

Palladium-Catalyzed Alkylation of sp^2 and sp^3 C-H Bonds with Methylboroxine and Alkylboronic Acids: Two Distinct C-H Activation Pathways

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C-H Functionalization

- C-H most fundamental linkage in organic chemistry
- Resistant to selective chemical transformations
- Bond Dissociation C-H is large

H-CH₃ 105 kcal/mol

H-C₆H₅ 110 kcal/mol

- C-H activation disconnection strategy that will provide alternatives to conventional methods---in a single preparative step

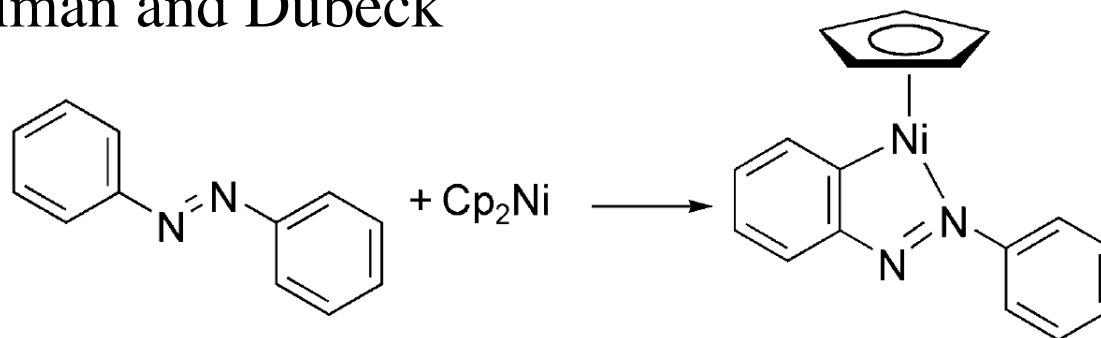
Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn
Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd
La	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg

For Reviews see: Dyker, G. *Angew. Chem. Int. Ed.* **1999**, *38*, 1698-1712.

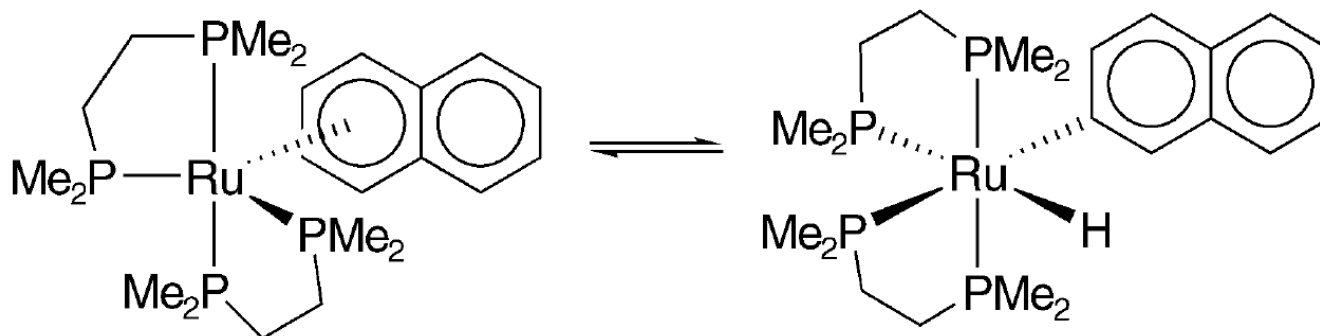
Pfeffer, M.; Ritleng, V. *Chem. Rev.* **2002**, *102*, 1731-1769.

Pioneering Studies

- 1963-Kleiman and Dubeck



- 1965-Chatt and Davidson



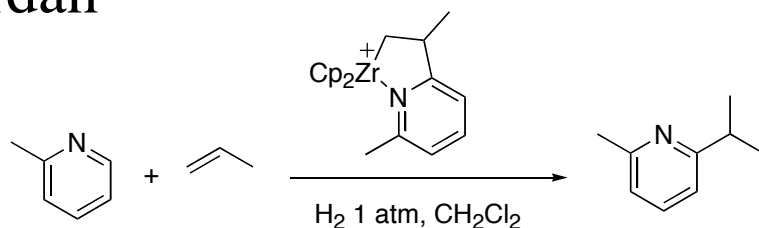
Kleiman, J.P.; Dubeck, M. *J. Am. Chem. Soc.* **1963**, 1544.

