

Pyridone Ligand-Accelerated C-H Functionalization

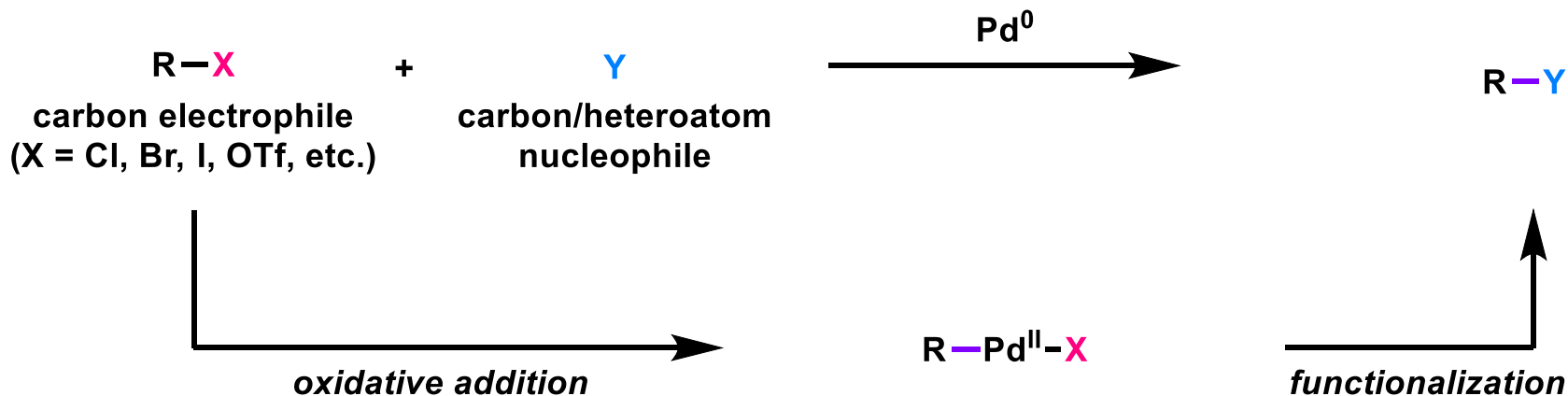
2021/8/21 Takumi Fukuda

Contents

1. Introduction
2. Ligand-accelerated non-directed C–H alkenylation
(Yu, 2017)
3. Directed C–H hydroxylation with molecular oxygen
(Yu, 2021, Main)

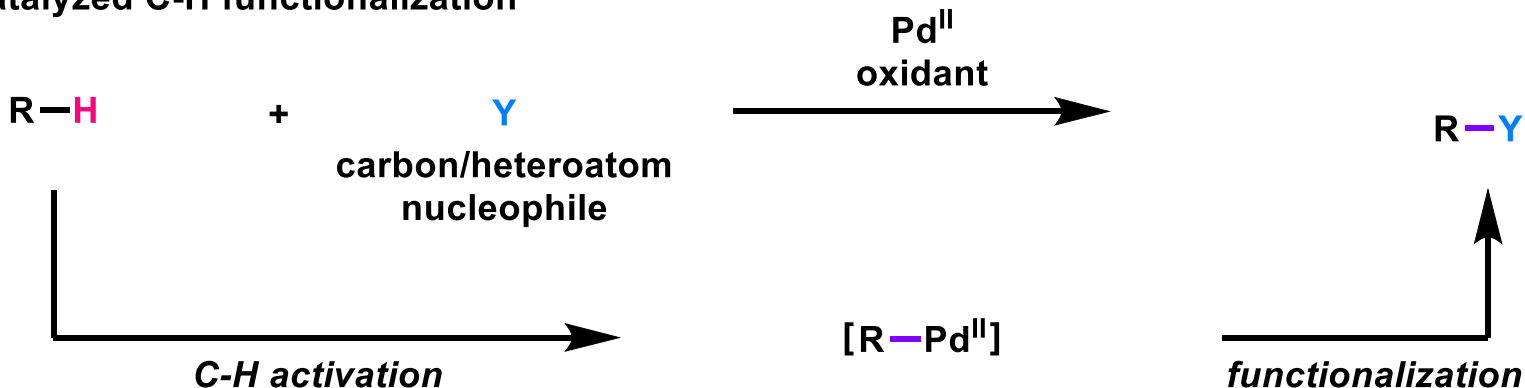
Introducton of C-H Functionalization

1. Pd^0 -catalyzed cross-coupling between carbon electrophiles and carbon/heteroatom nucleophiles.



Pre-functionalized substrates, electrophiles and nucleophiles, are required, resulting in lengthy syntheses.

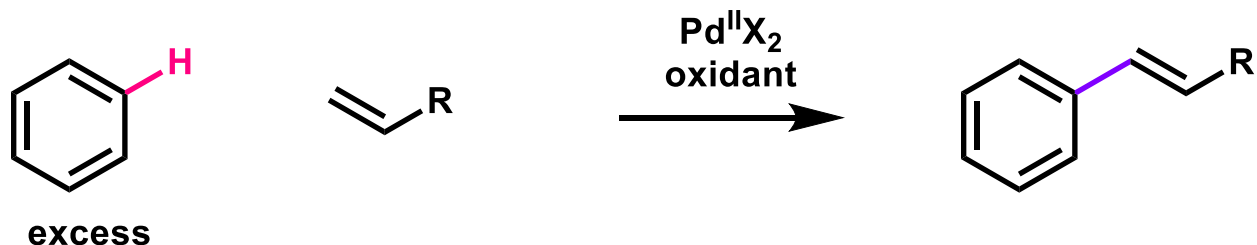
2. Pd^{II} -catalyzed C-H functionalization



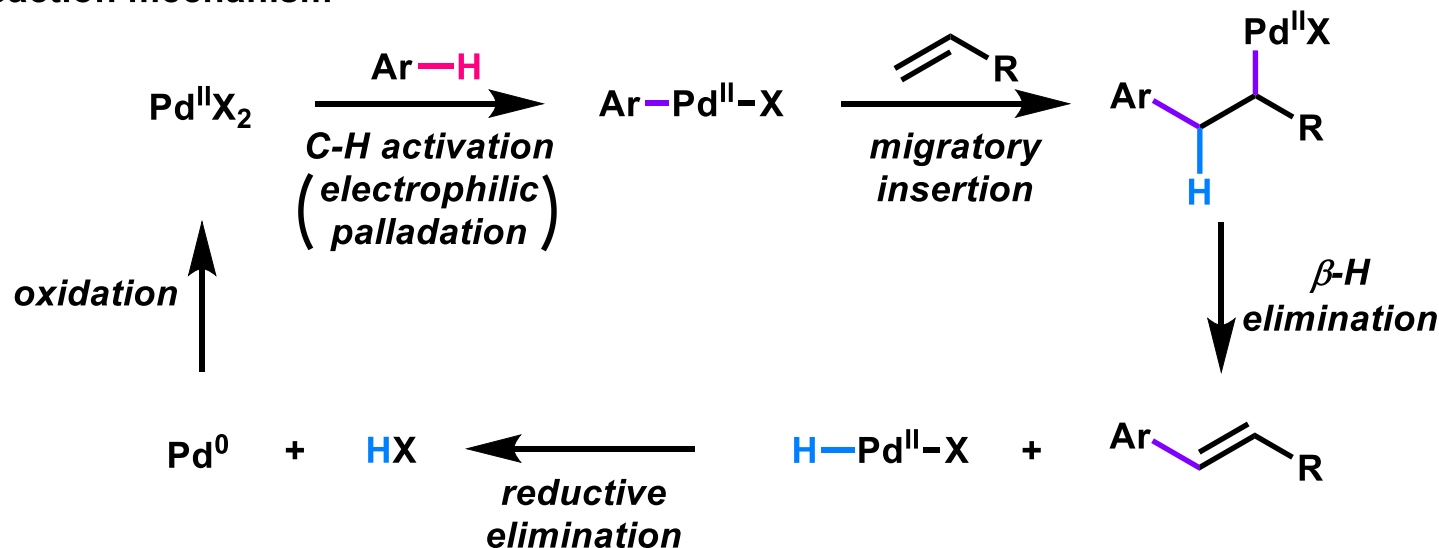
The selective activation of C-H bonds can avoid pre-functionalizations. However, the activation of thermodynamically stable C-H bonds is difficult.

Pioneering Work of C-H Functionalization

Fujiwara-Moritani reaction¹⁾²⁾



Reaction mechanism



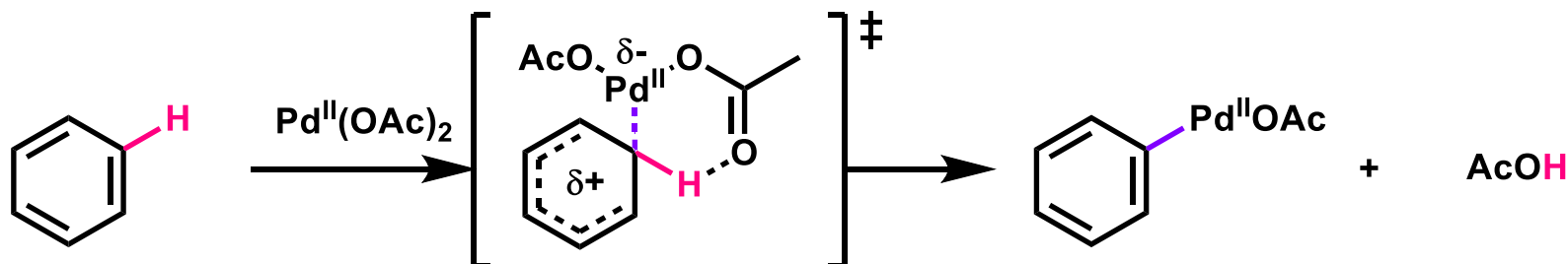
Limitation

1. A large excess of arenes is required for Fujiwara-Moritani reaction.
2. Fujiwara-Moritani reaction, which involves electrophilic palladation step, is limited to electron-rich arenes.

1) Moritani, I.; Fujiwara, Y. Tetrahedron Lett. 1967, 8, 1119. 2) Fujiwara, Y.; Moritani, I.; Danno, S.; Asano, R.; Teranishi, S. J. Am. Chem. Soc. 1969, 91, 7166.

Mechanisms of C-H Activation

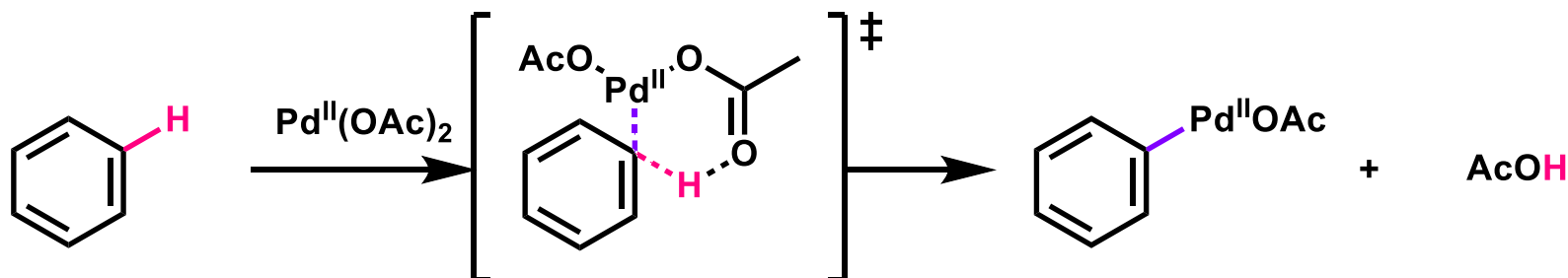
1. Electrophilic palladation¹⁾



Pd^{II} coordinates to the π -system of arenes, and the resulting arenium species transfers a proton to acetate to generate arylpalladium intermediate. In electrophilic palladation, the efficacy of C-H activation is highly dependent on the electronic properties of arenes, with electron-rich substrates giving better reactivity.

Dating back to the early work of Fujiwara and Moritani, reactivity trends consistent with electrophilic palladation.

