
Catalytic C-H Bond Functionalization with Palladium(II)

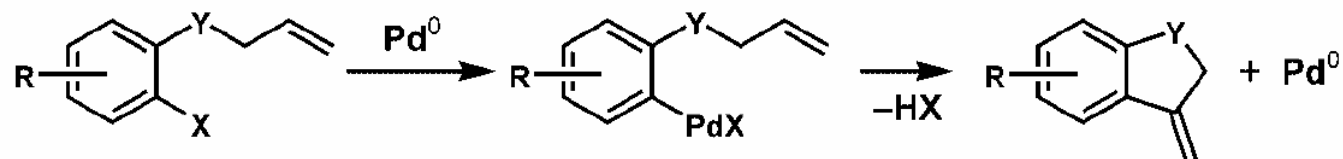
-- Latest development in the synthesis of functionalized indoles and benzofurans/dihydrobenzofurans

-- Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2003**, *125*, 9578

-- Zhang, H, Ferreira, E. M.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2004**, *43*, 6144

Introduction

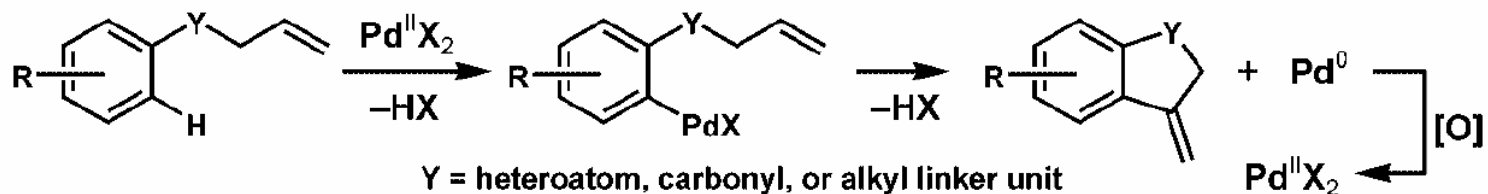
a) Heck Cyclization



Overall process involves two functionalization events:

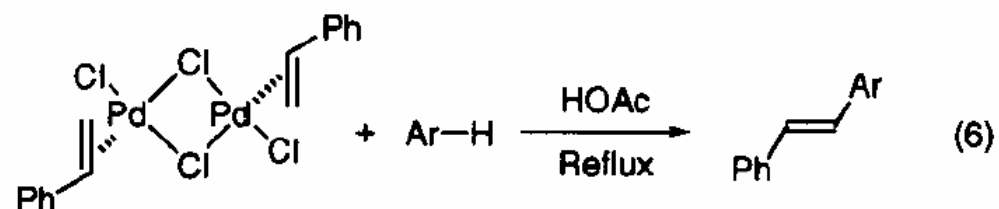
- Halogenation of aryl/vinyl precursor
- Palladium(0) catalyzed C-C bond formation.

b) Fujiwara-Moritani/Oxidative Heck Cyclization

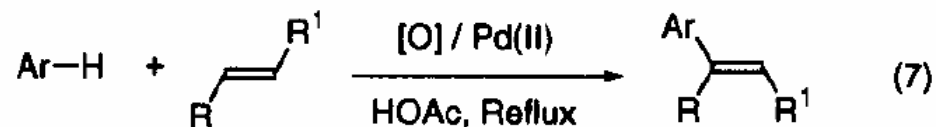


Oxidative coupling of unfunctionalized arene directly with alkene avoid prehalogenation.

