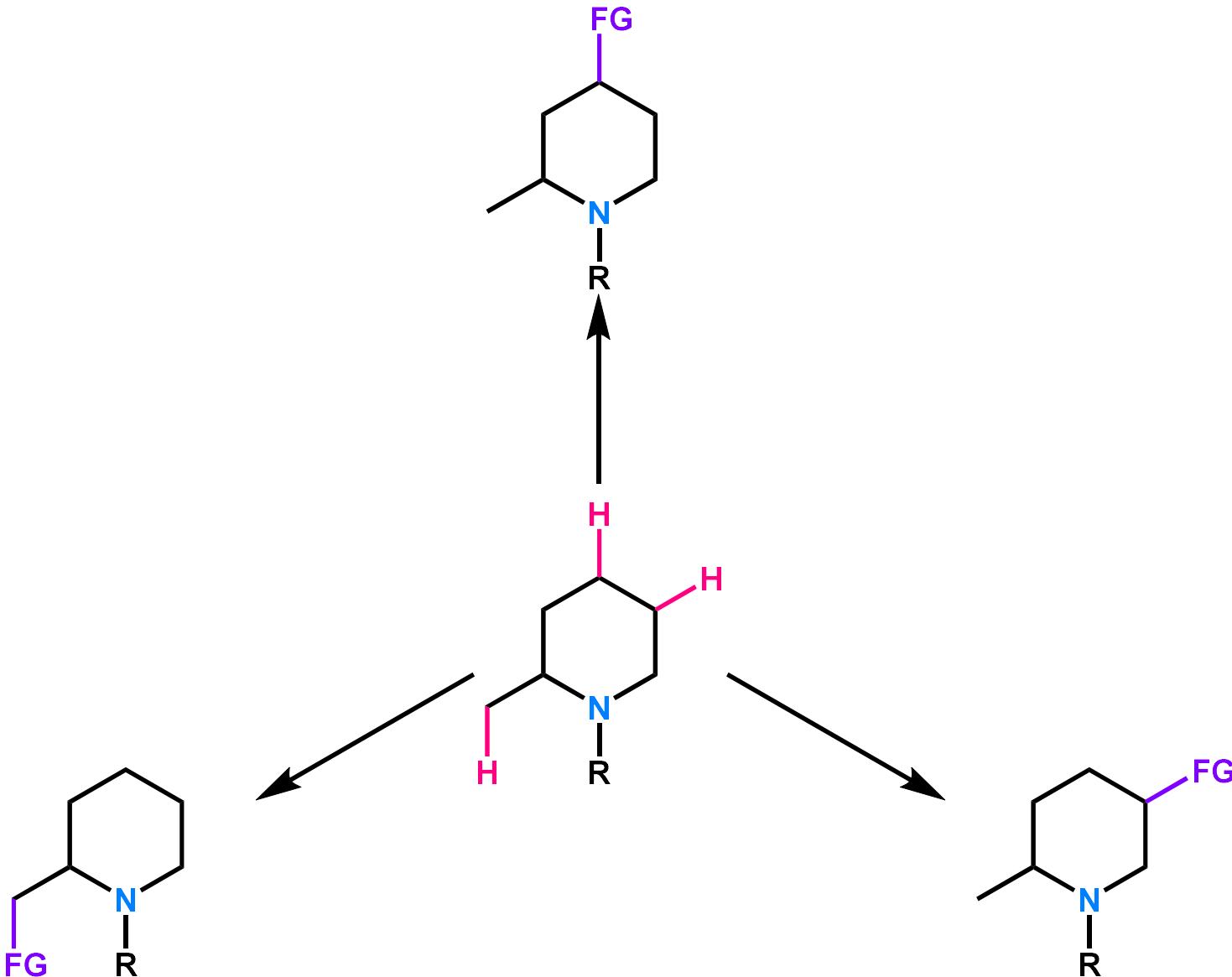


Remote C-H Functionalization of Alicyclic Amines



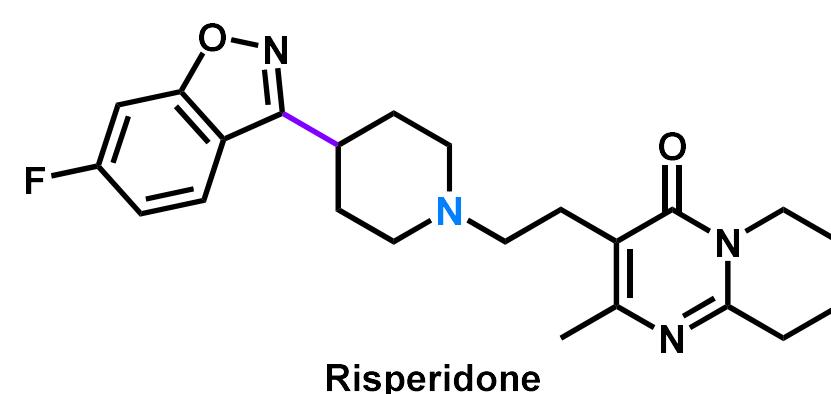
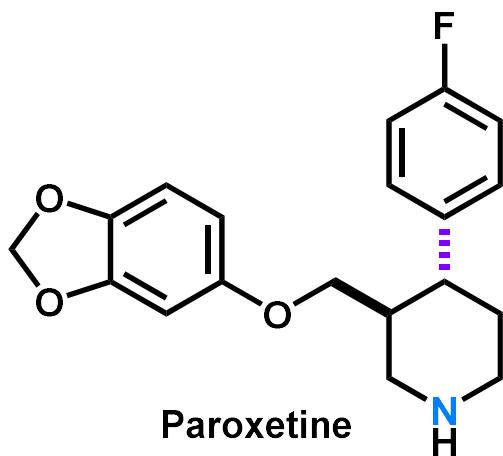
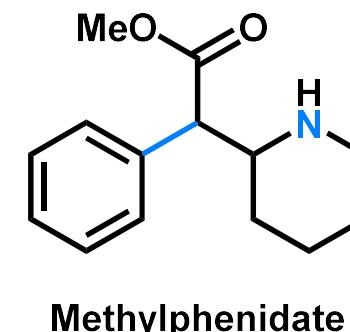
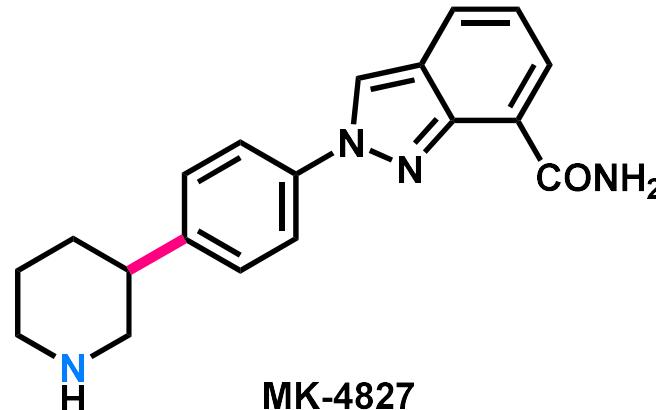
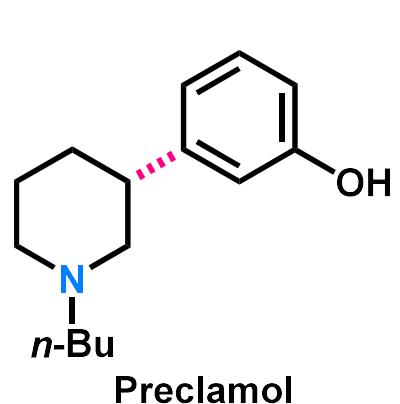
Contents

1. Introduction
2. β C-H functionalization (Baudoin, 2013)
3. Exo-cyclic C-H functionalization (Gaunt, 2015)
4. Transannular C-H activation (Sanford, 2016)

Contents

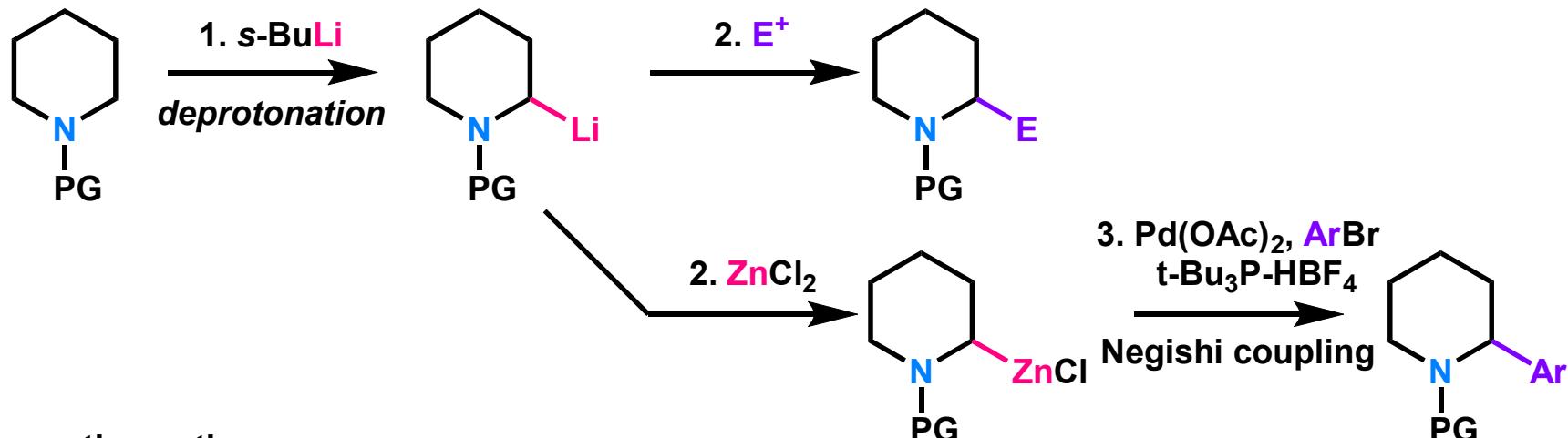
1. Introduction
2. β C-H functionalization (Baudoin, 2013)
3. Exo-cyclic C-H functionalization (Gaunt, 2015)
4. Transannular C-H activation (Sanford, 2016)

