

C(sp³)-H Arylation of Free Alcohols Enabled by Hydrogen-Bond-Acceptor Ligands

2023/11/4 Yuya Shiga

Contents

1. Introduction

**2. C(sp³)–H arylation of free alcohols enabled by hydrogen-bond-acceptor ligands
(Yu, 2023)**

Prof. Jin Quan Yu



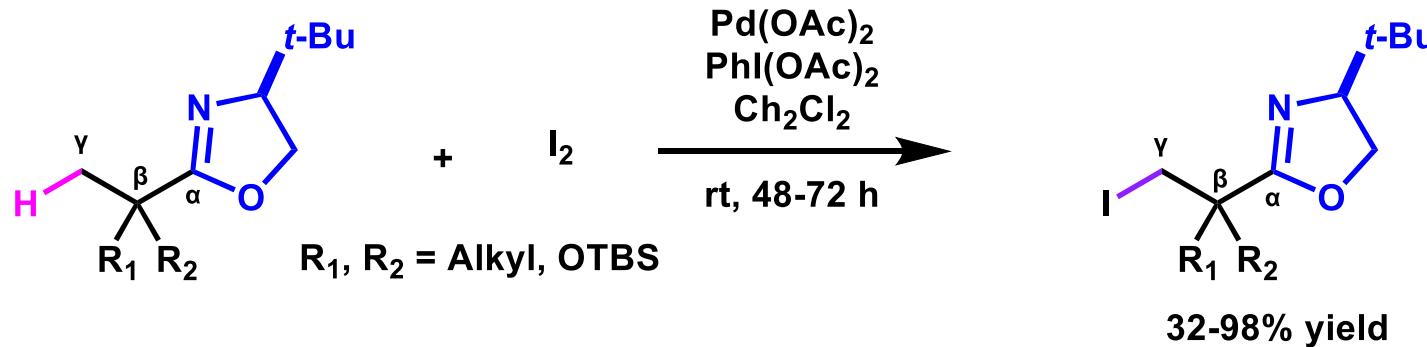
- 1982-1987 : East China Normal University
(B.Sc.) (Prof. L.-X. Dai and Prof. B. Q. Wu)**
- 1987-1988 : Shanghai Institute of Organic Chemistry**
- 1988-1900 : Guangzhou Institute of Chemistry (Prof. S.-D. Xiao)
(M.Sc.)**
- 1990-1994 : Teaching and research assistant
at Guangzhou Institute of Chemsitry**
- 1994-1999 : University of Cambridge (Prof. Jonathan B. Spencer)
(Ph.D.)**
- 1999-2003 : Junior Research Fellow of St. John's College
at University of Cambridge**
- 2001-2002 : Harberd 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 Profesor at Scripps Research Institute**
- 2010- : Professor at The Scripps Research Institute**

Reseach Topic:

- 1. Discovery and rational design of new reactions using C-H activation**
- 2. Synthetic applications for total synthesis**

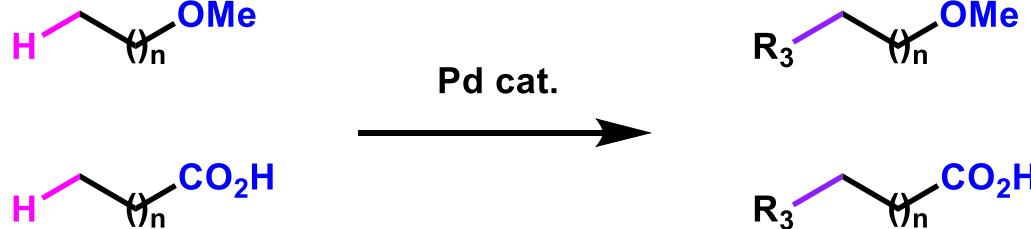
Directing Groups for Site-selective C–H Functionalization

1. Previously designed strong directing groups (DG)



Strong coordination of oxazoline to Pd^{II} enhances reactivities and site-selectivities.
However, it is necessary to install and remove specialized strong directing groups (DG).

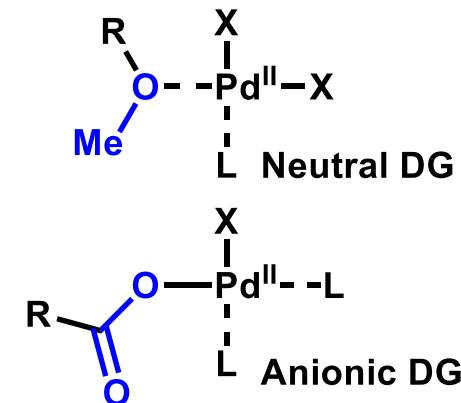
2. The use of native functional groups for the DGs



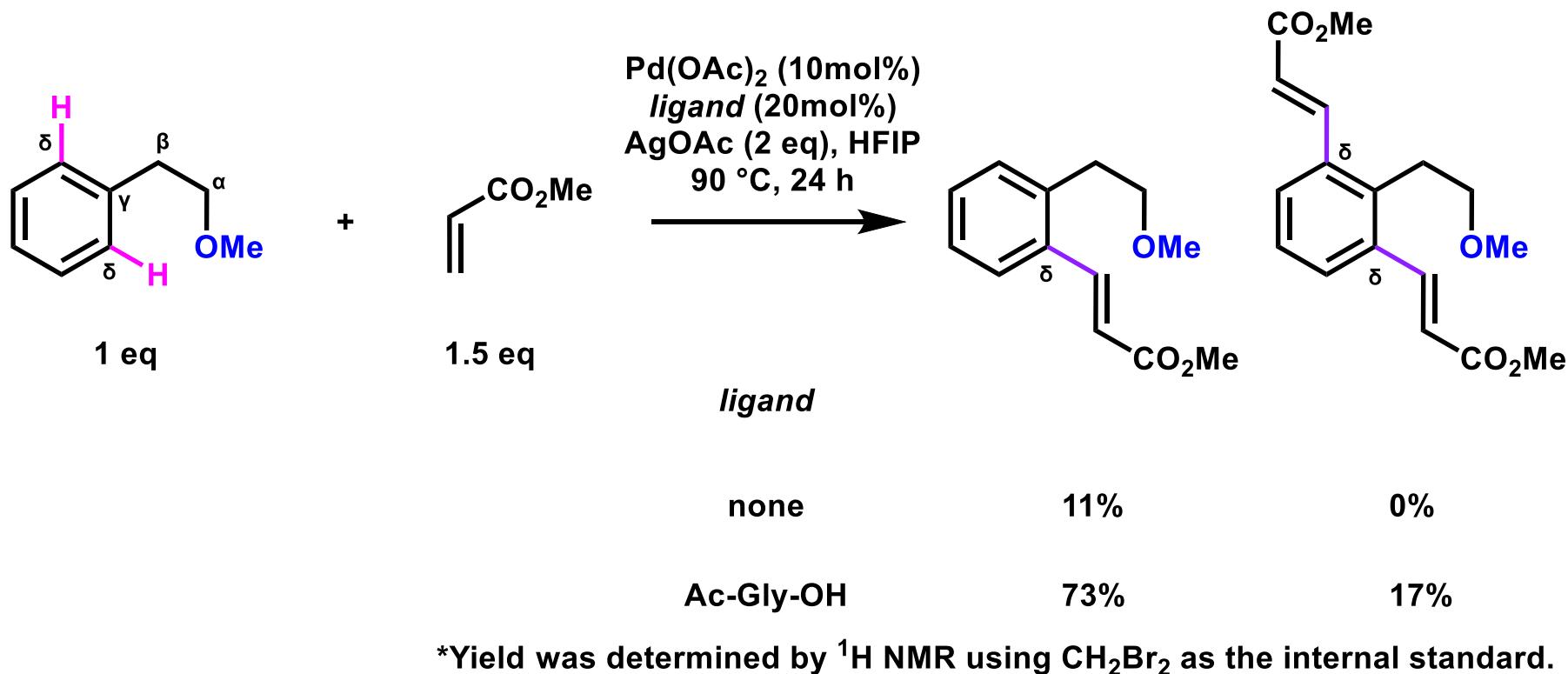
It is unnecessary to install and remove directing groups .

Problems

The weak coordinative ability of these functional groups to Pd(II).

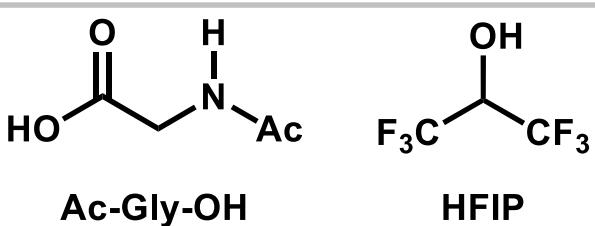


Ligands for Neutral Directing Groups (X,X Ligands)

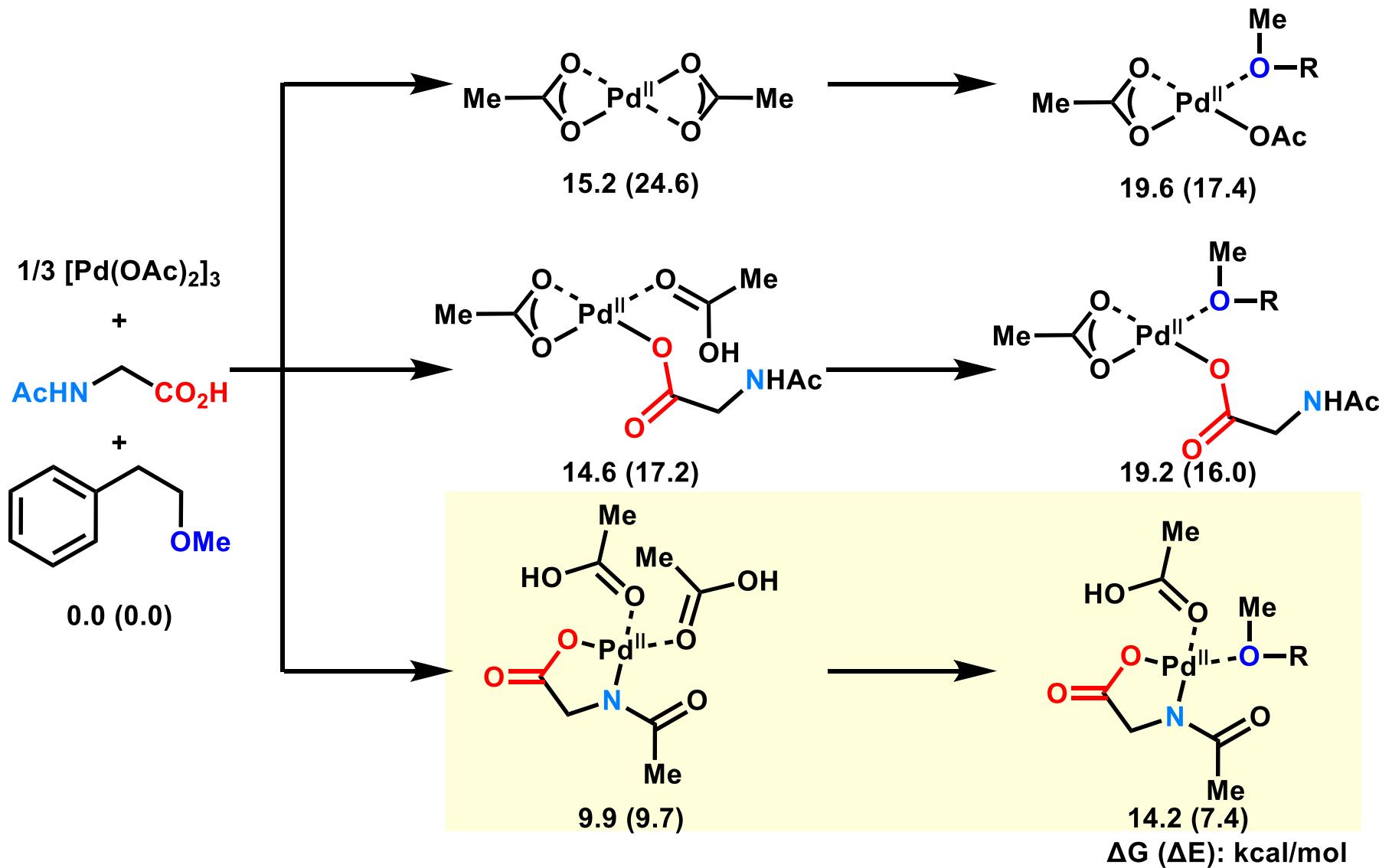


OMe acts as a neutral DG.