2. Concerted Metallation De protonation (CMD)²⁾

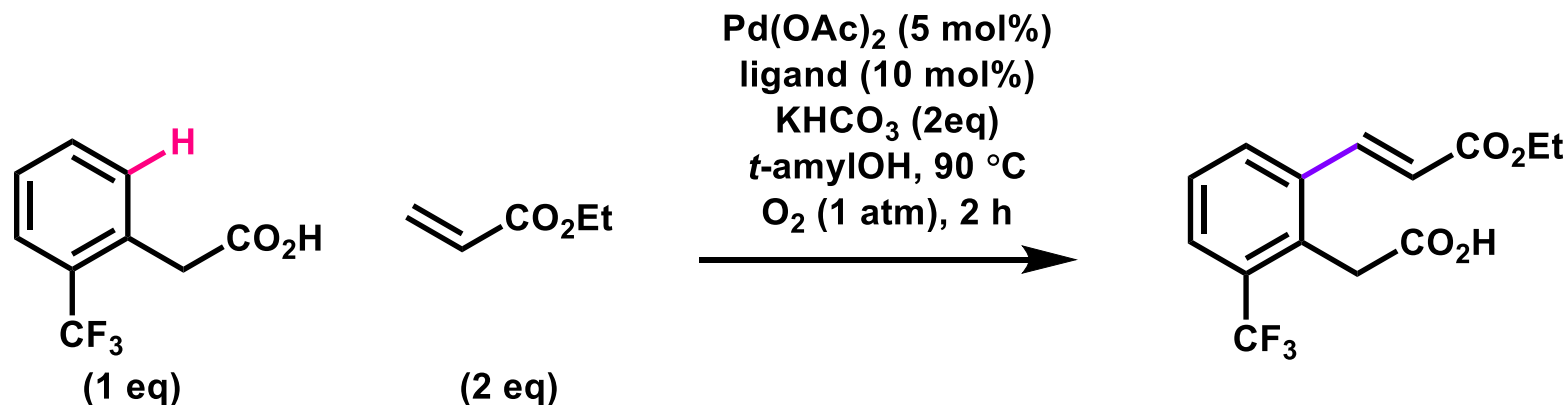


Anionic ligands on palladium, such as acetate or carbonate, assist C-H bond cleavage by acting as internal bases, particularly in the case of electron-deficient arenes.

1) Ryabov, A. D.; Sakodinskaya, I. K.; Yatsimirsky, A. K. *J. Chem. Soc., Dalton Trans.* **1985**, 2629.

2) Davies, D. L.; Donald, S. M. A.; Macgregor, S. A. *J. Am. Chem. Soc.* **2005**, 127, 13754.

Ligand Effect on C-H Activation (1)

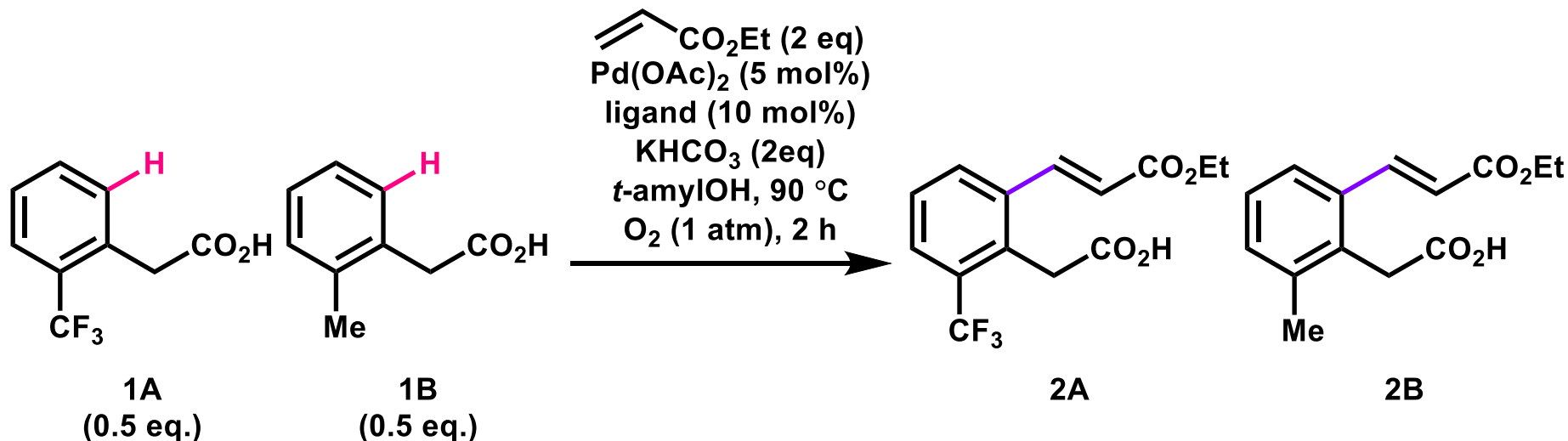


ligand	conversion ^{a)} (%)
none	7
Ac-Ile-OH	> 99 (96 ^{b)})

a) determined by ^1H NMR of crude mixture.
b) isolated yield.

Mono N-protected amino acid ligands (MPAA) accelerate the reaction.

Ligand Effect on C-H Activation (2)

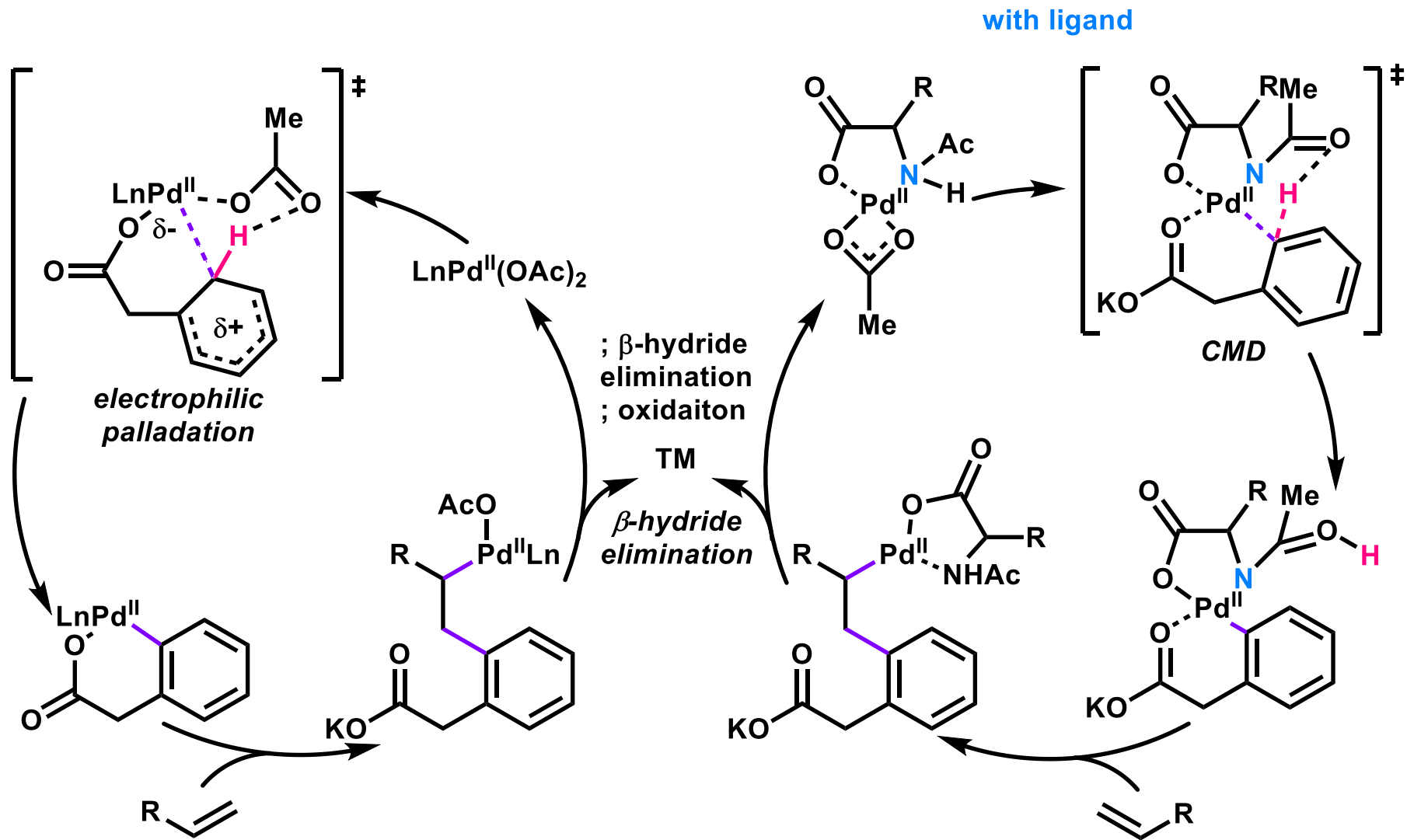


entry	ligand	time (min)	% conv. A	% conv. B	k _{2A} /k _{2B}
1	none	120	3	14	0.22
2	Ac-Ile-OH	10	40	21	1.87

The conversion was determined by ¹H NMR of crude mixture.

1. In the absence of ligand, electron-rich substrate 1B gave a higher initial rate.
→ C-H activation proceeds through an electrophilic palladation mechanism.
2. In the presence of Ac-Ile-OH, electron-poor substrate 1A gave a higher initial rate.
→ C-H activation proceeds through an electrophilic palladation mechanism.

Proposed Catalytic Cycle



Contents

1. Introduction
2. Ligand-accelerated non-directed C–H alkenylation
(Yu, 2017)
3. Directed C–H hydroxylation with molecular oxygen
(Yu, 2021, Main)

Prof. Jin-Quan Yu



**1982-1987 (B.Sc.): East China Normal University
(Prof. L.-X. Dai and Prof. B.-Q. Wu)**

**1987-1988 : Shanghai Institute of Organic Chemistry
1988-1990 (M.Sc.) Guangzhou Institute of Chemistry (Prof. S.-D. Xiao)**

**1990-1994 : Teaching and research assistant
at Guangzhou Institute of Chemistry**

1994-1999 (Ph.D.): University of Cambridge (Prof. Jonathan B. Spencer)

**1999-2003 : Junior Research Fellow of St. John's College
at University of Cambridge**

**2001-2002 : Harvard University (Prof. E. J. Corey)
(postdoc)**

**2003-2004 : Royal Society Research Fellow
at University of Cambridge**

2004-2007 : Assistant Professor at Brandeis University

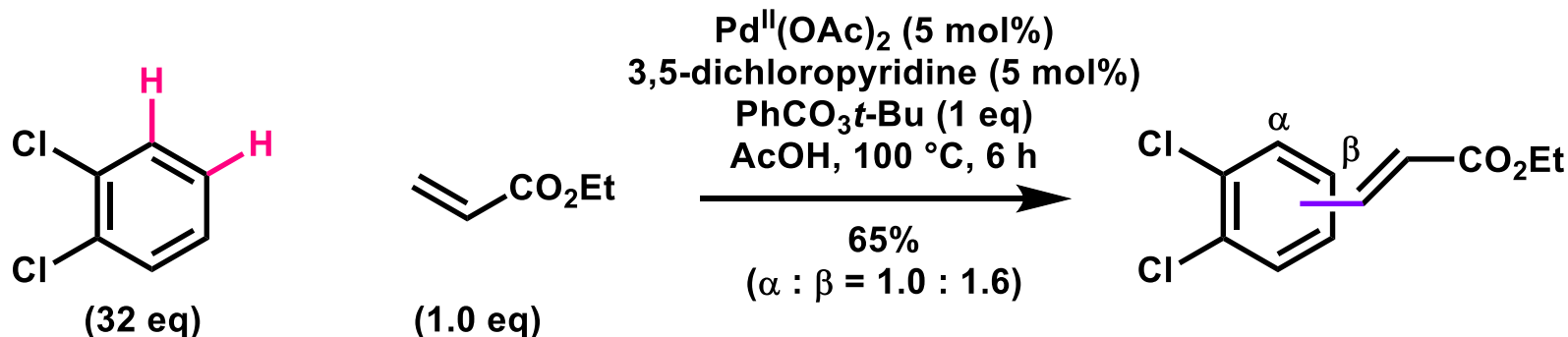
**2007-2010 : Associate Professor at The Scripps Research Institute
2010- : Professor at The Scripps Research Institute**

Research Topic:

Discovery and rational design of new reactions using C-H activation

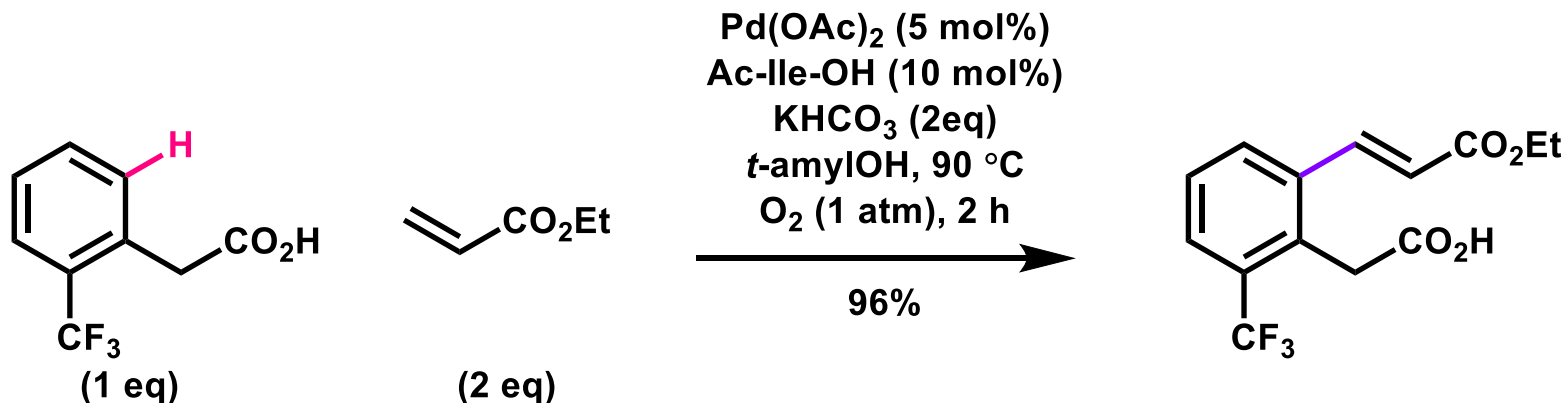
Background and Research Aim

1. Non-directed olefination (Sanford, 2012)¹⁾



A large excess of arenes is required to achieve sufficient reactivity with palladium catalysts.

