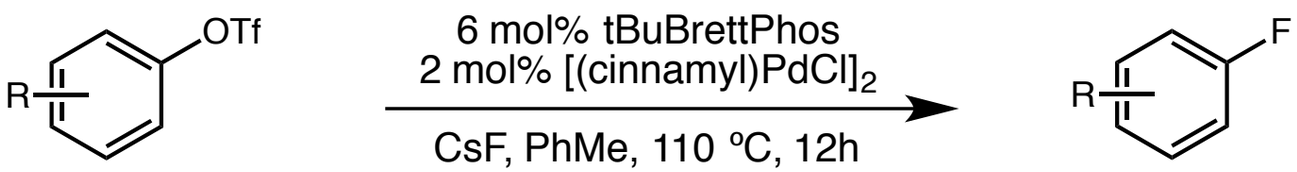


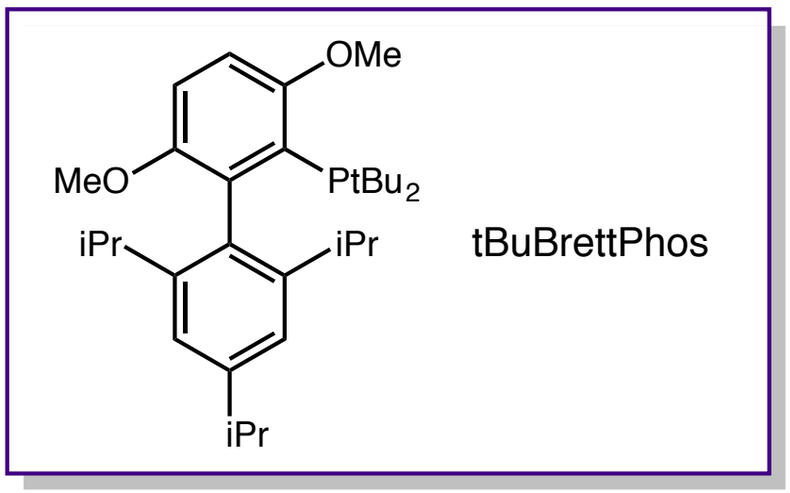
After working on this problem for ~10 years –

"Our work has shown that conventional tertiary phosphines, which are most widely used for Pd catalysis, are unlikely to be useful for the desired C–F bond formation at the metal center"

-Grushin 2007

Buchwald 2008





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Watson, D. A.; Su, M.; Teverovskiy G.; Zhang, Y.; Garcia-Fortanet, J.; Kinzel, T.; Buchwalk, S. L. *Science,* **2008**, 325, 1661.
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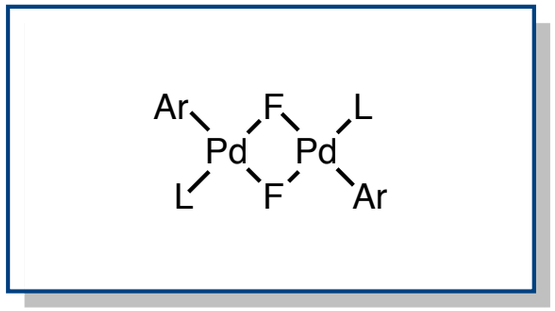

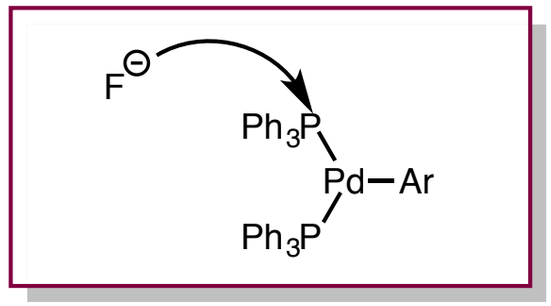

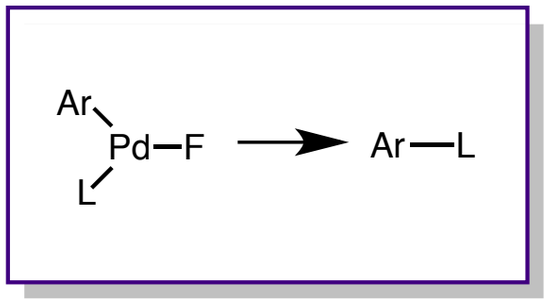

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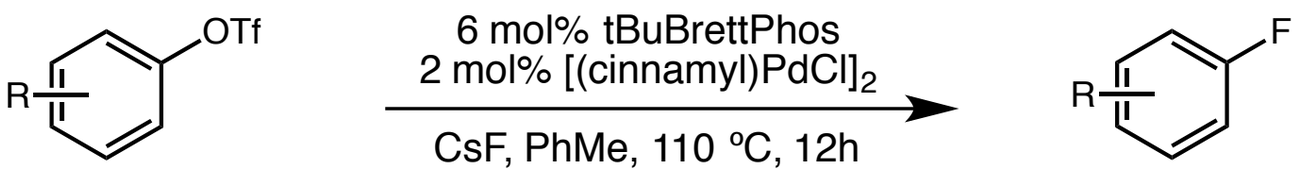

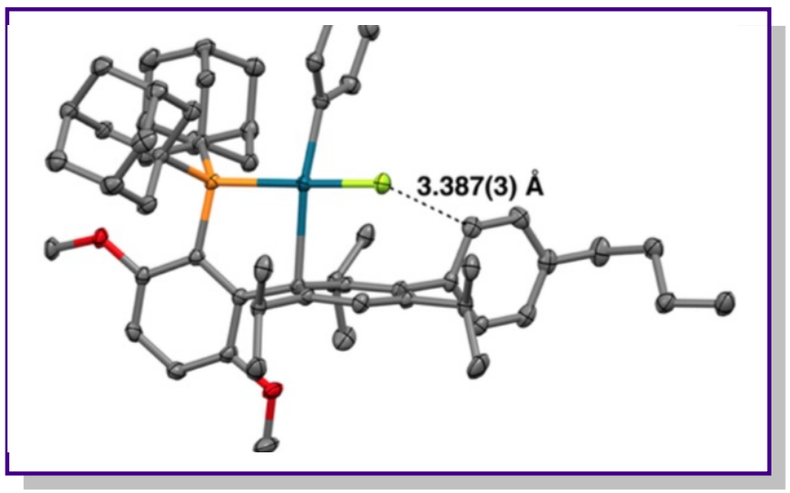

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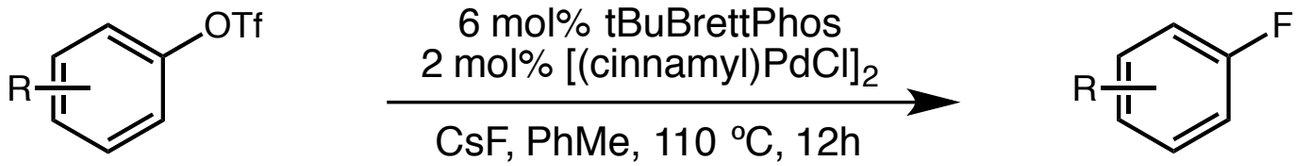
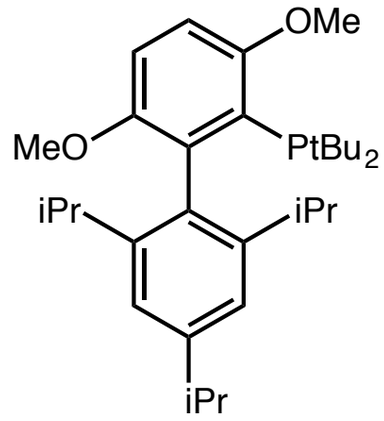
Grushin, V. V.; *Acc. Chem. Res.* **2010**, *43*, 160.

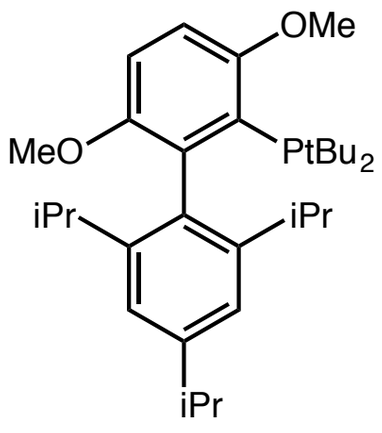
Palladium Mediated Aryl–F Bond Formation

Buchwald 2008



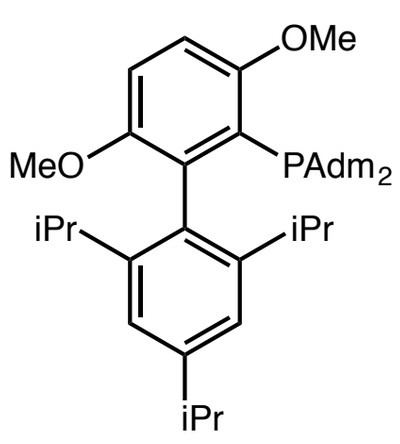


tBuBrettPhos



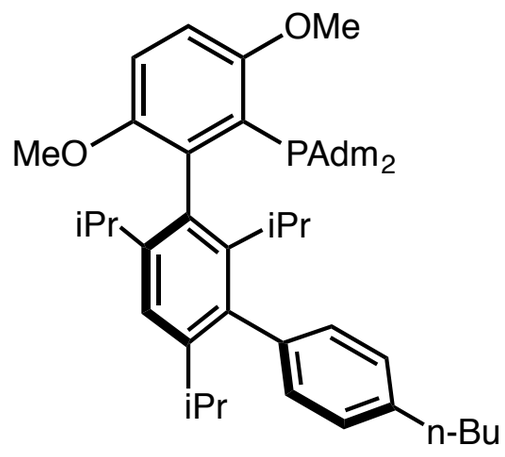
tBuBrettPhos – 2008

Aryl and select Heteroaryl Triflates



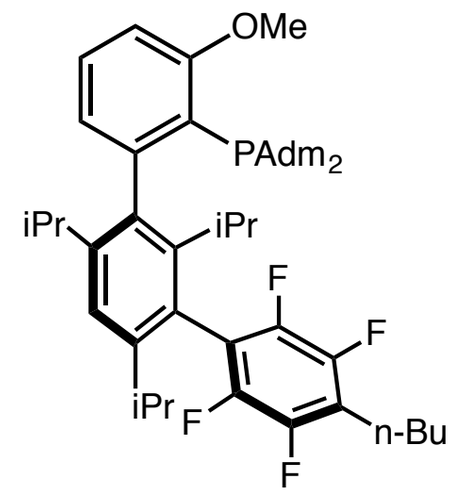
AdmBrettPhos – 2013

Aryl and Hetereoaryl Triflates



Arylated Ligand – 2014

Removes the induction period
Aryl bromides now work



AlPhos – 2015

Aryl and Hetereoaryl Bromides at **room temperature**

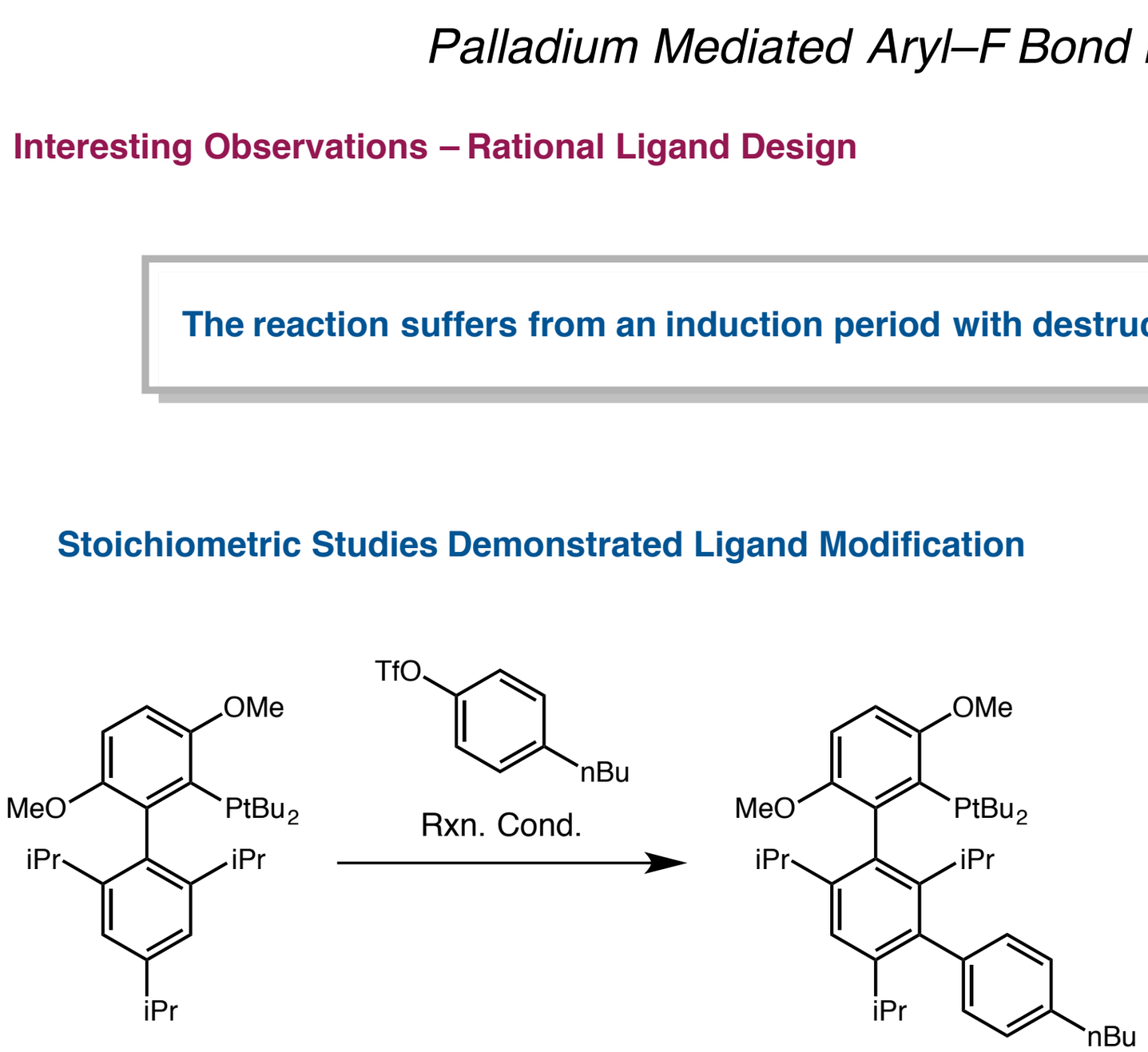
Watson, D. A.; Su, M.; Teverovskiy G.; Zhang, Y.; Garcia-Fortanet, J.; Kinzel, T.; Buchwald, S. L. *Science,* **2008**, 325, 1661.
Lee, H. G.; Milner, P. J.; Buchwald, S. L. *Org. Lett.* **2013**, 15, 5602.
Lee, H. G.; Milner, P. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2014**, 136, 3792.
Sather, A. C.; Lee, H. G.; De La Rosa, V. Y.; Yang, Y.; Muller, P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2015**, 137, 13433.
Milner, P. J.; Yang, Y.; Buchwald, S. L. *Organometallics.* **2015**, 34, 4775.