Mono Protected Amino Acid (MPAA) accelerates the reaction.

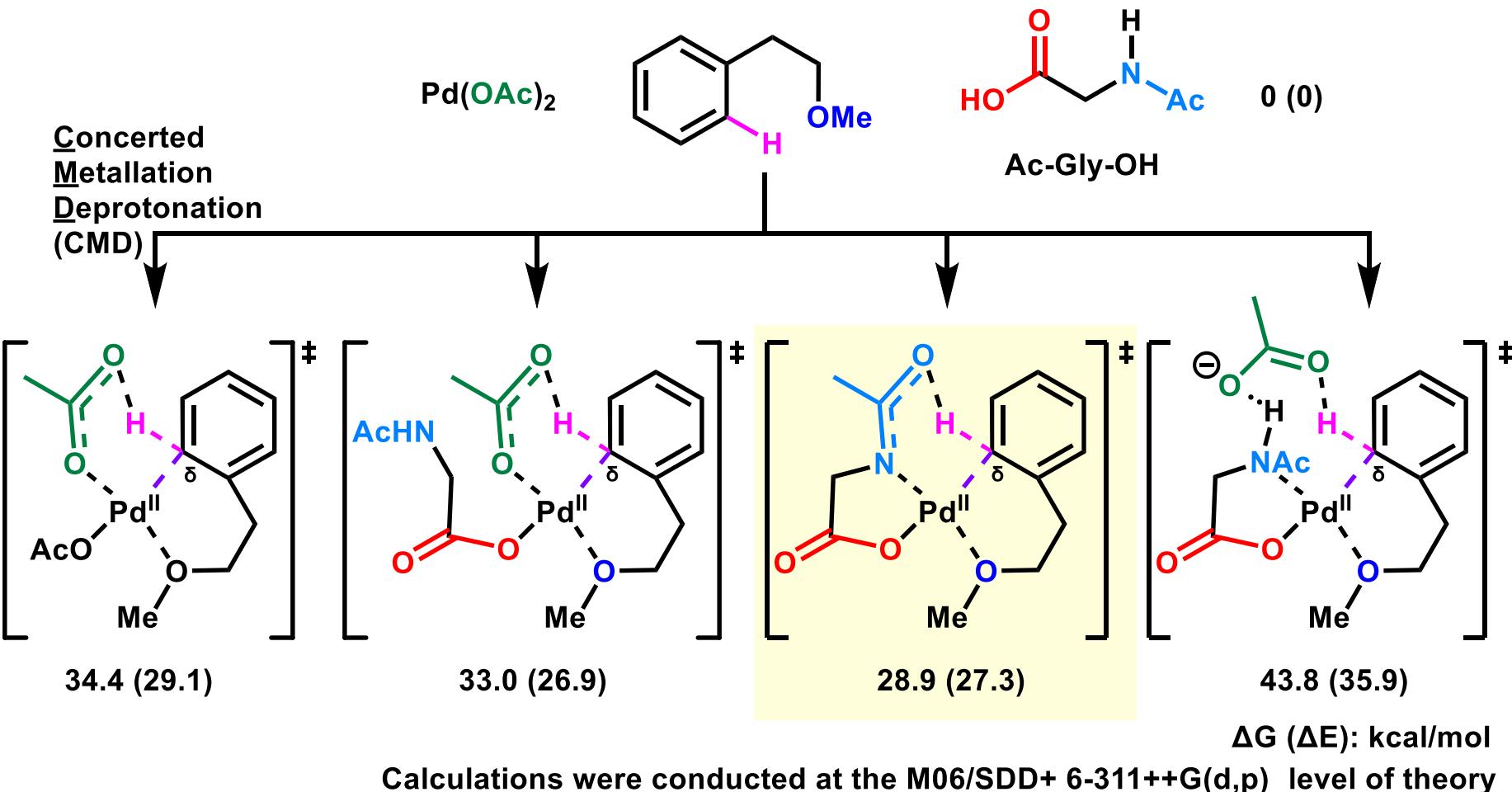


Computation Study of Reaction Mechanism (1)



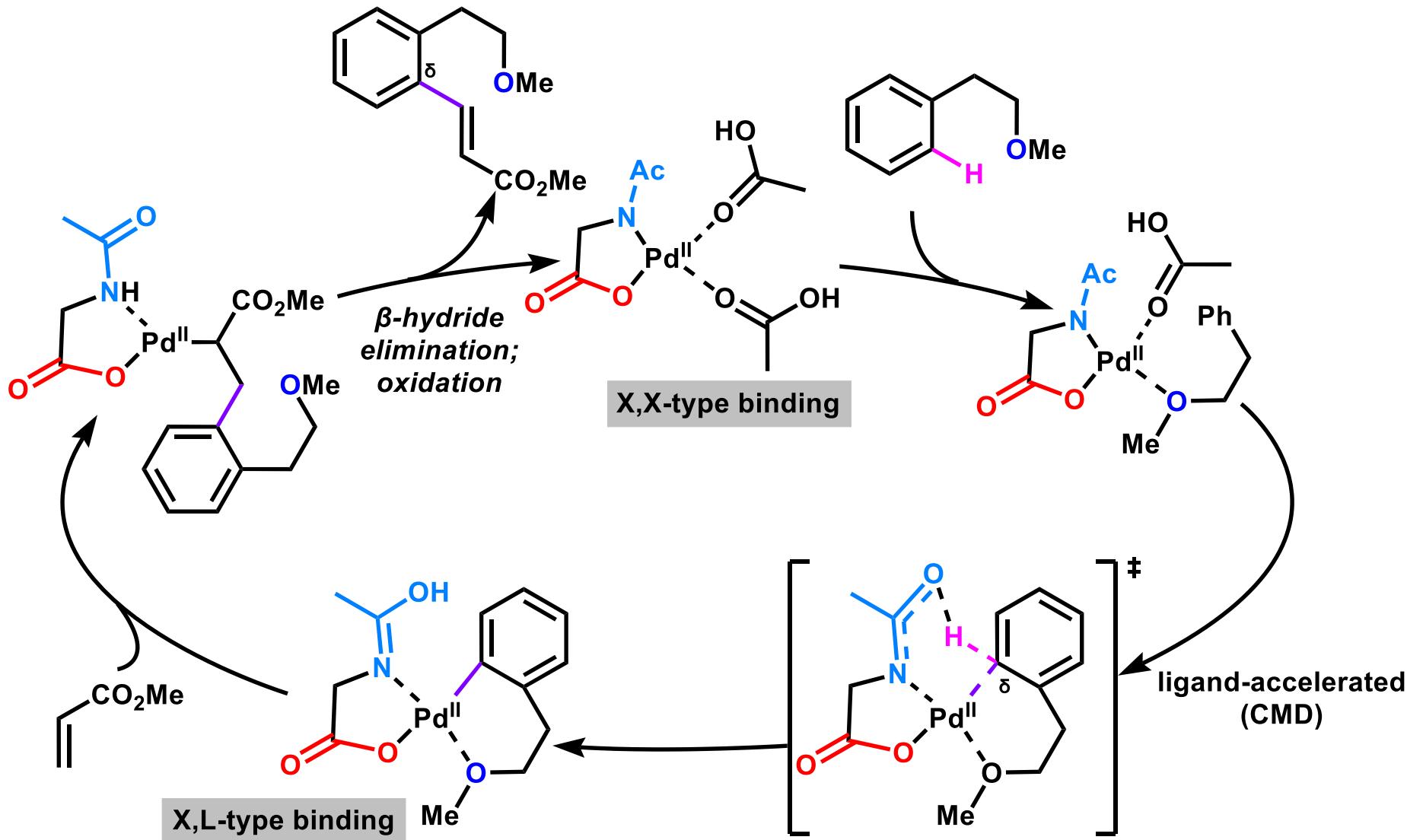
Calculations were conducted at the M06/SDD+ 6-311++G(d,p) level of theory

Computation Study of Reaction Mechanism (2)

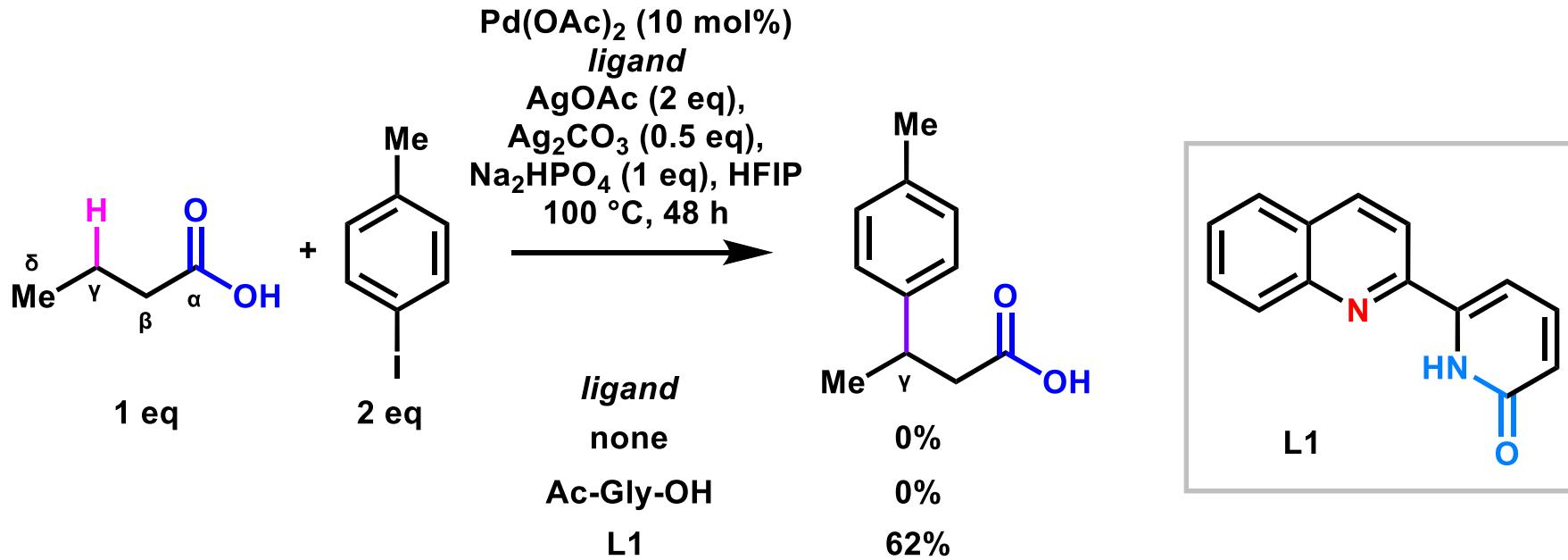


N-Acyl groups accelerate CMD step, acting as a base to deprotonate the C–H bond.