Chatt, J.M.; Davidson, M. *J. Am. Chem. Soc.* **1965**, 843.

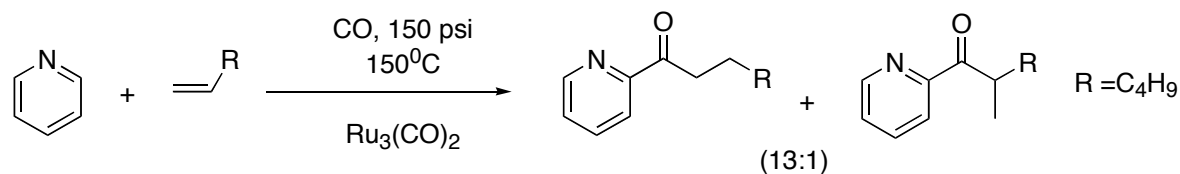
Stoichiometric cleavage of C-H bond: *Chem Rev.* **1997**, 97, 2879.

Catalytic C-H activation

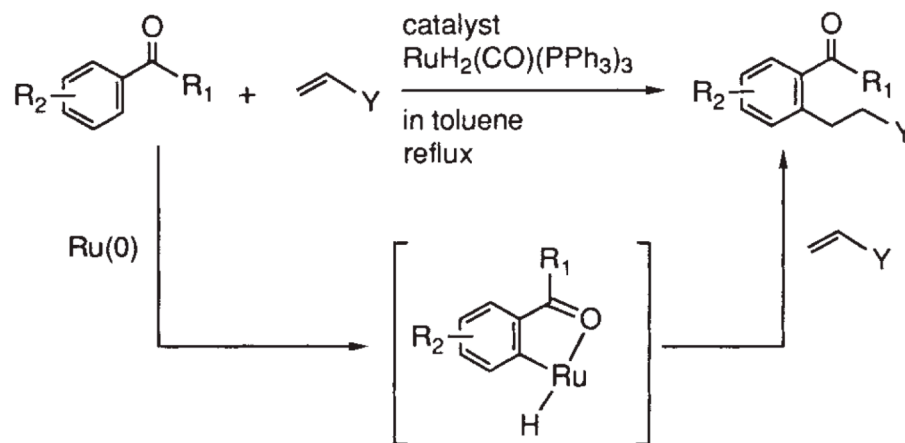
- 1989-Jordan



- 1992-Moore



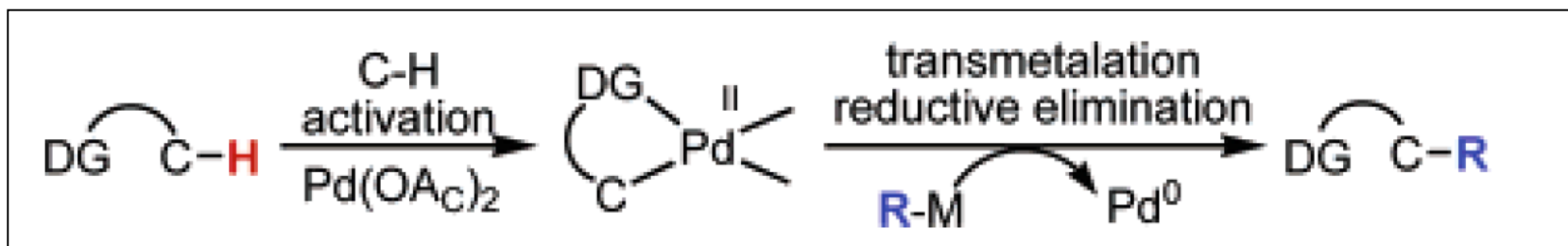
- 1993-Murai



