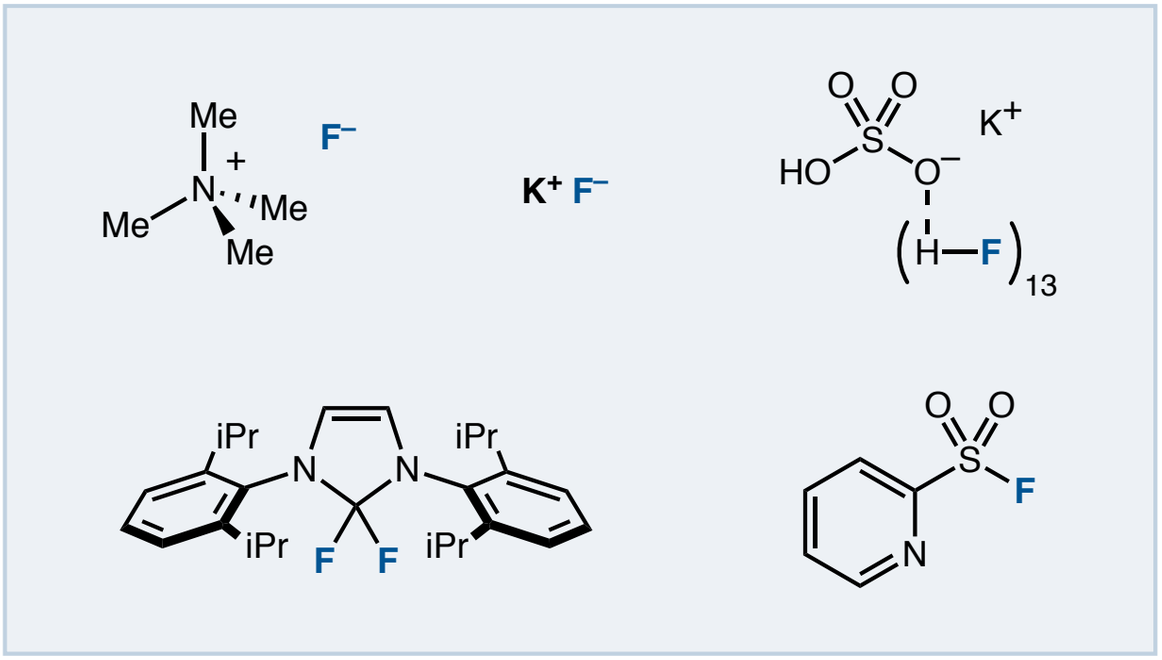
Recent Developments in Nucleophilic Fluorination



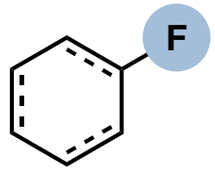
Vlad Bacauanu

MacMillan Research Group

Group Meeting

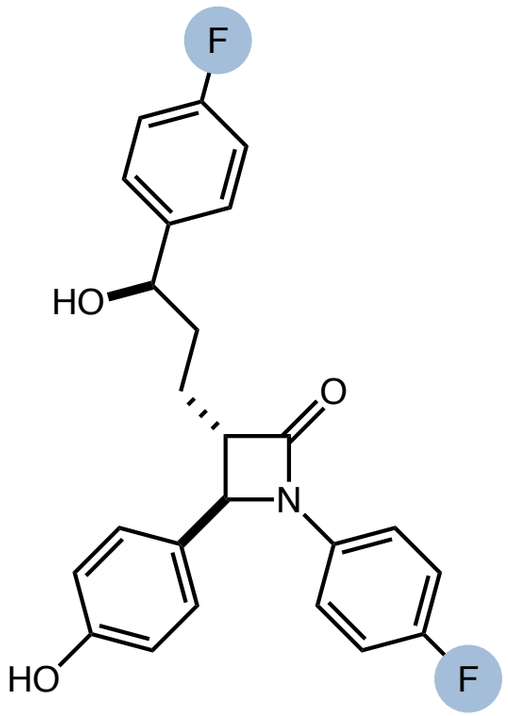
March 13th, 2018

Importance of Novel Fluorination Technologies

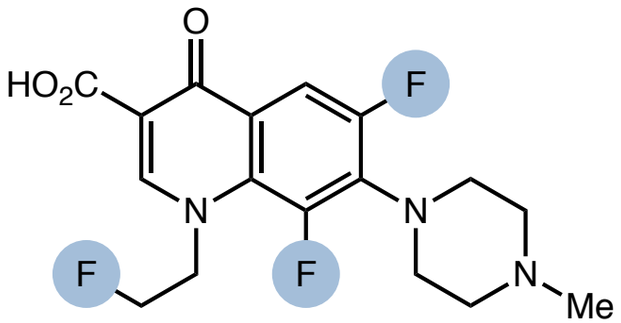


C–F bond

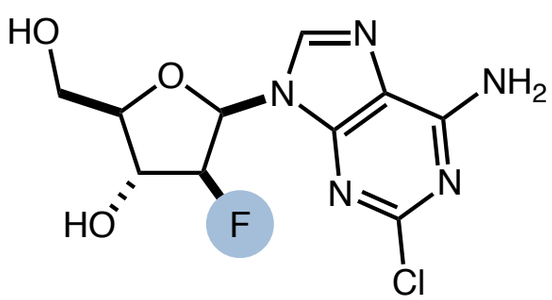
- ***Improved membrane permeance***
- ***Enhanced metabolic stability***
- ***Present in 20–30% new approved drugs***



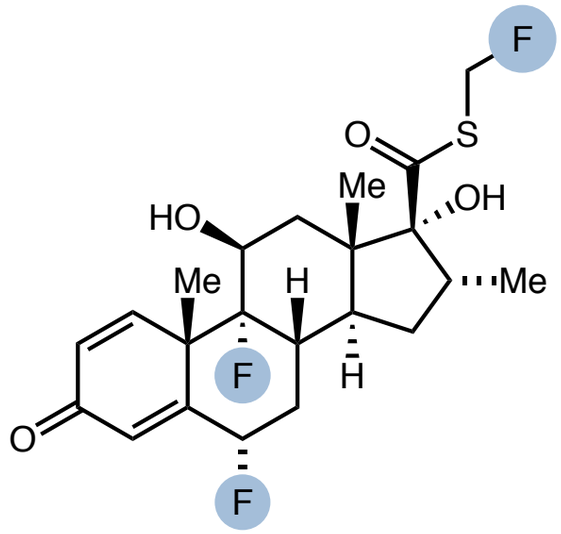
ezetimibe



fleroxacin



clofarabine

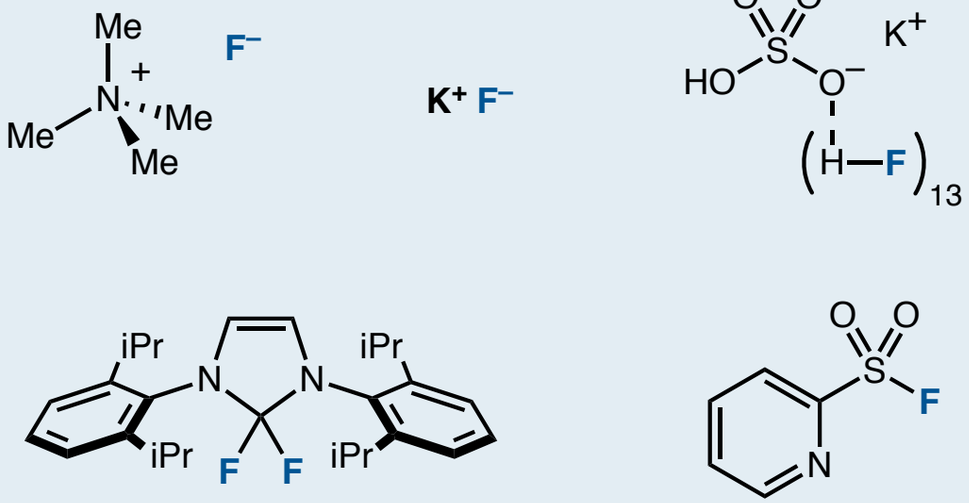


fluticasone

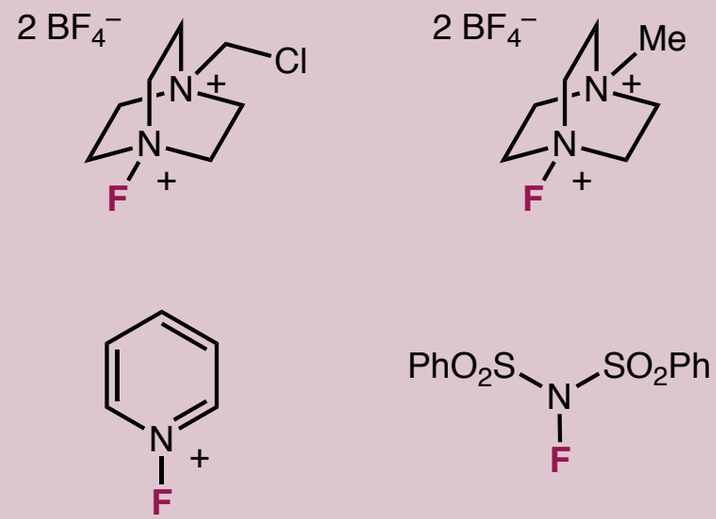
Fustero, S.; Soloshonok, V. A.; Liu, H. *et al. Chem. Rev.* **2014**, *114*, 2432.

Acena, J. L.; Soloshonok, V. A.; Izawa, K.; Liu, H. *et al. Chem. Rev.* **2016**, *116*, 422.

Importance of Developing Nucleophilic Fluorination Strategies



nucleophilic fluorination

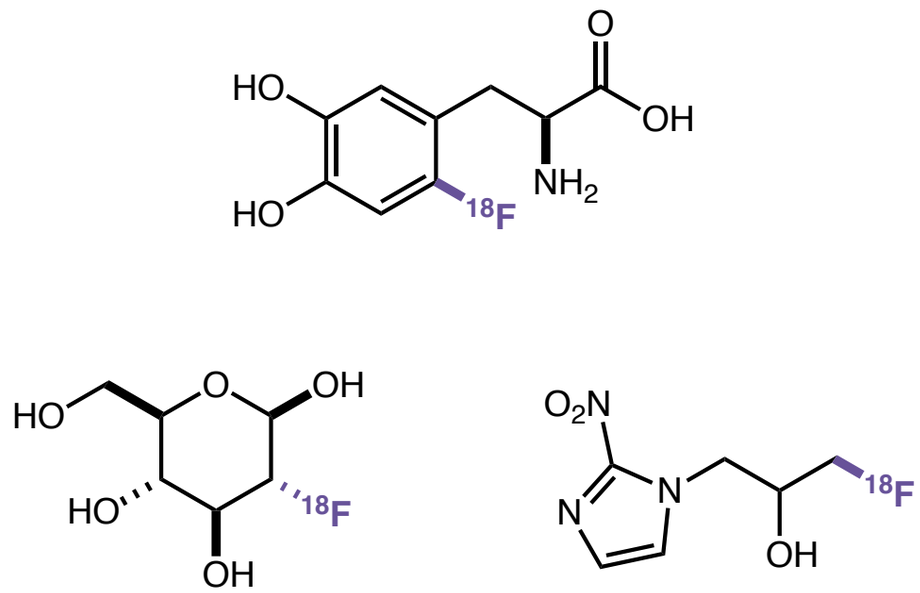


electrophilic fluorination

Why would you choose to do nucleophilic fluorination?

- Generally cheaper reagents vs. electrophilic
- Potentially better FG tolerance (F^+ is oxidizing)
- **Significantly more desirable for ^{18}F PET imaging**

($^{18}F^+$ reagents are inconveniently made from $^{18}F_2$)



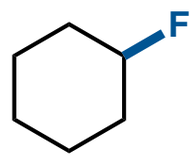
Campbell, M. G.; Ritter, T. *Chem. Rev.* **2015**, *115*, 612.

Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 8214.

Recent Developments in Nucleophilic Fluorination

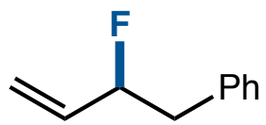
Construction of Alkyl C–F Bonds

Nucleophilic substitution promoted by hydrogen bonding

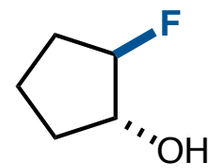


Deoxyfluorination of aliphatic alcohols

Transition metal-catalyzed allylic fluorination

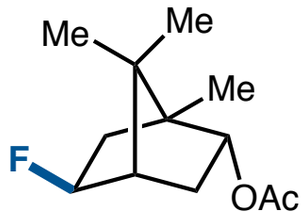


Direct hydrofluorination of alkenes



Metal-mediated aminofluorination of alkenes

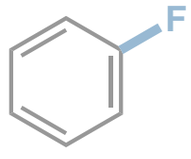
Asymmetric hydrofluorination of epoxides



Manganese-catalyzed C–H fluorination – see YYL group meeting

Construction of Aromatic C–F Bonds

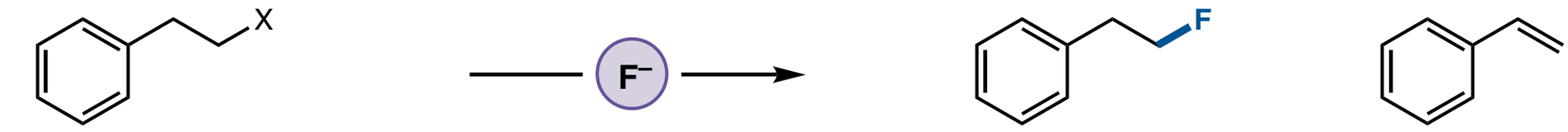
Metal-mediated fluorination of arenes – see JRT group meeting



Nucleophilic aromatic substitution of (pseudo)halides

Ritter's S_NAr deoxyfluorination of phenols

Aliphatic Nucleophilic Substitution Reactions with Fluoride



alkyl (pseudo)halide

substitution

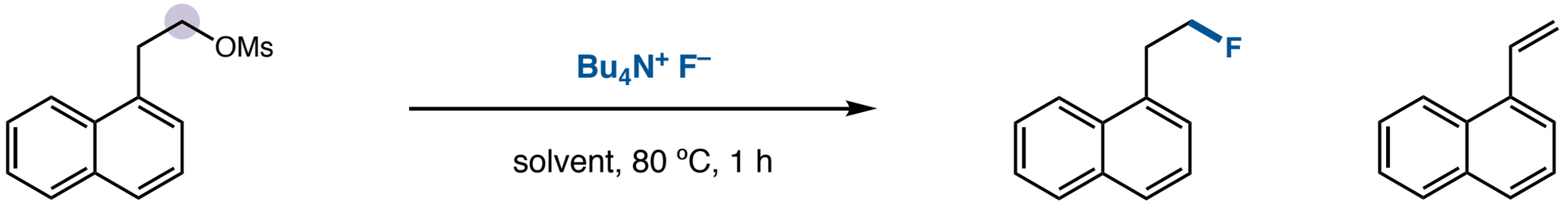
elimination

Why is an S_N2 reaction using a fluoride source not as straightforward as it looks?

F^-	***water / protic solvents*** hydrogen bonding	***polar aprotic solvents*** no hydrogen bonding
solubility	good	counterion dependent
nucleophilicity	poor **(no S_N2)**	good
basicity	weak	strong **(competitive E2)**

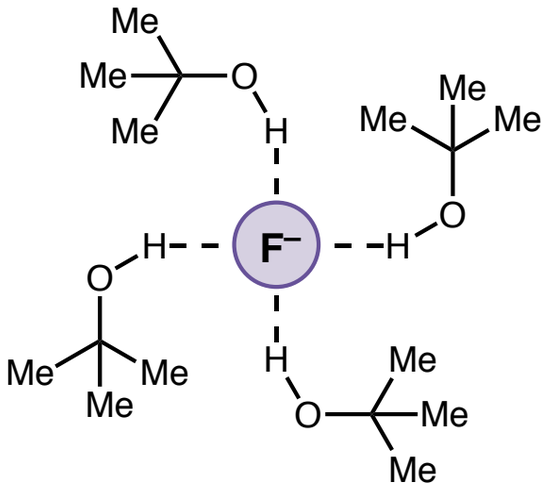
Lee, S.; Chi, D. Y. *et al. Chem. Soc. Rev.* **2016**, *45*, 4638.

Unexpected S_N2 Reactions with Fluoride in Alcohol Solvents



alkyl mesylate

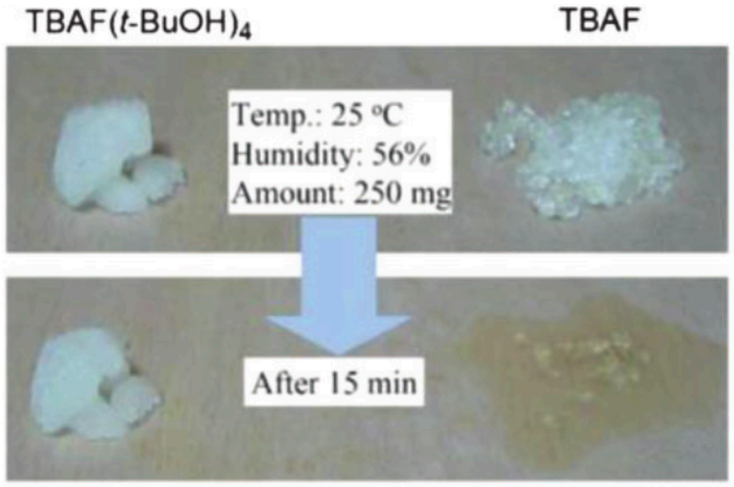
in MeCN:	*33%*	*61%*
in tBuOH:	***87%***	***9%***
TBAF•4(tBuOH), in MeCN:	*71%*	*29%*

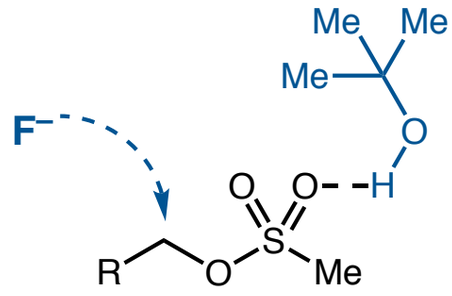


"controllable fluoride"

diminished basicity

decent nucleophilicity

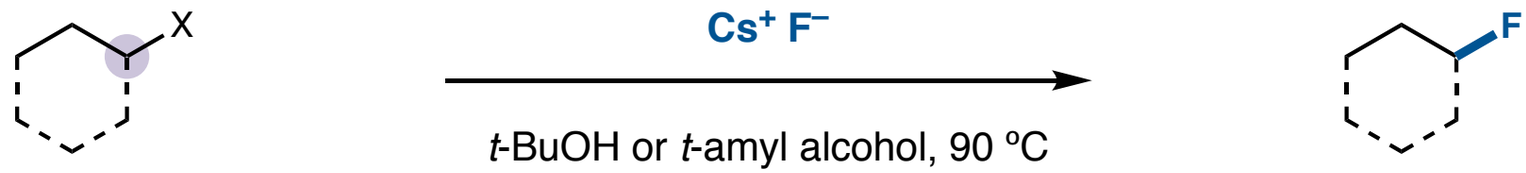


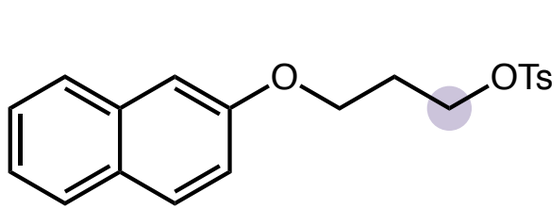


enhanced leaving group ability

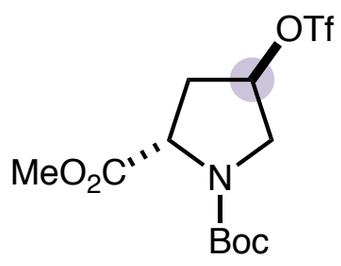
Lee, S.; Chi, D. Y. *et al. Chem. Soc. Rev.* **2016**, *45*, 4638.