Palladium Mediated Aryl–F Bond Formation

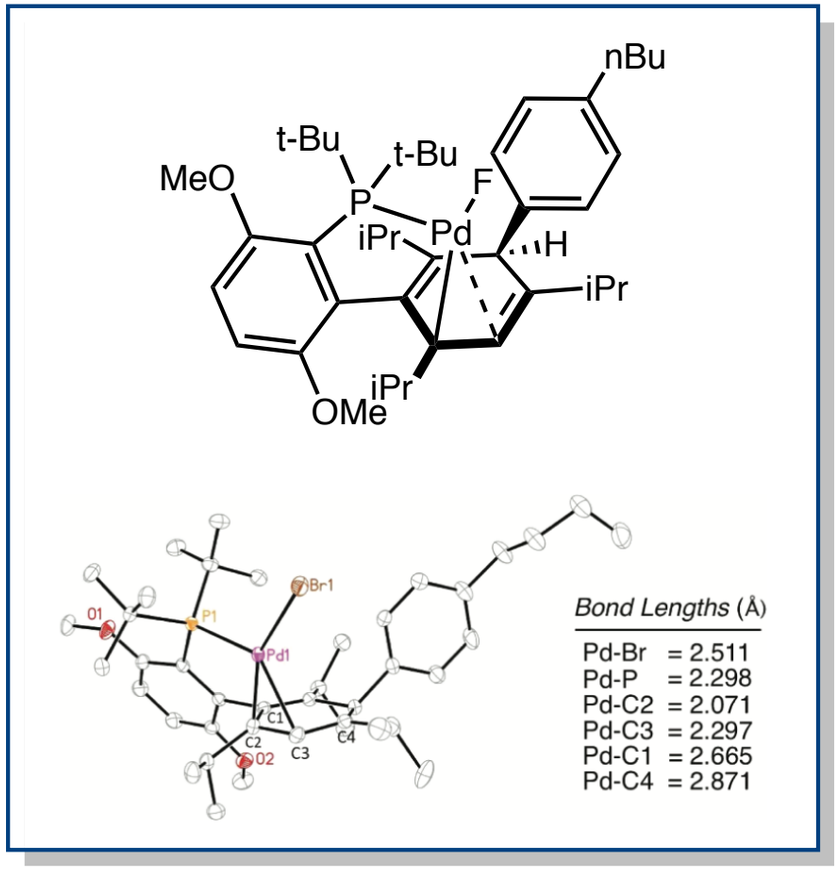
Interesting Observations – Rational Ligand Design

The reaction suffers from an induction period with destruction of the ArOTf susbtrate

Stoichiometric Studies Demonstrated Ligand Modification



tBuBrettPhos | **Functionalized Ligand**

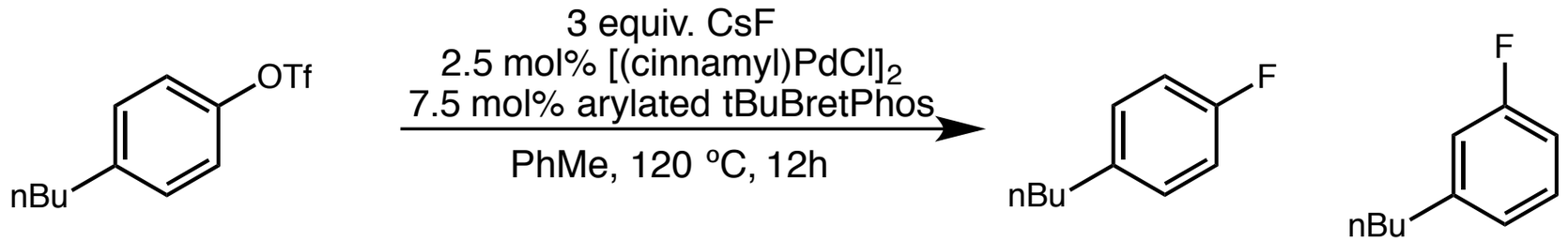


Watson, D. A.; Su, M.; Teverovskiy G.; Zhang, Y.; Garcia-Fortanet, J.; Kinzel, T.; Buchwald, S. L. *Science,* **2008**, 325, 1661.
Maimone, T. J.; Milner, P. J. Kinzel, T.; Zhang, Y.; Takase, M. K.; Buchwald, S. L. *J. Am. Chem. Soc.* **2011**, 133, 18106.
Milner, P. J.; Kinzel, T.; Zhang, Y.; Buchwald, S. L. *J. Am. Chem. Soc.* **2014**, 136, 15757.
Sather, A. C.; Lee, H. G.; De La Rosa, V. Y.; Yang, Y.; Muller, P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2015**, 137, 13433.

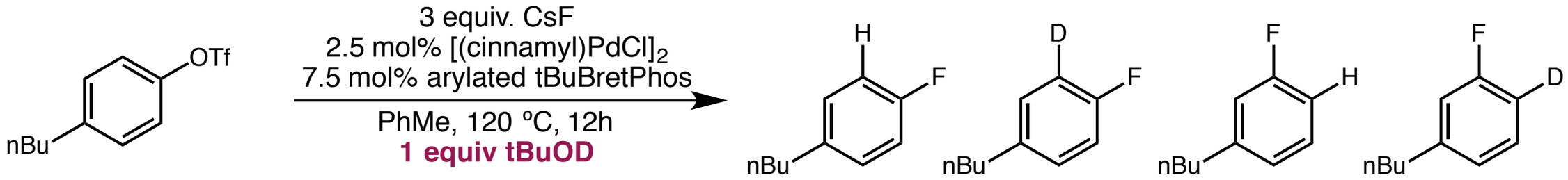
Palladium Mediated Aryl–F Bond Formation

Interesting Observations – Rational Ligand Design

Certain substrates lead to a mixture of regioisomers



70% Yield **1.5:1 rr**



30% 3% 14% 8%

2,6-dideutared aryl triflates show improved regioselecitivity compared to there non deuterated analogues

Watson, D. A.; Su, M.; Teverovskiy G.; Zhang, Y.; Garcia-Fortanet, J.; Kinzel, T.; Buchwald, S. L. *Science,* **2008**, 325, 1661.
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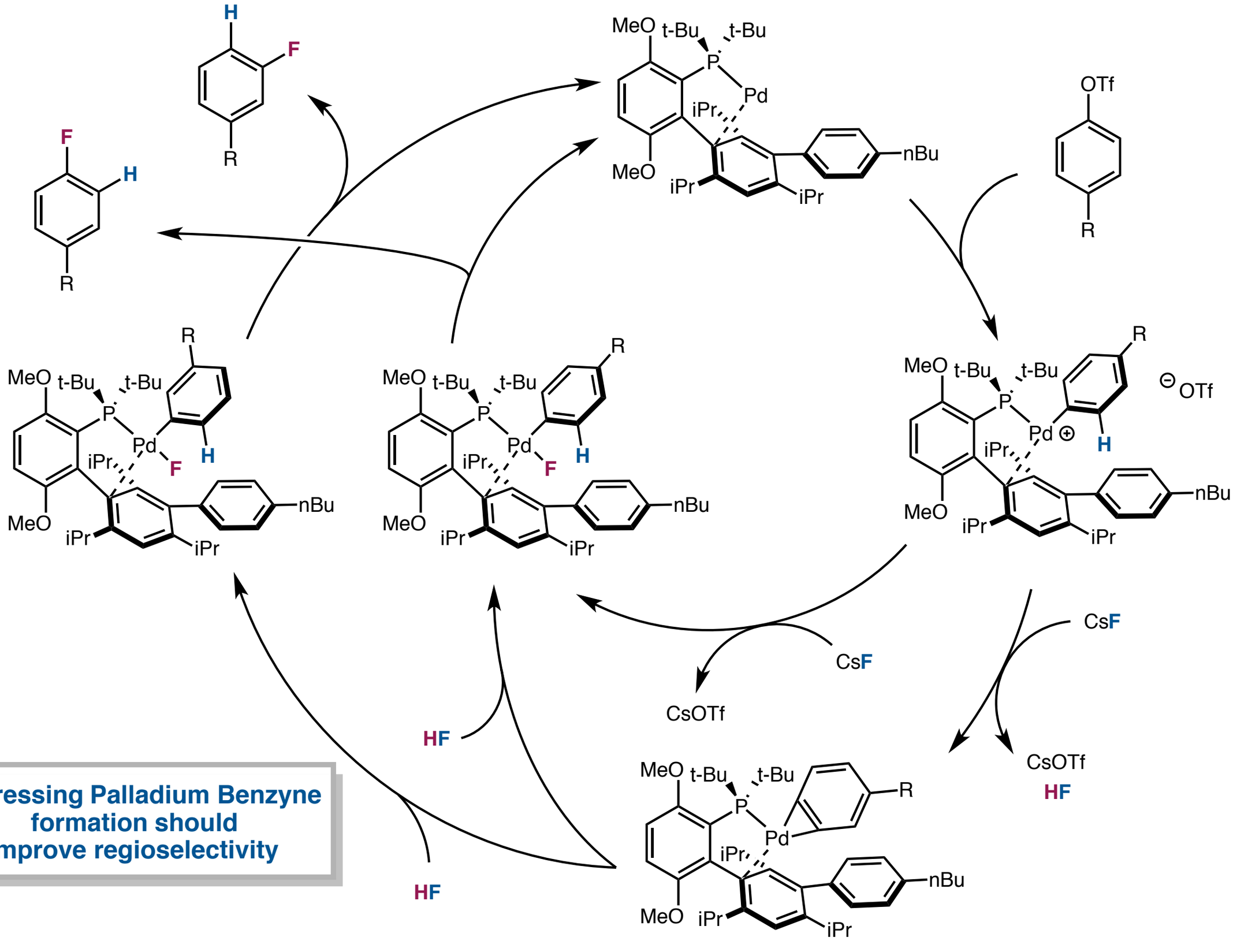
Palladium Mediated Aryl–F Bond Formation

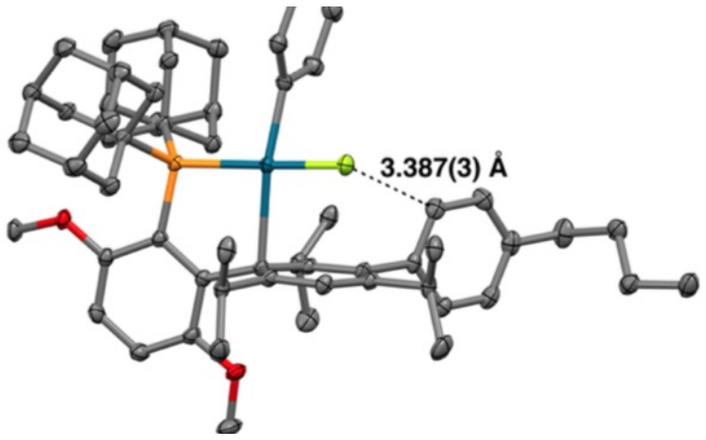


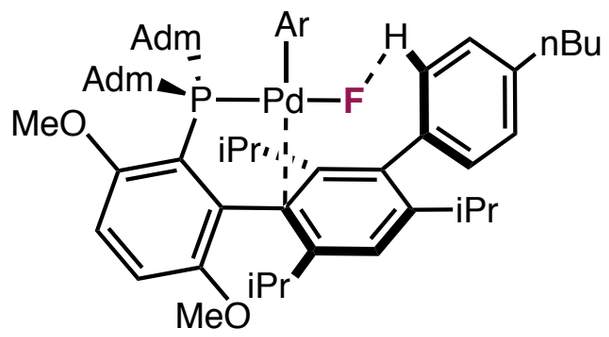
Supressing Palladium Benzyne formation should improve regioselectivity

Palladium Mediated Aryl–F Bond Formation

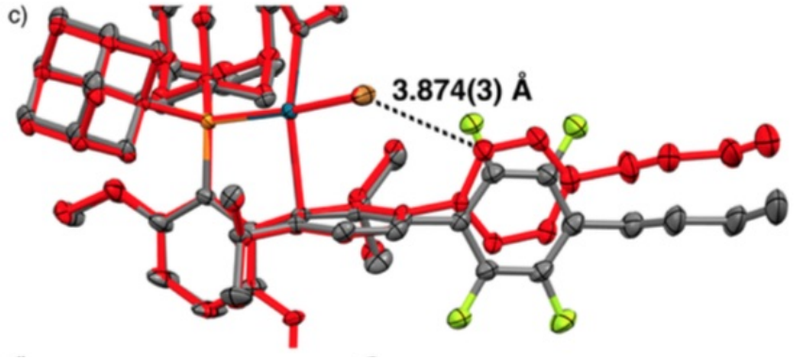
Rational Ligand Design

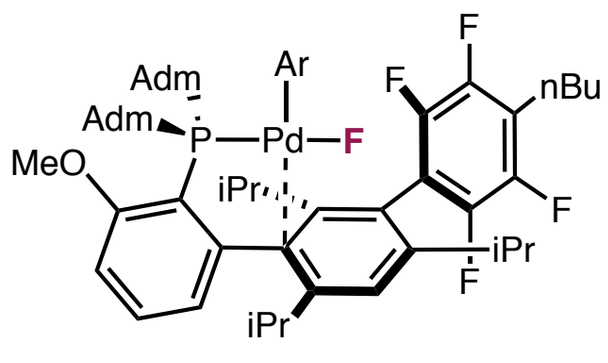
High reaction temperatures required for reductive elimination





Internal H-bonding interaction stabilizes fluoride ligand – retards reductive elimination



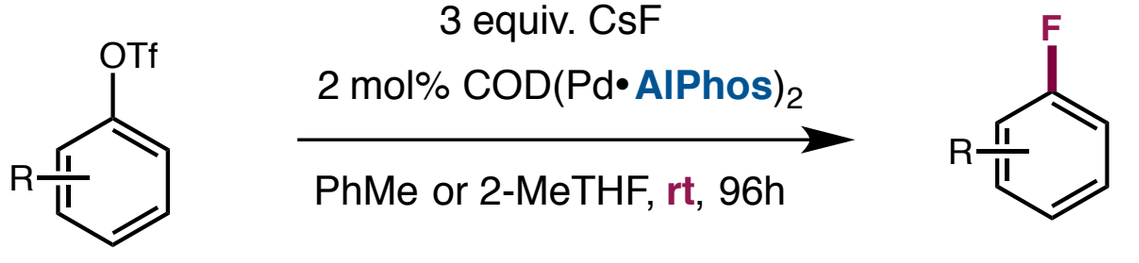


This complex reductively eliminates at room temperature !

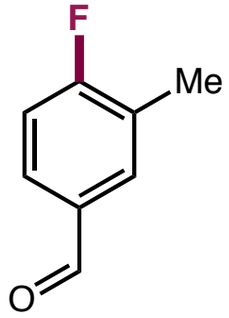
Sather, A. C.; Lee, H. G.; De La Rosa, V. Y.; Yang, Y.; Muller, P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2015**, 137, 13433.