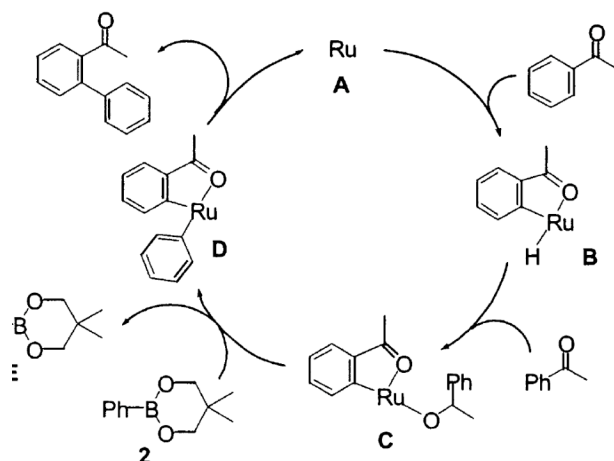
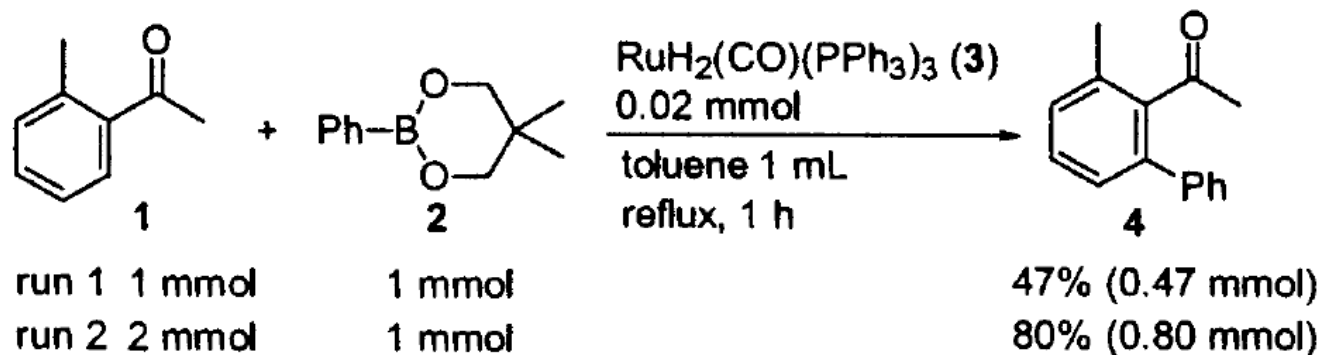
Taylor, D.; Jordan, R. *J. Am. Chem. Soc.* **1989**, *111*, 778-779.;

Moore et al. *J. Am. Chem. Soc.* **1992**, *114*, 5888.

Murai, S.; Kakiuchi, S.; Sekine, S.; Tanaka, A.; Kamatani, M.; Chatani, N. *Nature*, **1993**, *366*, 529.