Scope of Hydrogen Bond-Promoted Nucleophilic Flourination

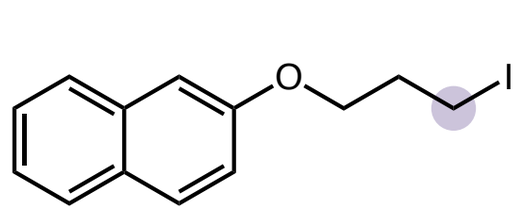




93% yield
(2 h)

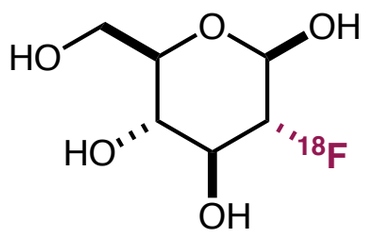


69% yield
(1.5 h, 25 ºC)

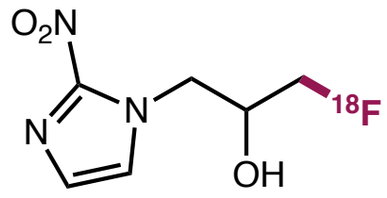


90% yield
(24 h)

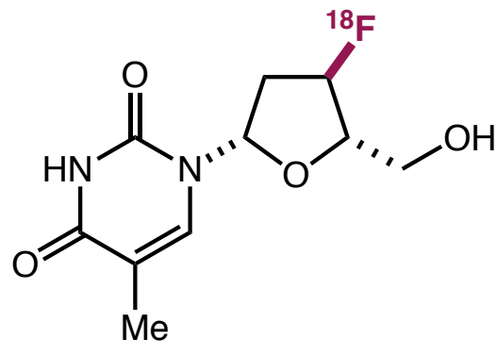
Applications in radio-labelling



85% RCY



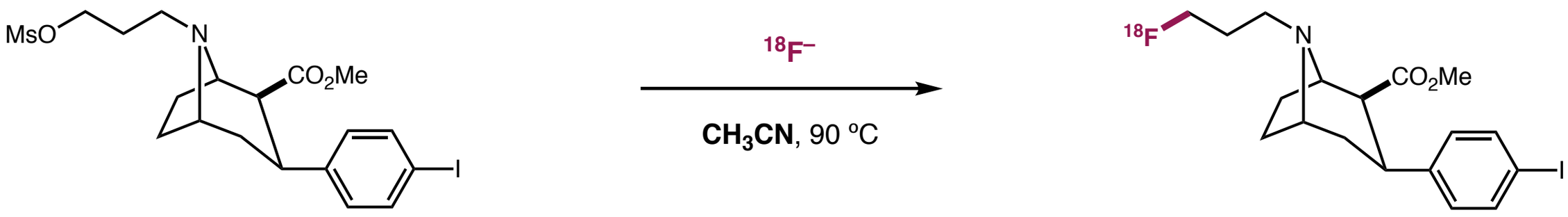
70% RCY



66% RCY

Lee, S.; Chi, D. Y. *et al. J. Am. Chem. Soc.* **2006**, *128*, 16394.

Application of Hydrogen Bond-Promoted Nucleophilic Flourination

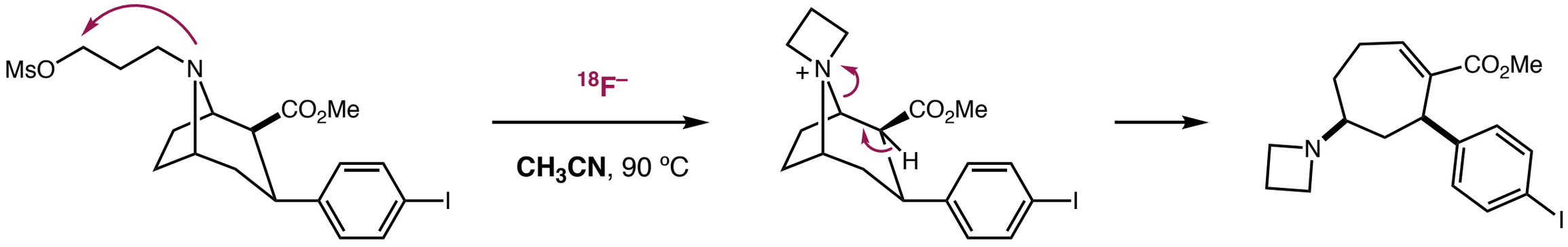


Desired fluorinated producted obtained in 1% yield

PET imaging of dopamine transporters

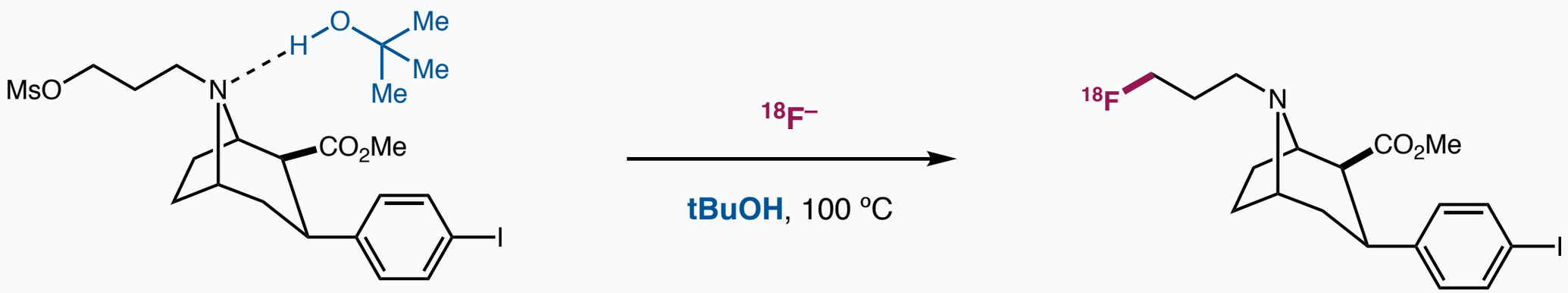
Lee, S.; Chi, D. Y. *et al. J. Am. Chem. Soc.* **2006**, *128*, 16394.

Application of Hydrogen Bond-Promoted Nucleophilic Flourination



competitive N-alkylation

major product

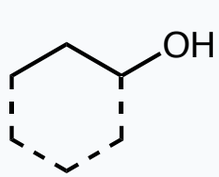


amine inhibited via H-bonding

36% RCC

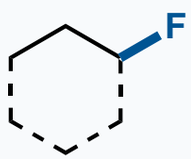
Lee, S.; Chi, D. Y. *et al. J. Am. Chem. Soc.* **2006**, *128*, 16394.

General Deoxyfluorination of Aliphatic Alcohols



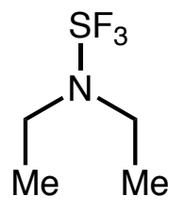
direct

deoxyfluorination



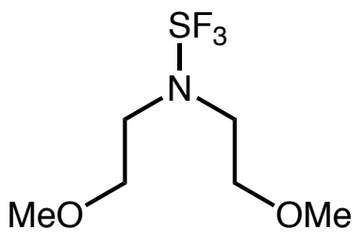
- ***Ubiquitous functional group***
- ***Circumvent prefunctionalization***

Deoxyfluorination reagents



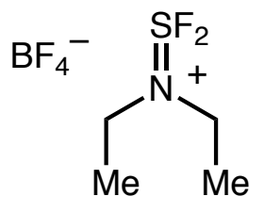
DAST

(1975)



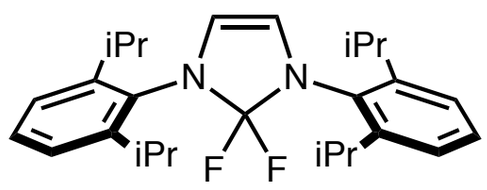
Deoxo-Fluor

(1999)



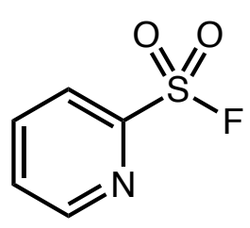
XtalFluor-E

(2009)



PhenoFluor

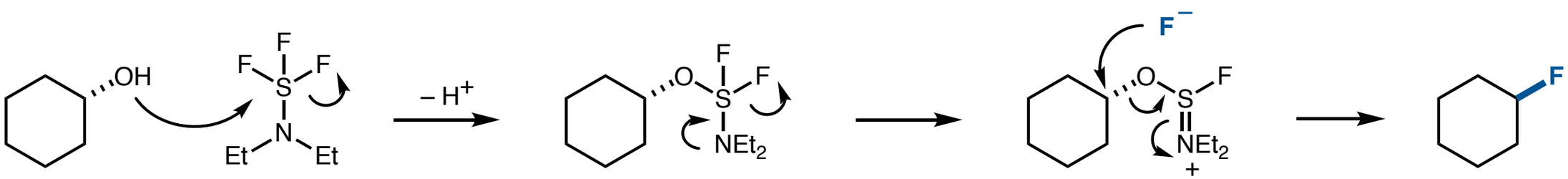
(2011)



PyFluor

(2015)

Example of mechanism



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

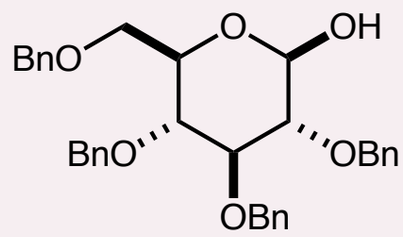
Doyle, A. G. *et al. J. Am. Chem. Soc.* **2015**, *137*, 9571.

Couturier, M. *et al. J. Org. Chem.* **2010**, *75*, 3401.

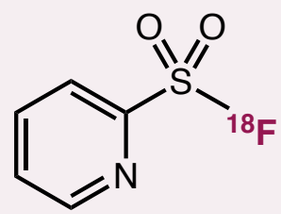
Ritter, T. *et al. J. Am. Chem. Soc.* **2013**, *135*, 2470.

Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 8214.

Selected Examples of Alcohol Deoxyfluorination

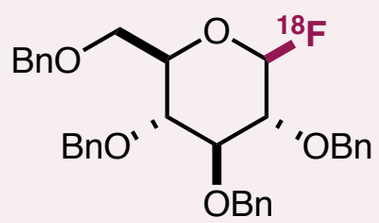


protected glucose

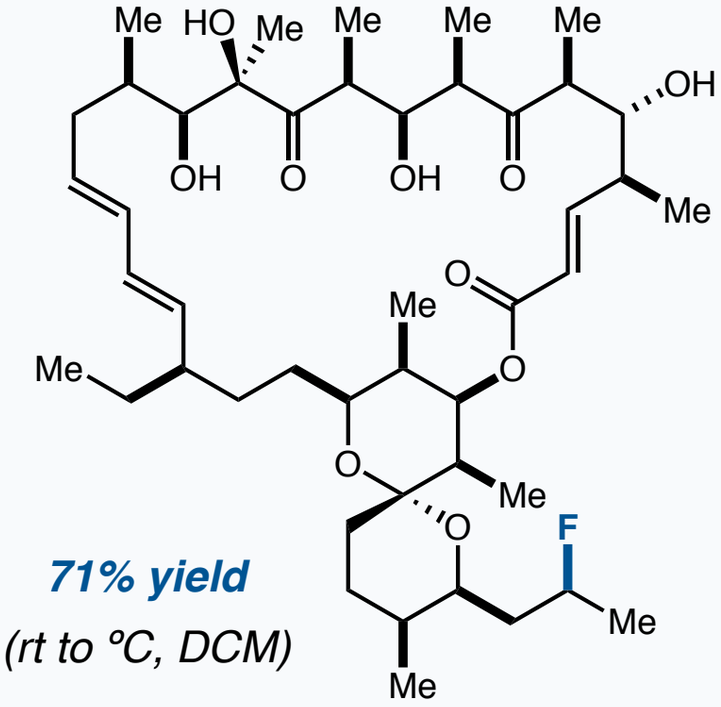


MTBD, MeCN

80 °C, 20 min

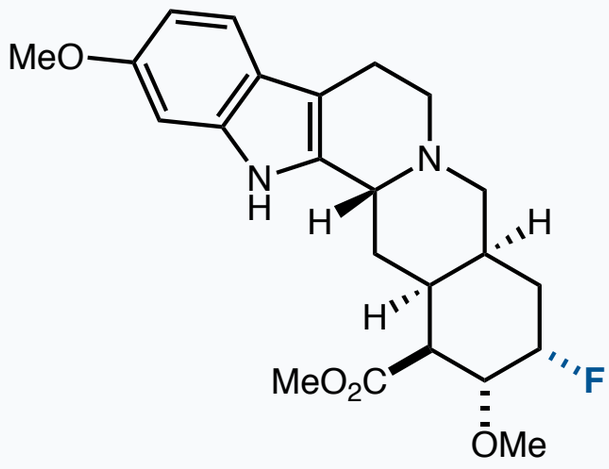


15% RCC



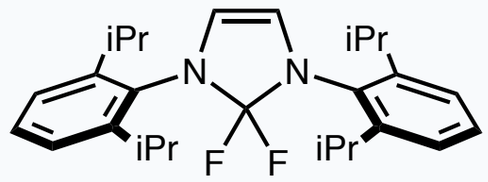
71% yield

(rt to °C, DCM)



82% yield

(80 °C, in toluene)



2.0 equiv. DIPEA

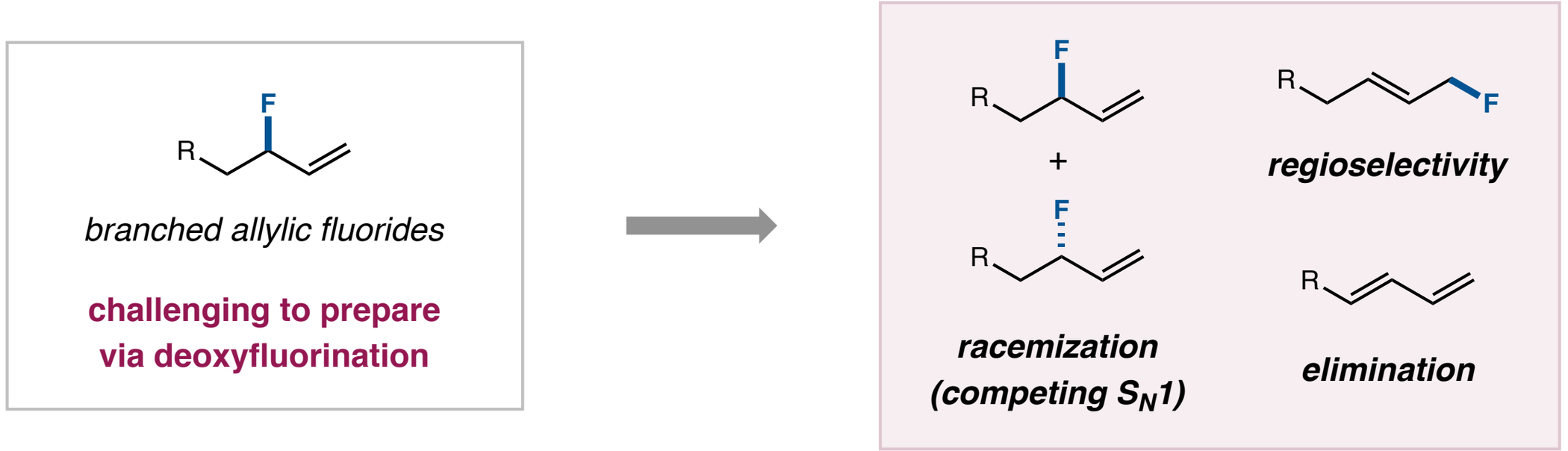
2.0 equiv. KF

2–20 h

Nielsen, M. K.; Ugaz, C. R.; Li, W.; Doyle, A. G. *J. Am. Chem. Soc.* **2015**, *137*, 9571.

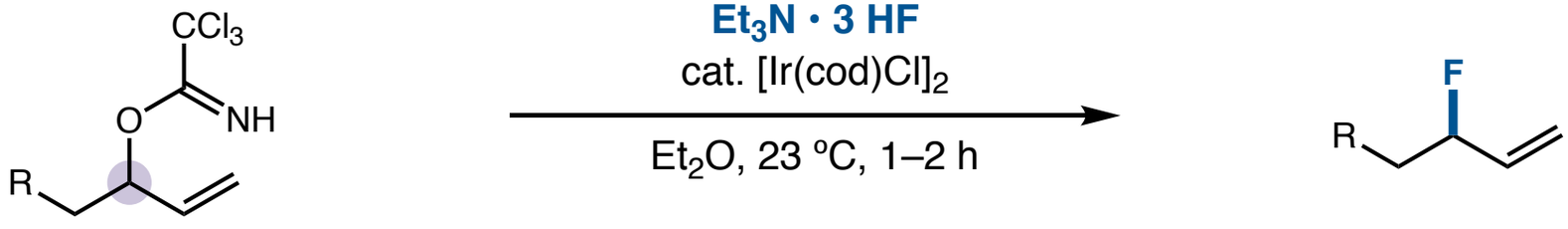
Sladojevich, F.; Arlow, S. I.; Tang, P.; Ritter, T. *J. Am. Chem. Soc.* **2013**, *135*, 2470.

Metal-Catalyzed Nucleophilic sp^3 Fluorination via π-Allyl Chemistry

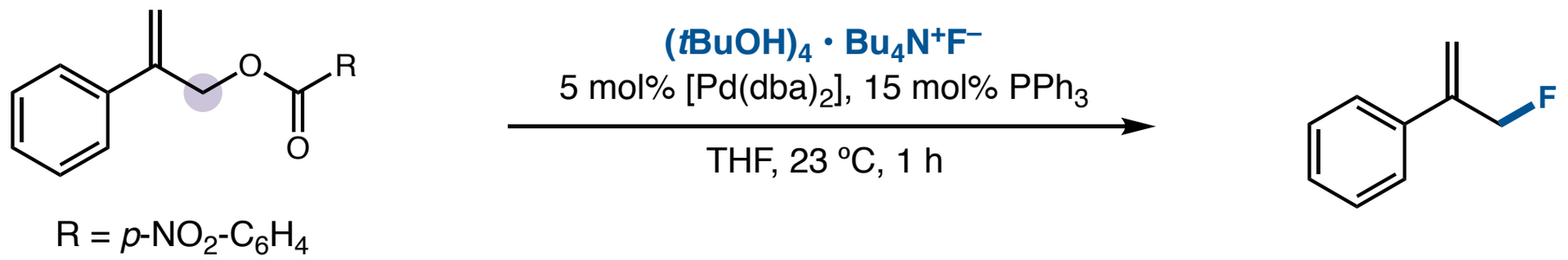


- Application of established π-allyl chemistry towards nucleophilic fluorination
- Potential control over regioselectivity by modulating nature of catalytic species
- Opportunities for asymmetric construction of fluorinated products

π-Allyl Methodologies for Nucleophilic sp³ Fluorination

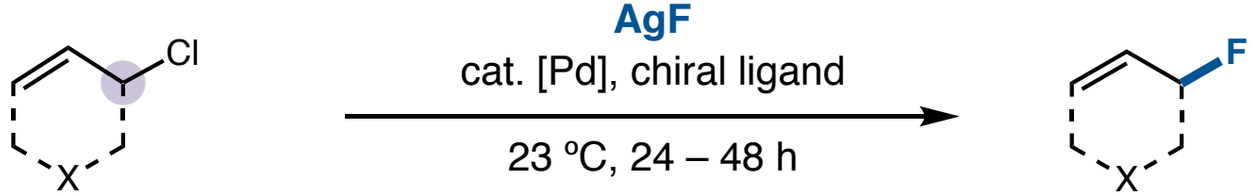


Topczeswki, J. J.; Tweson, T. J.; Nguyen, H. M. *J. Am. Chem. Soc.* **2011**, *133*, 19318.



Brown, J. M.; Gouverneur, V. *et al. Angew. Chem., Int. Ed.* **2011**, *123*, 2661.

racemic material

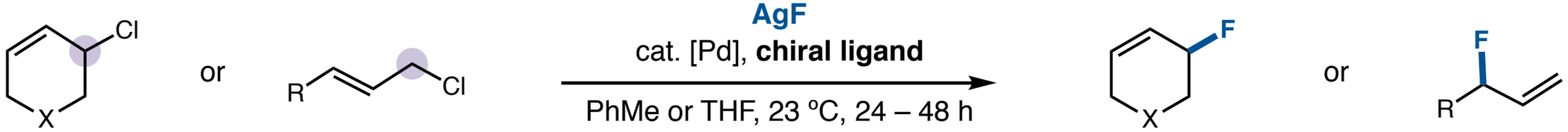


enantio-enriched

Katcher, M. H.; Doyle, A. G. *J. Am. Chem. Soc.* **2010**, *132*, 17402.

Katcher, M. H.; Sha, A.; Doyle, A. G. *J. Am. Chem. Soc.* **2011**, *133*, 15902.

