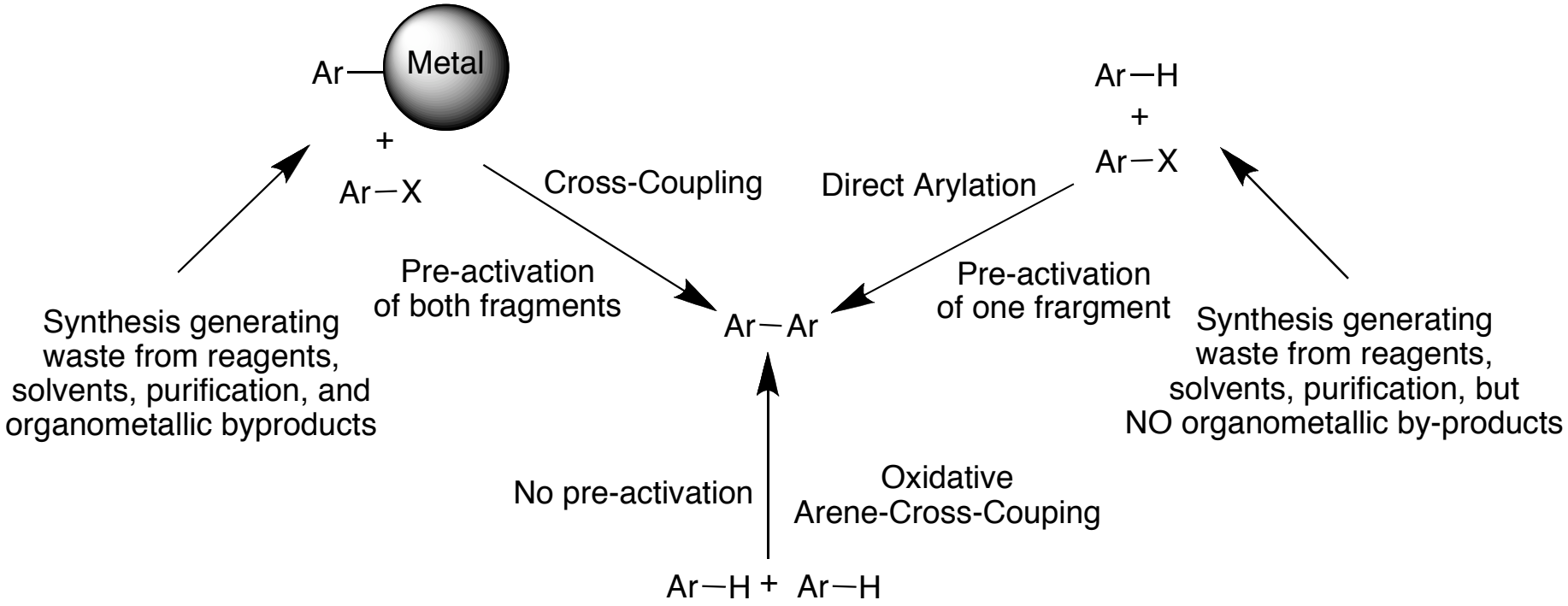
Palladium-Catalyzed Intramolecular Coupling of Arenes and Unactivated Alkanes in Air

Benoit Liegault and Keith Fagnou, Organomettalics, ASAP

Jared Hammill
Current Literature Presentation
9/27/08

Requirement for Pre-Activation

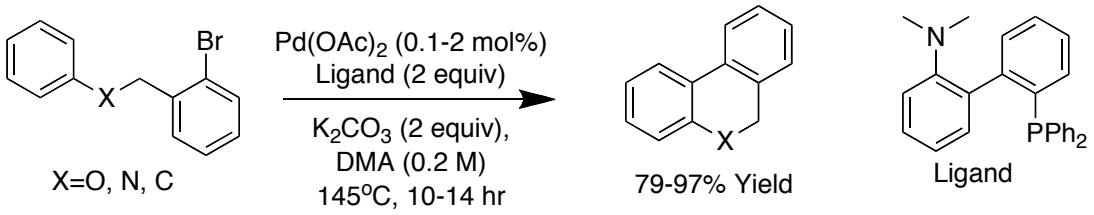
- The scientific and commercial value of biarys has led to the discovery of a variety of transition metal catalyzed coupling reactions
  - Suzuki, Stille, Negishi, Kumada, etc.