Palladium Mediated Aryl–F Bond Formation

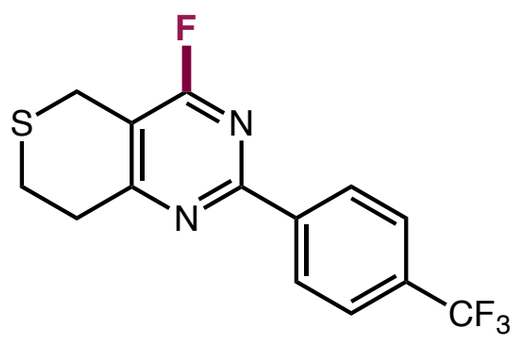
State of the art technology



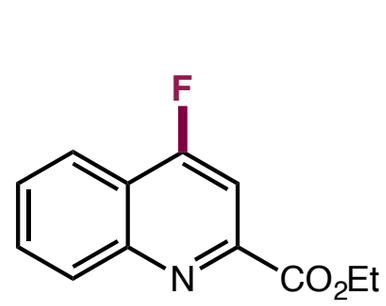
>100:1 rr



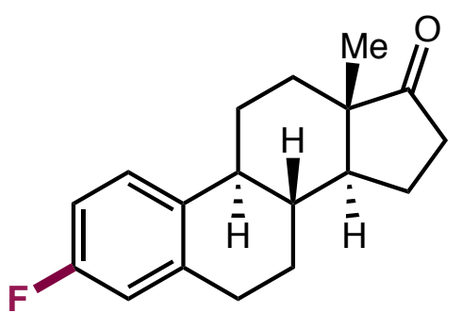
82% yield



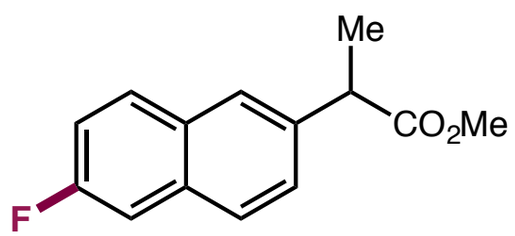
89% yield



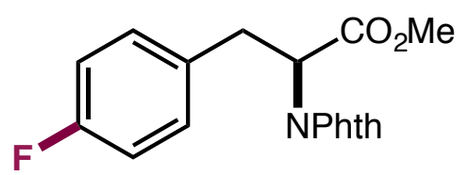
95% yield



81% yield



96% yield



92% yield

Sather, A. C.; Lee, H. G.; De La Rosa, V. Y.; Yang, Y.; Muller, P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2015**, 137, 13433.

Transition Metals Mediated Fluorination of Arenes and Heteroarenes

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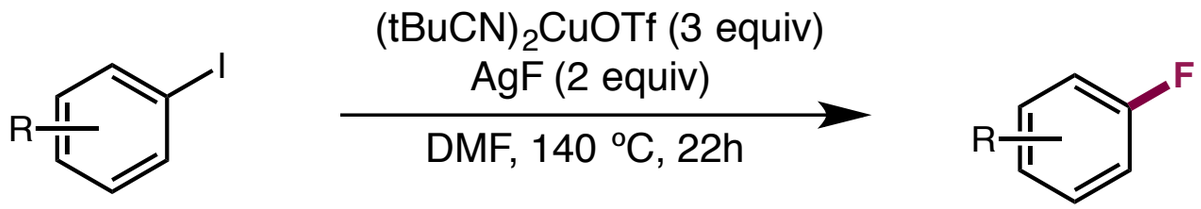
Paquin, J-R. et al. *Chem. Rev.* **2015**, *115*, 9073.
Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2015**, *54*, 2.

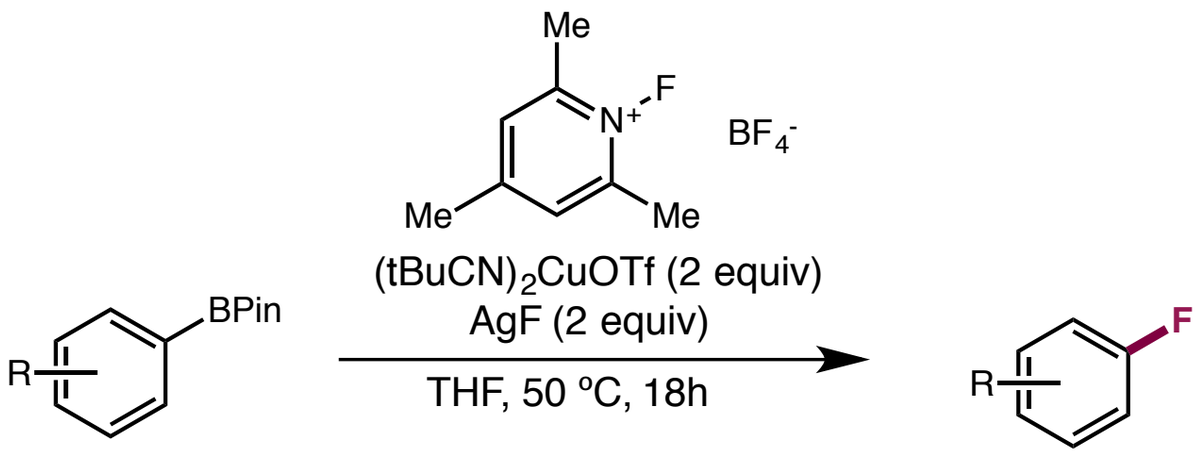
Copper Catalyzed Aryl–F Bond Formation

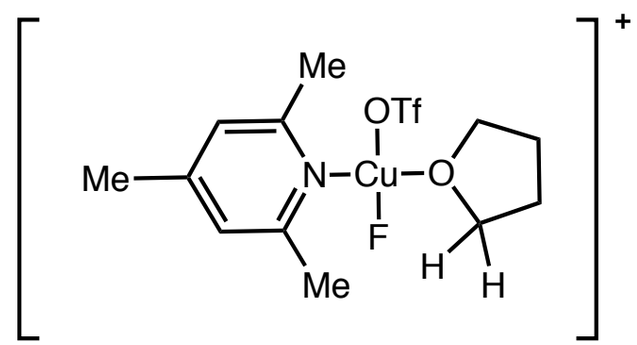
Reactions I'm not going to talk about in depth – Copper Mediated

Hartwig – 2012



Hartwig – 2013





Cu(III) observed spectrascopically

Mass Spec

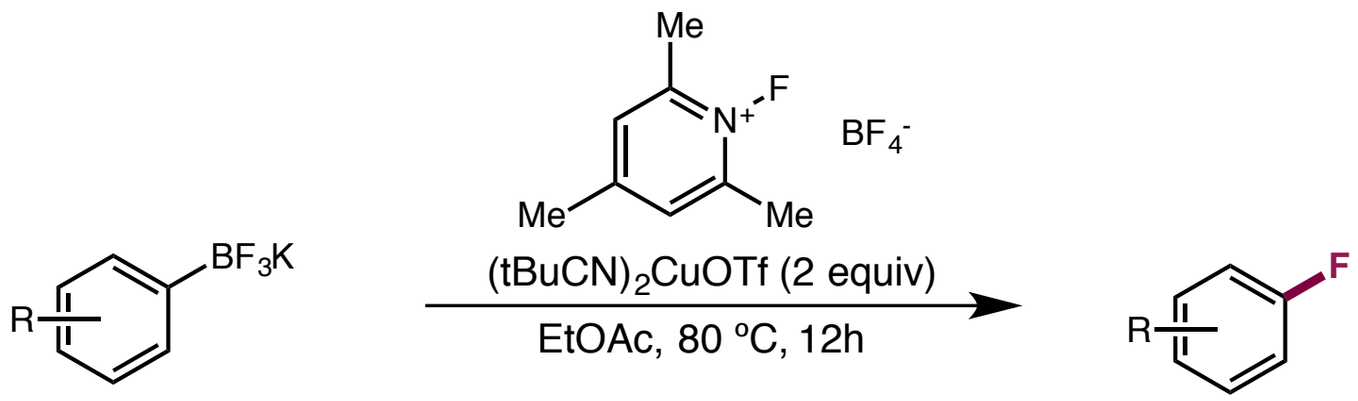
^{19}F and ^{1}H NMR

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

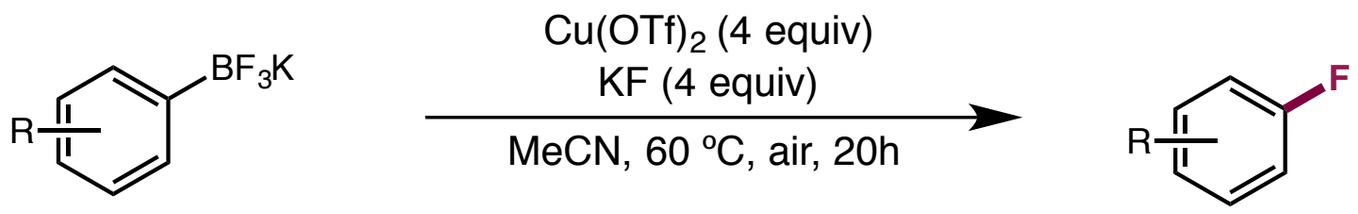
Copper Catalyzed Aryl–F Bond Formation

Reactions I'm not going to talk about in depth – Copper Mediated

Sanford – 2013



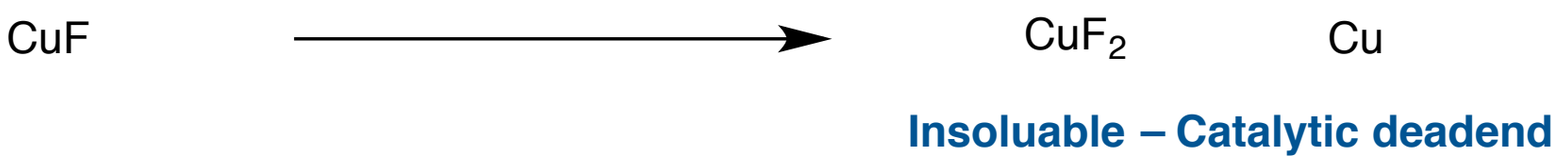
Sanford – 2013



Ye, Y.; Schimler, S. D.; Hanley, P. S.; Sanford, M. S. *J. Am. Chem. Soc.* **2013**, 135, 16292.
Ye, Y.; Sanford, M. S *J. Am. Chem. Soc.* **2013**, 135, 4848.

Copper Catalyzed Aryl–F Bond Formation

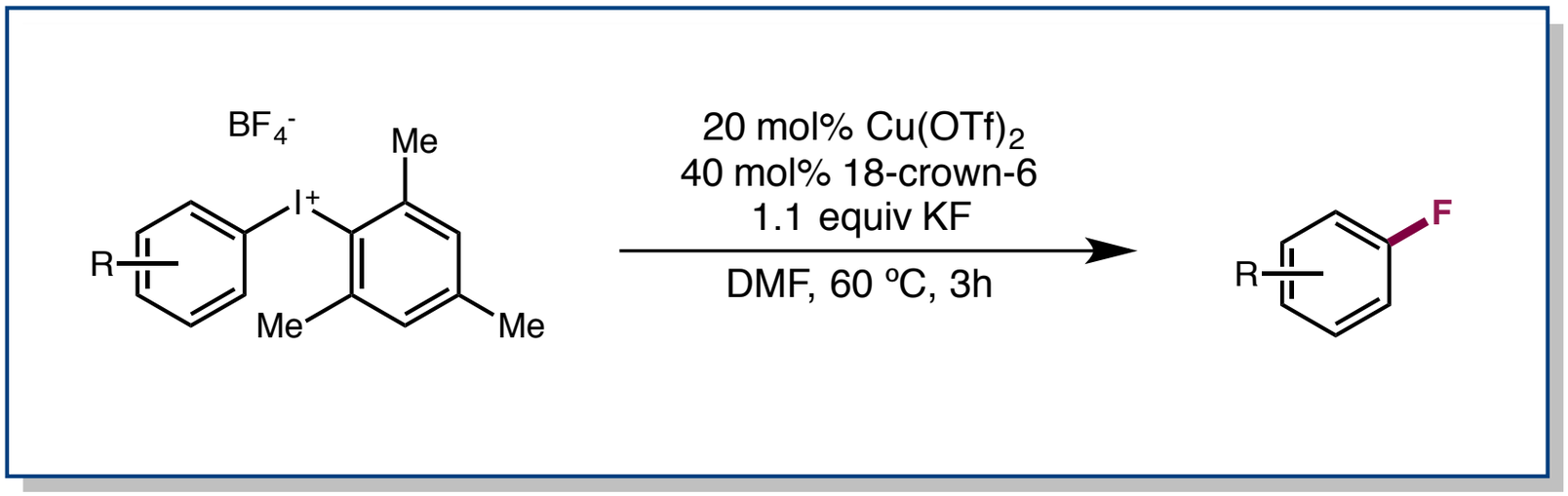
All of these methods are super–stoichiometric in copper – Copper Fluoride is prone to disproportionation



Insoluable – Catalytic deadend

Complexation can stabilized Cu(I) fluorides but heating induces disproportionation

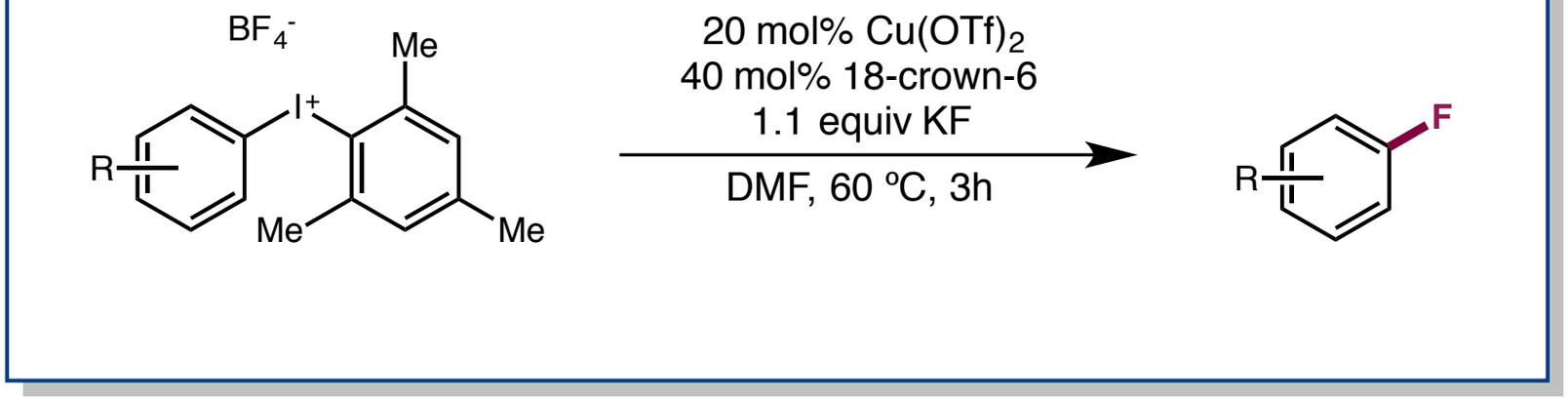
Sanford – 2013 First Method Catalytic in Copper

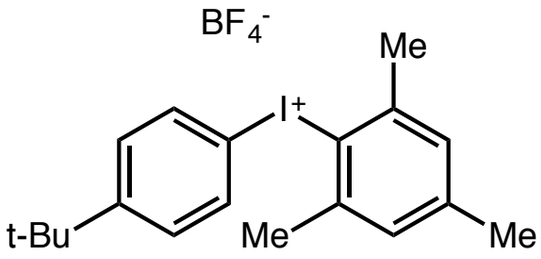


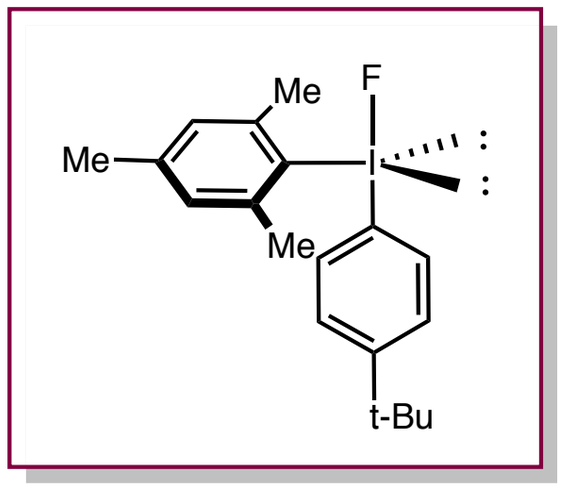
Ichiishi, N.; Canty, A. J.;Yates, B. F.; Sanford, M. S. *Org. Lett.* **2013**, *15,* 5134.
Ichiishi, N.; Canty, A. J.;Yates, B. F.; Sanford, M. S. *Organometallics* **2014**, *33,* 5525.