Biologically Significant Compounds Containing Alicyclic Amines

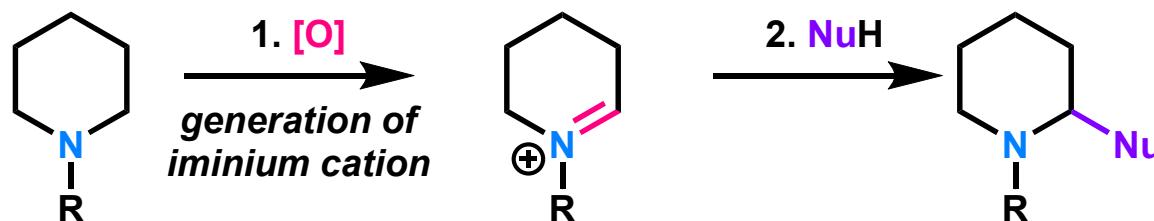


α C-H Functionalization of Alicyclic Amines

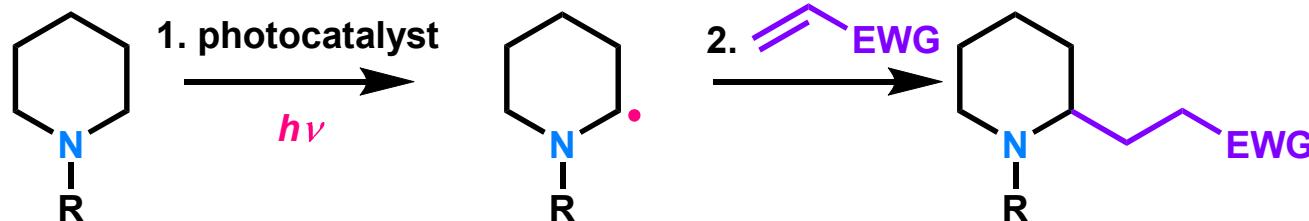
(1) α -ainon path



(2) α -cation path



(3) α -radical path

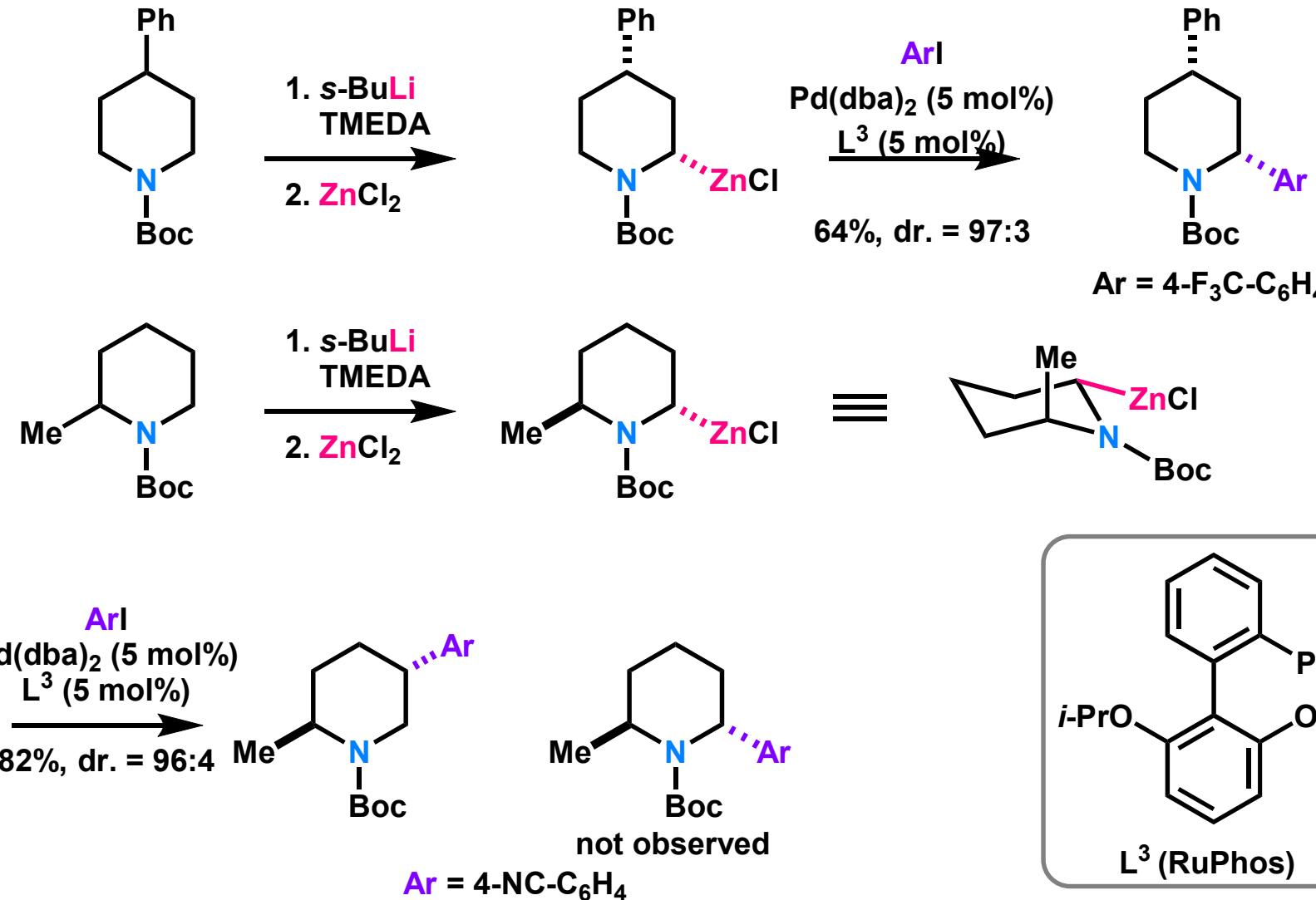


Methods for C-H functionalization of alicyclic amines are dominated by functionalization of the highly activated C-H bonds α to nitrogen

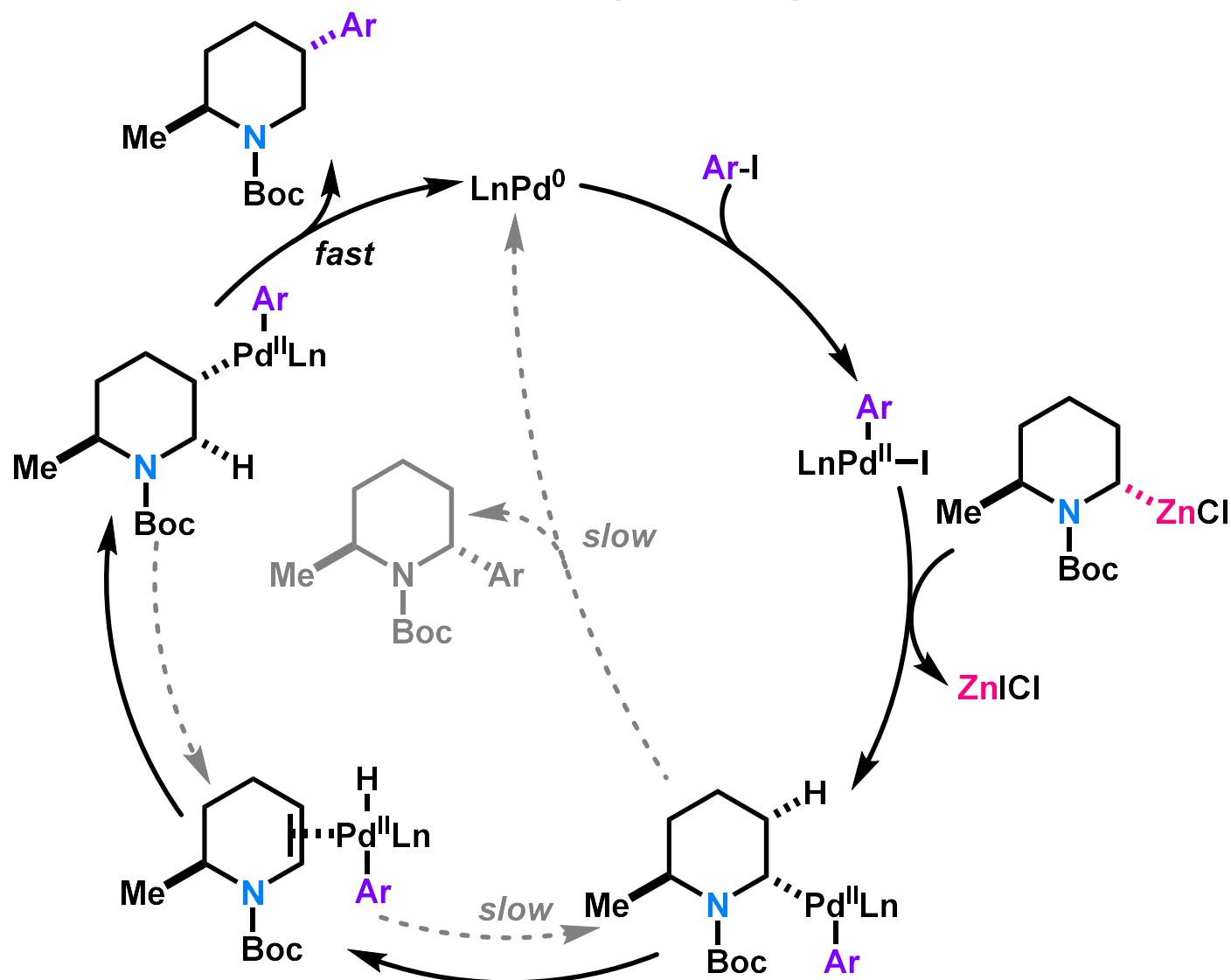
Contents

1. Introduction
2. β C-H functionalization (Baudoin, 2013)
3. Exo-cyclic C-H functionalization (Gaunt, 2015)
4. Transannular C-H activation (Sanford, 2016)

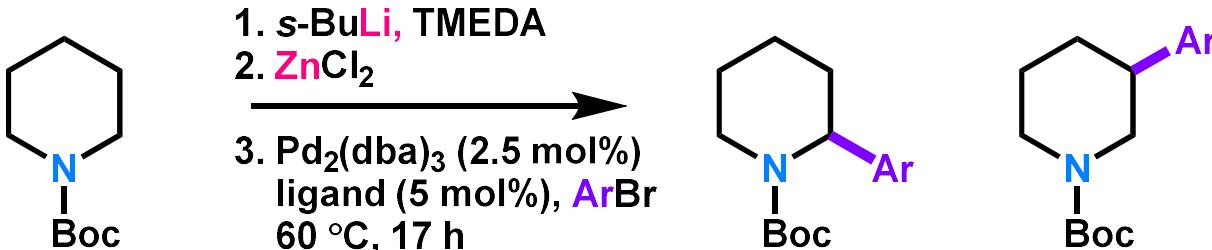
Substrate-Controlled β -Arylation



Proposed Catalytic Cycle

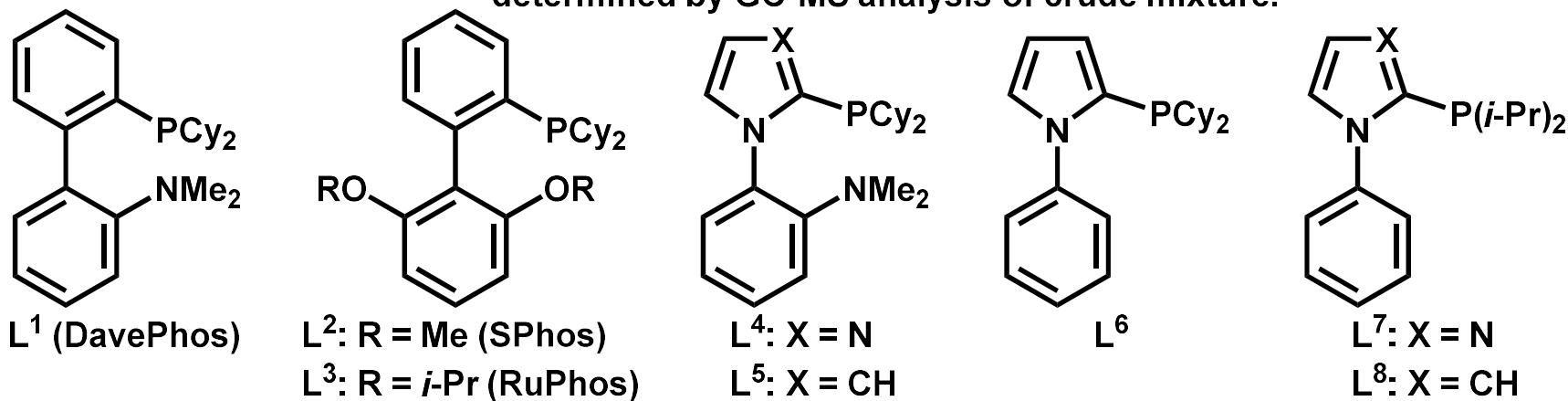


Ligand-Controlled β -Arylation

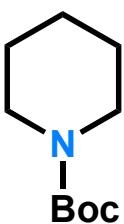


entry	ligand	$\alpha:\beta^*$	yield	($Ar = 4-F_3C-C_6H_5$)
1	L^1	61 : 39	68	
2	L^2	94 : 6	78	
3	L^3	90 : 10	65	
4	L^4	17 : 83	57	
5	L^5	17 : 83	65	
6	L^6	10 : 90	44	
7	L^7	17 : 83	56	
8	L^8	9 : 91	59	

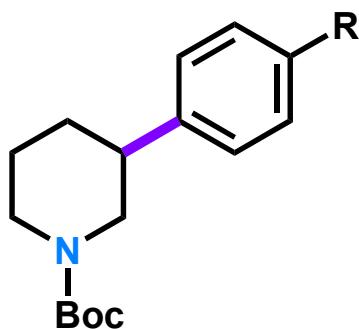
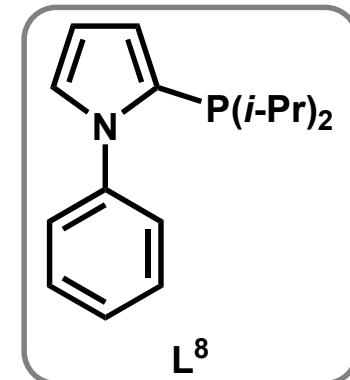
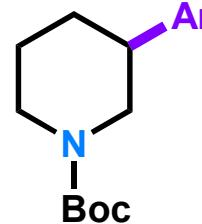
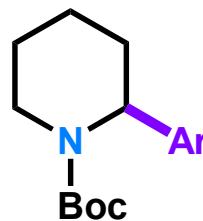
* determined by GC-MS analysis of crude mixture.