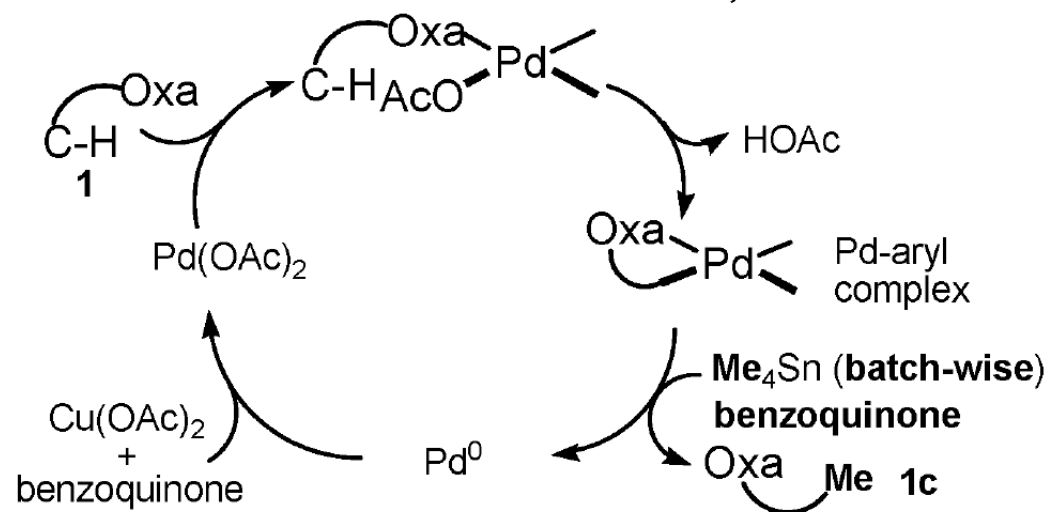
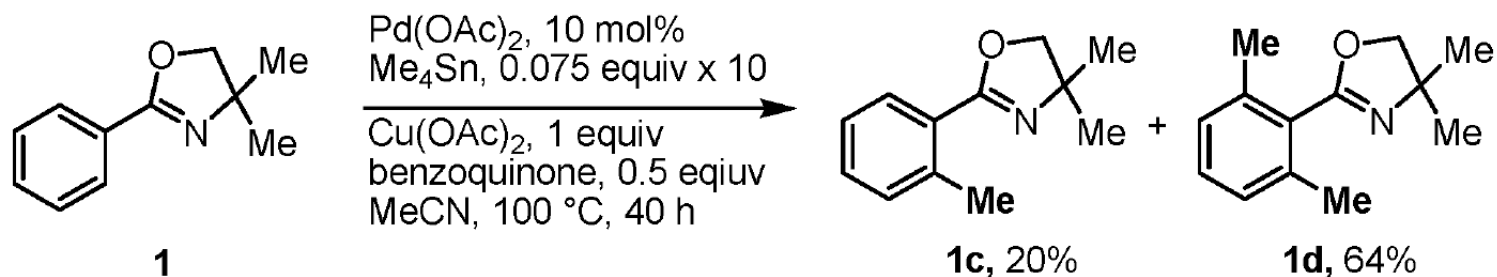


- Directed C-H activation is favored by a σ -chelating heteroatom that is conjugated to the aryl rings
- Direct coupling of C-H bonds with organometallic reagents
- Many recent examples of pyridine and carbonyl directed arylation of sp^2 and sp^3 C-H bonds



Kakiuchi, F.; Kan, S.; Igi, K.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* **2003**, *125*, 1698.

Alkylation using Organotin



Chen, X.; Li, J-J.; Hao, X-S.; Goodhue, C. E.; Yu, Jin-Quan *J. Am. Chem. Soc.* **2006**, *128*, 78-79.

Pd-catalyzed Alkylation of Aryl C-H Bonds

Entry	Substrate	Methylation product	Yield%	Entry	Product	Yield%
1		 	84	8	 	89
2		 	87	9	 	86
3			62	10		60
4			88	11		84
5			76	12		90
6			78	13		85
7			86	14		78

^a Oxa = 4,4-dimethyloxazoline-2-, Pd(OAc)₂ (10 mol %), organotin agents (0.075 equiv × 10), Cu(OAc)₂ (1 equiv), benzoquinone, 1 equiv, MeCN, 100 °C, 40 h.

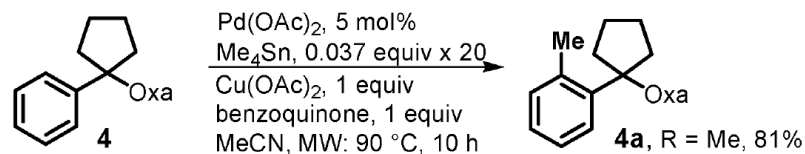
- Non- π -conjugated chelation assisted catalytic C-H activation are still rare but is possible in this instance