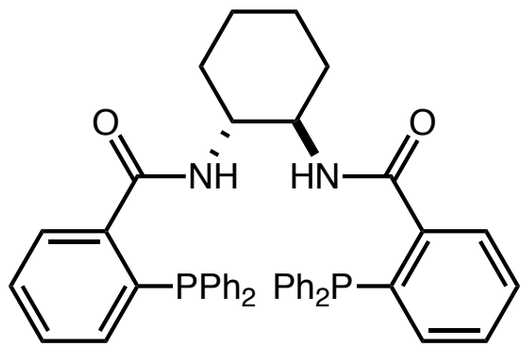
Doyle's Palladium-Catalyzed Asymmetric Allylic Fluorination

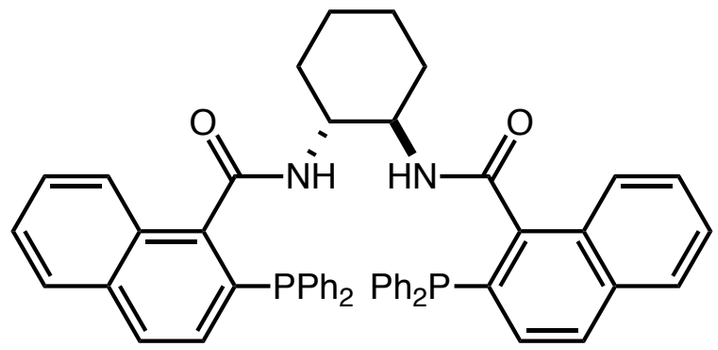


racemic mixture

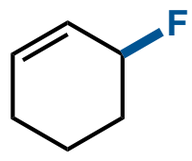
enantioenriched products

chiral ligand

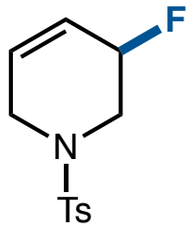




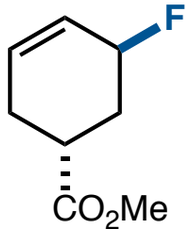
chiral ligand



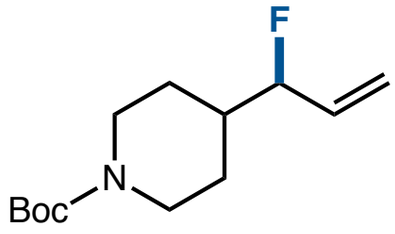
85% yield
88% ee



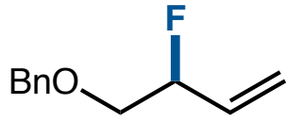
74% yield
96% ee



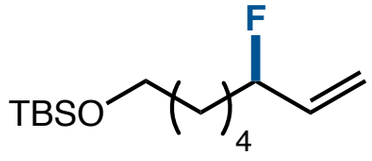
68% yield
14:1 dr, 90% ee



85% yield
10:1 b:l, 93% ee



50% yield
16:1 b:l, 90% ee

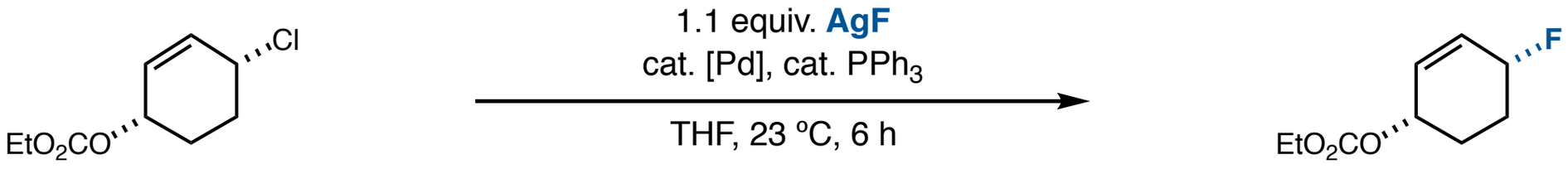


84% yield
>20:1 b:l, 58% ee

Katcher, M. H.; Doyle, A. G. *J. Am. Chem. Soc.* **2010**, *132*, 17402.

Katcher, M. H.; Sha, A.; Doyle, A. G. *J. Am. Chem. Soc.* **2011**, *133*, 15902.

Doyle's Palladium-Catalyzed Asymmetric Allylic Fluorination

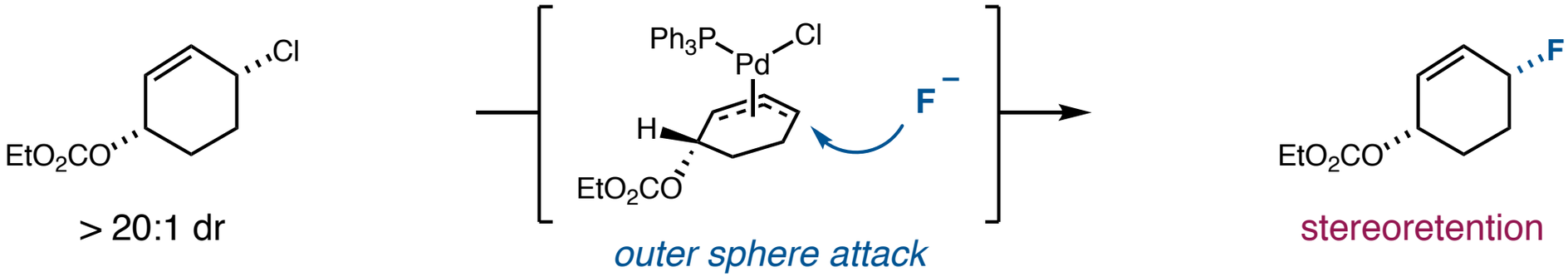


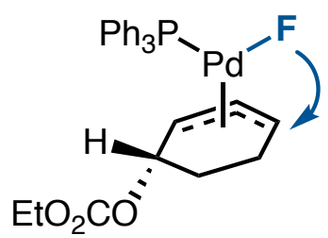
> 20:1 dr

stereoretention

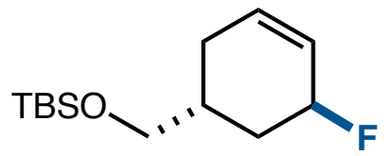
Katcher, M. H.; Norrby, P. O.; Doyle, A. G. *Organometallics* **2014**, *33*, 2121.

Doyle's Palladium-Catalyzed Asymmetric Allylic Fluorination



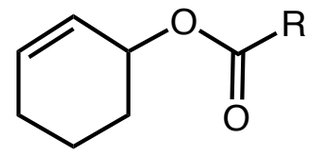


expected for "hard" nucleophile



56% yield

silyl ethers are tolerated



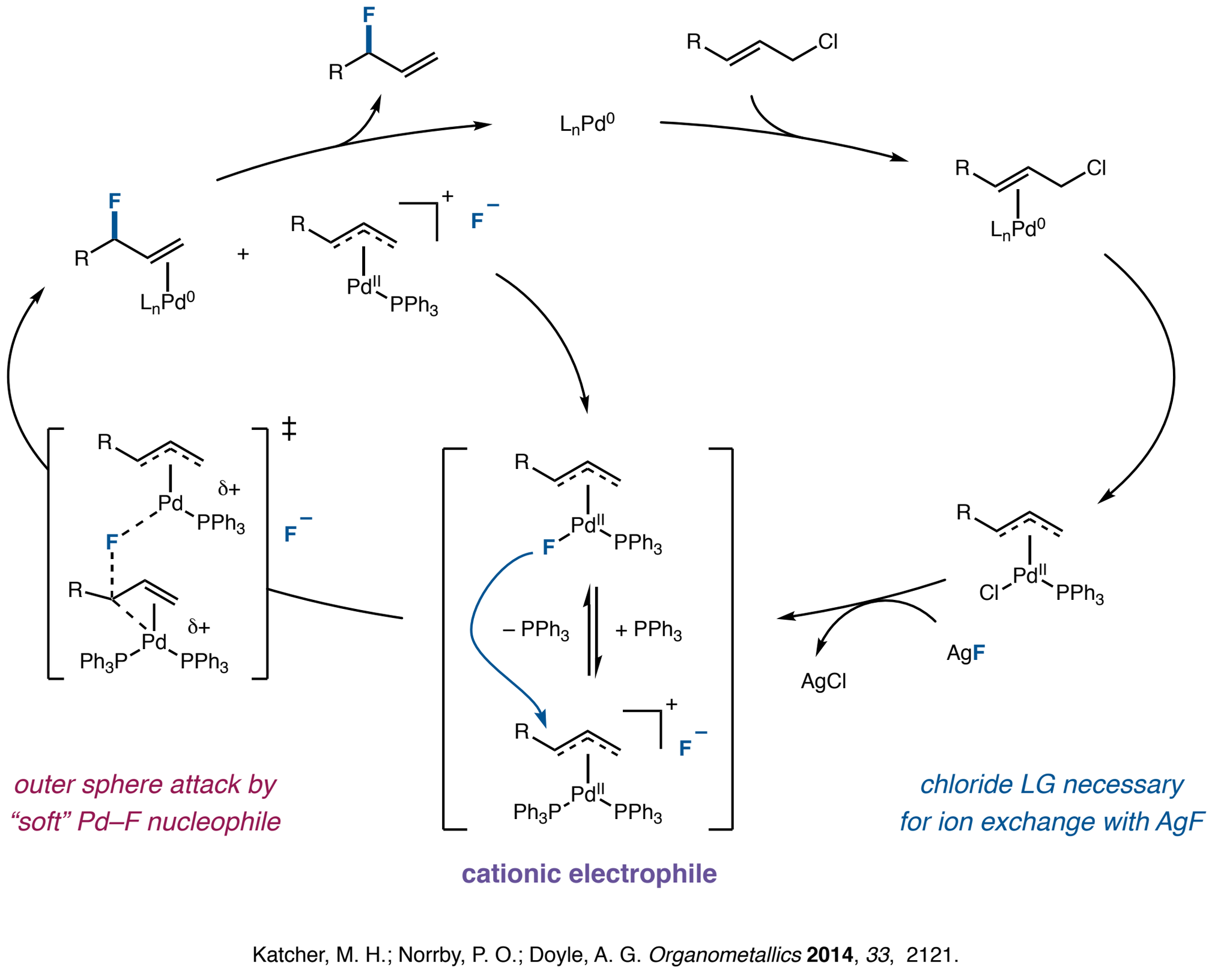
no product

typical π-allyl substrates incompatible

Typical π-allyl mechanism involving "naked" F^- as nucleophile unlikely

Katcher, M. H.; Norrby, P. O.; Doyle, A. G. *Organometallics* **2014**, *33*, 2121.

Proposed Mechanism for Palladium-Catalyzed Allylic Fluorination



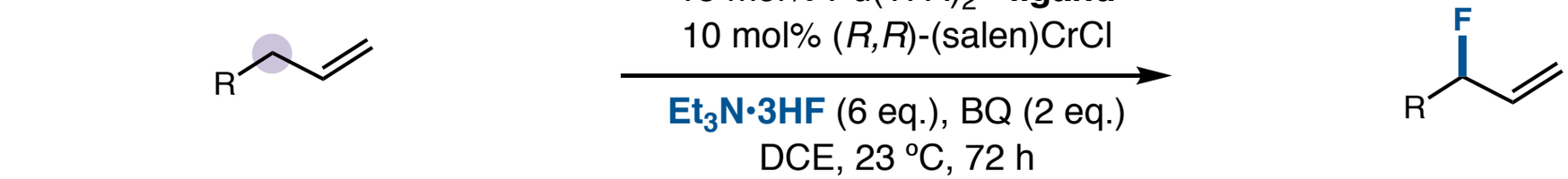
outer sphere attack by "soft" Pd–F nucleophile

cationic electrophile

chloride LG necessary for ion exchange with AgF

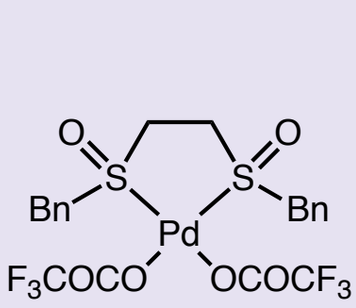
Katcher, M. H.; Norrby, P. O.; Doyle, A. G. *Organometallics* **2014**, *33*, 2121.

Palladium-Catalyzed Allylic C–H Fluorination

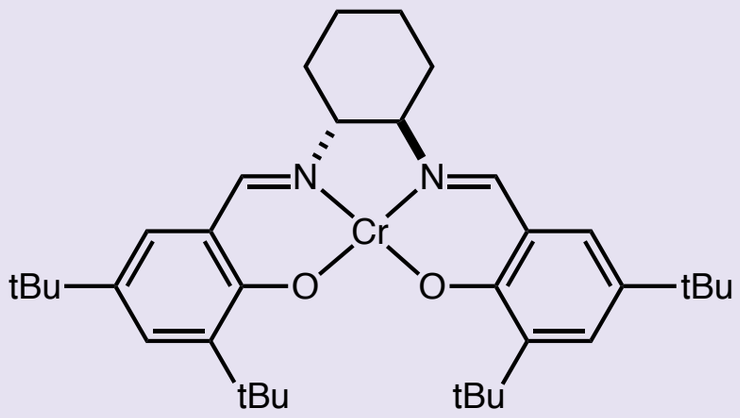


allylic C–H substrate

branched product

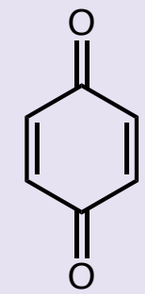


Pd(TFA)$_2$ • **ligand**



(*R,R*)-(salen)CrCl

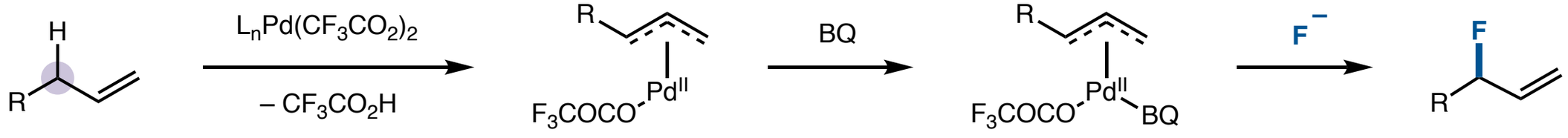
Lewis acid



benzoquinone (BQ)

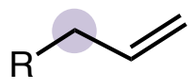
oxidant + ligand

Potential reaction pathway



Braun, M. G.; Doyle, A. G. *J. Am. Chem. Soc.* **2013**, *135*, 12990.

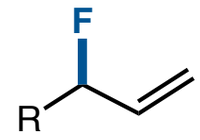
Palladium-Catalyzed Allylic C–H Fluorination



allylic C–H substrate

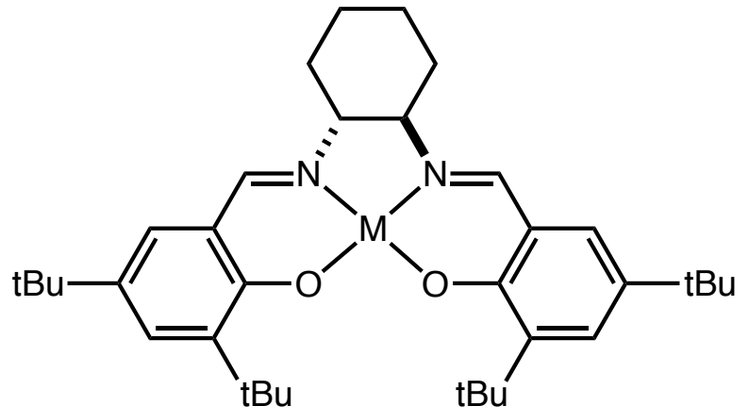
15 mol% $Pd(OAc)_2 \cdot (PhSOCH_2)_2$
10 mol% **co-catalyst**

F^- source (6 eq.), BQ (2 eq.)
DCE, 23 °C, 72 h



branched product

F^- source	**co-catalyst**	**yield**
AgF	—	0%
KF	—	0%
$Et_3N \cdot 3HF$	—	33%
$Et_3N \cdot 3HF$	(salen)MnCl	14%
$Et_3N \cdot 3HF$	**(salen)CrCl**	**51%**
$Et_3N \cdot 3HF$	(salen)CrF	28%

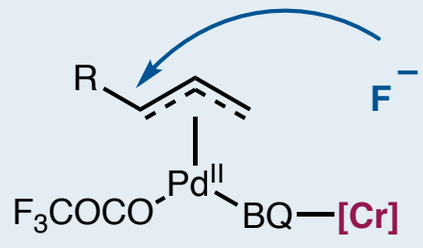


(salen)M

(salen)Cr—F

potentially generated *in situ*

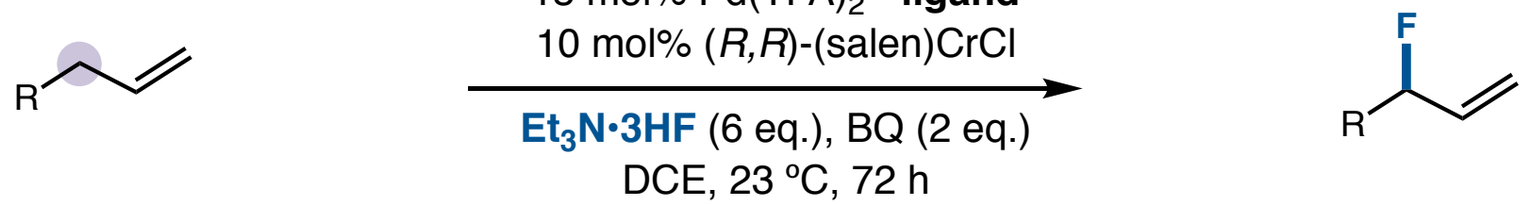
unlikely nucleophile



Lewis acid increases [Pd] electrophilicity

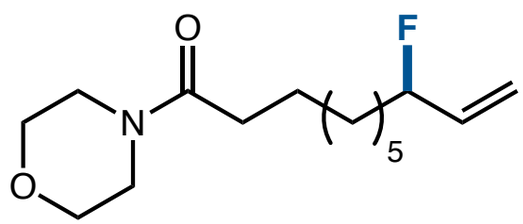
Braun, M. G.; Doyle, A. G. *J. Am. Chem. Soc.* **2013**, *135*, 12990.

Palladium-Catalyzed Allylic C–H Fluorination

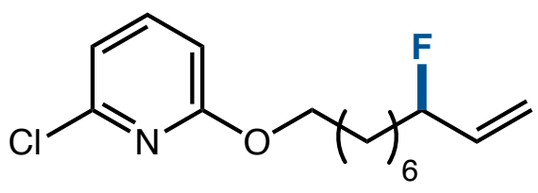


allylic C–H substrate

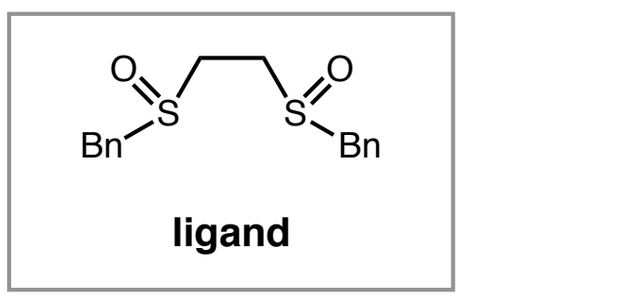
branched product



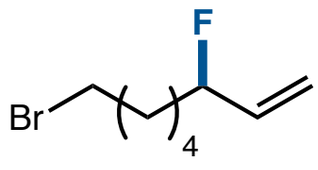
53% yield
7.0:1 b:l



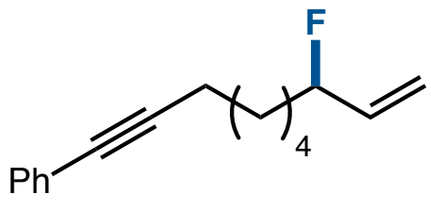
54% yield
7.8:1 b:l



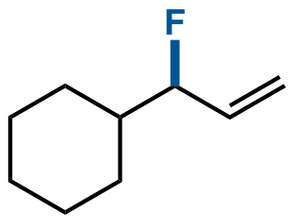
ligand



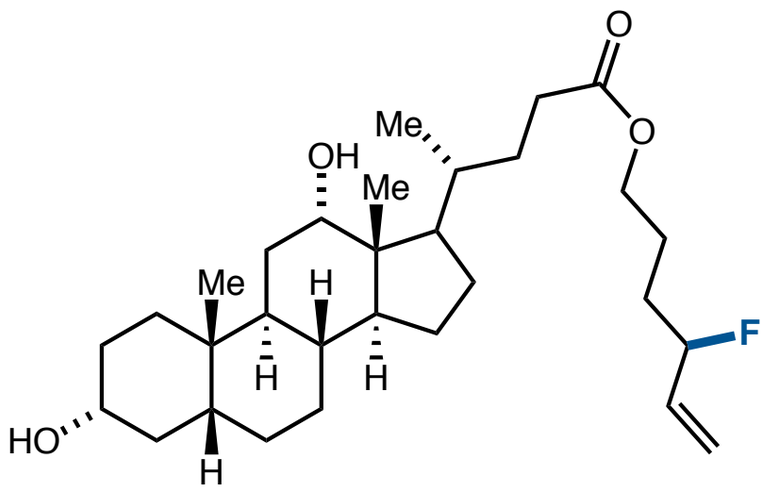
54% yield
7.0:1 b:l



47% yield
7.5:1 b:l



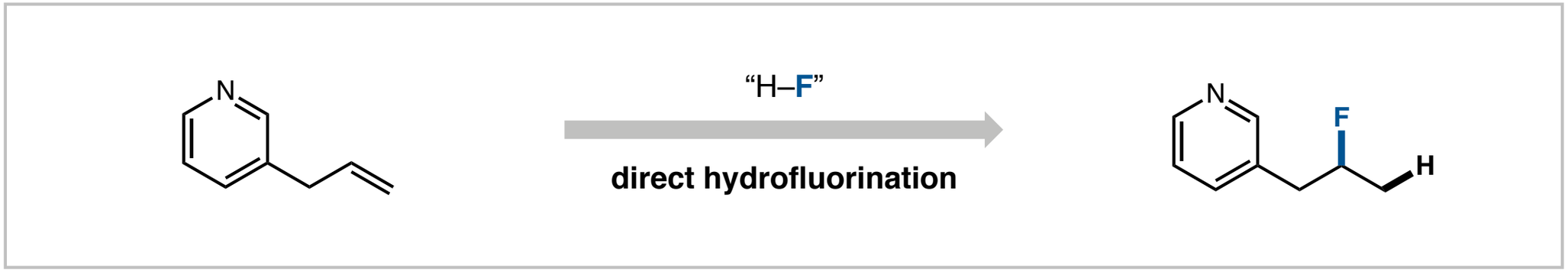
33% yield
2.0:1 b:l



43% yield
6.8:1 b:l

Braun, M. G.; Doyle, A. G. *J. Am. Chem. Soc.* **2013**, *135*, 12990.