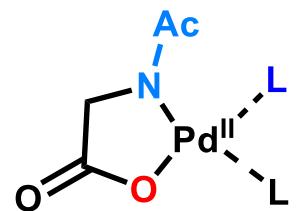
Proposed Reaction Mechanism (X,X Ligands)



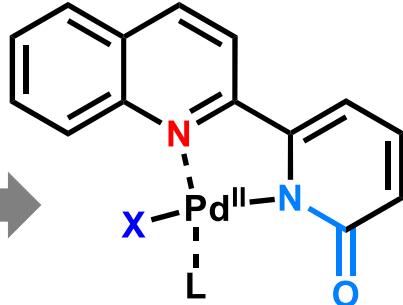
Ligand for Anionic Directing Groups (L,X Ligands)



Ligands type

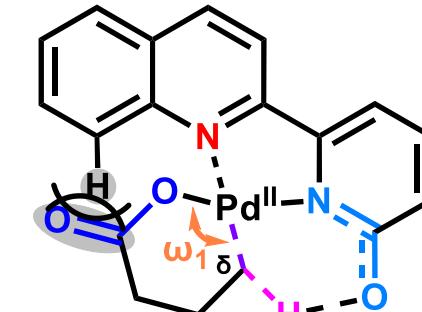


MPAA
bisanionic chelates
(X,X type binding)

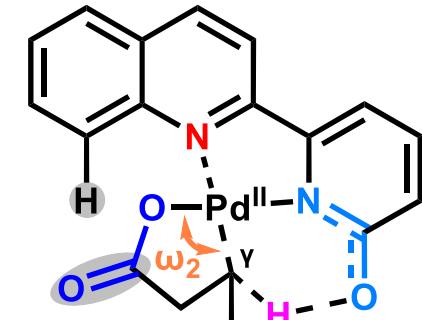


L1
monoanionic chelates
(L,X type binding)

Site selectivity



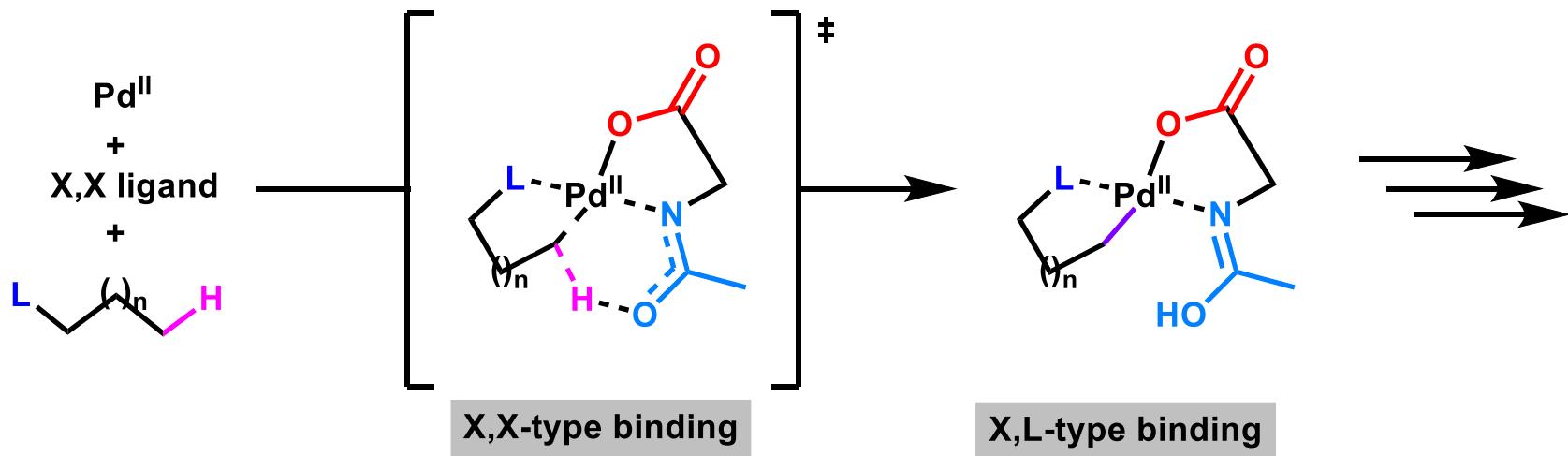
$\omega_1 > \omega_2$
5 membered palladacycle
is more favored



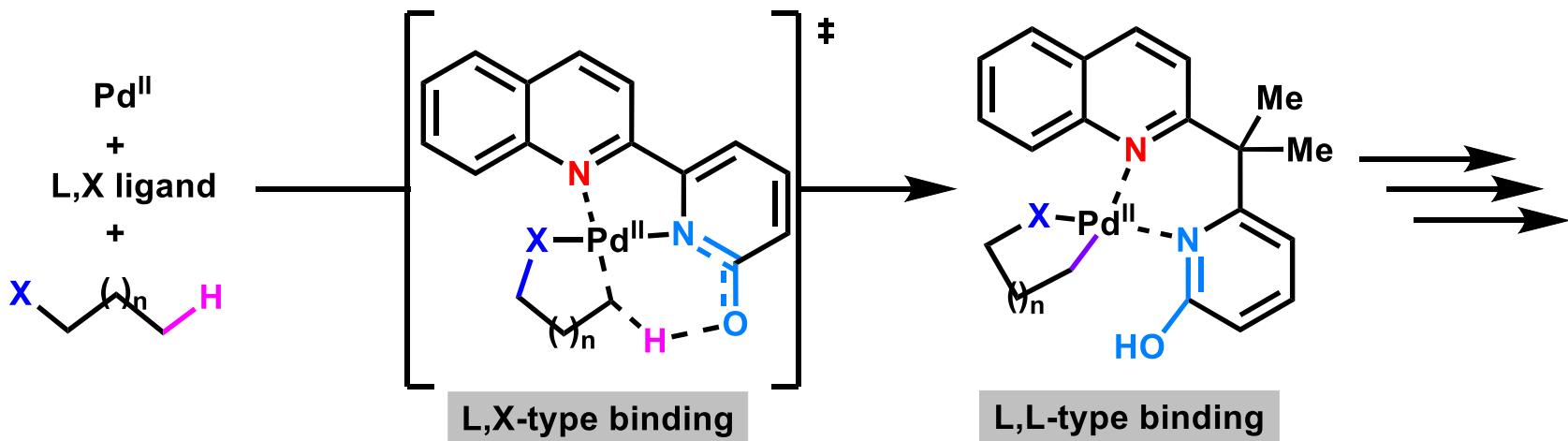
favored

Short Summary

1. Bisanionic X,X ligand are useful for neutral directing group¹⁾



2. Monoanionic L,X ligand are useful for anionic directing group²⁾



1) Li, G.; Leow, D.; Wan, L.; Yu, J.Q.; *Angew. Chem. Int. Ed.* **2013**, 52, 1245.

2) Hu, L.; Meng, G.; Yu, J.Q.; *J. Am. Chem. Soc.* **2022**, 144, 20550.

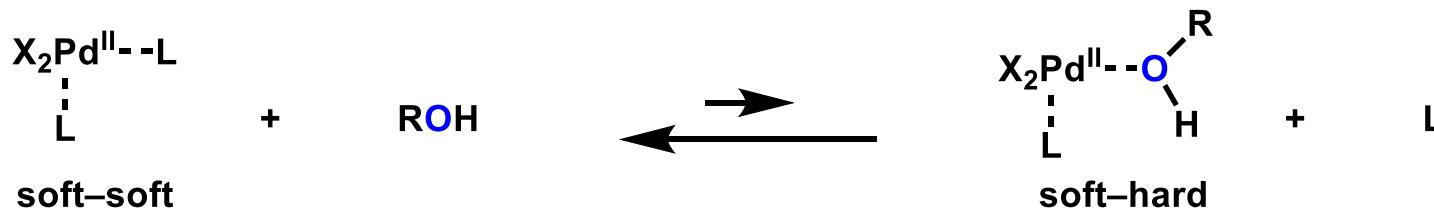
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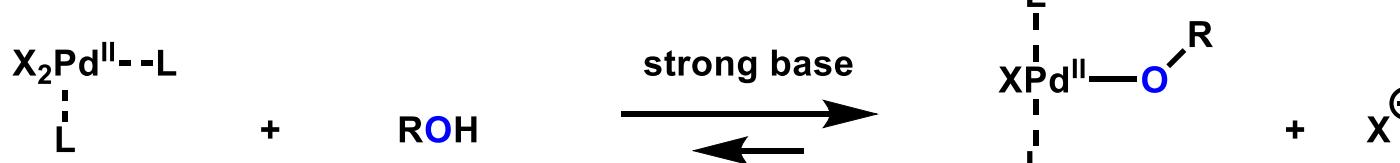
Alcohols as Directing Groups

1. Neutral (L-type) coordination



The binding affinity of neutral alcohol to Pd^{II} is low.¹⁾

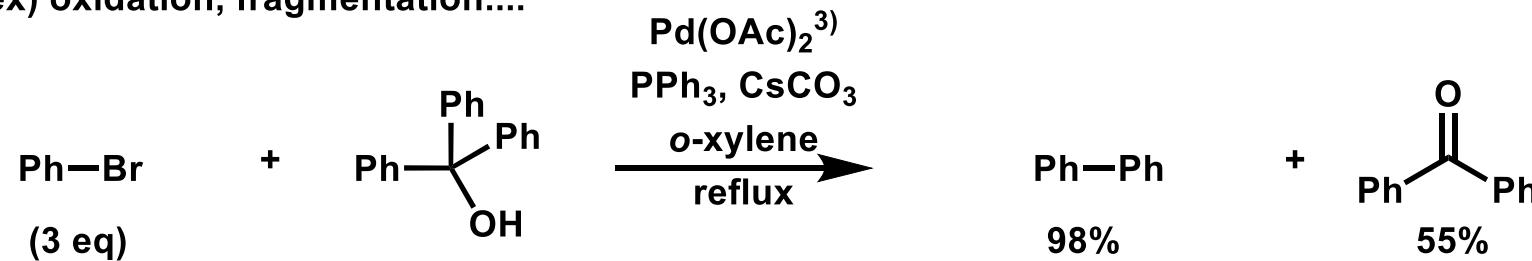
2. Anionic (X-type) coordination



The binding affinity of anionic alcohols (alkoxides) to Pd^{II} is higher than neutral alcohols.²⁾

However, Pd-alkoxides are prone to undesired side reactions.

ex) oxidation, fragmentation....

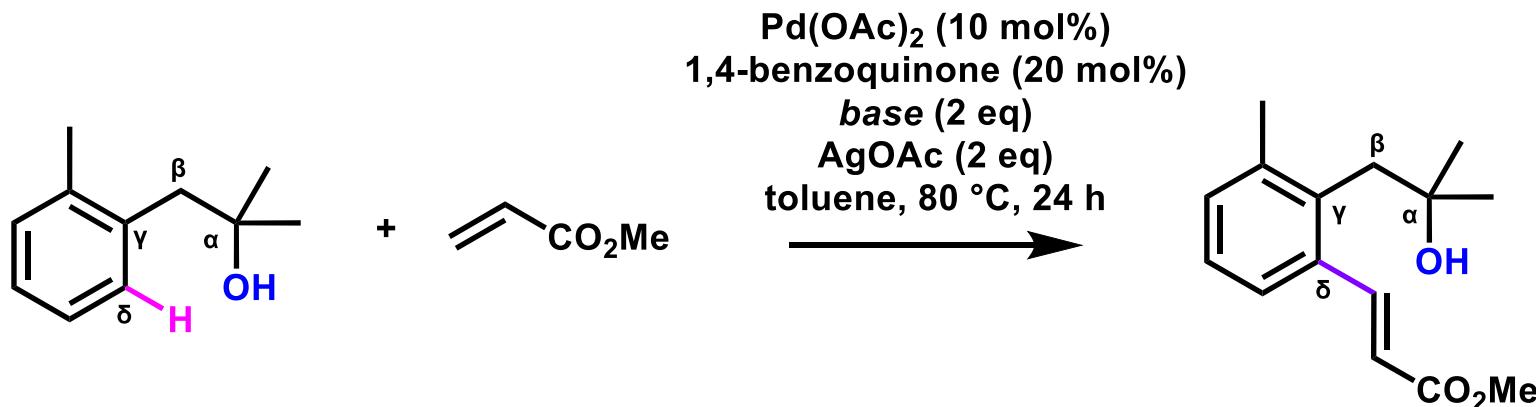


1) Mo, F.; Tabor, J.; Dong, G. *Chem. Lett.* **2014**, 43, 264.

2) Bryndza, H. E.; Tam, W. *Chem. Rev.* **1988**, 88, 1163.

3) Terao, Y.; Qakui, H.; Satoh, T.; Mirua, M.; Nomura, M. *J. Am. Chem. Soc.* **2001**, 123, 10407.