Introduction – Fujiwara-Moritani Oxidative Heck Reaction



Ar = phenyl, *p*-tolyl, 2,5-dimethylphenyl
Yield: 15-26% on Pd-complex



ArH : benzenoid and non-benzenoid

R = H, CH₃, Ph. R' = Ph, CO₂Et, COMe, CHO, CO₂H, CN

Yield: 10-90% on olefin

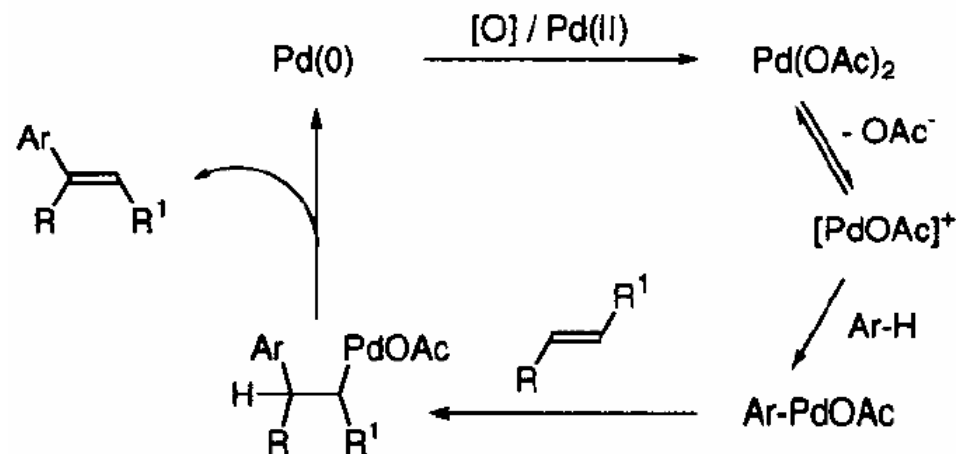
TON: 3-280

Early Report: Fujiwara, Moritani, et al. *TL*, 1967, 1119; *JACS*, 1969, 91, 7166.

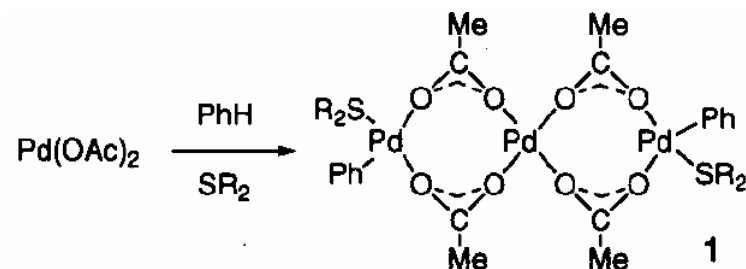
Latest Review: Fujiwara et al. *Acc. Chem. Res.* **2001**, 34, 633

Introduction – Fujiwara-Moritani Oxidative Heck Reaction

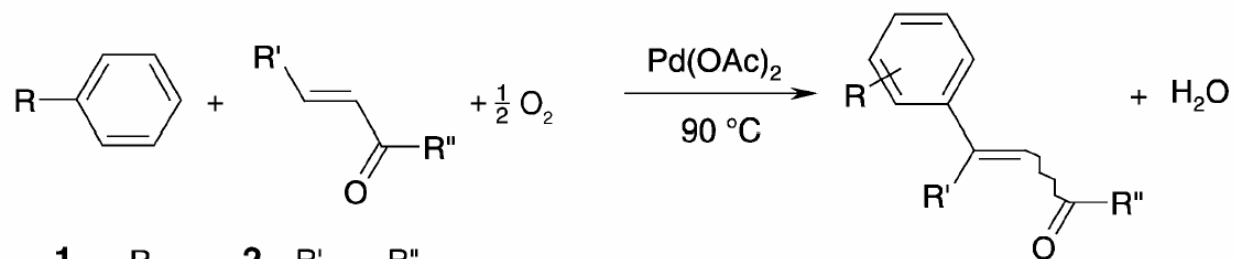
Mechanism for Pd catalyzed coupling of arene with olefin:



σ -Aryl-Pd complexes formed via electrophilic substitution of aromatic C-H bonds by cationic [PdOAc]⁺ species have been proved to be the intermediates in the catalytic cycle.

