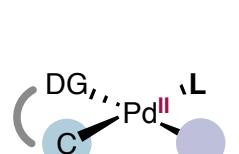


Reductive Elimination from High-Valent Palladium

**Kazunori Nagao
MacMillan Group Meeting**

Why do people focus on Pd^{IV}

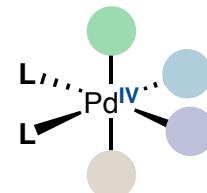
- Merging with C–H activation



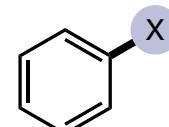
palladacycle



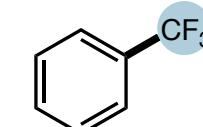
oxidant



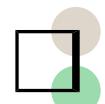
Pd^{IV} complex



C–Hetero



C– CF_3



small ring

Oxidative C–H Functionalization

- Facile reductive elimination

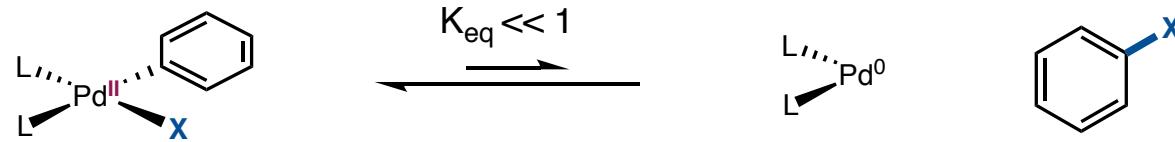
Challenging Bond Formation

Mechanistic Curiosity for Reductive Elimination

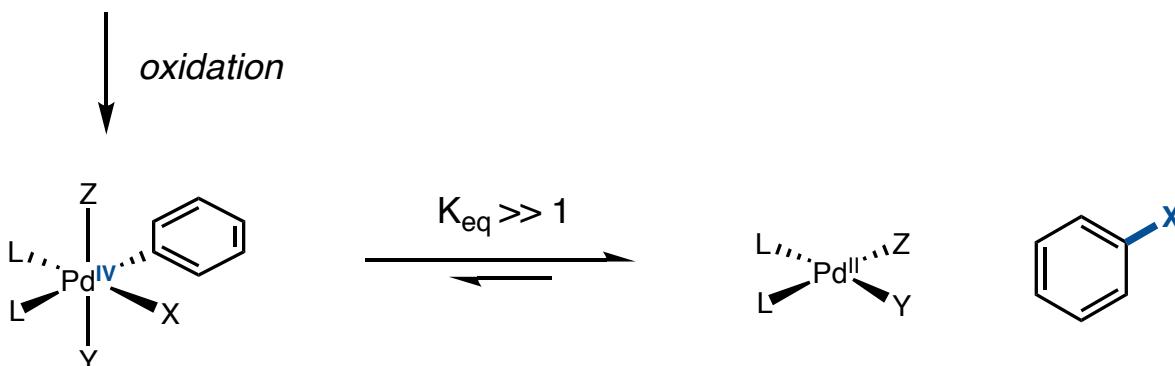
- Mononuclear Pd^{IV} or Binuclear Pd^{III} ?
- How do they work?
- Origin of Chemoselectivity

C–X Reductive Elimination

Carbon–Halogen Reductive Elimination

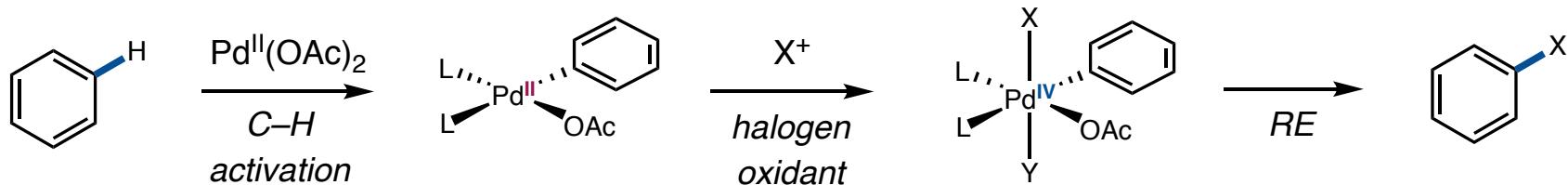


kinetically *slow* and thermodynamically *unfavored*

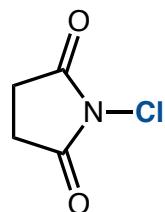
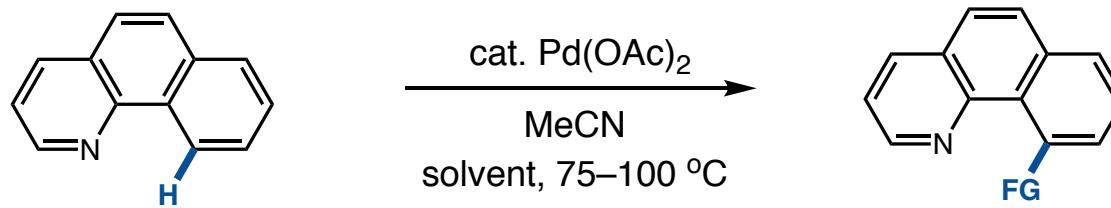


kinetically *fast* and thermodynamically *favored*

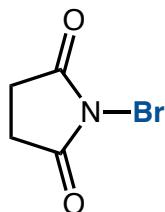
C–H activation (Pd^{II} catalysis) and Oxidative Functionalization (Pd^{IV} catalysis)