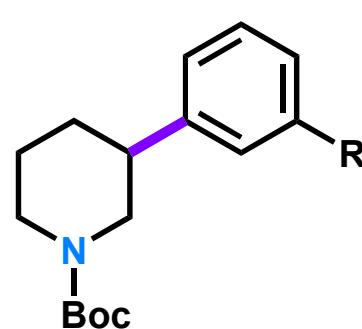
Substrate Scope



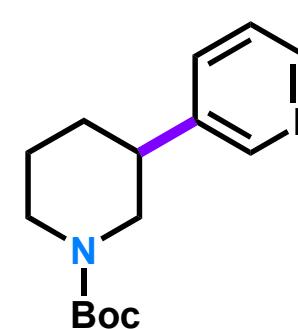
1. *s*-BuLi, TMEDA
2. ZnCl₂
3. Pd₂(dba)₃ (2.5 mol%), ligand (5 mol%), ArBr
60 °C, 17 h



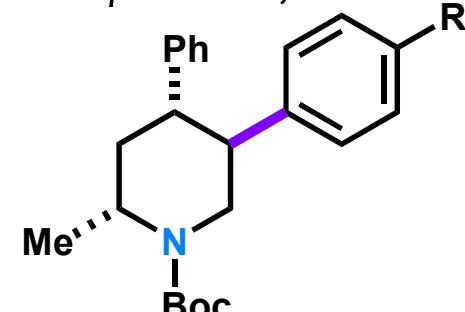
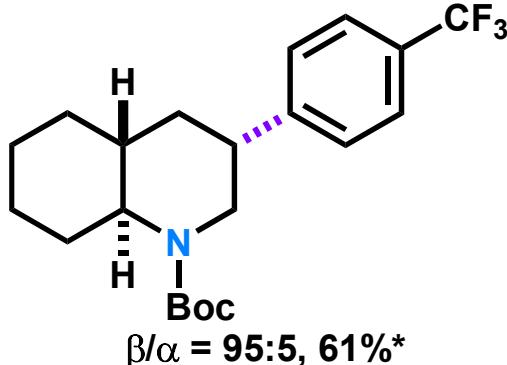
R = CF₃ : β/α = 91:9, 59%
R = CN : β/α = 85:15, 51%
R = OMe : β/α = 88:12, 55%
R = NMe₂ : β/α = 78:22, 48%



R = F : β/α = 90:10, 63%
R = OMe : β/α = 86:14, 71%



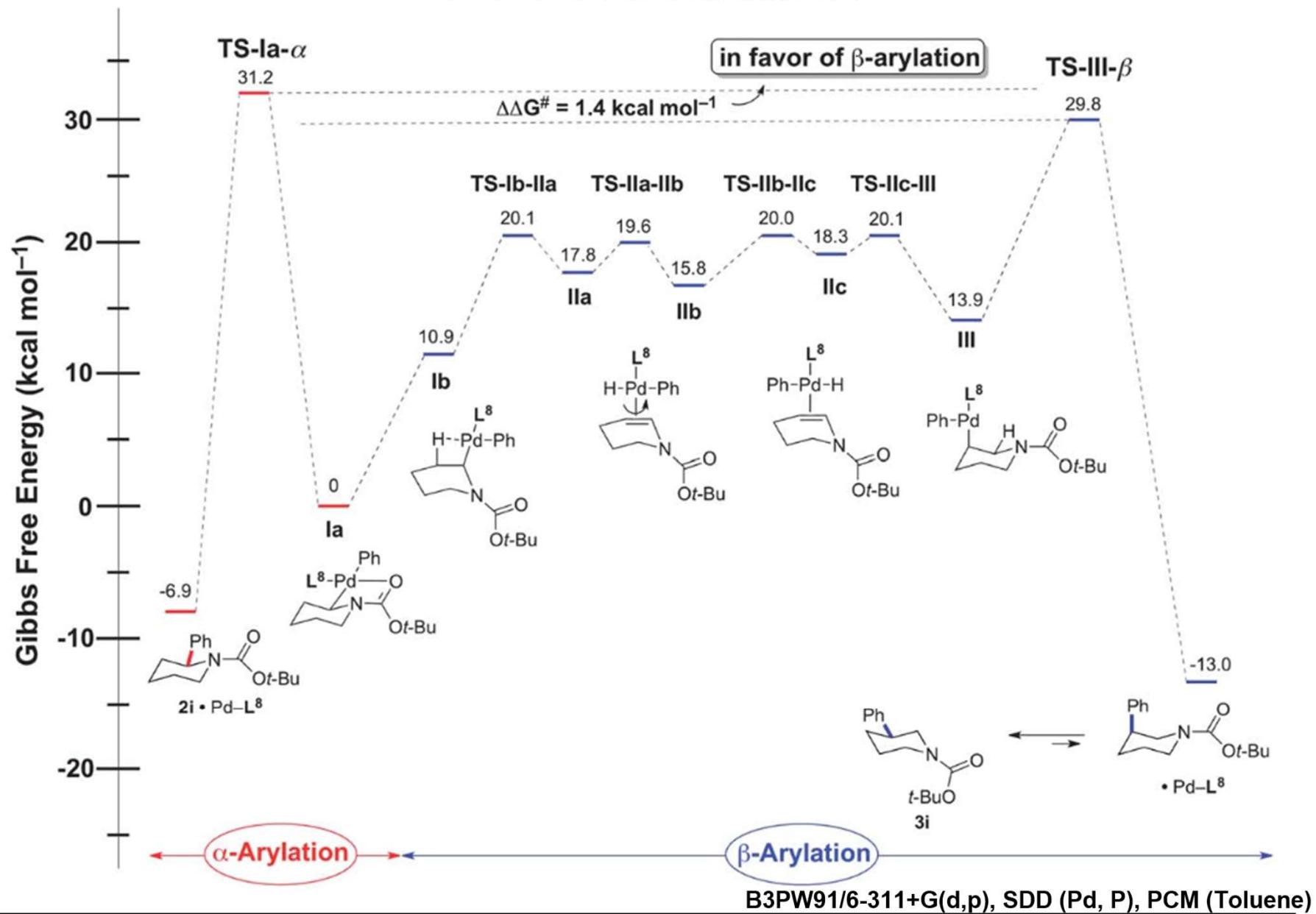
β/α = 91:9, 62%



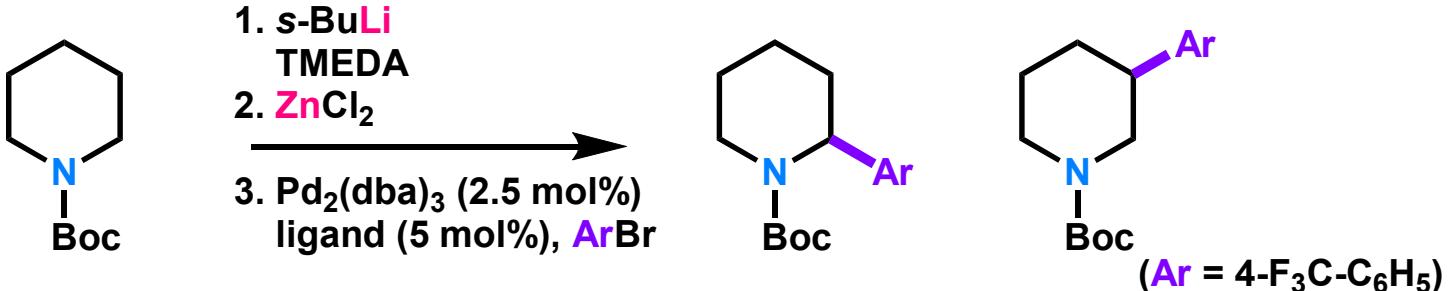
R = CF₃ : β/α > 98:2, 57%*
R = OMe : β/α > 98:2, 61%*

* Reaction performed at 80 °C.

DFT Calculation



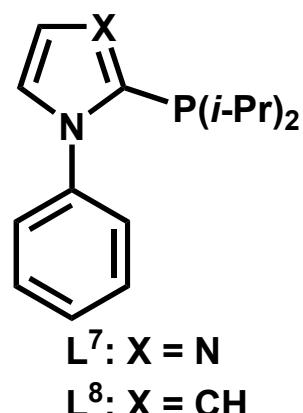
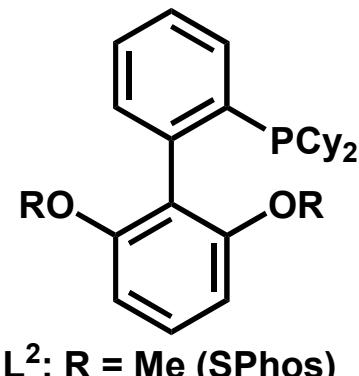
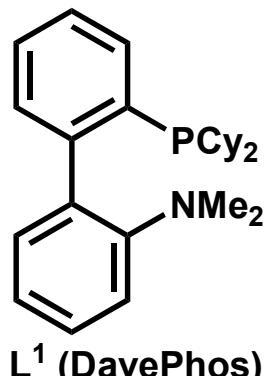
Rationale for Stereoselectivity



entry	ligand	ΔG_α	ΔG_β	$\Delta\Delta G_{\text{calc}}^{\text{a}}$	$\alpha/\beta_{\text{calcd}}$	$\alpha/\beta_{\text{exp}}^{\text{b}}$
1	L^8	31.1	29.6	-1.5	9 : 91	10 : 90
2	L^7	30.5	30.2	-0.3	39 : 61	20 : 80
3	L^1	26.3	26.3	0.0	50 : 50	50 : 50
4	L^2	23.5	24.4	0.9	80 : 20	97 : 3