C(sp²)-H Activation Using Free Alcohol as Anionic Directing Groups

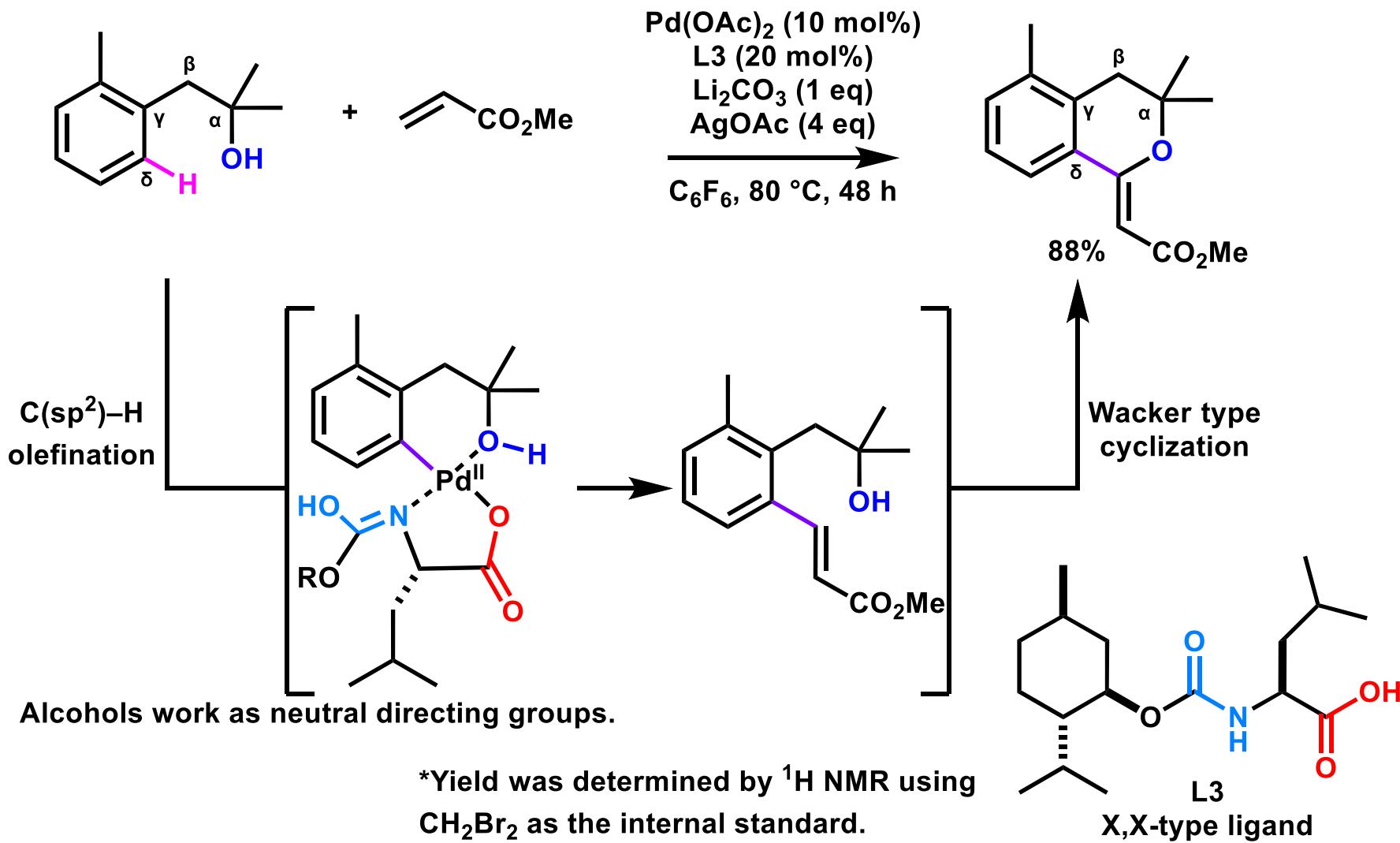


entry	base	yield*
1	Li ₂ CO ₃	16%
2	K ₂ CO ₃	1%
3	<i>t</i> -BuONa	0%
4	<i>t</i> -BuOLi	0%

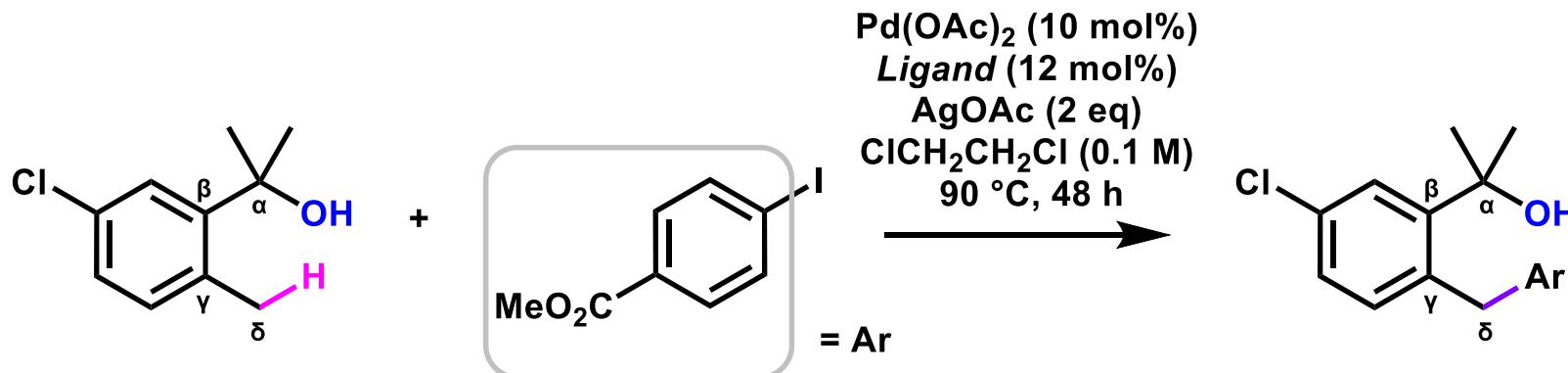
*Yield was determined by ¹H NMR using CH₂Br₂ as the internal standard.

Pd-Alcoxide coordinations are not useful as directing groups.

C(sp²)-H Activation Using Free Alcohols as Neutral Directing Groups



C(sp³)-H Arylation of Free Alcohol with X,X Ligands



Ligand

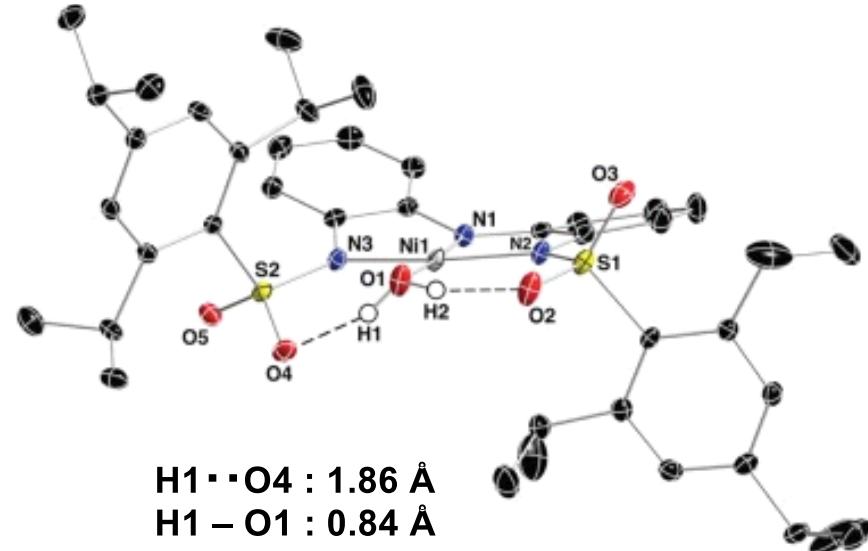
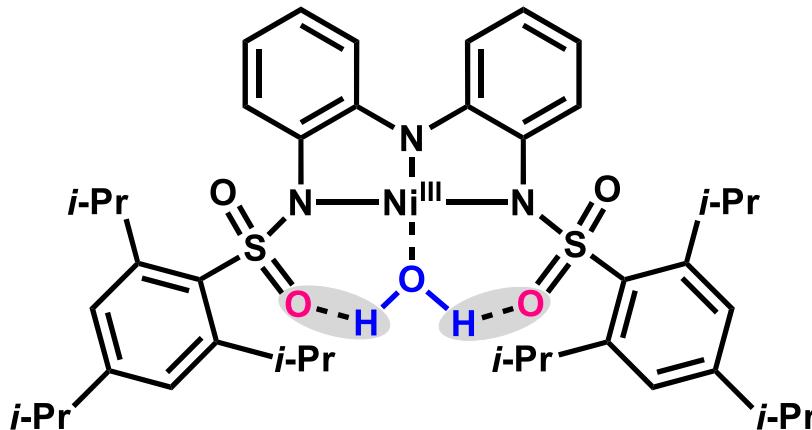
none			
4%			
	3%	R = Me : 6% R = OMe : 2%	3%

X,X ligands do not work well in C(sp³)-H activation.

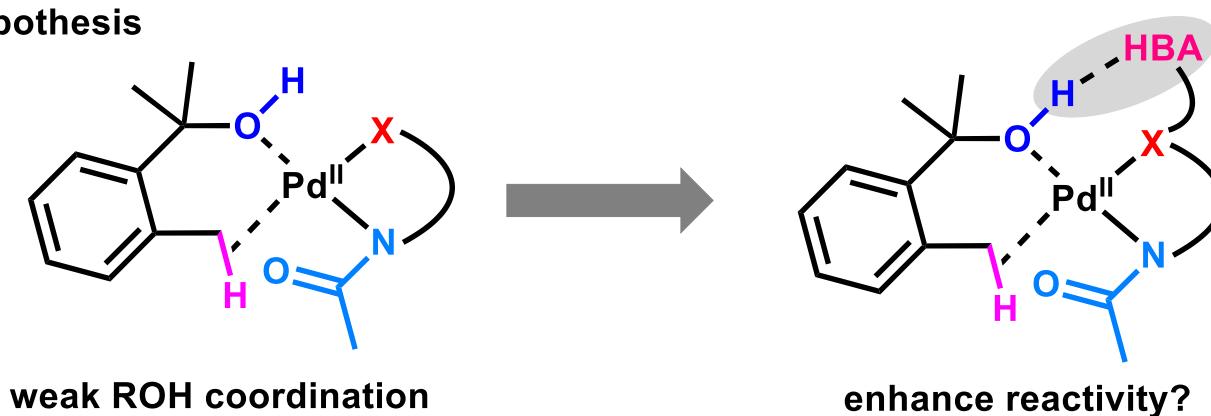
→ The development of new ligands that enhance coordination of neutral alcohol to Pd is necessary.

New Ligand Design Based on Intramolecular Hydrogen Bond

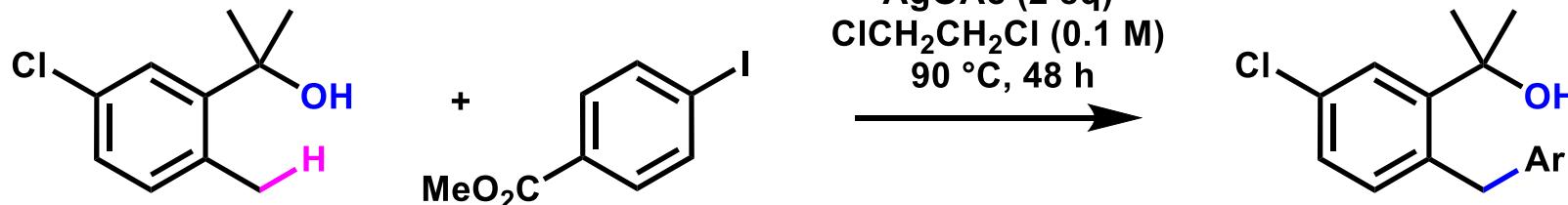
Stabilization of a transition metal-aqua complex via intramolecular hydrogen bonds