Regioselective C–H Oxidative Functionalization



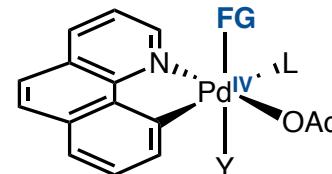
chlorination
95%



bromination
95%



acetoxylation
86%



Proposed Pd^{IV} Intermediate

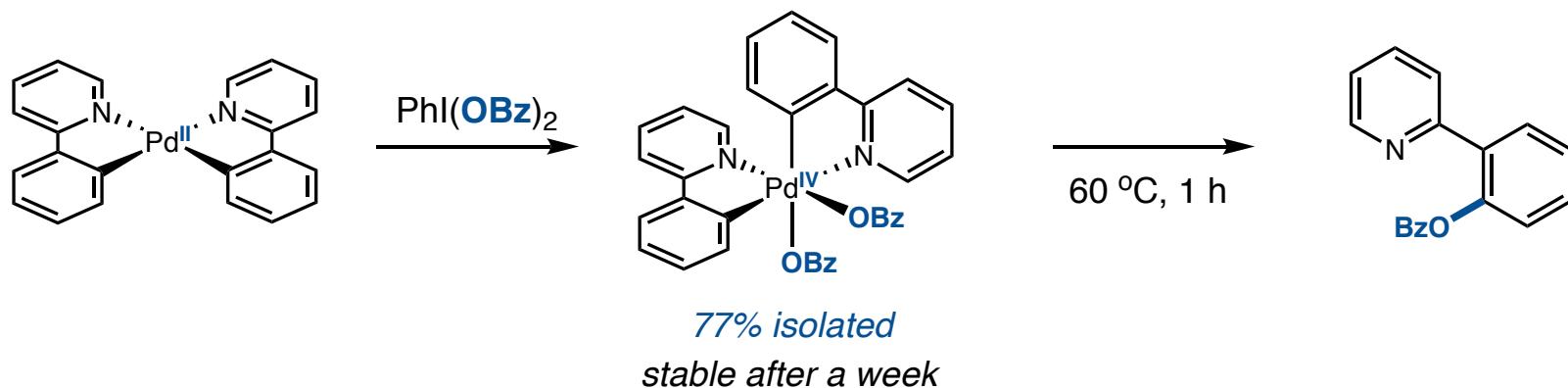


Mechanistic Investigation

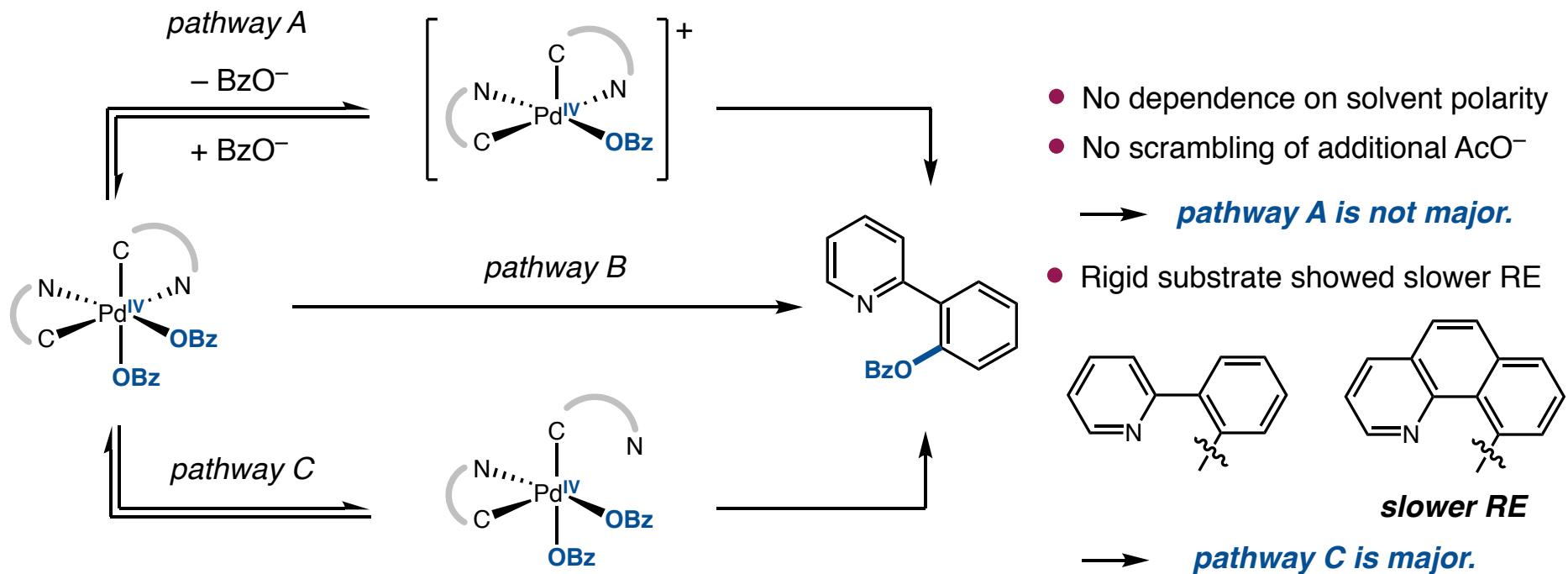
Isolation of Pd^{IV} complex

Study of Reductive Elimination

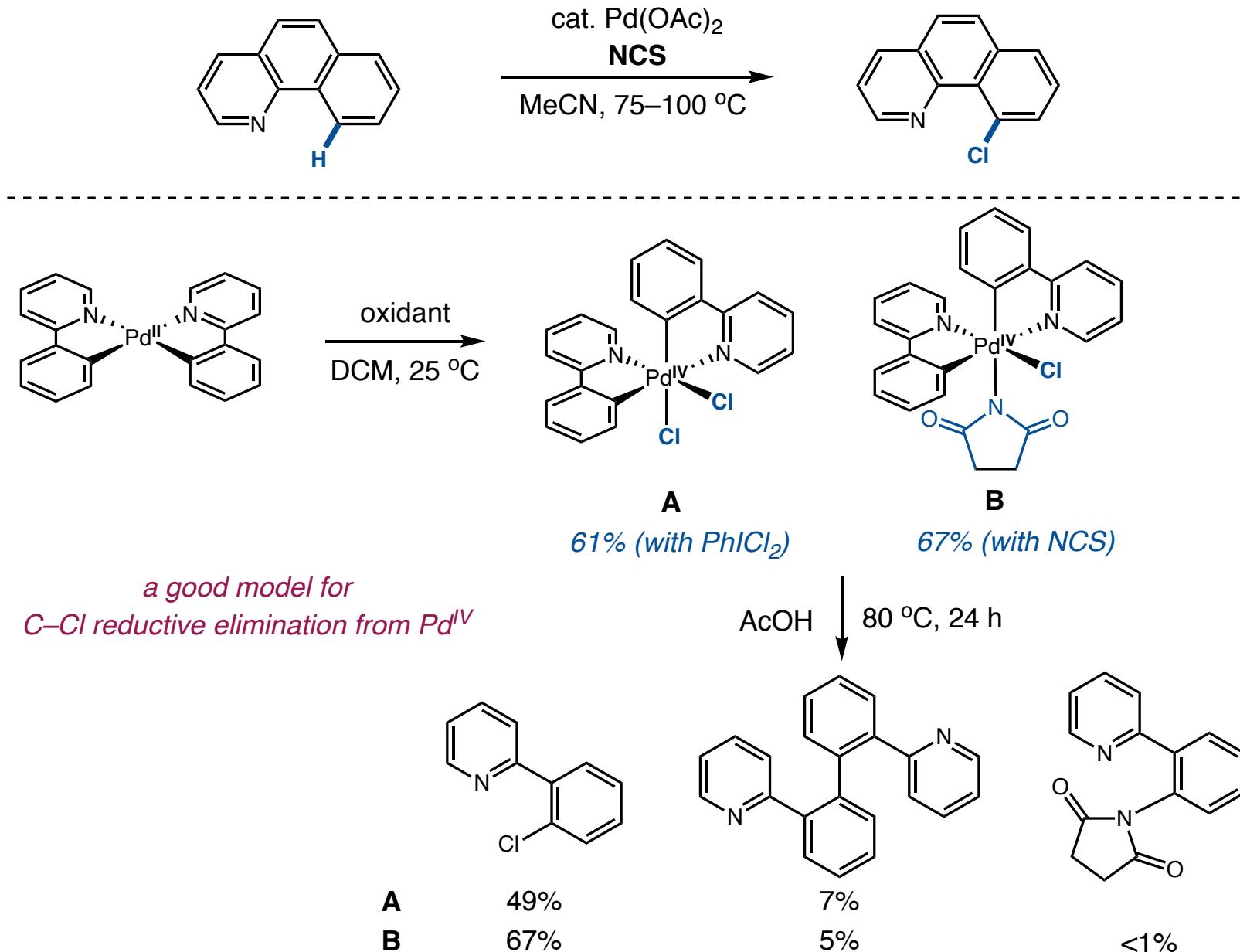
Isolation of Pd^{IV} Complex



Possible Mechanism of C–O Reductive Elimination

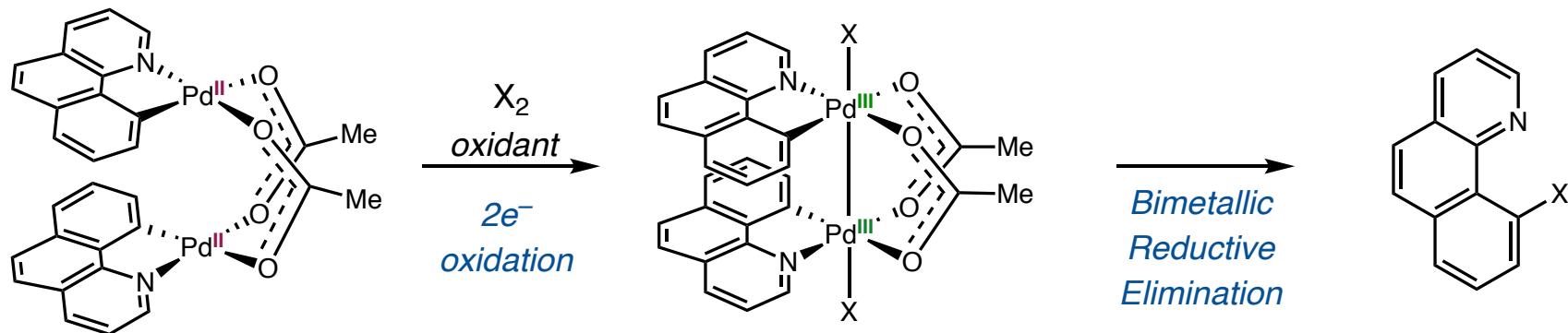


Isolation of Pd^{IV} Complex



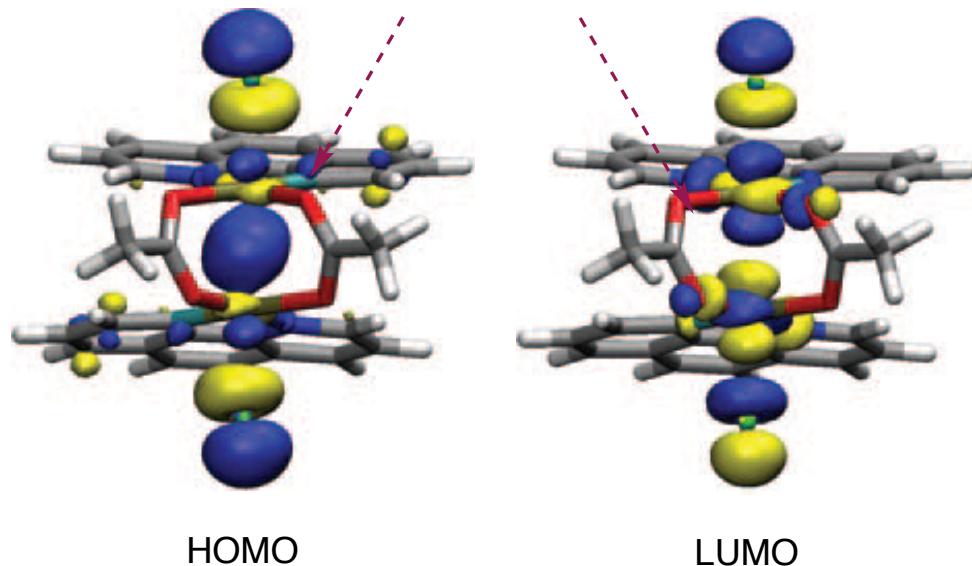
Bimetallic Pd^{III} Intermediate

Ritter suggested Bimetallic Pd^{II/III} Mechanism



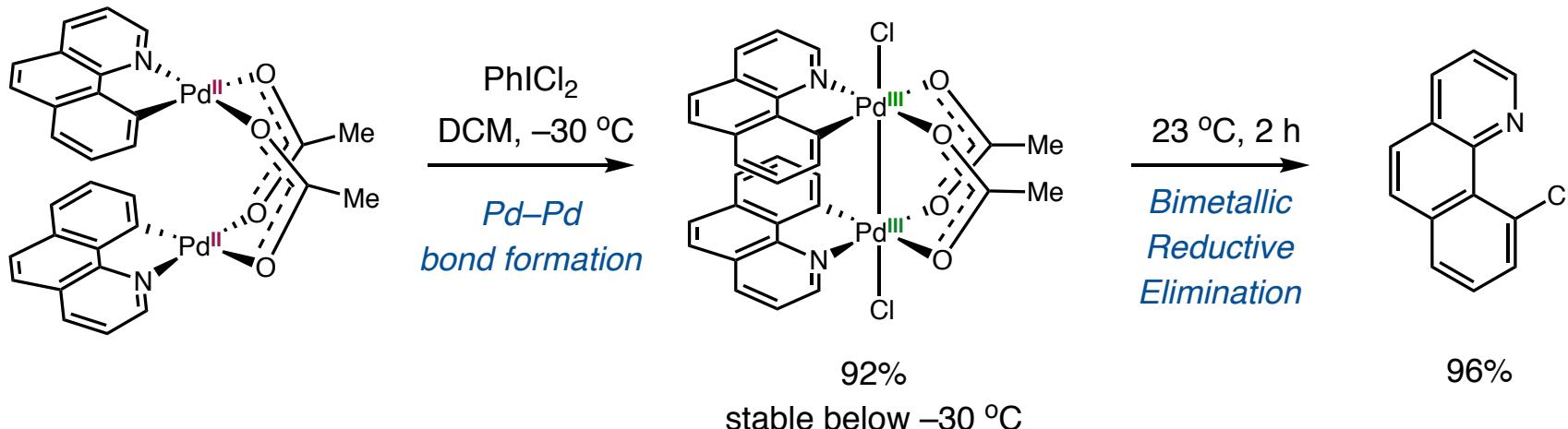
Molecular Orbital of Bimetallic Pd^{III} Complex

Pd–Pd bond corresponds to redox state of Pd

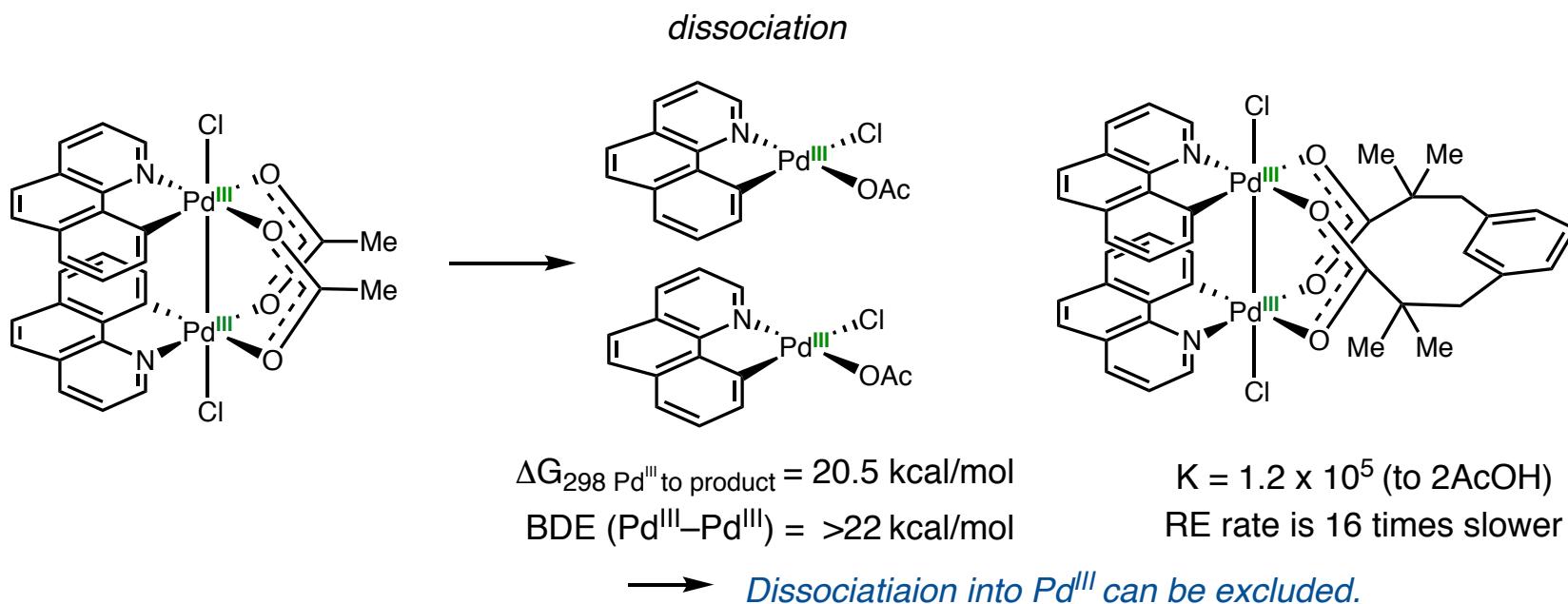


Synergistic effect by two Pd metals may facilitate redox transformation.

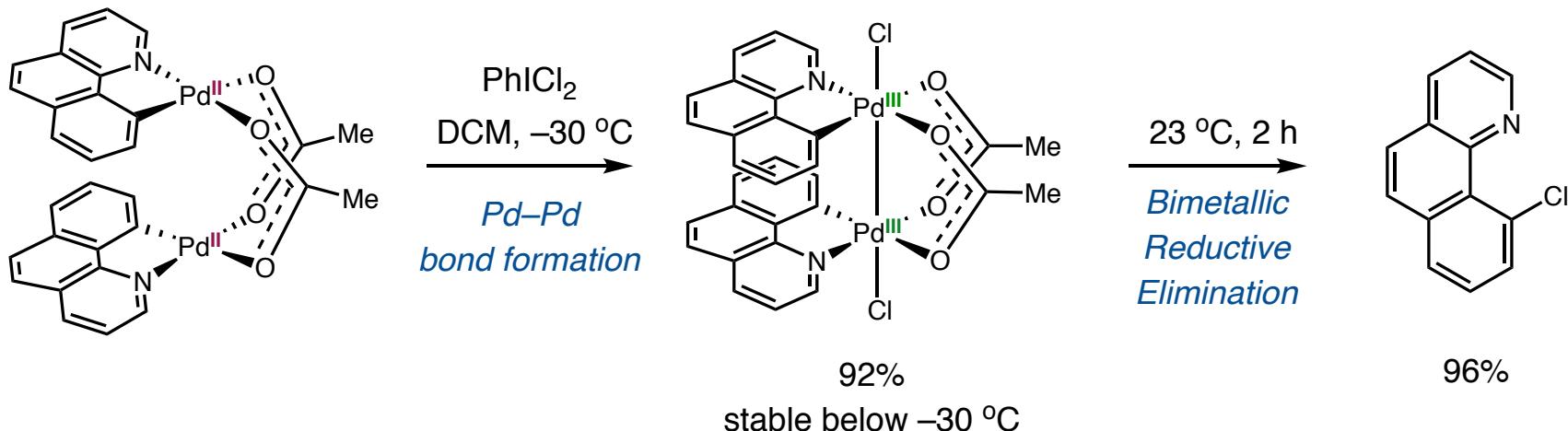
Identification of Pd^{III} Dimer and Bimetallic Reductive Elimination