2. Directed olefination using N-protected amino acid ligands (Yu, 2010)²⁾



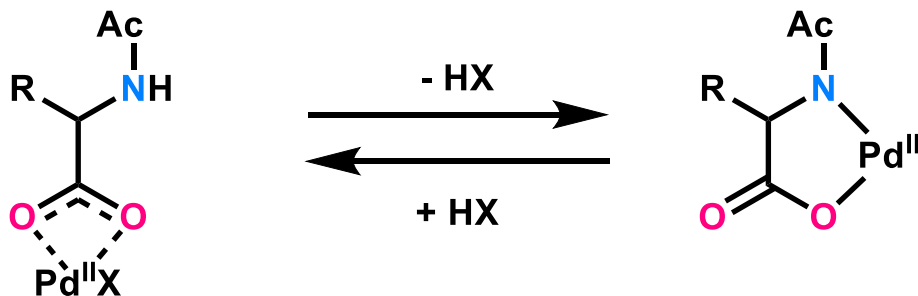
N-protected amino acid ligands enabled carboxylate-directed C-H olefination, allowing arenes to be used as the limiting reagent.

→ Further screening of ligands was conducted using 1,2-dichlorobenzene as a model substrate to realize non-directed C-H functionalization of arenes.

1) Kubota, A.; Emmert, M. H.; Sanford, M. S. *Org. Lett.* **2012**, 14, 1760. 2) Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, 132, 14137. 3) Wang, P.; Verma, P.; Xia, G.; Shi, J.; Qiao, J. X.; Tao, S.; Cheng, P. T. W.; Poss, M. A.; Farmer, M. E.; Yeung, K.-S.; Yu, J.-Q. *Nature* **2017**, 23, 551.

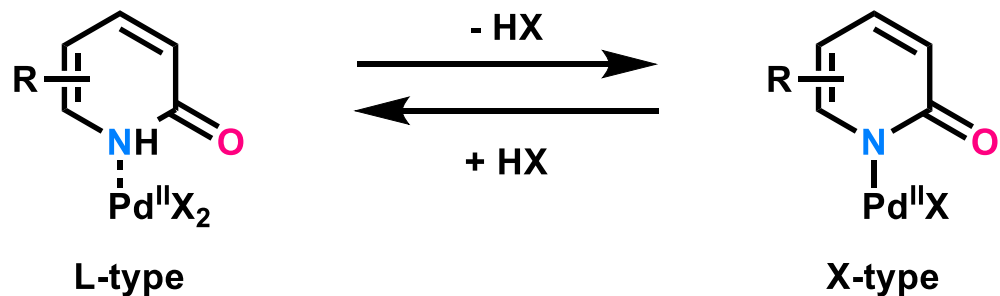
Design of Ligands

1. Mono N-Protected Amino Acid ligand (MPAA)¹⁾²⁾



Coordination modes can be sterically controlled.

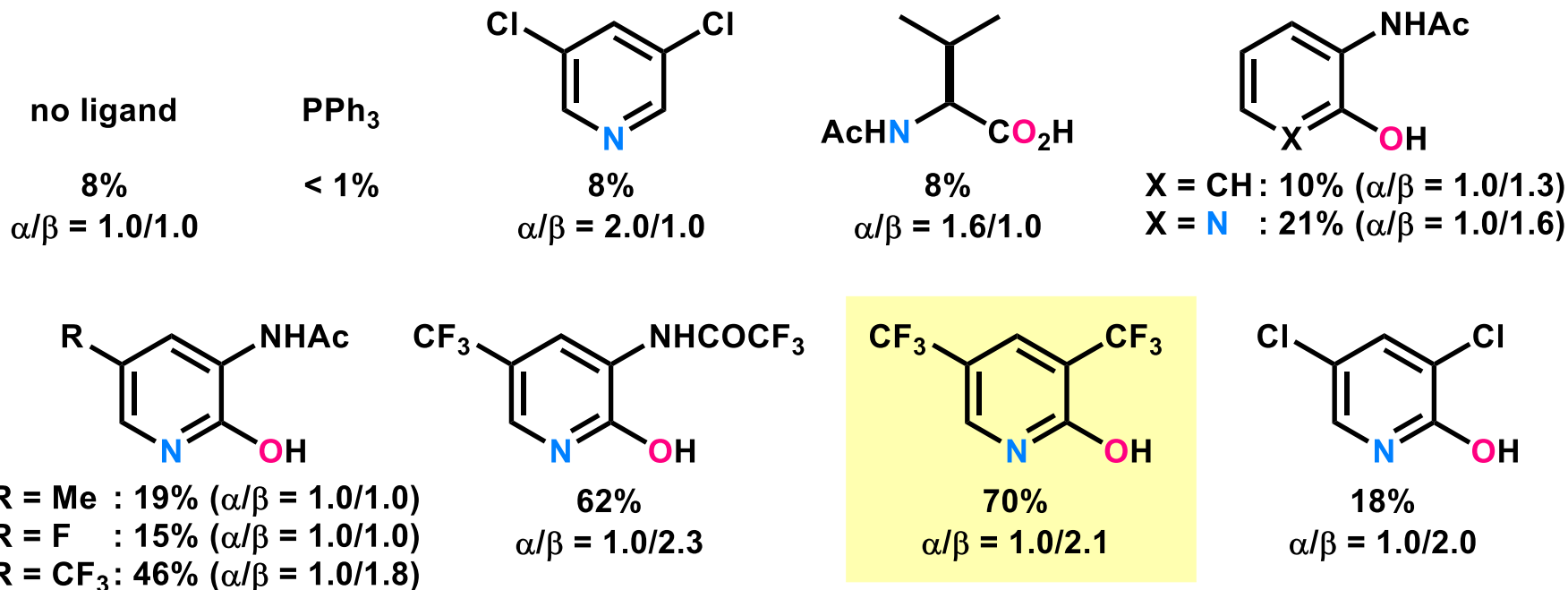
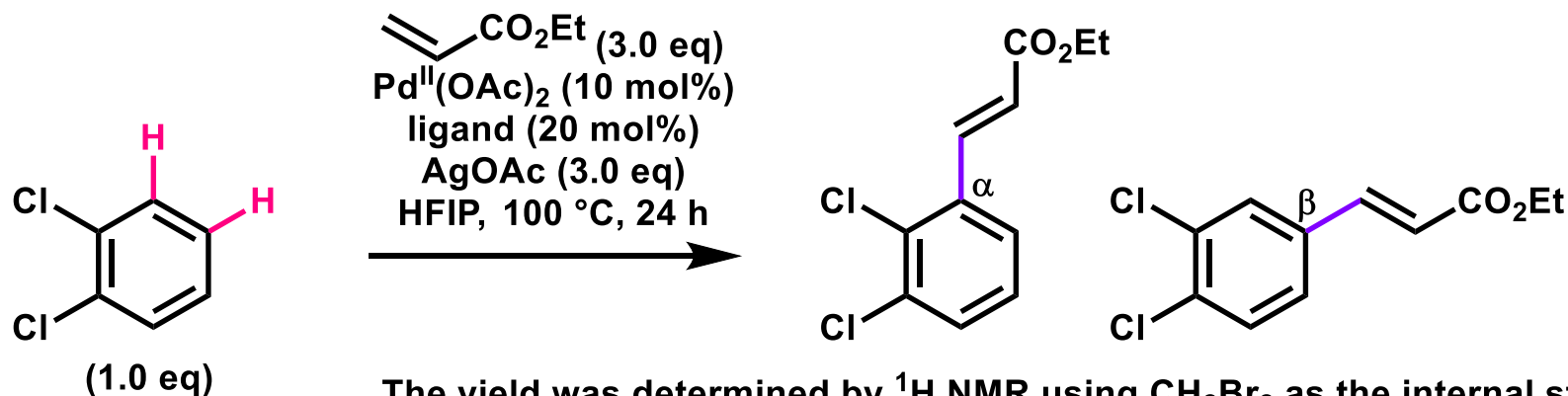
2. Pyridone ligand



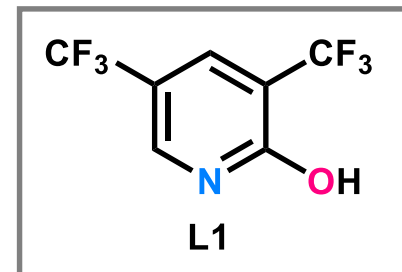
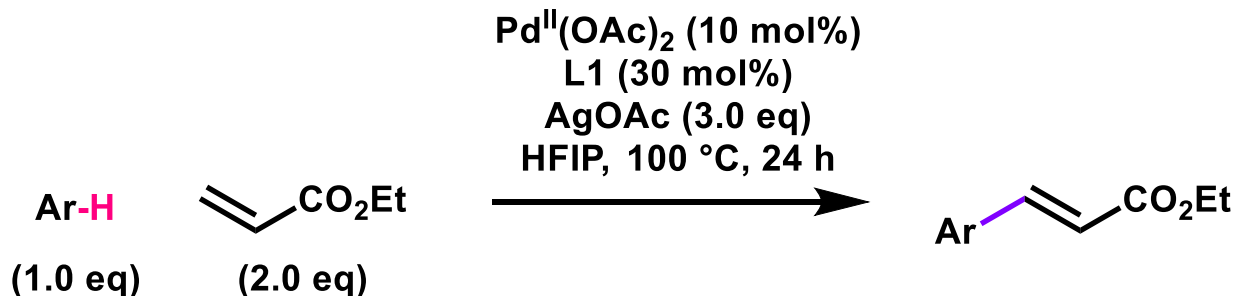
Coordination modes can be electronically controlled.

1) Wang, D.-H.; Engle, K. M.; Shi, B.-F.; Yu, J.-Q. *Science* **2010**, 327, 315. 2) Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, 132, 14137. 3) Wang, P.; Verma, P.; Xia, G.; Shi, J.; Qiao, J. X.; Tao, S.; Cheng, P. T. W.; Poss, M. A.; Farmer, M. E.; Yeung, K.-S.; Yu, J.-Q. *Nature* **2017**, 23, 551.

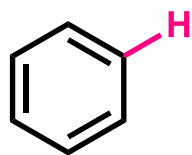
Screening of Ligands



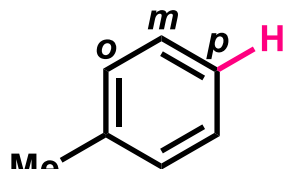
Substrate Scope



The yield was determined by ^1H NMR using CH_2Br_2 as the internal standard.