a) $\Delta\Delta G_{\text{calc}} = \Delta G_\beta - \Delta G_\alpha$

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



1. The selectivity observed experimentally was well reproduced by the calculation.

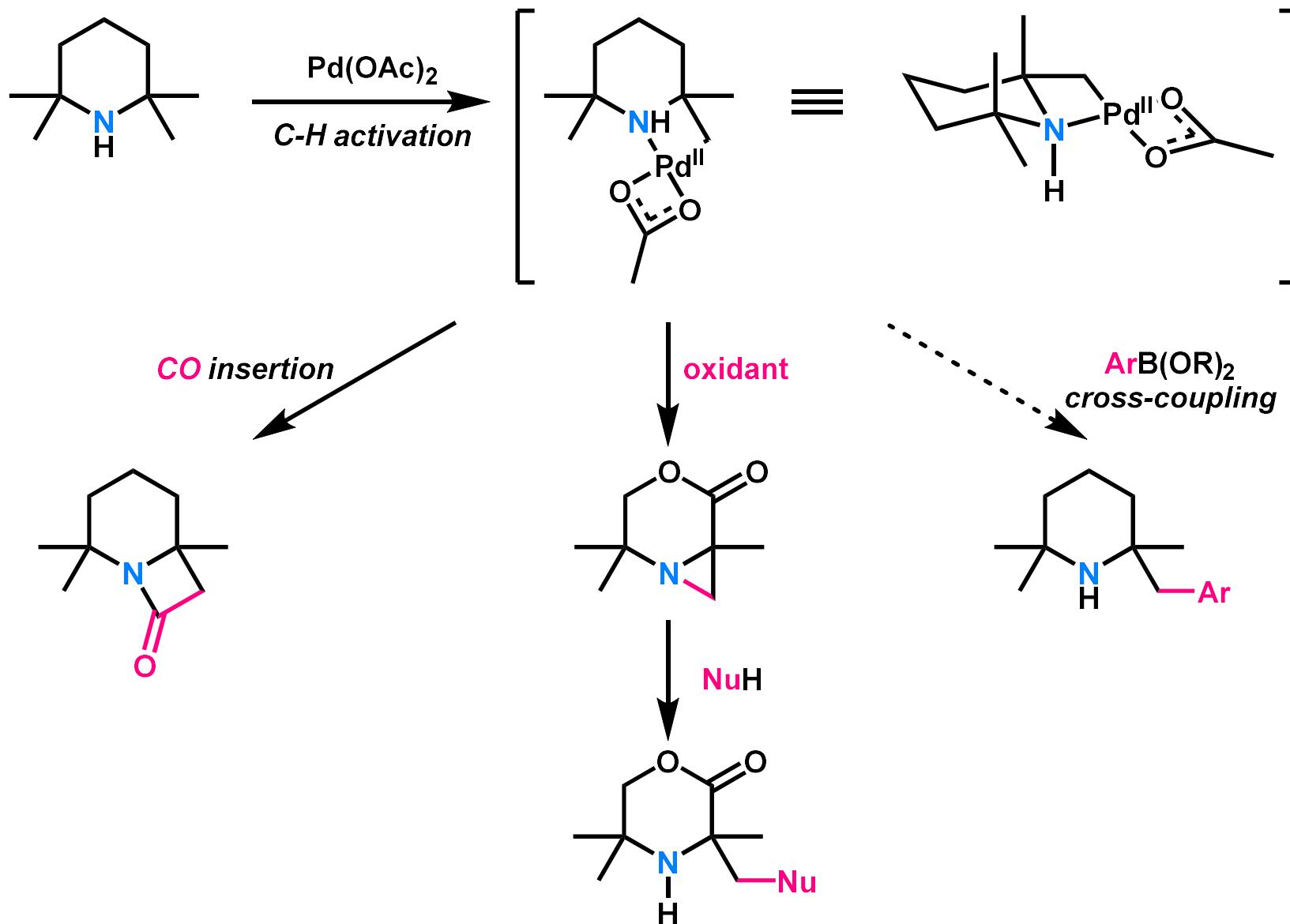
2. Reductive elimination was suppressed by using more electron-rich ligands.

3. Less sterically hindered ligands (L^7 and L^8) improve the coupling selectivity by disfavoring reductive elimination.

Contents

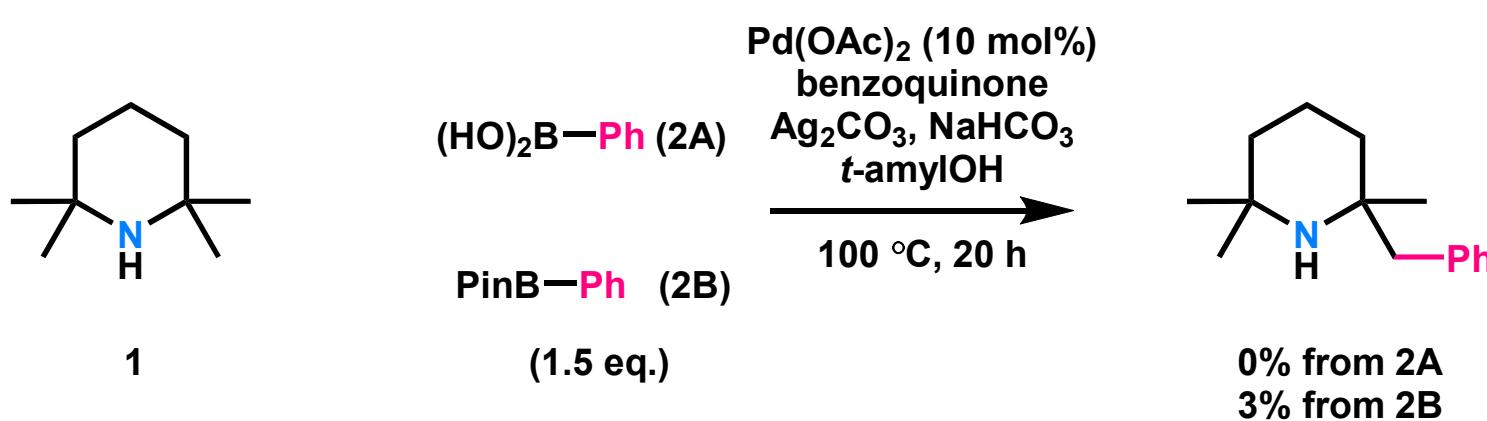
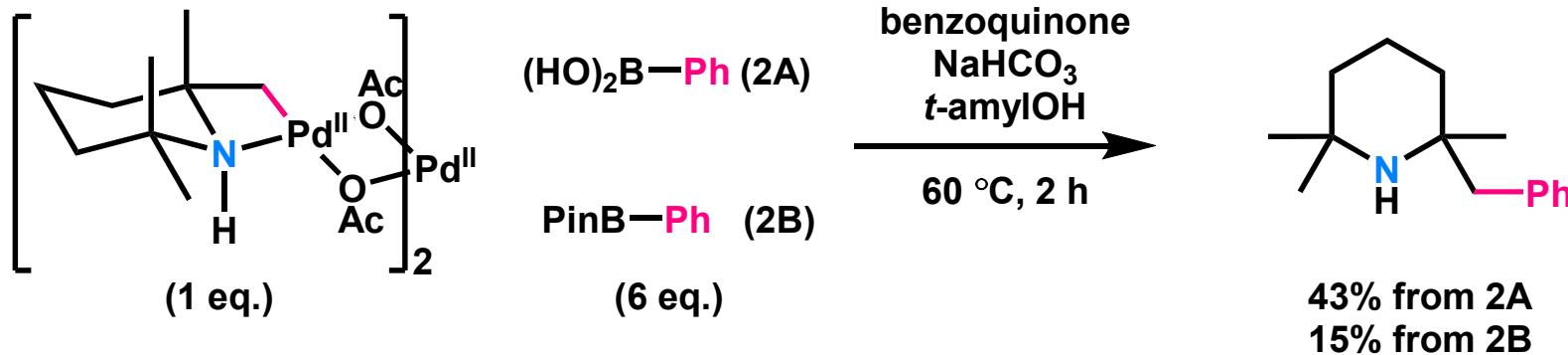
1. Introduction
2. β C-H functionalization (Baudoin, 2013)
3. Exo-cyclic C-H functionalization (Gaunt, 2015)
4. Transannular C-H activation (Sanford, 2016)

Previous Work



- 1) Willcox, D.; Chappell, B. G. N.; Hogg, K. F.; Calleja, J.; Smalley, A. P.; Gaunt, M. J. *Science* **2016**, *354*, 6314.
2) McNally, A.; Haffemayer, B.; Collins, B. S. L.; Gaunt, M. J. *Nature* **2014**, *510*, 129.

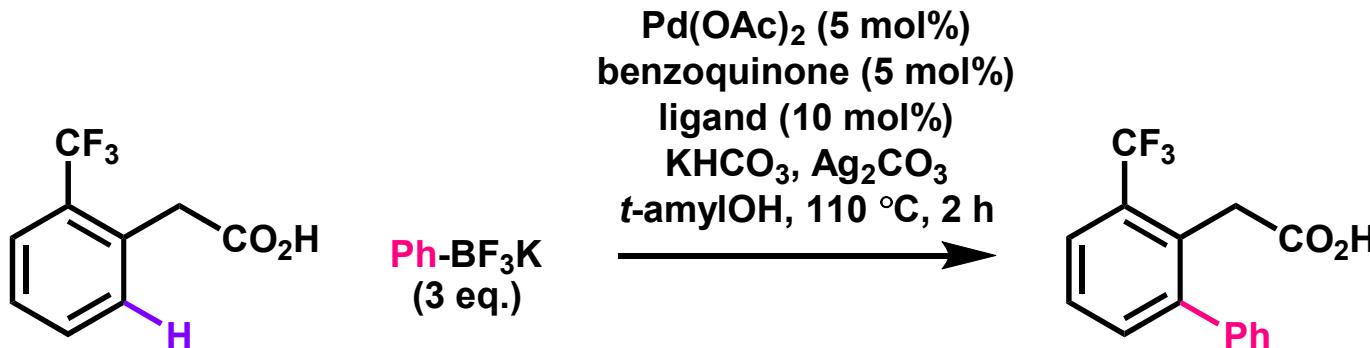
Initial Attempt



Based on this result, C-H activation step doesn't work well.

→ Mono N-protected amino acid ligand invented by Yu group was employed.

Amino Acid Ligand

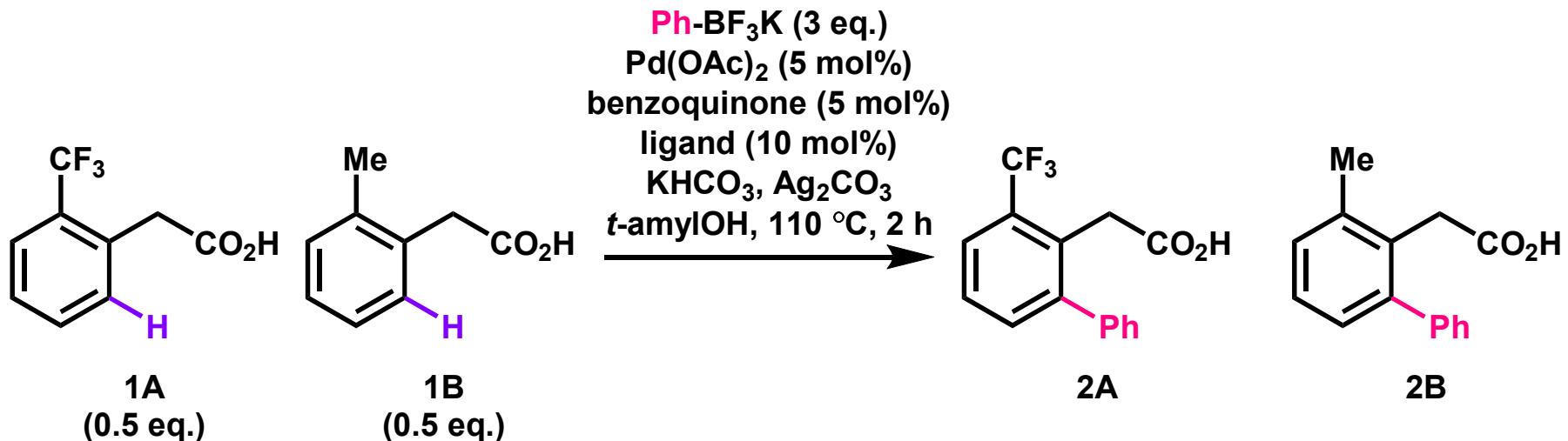


entry	ligand	% conv.	entry	ligand	% conv.
1	none	13	9	H-Ile-OH	0
2	Boc-Gly-OH	61	10	Me-Ile-OH	0
3	Boc-Ala-OH	77	11	formyl-Ile-OH	62
4	Boc-Phe-OH	83	12	Ac-Ile-OH	89
5	Boc-Val-OH	82	13	Fmoc-Ile-OH	79
6	Boc-Leu-OH	81	14	Cbz-Ile-OH	76
7	Boc-t-Leu-OH	79	15	Ac-Val-OH	79
8	Boc-Ile-OH	81	16	Ac-Leu-OH	87

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

1. Mono N-protected amino acid ligands accelerate the reaction.
2. Substitution of the nitrogen atom with an electron-withdrawing group is necessary for reactivity.