- Various primary alkyl tin reagents were used



- Drawback

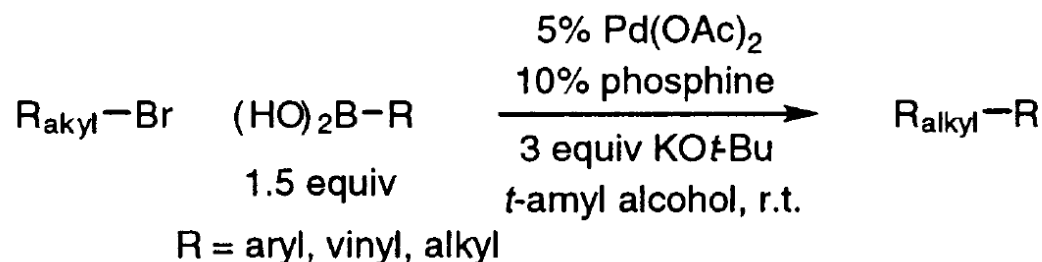
Long reaction time—batchwise addition



==> still drawbacks---batchwise addition, toxicity of Organotin reagents

Alkylation with alkylboroxine and boronic acids

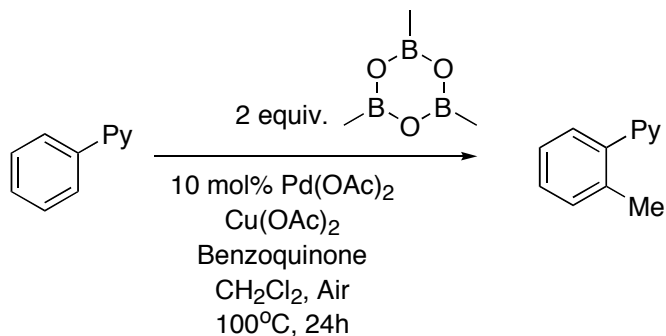
- C-H activation/C-C coupling using boronic acids is plausible



- Challenge:
 - Pd(II) catalyzed homocoupling of organometallic reagent is faster than C-H activation
 - The palladacycle formed from the C-H activation step can also catalyze homocoupling (transmetalation and reductive elimination must be faster)

Kirchhoff, J. H.; Netherton, M. R.; Hills, I. D.; Fu, G.C. *J. Am. Chem. Soc.* **2002**, *124*, 13662.

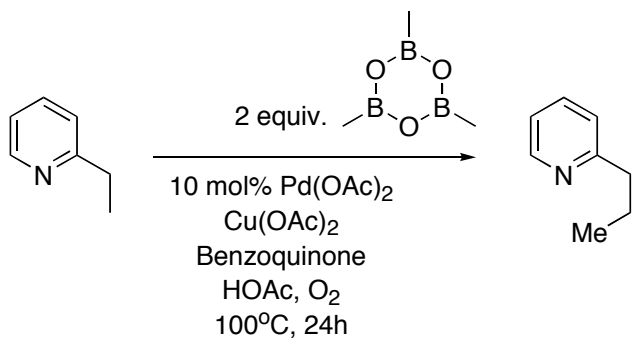
Methylation of sp^2 C-H



entry	substrate	product	yield(%)	entry	substrate	product	yield(%)
1			72 ^b	7			82
2			66	8			65
3			64	9			84
4			62	10			78
5			38	11			93
6			50	12			38

^a 10 mol % of Pd(OAc)₂, 1 equiv of benzoquinone, 1 equiv of Cu(OAc)₂, 1 equiv of methylboroxine, 100 °C, 24 h, CH₂Cl₂, air. ^b 10% dimethylated product was isolated.

Methylation of sp^3 C-H

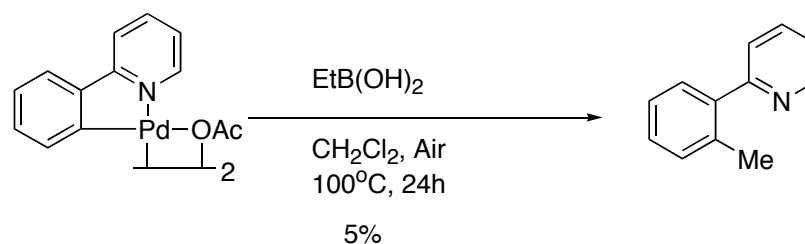
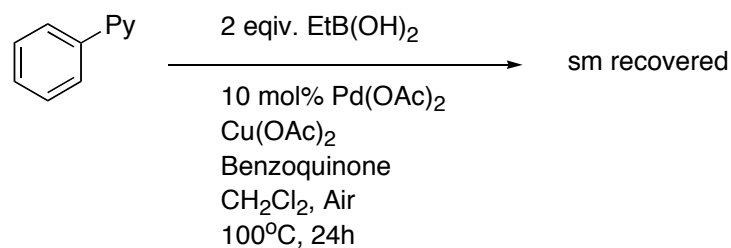


- no alkylation products were observed with ethyl or butylboroxine

entry	substrate	product	yield(%)	entry	substrate	product	yield(%)
1			79	5			60
			11				50
2			50	7			51
			20				70
3			33	8			70
4			70	9			22
				10			80

^a 10 mol % of Pd(OAc)₂, 2 equiv of benzoquinone, 2 equiv of Cu(OAc)₂, equiv of methylboroxine, 100 °C, 24 h, HOAc, O₂.