Recent Advances in Direct Hydrofluorination of Alkenes



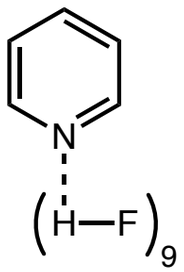
H—F

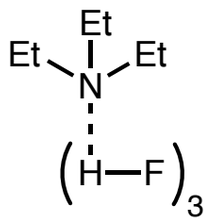
hydrofluoric acid

pK_a = 3.2

toxic and corossive gas

difficult alkene protonation

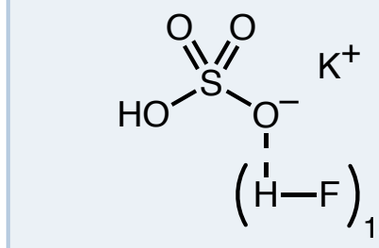




convenient liquid F⁻ source

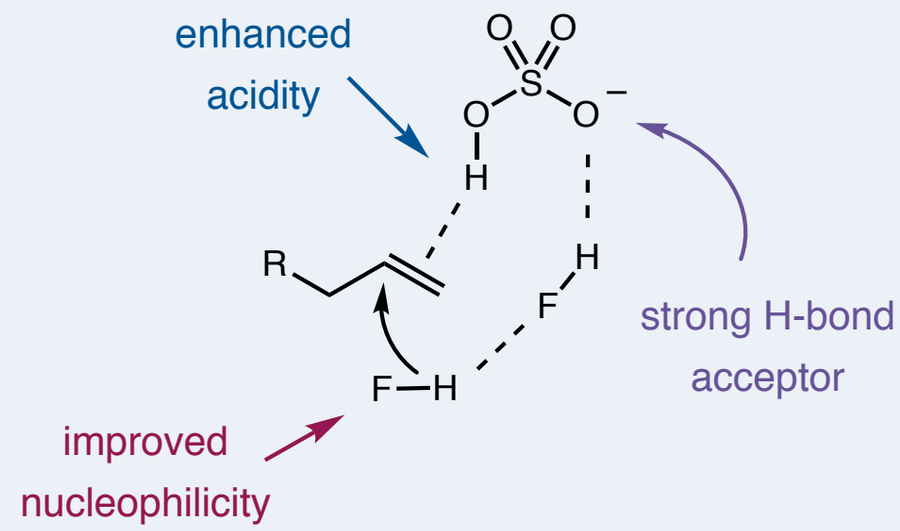
acidity further diminished

large excess required



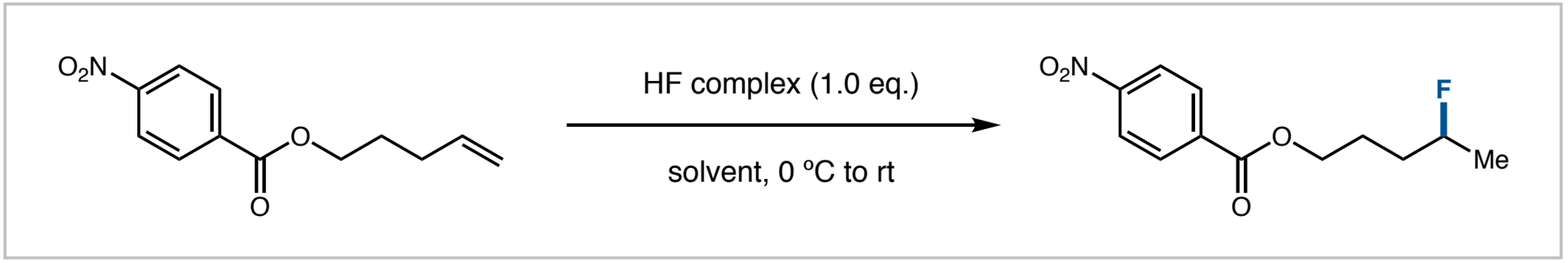
pK_a ($KHSO_4$) = 1.9

liquid reagent



Lu, Z.; Zeng, X.; Hammond, G. B.; Xu, B. *J. Am. Chem. Soc.* **2017**, *139*, 18202.

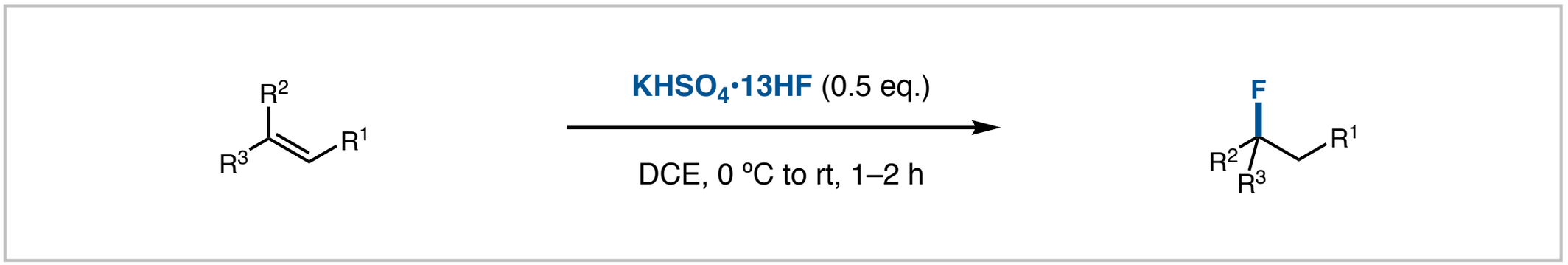
Direct Hydrofluorination of Alkenes Using a $KHSO_4$–HF Complex

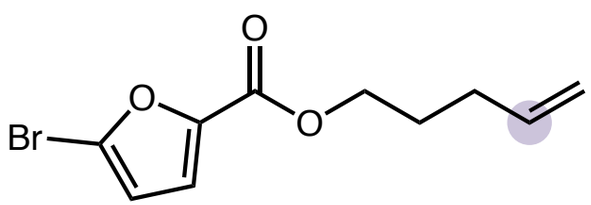


solvent	HF complex	time	alkene SM	product
DCM	Py•3HF	0.5 h	100%	0%
DCM	K_2SO_4•14HF	18 h	84%	16%
DCM	$KHSO_4$•13HF	0.5 h	57%	43%
DCE	$KHSO_4$•13HF	0.5 h	29%	71%
DCE	**$KHSO_4$•13HF**	**2 h**	3%	**83%**
DCE	KH_2PO_4•9HF	0.5 h	100%	0%

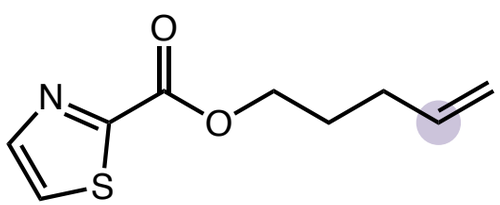
Lu, Z.; Zeng, X.; Hammond, G. B.; Xu, B. *J. Am. Chem. Soc.* **2017**, *139*, 18202.

Direct Hydrofluorination of Alkenes Using a $KHSO_4$–HF Complex

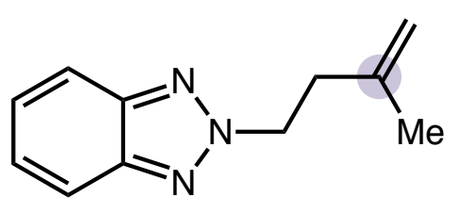




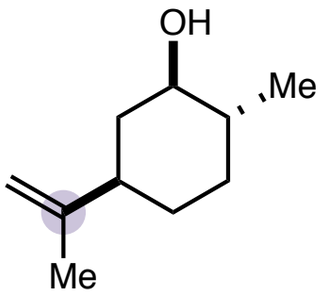
79% yield



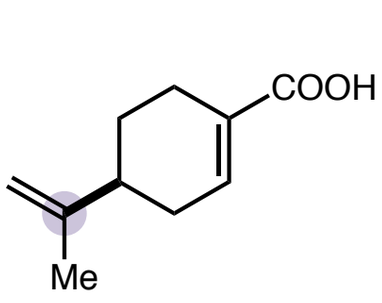
72% yield



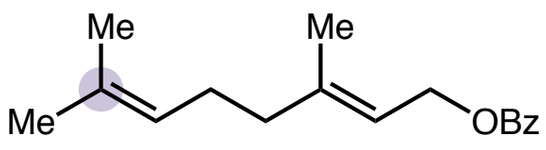
61% yield



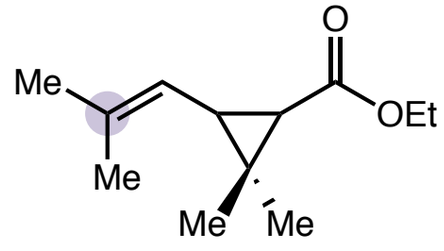
53% yield



62% yield



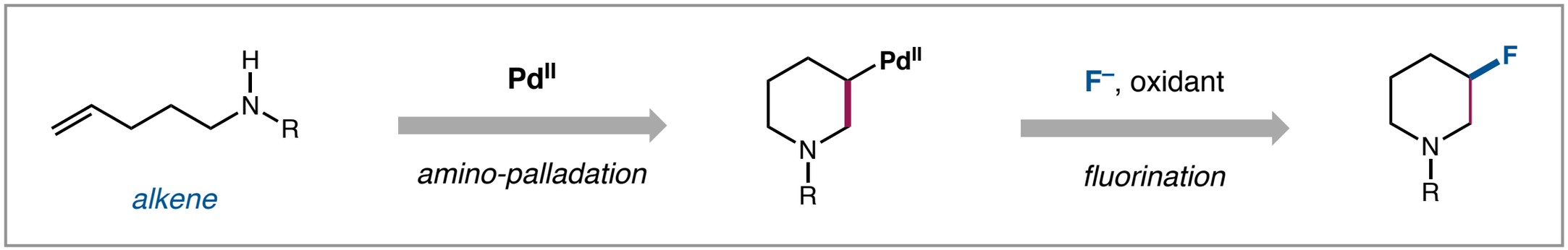
45% yield



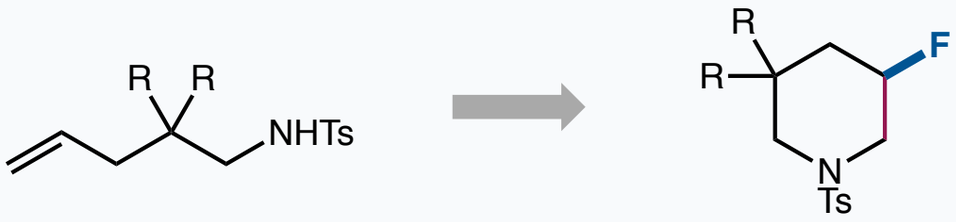
61% yield

Lu, Z.; Zeng, X.; Hammond, G. B.; Xu, B. *J. Am. Chem. Soc.* **2017**, *139*, 18202.

Palladium-Catalyzed Aminofluorination of Alkenes



Nucleophilic amino-fluorination of alkenes containing tosyl-protected amines



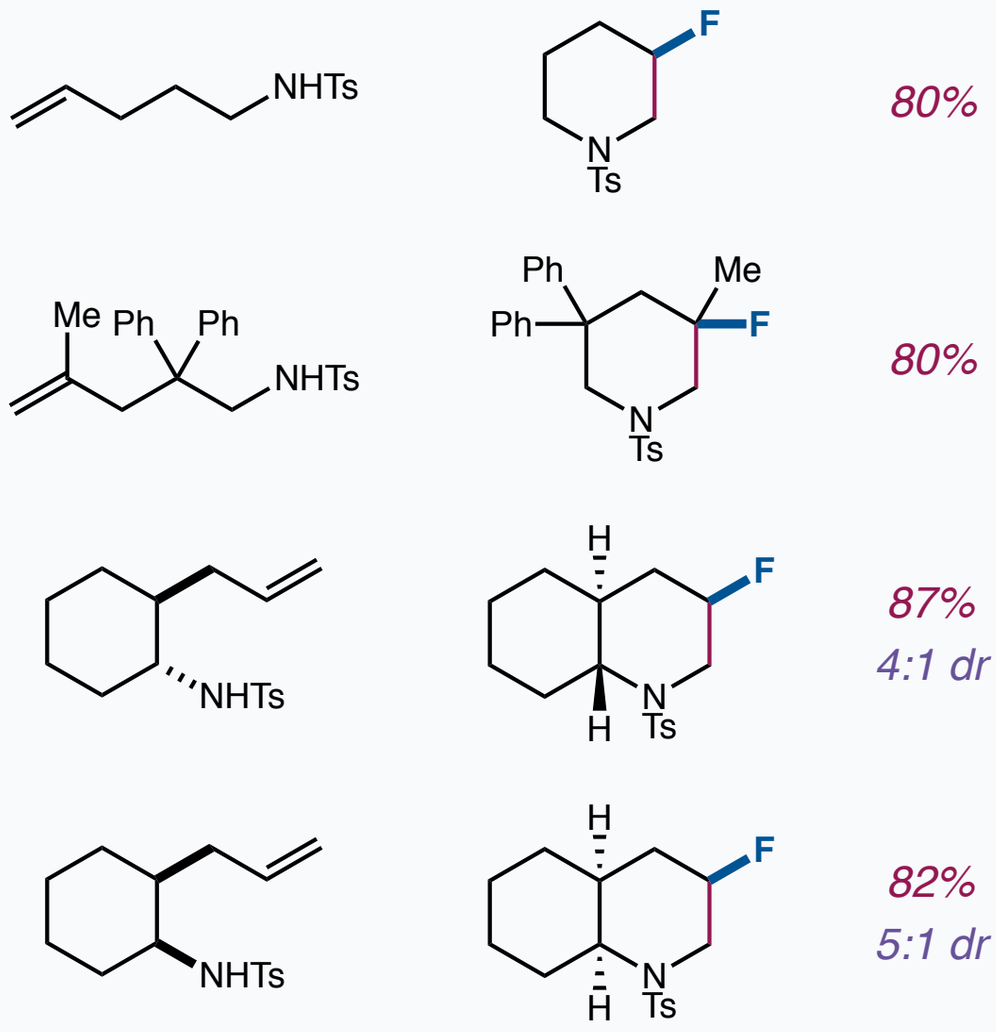
alkene *fluoroamine*

conditions

10 mol% $Pd(OAc)_2$ 2 eq. $PhI(OPiv)_2$

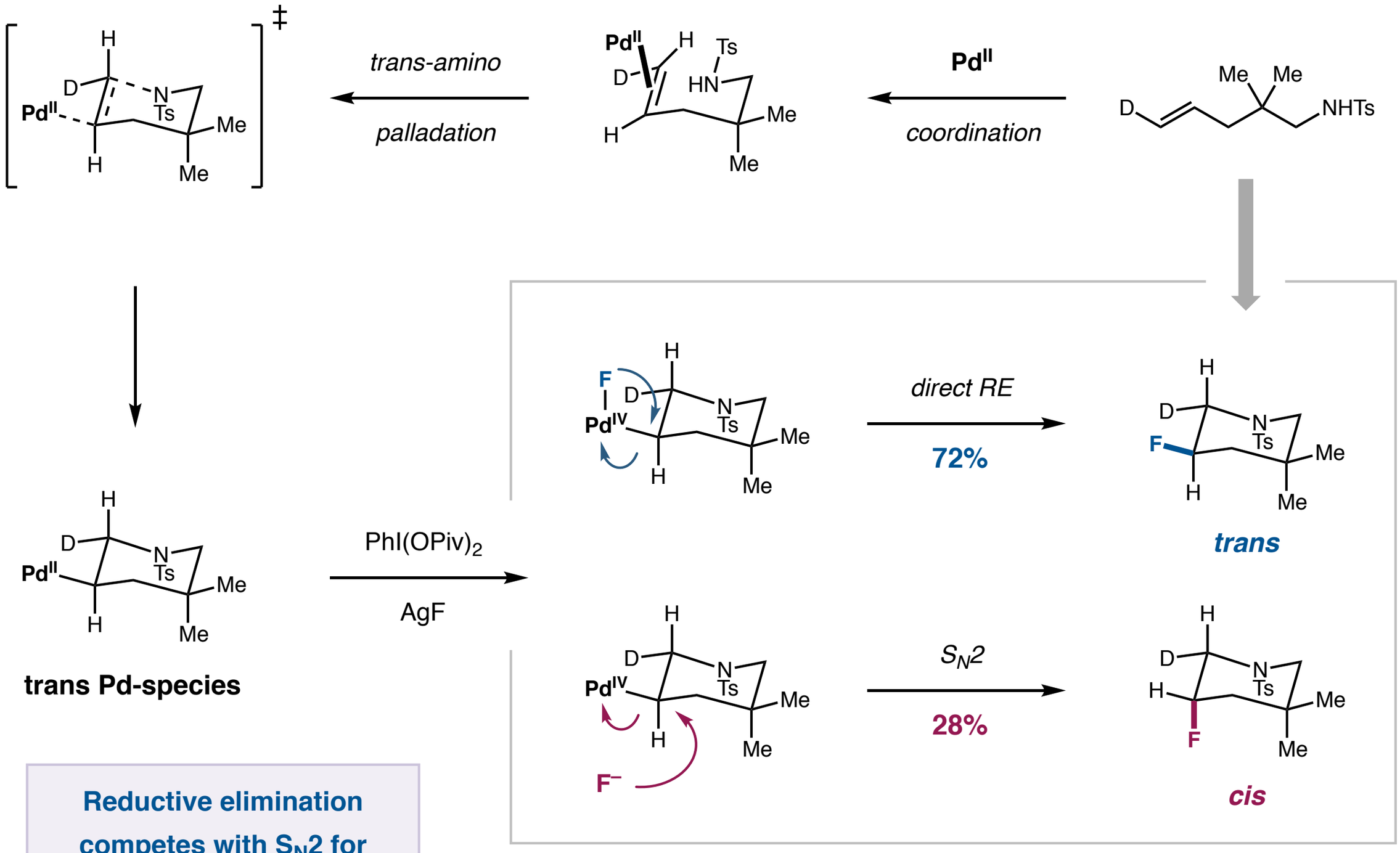
$MgSO_4$ 5 eq. AgF

CH_3CN, rt



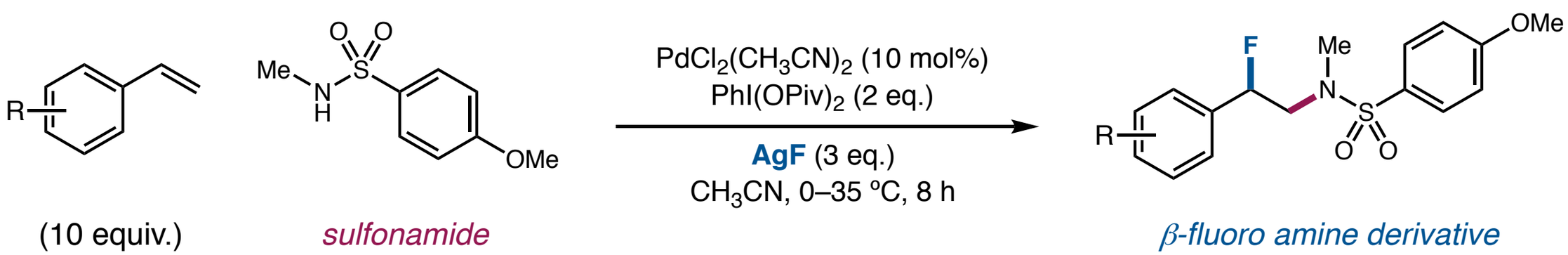
Wu, T.; Yin, G.; Liu, G. *J. Am. Chem. Soc.* **2009**, *131*, 16354.

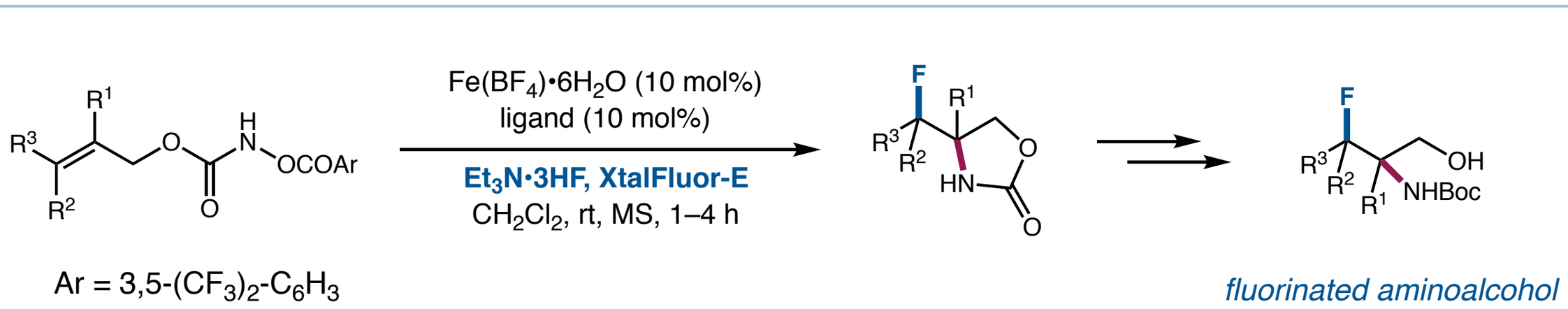
Mechanism for Palladium-Catalyzed Aminofluorination of Alkenes



Wu, T.; Yin, G.; Liu, G. *J. Am. Chem. Soc.* **2009**, *131*, 16354.