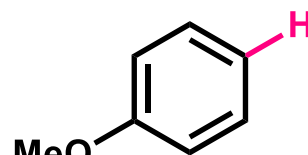


64%



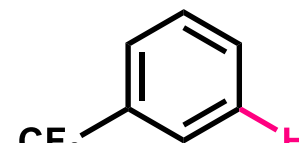
83%

(*o*/*m*/*p* = 1.0/12.2/13.8)



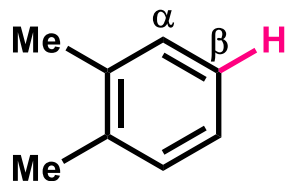
67%

(*o*/*m*/*p* = 1.8/1.0/3.7)



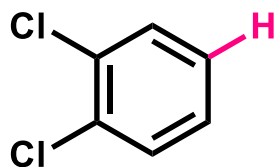
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(*m*/*p* = 3.3/1.0)



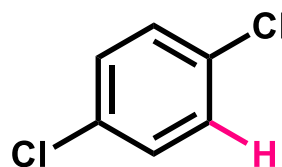
81%

($\alpha/\beta < 1/20$)

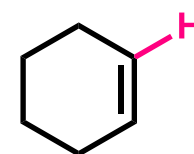


81%

($\alpha/\beta = 1.0/3.0$)



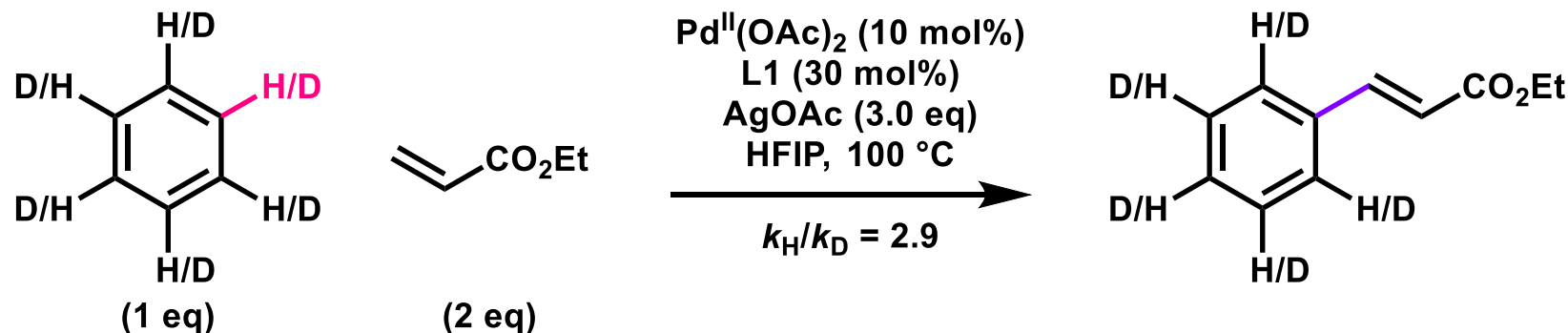
60%



64%

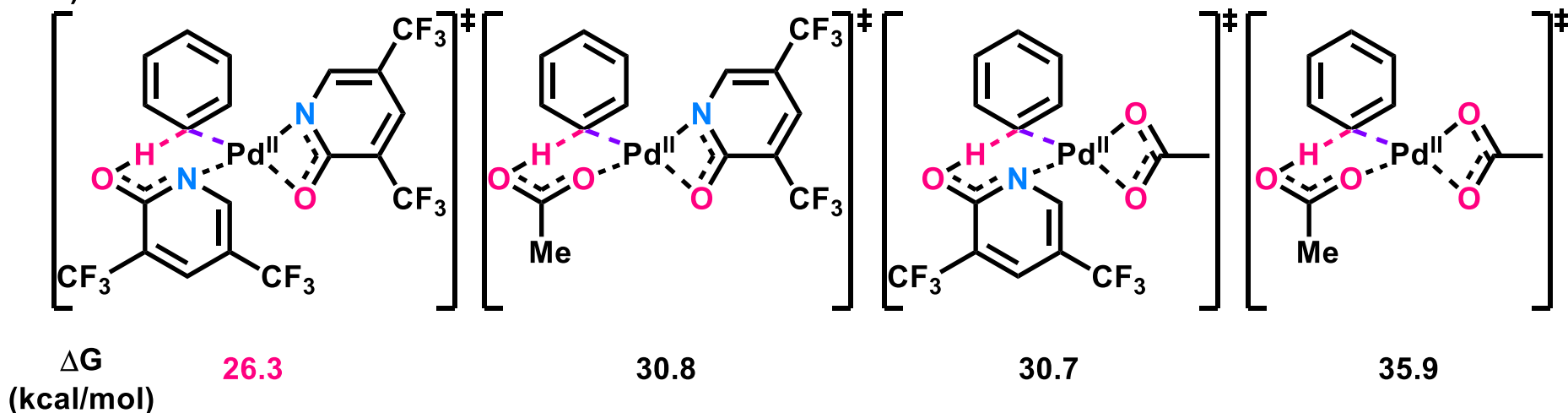
Mechanistic Study (1)

1) Kinetic isotope effect (KIE)



The kinetic-isotope-effect experiments ($k_{\text{H}}/k_{\text{D}} = 2.9$) using benzene as a model substrate with ethyl acrylate indicate that the C-H bond cleavage is the late-limiting step.

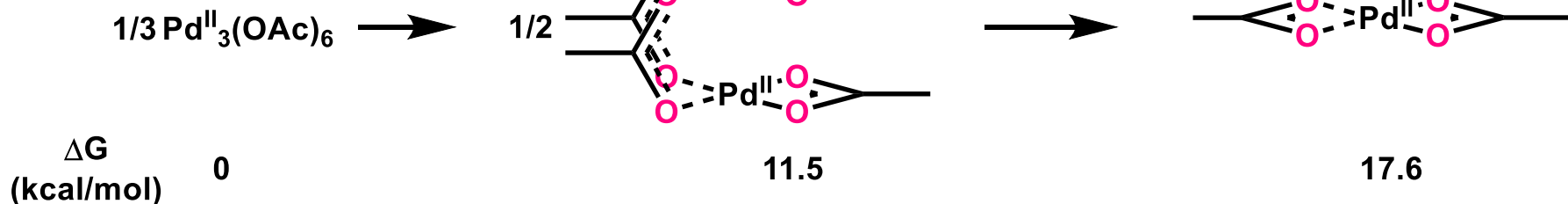
2) DFT calculation of TS structures



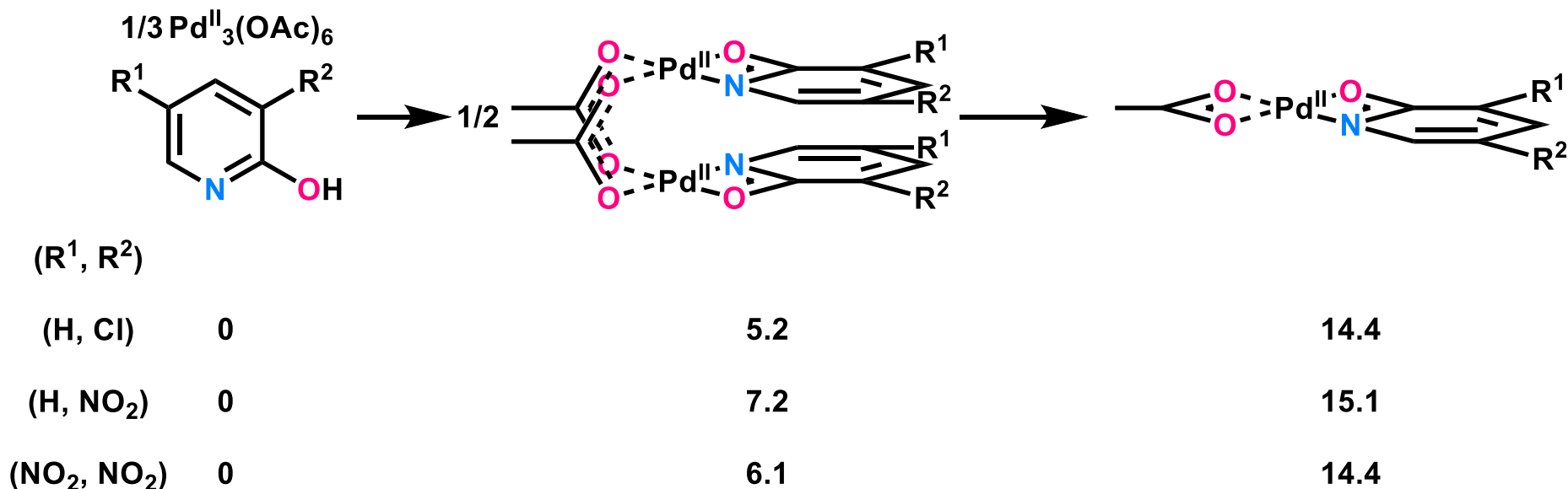
Calculation was conducted at the M06/SDD,6-311+G(d,p)(SMD)//B3LYP/LANL2DZ,6-31-G(d) level of theory.

Mechanistic Study (2)

1) Without pyridone ligand



2) With pyridone ligand



With pyridone ligands, π - π stacking interactions stabilize dimeric Pd species.

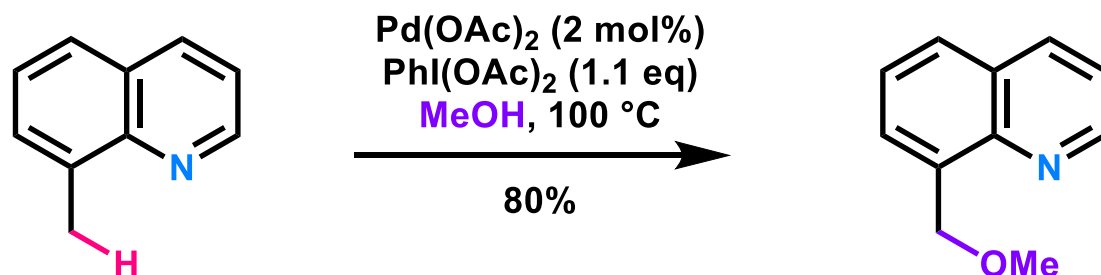
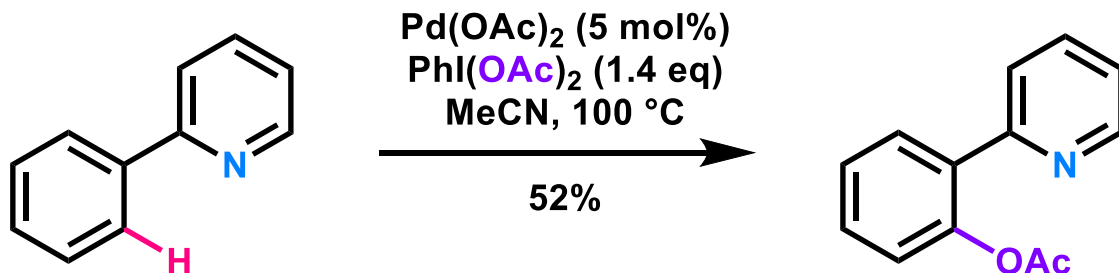
Pyridone ligands promote not only CMD process, but also generation of reactive monomeric Pd species.

Contents

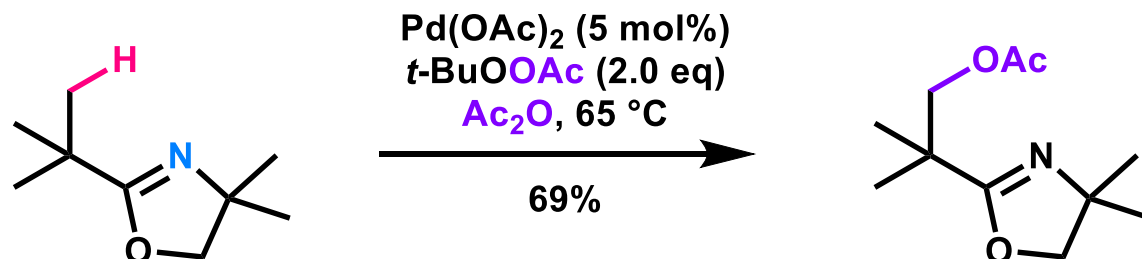
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(Yu, 2017)
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C-H Oxidation with Stoichiometric Oxidant

1. with $\text{PhI}(\text{OAc})_2$ (Sanford, 2004)¹⁾

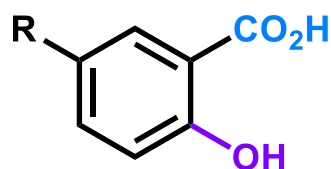
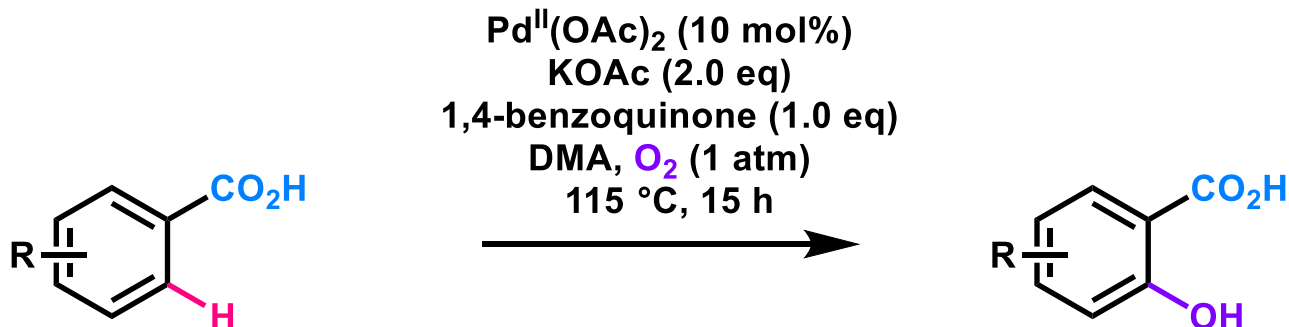


2. with $t\text{-BuOOAc}$ (Yu, 2005)²⁾

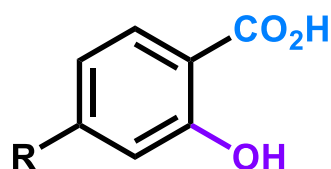


1) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* 2004, 126, 2300. 2) Giri, R.; Liang, J.; Lei, J.-G.; Li, J.-J.; Wang, D.-H.; Chen, X.; Naggar, I. C.; Guo, C.; Foxman, B. M.; Yu, J.-Q. *Angew. Chem. Int. Ed.* 2005, 44, 7420.