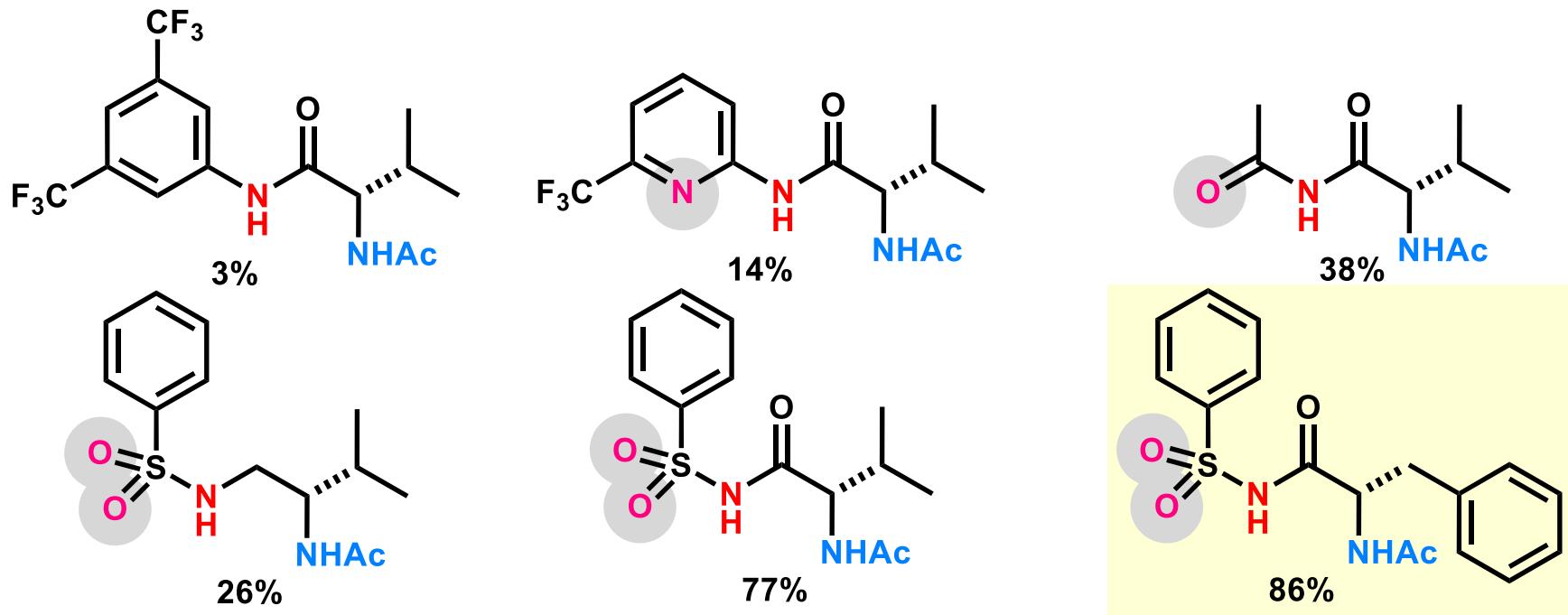
Working hypothesis



Ligands Screening with Potential HBAs Moiety



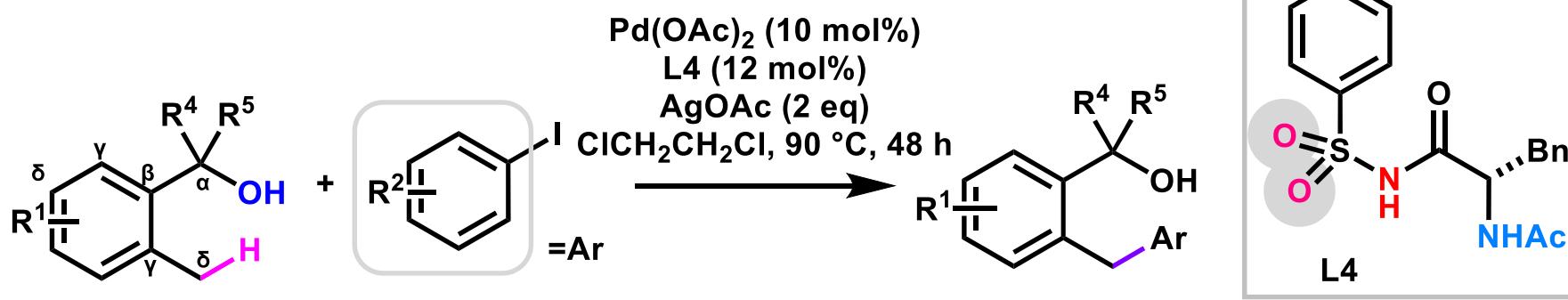
Ligand



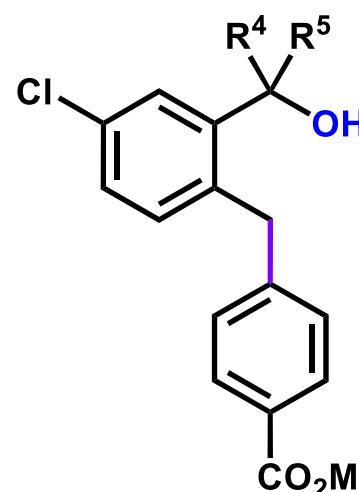
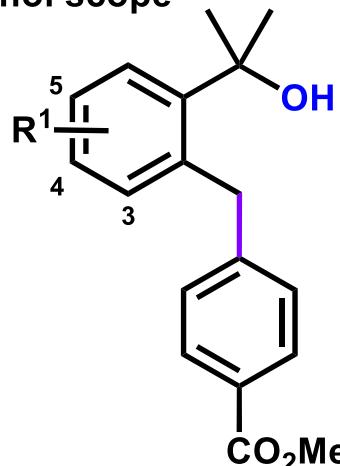
Ligands bearing potential HBAs improve yield

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

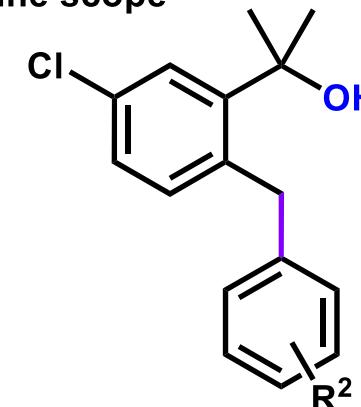
Substrate Scope (1)



alcohol scope



aryl iodine scope



$\text{R}^1 = 5\text{-CF}_3$

56%

$\text{R}^1 = 5\text{-OMe}$

not detected

$\text{R}^1 = 3\text{-Cl}$

37%

$\text{R}^1 = 4\text{-Cl}$

54%*

$\text{R}^4, \text{R}^5 = \text{Et}$

42%**

$\text{R}^2 = p\text{-CO}_2\text{Me}$

72%

(\pm) $\text{R}^4 = \text{Me}, \text{R}^5 = \text{H}$

<5%**

$\text{R}^2 = p\text{-OMe}$

66%

$\text{R}^4, \text{R}^5 = \text{H}$

14%**

$\text{R}^2 = o\text{-Me}$

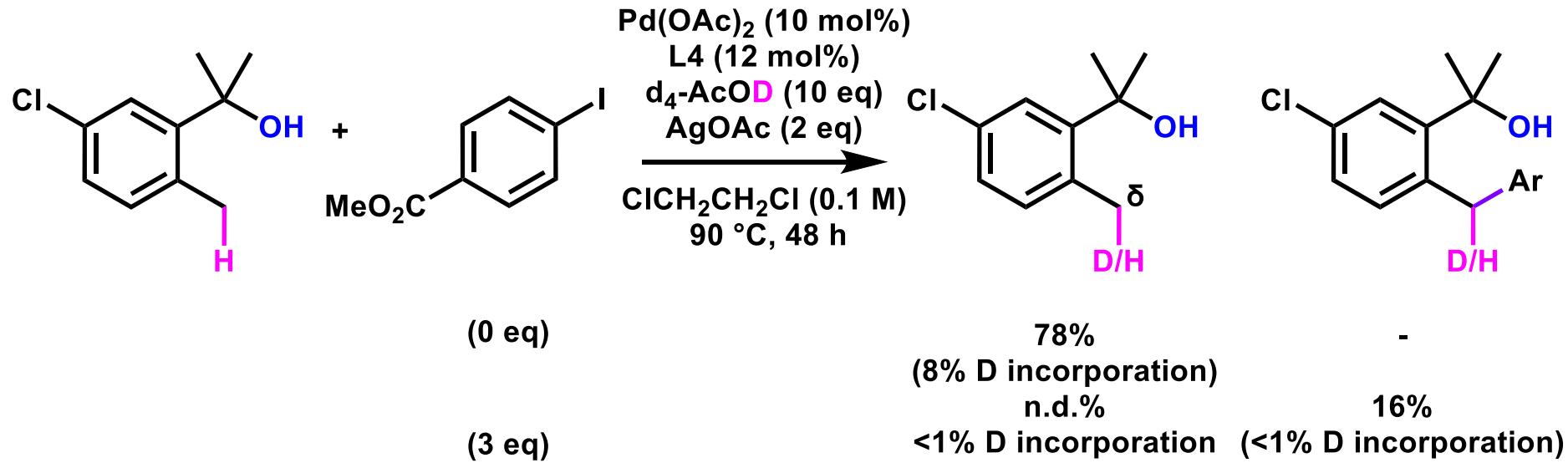
24%*

* Reaction run at 100°C , 3 days

**Reaction run at 85°C , 3 days

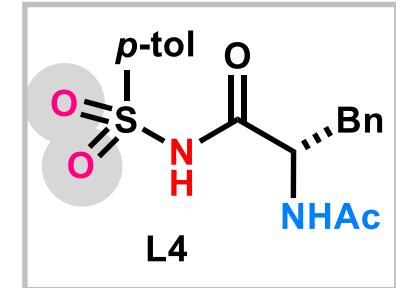
Yield was determined by ${}^1\text{H}$ NMR using CH_2Br_2 as the internal standard.

Mechanistic Study



**Without coupling partner, CH activation is reversible.
With coupling partner, CH activation is irreversible.**

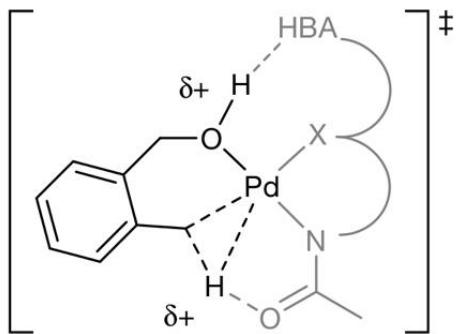
Kinetic data analysis reveals that the reaction rate is approximately 1st order in [alcohol]. (c.f. appendix)



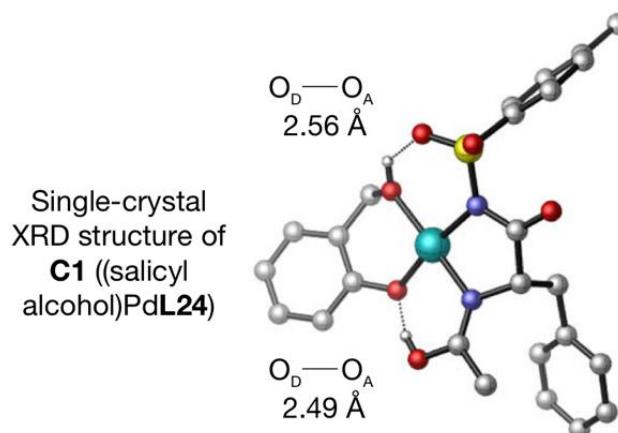
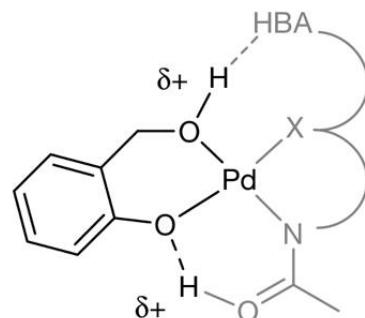
→ C-H activation is rate determining step.