Other Examples of Metal-Catalyzed Alkene Aminofluorination



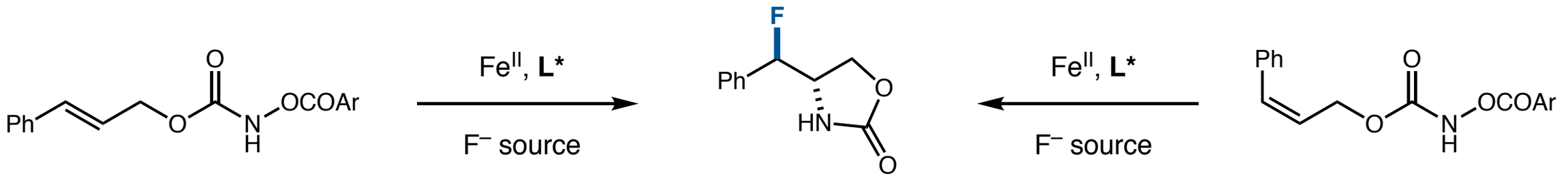


Zhu, H.; Liu, G. *Acta. Chim. Sinica* **2012**, *70,* 2404.

Fu, D.-F.; Liu, G.-S.; Zhu, C.-L.; Yuan, B.; Xu, H. *Org. Lett.* **2014**, *16*, 2912.

Chen, P.; Liu, G. *Eur. J. Org. Chem.* **2015**, 4295.

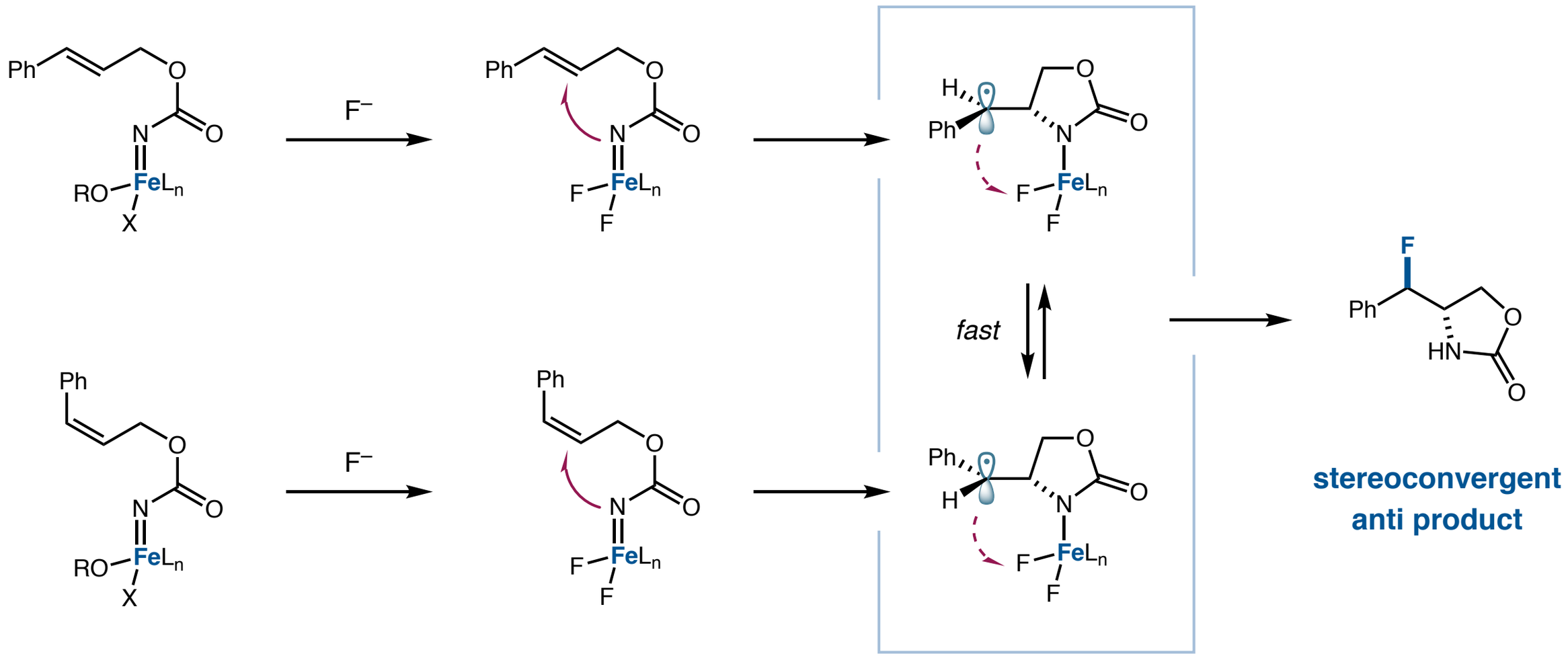
Mechanistic Insight for Iron-Catalyzed Aminofluorination of Alkenes



■ **Iron involved in bond-forming step**

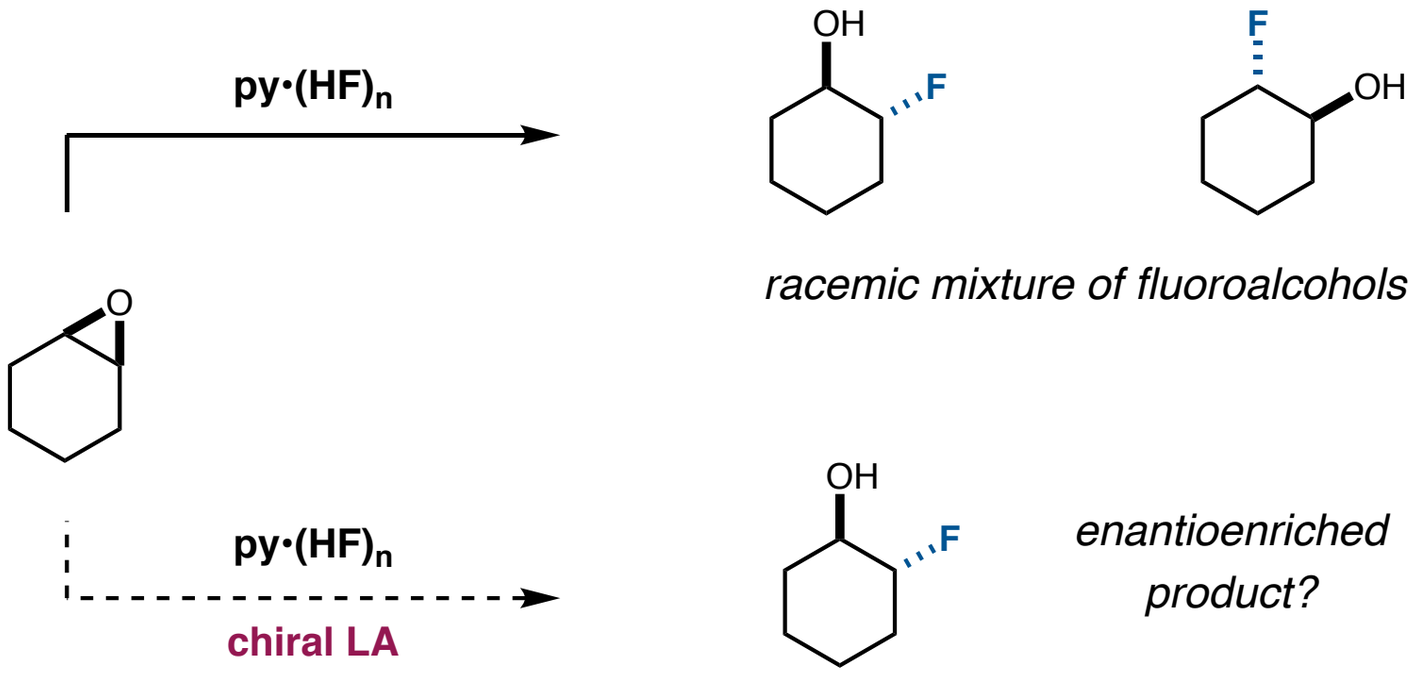
3.2:1 dr, 81% ee

■ **Ablation of alkene stereochemistry**



Fu, D.-F.; Liu, G.-S.; Zhu, C.-L.; Yuan, B.; Xu, H. *Org. Lett.* **2014**, *16*, 2912.

Opportunities for Asymmetric Hydrofluorination of Epoxides



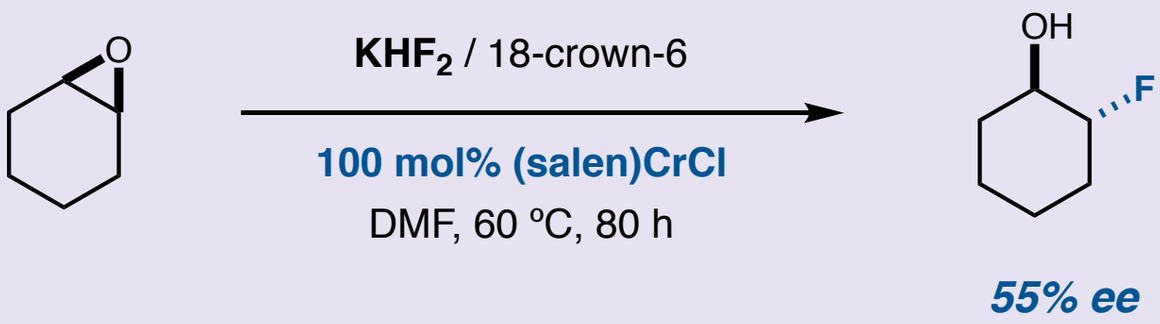
Precedented

Remarkable reactivity

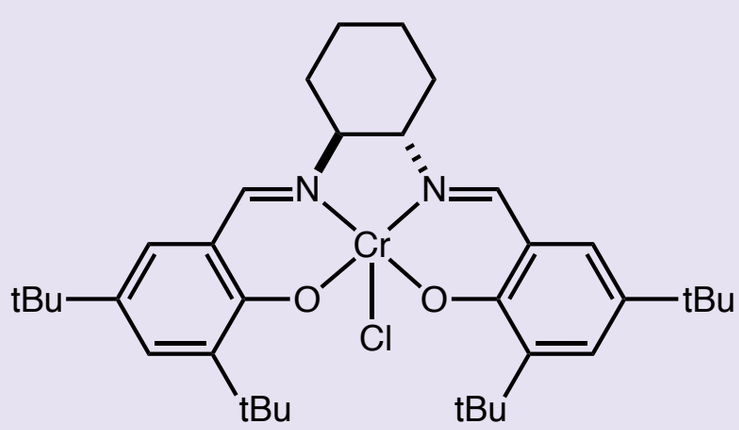
Fast background rxn

Catalyst inhibition

Haufe – the first asymmetric hydrofluorination of epoxides



55% ee



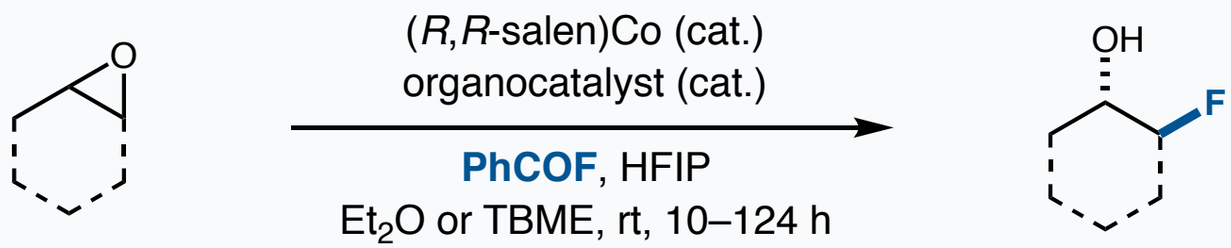
(salen)CrCl

Bruns, S.; Haufe, G. *J. Fluor. Chem.* **2000**, *104*, 247.

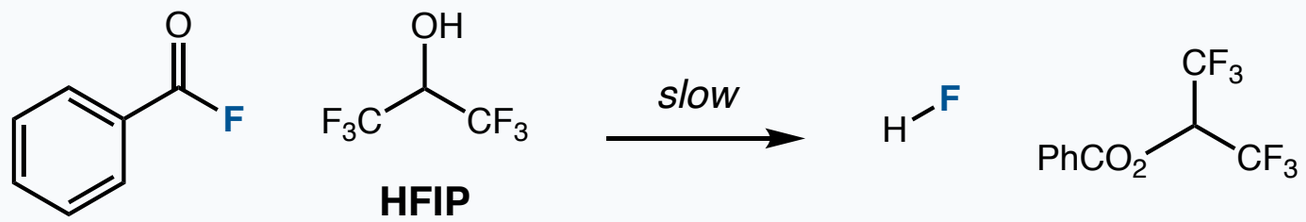
Hollingworth, C.; Gouverneur, V. *Chem. Commun.* **2012**, *48*, 2929.

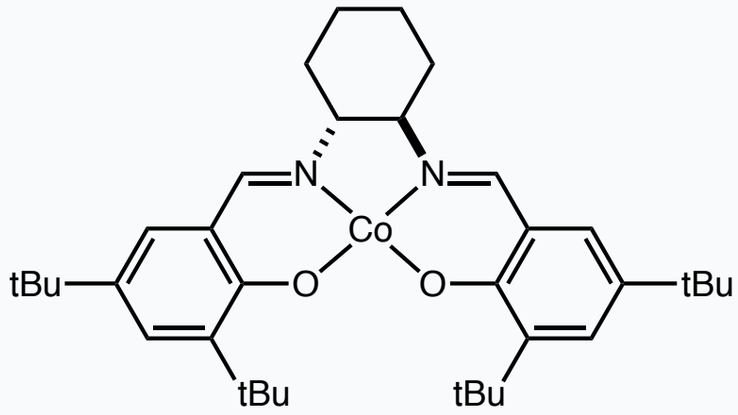
Doyle's Lewis Acid-Catalyzed Asymmetric Hydrofluorination of Epoxides

Doyle's Catalytic Asymmetric Epoxide Hydrofluorination

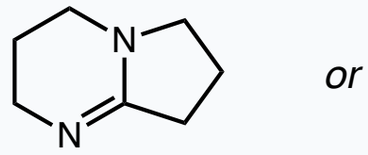


Key design element: slow generation of active "HF"



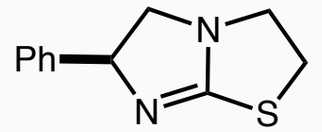


(*R*,*R*-salen)Co



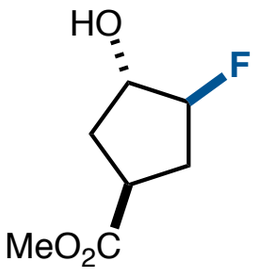
DBN

or

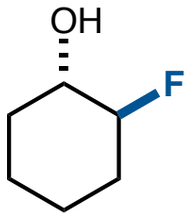


(–)-tetramisole

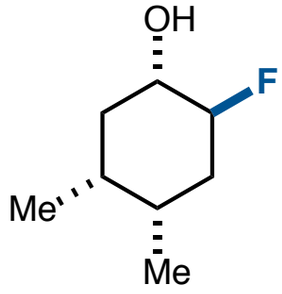
Desymmetrization



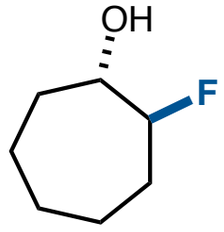
88% yield
86% ee



65% yield
93% ee

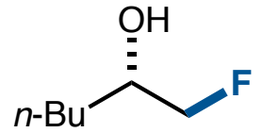


75% yield
90% ee

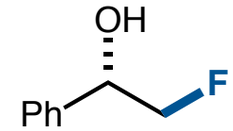


82% yield
90% ee

Kinetic resolution



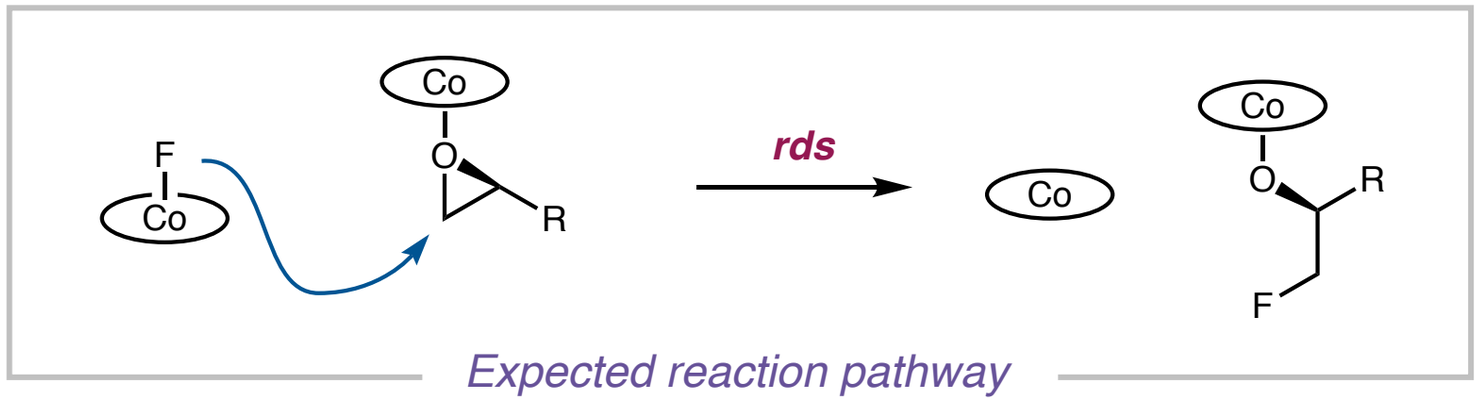
47% yield (GC)
99% ee



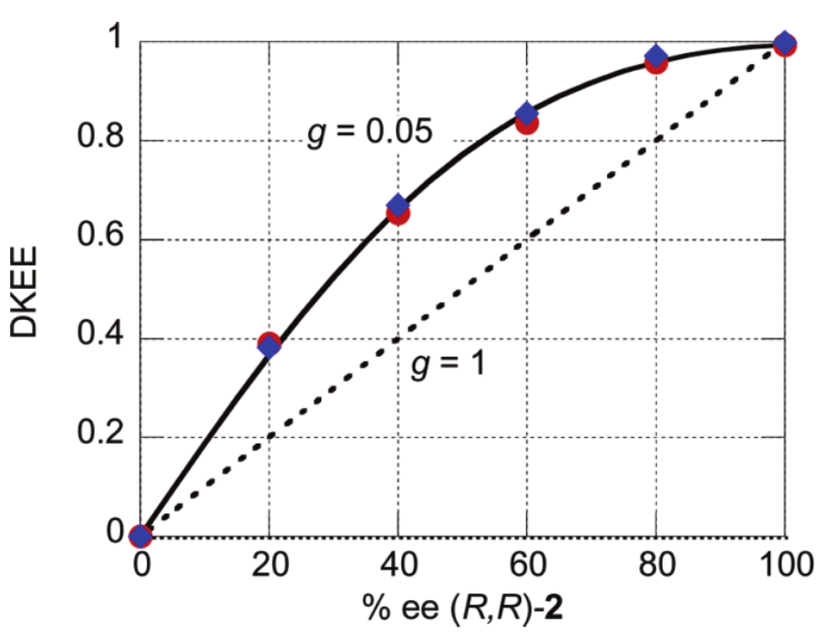
44% yield
99% ee

Kalow, J. A.; Doyle, A. G. *J. Am. Chem. Soc.* **2010**, *132*, 3268.