Possible Mechanism of Bimetallic Reductive Elimination

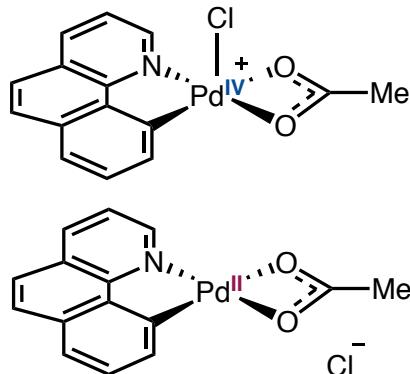


Identification of Pd^{III} Dimer and Bimetallic Reductive Elimination



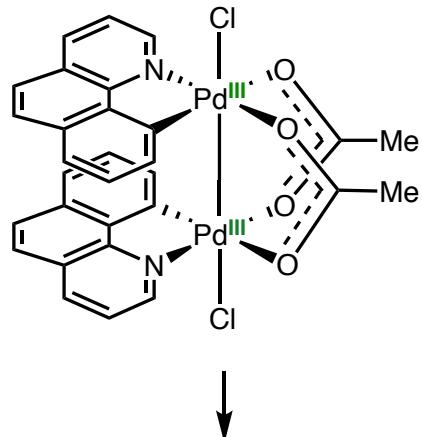
Possible Mechanism of Bimetallic Reductive Elimination

disproportionation



Pd^{II}-Pd^{IV} dimer resonance
can not suppress the Pd-Pd
electronic communication

RE from cationic Pd^{III}

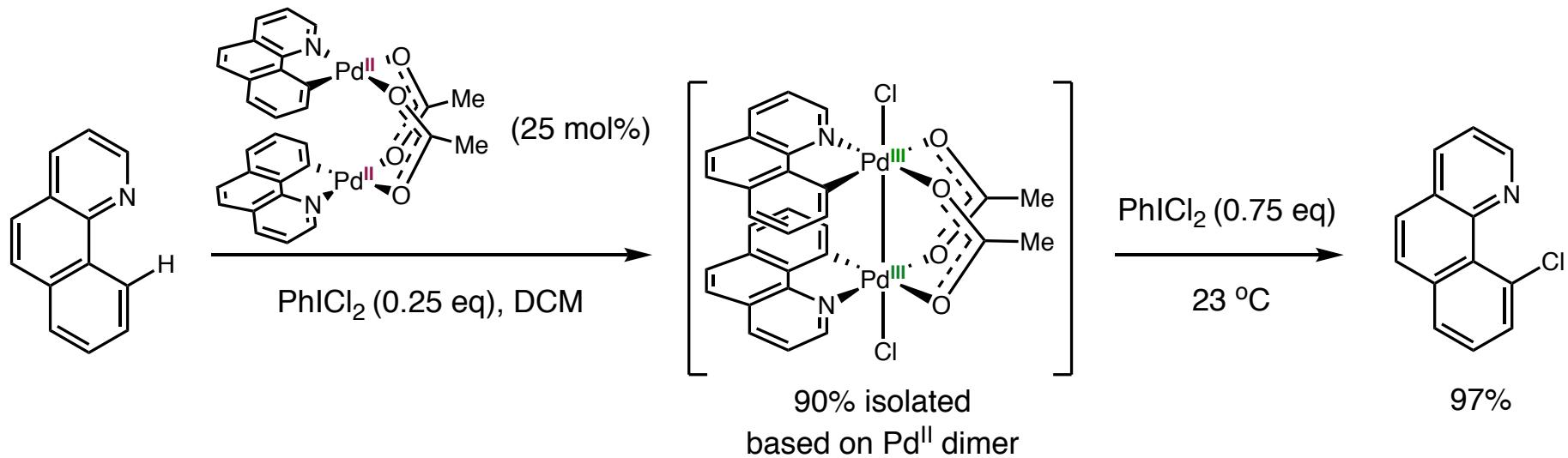


Concerted Reductive Elimination

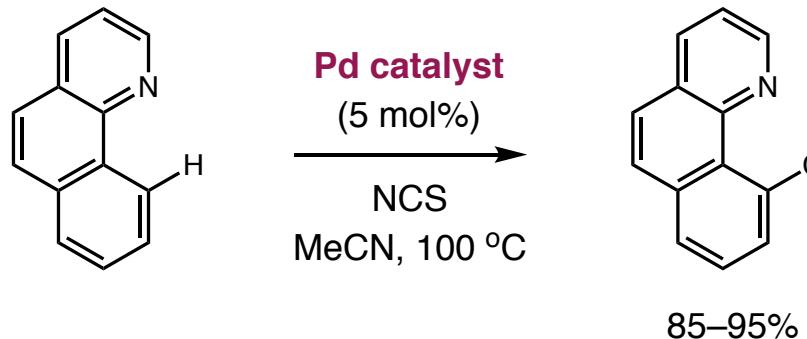
The RE rate is independent
of Cl⁻ and AcO⁻

Catalytic C–H Chlorination

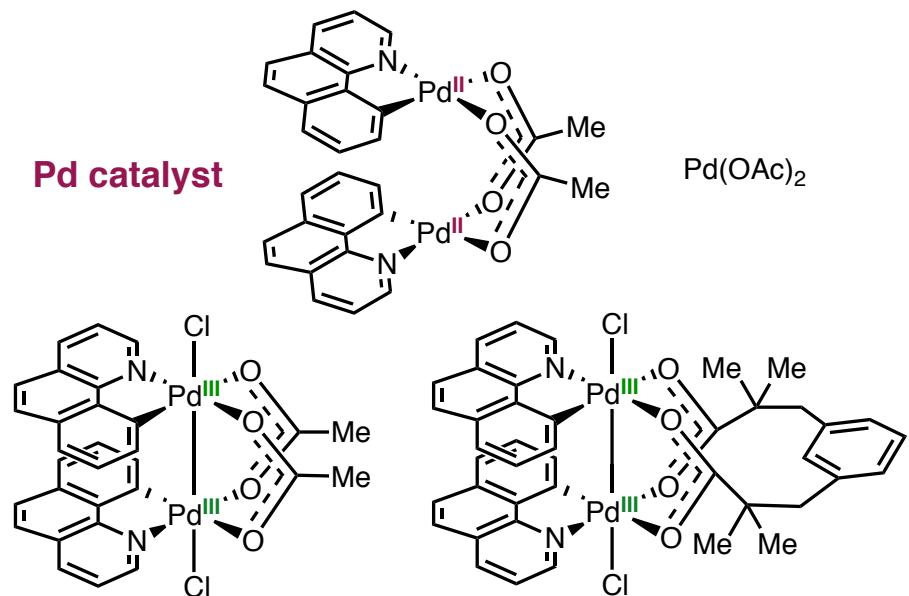
Catalysis with $\text{PhI}(\text{Cl})_2$



Catalysis with NCS

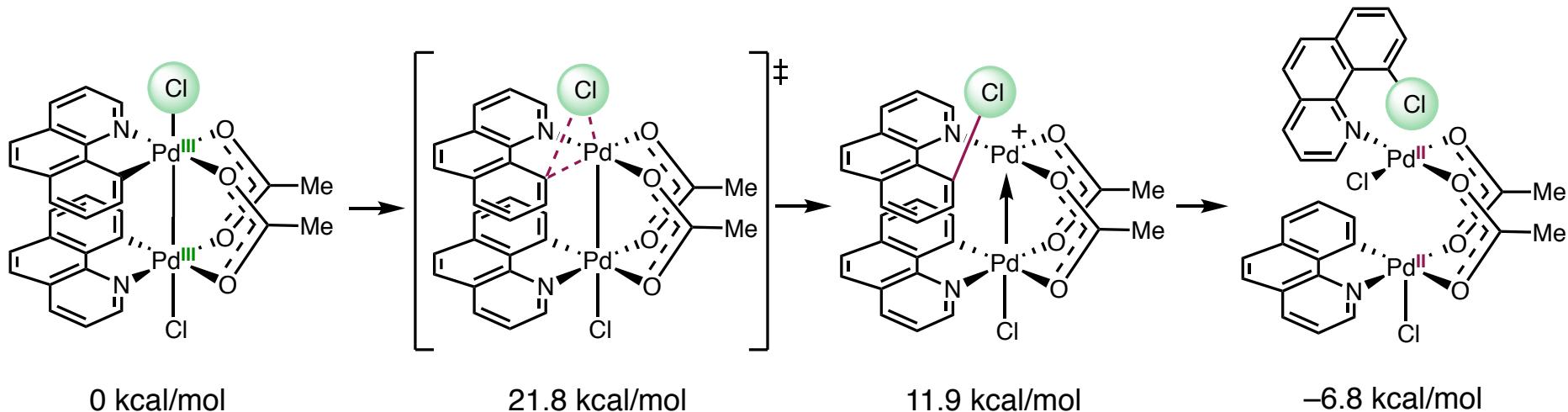


Pd catalyst



Computational Study

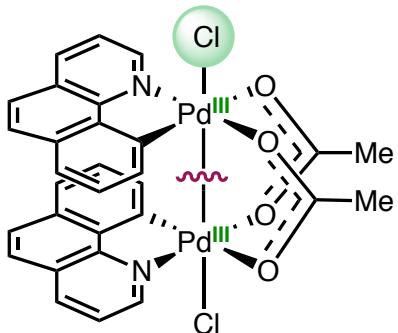
Bimetallic Reductive Elimination



The electron binding energies of two Pd atoms monotonically decrease

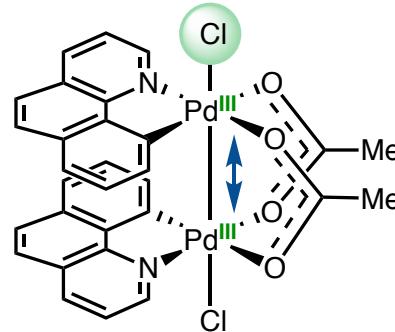


Redox synergy between 2 Pd centers



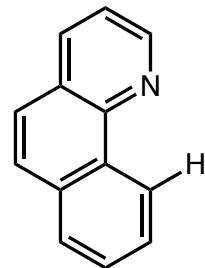
Pd–Pd Cleavage

33.2 kcal/mol (Homolytic)
29.5 kcal/mol (Heterolytic)

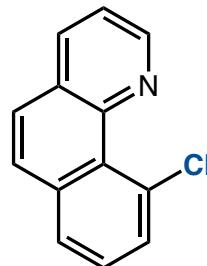


Pd–Pd distance Activation Energy RE

Mechanistic Studies for C–H Chlorination with NCS



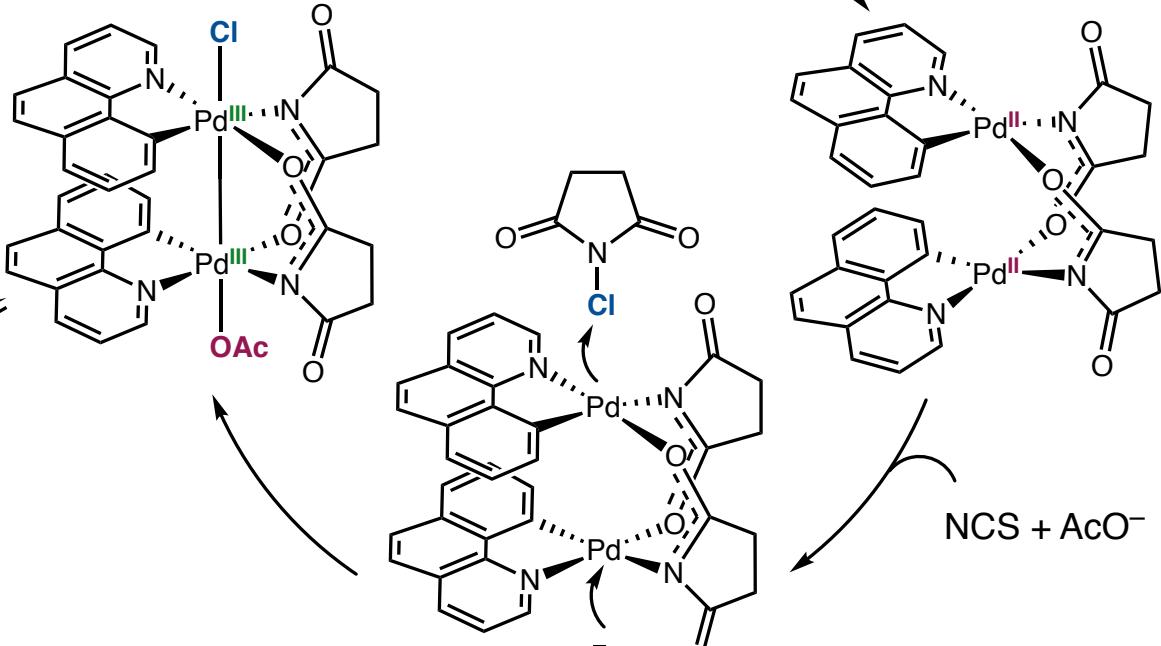
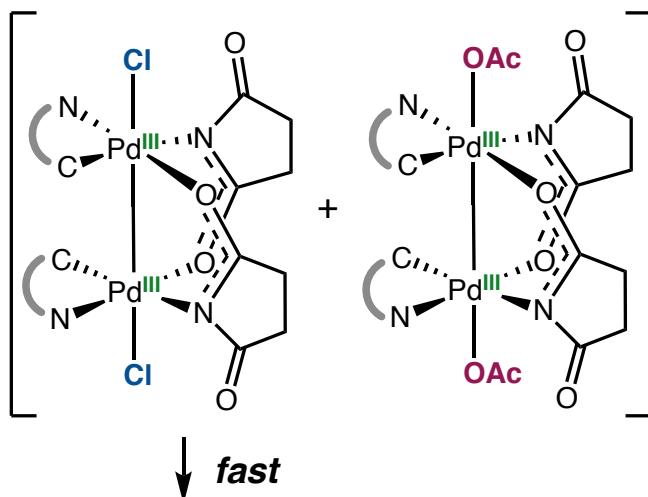
$\xrightarrow[\text{MeCN, 100 } \text{°C}]{\text{Pd(OAc)}_2 \text{ (5 mol\%)}}$
NCS



No acetoxylated product

Why chemoselective C–Cl RE?