X-Ray Crystallography

Proposed TS for benzylic CMD

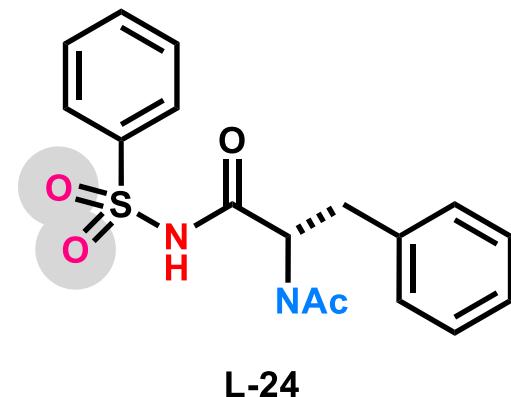
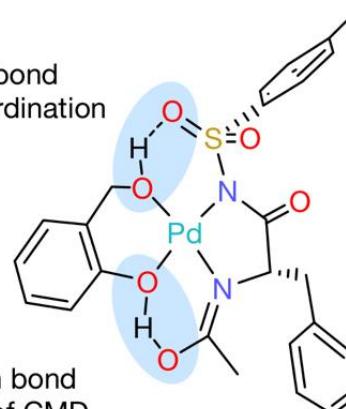


TS analogue salicyl alcohol



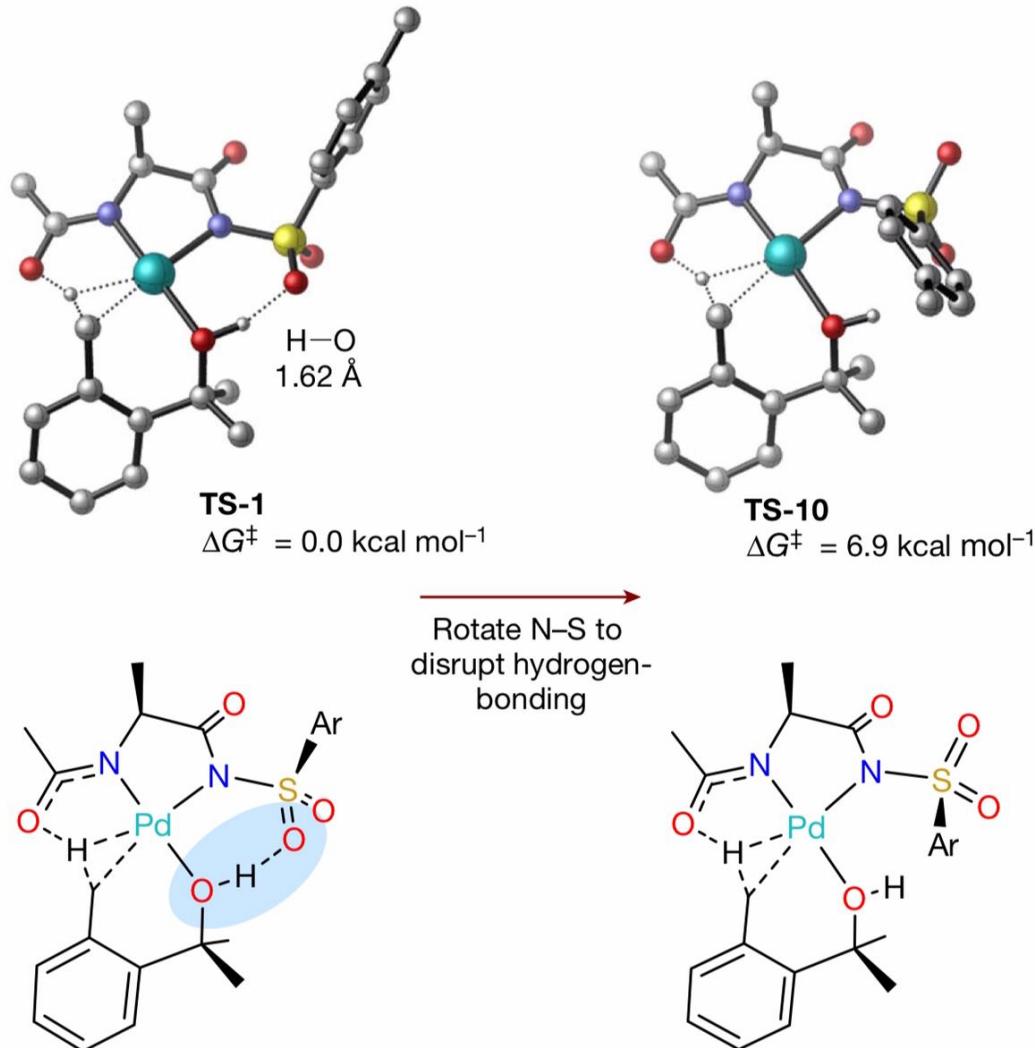
Hydrogen bond stabilizes coordination

Hydrogen bond analogue of CMD



Proposed hydrogen bond is observed at CMD immitating complex.

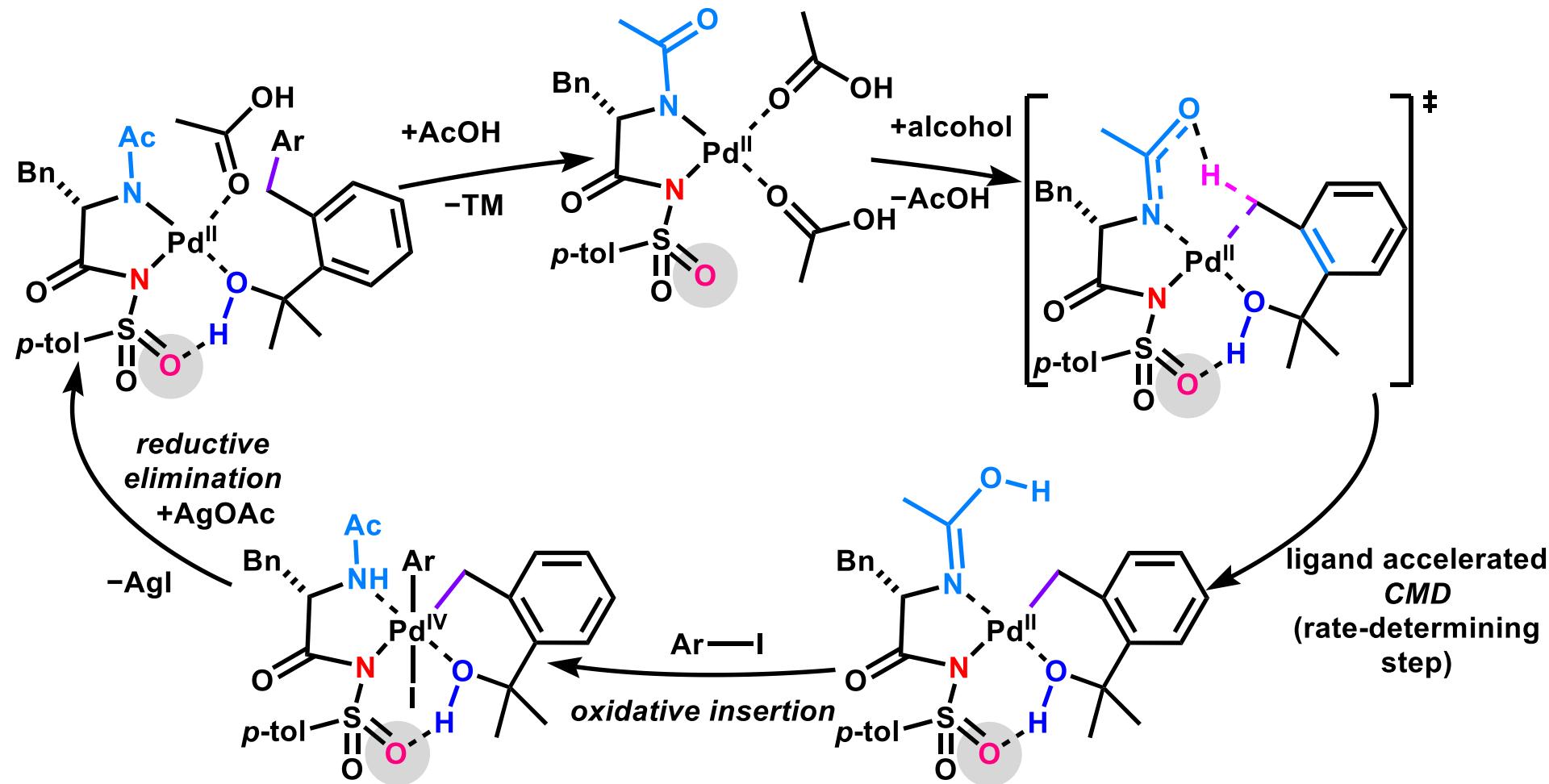
DFT Calculation



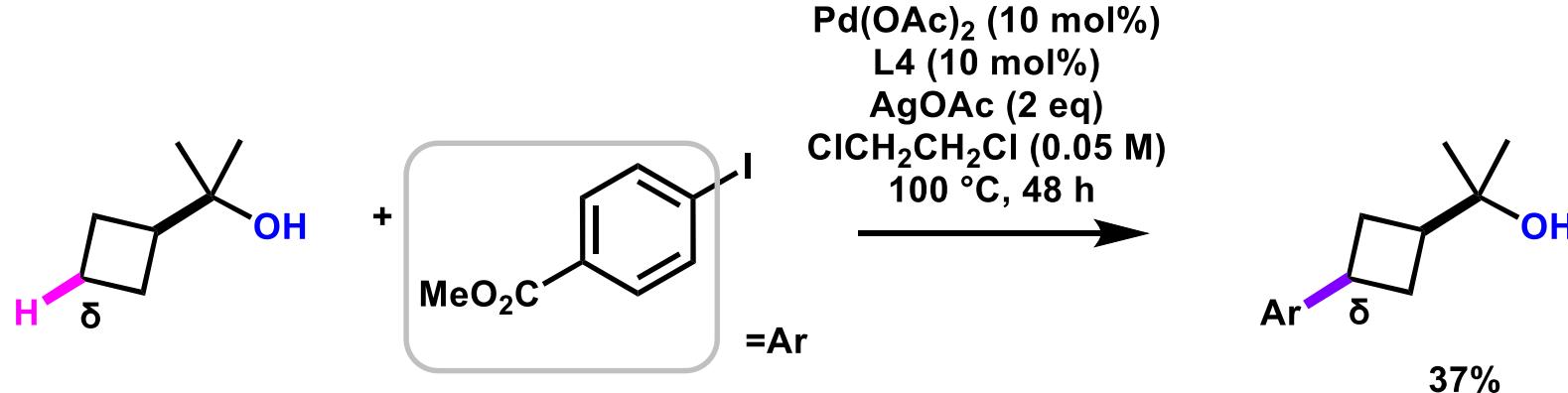
Hydrogen bond stabilize TS approximately 6.9 kcal/mol.

Calculations were conducted at the $\omega\text{B97XD}/6-311++\text{G}(2\text{d},\text{p})$ level of theory