Mechanistic Investigation for Asymmetric Hydrofluorination of Epoxides

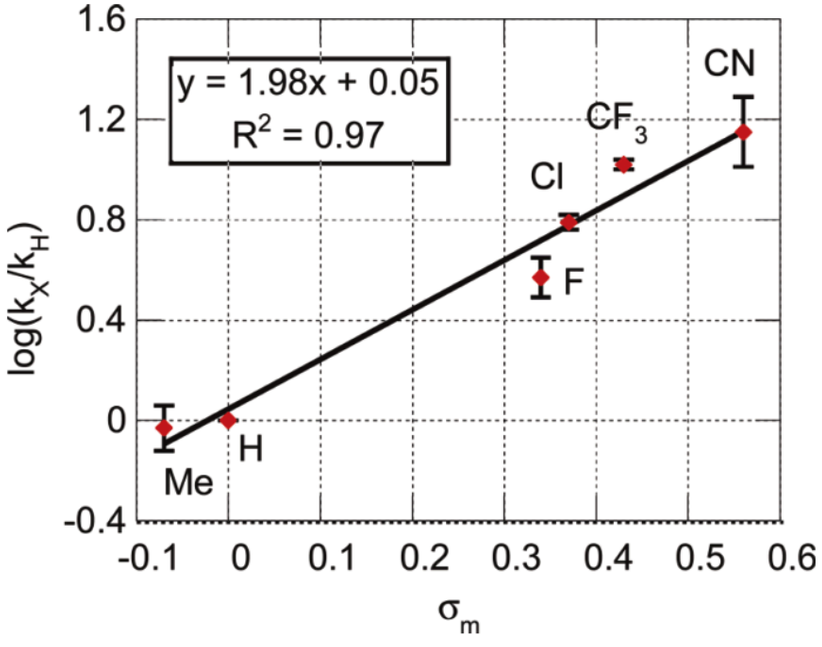


Expected reaction pathway



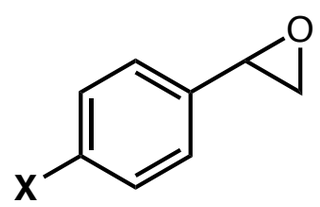
*non-linear effects with (salen)Co (**2**)*

consistent with bimetallic rds

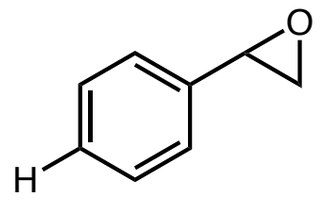


buildup of negative charge on substrate

consistent with epoxide opening in rds



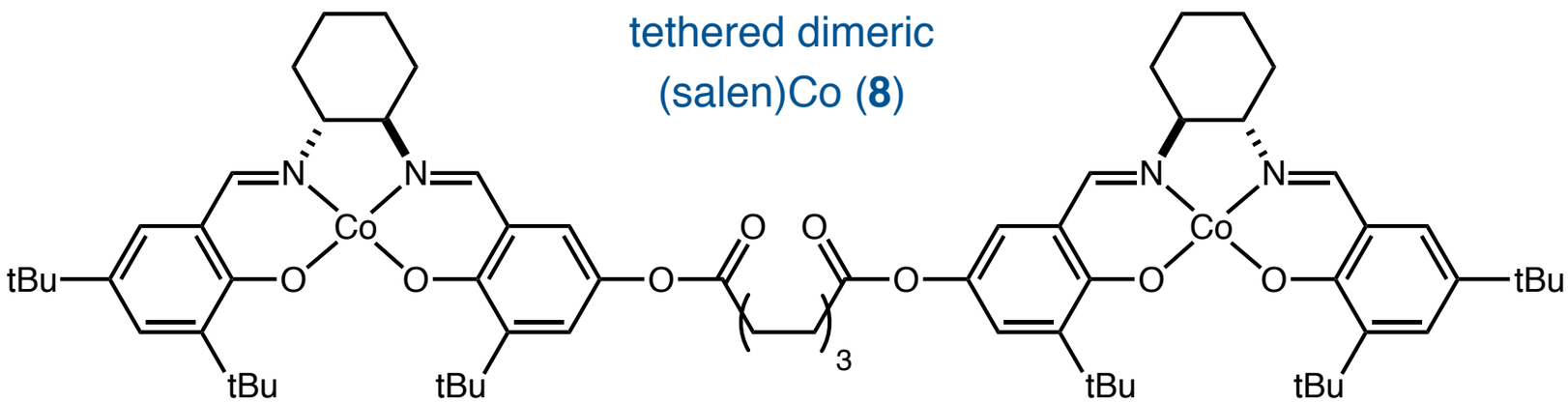
vs



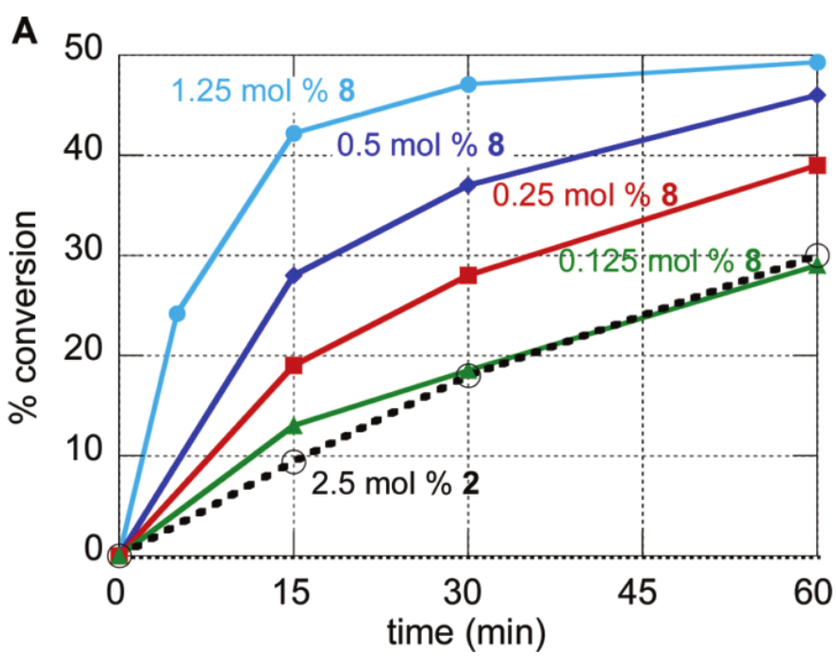
Discrepancy: kinetic studies show first order in (salen)Co catalyst!

Kalow, J. A.; Doyle, A. G. *J. Am. Chem. Soc.* **2011**, *133*, 16001.

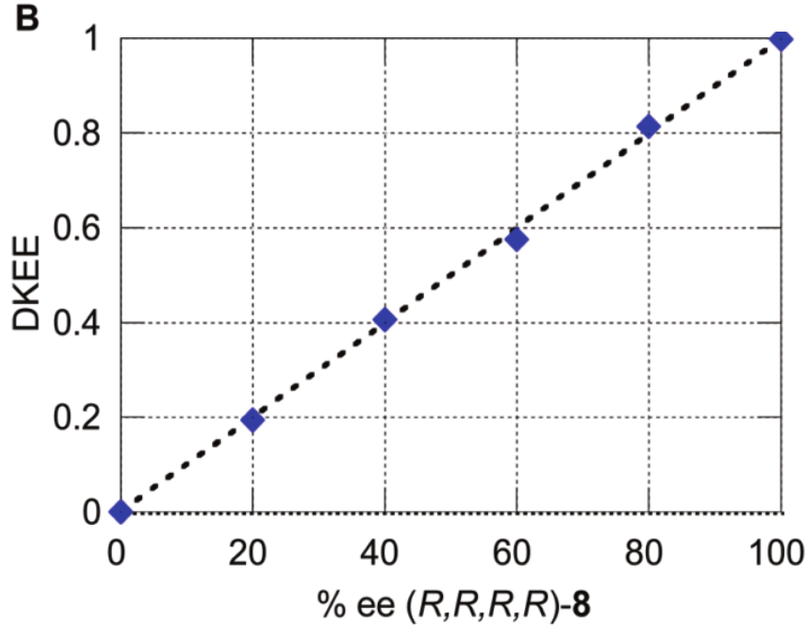
Mechanistic Investigation for Asymmetric Hydrofluorination of Epoxides



(!!!) rate data show ***half-order*** dependence on **8 (!!!)**



rate ehhancement relative to monomer

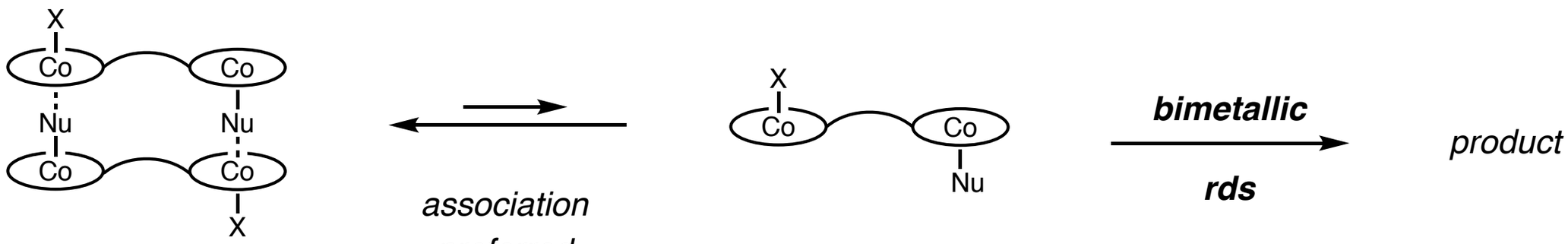


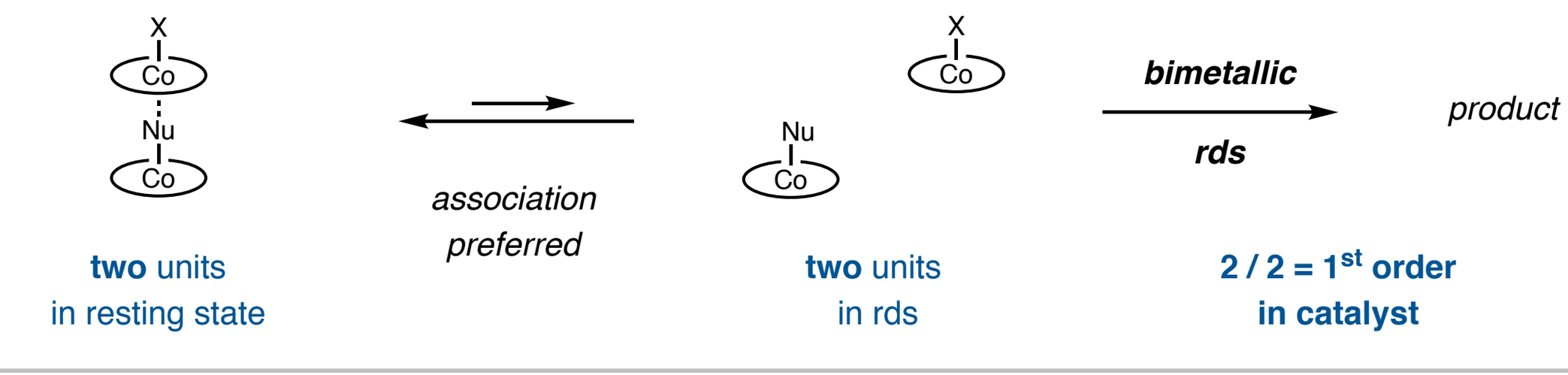
absence of non-linear effects

consistent with bimetallic mechanism

Kalow, J. A.; Doyle, A. G. *J. Am. Chem. Soc.* **2011**, *133*, 16001.

Mechanistic Investigation for Asymmetric Hydrofluorination of Epoxides



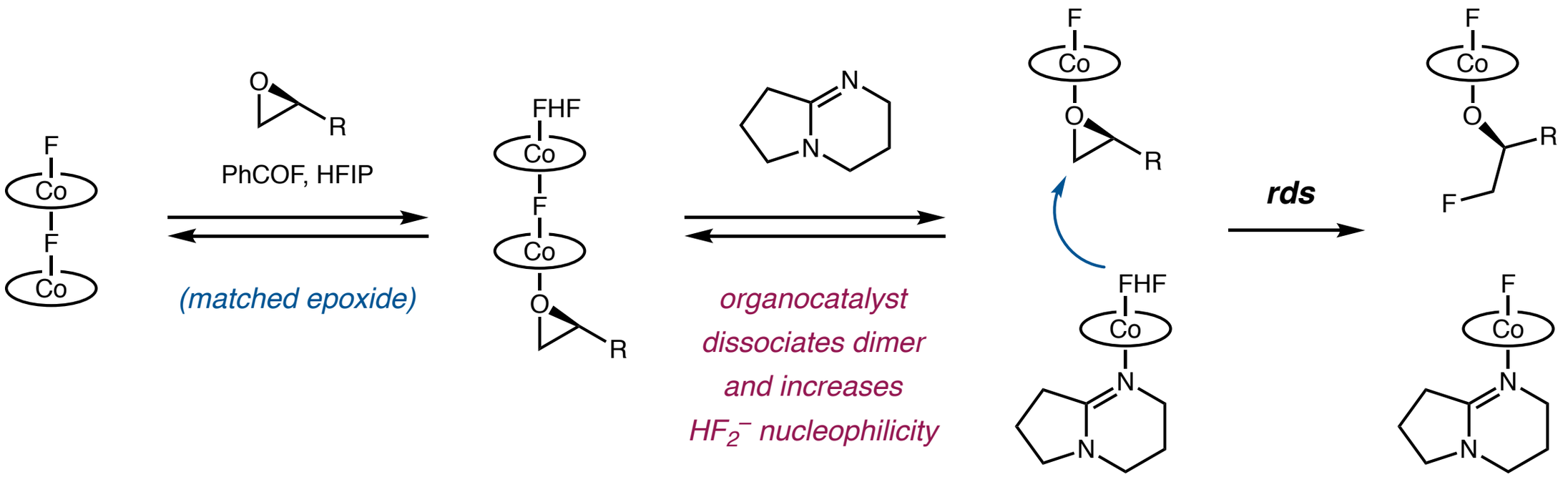


Bimetallic rate-determining step + dimeric resting state = first order kinetics

Kalow, J. A.; Doyle, A. G. *J. Am. Chem. Soc.* **2011**, *133*, 16001.

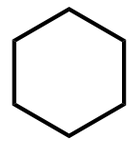
Mechanistic Investigation for Asymmetric Hydrofluorination of Epoxides

Simplified mechanistic picture



Kalow, J. A.; Doyle, A. G. *J. Am. Chem. Soc.* **2011**, *133*, 16001.

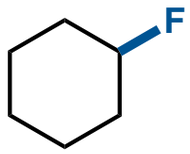
Aliphatic C–H Nucleophilic Fluorination with Manganese Complexes



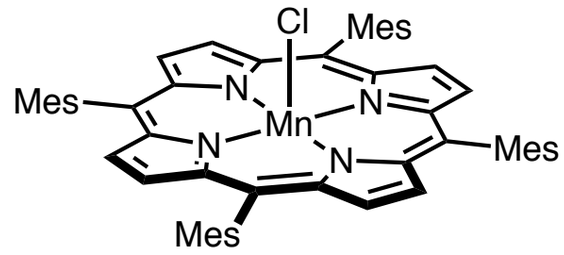
C–H substrate

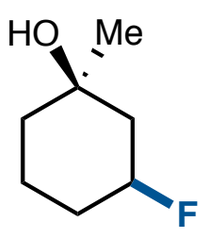
AgF
cat. Mn(TMP)Cl

PhIO, $TBAF{\cdot}3H_2O$
MeCN / DCM, 50 °C

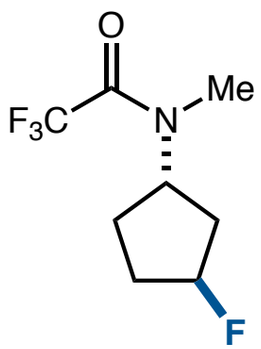


sp^3 C–F product

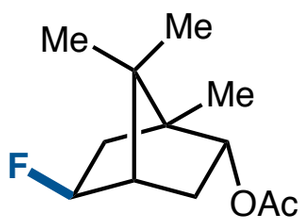




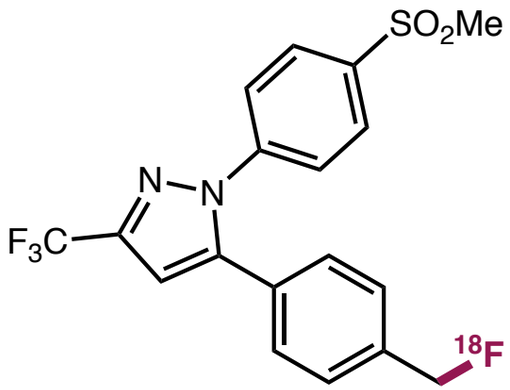
44% yield
8:1 dr, 4:1 rr



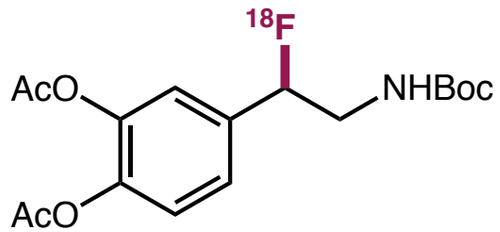
51% yield
1.5:1 dr



57% yield



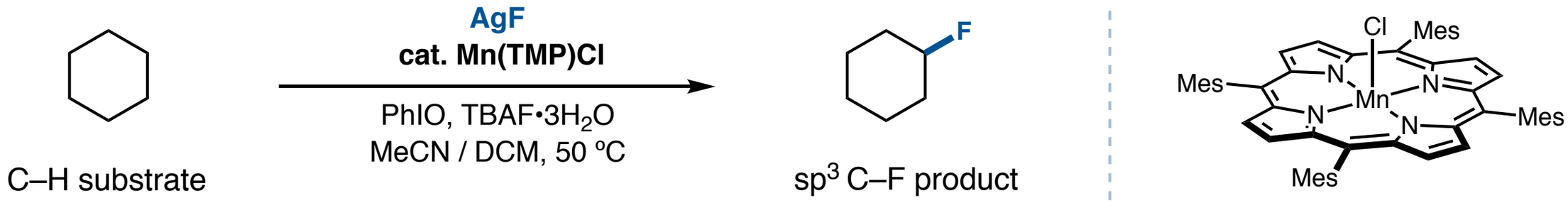
23% RCC



51% RCC

Liu, W.; Huang, X.; Cheng, M.-J.; Nielsen, R. J.; Goddard, W. A.; Groves, J. T. *Science* **2012**, *337*, 1322.
Huang, X.; Liu, W.; Ren, H.; Neelamegam, R.; Hooker, J. M.; Groves, J. T. *J. Am. Chem. Soc.* **2014**, *136*, 6842.

Aliphatic C–H Nucleophilic Fluorination with Manganese Complexes



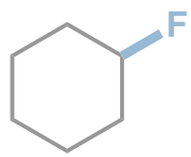
For more details,
see Yong's group meeting
on manganese catalysis

Liu, W.; Huang, X.; Cheng, M.-J.; Nielsen, R. J.; Goddard, W. A.; Groves, J. T. *Science* **2012**, *337*, 1322.
Huang, X.; Liu, W.; Ren, H.; Neelamegam, R.; Hooker, J. M.; Groves, J. T. *J. Am. Chem. Soc.* **2014**, *136*, 6842.

Recent Developments in Nucleophilic Fluorination

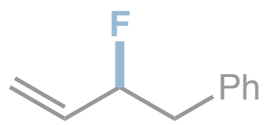
Construction of Alkyl C–F Bonds

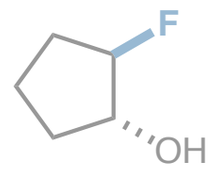
Nucleophilic substitution promoted by hydrogen bonding



Deoxyfluorination of aliphatic alcohols

Transition metal-catalyzed allylic fluorination

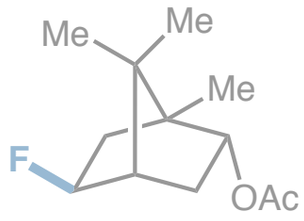




Direct hydrofluorination of alkenes

Metal-mediated aminofluorination of alkenes

Asymmetric hydrofluorination of epoxides

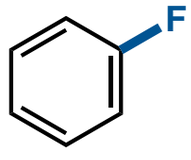


Manganese-catalyzed C–H fluorination – see YYL group meeting

Construction of Aromatic C–F Bonds

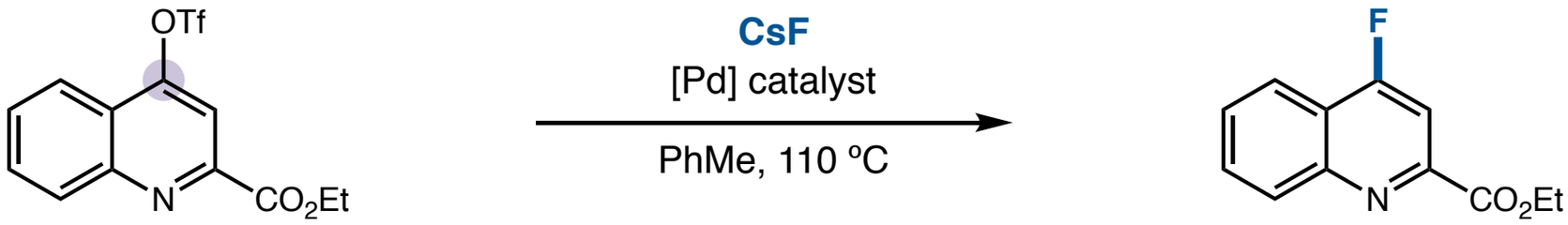
Metal-mediated fluorination of arenes – see JRT group meeting

Nucleophilic aromatic substitution of (pseudo)halides

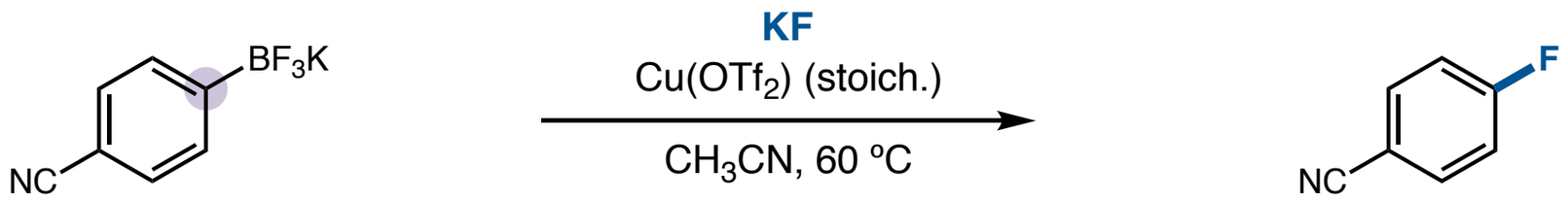


Ritter's S_NAr deoxyfluorination of phenols

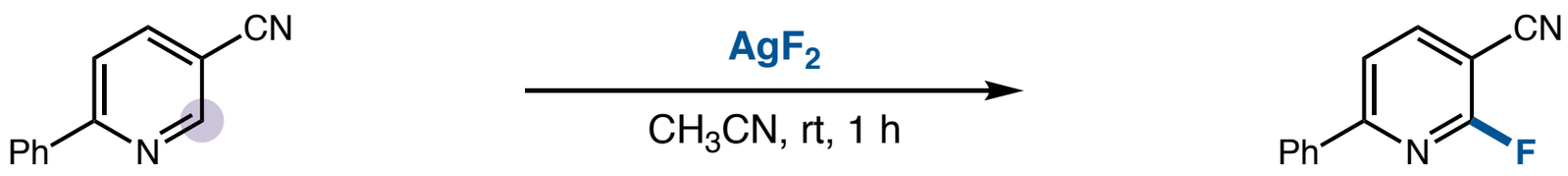
Transition Metal-Mediated Nucleophilic Flourination of Arenes



Buchwald, S. L. *et al. Science* **2008**, *325*, 1661.