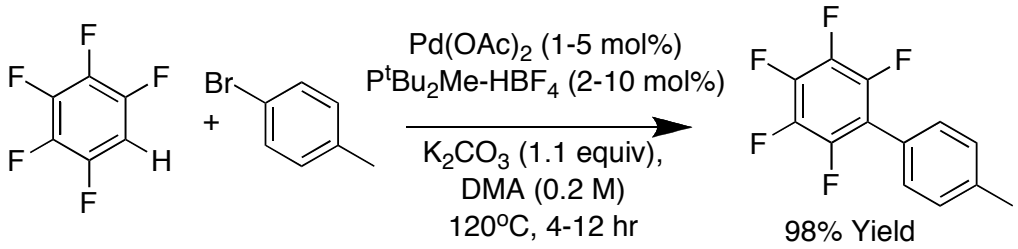
Stuart, et al., Science, 316, 1172

Fagnou Group

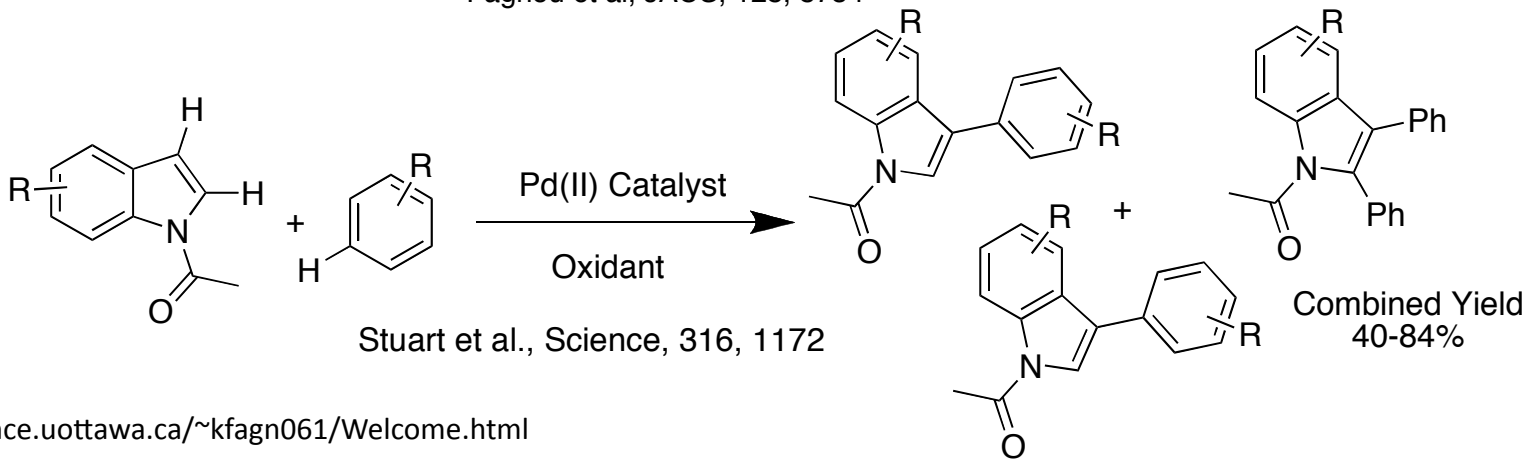
"A major focus of ongoing research is directed at changing the current practice of molecule pre-activation in the construction of new carbon-carbon bonds."