*Schoenebeck suggests
ligand scrambling mechanism*

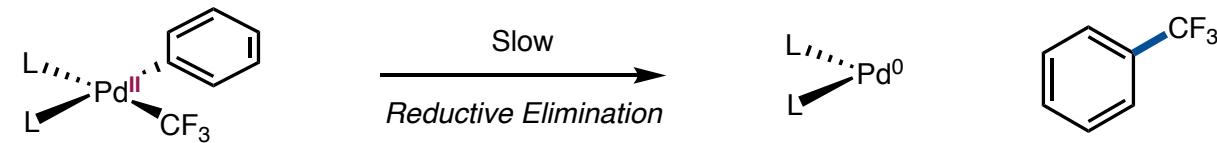


Turnover-Limiting Acetate-Assisted Oxidation

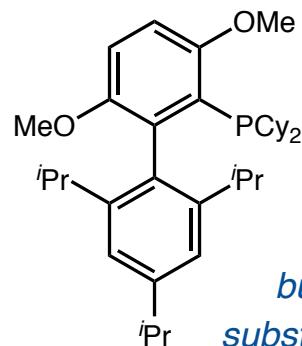
Nielsen, M. C.; Lyngvi, E.; Schoenbeck. *J. Am. Chem. Soc.* **2013**, 135, 1978.

Powers, D. C.; Benitez, D.; Tkatchouk, E.; Goddard III, W. A.; Ritter, T. *J. Am. Chem. Soc.* **2010**, 132, 14092.

Ar–CF₃ Reductive Elimination from Pd^{II}

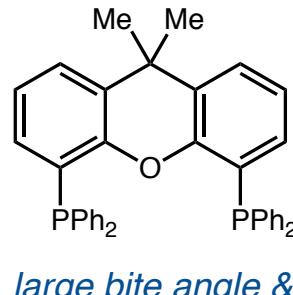


Successful Examples of Ar–CF₃ RE from Pd^{II}



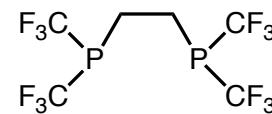
*bulky
substituents*

Brettphos
stoichiometric (80 °C)
catalytic (Et₃SiCF₃, 80 – 140 °C)



*large bite angle &
bulky substituents*

Xantphos
stoichiometric (80 °C)



*small bite angle &
electronic repulsion*

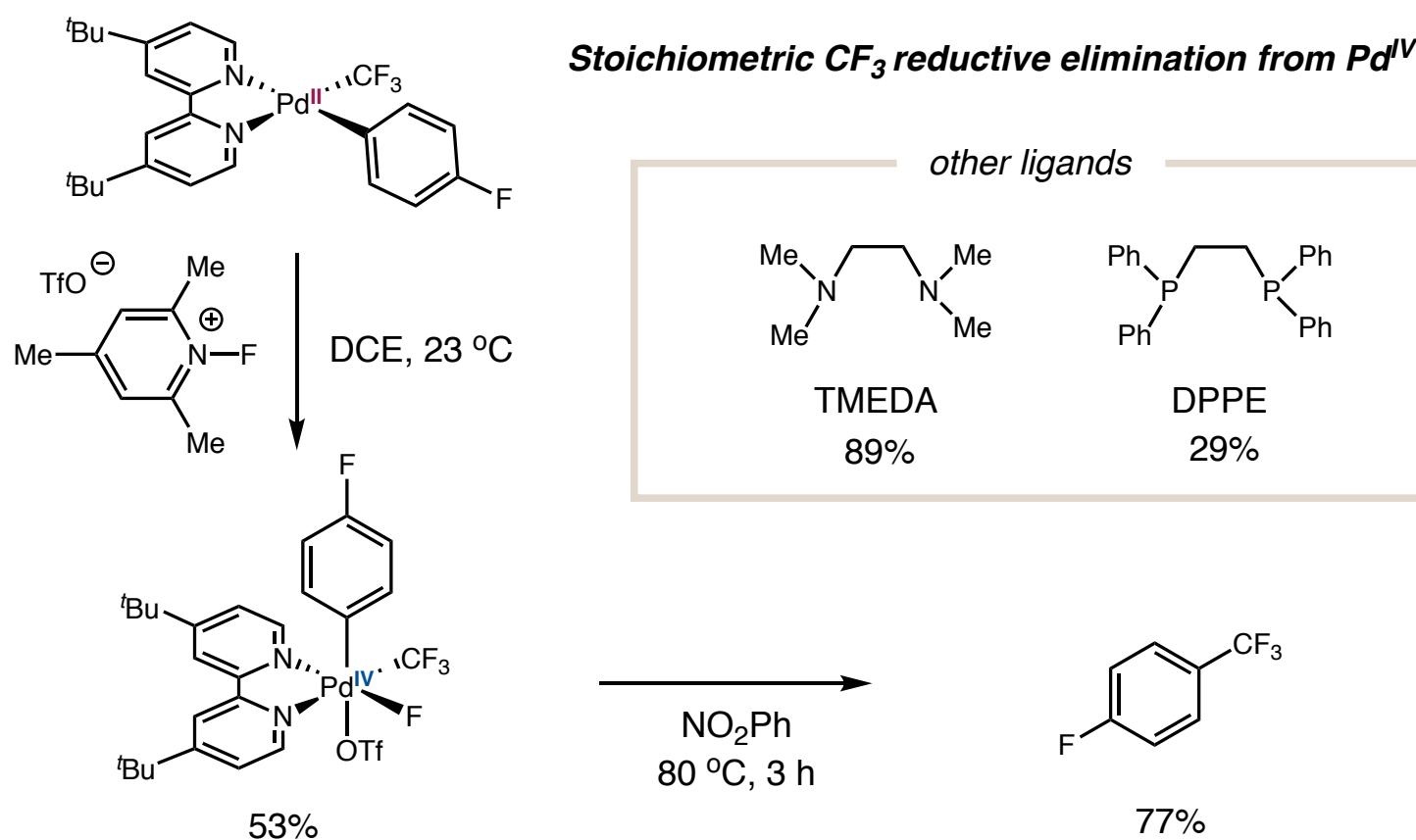
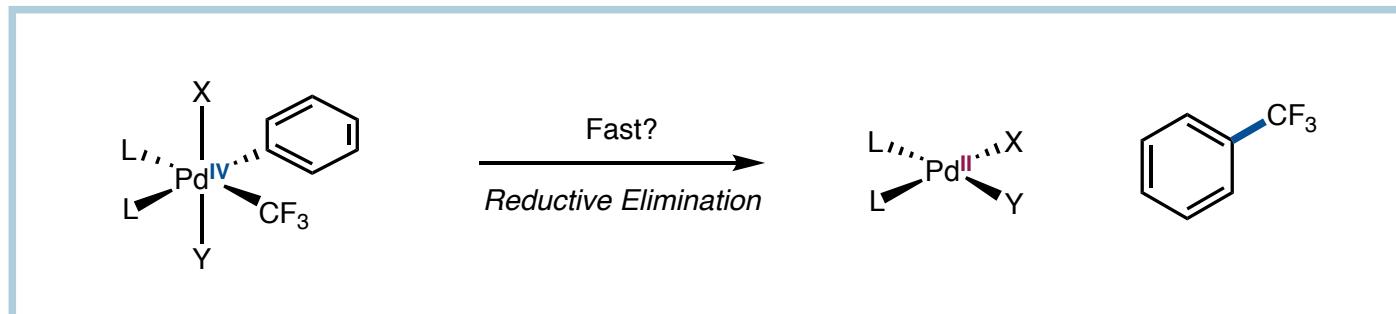
DFMPE
stoichiometric (60 – 90 °C)

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

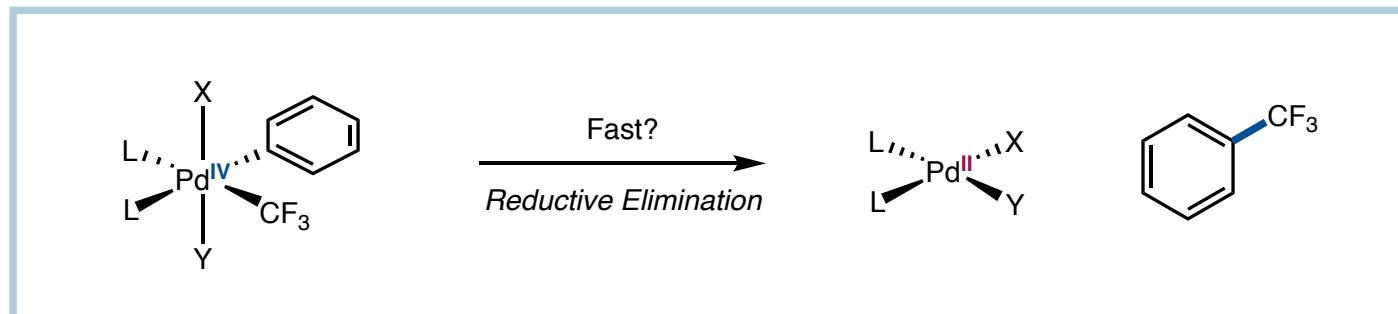
Glushin, V. V.; Marshall, W. J. *J. Am. Chem. Soc.* **2006**, *128*, 12644.

Nielsen, M. C.; Bonney, K. J.; Schoenebeck, F. *Angew. Chem. Int. Ed.* **2014**, *53*, 5903.

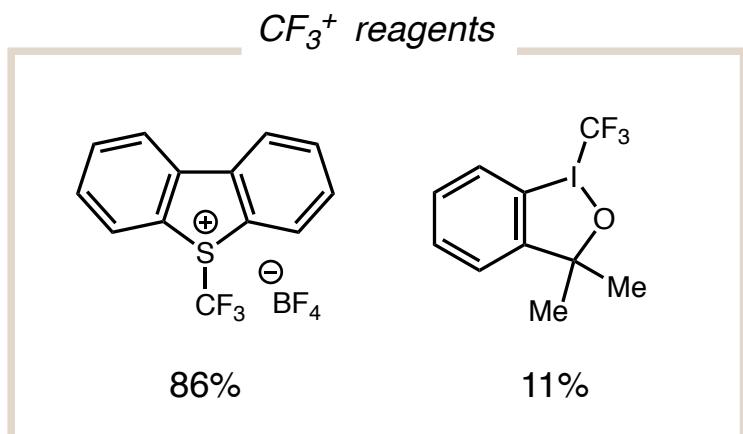
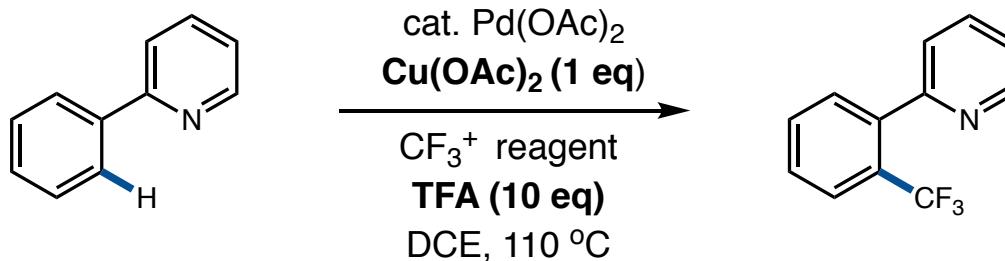
Ar-CF₃ Reductive Elimination from Pd^{IV}