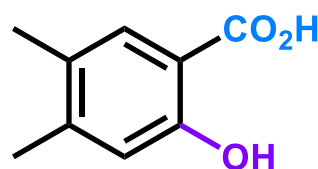
Successful C-H Hydroxylation with O₂



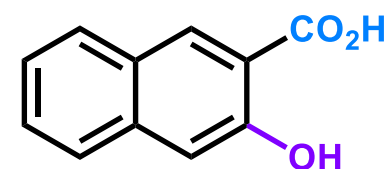
R = Me : 78%
 R = OMe: 73%



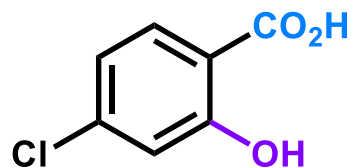
R = Me : 82%
 R = NHAc: 52%



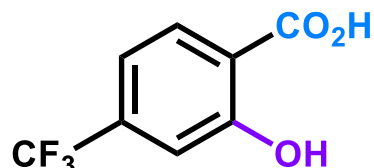
76%



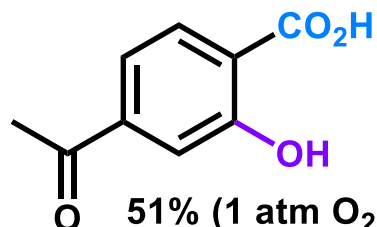
62%



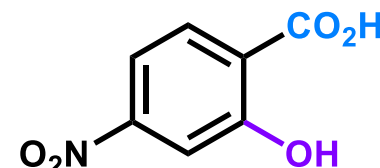
X = F : 82%
 X = Cl: 78%



50% (1 atm O₂)
 86% (5 atm O₂)



51% (1 atm O₂)
 63% (5 atm O₂)

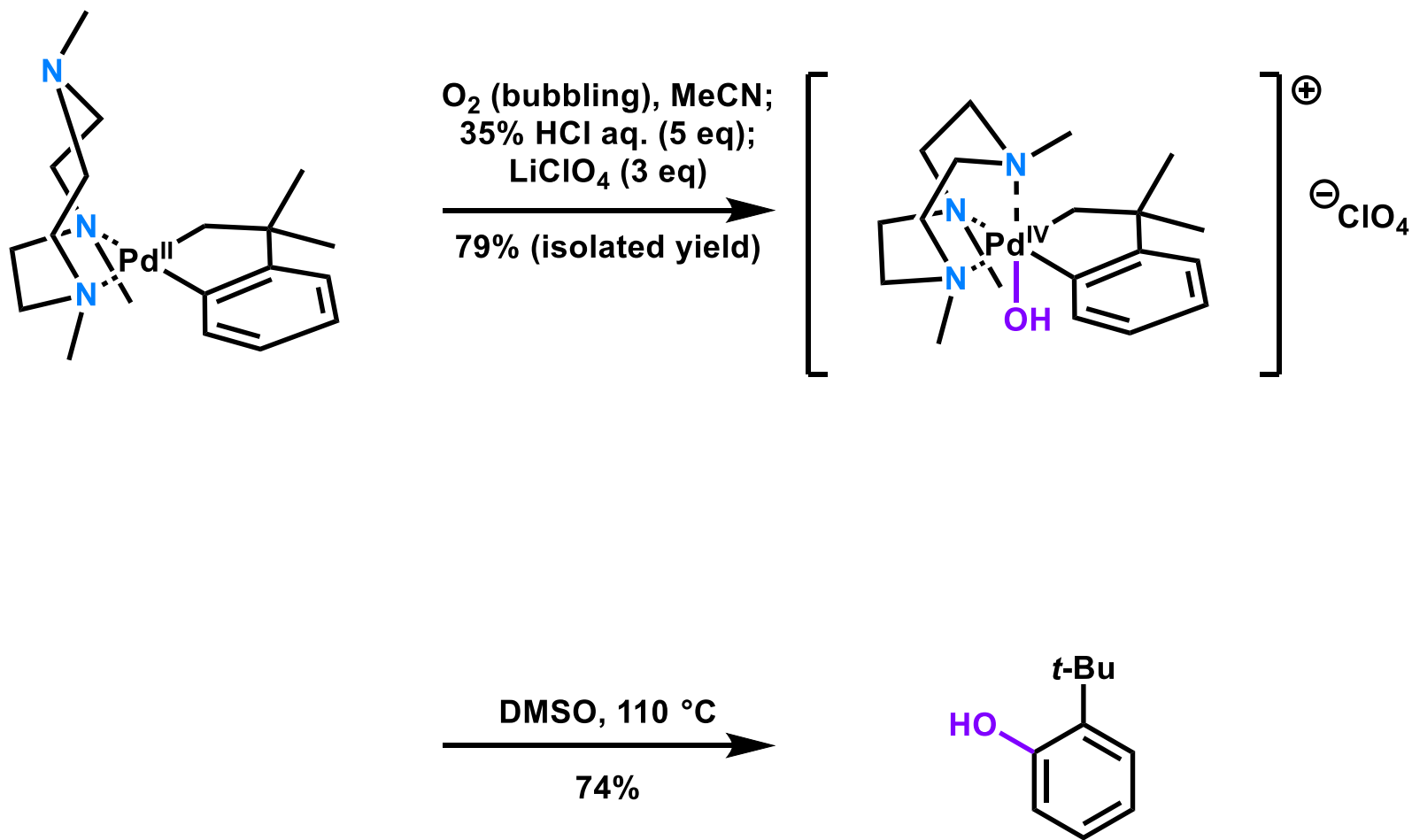


54% (1 atm O₂)
 91% (5 atm O₂)

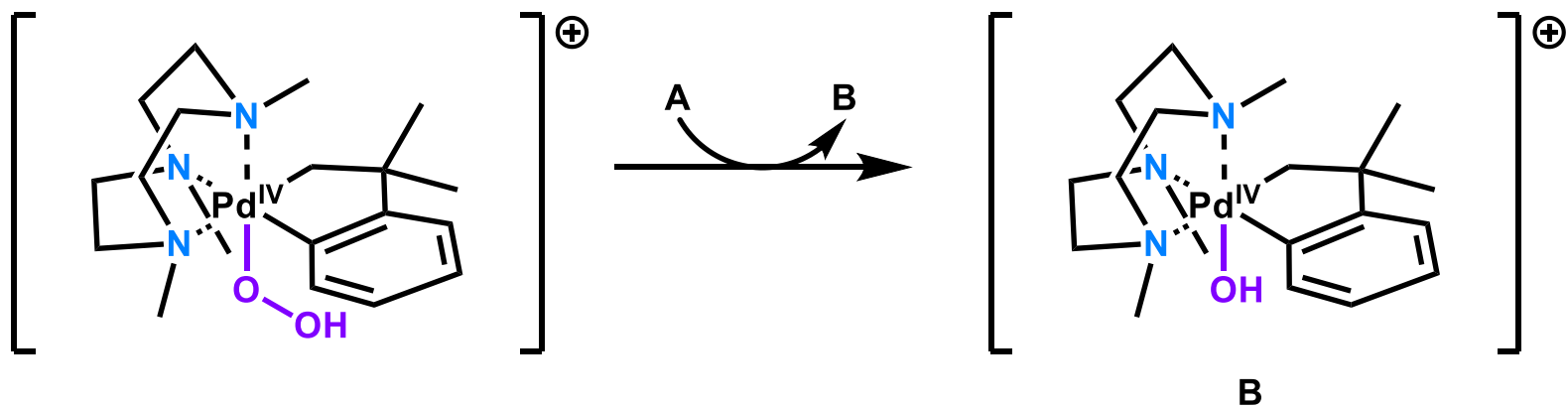
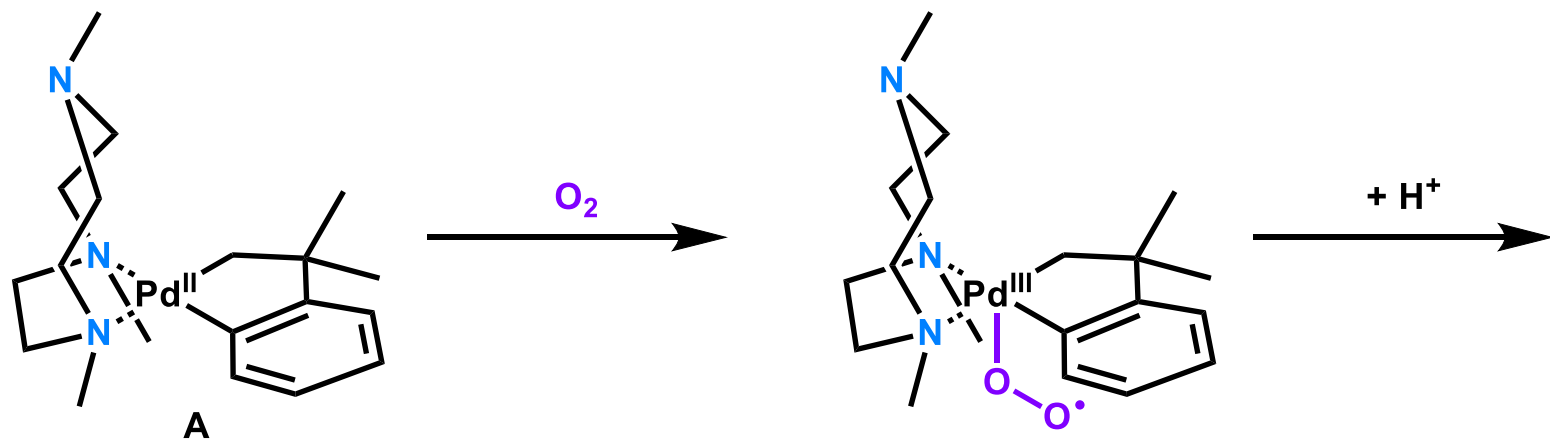
Limitation

1. Electron-deficient arenes have low reactivity to C-H hydroxylation.
2. Heteroaryl acids show no reactivity under the reaction conditions.

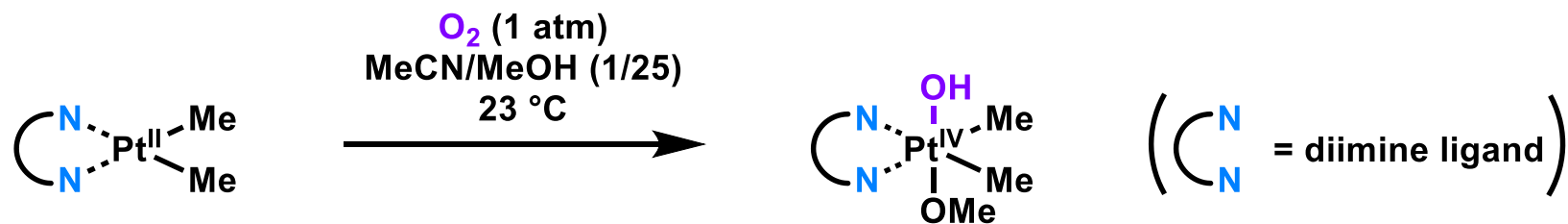
Oxidation of Pd(II) with O₂ (Mirica's group)



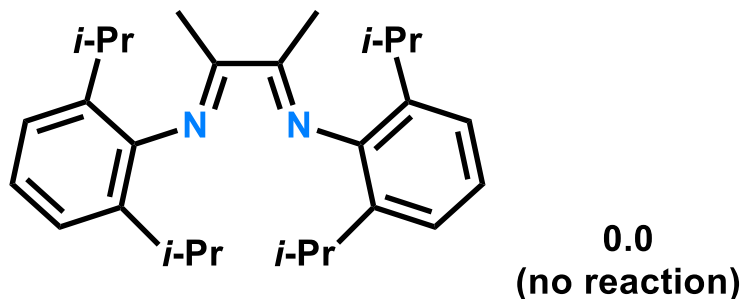
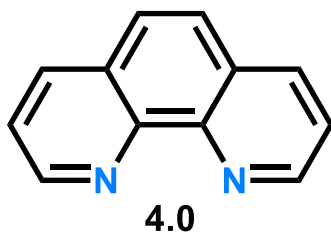
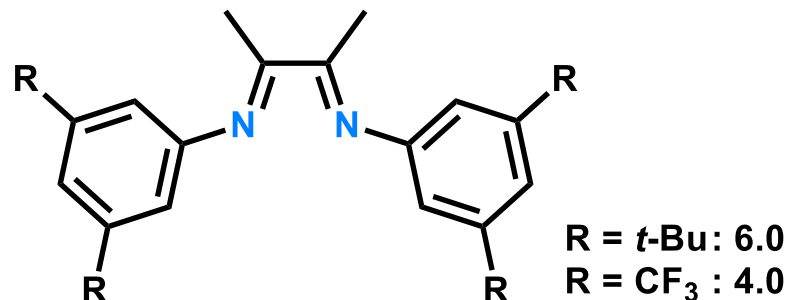
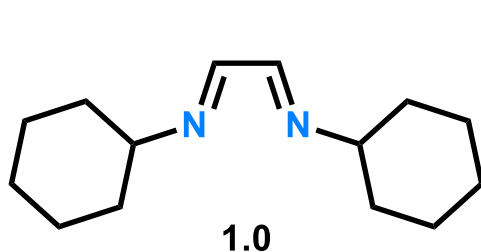
Proposed Mechanism