Alkylation of C-H Bonds



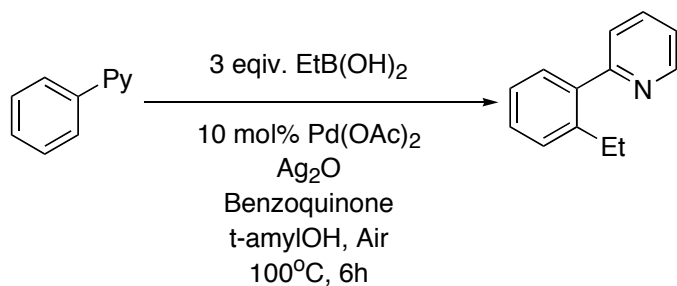
Indication that transmetalation is problematic

Optimization:

Solvents: **t-Amyl alcohol**, t-Butyl alcohol, DMF, Dioxane, Toluene, HOAc

Oxidants & Additives: **Ag₂O**, Cu(OAc)₂, H₂O, K₂CO₃, KOAc, Cu₂O, MnO₂, AgOAc, **Ag₂CO₃**

Alkylation of C-H Bonds



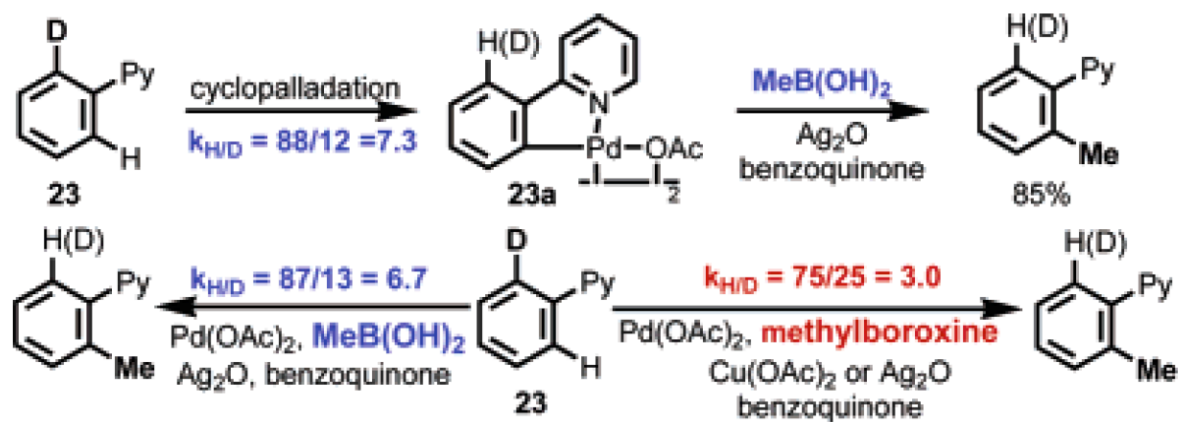
- couples both sp² and sp³ C-H bonds
- Ag₂O plays a dual role as an efficient promoter for the transmetalation as well as a co-oxidant.
- benzoquinone promotes reductive elimination
- no dialkylated products were observed

entry	RB(OH) ₂	product	yield(%)	entry	RB(OH) ₂	product	yield(%)
1	Me-B(OH) ₂		67	8	n-Bu-B(OH) ₂		55
2	Et-B(OH) ₂		64	9	Me-B(OH) ₂		40
3	n-Bu-B(OH) ₂		75	10	n-Bu-B(OH) ₂		43
4	n-Hex-B(OH) ₂		51	11	Me-B(OH) ₂		48
5	Ph(CH ₂) ₂ B(OH) ₂		53	12	n-Bu-B(OH) ₂		56
6	-B(OH) ₂		52	13	-B(OH) ₂		35
7	Me-B(OH) ₂		48				

^a 10 mol % of Pd(OAc)₂, 1 equiv of Ag₂O, 0.5 equiv of benzoquinone, equiv of boronic acid, 100 °C, 6 h, *tert*-amyl alcohol, air.