Competition Experiment



entry	ligand	time (min)	% conv. A	% conv. B	k_{2A}/k_{2B}
1	none	60	9	18	0.48
2	Ac-Ile-OH	20	36	16	2.17

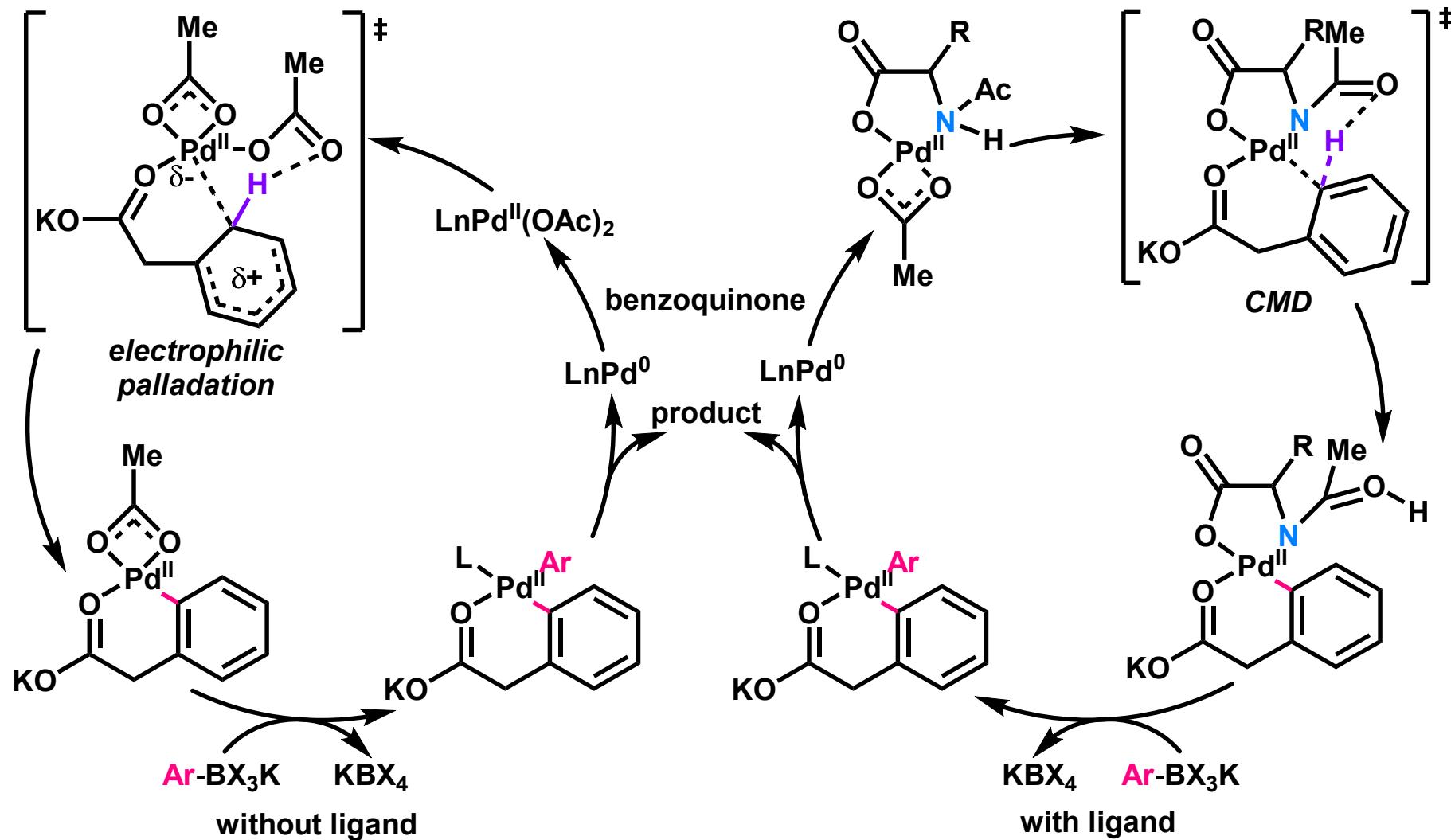
The conversion was determined by ¹H NMR of crude mixture.

1. In the absence of ligand, electron-rich substrate 1B gave a higher initial rate.

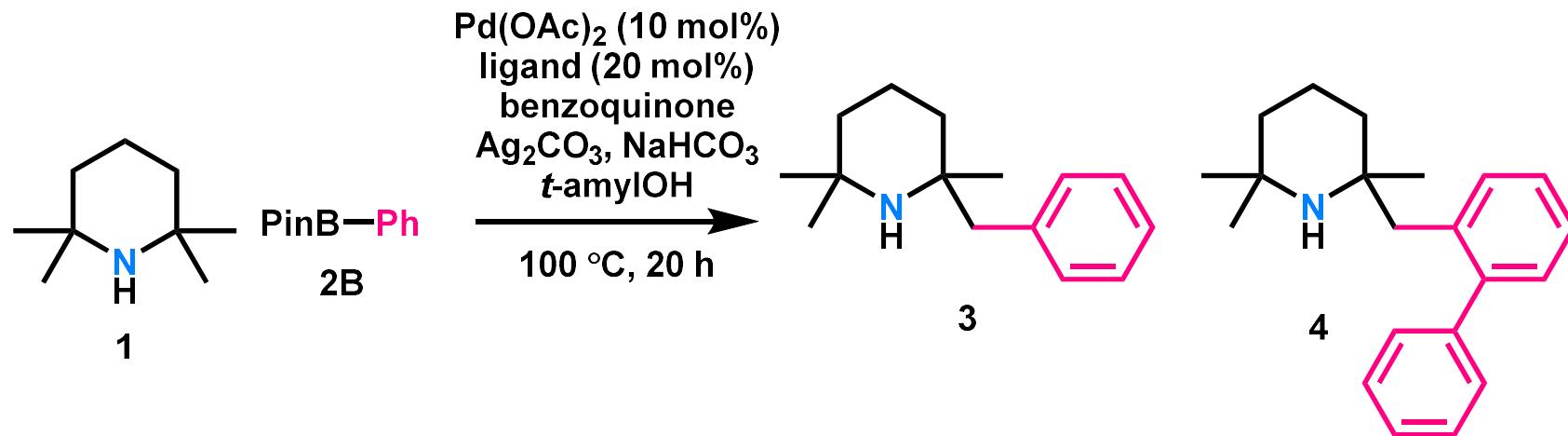
2. In the presence of Ac-Ile-OH, electron-poor substrate 1A gave a higher initial rate.

→ These date indicate a change in mechanism of the C-H activation step when amino acid ligands are added to the reaction.

Proposed Catalytic Cycle



Optimization for C-H Arylation



entry	1 (eq.)	2B (eq.)	ligand	3 (%) ^a	4 (%) ^a
1	1.0	1.5	none	3	0
2	1.0	1.5	Ac-Gly-OH	33	19
3	1.0	1.5	Ac-Val-OH	34	21
4	1.0	1.5	Ac-Leu-OH	35	19
5	2.0	1.0	Ac-Gly-OH	50	7
6	2.0	1.0	Ac-Val-OH	56	10
7	2.0	1.0	Ac-Leu-OH	53	10
8^b	2.0	1.0	Ac-Phe-OH	61	11

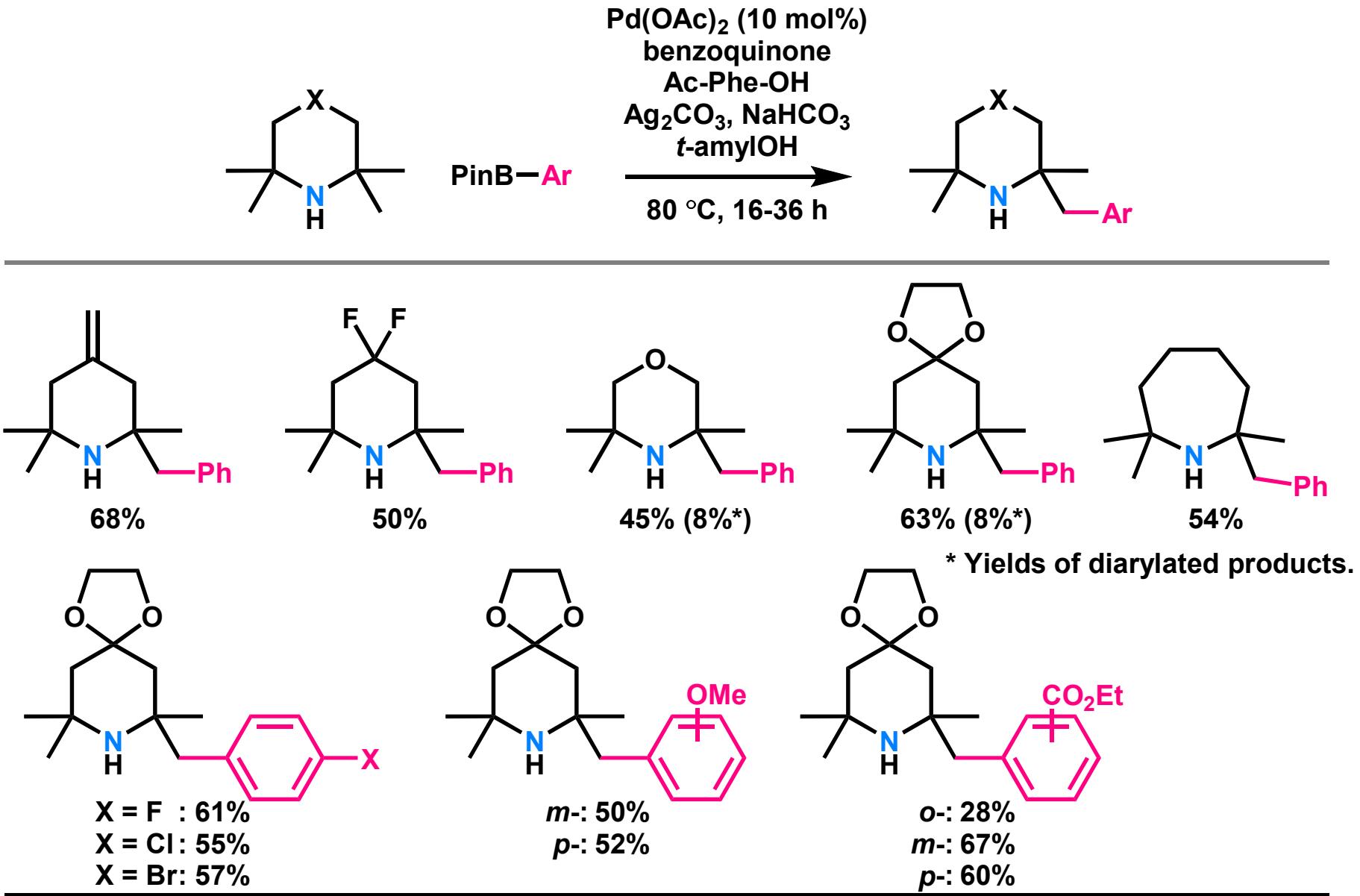
a) Yield was determined by GC or ^1H NMR of crude mixture.

b) Reaction at 80°C .