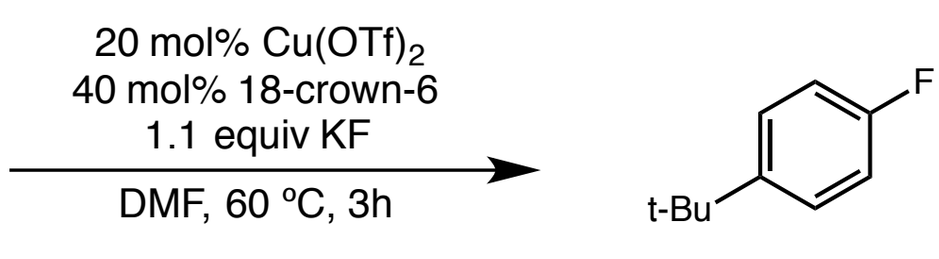
Copper Catalyzed Aryl–F Bond Formation

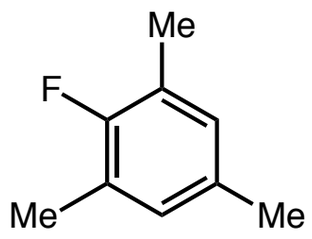
Sanford – 2013 First Method Catalytic in Copper











	73% Yield	>1% Yield
without [Cu]	2% Yield	40% Yield

The ratio of products in the absence of copper is strongly dependent on substrate electronics

Ichiishi, N.; Canty, A. J.;Yates, B. F.; Sanford, M. S. *Org. Lett.* **2013**, *15,* 5134.
Ichiishi, N.; Canty, A. J.;Yates, B. F.; Sanford, M. S. *Organometallics* **2014**, *33,* 5525.
Grushin, V. V.; Demkina, I. I.; Tolstaya, T. P. *J. Chem. Soc., Perkin Trans. 2* **1992**, 505.

Copper Catalyzed Aryl–F Bond Formation

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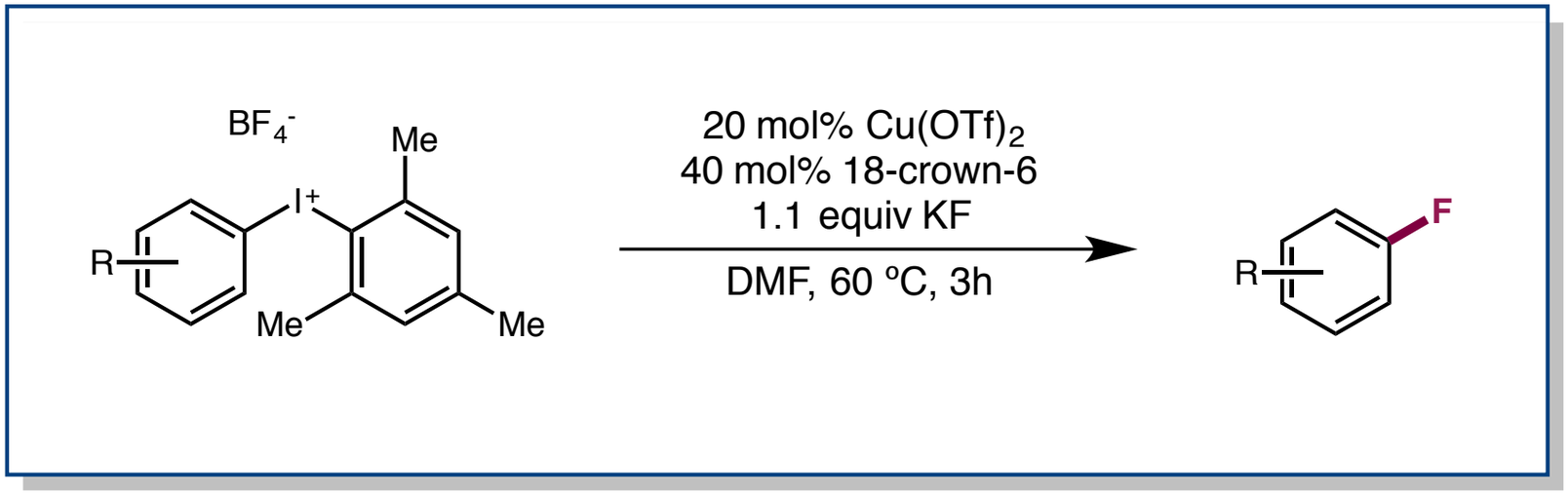

Cu(I) is formed in situ

Concentration of fluoride is kept low due to insolubility of KF in DMF

Ichiishi, N.; Canty, A. J.;Yates, B. F.; Sanford, M. S. *Org. Lett.* **2013**, *15,* 5134.
Ichiishi, N.; Canty, A. J.;Yates, B. F.; Sanford, M. S. *Organometallics* **2014**, *33,* 5525.
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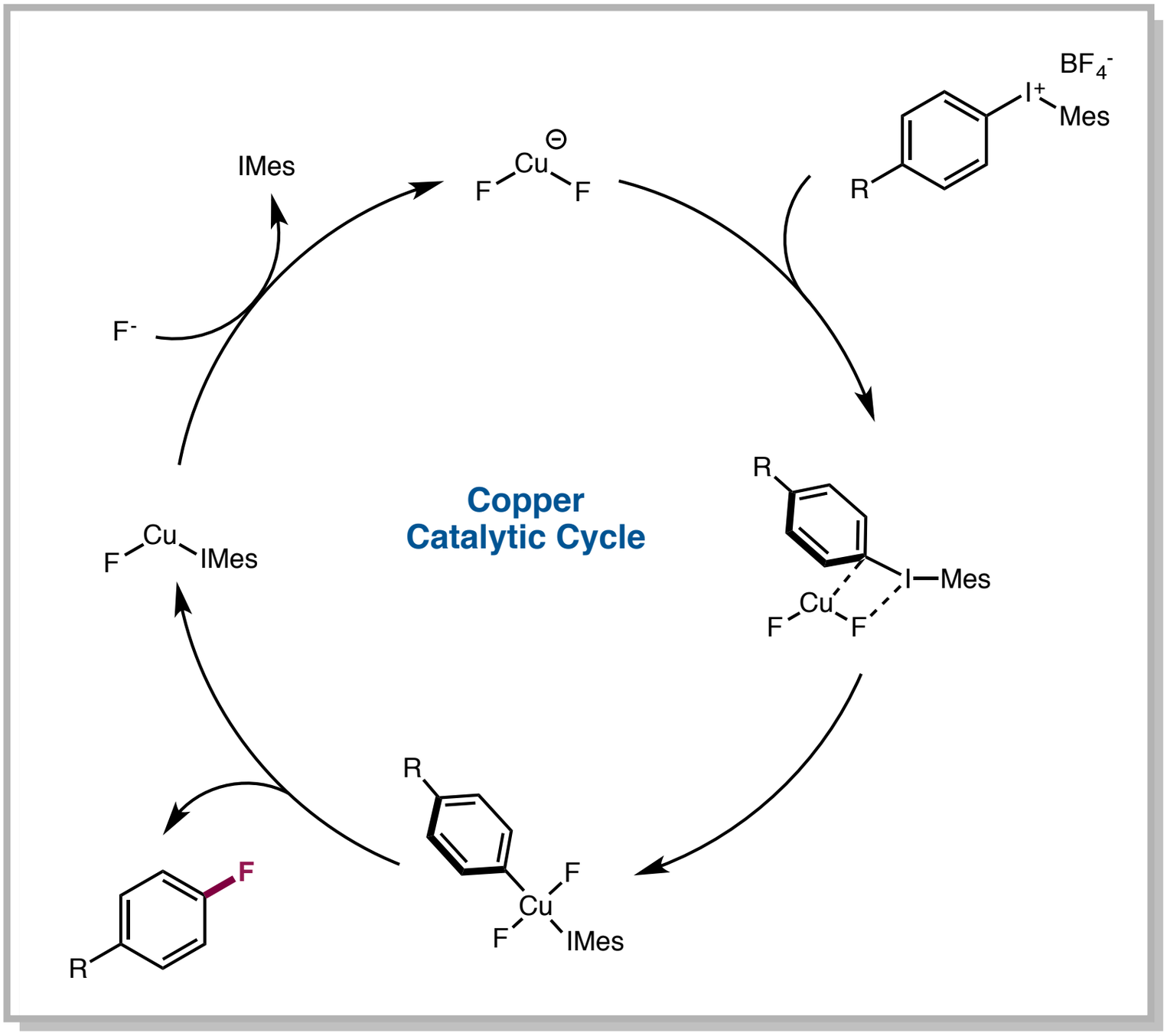
Copper Catalyzed Aryl–F Bond Formation



Rapid oxidative addition

Faster then Cu(I) disproportionation

Faster than backgroup reaction

18-Crown-6 allows for concentration of fluoride in solution to be controlled

Ichiishi, N.; Canty, A. J.;Yates, B. F.; Sanford, M. S. *Org. Lett.* **2013**, *15,* 5134.
Ichiishi, N.; Canty, A. J.;Yates, B. F.; Sanford, M. S. *Organometallics* **2014**, *33,* 5525.

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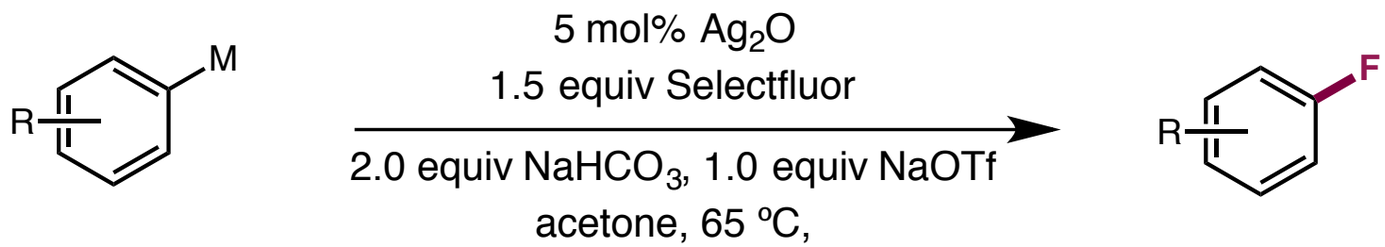
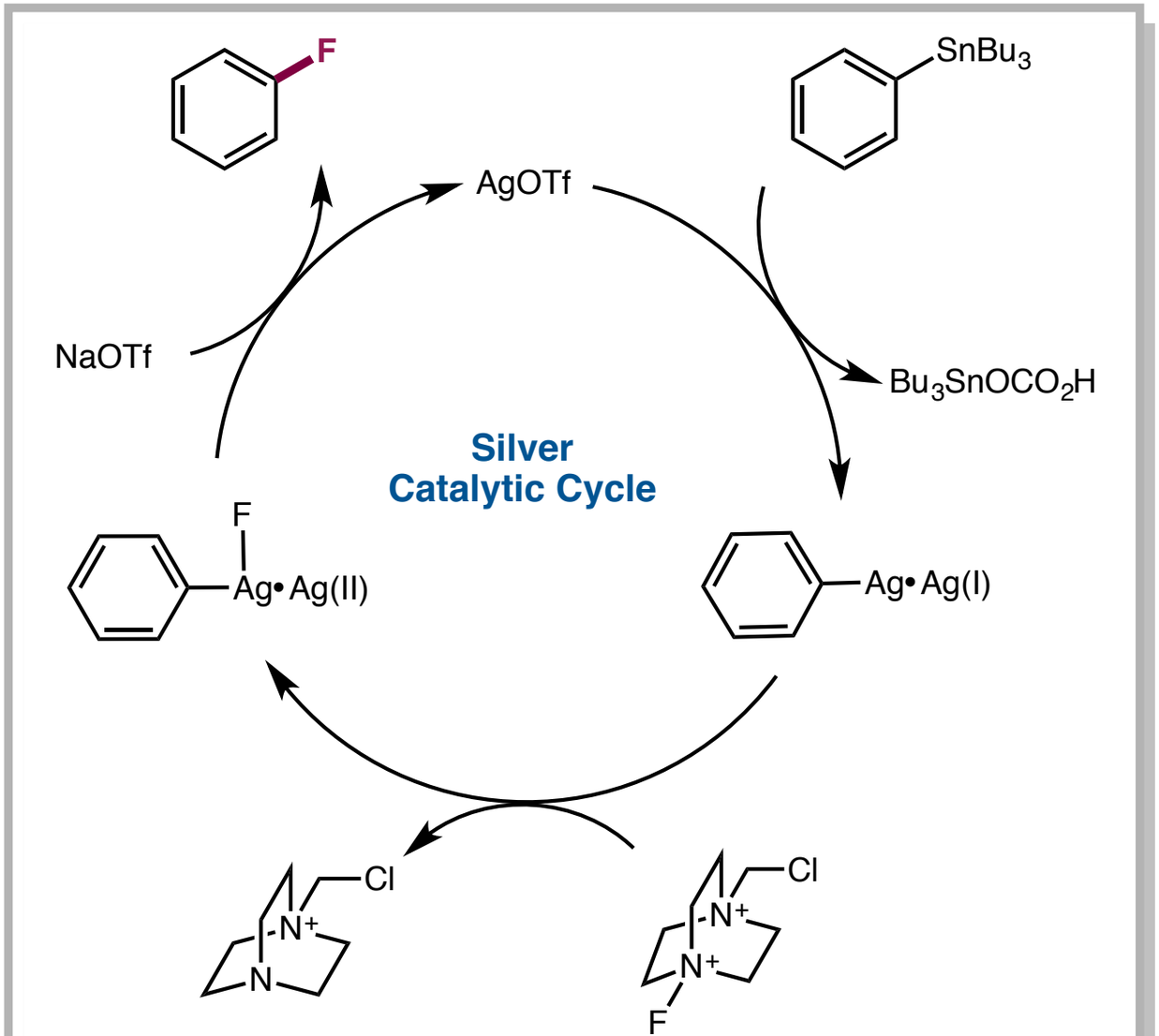
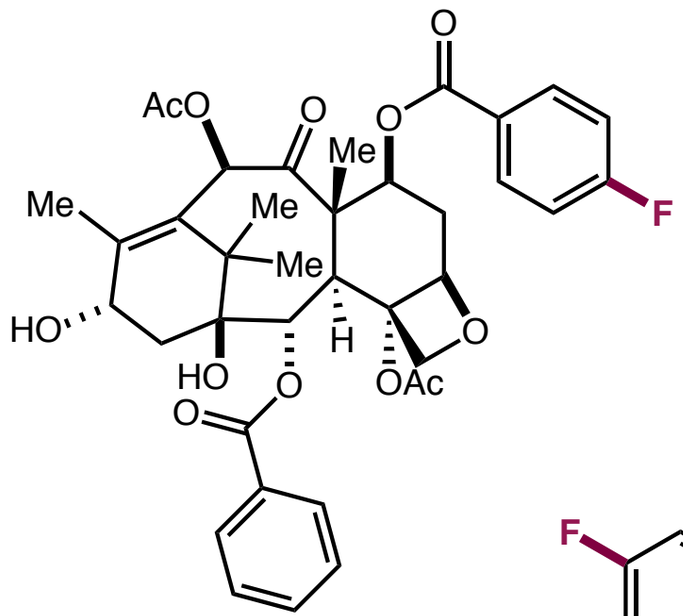
Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2015**, *54*, 2.