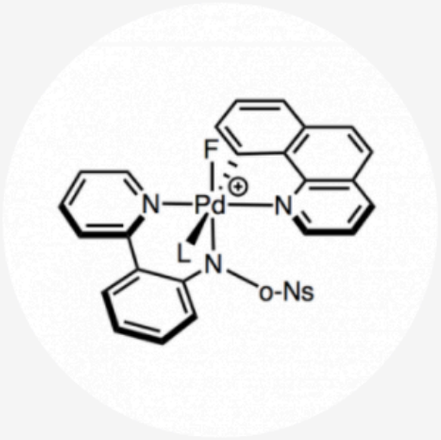


Ye, Y.; Schimler, S. D.; Hanley, P. S.; Sanford, M. S. *J. Am. Chem. Soc.* **2013**, *135*, 16292.



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

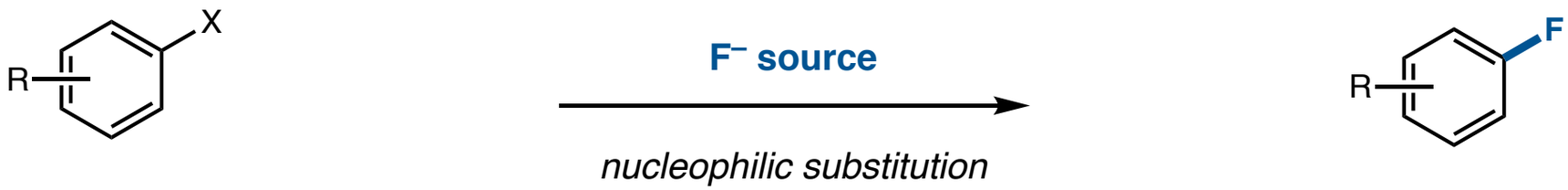
Transition Metal-Mediated Nucleophilic Flourination of Arenes



Transition Metal Mediated Fluorination of Arenes

Jack Twilton →

Nucleophilic Aromatic Substitution of Haloarenes with "Naked" Fluoride

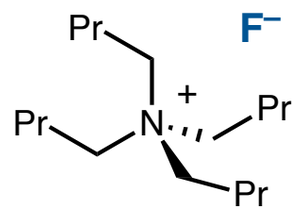


Cs^+ F^-

K^+ F^-

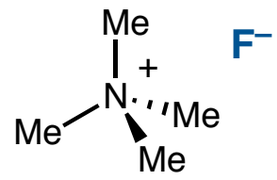
low solubility in organics

requires high temperatures



good solubility

Hoffmann elimination when drying

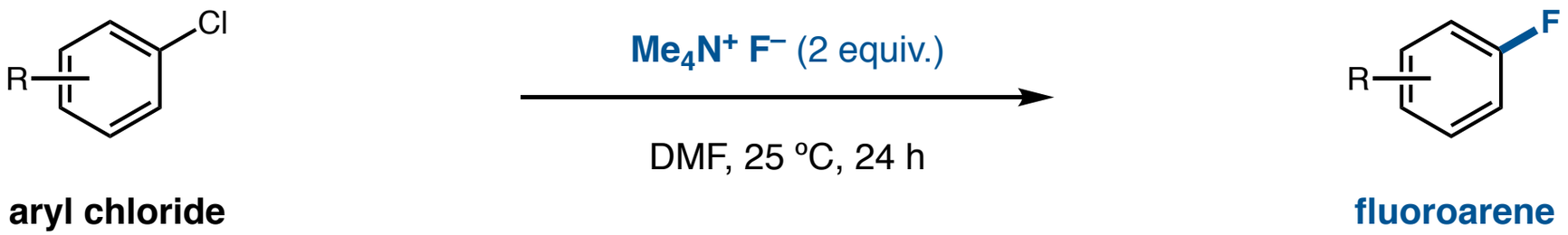


good solubility

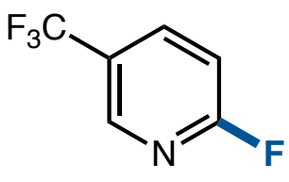
easy preparation and drying

Schimler, S. D.; Ryan. S. J.; Bland, D. C.; Anderson, J. E.; Sanford, M. S. *J. Org. Chem.* **2015**, *80*, 12137.

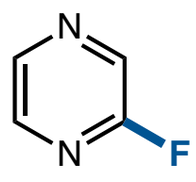
Sanford's Nucleophilic Aromatic Substitution of Haloarenes with NMe_4F



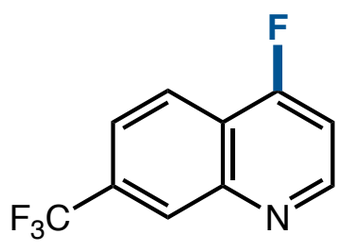
aryl chloride **fluoroarene**



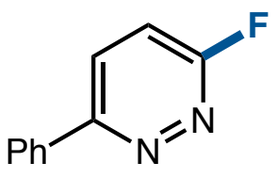
98% yield



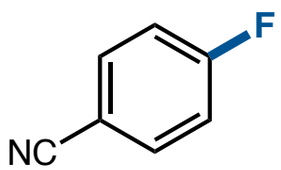
92% yield



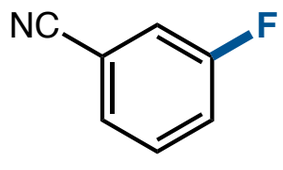
79% yield



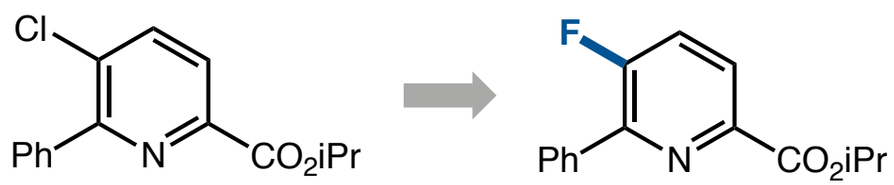
90% yield



80% yield
(at 80 °C)



7% yield
(at 80 °C)

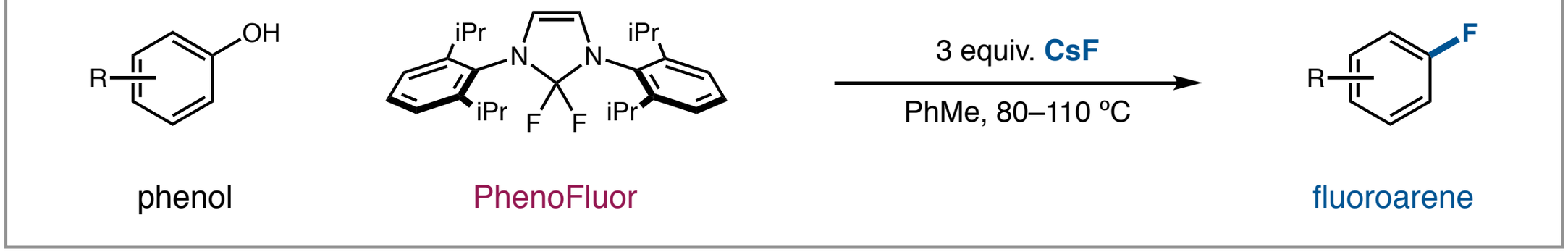


equiv. H_2O	*yield*
0	99%
1	76%
2	1%

"Naked" fluoride S_NAr very sensitive to presence of water

Schimler, S. D.; Ryan. S. J.; Bland, D. C.; Anderson, J. E.; Sanford, M. S. *J. Org. Chem.* **2015**, *80*, 12137.

Ritter's Deoxyfluorination of Phenols



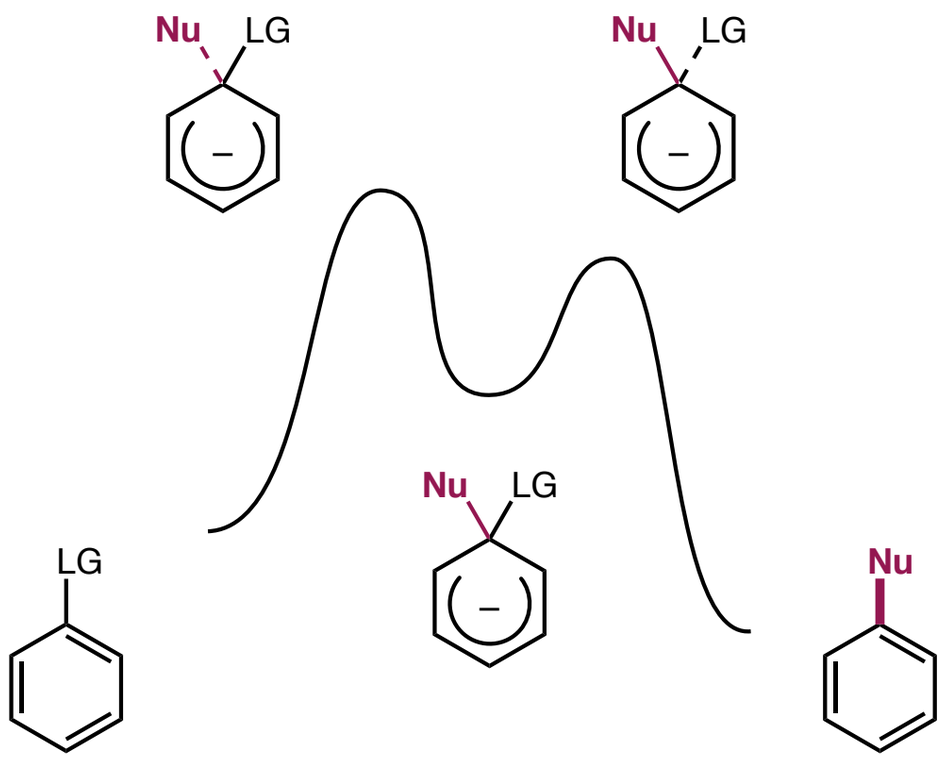
- ***Adaptable towards fluorination with nucleophilic ^{18}F***
- ***Compatible with wide range of electronically distinct arenes***
- ***Unique S_NAr approach for deoxyfluorination of phenols***

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

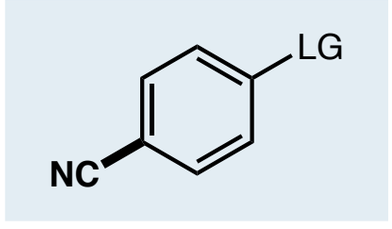
Neumann, C. N.; Hooker, J. M.; Ritter, T. *Nature* **2016**, *534*, 369.

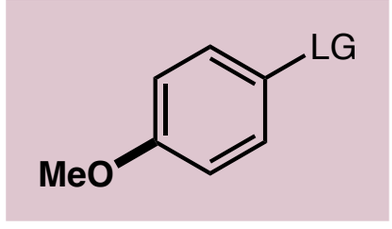
A Concerted Nucleophilic Aromatic Substitution Approach

Traditional S_NAr

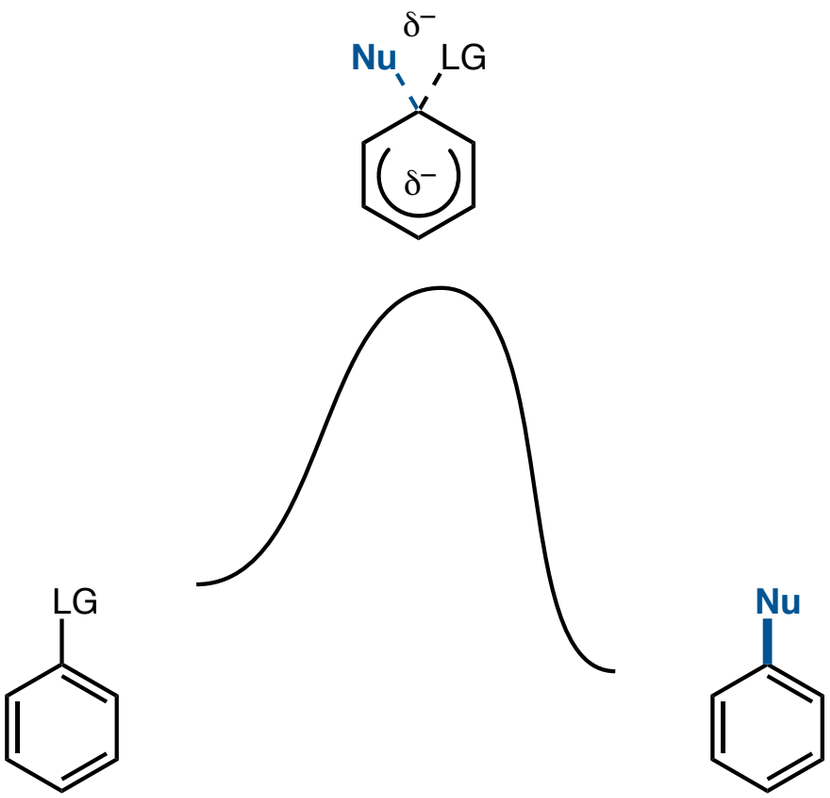


- ***Well-established stepwise substitution***
- ***Stabilization of TS charge by ring***
- ***High sensitivity to arene substituents***

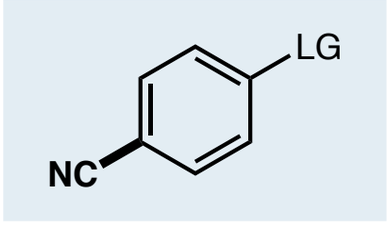


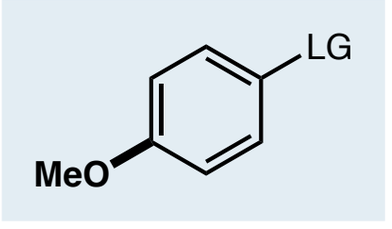


Concerted S_NAr



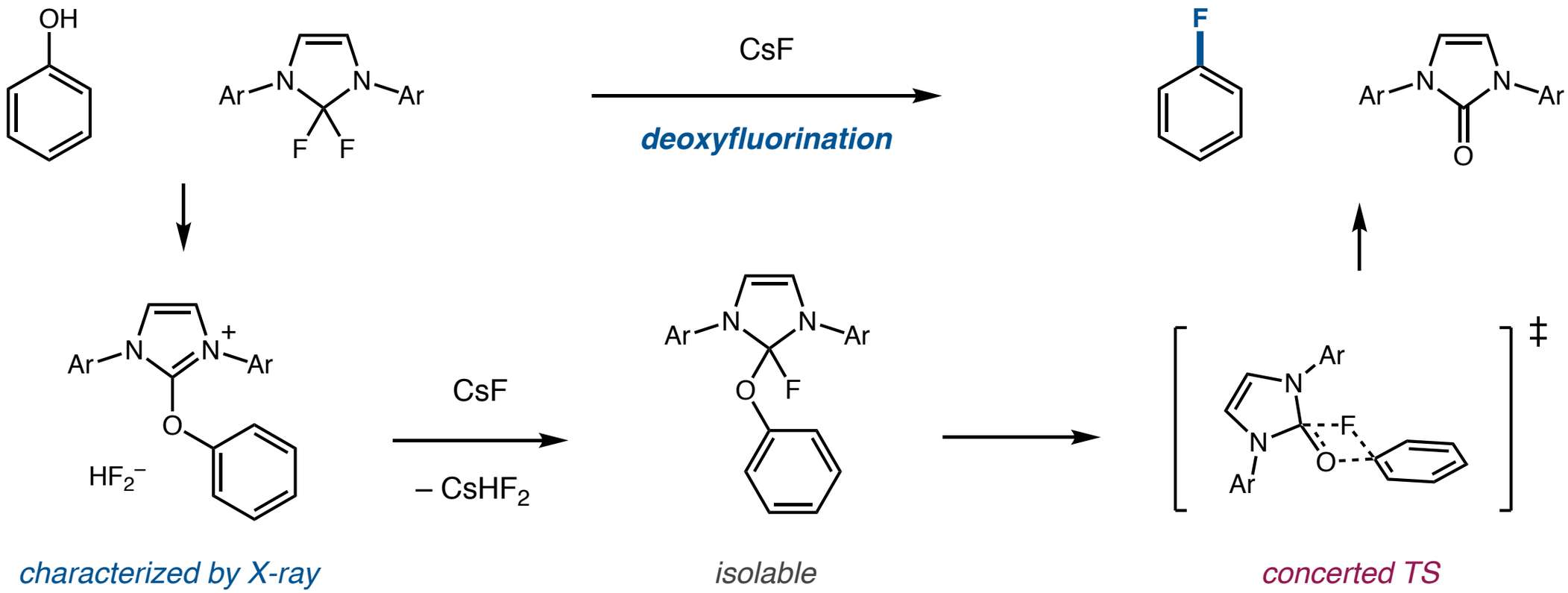
- ***Underexplored concerted pathway***
- ***Charge distributed among ring, Nu and LG***
- ***Good tolerance of arene electronics***

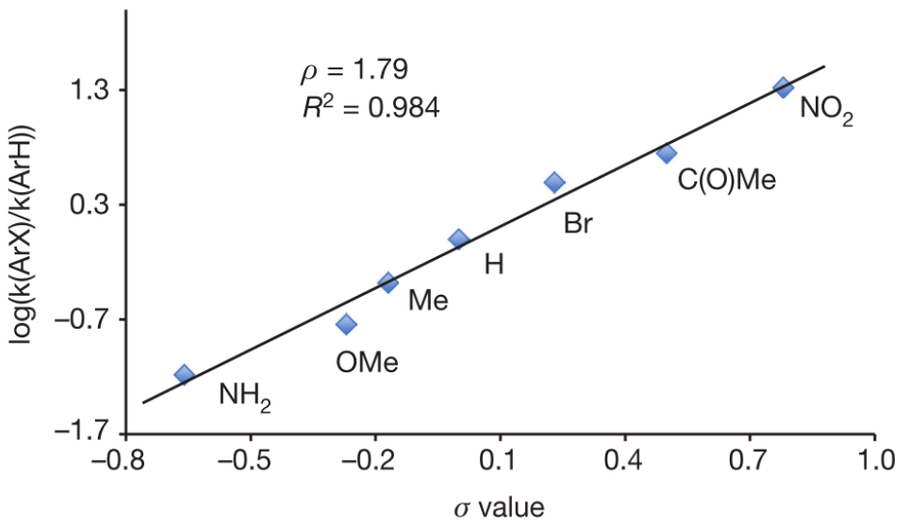




Neumann, C. N.; Hooker, J. M.; Ritter, T. *Nature* **2016**, *534*, 369.