Fagnou et al, JACS, 126, 9186 & Fagnou et al, JACS, 128, 581



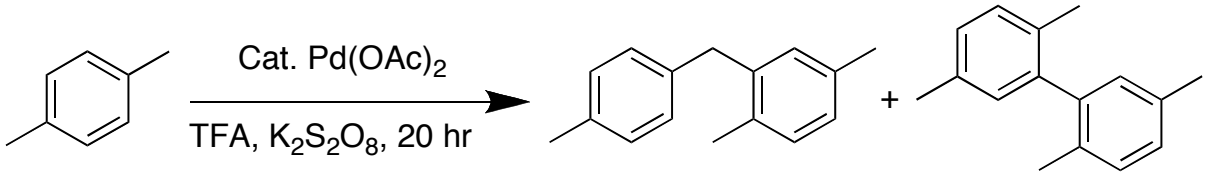
Fagnou et al, JACS, 128, 8754



Stuart et al., Science, 316, 1172

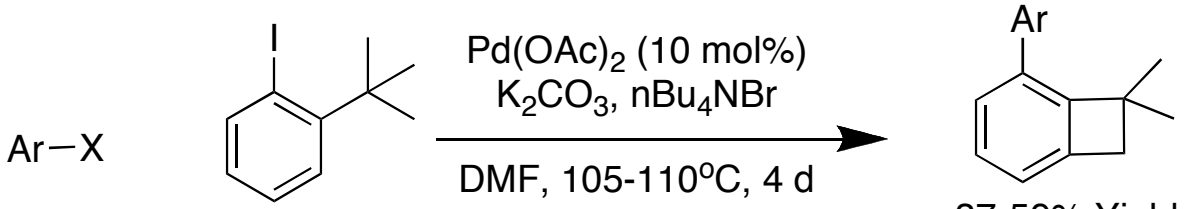
http://www.science.uottawa.ca/~kfagn061/Welcome.html