Mechanistic Insights

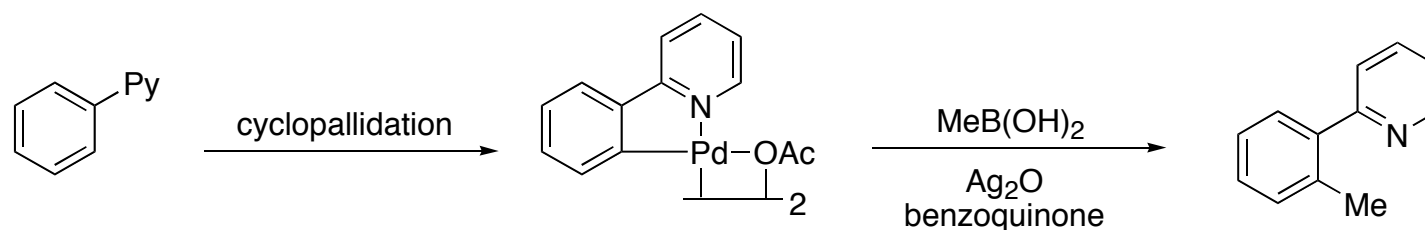
- **Kinetic Isotope Effect:** changes in rate observed when a ^1H is replaced by a ^2D in the same reaction.
- This change can affect the rate of the reaction only if H(or D) is involved in the rate determining step



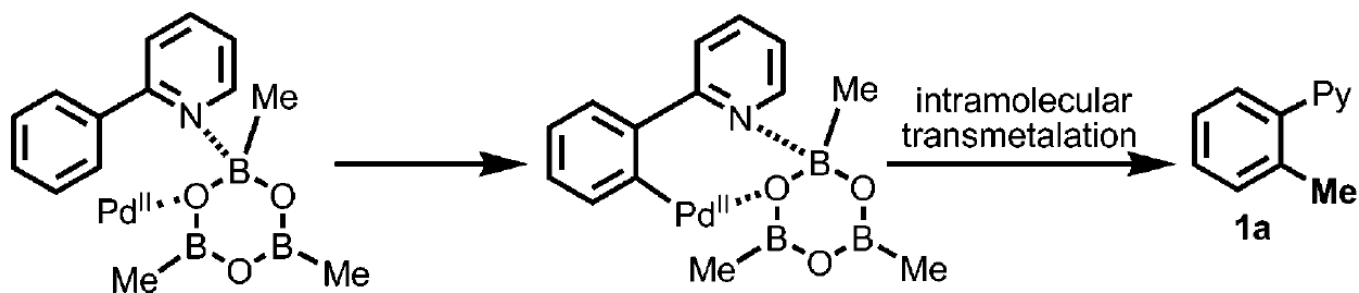
- $K_{\text{H/D}}$ for cyclopallidation with MeB(OH)_2 is 7.3.
- Dimeric palladacycle reacts only with boronic acids under the optimized conditions, not the conditions used for methylboroxine.
- $K_{\text{H/D}}$ for methylation with MeB(OH)_2 is 6.7 and with methylboroxine is 3.0.
- Intermolecular KIE with MeB(OH)_2 is 4.0 and with methylboroxine is 3.5. suggests that C-H cleavage is the rate determining step in both reactions

C-H Activation Pathways

Boronic Acids



Methylboroxine



Summary

- One pot procedure for the coupling of sp^2 and sp^3 C-H bonds with alkylboroxines and alkylboronic acids has been developed using Pd(II).
- Mechanistic studies utilizing kinetic isotope effects indicate two distinct pathways for C-H activation.
- Expand scope by using other directing groups and organometallic reagents
- Many reports focused on investigations on the scope and limitations of these types of reactions, only a few cases of applications towards natural products.