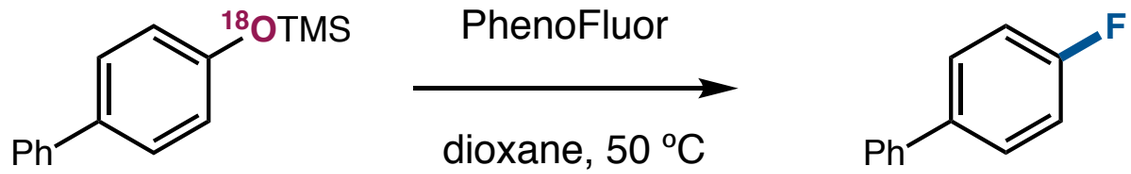
A Concerted Nucleophilic Aromatic Substitution Approach





Negative charge buildup on ring in rds

(ρ = 1.8 vs ρ = 3–8 for step-wise S_NAr)

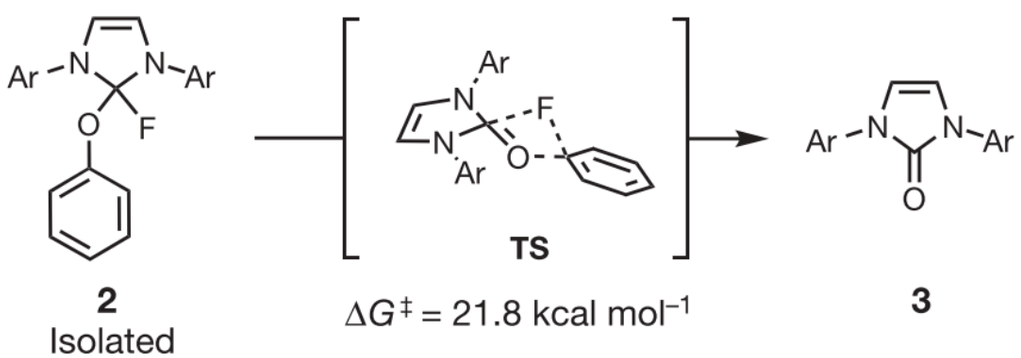


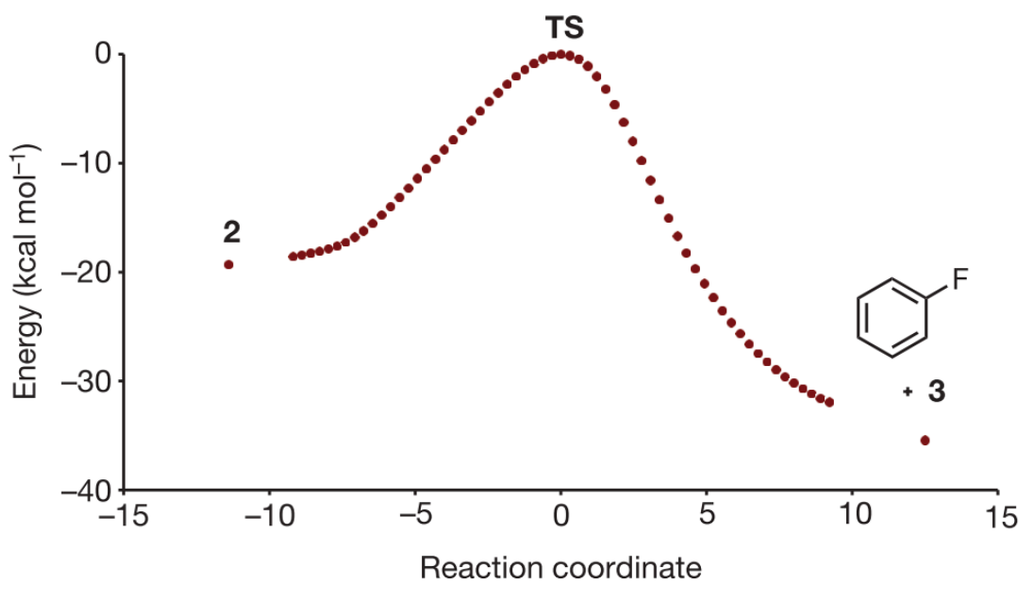
$k(^{16}O) / k(^{18}O) = 1.080 \pm 0.021$

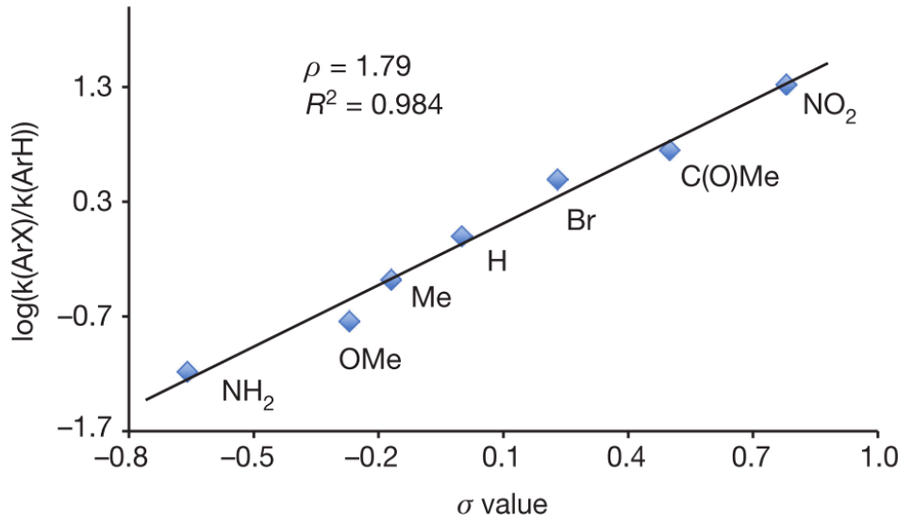
C–O bond cleavage occurs in rds

Neumann, C. N.; Hooker, J. M.; Ritter, T. *Nature* **2016**, *534*, 369.

A Concerted Nucleophilic Aromatic Substitution Approach

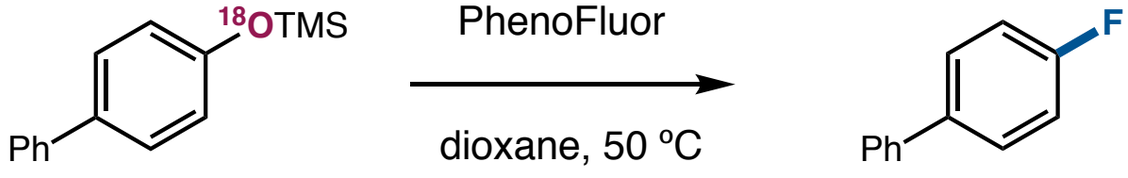






Negative charge buildup on ring in rds

(ρ = 1.8 vs ρ = 3–8 for step-wise S_NAr)

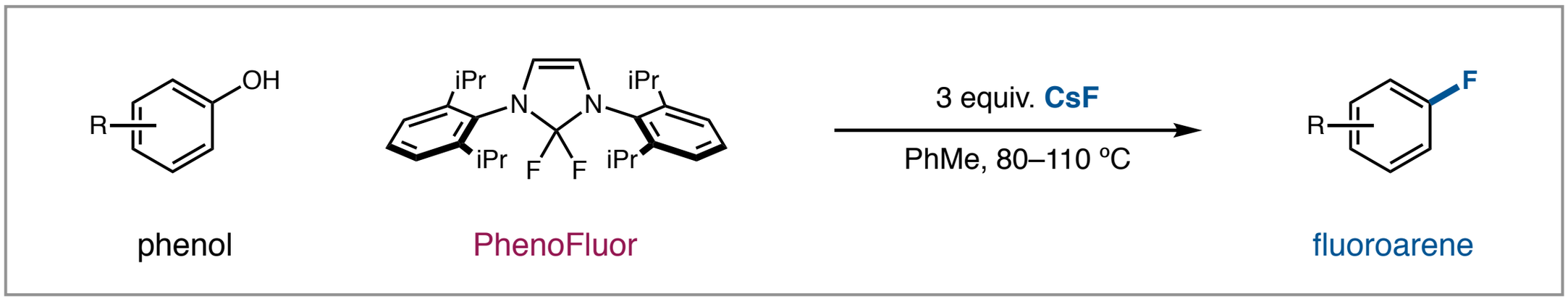


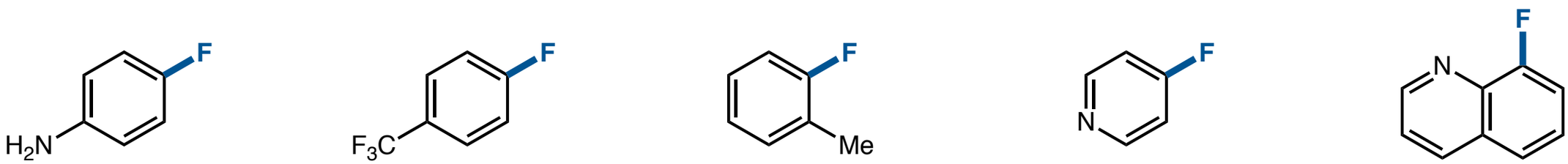
$k(^{16}O) / k(^{18}O) = 1.080 \pm 0.021$

C–O bond cleavage occurs in rds

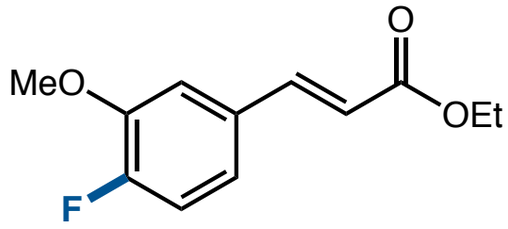
Neumann, C. N.; Hooker, J. M.; Ritter, T. *Nature* **2016**, *534*, 369.

Substrate Scope for Ritter's Deoxyfluorination of Phenols

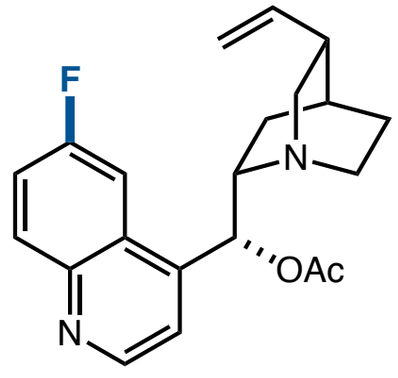




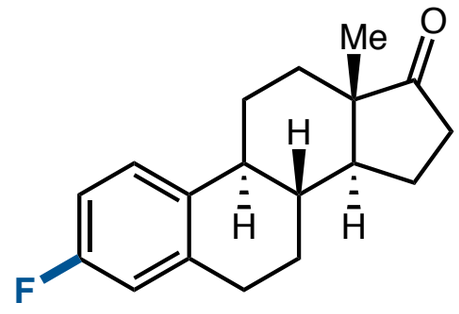
75% yield *92% yield* *87% yield* *90% yield* *92% yield*



88% yield



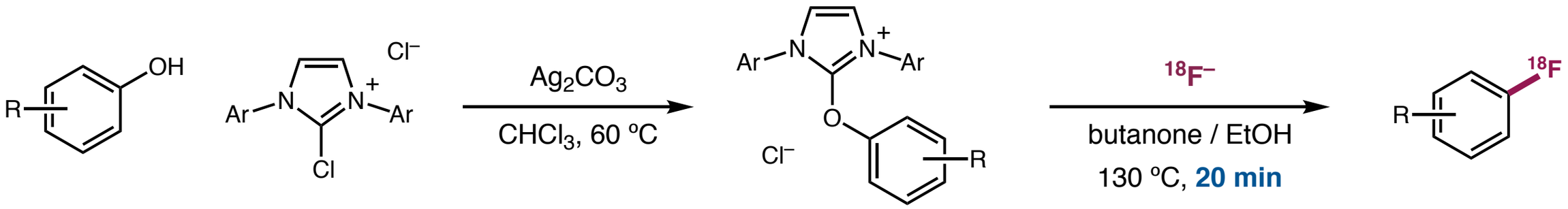
95% yield

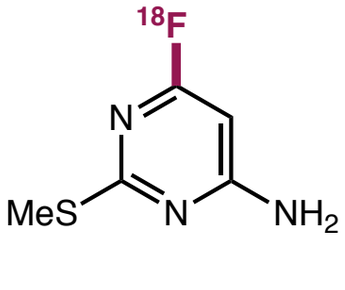


90% yield

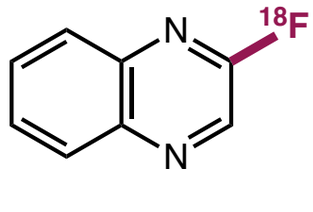
Tang, P.; Wang, W.; Ritter, T. *J. Am. Chem. Soc.* **2011**, *133*, 11482.

Adaption of Deoxyfluorination For ^{18}F Labelling

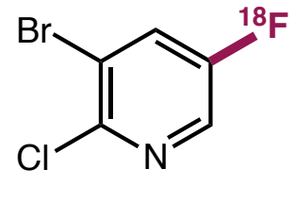




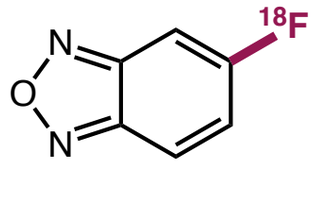
98% RCC



87% RCC

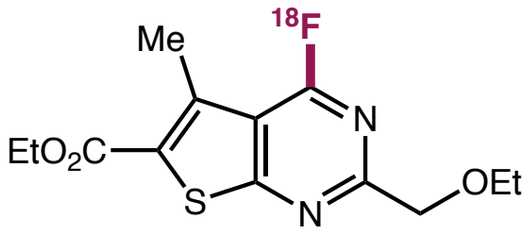


90% RCC

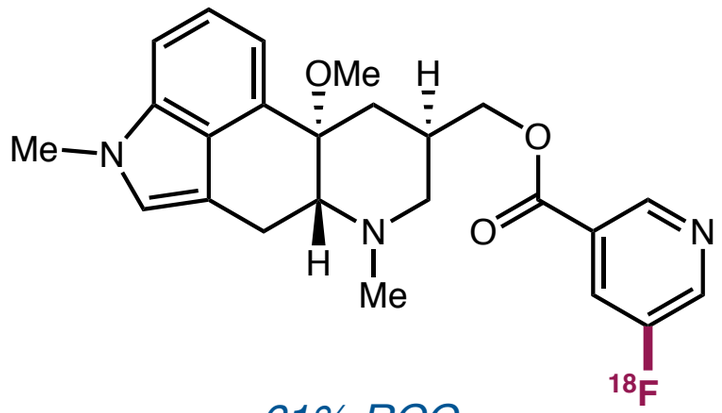


98% RCC

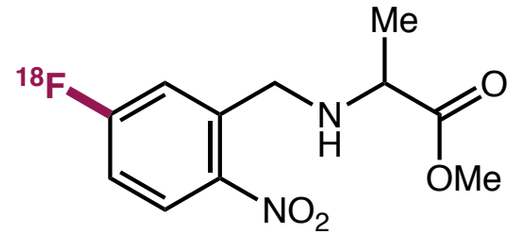
27% isolated RCY



81% RCC



61% RCC

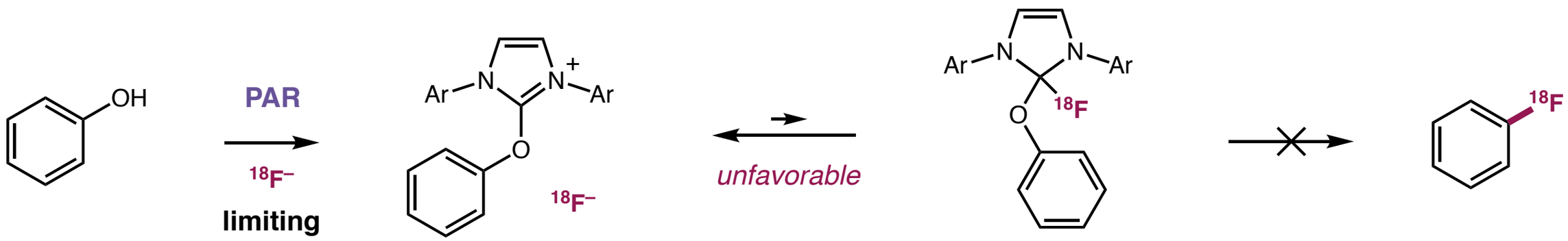


86% RCC

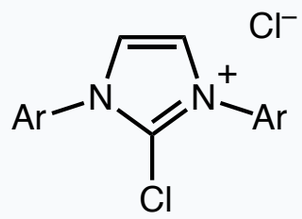
Neumann, C. N.; Hooker, J. M.; Ritter, T. *Nature* **2016**, *534*, 369.

Problems with ^{18}F Labelling of More Electron-Rich Substrates

Limitation in ^{18}F labelling: electron-rich/-neutral substrates

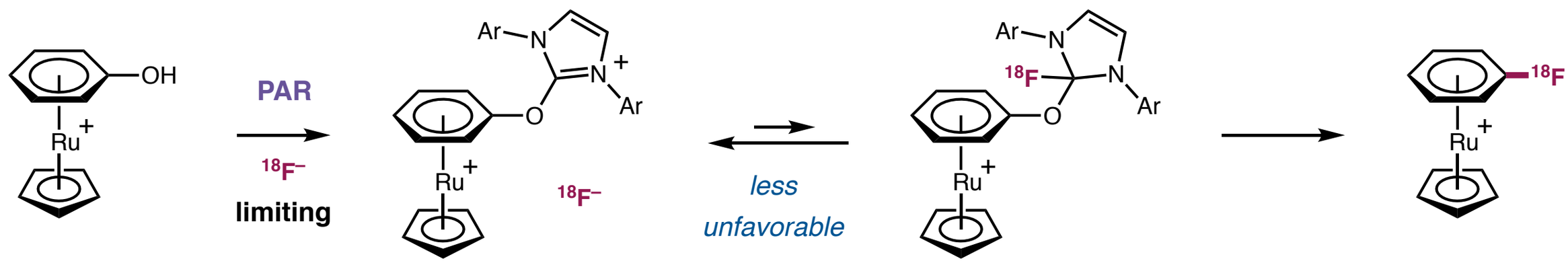


PAR *(phenol activation reagent)*



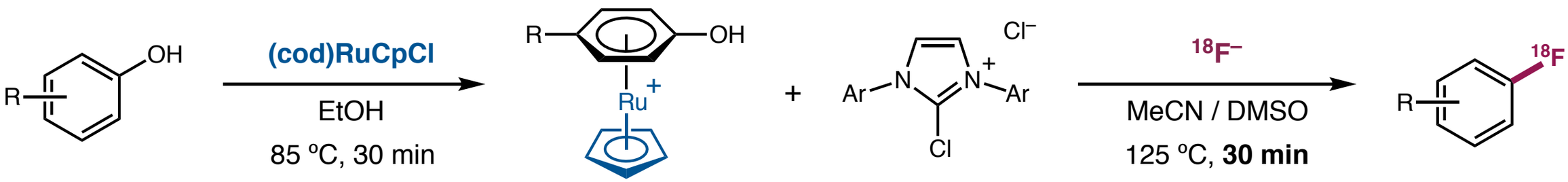
- ***More electron-rich substrates do not react sufficiently fast***
- ***Coordination with $CpRu^+$ restores a favorable enough equilibrium***

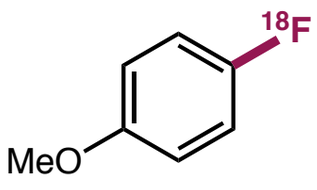
Solution: coordination with $CpRu^+$ increases electrophilicity



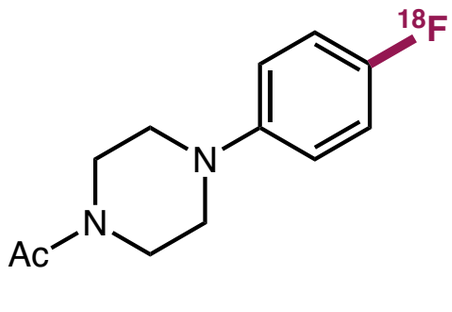
Hooker, J. M.; Ritter, T. *et al. ACS Cent. Sci.* **2017**, *3*, 944.

Scope of Improved ^{18}F Labelling of Phenols

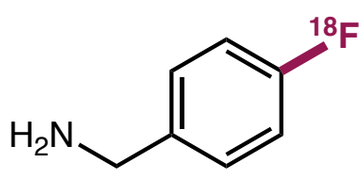




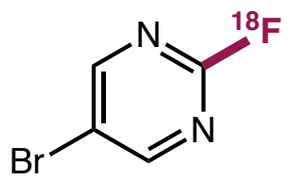
89% RCC



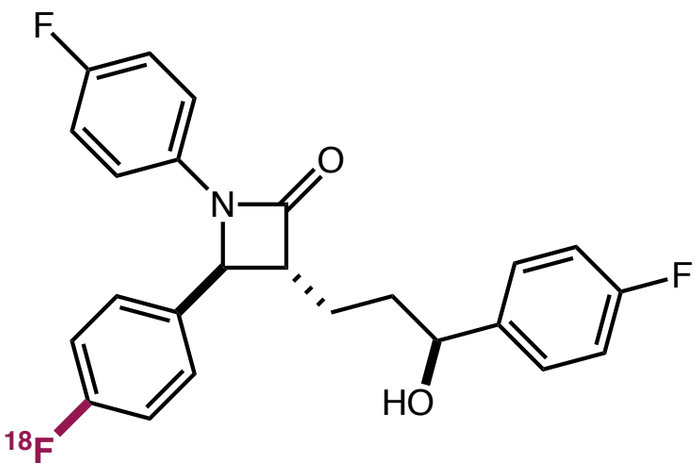
99% RCC



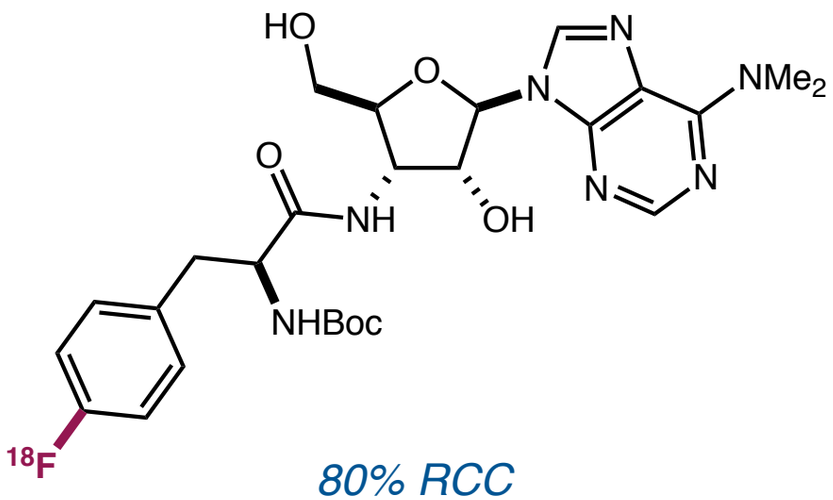
30% RCC



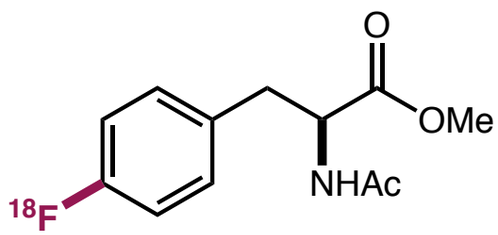
43% RCC



98% RCC



80% RCC



24% isolated RCY

Hooker, J. M.; Ritter, T. *et al. ACS Cent. Sci.* **2017**, *3*, 944.

Recent Developments in Nucleophilic Fluorination

Construction of Alkyl C–F Bonds

Nucleophilic substitution promoted by hydrogen bonding

Deoxyfluorination of aliphatic alcohols

Transition metal-catalyzed allylic fluorination

Direct hydrofluorination of alkenes

Metal-mediated aminofluorination of alkenes

Asymmetric hydrofluorination of epoxides

Manganese-catalyzed C–H fluorination

Construction of Aromatic C–F Bonds

Metal-mediated fluorination of arenes

Nucleophilic aromatic substitution of (pseudo)halides

Ritter's S_NAr deoxyfluorination of phenols