Unactivated Sp^3 C-H Coupling



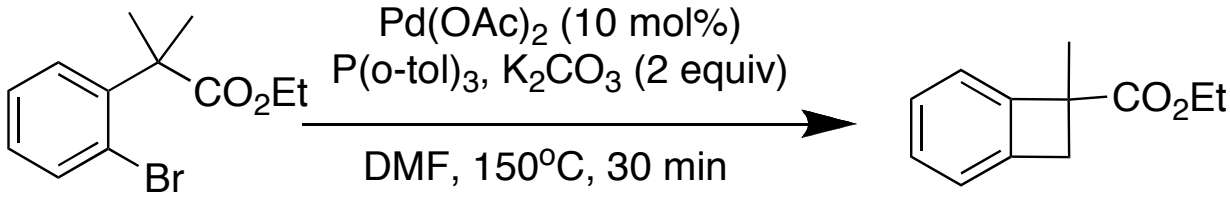
Lu, Organometallics, 26, 4376

yields <30%



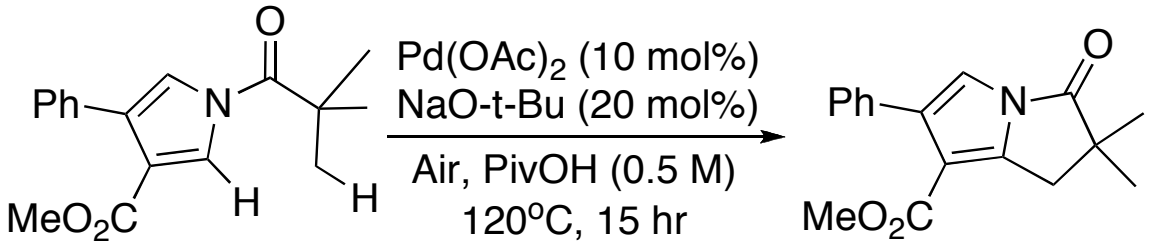
37-59% Yield

Dyker, ACIE, 33, 103



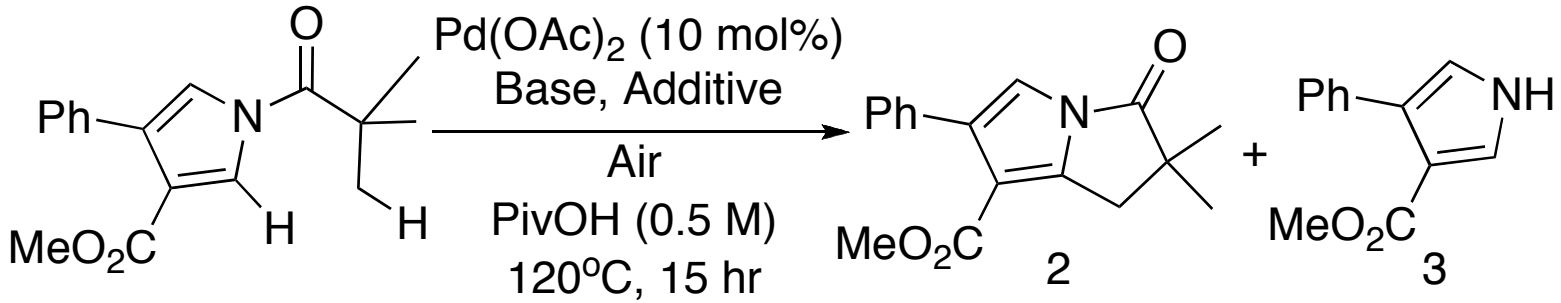
60% Yield

Gueritte, ACIE, 42, 5736



Fagnou et al, Organometallic, ASAP

Reaction Optimization



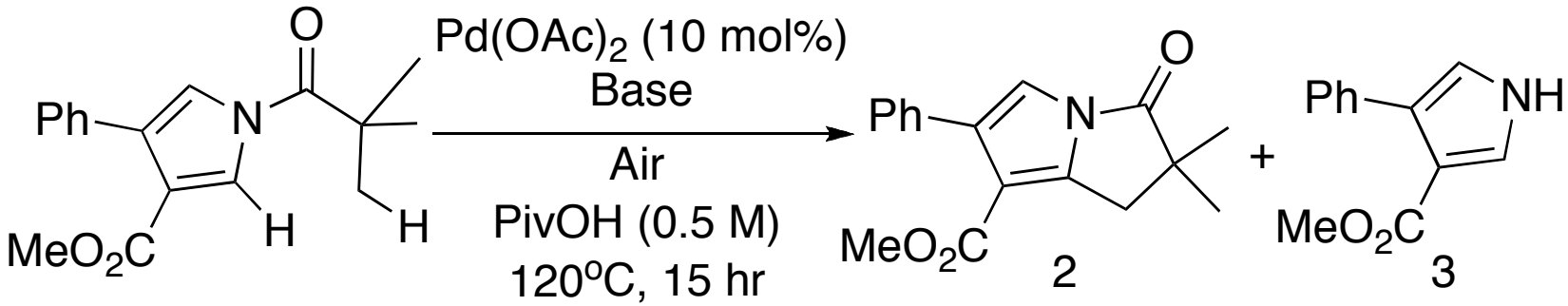
Base Screen:

NaO-tBu, Na_2CO_3, Rb_2CO_3 NaOPiv, KOPiv, CsOPiv, $(i\text{-}Pr)_2NEt$, DABCO

Terminal Oxidant Screen:

Base (20%)	Additive	SM Consumption	NMR Yield of 2	NMR Yield of 3
NaO-t-Bu	Dry O_2 (Balloon)	83	49	0
NaO-t-Bu	$Cu(OAc)_2$ Sealed Vial	62	25	2
NaO-t-Bu	Ag(Oac) Sealed Vial	67	35	4
NaO-t-Bu	-	97	82 (67 isolated)	0