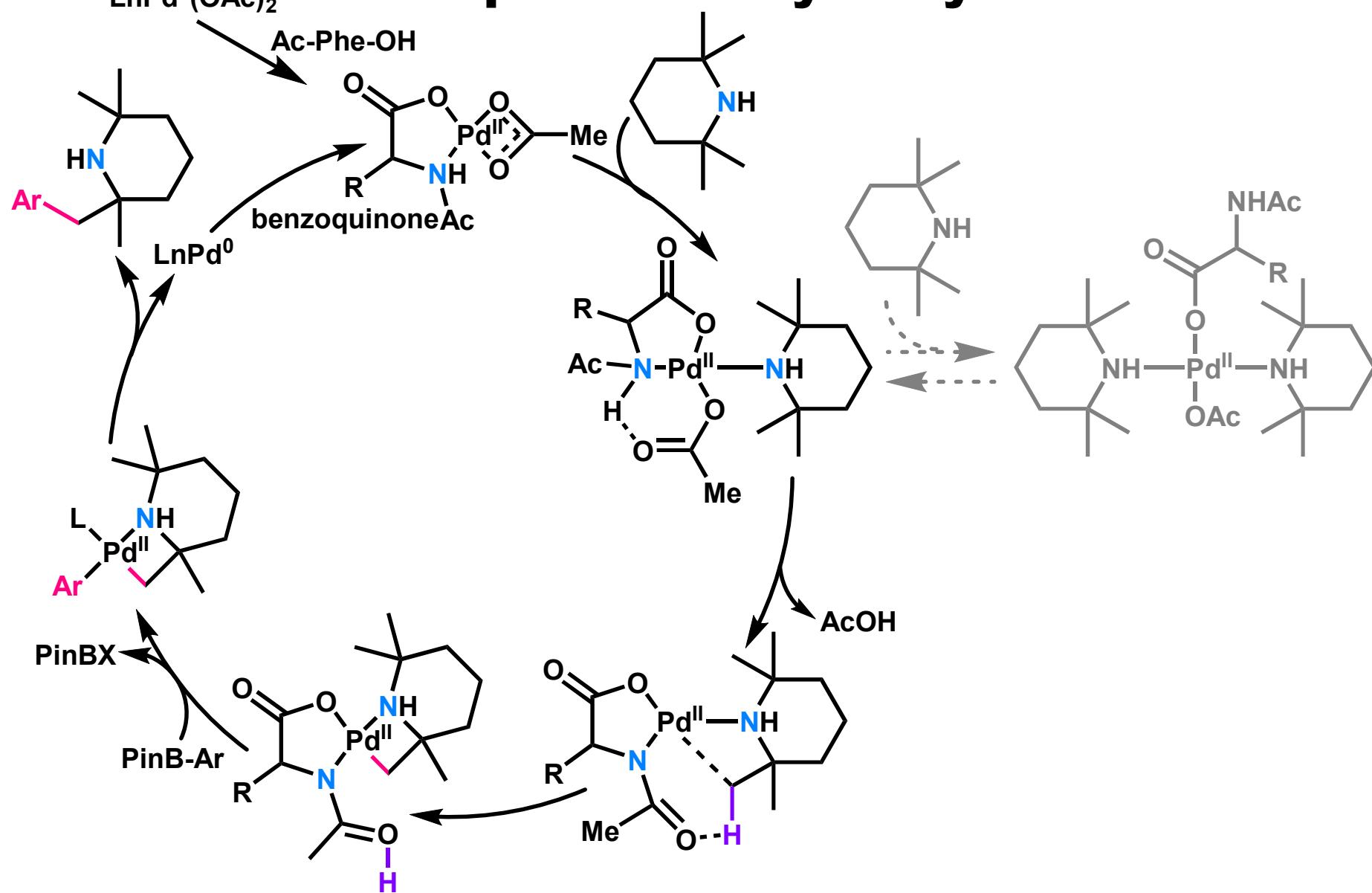
The second arylation took place on the *ortho* sp²-carbon atom of the new phenyl group.

Over-arylation was suppressed by changing the stoichiometry of the reaction (entry 5-8).

Substrate Scope

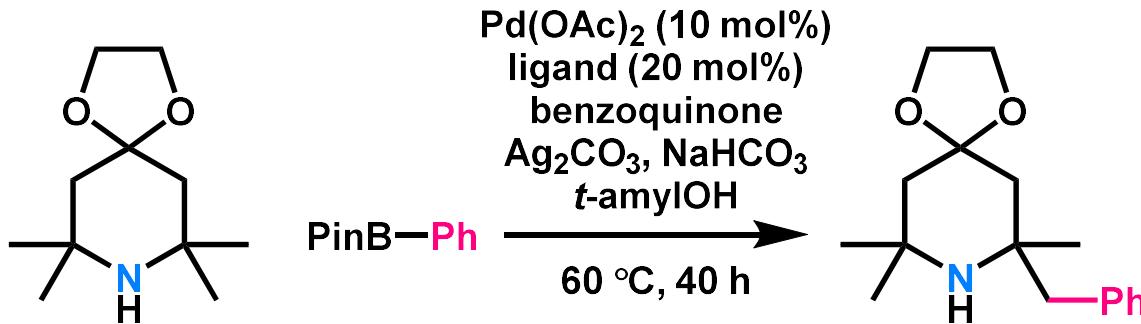


Proposed Catalytic Cycle

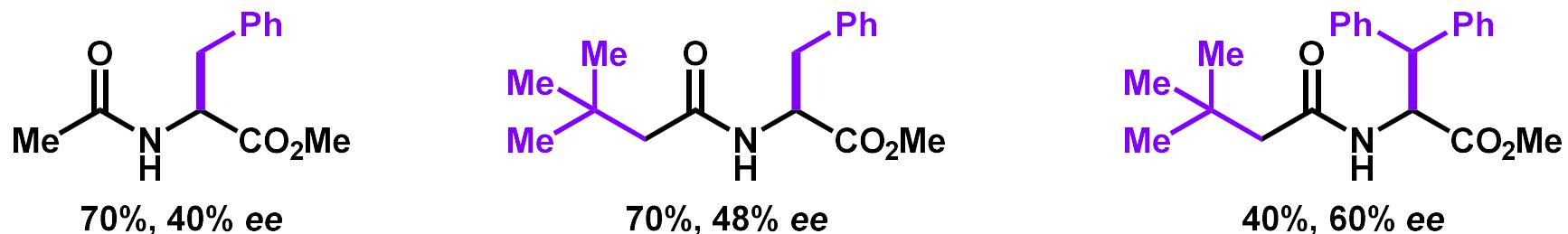
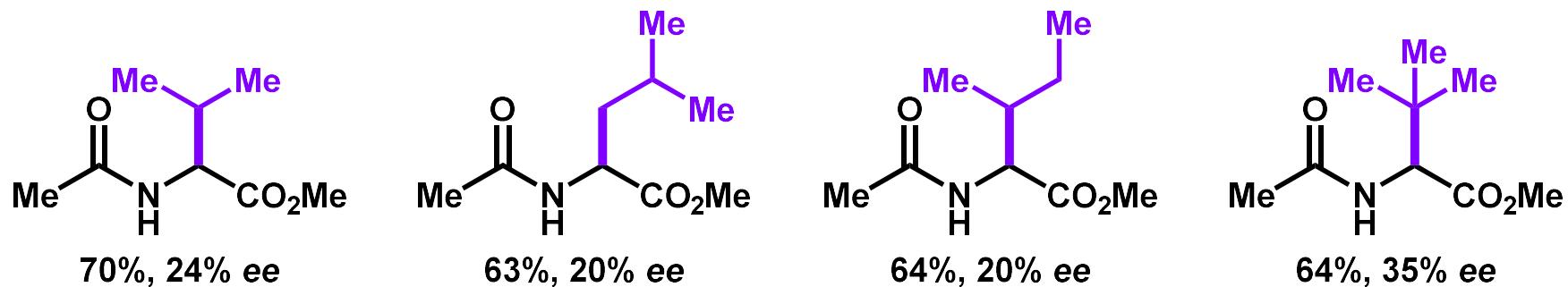


1) Smalley, A. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2015**, *137*, 10632. 2) He, C.; Gaunt, M. J. *Angew. Chem. Int. Ed.* **2015**, *54*, 15840. 21

Enantioselective C-H Arylation



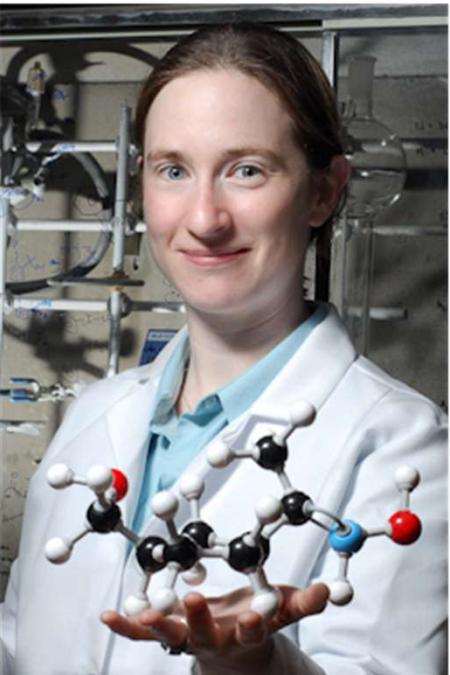
Yield was determined by ^1H NMR of crude mixture.



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Melanie S. Sanford



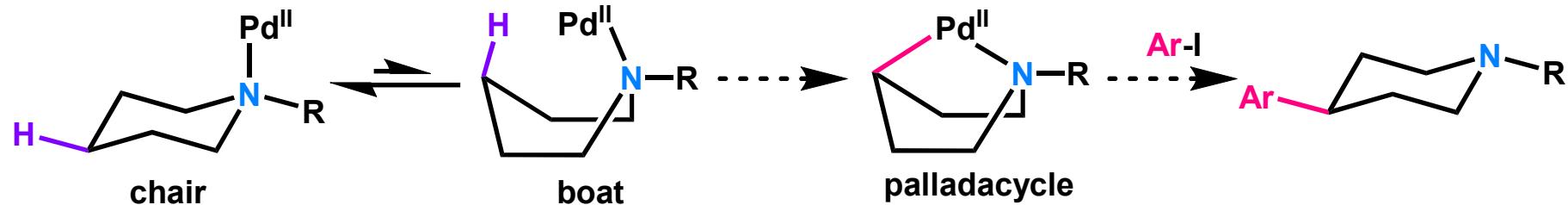
- 1996 : BS Yale University (Prof. Crabtree, R. H.)
2001 : Ph.D. Caltech (Prof. Grubbs, R. H.)
2001 - 2003: Postdoc. Princeton University (Prof. Groves, J.)
2003 - 2007: Assistant Prof. The University of Michigan
2007 - 2010: Associate Prof. The University of Michigan
2010 - : Prof. The University of Michigan

Research Topic:

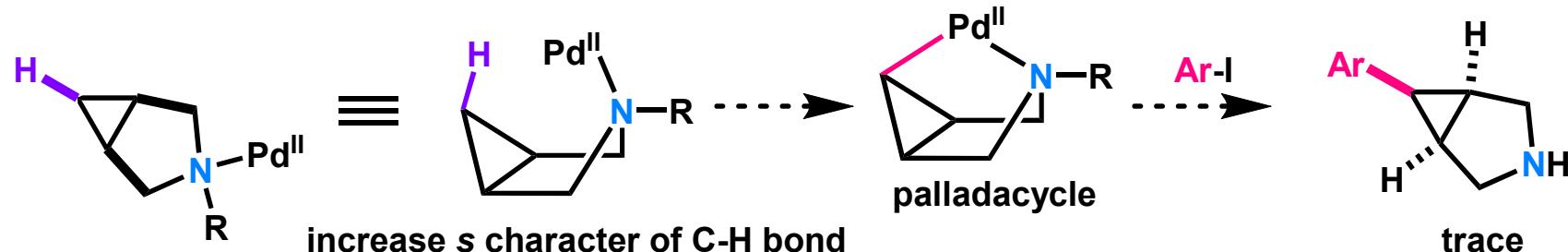
1. C-H Functionalization
2. Organometallics
3. Fluorination
4. Flow Batteries

Working Hypothesis

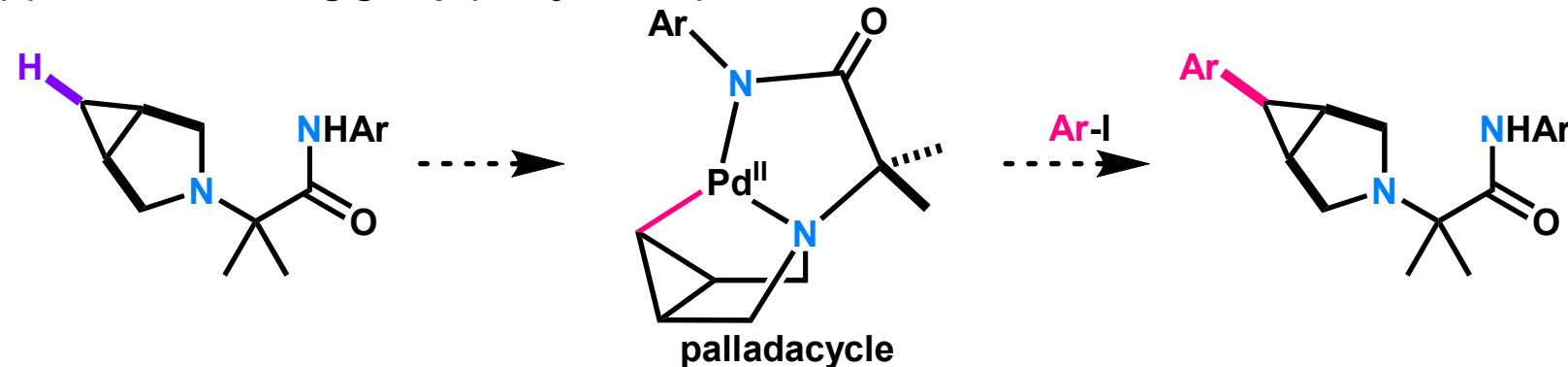
(1) Concept



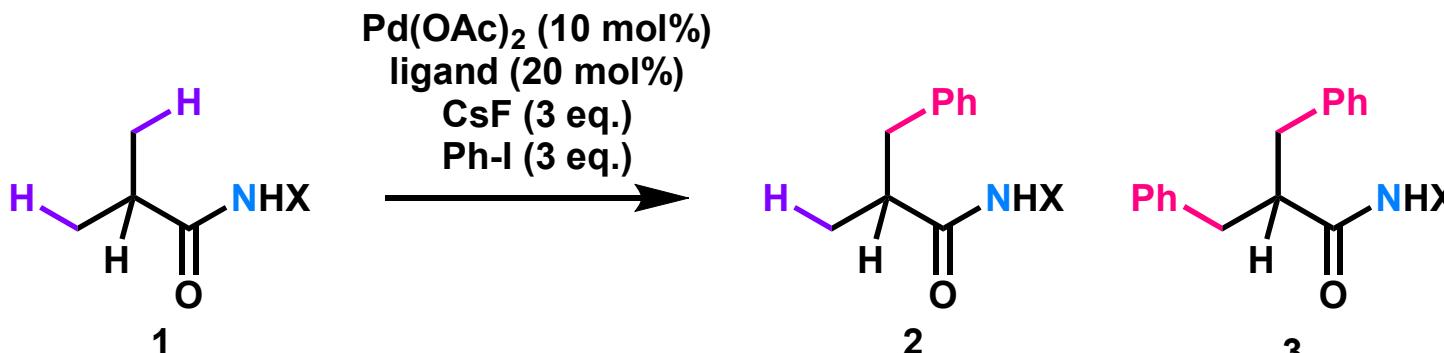
(2) Pre-arrangement of conformation



(3) Second directing group (N-aryl amide)

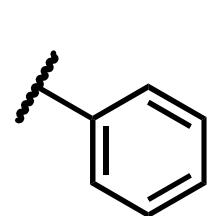


N-aryl Amide as a Directing Group

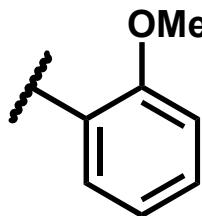


Yield was determined by ¹H NMR of crude mixture.

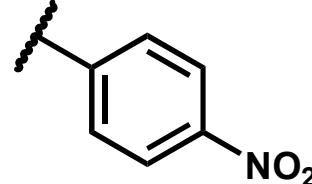
X = OMe



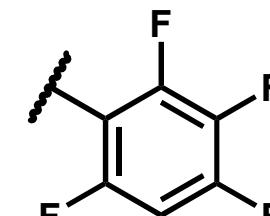
2: 0%
3: 0%



2: 3%
3: 0%

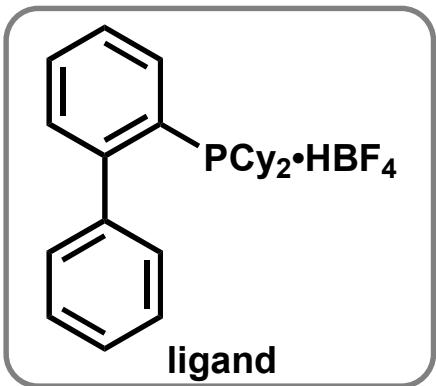


2: 0%
3: 0%



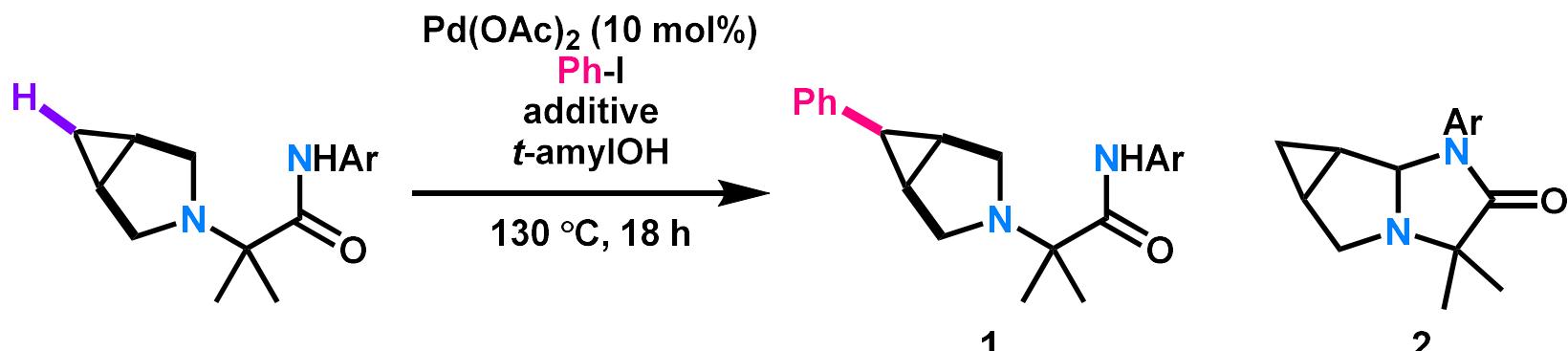
2: 12%
3: 0%

2: 34%
3: 54%

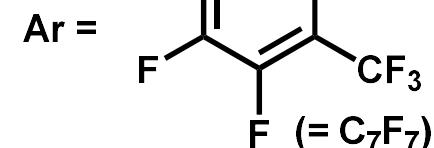


Buchwald-Hartwig amination pathway with ArI was suppressed by reducing the nucleophilicity of the amide N-H bond.

Optimization of Reaction Conditions



entry	Ar-I (eq.)	additive	1 (%) ^a	2 (%) ^a
1	20	none	7	18
2	20	AgOPiv	18	23
3	20	AgOPiv (no Pd)	ND	41
4	20	NaOPiv	1	41
5	20	KOPiv	18	10
6	20	CsOPiv	71	6
7 ^b	20	CsOPiv	98	< 2
8 ^b	1.0	CsOPiv	92	< 2



M^+	E°
Ag^+	0.7991 V
Na^+	-2.714 V
K^+	-2.925 V
Cs^+	-2.923 V

a) Yield was determined by GC of crude mixture.

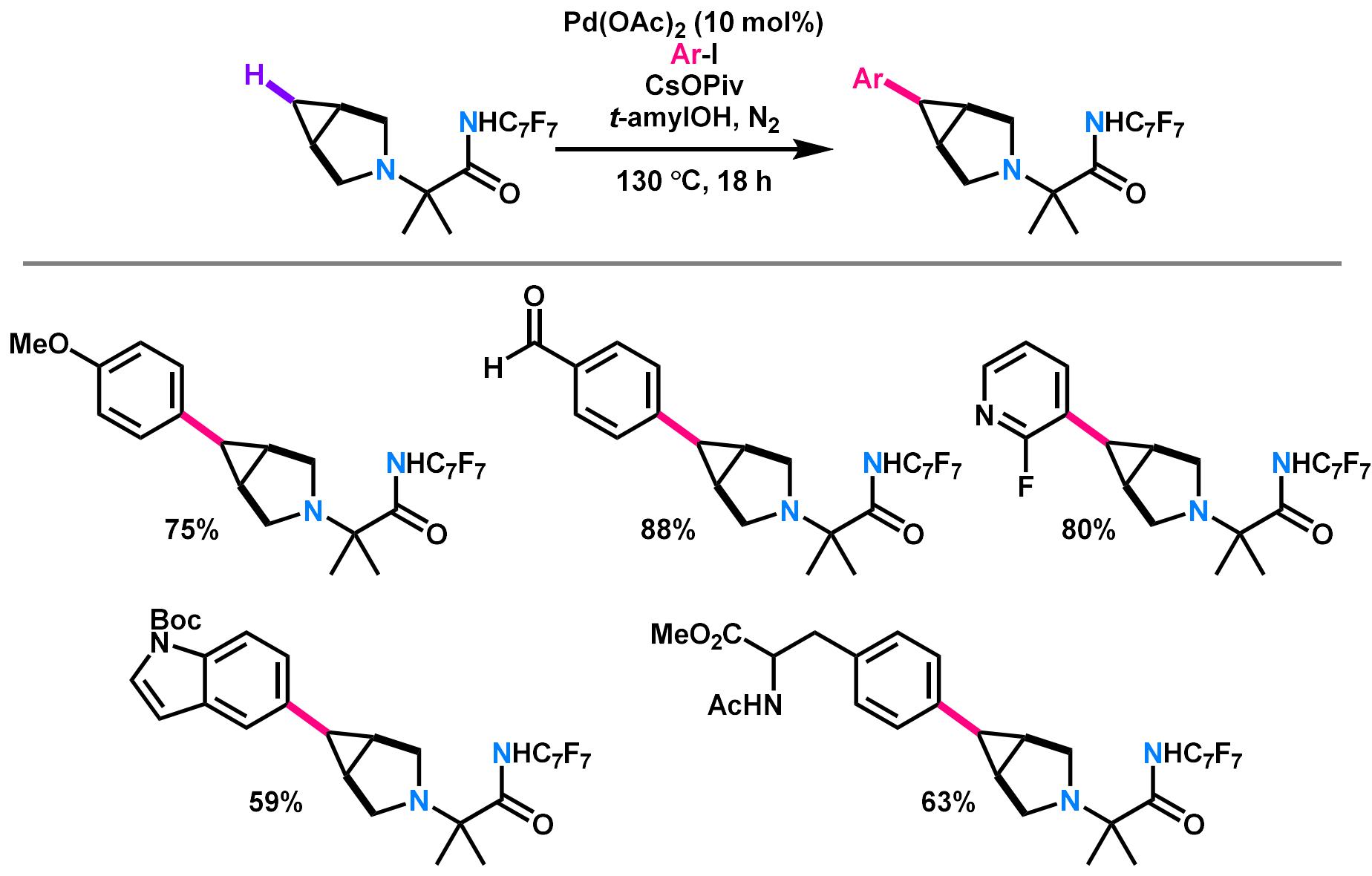
b) set up in glove box under N_2 .