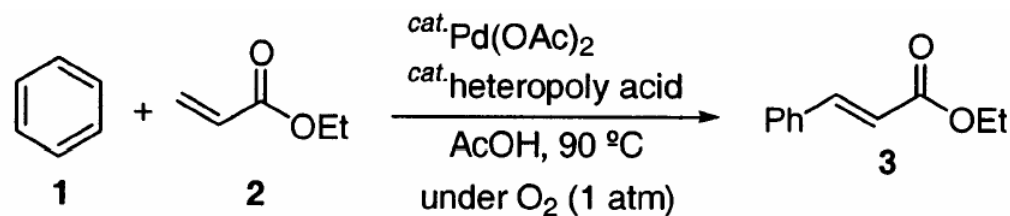


Introduction – Fujiwara-Moritani Oxidative Heck Cyclization



1	R	2	R'	R''
a	H	a	H	OBu
b	Me	b	Ph	OEt
c	OMe	c	Ph	Me

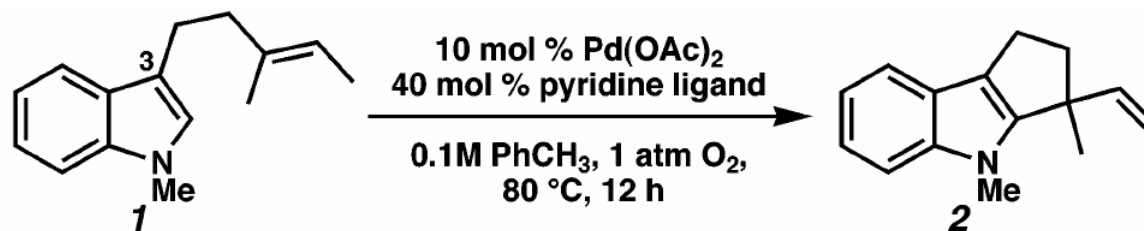
Jacobs, P. A. et al. *Ang*, 2003, 3512.



Ishii, Y. et al *JACS*, 2003, 1476.

- Latest studies largely focused on coupling of benzene with activated olefins.
- Direct intramolecular oxidative Heck cyclization between arene and unactivated olefins not thoroughly studied.

Catalytic Pd(II)-mediated Aerobic Indole Annulation.



entry	pyridine ligand	p <i>K</i> _a (pyrH ⁺)	conversion (%) ^a
1	4-MeO	6.47	3
2	4- <i>t</i> -Bu	5.99	1
3	unsubstituted	5.25	23
4	4-CO ₂ Et	3.45	52
5	3-CO ₂ Et	3.35	76
6	3-COCH ₃	3.18	58
7	3-F	2.97	64
8	3-CN	1.39	55
9	3,5-di-Cl	0.90	22

-- electron-poor ligands resulted in a more electrophilic, and therefore more reactive, palladium catalyst.

-- Ligands that were too electron-deficient, however, were unable to sufficiently ligate palladium, likely hampering both reactivity and Pd(0) reoxidation.

Catalytic Pd(II)-mediated Aerobic Indole Annulation.

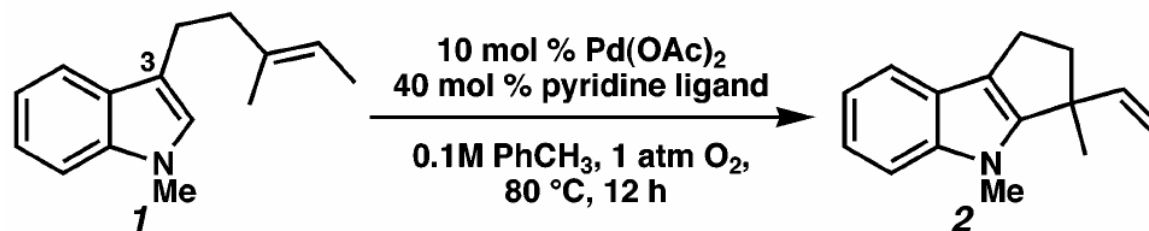
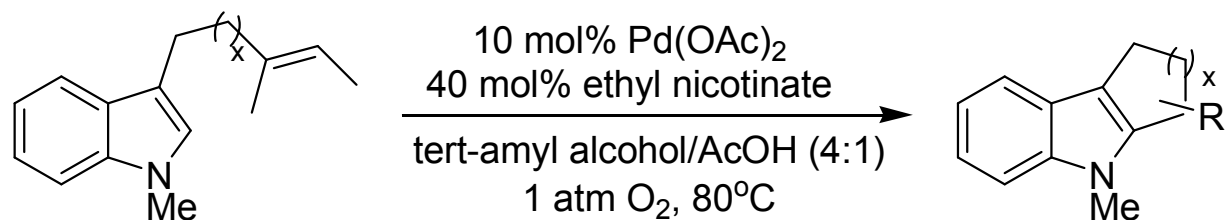


Table 2. Solvent Effects in the Reaction of **1** to **2**

entry	solvent	% conversion	% yield (GC)
1	toluene	88	33
2	chlorobenzene	85	40
3	butyl acetate	95	49
4	<i>tert</i> -amyl alcohol	94	53
5	pinacolone	95	58
6	AcOH	86	25
7.	pinacolone/AcOH (4:1)	91	76
8	<i>tert</i> -amyl alcohol/AcOH (4:1)	99	82 ^b

^a 10 mol % Pd(OAc)₂, 40 mol % ethyl nicotinate, 1 atm O₂, 80 °C, 24 h, 0.1 M substrate **1** in solvent. ^b Isolated yield.