Ar-CF₃ Reductive Elimination from Pd^{IV}



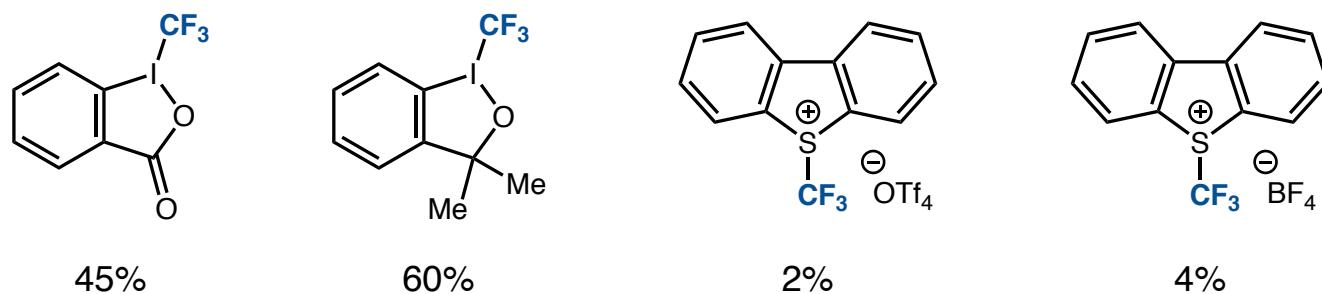
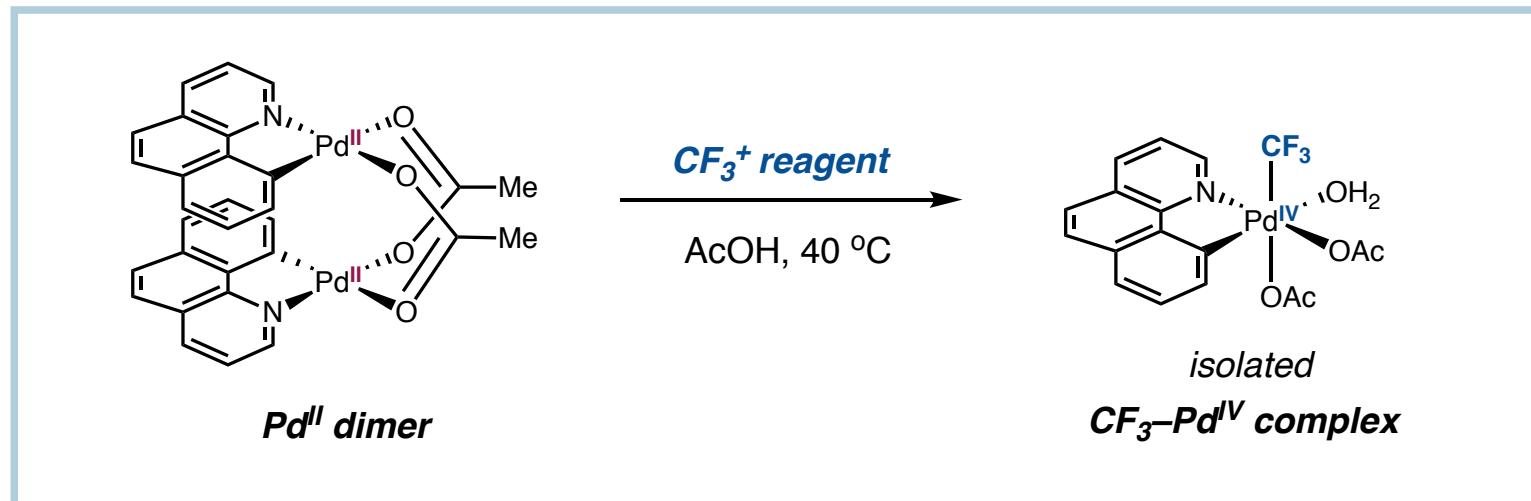
Catalytic C–H Trifluoromethylation



- TFA (10 eq) is essential for the reaction
- Cu(OAc)₂ (1 eq) also improves the yield

*What's the role of these reagents?
How does the reaction work?*

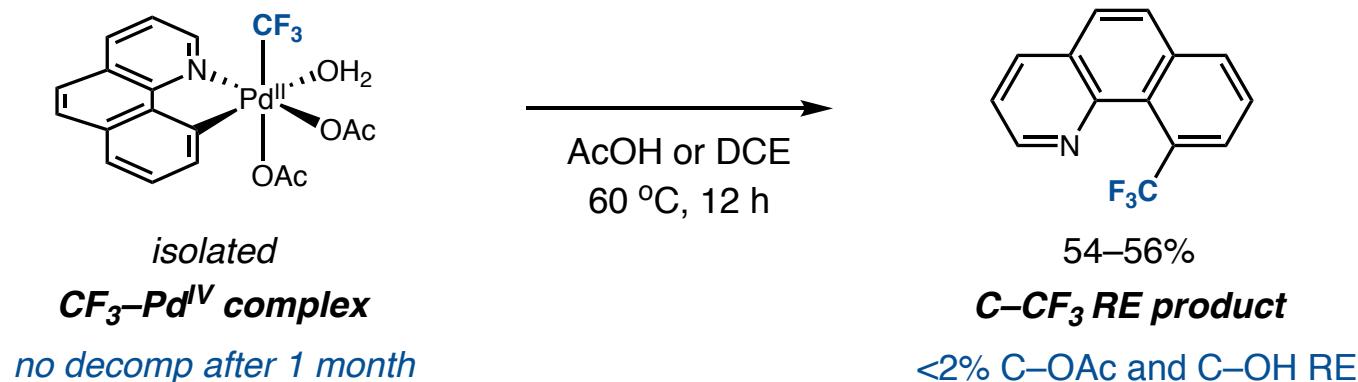
Isolation of CF₃-Pd^{IV} Intermediate



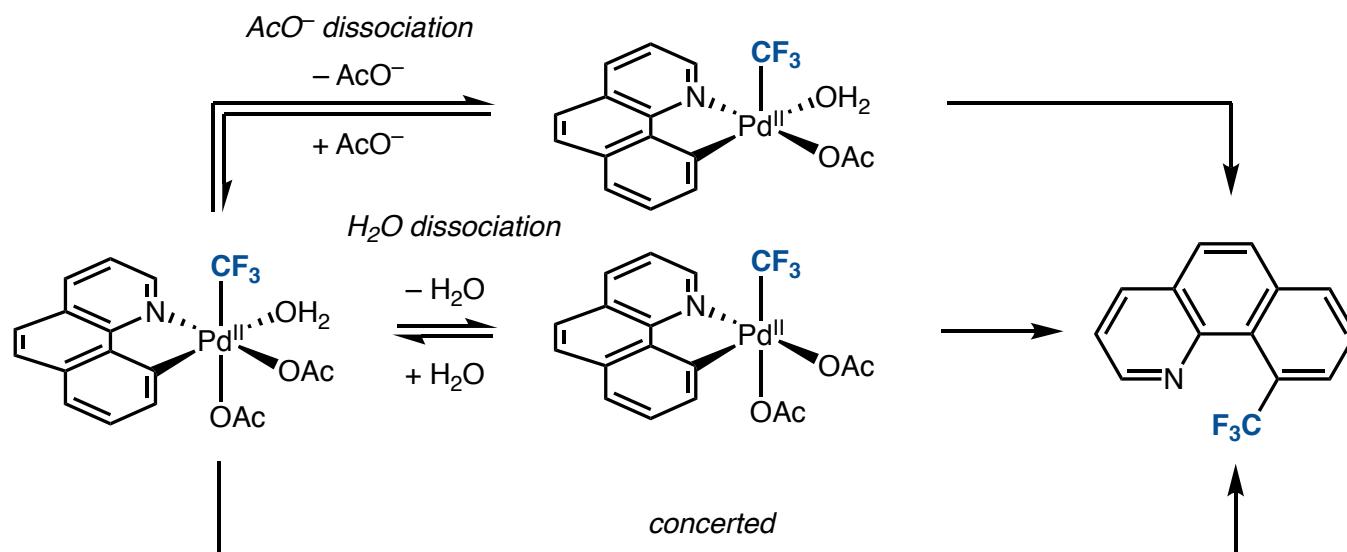
DCE instead of AcOH : <2%
DCE / 1 eq AcOH : 48%
DCE / 20 eq AcOH : 65%

Additional AcOH is important.

Reductive Elimination from Isolated CF₃–Pd^{IV} complex



Mechanism for Reductive Elimination

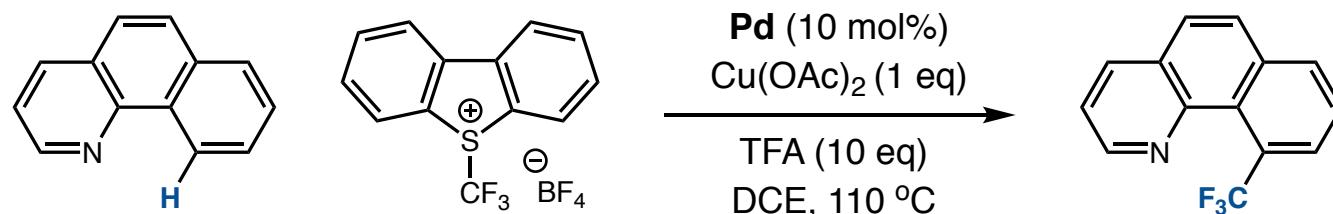


Increase of [AcO⁻] significantly slowed C–CF₃ RE

→ *AcO⁻ dissociative RE Pathway*

Addition of acidic additive [TFA, TFAA, Yb(OTf)₃] accelerated C–CF₃ RE

Catalytic Activity of Isolated CF_3-Pd^{IV} Complex



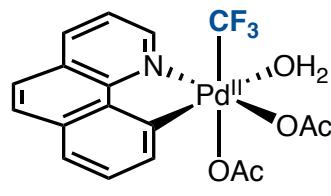
$Pd(OAc)_2 : 0.08 \times 10^{-4} \text{ M/s}$

$CF_3-Pd^{IV} : 1.40 \times 10^{-4} \text{ M/s}$

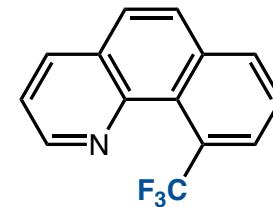
18 fold times Initial rates

CF_3-Pd^{IV} complex is a kinetically compete catalyst

The role of $Cu(OAc)_2$ and TFA



additive
 DCE
 $60^\circ C, 12 \text{ h}$



CF_3-Pd^{IV} complex

$C-CF_3$ RE product

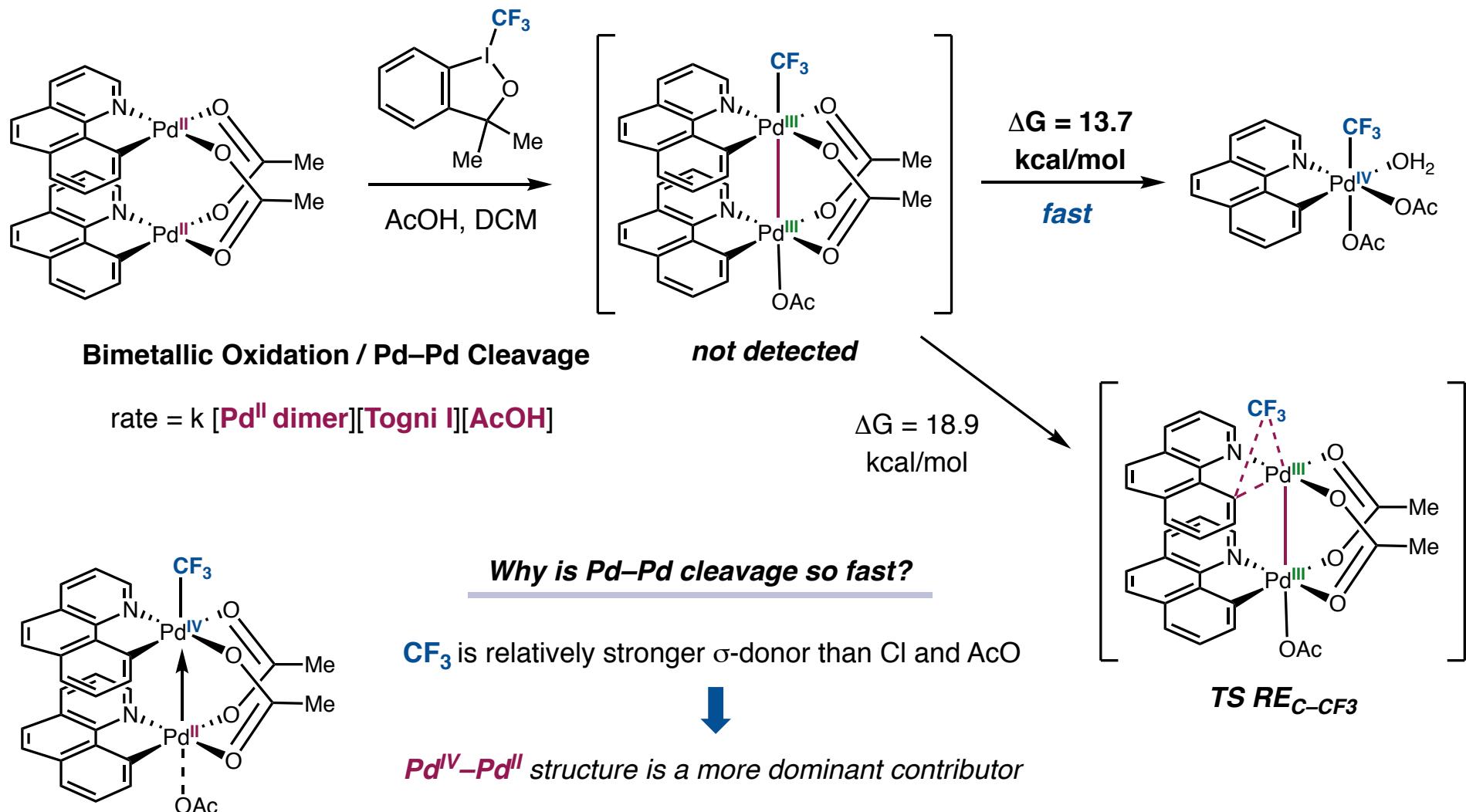
Acceleration of RE
Surpressing decomp pathway



none	54%
$Cu(OAc)_2$ (10 eq)	36%
TFA (100 eq)	89%
$Cu(OAc)_2$ (10 eq) + TFA (100 eq)	94%