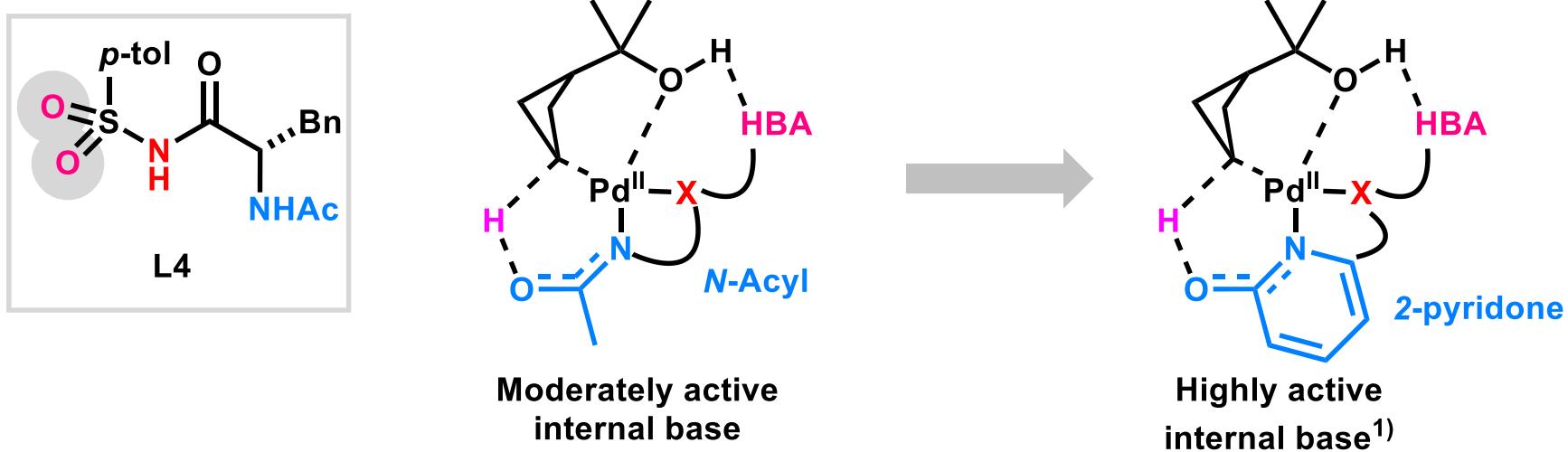
Proposed Reaction Mechanism



Application for Cyclobutyl Alcohols



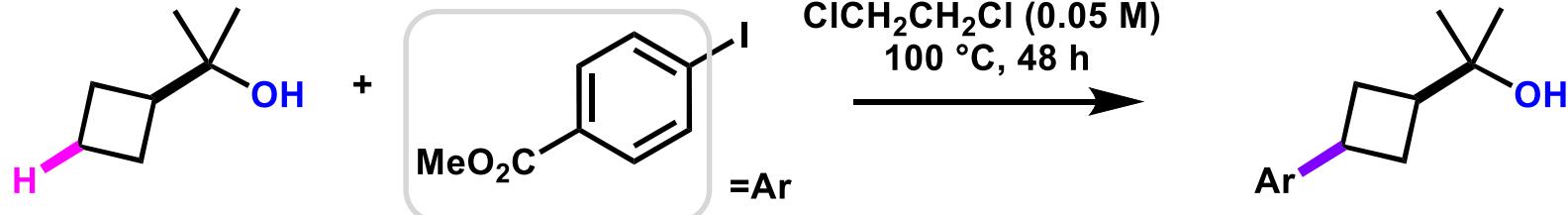
Working hypothesis



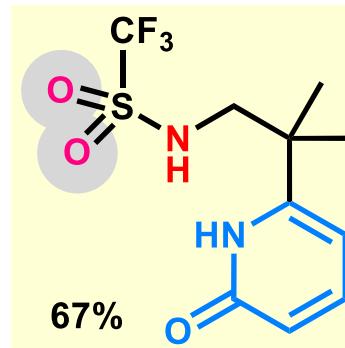
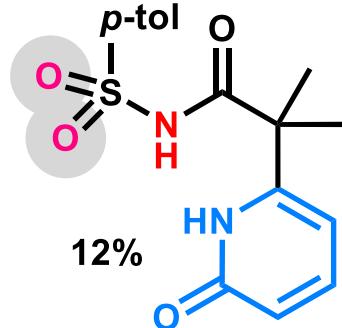
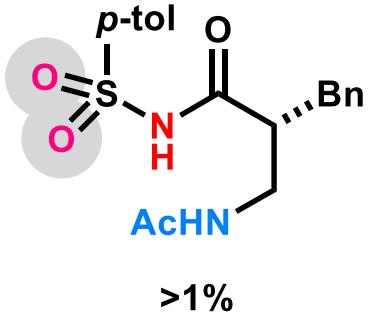
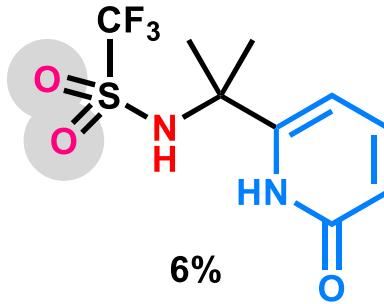
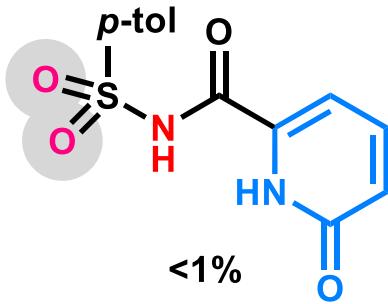
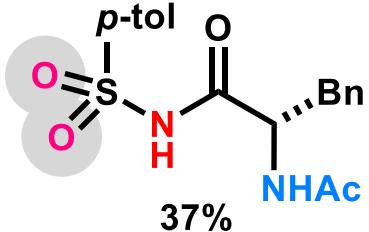
1) Wang, Z.; HU, L.; Chekshin, N.; Zhuang, Z.; Qian, S.; Ziao, J. X.; Yu, J. -Q. *Science*, **2021**, 374, 1281.

2) Strassfeld, D. A.; Chen, C.-Y.; Park, H. S.; Phan, D. Q.; Yu, J. -Q.; *Nature* **2023**, 1622, 80.

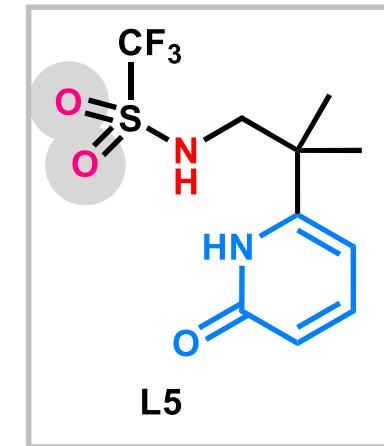
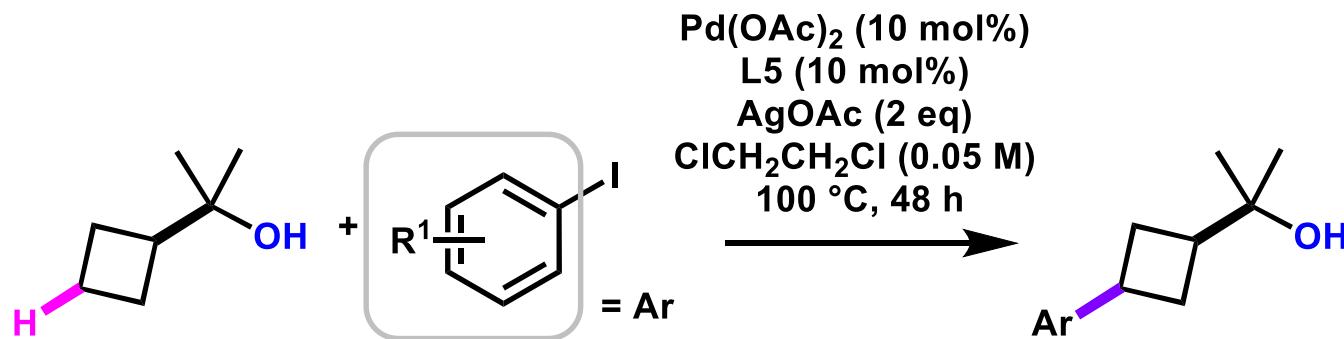
Ligands Screening (2)



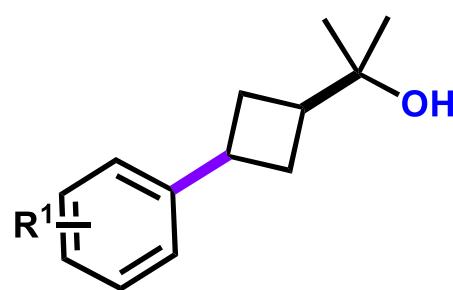
Ligand



Substrate Scope (2)

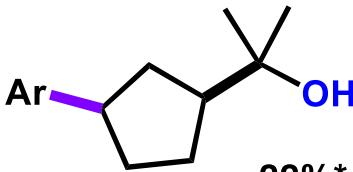
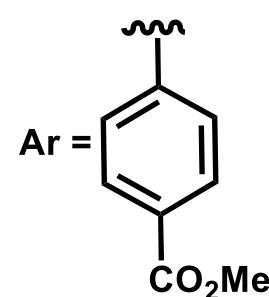
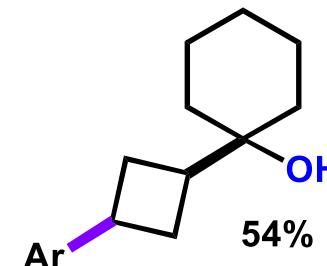
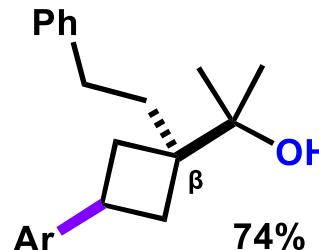


Aryl iodine scope



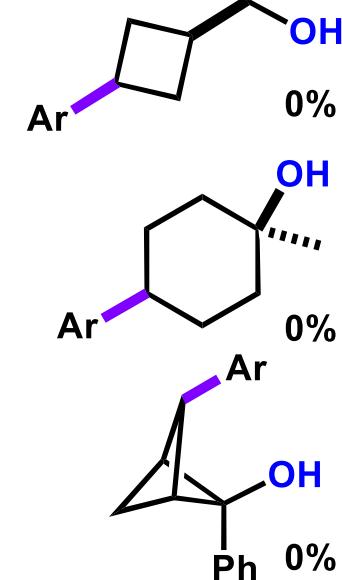
$\text{R}^1 = p\text{-CF}_3$
 $\text{R}^1 = p\text{-OMe}$
 $\text{R}^1 = m\text{-CF}_3$
 $\text{R}^1 = o\text{-CF}_3$

Alcohol scope

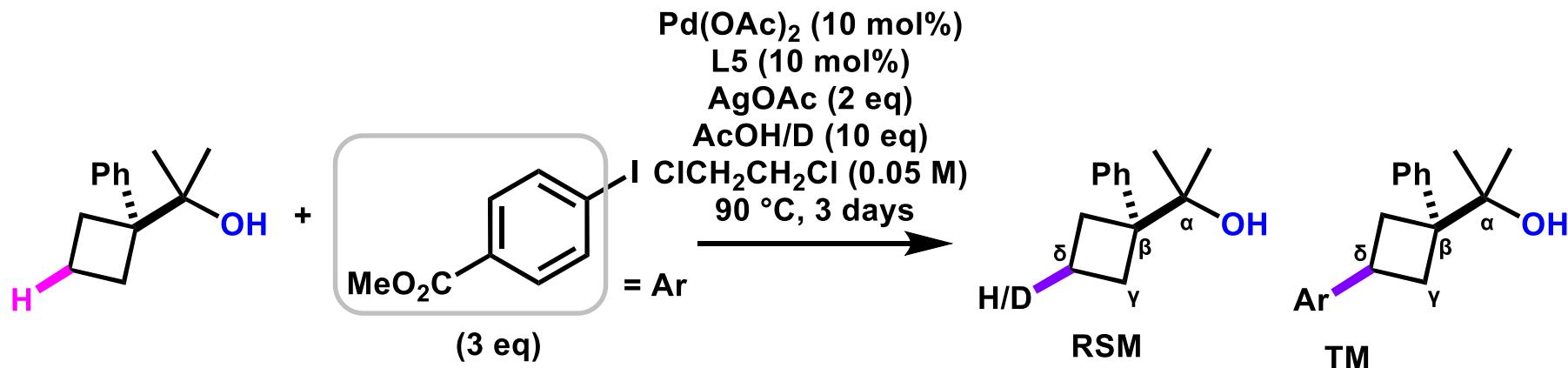


* 24 h reaction time

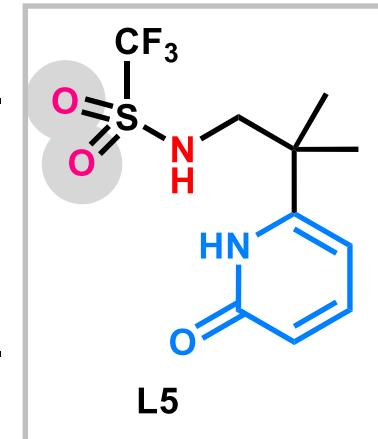
Unsuccessful substrate



Mechanistic Study (2)