Effect of Bidentate Ligands on Oxidation of Pt(II)

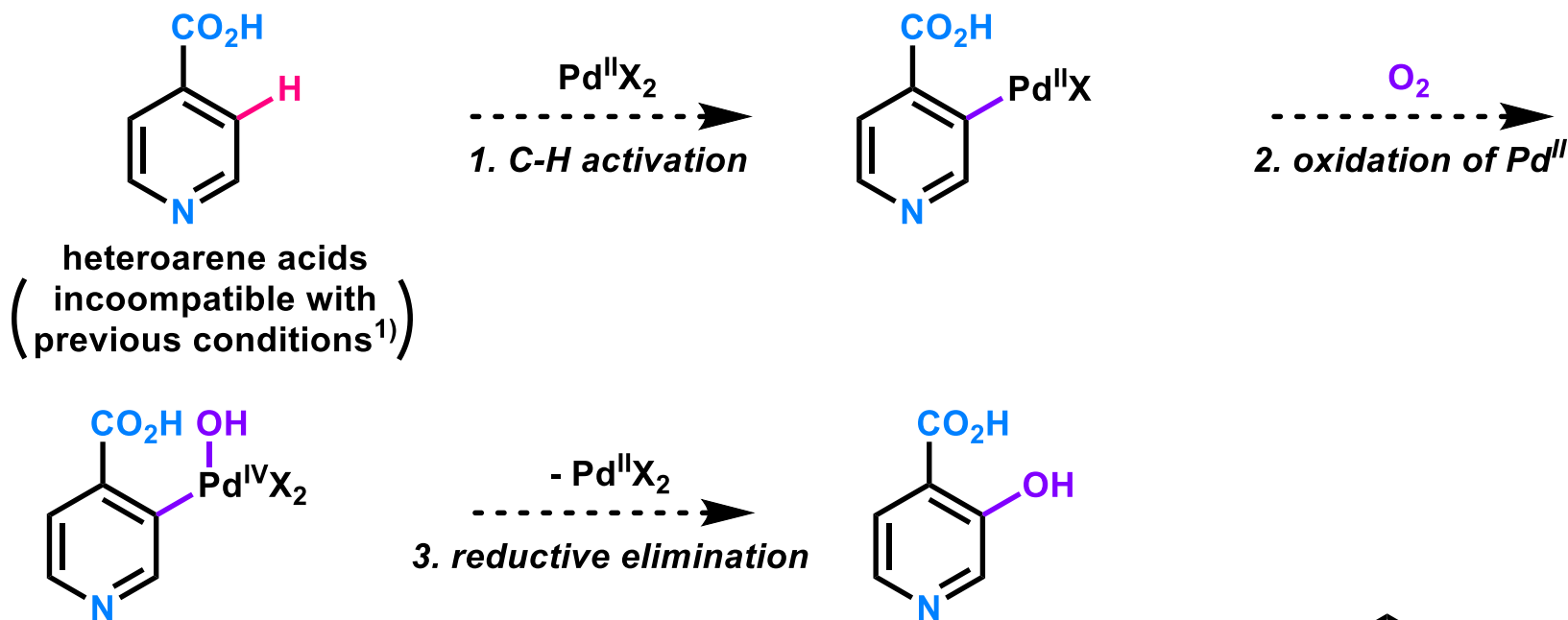


relative rate constant of (diimine)PtMe₂ with O₂ (1 atm).



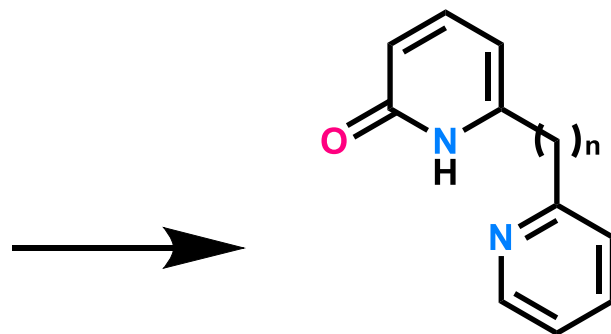
The rate of oxidation of Pt(II) is influenced by electronic and steric characters of ligands.

Working Hypothesis



Problem

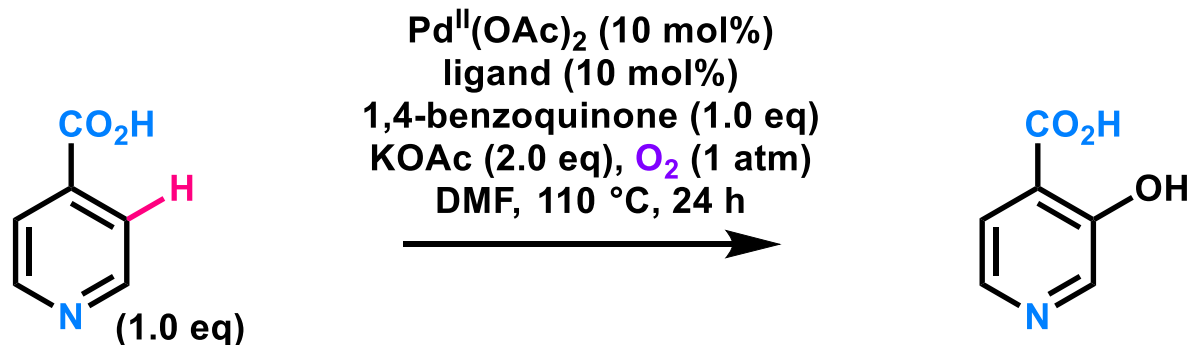
1. Slow C-H activation with electron-deficient arenes
→ use of pyridone ligand²⁾
2. Slow oxidation of Pd^{II}
→ use of electron-donating bidentate ligand³⁾



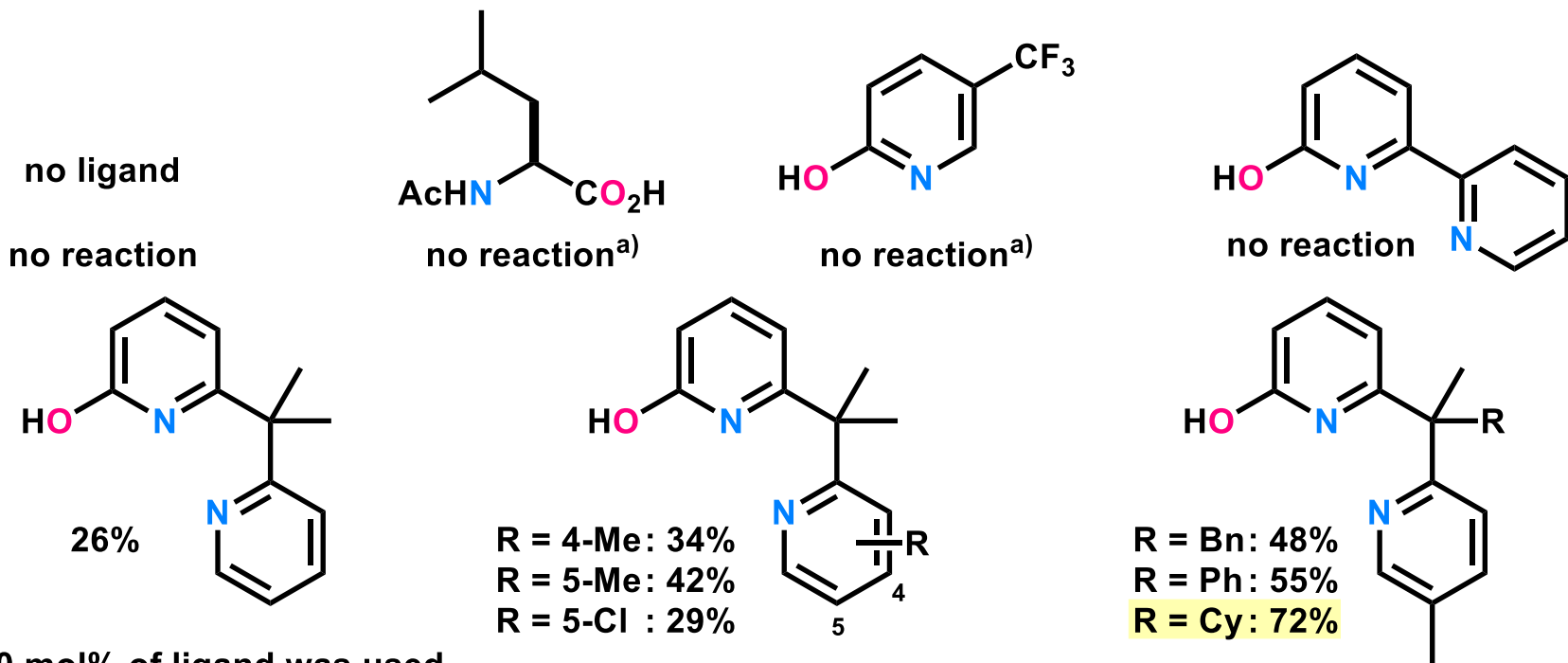
pyridine-pyridone ligand (n = 0, 1)

1) Wang, P.; Verma, P.; Xia, G.; Shi, J.; Qiao, J. X.; Tao, S.; Cheng, P. T. W.; Poss, M. A.; Farmer, M. E.; Yeung, K.-S.; Yu, J.-Q. *Nature* **2017**, 23, 551. 2) Rostovtsev, V. V.; Henling, L. M.; Labinger, J. A.; Bercaw, J. E. *Inorg. Chem.* **2002**, 41, 3608. 3) Li, Z.; Wang, Z.; Chekshin, N.; Qian, S.; Qiao, J. X.; Cheng, P. T.; Yeung, K.-S.; Ewing, W. R.; Yu, J.-Q. *Science* **2021**, 372, 1452.

Screening of Ligands

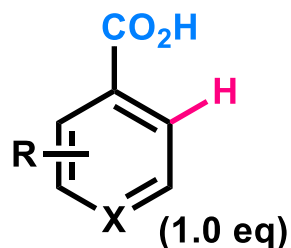


The yield was determined by ^1H NMR using 1,3,5-trimethoxybenzene as the internal standard.

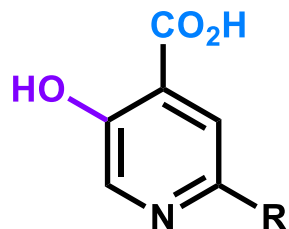
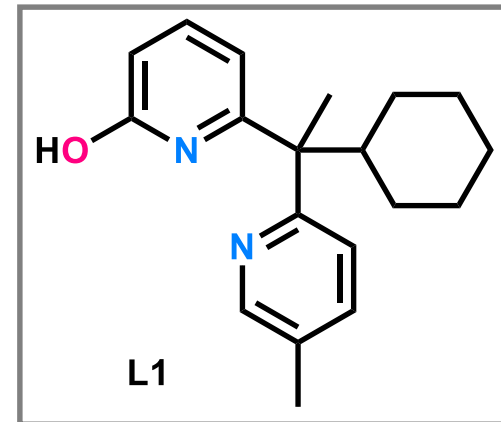
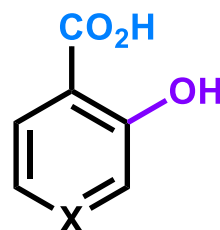


a) 20 mol% of ligand was used.