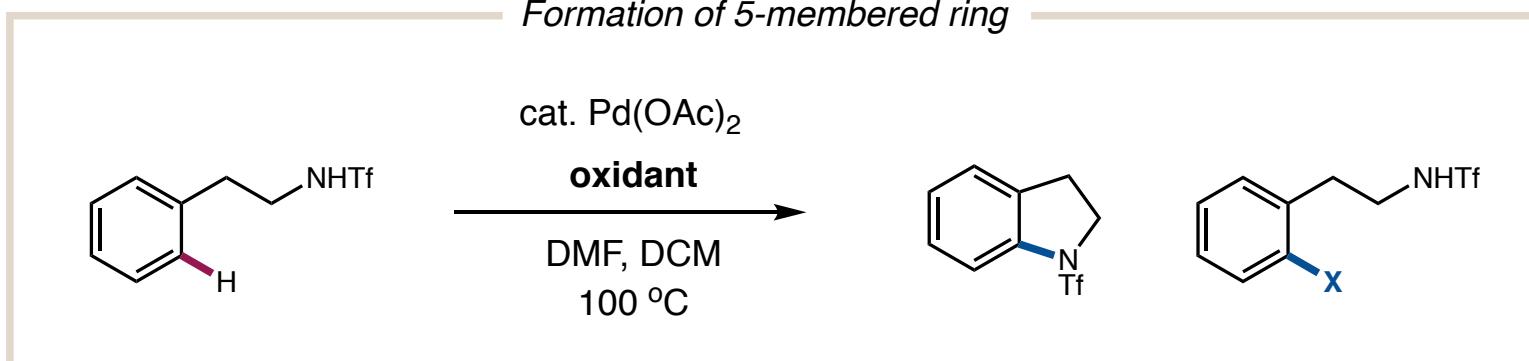
Binuclear Pd^{III} or Mononuclear Pd^{IV}

Kinetic study and DFT calculation suggests Reductive elimination from Pd^{IV}

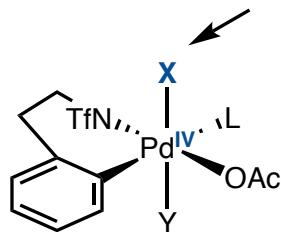


Small Ring Formation

Formation of 5-membered ring



Problematic RE partner



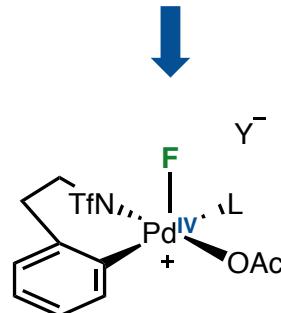
PhI(OAc)_2 15 45 (**OAc**)

AcO^tBu 13 50 (**OAc**)

NCS 0 20 (**Cl**)

NIS 0 35 (**I**)

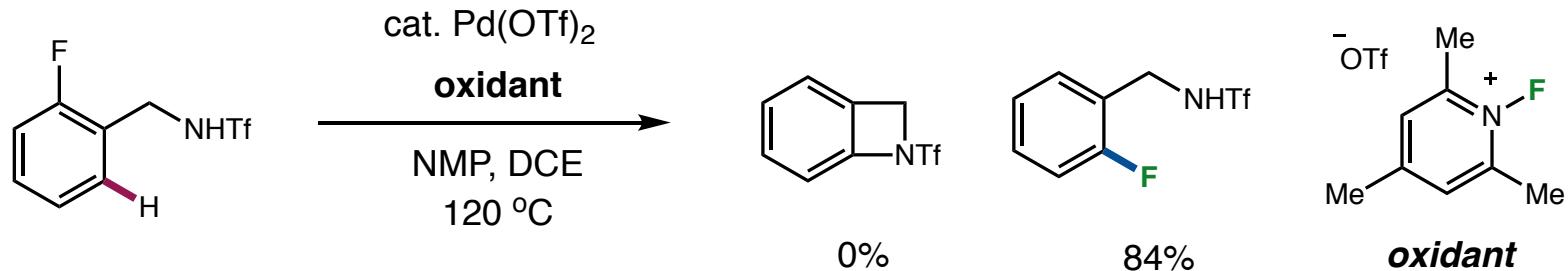
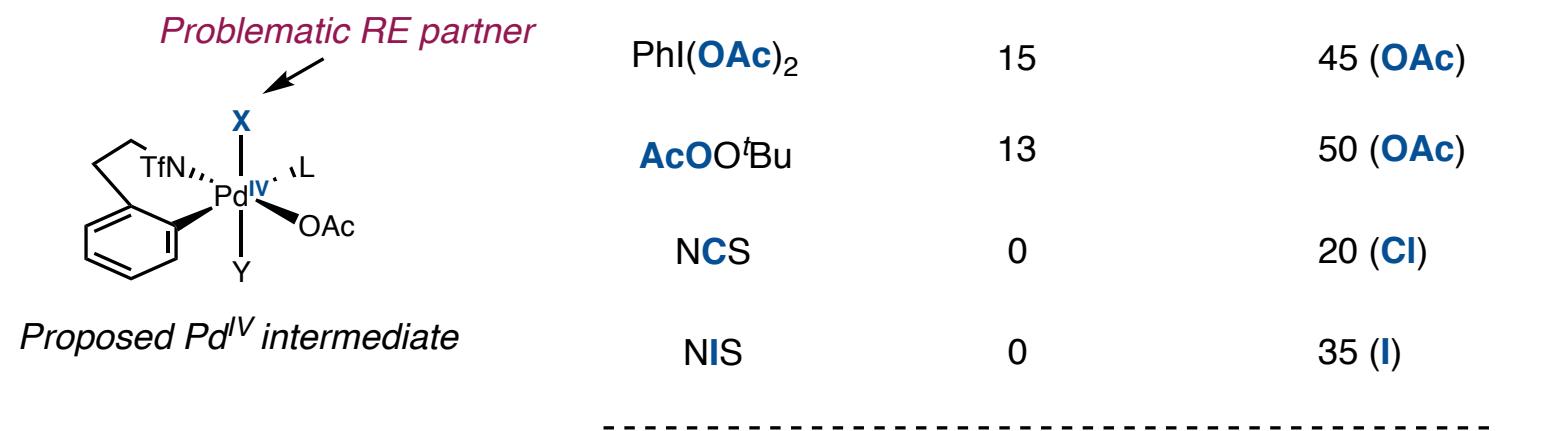
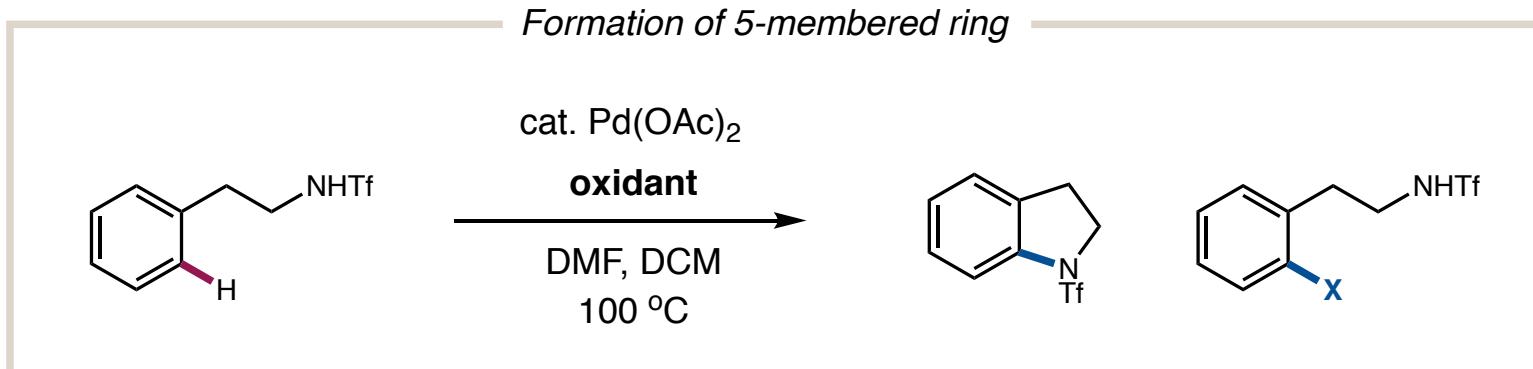
Proposed Pd^{IV} intermediate



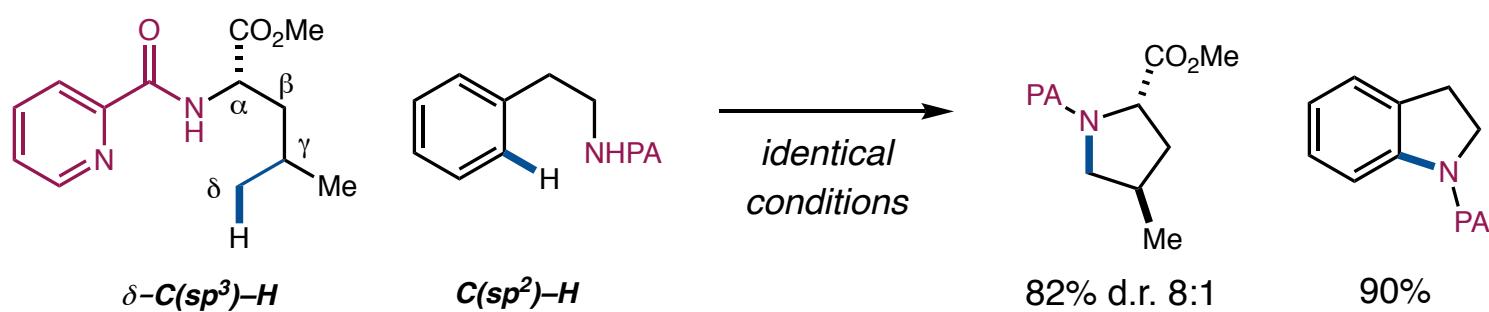
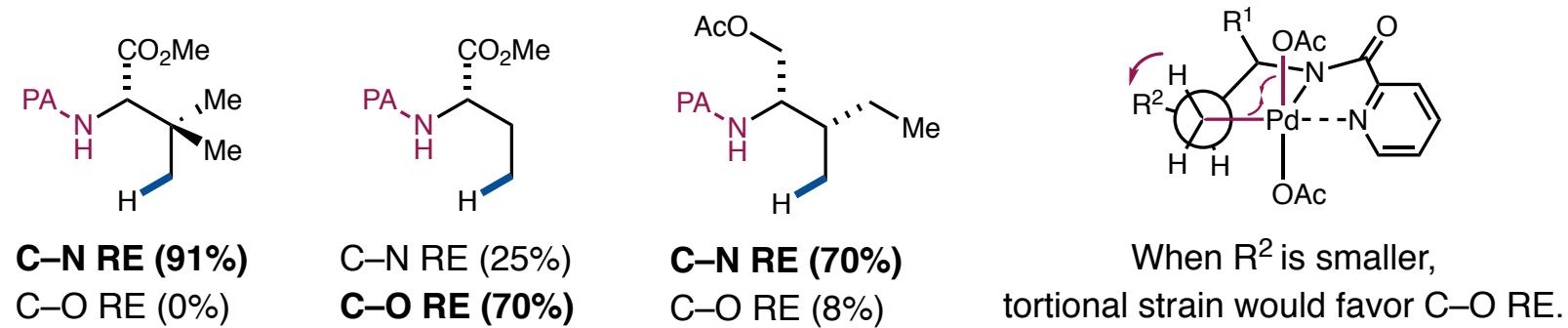
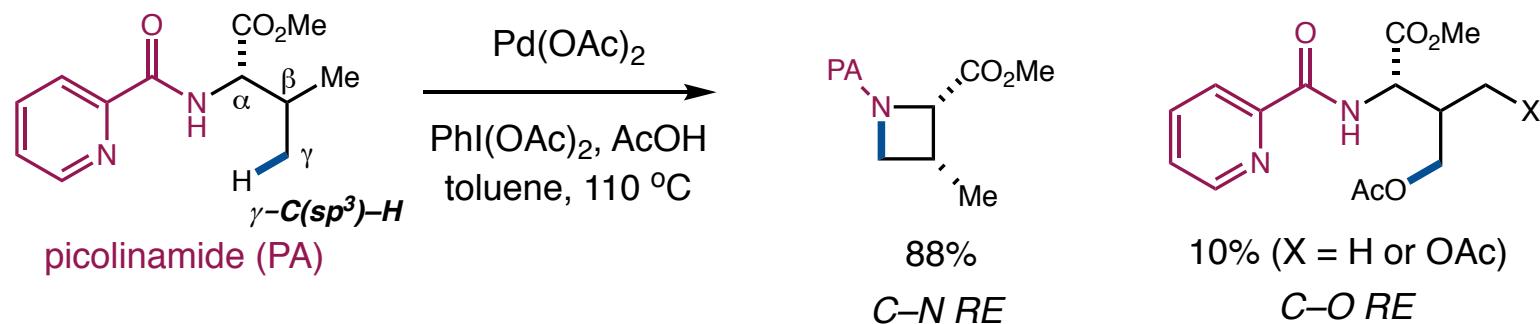
C–F is relatively inert for RE

How about 4-membered ring?