Quantity of Base, The Goldilocks Scenario



- Too little

Base	SM Consumption	NMR Yield of 2	NMR Yield of 3
None	32	15	0

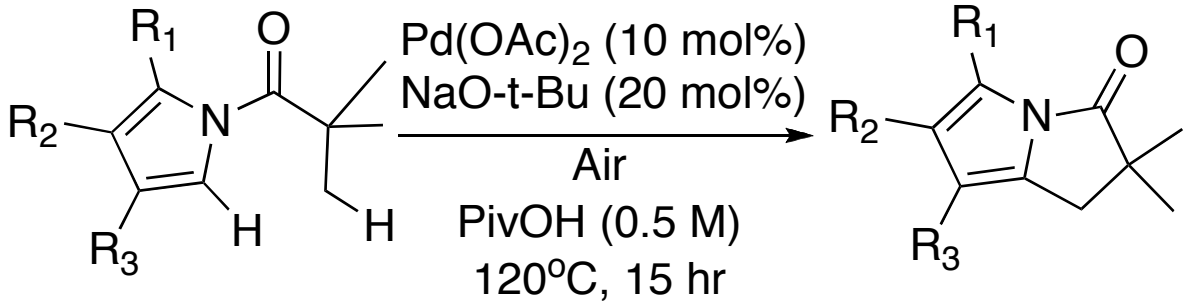
- Too much

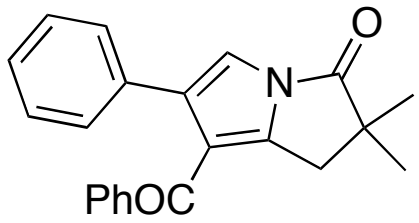
Base	SM Consumption	NMR Yield of 2	NMR Yield of 3
NaO-t-Bu (200%)	88	32	32

- Just right

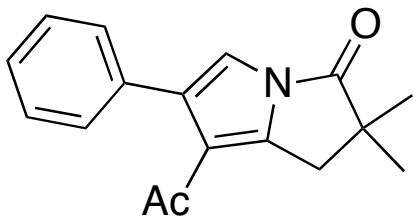
Base	SM Consumption	NMR Yield of 2	NMR Yield of 3
NaO-t-Bu (20%)	97	82(67 isolated)	0

Reaction Scope

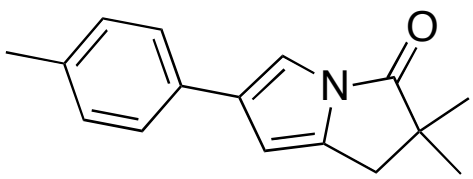




59%

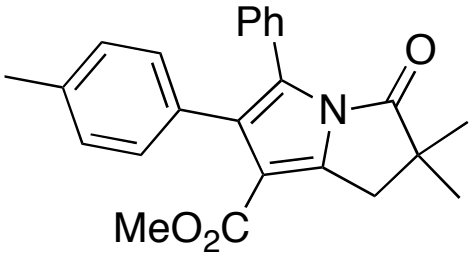


47%

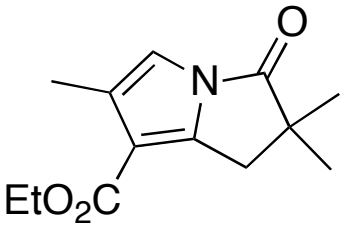


Needs EWG

12%

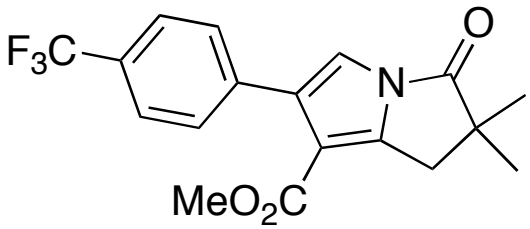


69%



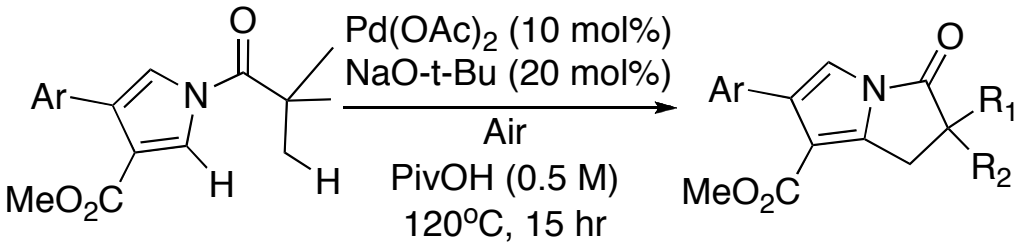
29%

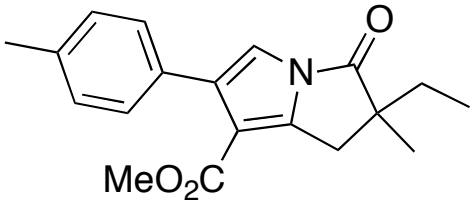
Needs Arene



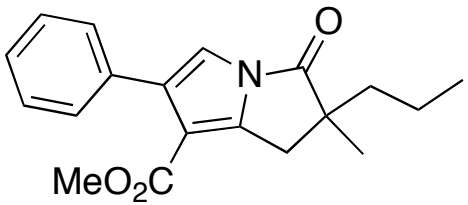
55%

Reaction Scope (cont.)