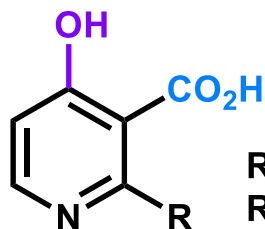
Substrate Scope (1)



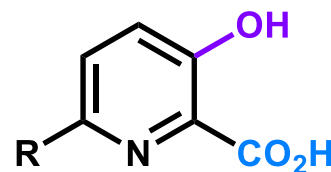
$\text{Pd}^{\text{II}}(\text{OAc})_2$ (10 mol%)
 L1 (10 mol%)
 1,4-benzoquinone (1.5 eq)
 KOAc (2.0 eq), O_2 (1 atm)
 DMF , 110°C , 24 h



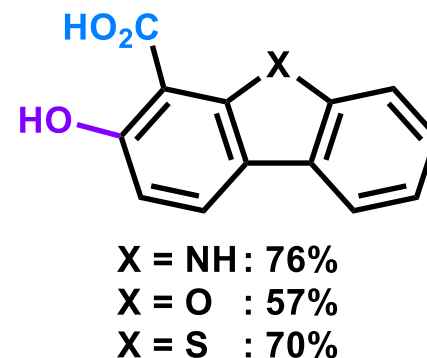
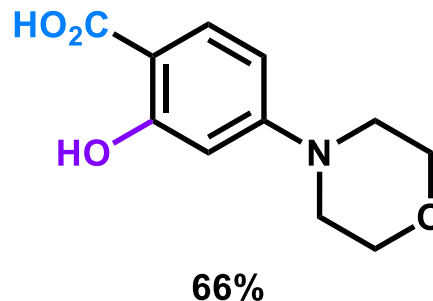
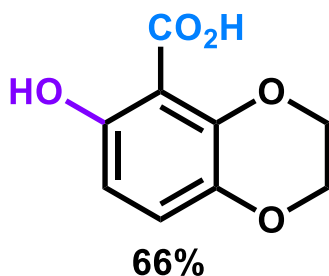
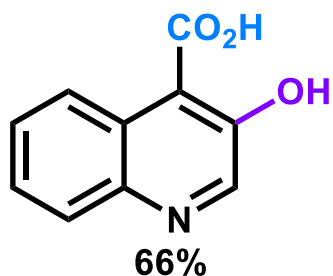
$\text{R} = \text{H}$: 72%
 $\text{R} = \text{CF}_3$: 76%
 $\text{R} = t\text{-Bu}$: 52%
 $\text{R} = \text{Cl}$: 67%



$\text{R} = \text{Me}$: 75%
 $\text{R} = \text{CF}_3$: 81%

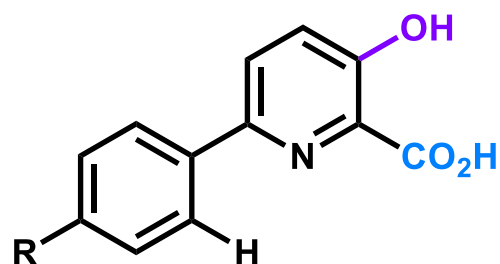
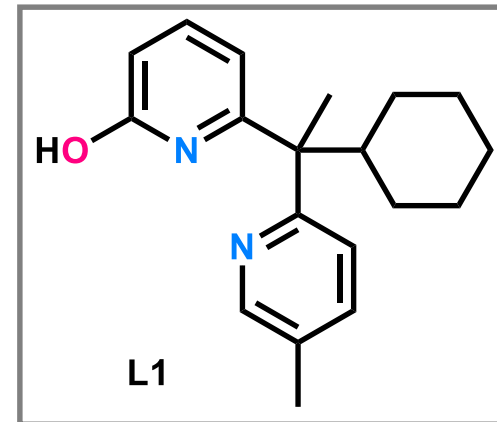
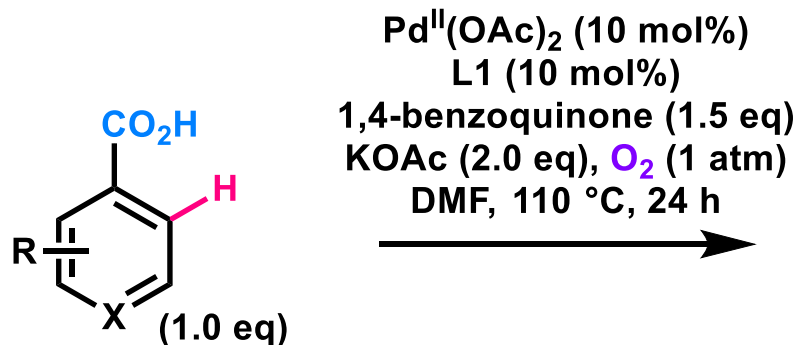


$\text{R} = \text{Me}$: 54%
 $\text{R} = \text{OMe}$: 61%
 $\text{R} = \text{CF}_3$: 70%

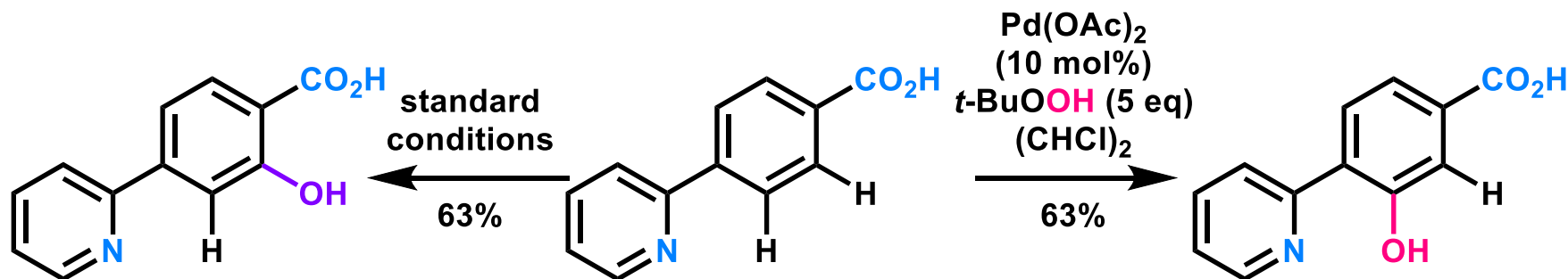
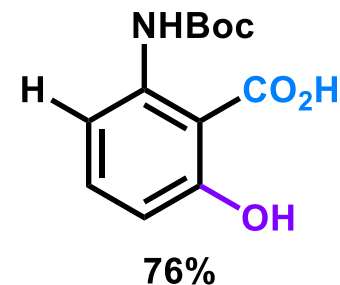
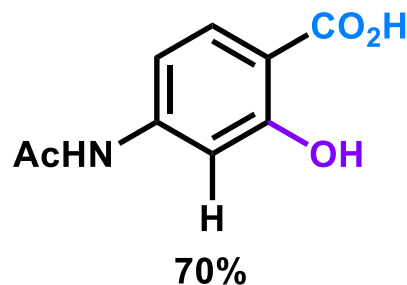


$\text{X} = \text{NH}$: 76%
 $\text{X} = \text{O}$: 57%
 $\text{X} = \text{S}$: 70%

Substrate Scope (2)

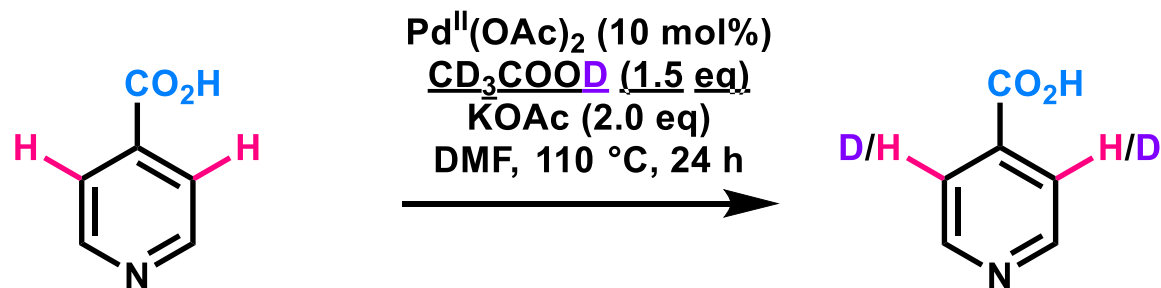


$\text{R} = \text{H}$: 52%
 $\text{R} = \text{Me}$: 63%
 $\text{R} = \text{OMe}$: 65%
 $\text{R} = \text{CF}_3$: 79%



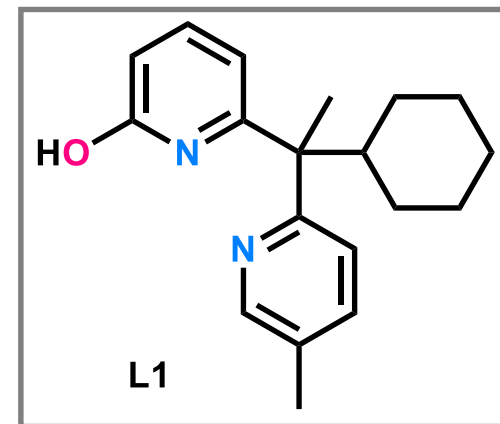
Mechanistic Study

1) Deuterium-labelling experiment

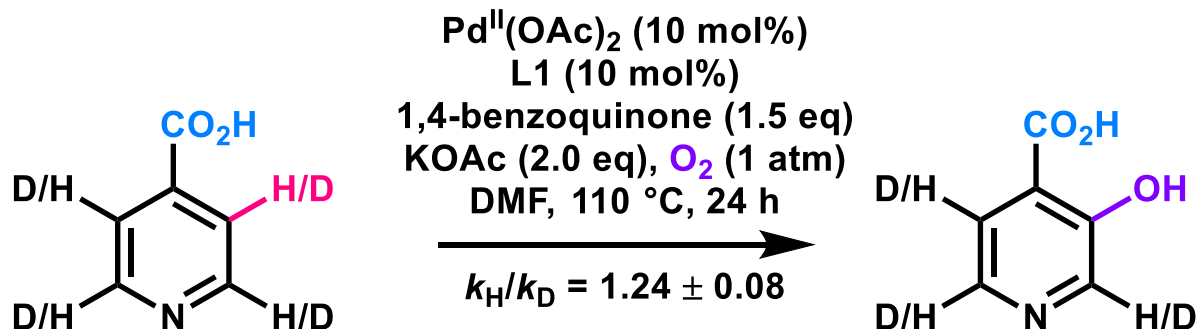


(1.0 eq)

w/o ligand : 0% D incorporation
10 mol% L1: 42% D incorporation



2) Kinetic isotope effect (KIE) experiment

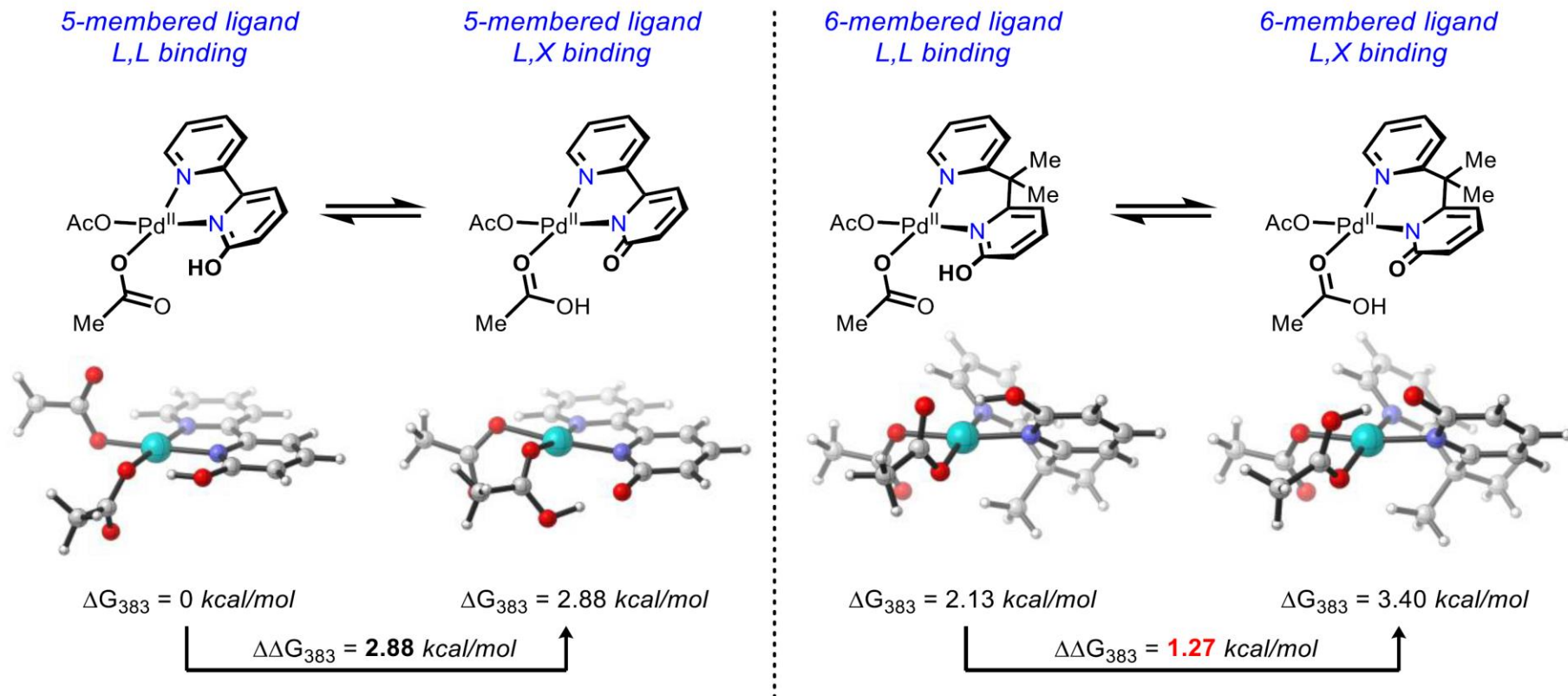


(1.0 eq)

$$k_H/k_D = 1.24 \pm 0.08$$

DFT Calculation (1)