Silver Mediated Aryl–F Bond Formation

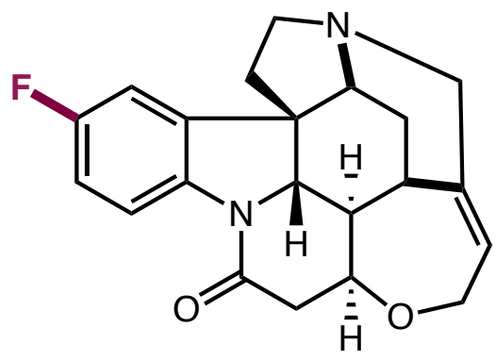
Silver (II) as a site for C–F bond formation







72% yield

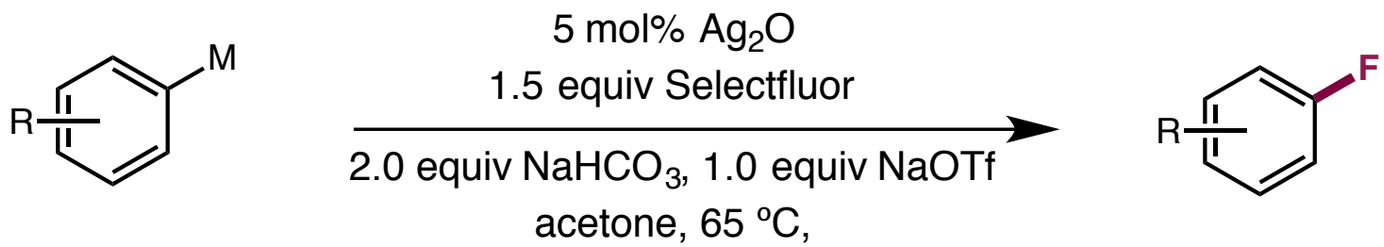


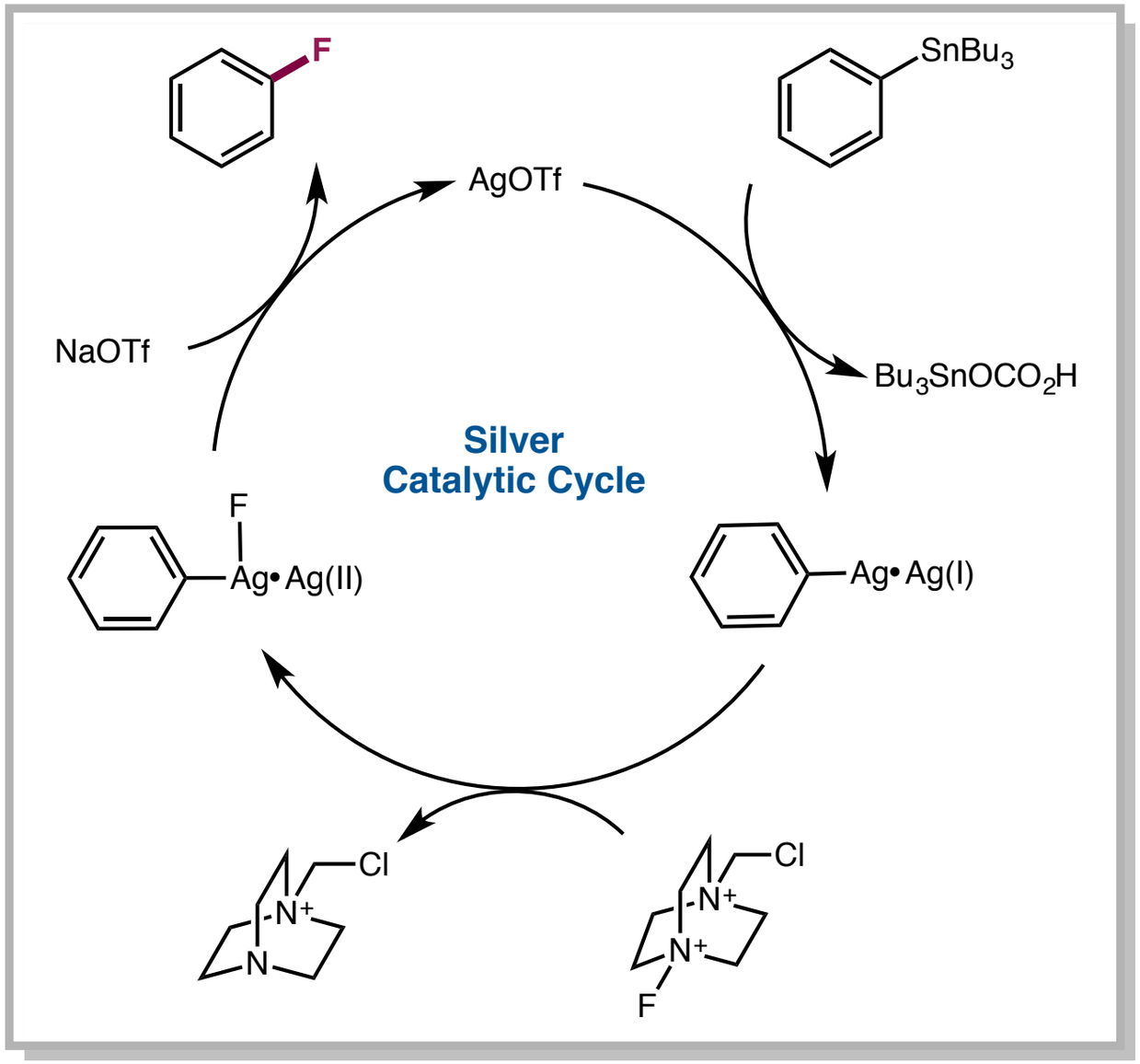
60% yield

Furuya, T.; Strom, A. E.; Ritter, T. *J. Am. Chem. Soc.*, **2009**, *131*, 1662
Furuya, T.; Ritter, T. *Org. Lett*, **2009**, *11*, 2860
Pingping, T.; Furuya, T.; Ritter, T. *J. Am. Chem. Soc.*, **2010**, *132*, 12150

Silver Mediated Aryl–F Bond Formation

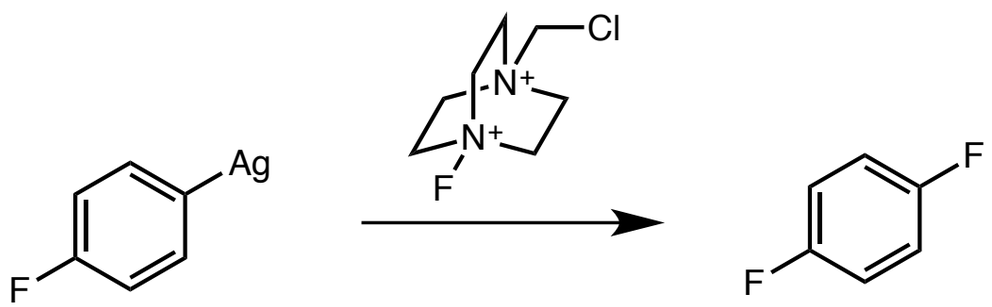
Silver (II) as a site for C–F bond formation





Radical scavengers did not impede the reaction

Addition of water lead to preferential phenol formation



47% yield

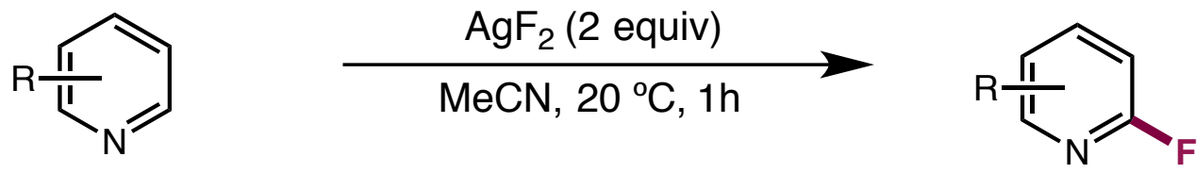
Addition of AgOTf 84% yield

Furuya, T.; Strom, A. E.; Ritter, T. *J. Am. Chem. Soc.*, **2009**, *131*, 1662
Furuya, T.; Ritter, T. *Org. Lett*, **2009**, *11*, 2860
Pingping, T.; Furuya, T.; Ritter, T. *J. Am. Chem. Soc.*, **2010**, *132*, 12150

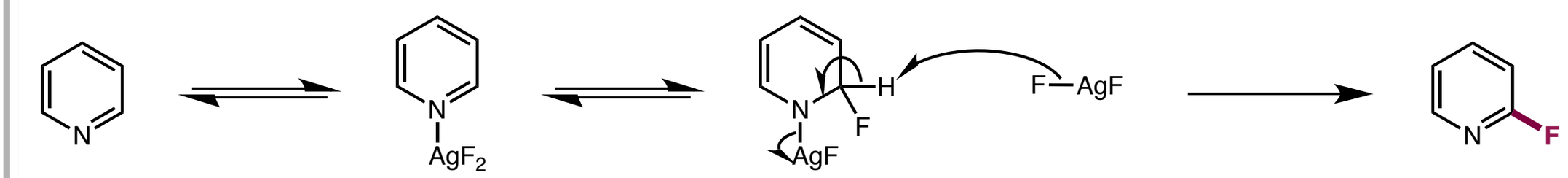
Silver Mediated Aryl–F Bond Formation

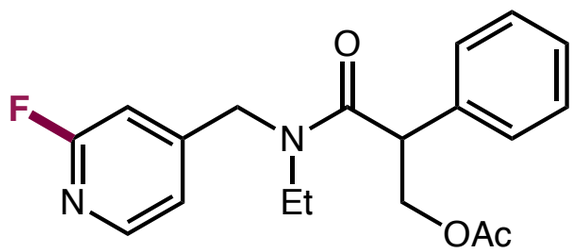
Silver (II) as a site for C–F bond formation

Hartwig – 2013

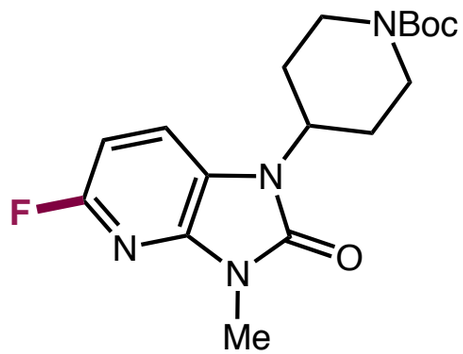


Pyridines and Diazenes

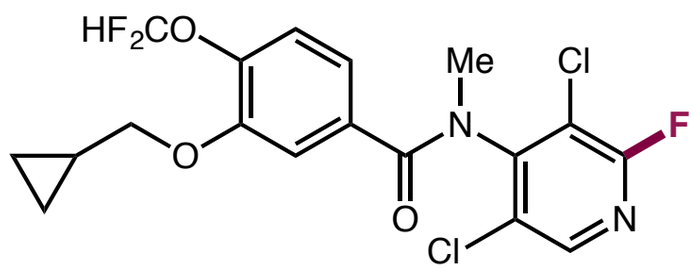




74% yield



75% yield



67% yield

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

Transition Metals Mediated Fluorination of Arenes and Heteroarenes

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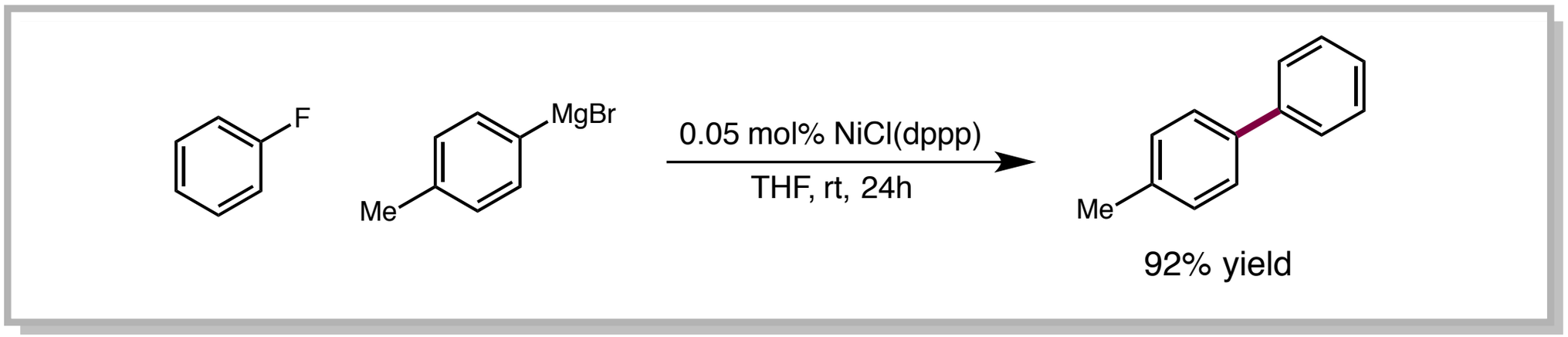
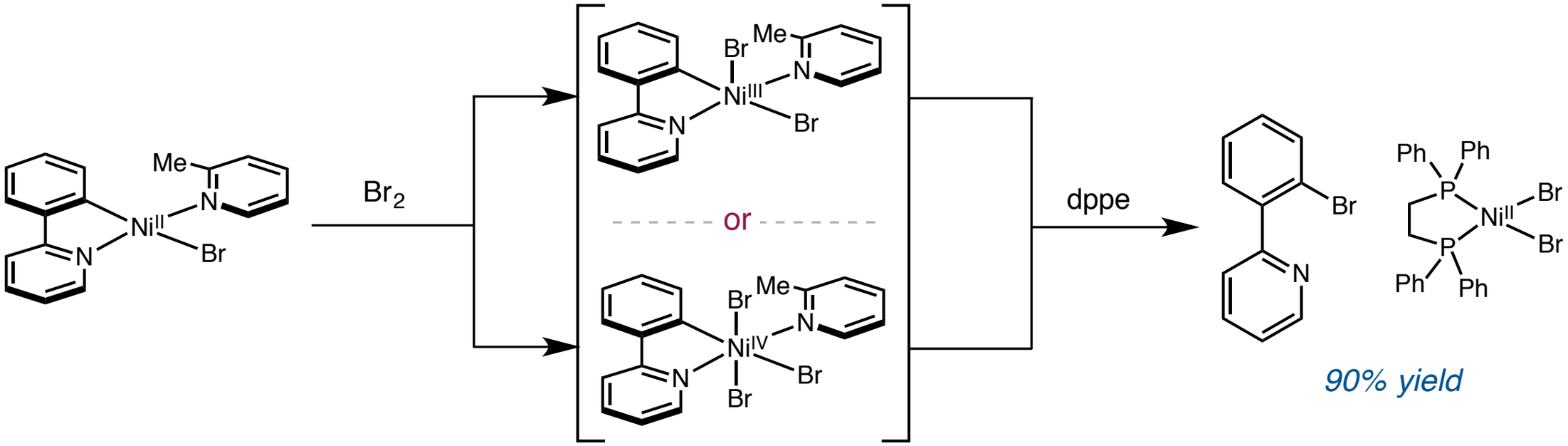
Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2015**, *54*, 2.