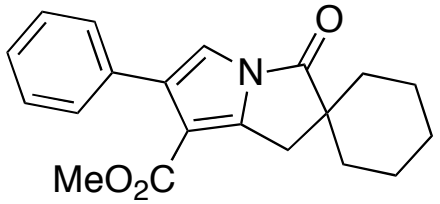




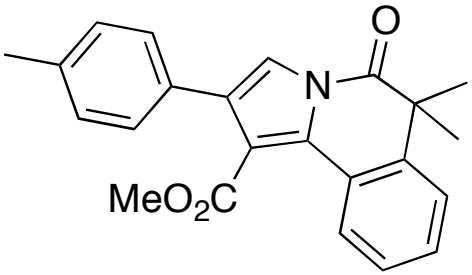
41%



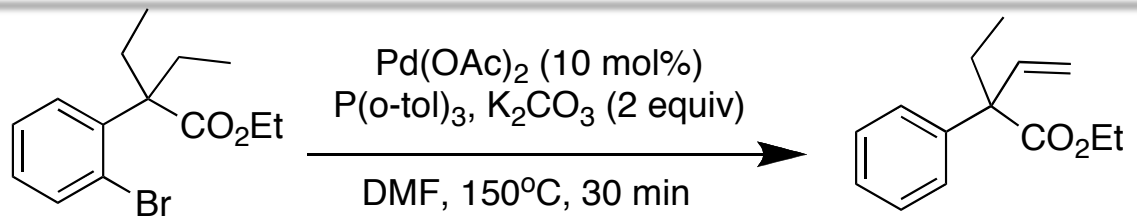
59%



45%



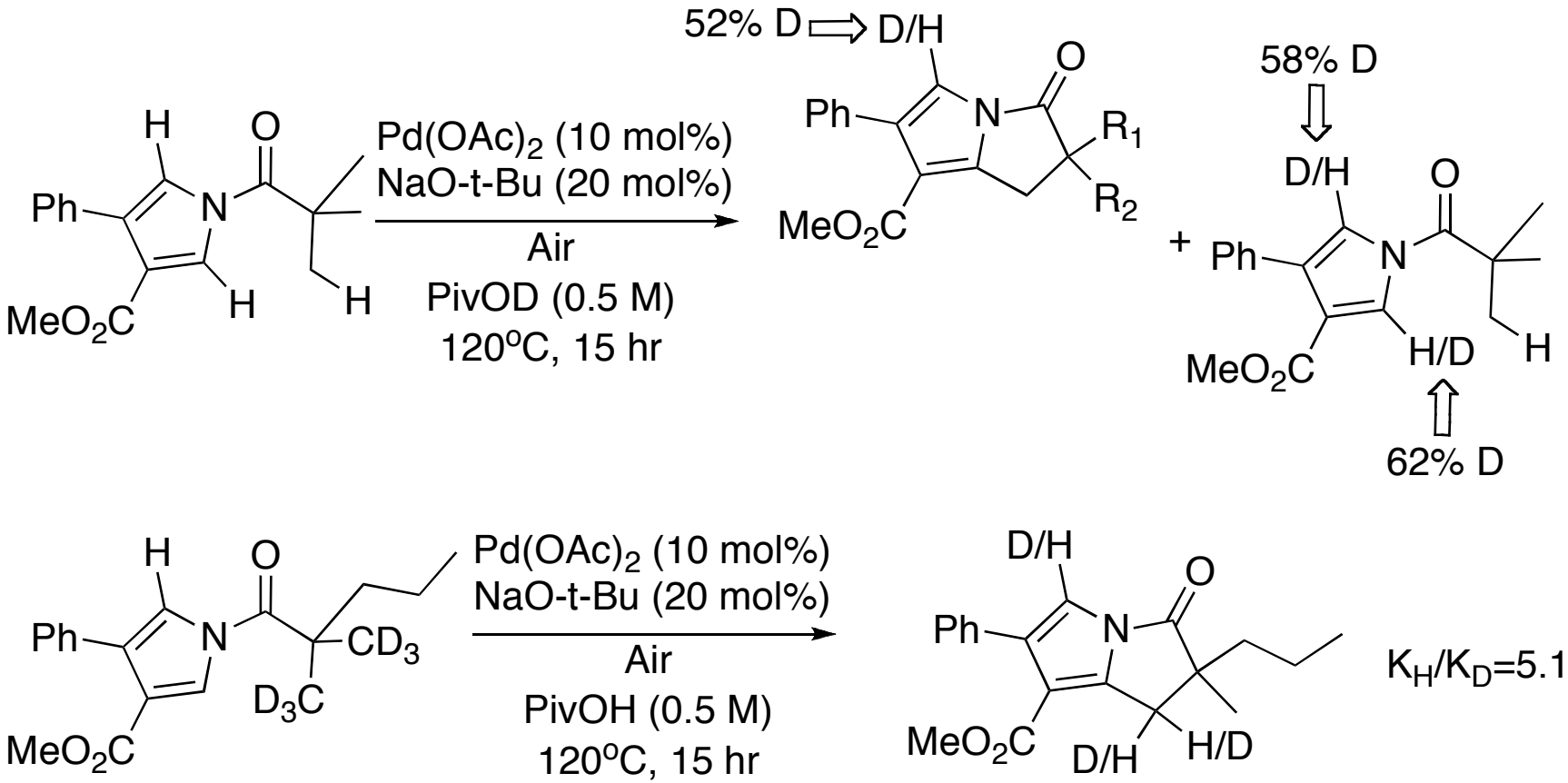
92%



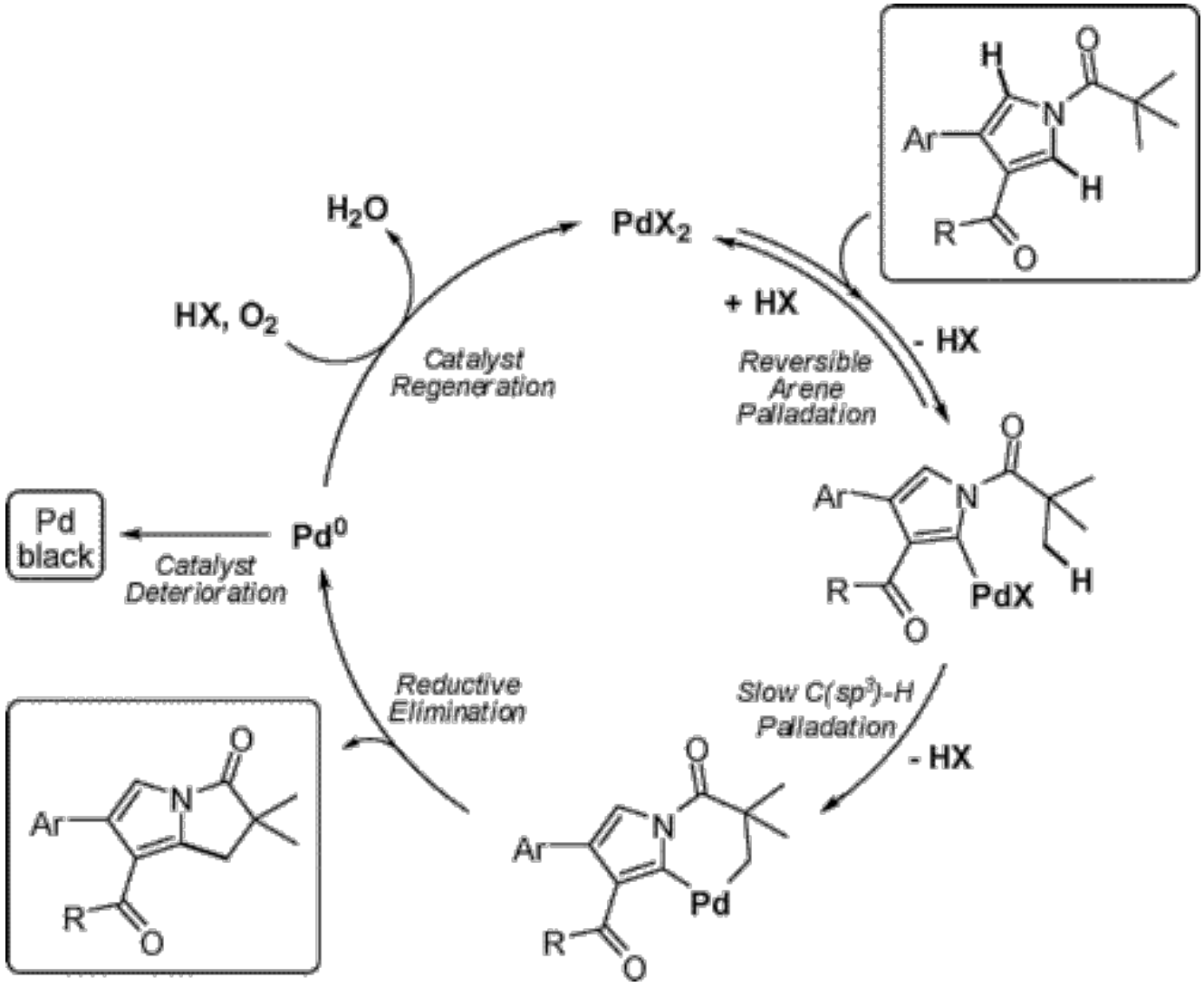
93% Yield

Don't see B-elimination product

Mechanistic Studies