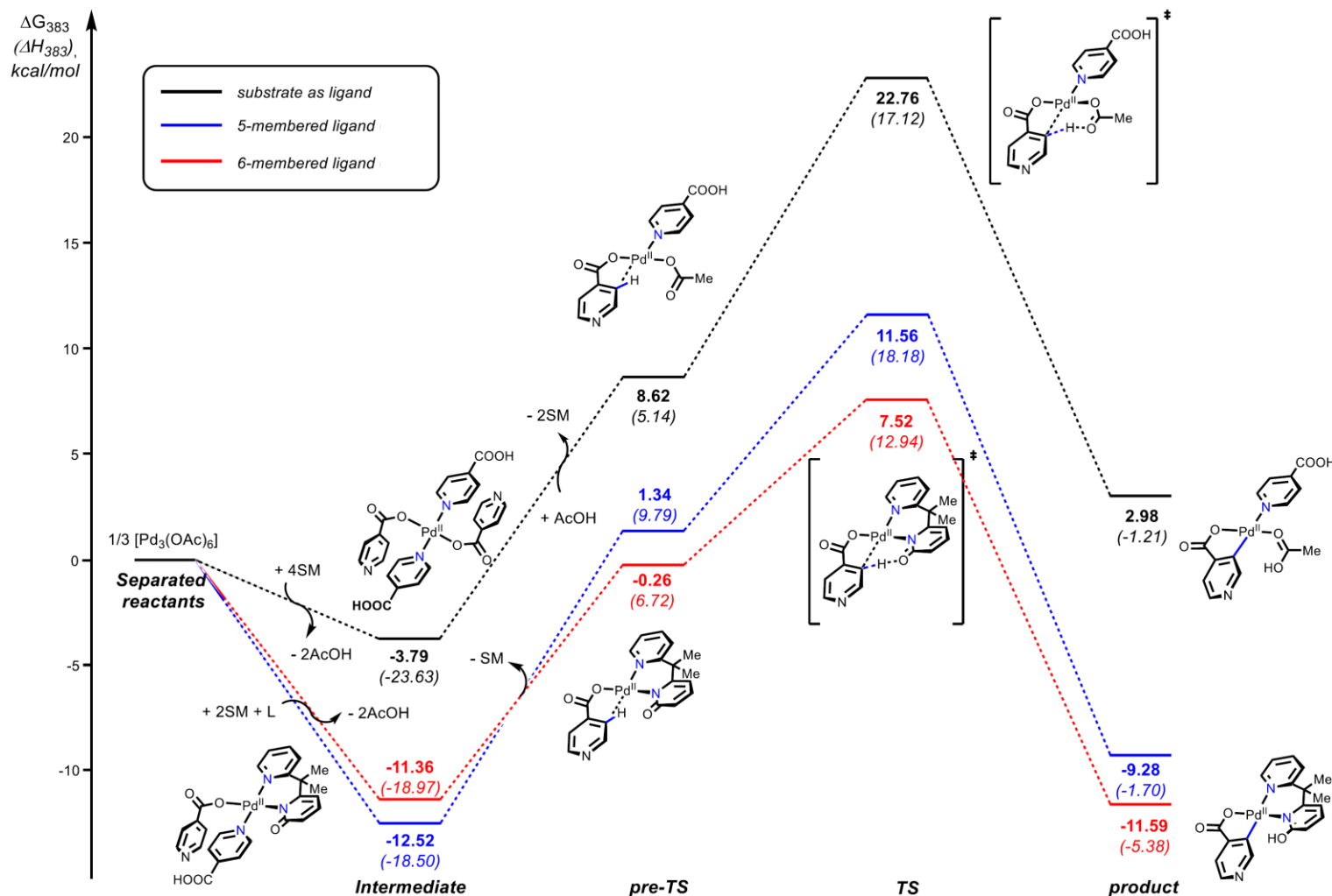
1) Binding modes of bidentate ligand



Calculations were conducted at the $\text{SMD}_{\text{DMF}}\text{-M06/6-311++G(d,p)/SDD(Pd)}/\text{SMD}_{\text{DMF}}\text{-B3LYP-D3(BJ)/6-31+G(d,p)/SDD(Pd)}$ level of theory.

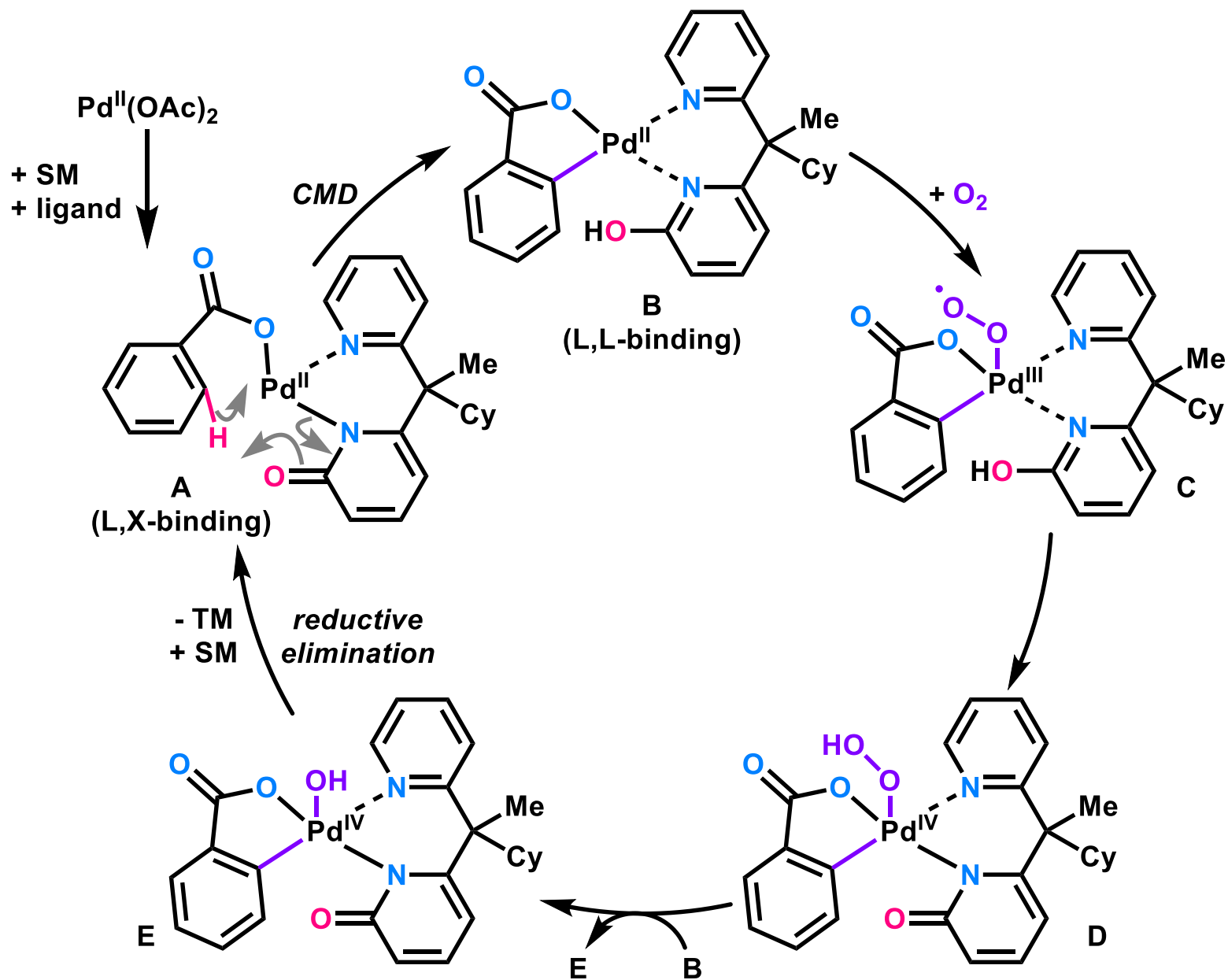
DFT Calculation (2)

2) Energy profiles on the C-H cleavage step



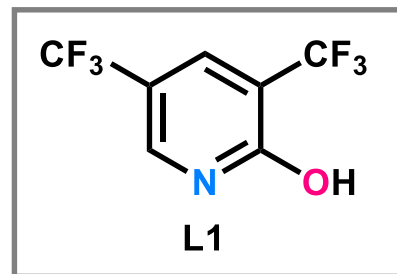
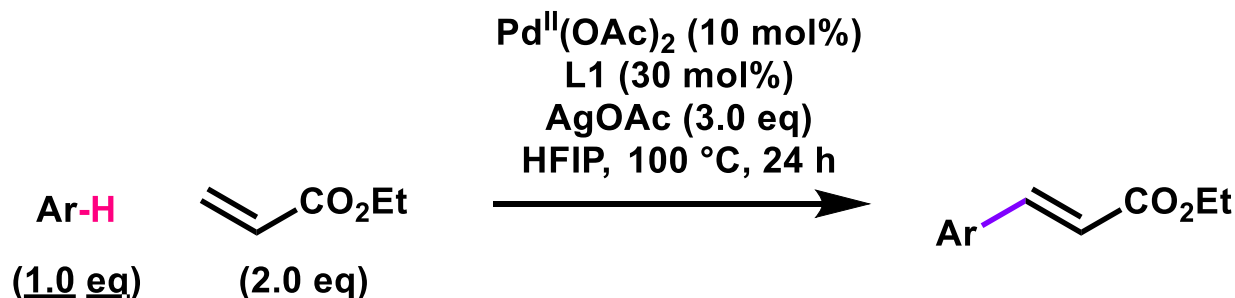
Calculations were conducted at the SMD_{DMF}-M06/6-311++G(d,p)/SDD(Pd)//SMD_{DMF}-B3LYP-D3(BJ)/6-31+G(d,p)/SDD(Pd) level of theory.

Proposed Mechanism

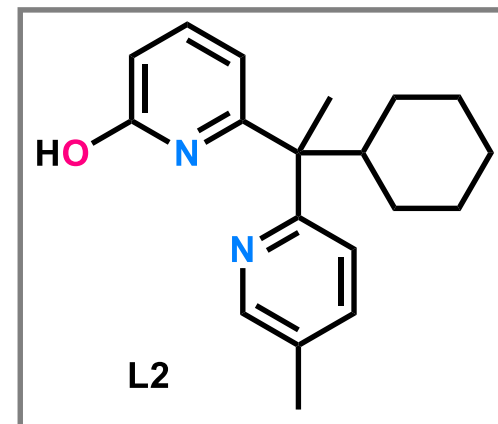
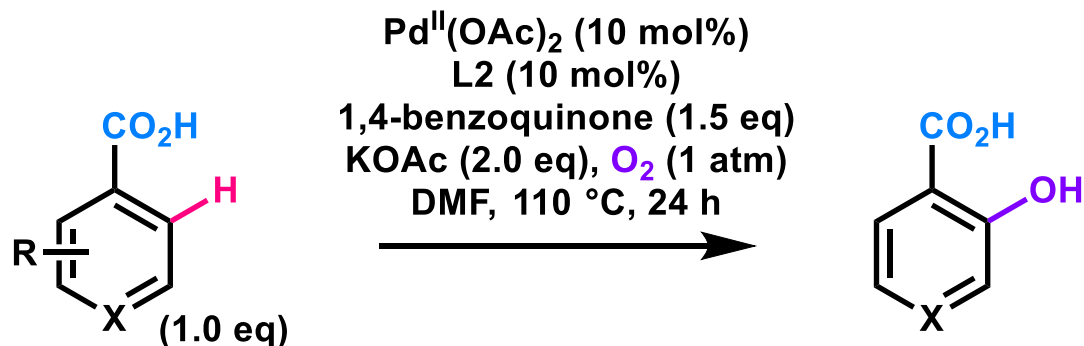


Summary

1. Non-directed C-H alkenylation (Yu, 2017)¹⁾



2. Directed C-H hydroxylation with molecular oxygen (Yu, 2021)²⁾



1) Wang, P.; Verma, P.; Xia, G.; Shi, J.; Qiao, J. X.; Tao, S.; Cheng, P. T. W.; Poss, M. A.; Farmer, M. E.; Yeung, K.-S.; Yu, J.-Q. *Nature* **2017**, 23, 551. 2) Li, Z.; Wang, Z.; Chekshin, N.; Qian, S.; Qiao, J. X.; Cheng, P. T.; Yeung, K.-S.; Ewing, W. R.; Yu, J.-Q. *Science* **2021**, 372, 1452.