Nickel Mediated Aryl–F Bond Formation

Nickel will actually undergo oxidative addition into simple unactivated Ar–F bonds – 1973



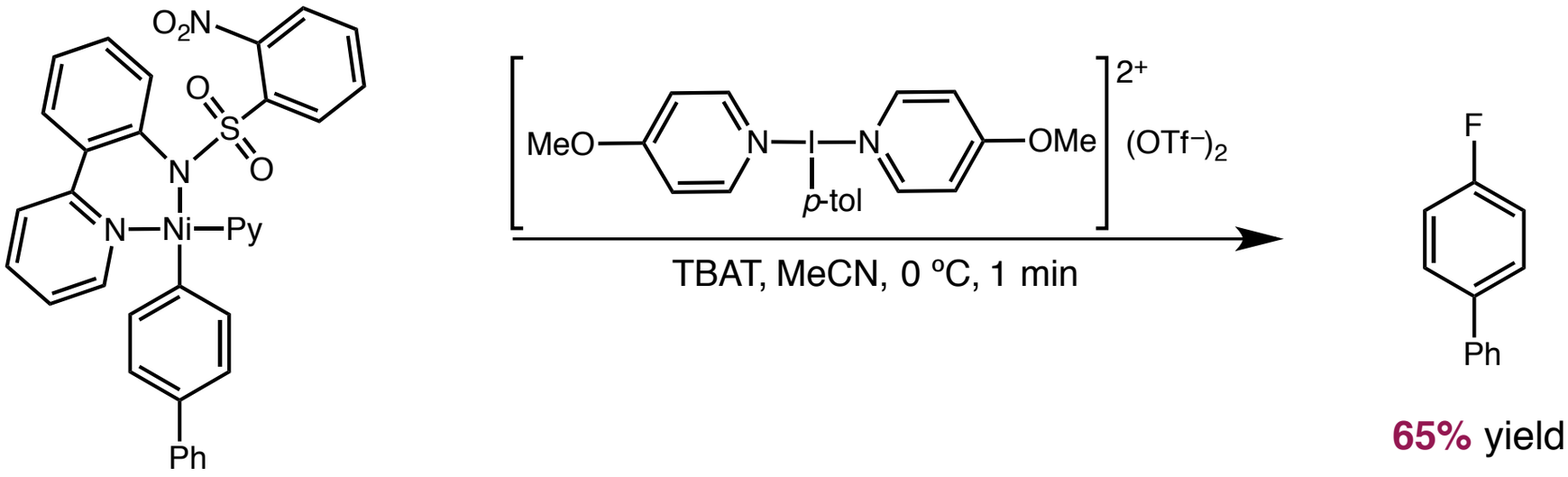
C–X bond formation fron Nickel (II) is unknown.

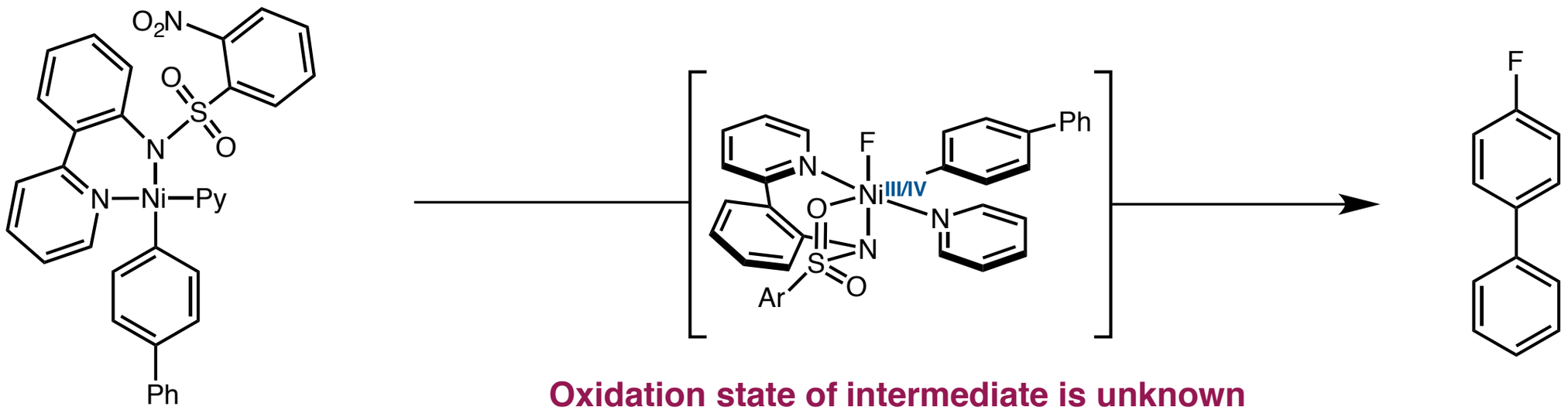


Amii, H.; Uneyama, K. *Chem. Rev.* **2009**, *109, 2119.*
Kiso, Y.; Tamao, K.; Kumada, M. *J. Organomet. Chem.* **1973,** *50*, C12.
Higgs, A. T.; Zinn, P. J.; Simmons, S. J.; Sanford, M. S. *Organometallics,* **2009**, *21*, 2009.
Camasso, N. M.; Sanford, M. S. *Science,* **2015**, *347*, 6227.
Lee, E.; Hooker, J. M.; Ritter, T. *J. Am. Chem. Soc.,* **2012**, *134*, 17456.

Nickel Mediated Aryl–F Bond Formation

Oxidative Fluorination of Nickel Aryl Complexes





Oxidation state of intermediate is unknown

Amii, H.; Uneyama, K. *Chem. Rev.* **2009**, *109, 2119.*
Kiso, Y.; Tamao, K.; Kumada, M. *J. Organomet. Chem.* **1973,** *50*, C12.
Higgs, A. T.; Zinn, P. J.; Simmons, S. J.; Sanford, M. S. *Organometallics,* **2009**, *21*, 2009.
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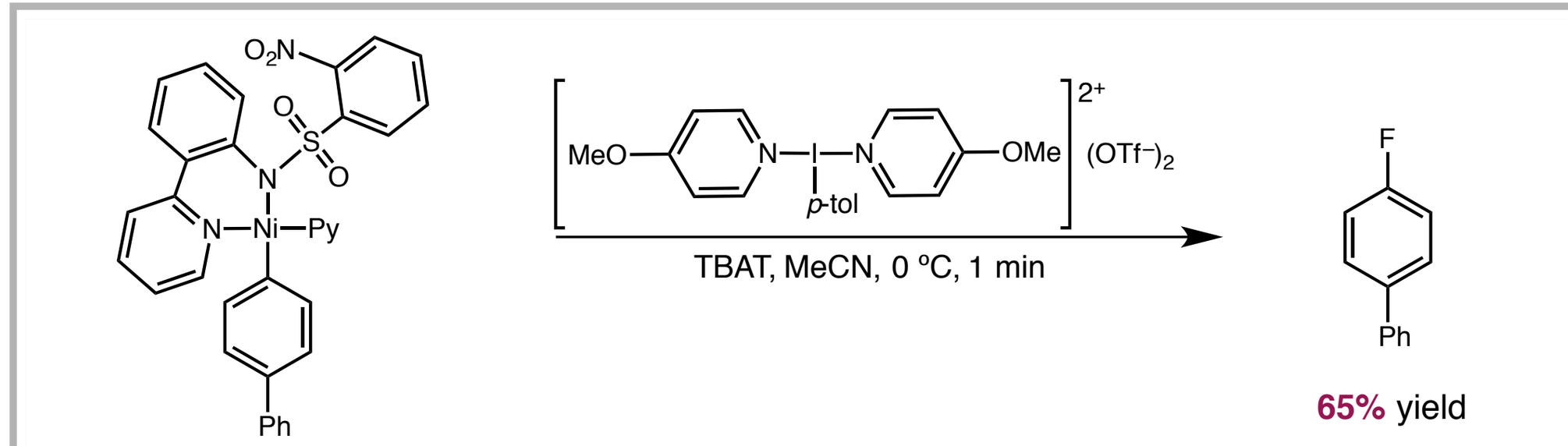

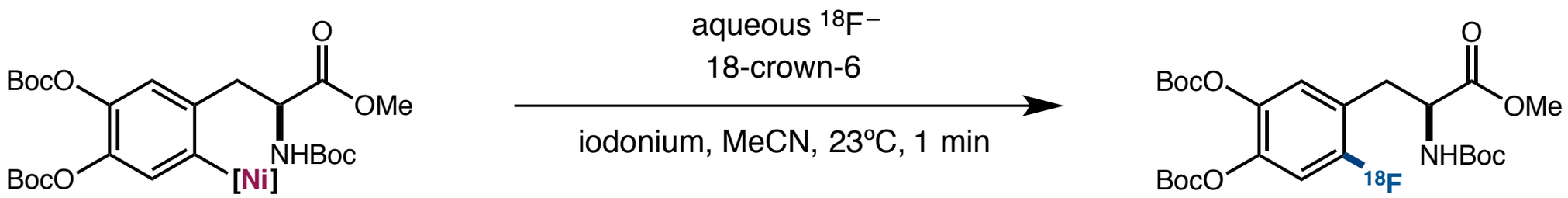

18F–L-DOPA
15% RCY

Amii, H.; Uneyama, K. *Chem. Rev.* **2009**, *109, 2119.*
Kiso, Y.; Tamao, K.; Kumada, M. *J. Organomet. Chem.* **1973,** *50*, C12.
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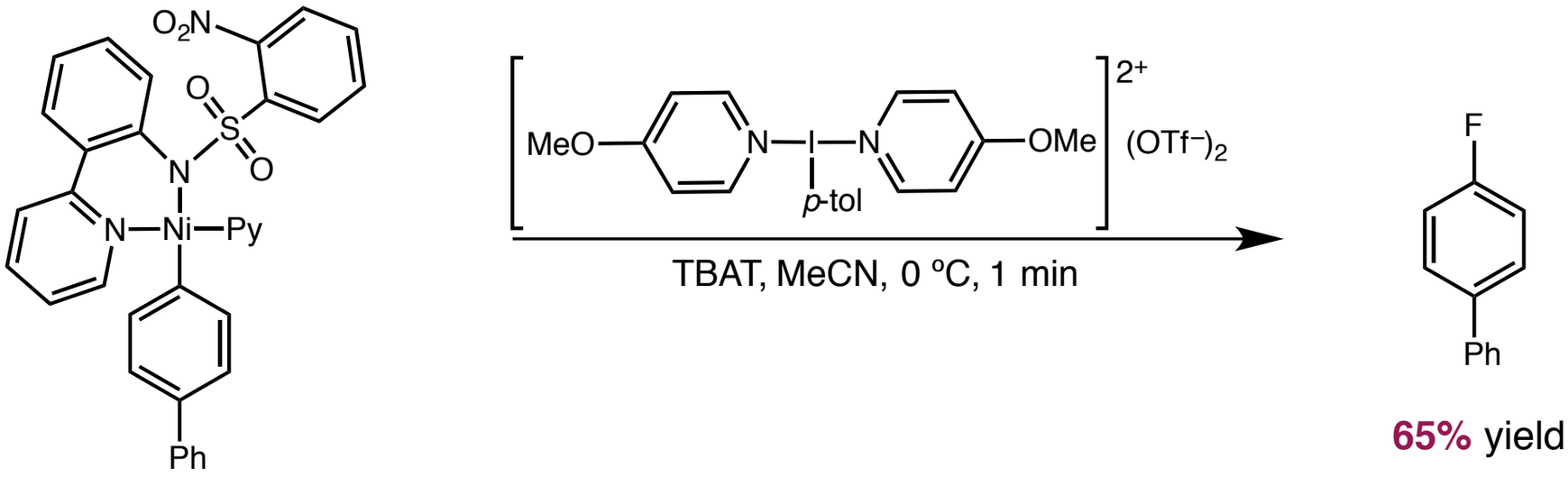
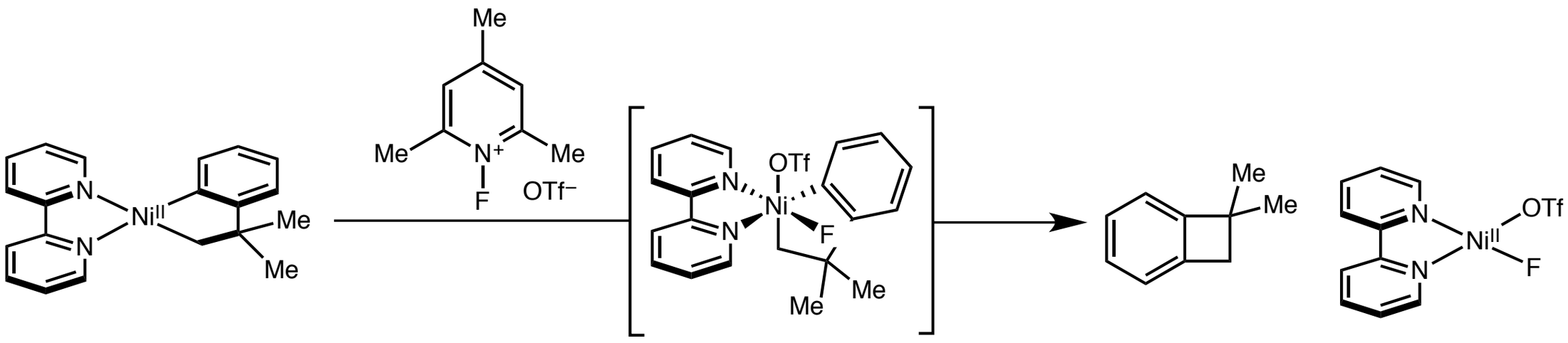


65% yield



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Kiso, Y.; Tamao, K.; Kumada, M. *J. Organomet. Chem*. **1973,** *50*, C12.
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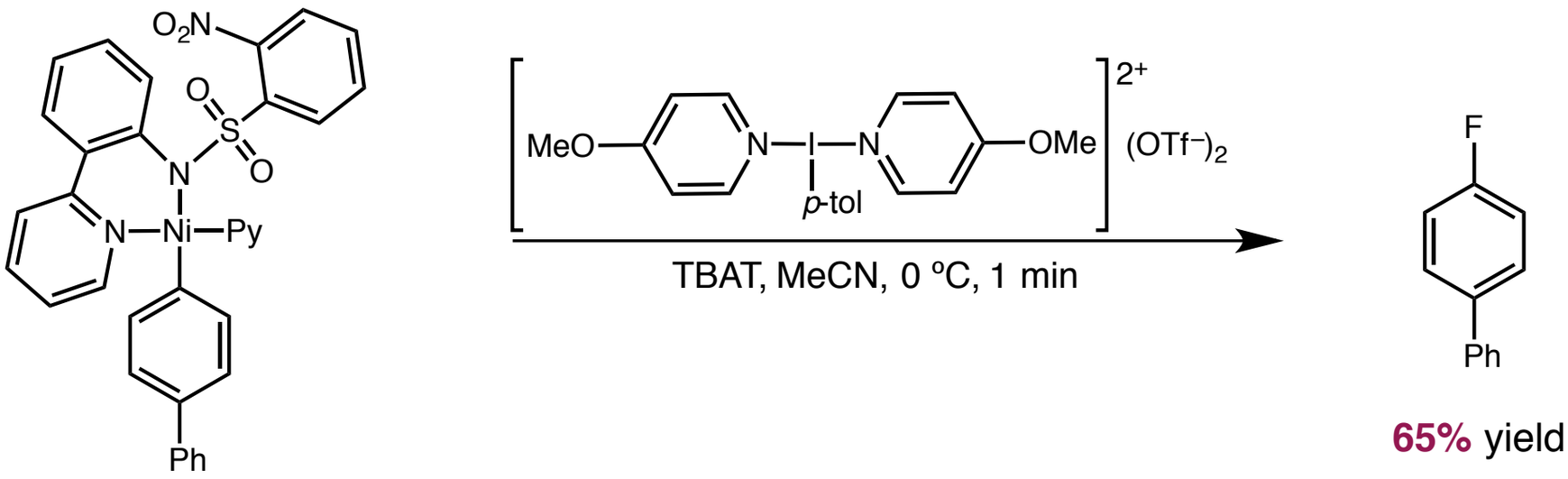