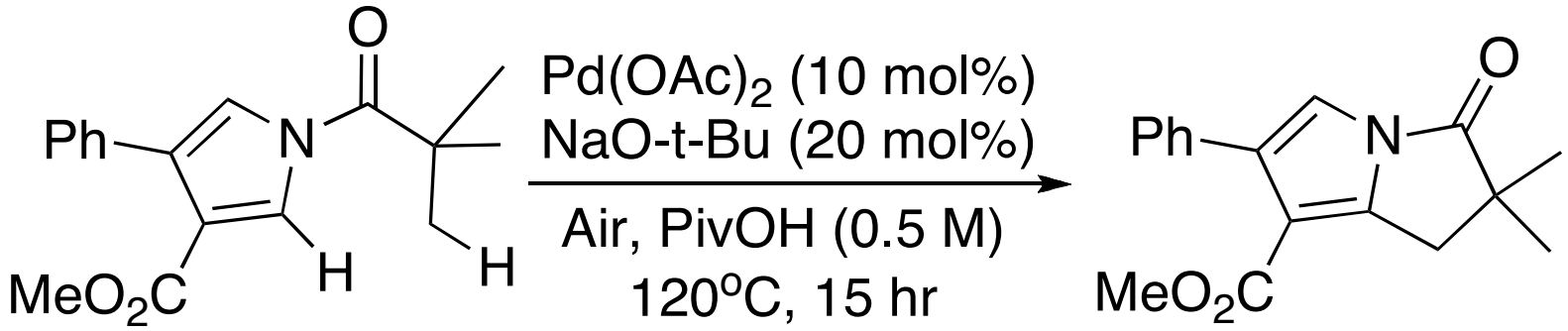


Proposed Mechanism



Reaction Limitations

- Need for EWG
- Need for Arene
- Pre-organization
  - Thorpe-Ingold effect, forced planarity



Summary

- Developed an oxidative coupling of an arene with an unactivated methyl group using Pd catalysis and air as a terminal oxidant

- Such reaction can provide economical and environmental benefits by decreasing waste and cost in preparation of pre-activated substrates

- Should prompt further investigation of C-H, C-H coupling in an effort to increase the applicability in organic synthesis