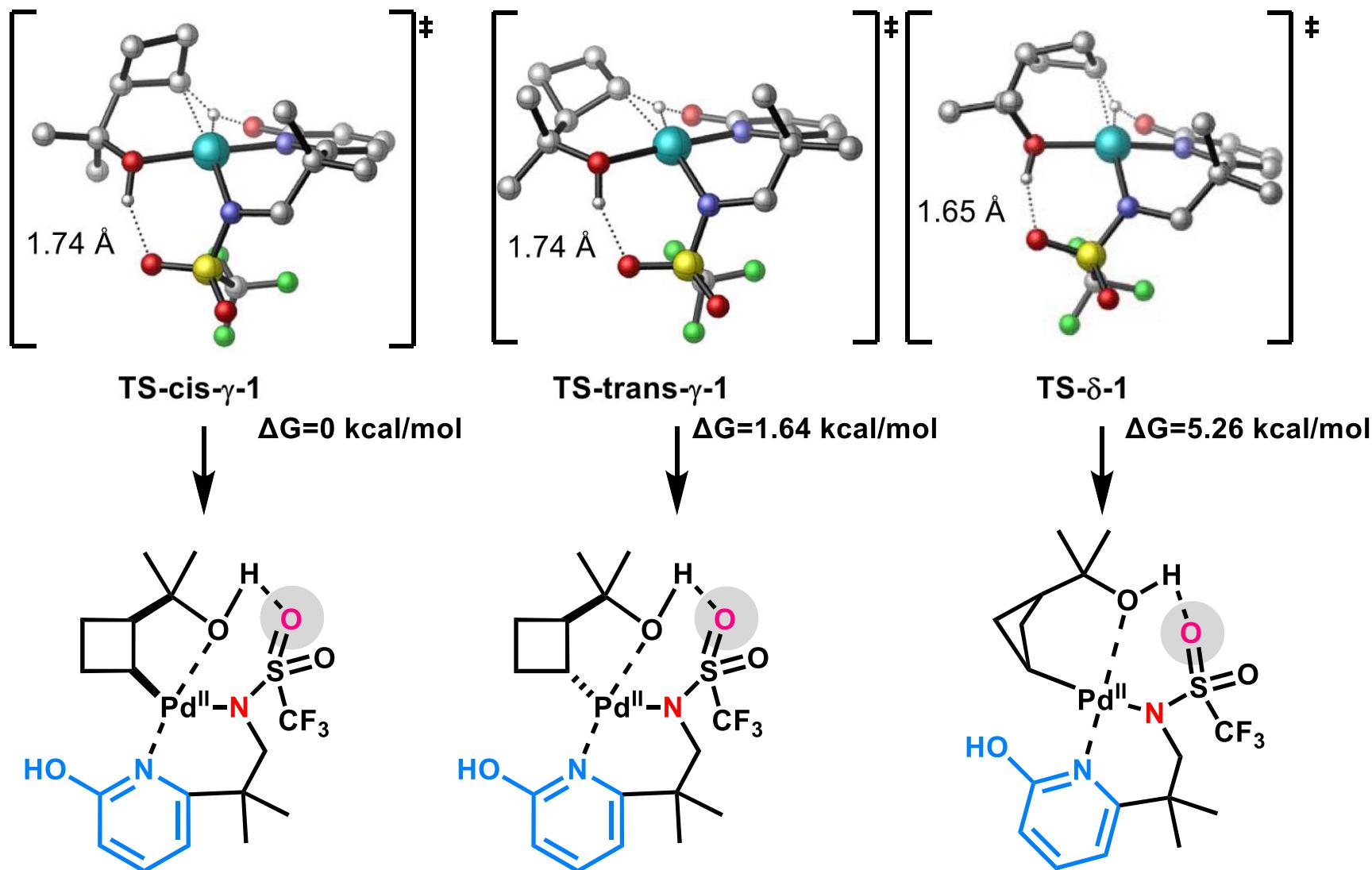


AcOH/D	Yield of TM	RSM γ-cis / γ-trans / δ-cis %D	TM γ-cis / γ-trans %D
AcOH	51%	-	-
d4-AcOD	51%	23% / 2% / <1%	15% / 25%

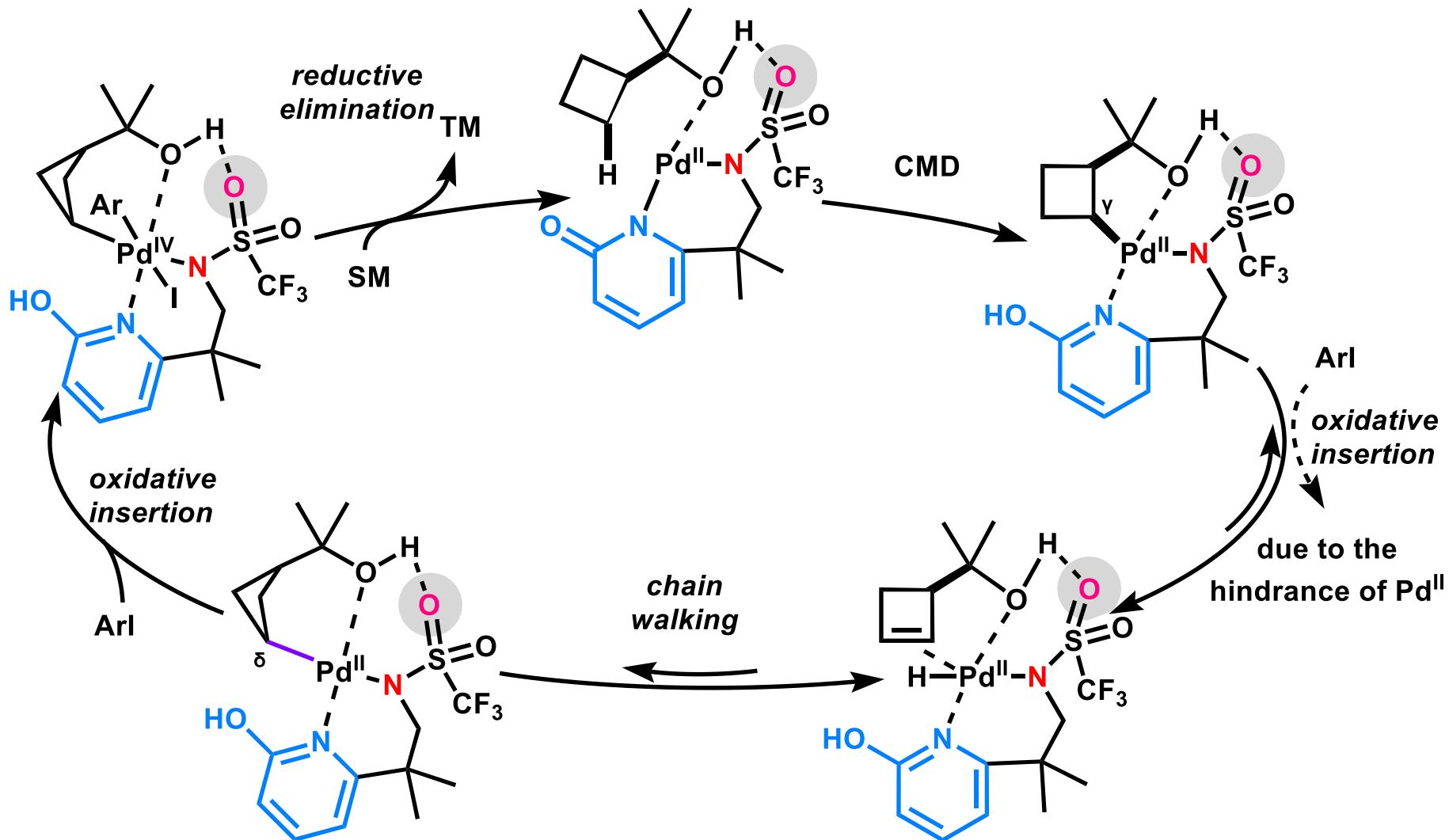


Deutrium incorporation was observed into the γ -position.

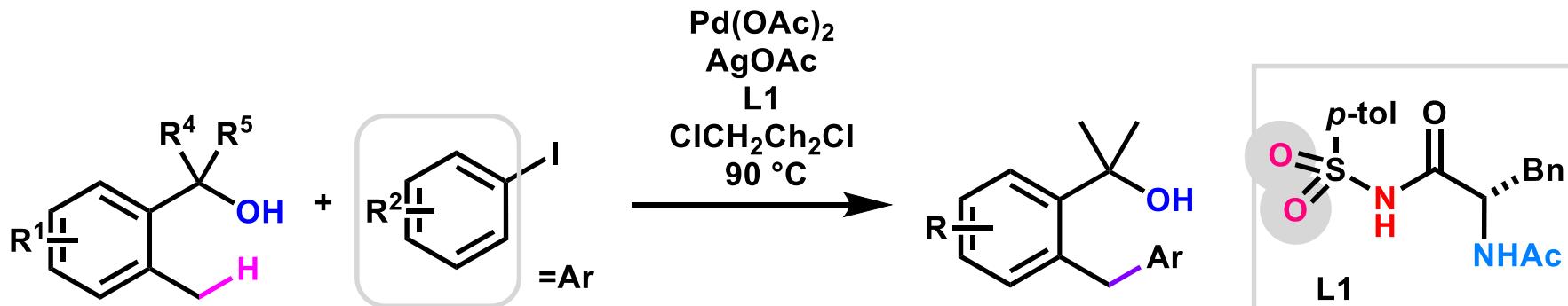
DFT Calculation (2)



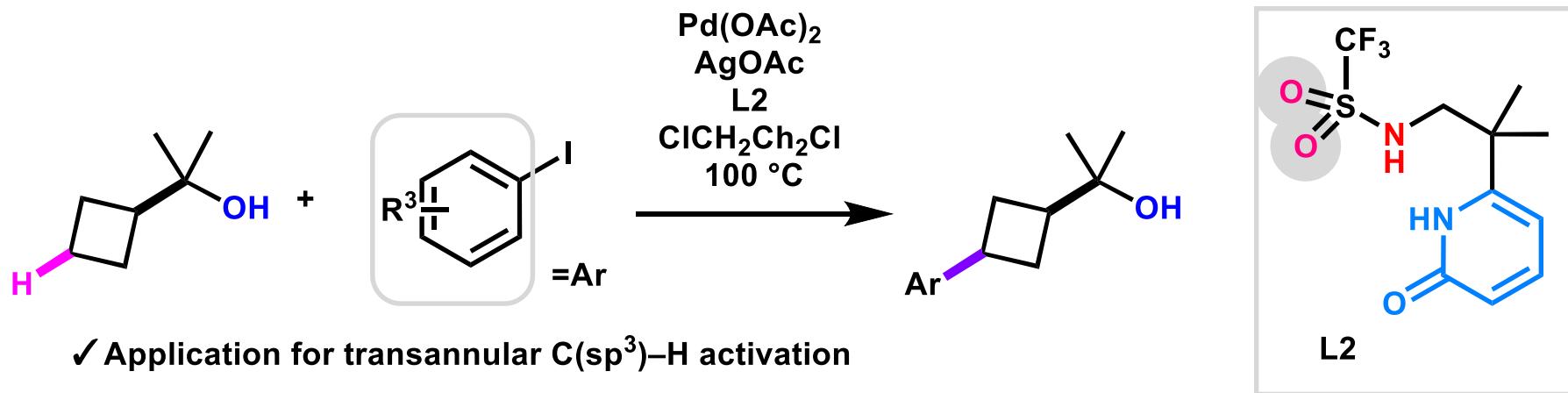
Proposed Reaction Mechanism (Cyclobutyl Alcohols)



Summary



✓ First report on alcohol directed $\text{C}(\text{sp}^3)\text{-H}$ activation



✓ Application for transannular $\text{C}(\text{sp}^3)\text{-H}$ activation

Key

- Non-covalent interactions between ligands and substrate
- Alcohols as neutral directing groups

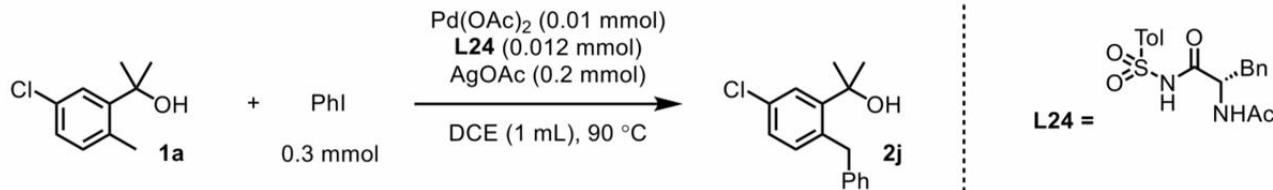
Future work:

- Expansion of the substrate scope
ex) primary or secondary alcohols, linear alcohols

appendix

Kinetic Data Analysis

Measurements of kinetic order in alcohol substrates:



	$[\text{1a}]_0 = 0.05 \text{ M}$		$[\text{1a}]_0 = 0.1 \text{ M}$		$[\text{1a}]_0 = 0.2 \text{ M}$	
Time (h)	$[\text{1a}] \text{ (mM)}$	$[\text{2j}] \text{ (mM)}$	$[\text{1a}] \text{ (mM)}$	$[\text{2j}] \text{ (mM)}$	$[\text{1a}] \text{ (mM)}$	$[\text{2j}] \text{ (mM)}$
2	10.92	35.03	19.45	67.50	45.02	140.71
4	15.57	30.29	29.97	62.38	56.60	127.76
6	14.93	32.59	37.98	53.37	64.00	106.12
8	24.58	17.57	48.21	44.46	99.92	83.40