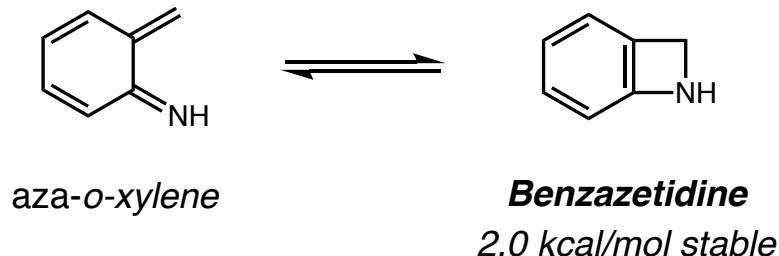
Small Ring Formation



Construction of Azetidine

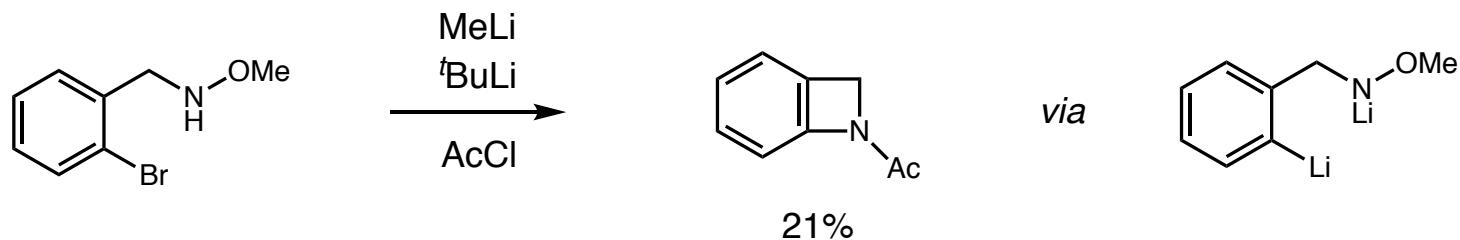
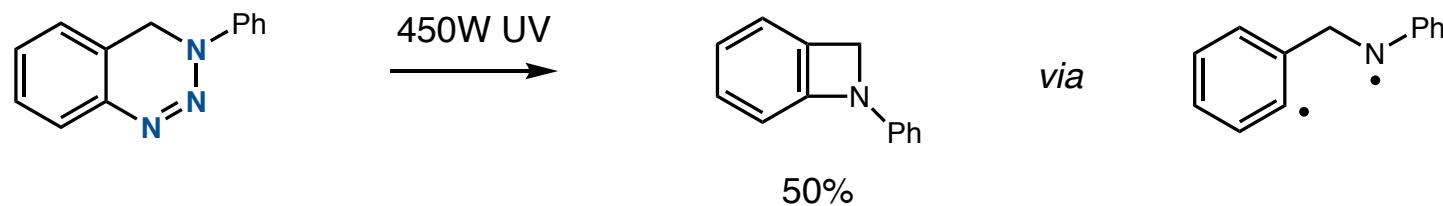


Construction of Benzazetidine

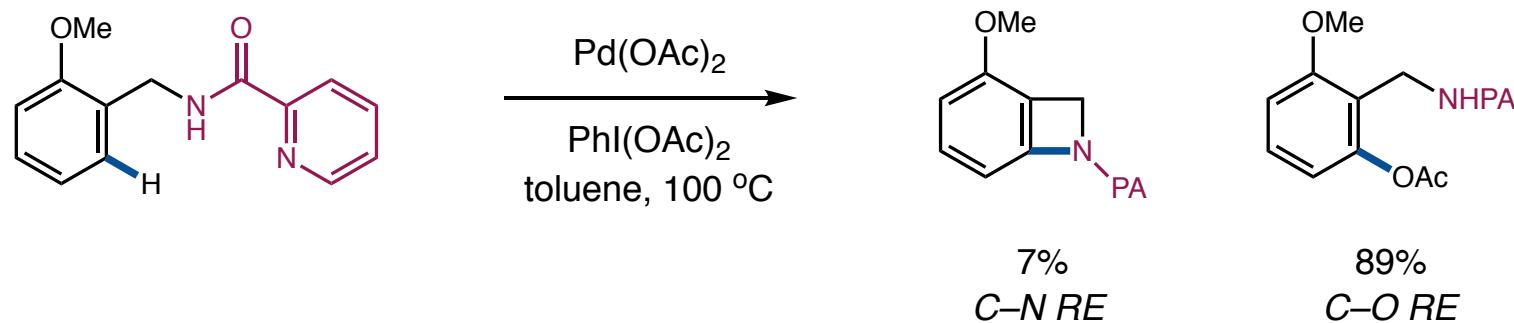


- A lack of practical synthesis due to ring strain
- underexplored N-heterocycle

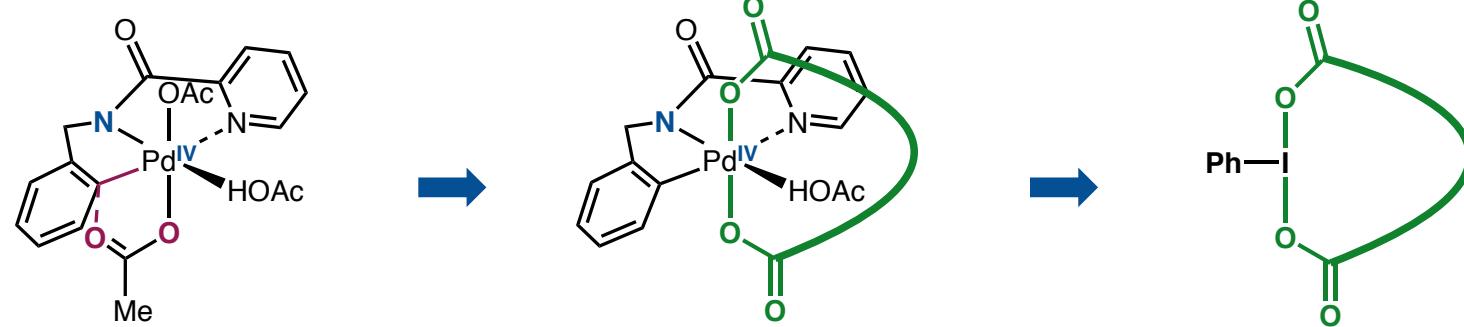
Previous Synthesis



Synthesis of Benzazetidine



Idea to C–N Selective Reductive Elimination

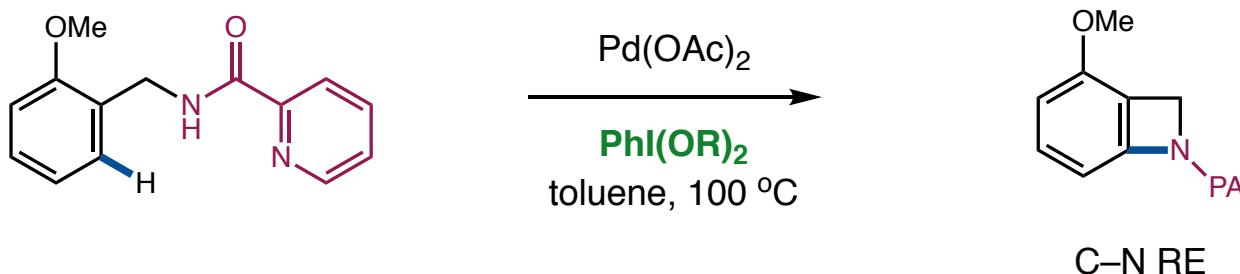


Favoured C–O RE
5-memberd TS

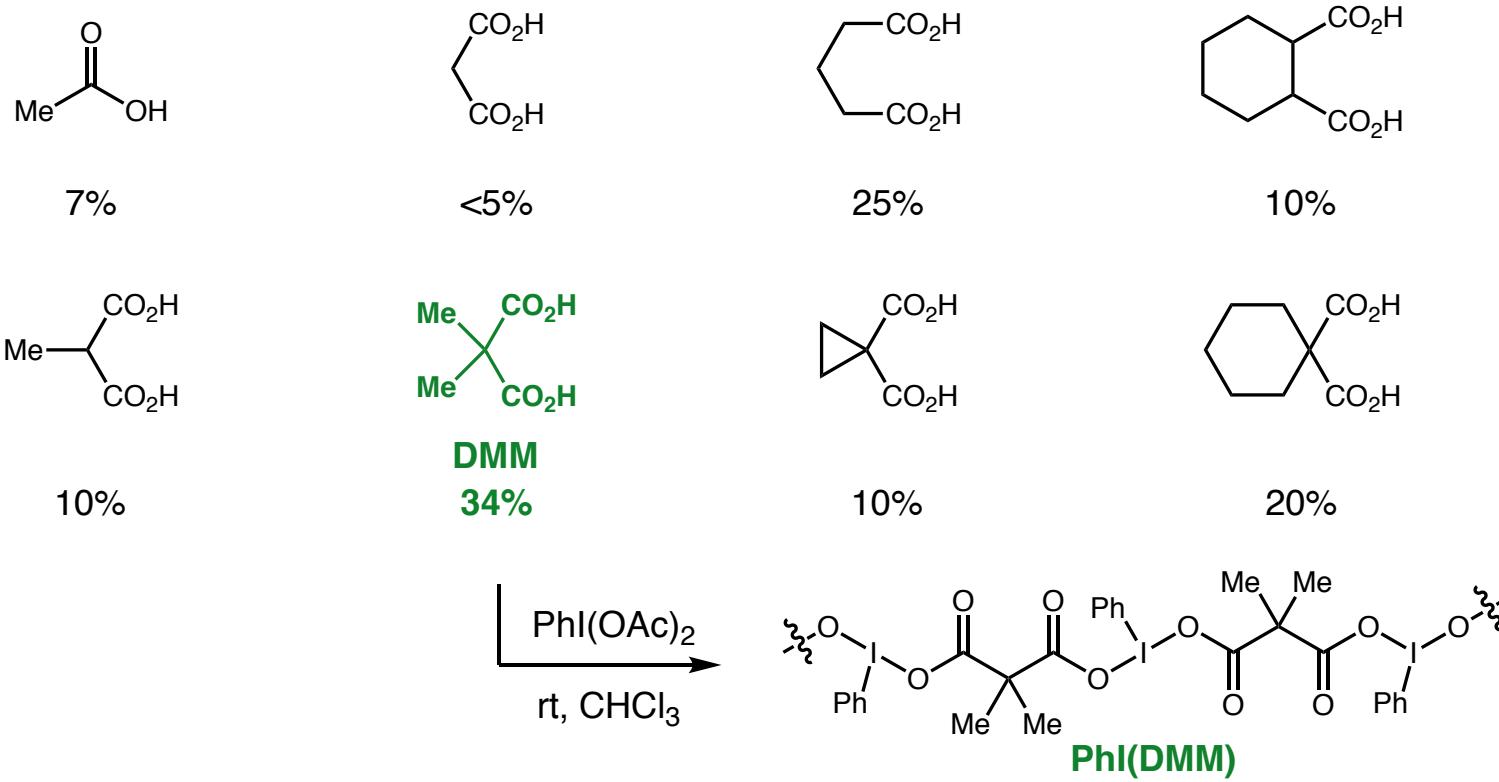
Spacer's strain overcome C–O RE?