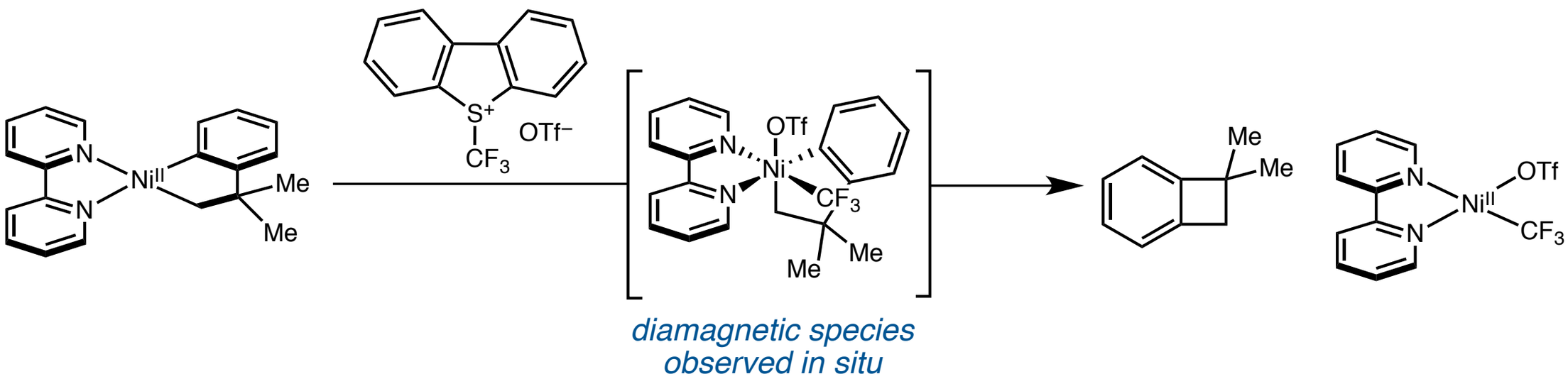

diamagnetic species observed in situ

Amii, H.; Uneyama, K. *Chem. Rev.* **2009**, *109, 2119.*
Kiso, Y.; Tamao, K.; Kumada, M. *J. Organomet. Chem.* **1973,** *50*, C12.
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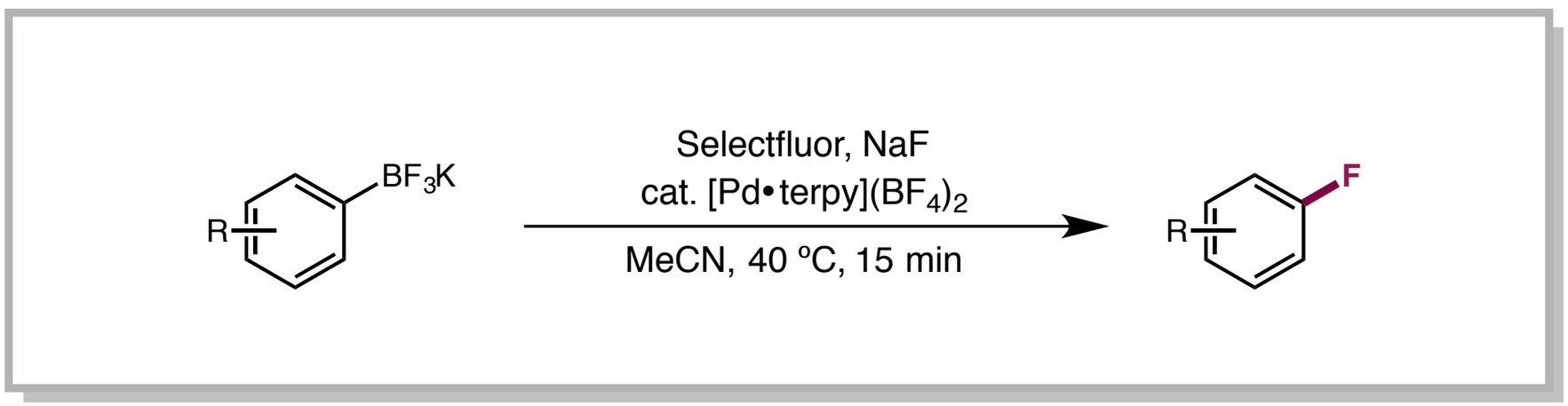
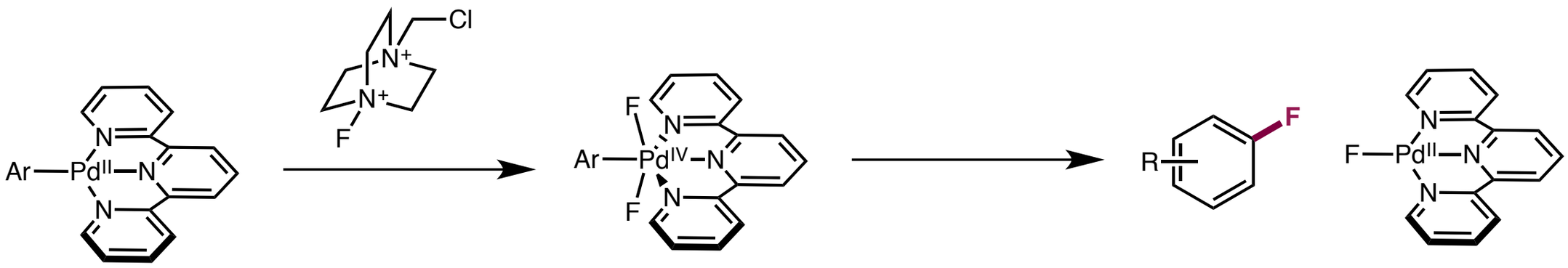
Radical Fluorination of Arenes

Ritters Catalytic Palladium Chemistry – Unexpected Mechanism: no reductive elimination at the metal



Logical Catalytic Proposal



Stoichiometric Studies Suggest an Alternate Mechanism

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

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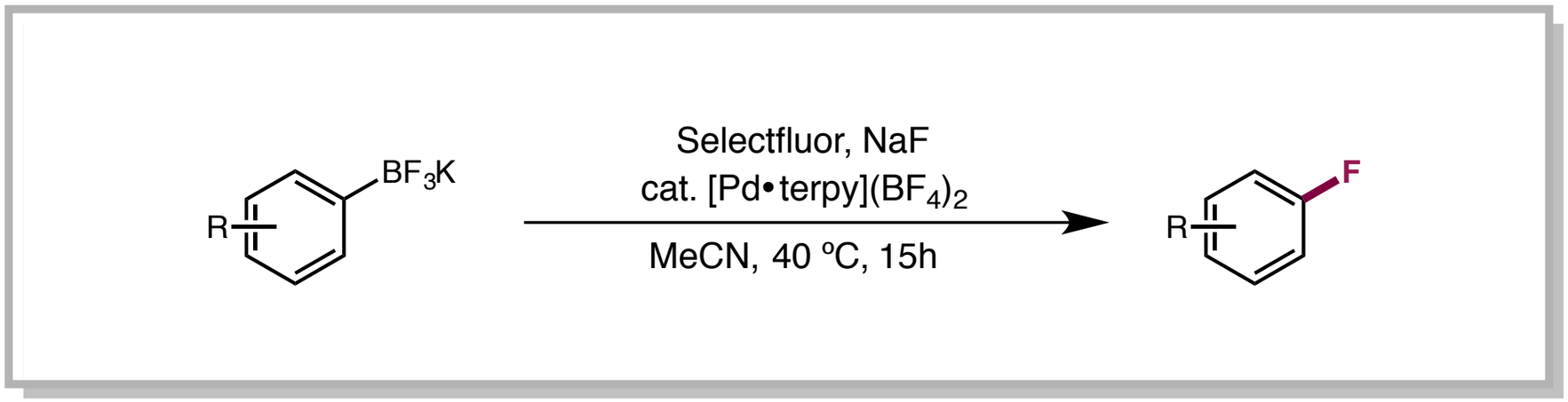
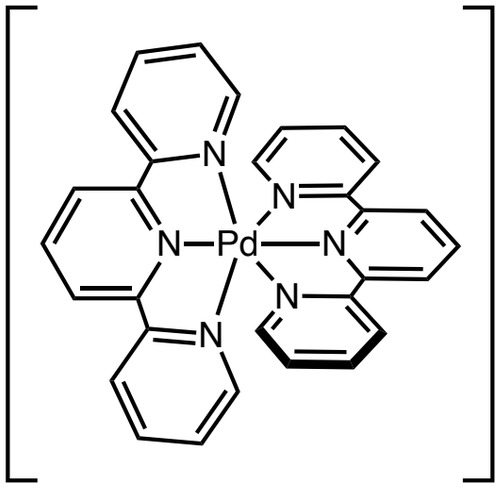
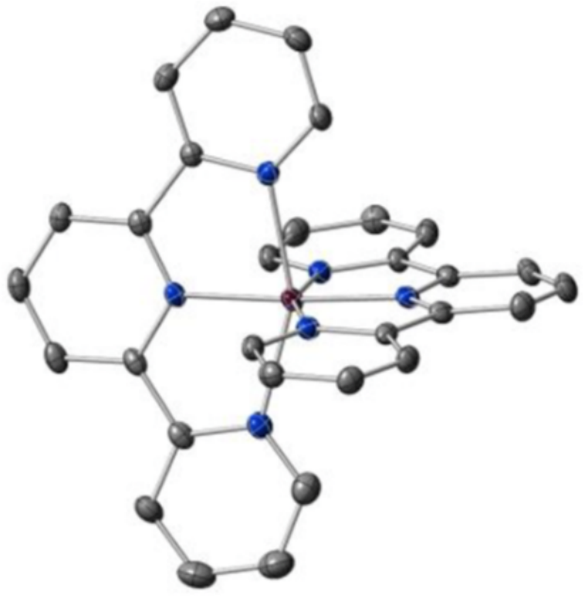




3 BF_4^-

Isolated Pd(III) Intermediate



coordinatively saturated Pd(III) complex isolated

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

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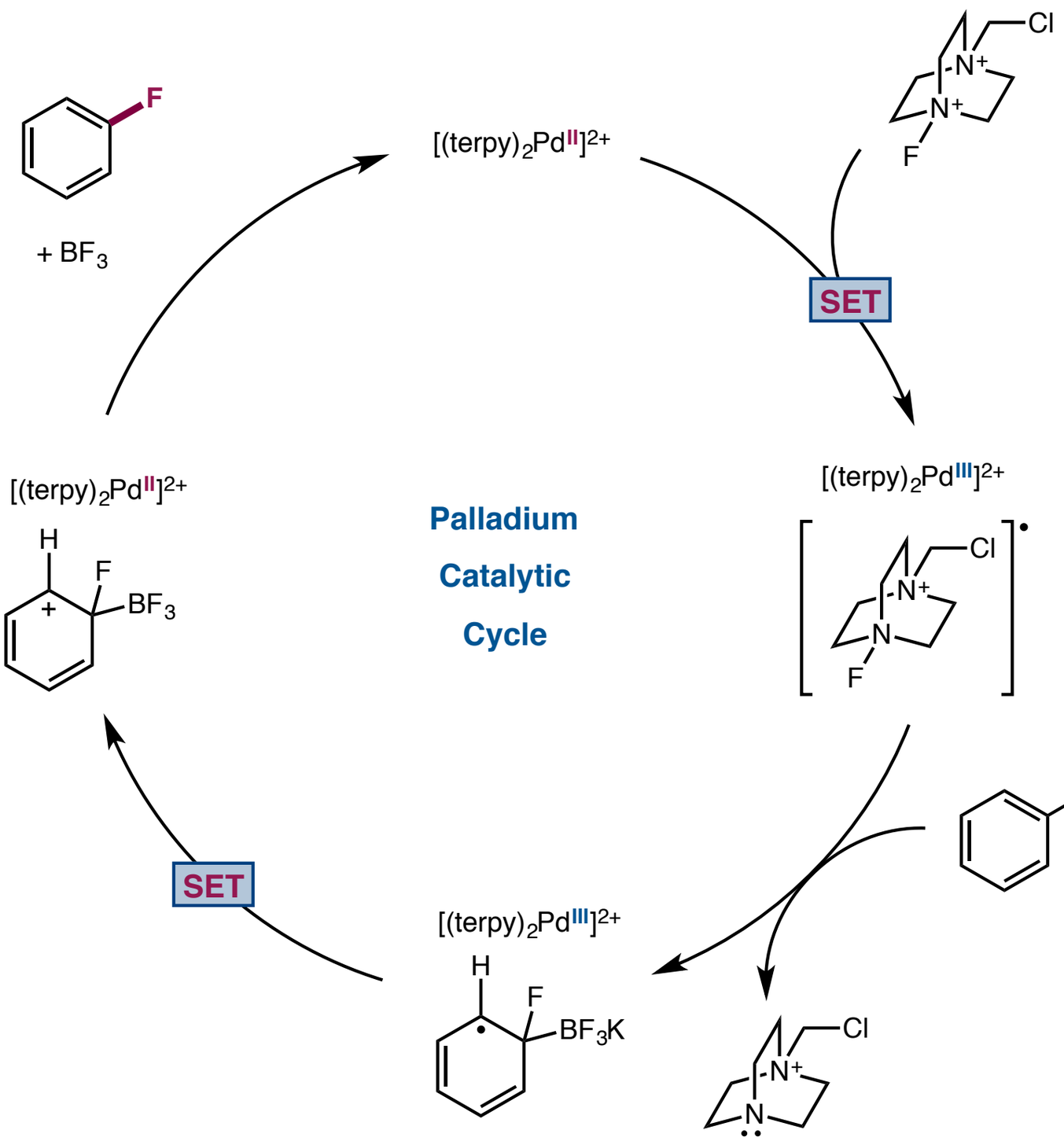
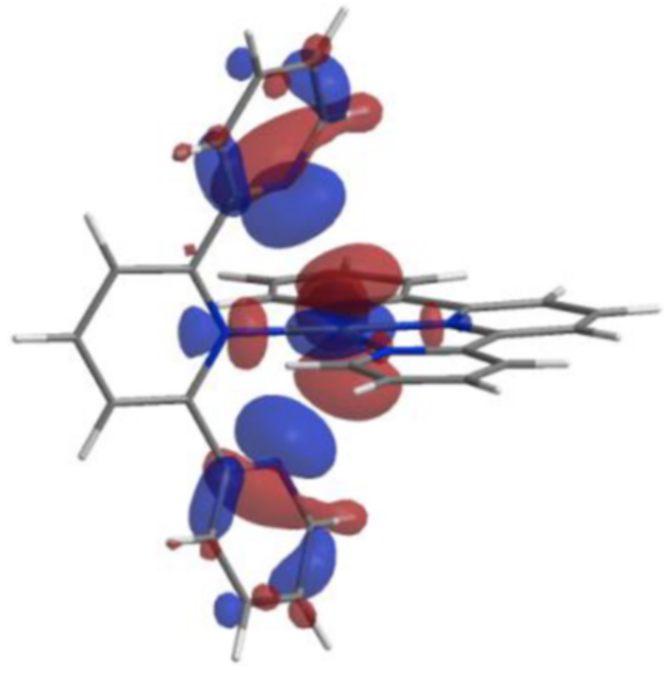