The role of carboxylate is to regenerate the Pd carboxylate catalyst by abstraction of iodide from the Pd centre.

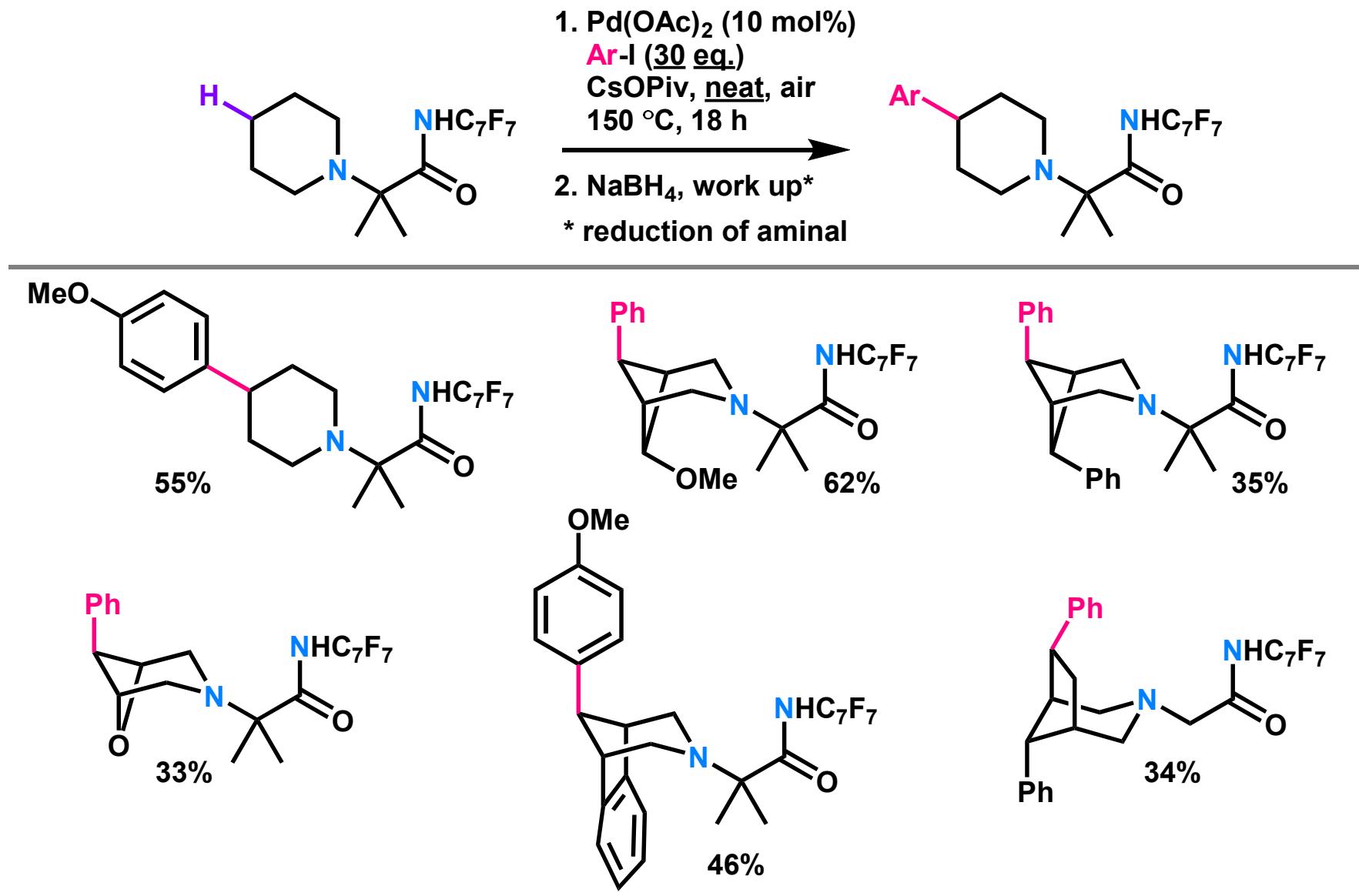
α -oxidation was suppressed by replacing Ag with non-oxidizing metal.

1) Topczewski, J. J.; Cabrera, P. J.; Saper, N. I.; Sanford, M. S. *Nature* **2016**, *531*, 220. 2) Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496. 27

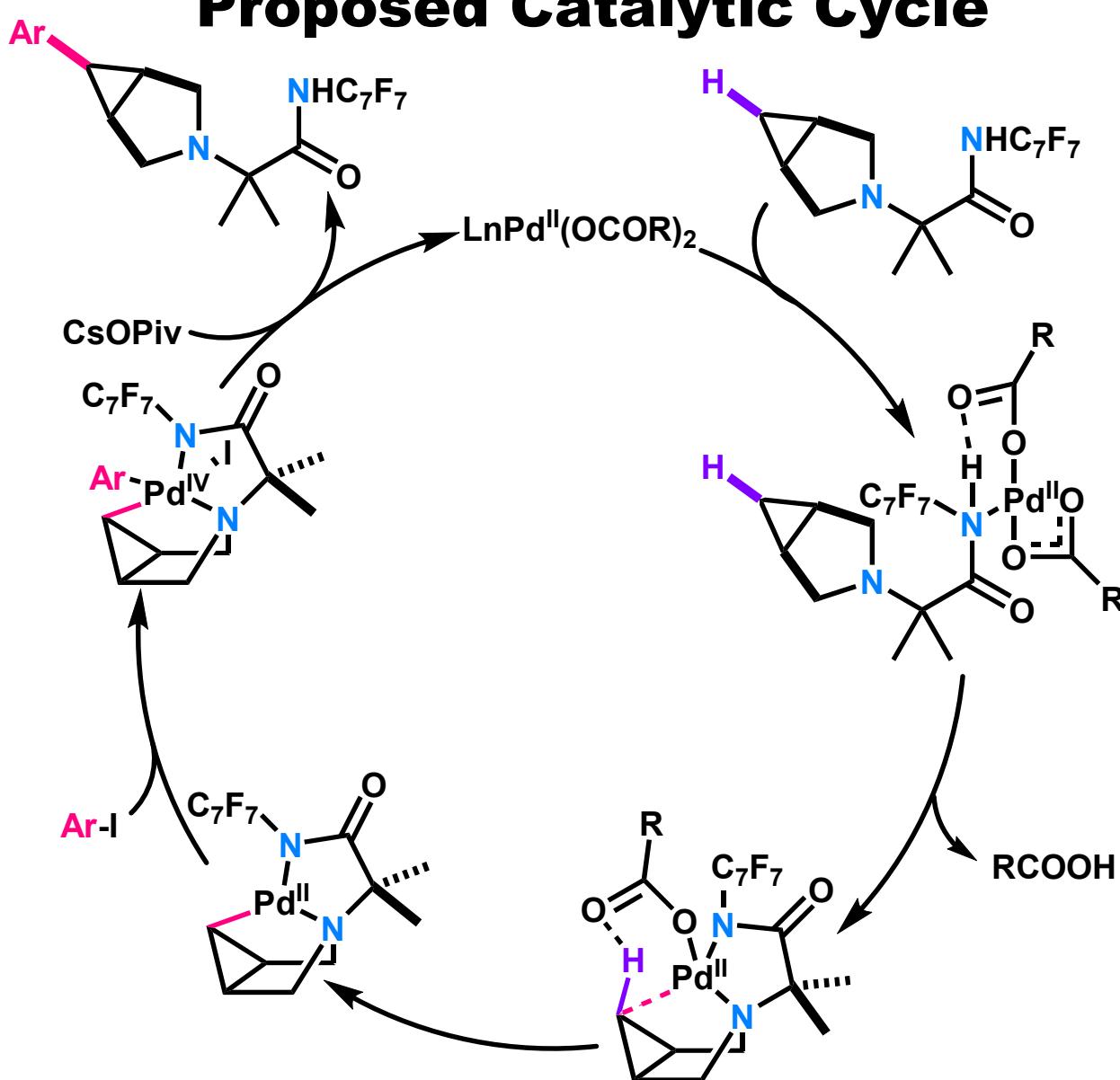
Substrate Scope



Expanding Substrate Scope

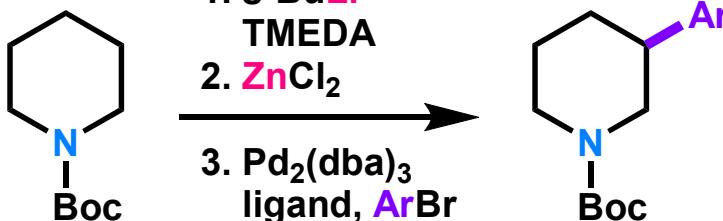


Proposed Catalytic Cycle



Summary

(1) β C-H functionalization

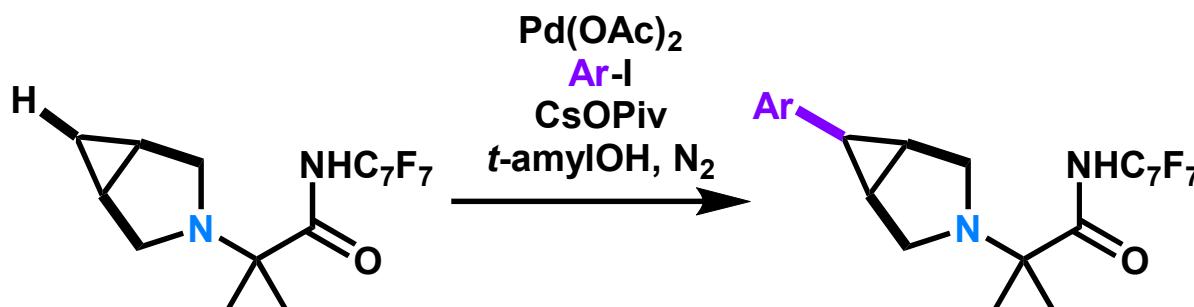


(2) exocyclic C-H functionalization



Ligands enable remote C-H functionalization.

(3) transannular C-H functionalization



Substrate design and directing group enable remote C-H functionalization.

1) Millet, A.; Larini, P.; Clot, E.; Baudoin, O. *Chem. Sci.* **2013**, *4*, 2241. 2) He, C.; Gaunt, M. J. *Angew. Chem. Int. Ed.* **2015**, *54*, 15840. 3) Topczewski, J. J.; Cabrera, P. J.; Saper, N. I.; Sanford, M. S. *Nature* **2016**, *531*, 220.