Design of $\text{PhI}(OR)_2$

Discovery of PhI(DMM)₂

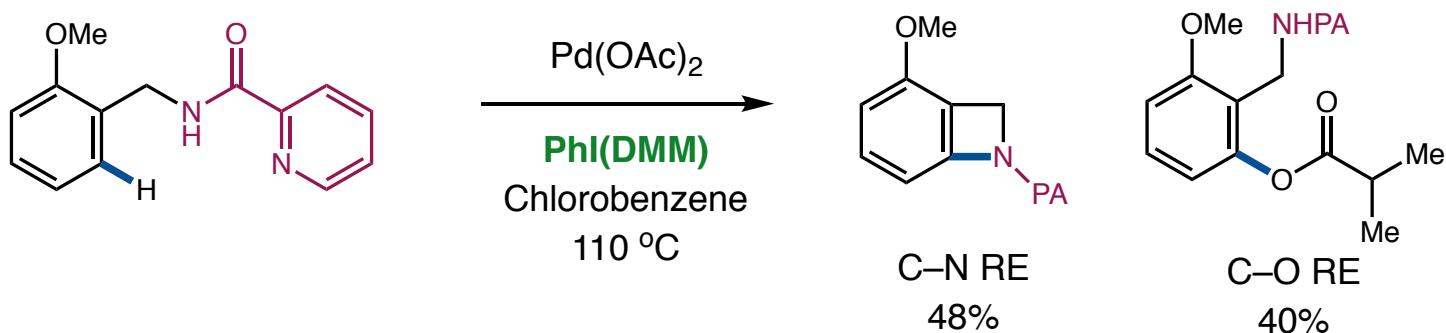


----- *diacidic-derived iodonium oxidants* -----

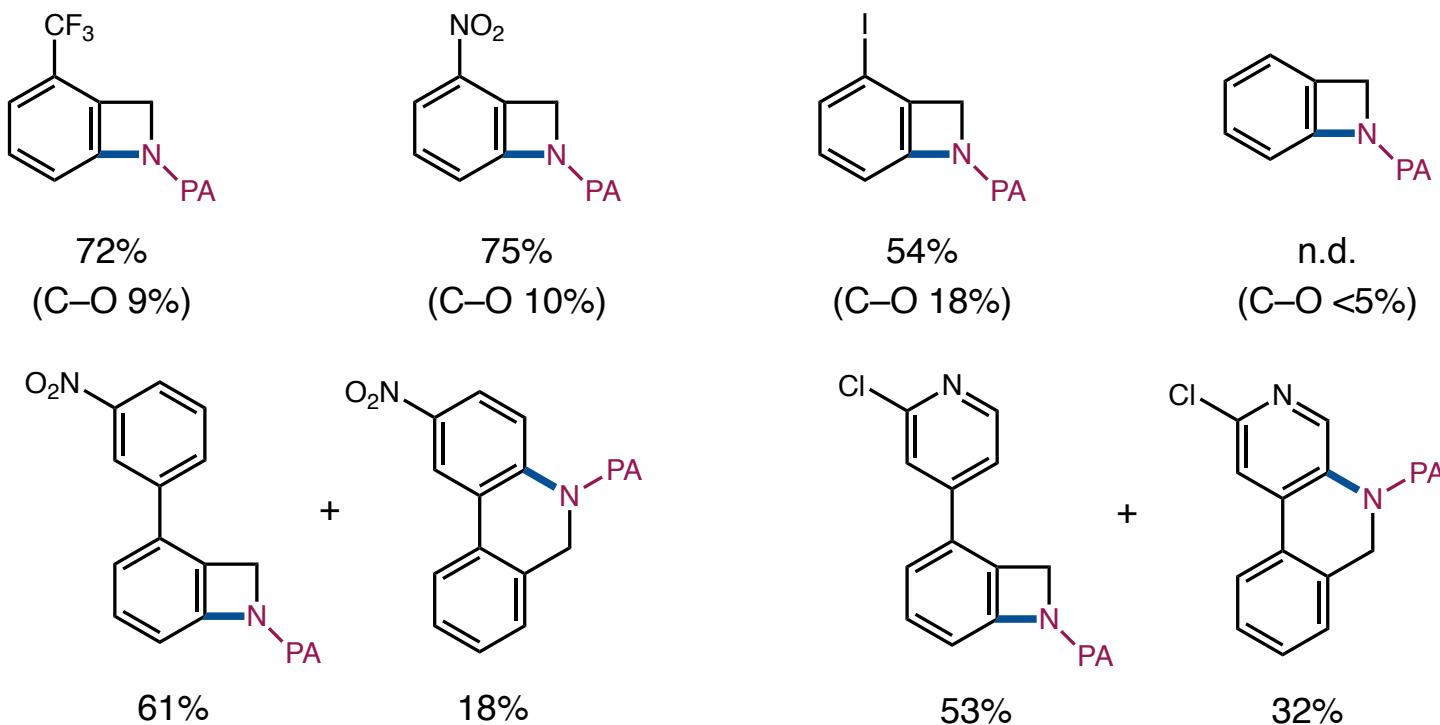


He, G.; Lu, G.; Guo, Z.; Liu, P.; Chen, G. *Nat. Chem.* **2016**, *8*, 1131.

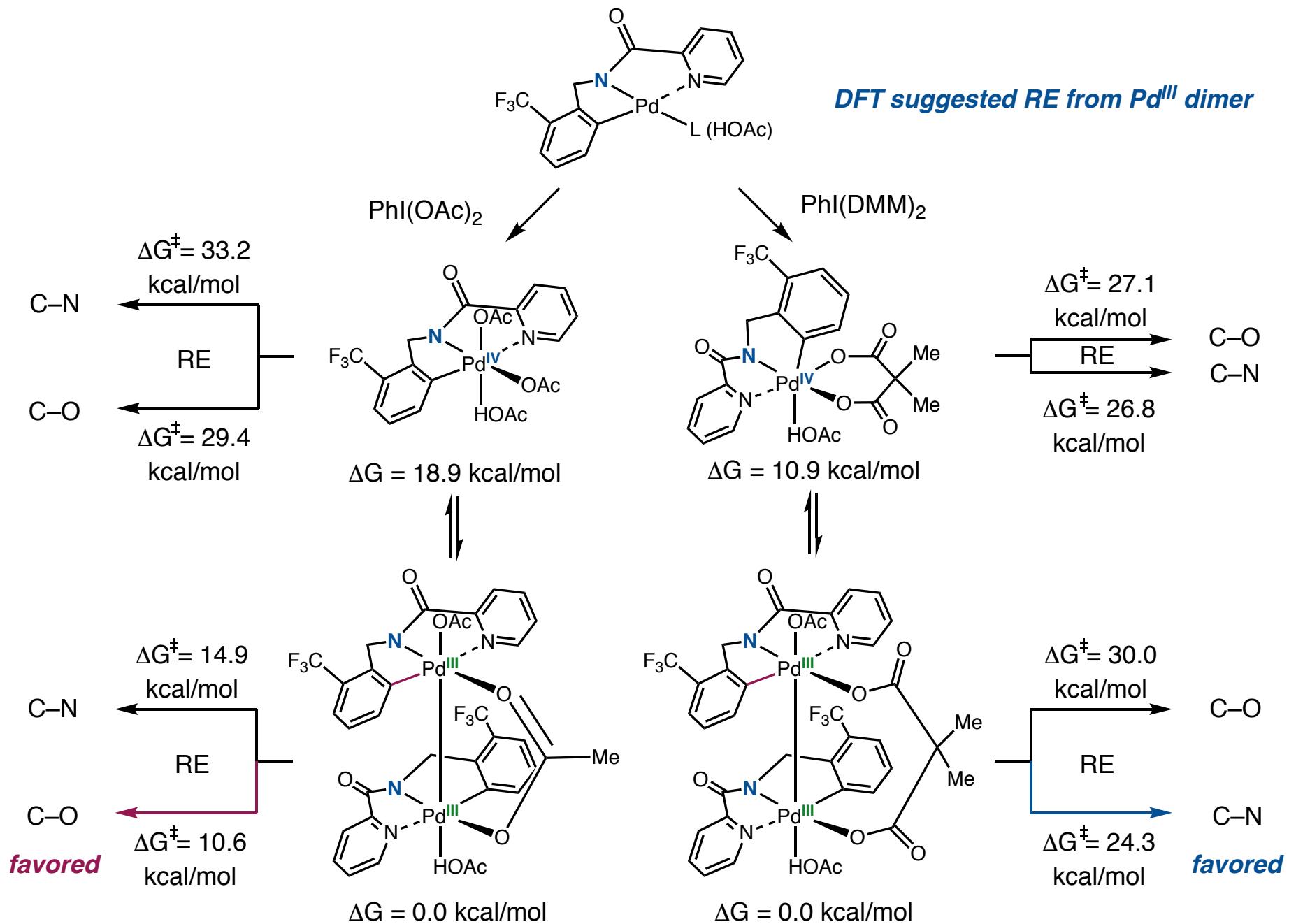
Substrate Scope



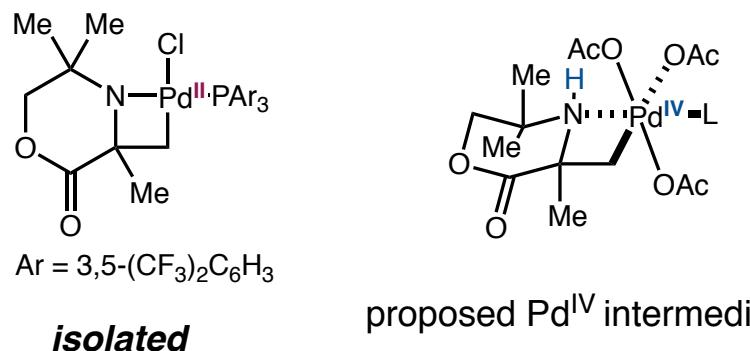
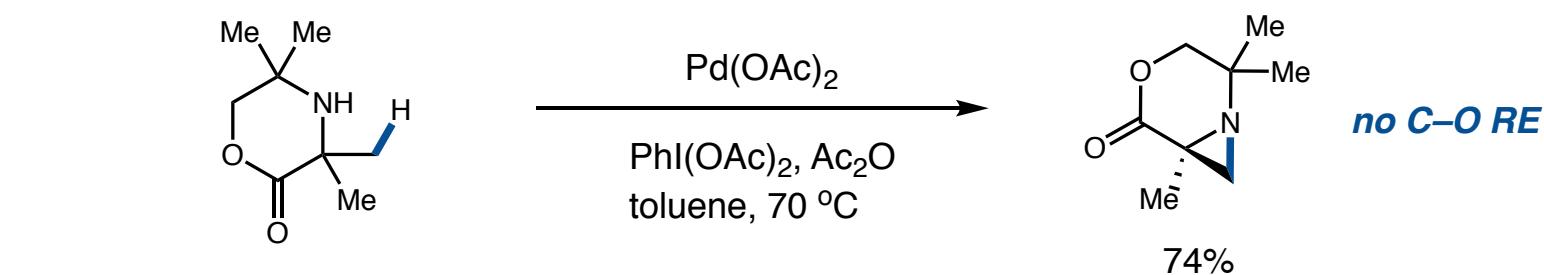
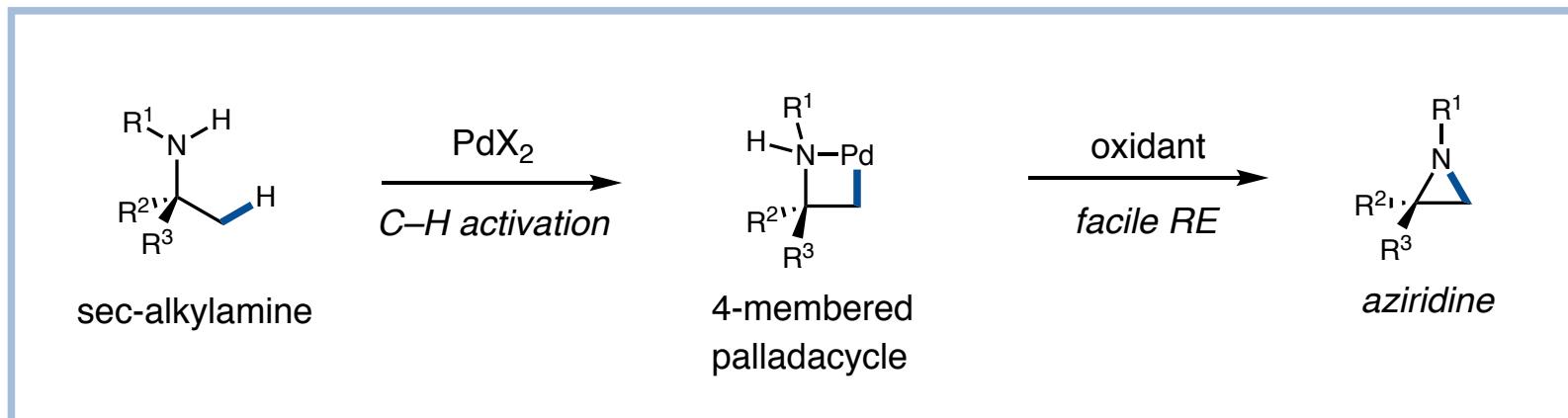
Substrate Scope



Computational Studies



Construction of Aziridine



- *Chemosselectivity of RE (C–N vs C–O)*
- *RE from Pd^{III} dimer or Pd^{IV}*

Computational Studies