Sodium Fluoride required to mop up BF_3 generated



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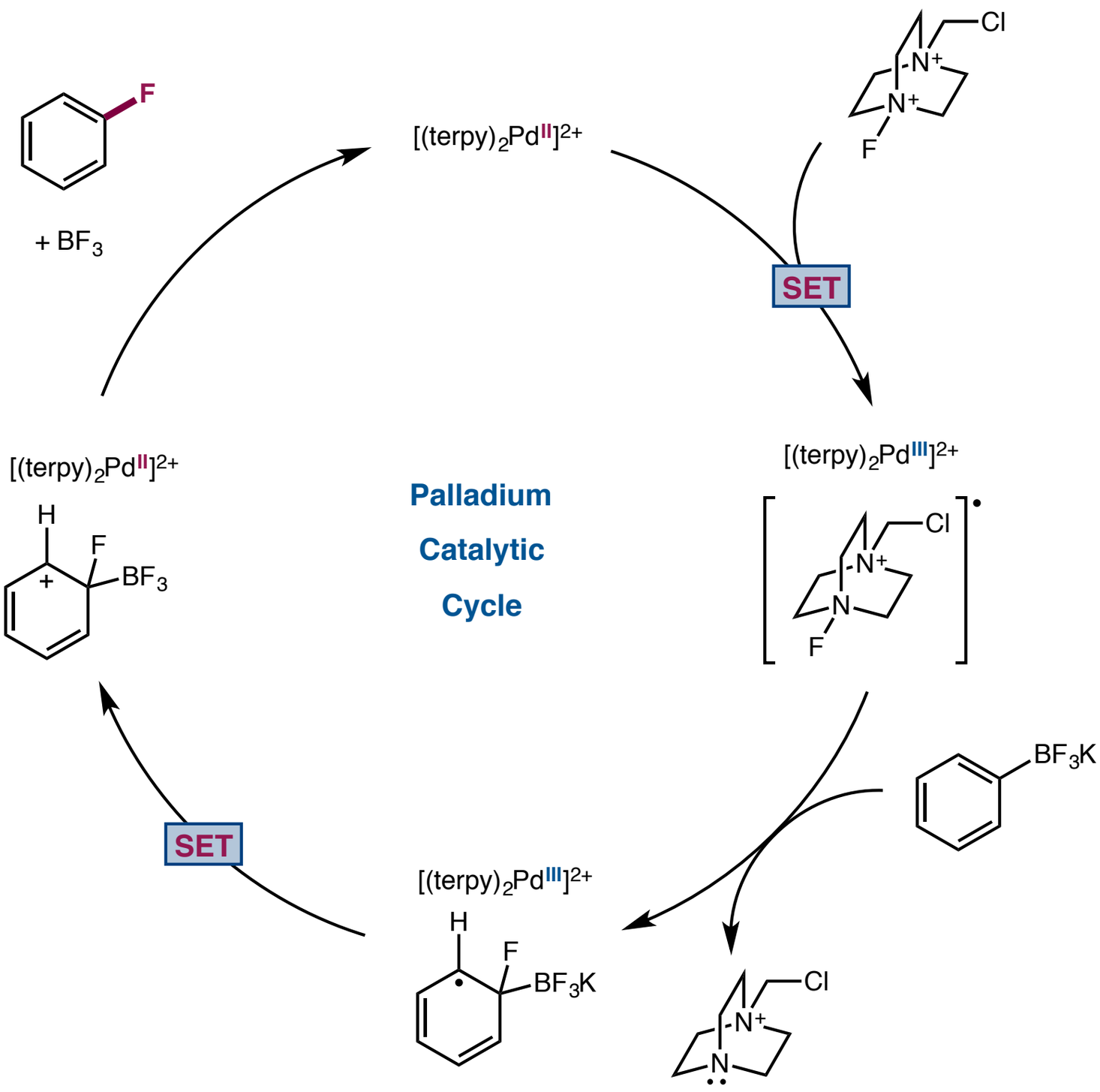

Sodium Fluoride required to mop up BF_3 generated

No organometallic intermediates

C–F bond not formed via reductive elimination

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

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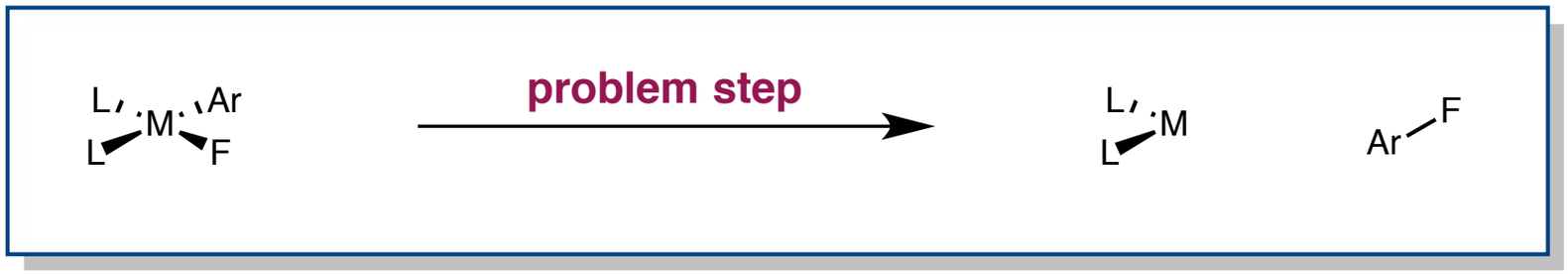
Conclusions

Reductive elimination to from the C–F bond is kinetically difficult



High oxidation state metal center Pd(IV), Ag(II), Ni(III) – Facilitates problematic step

Limited to organometallic nucleophiles and molecules with directing groups

Pd(II) catalysis allows the use of more diverse aryl halide electrophiles

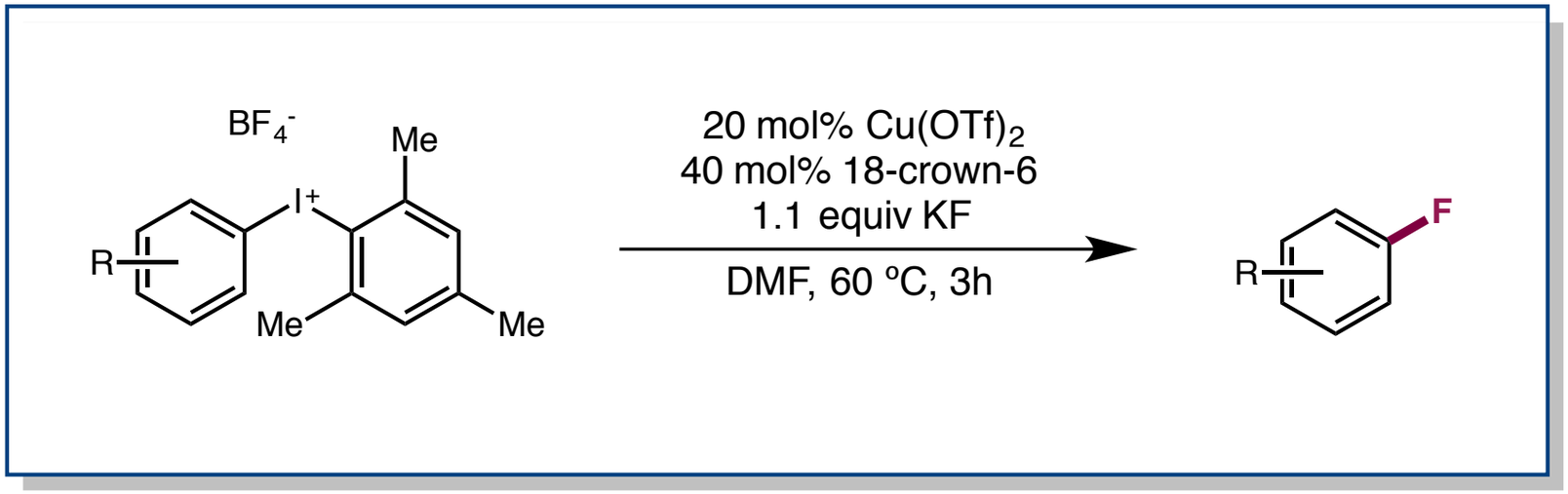
Ligand design incredibly important to get high efficiency

Cu(I)/Cu(III) catalysis – Cu prone to disproportionation

Highly reactive electrophiles enable catalysis but shortening reaction times

Copper Catalyzed Aryl–F Bond Formation

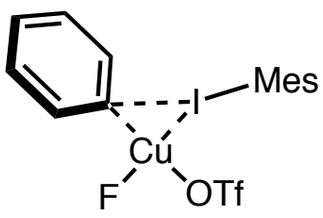
Sanford – 2013 First Method Catalytic in Copper



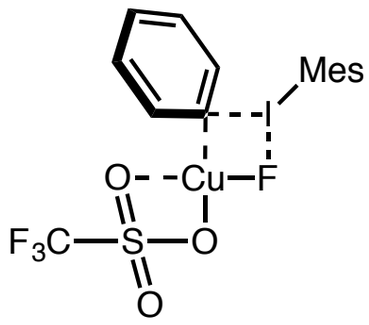
Cu(I) is formed in situ

Concentration of fluoride is kept low due to insolubility of KF in DMF

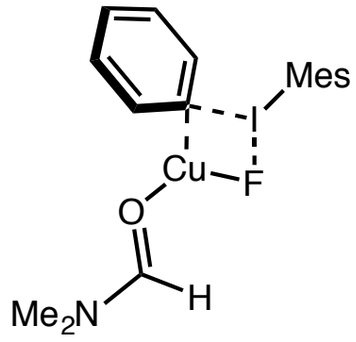
Transition State for Oxidative Addition



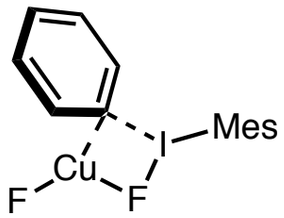
ΔG‡ 9.7 kcalmol-1



10.9 kcalmol-1



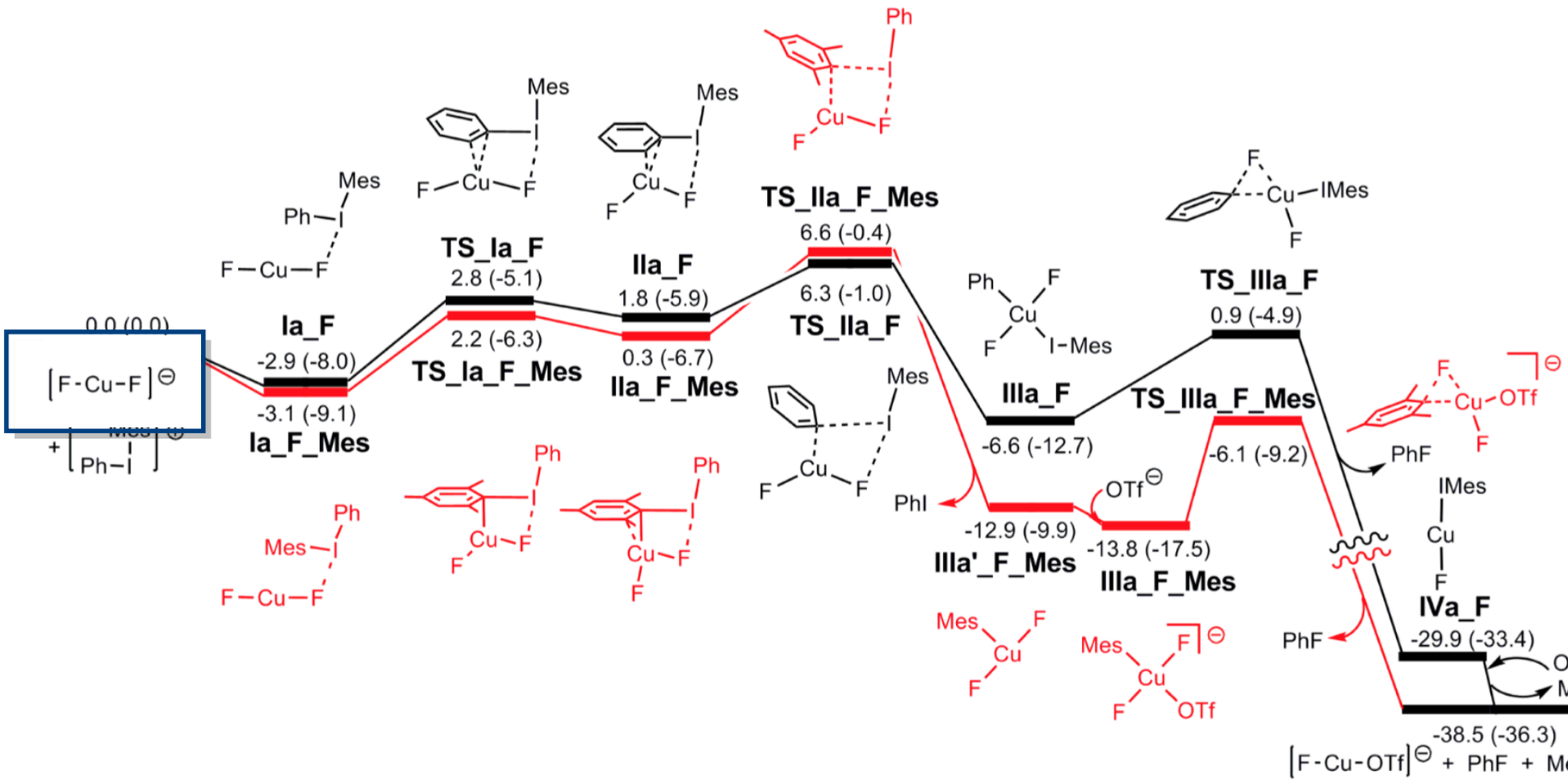
13.1 kcalmol-1

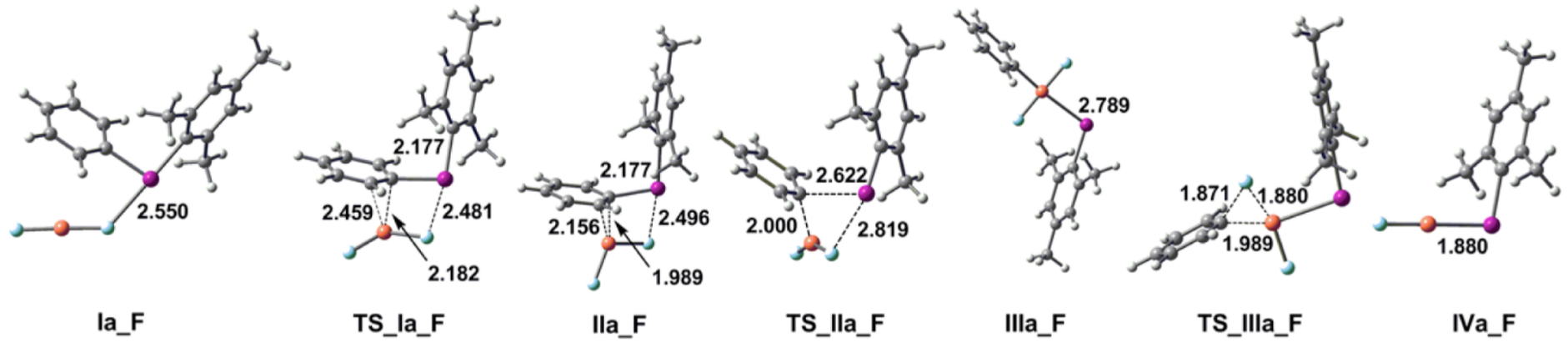


9.4 kcalmol-1

Ichiishi, N.; Canty, A. J.;Yates, B. F.; Sanford, M. S. *Org. Lett.* **2013**, *15,* 5134.
Ichiishi, N.; Canty, A. J.;Yates, B. F.; Sanford, M. S. *Organometallics* **2014**, *33,* 5525.
Grushin, V. V.; Demkina, I. I.; Tolstaya, T. P. *J. Chem. Soc., Perkin Trans. 2* **1992**, 505.

Copper Catalyzed Aryl–F Bond Formation





Barrier to oxidative addition to the I–Mes bond is ~ 4 kcal mol^{-1} higher in energy

Ichiishi, N.; Canty, A. J.;Yates, B. F.; Sanford, M. S. *Org. Lett.* **2013**, *15,* 5134.
Ichiishi, N.; Canty, A. J.;Yates, B. F.; Sanford, M. S. *Organometallics* **2014**, *33,* 5525.