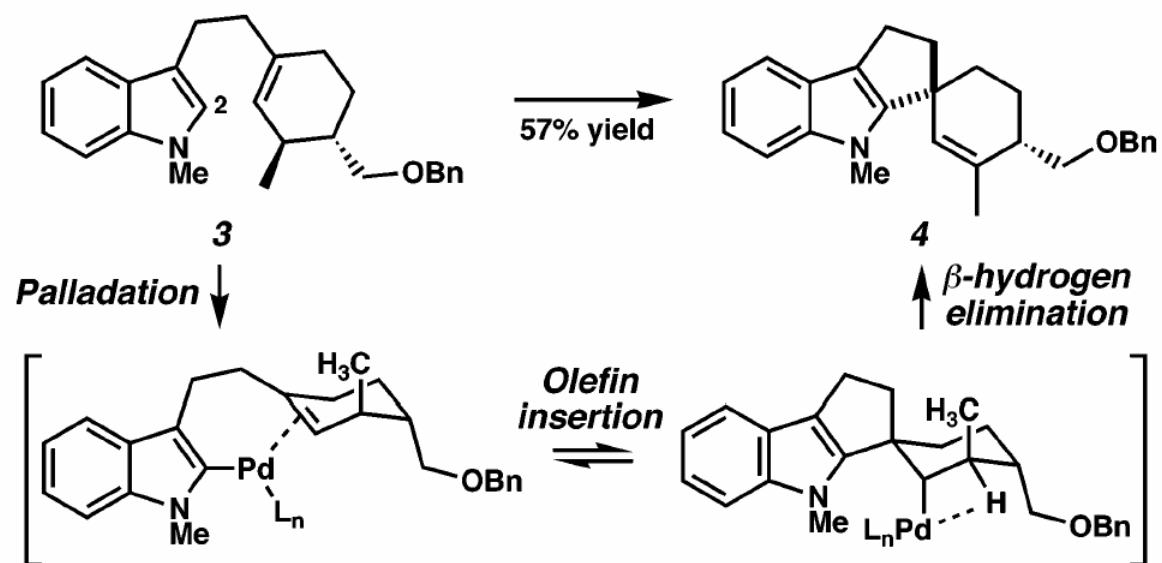
Catalytic Pd(II)-mediated Aerobic Indole Annulation.



entry	substrate ^b	product	time	% yield	entry	substrate ^b	product	time	% yield ^c	
1.			R = Me	24 h	82	9.			53 h	64 (1:1 dr)
2.			R = Et	18 h	74	10.			39 h	66 ^e
3.			R = CH ₂ OBn	24 h	60	11.			6 h	73 ^f
4.			R = 6-Cl	32 h	62	12.			5 h	68 ^f
5.			R = 5-OBn	20 h	73	13.			18 h	74
6.			<i>n</i> -Pent	30 h	79 ^d					
7.				48 h	69					
8.				18 h	76 (6:1 dr)					

Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2003**, *125*, 9578

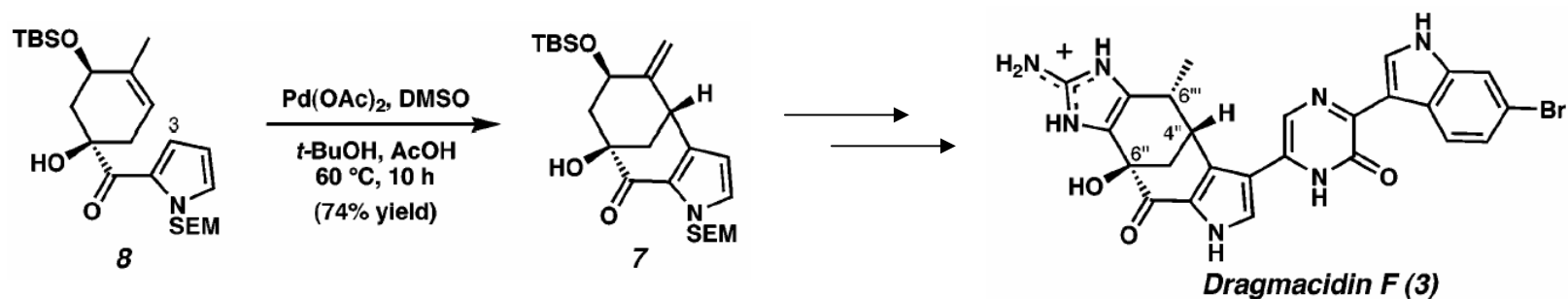
Catalytic Pd(II)-mediated Aerobic Indole Annulation.



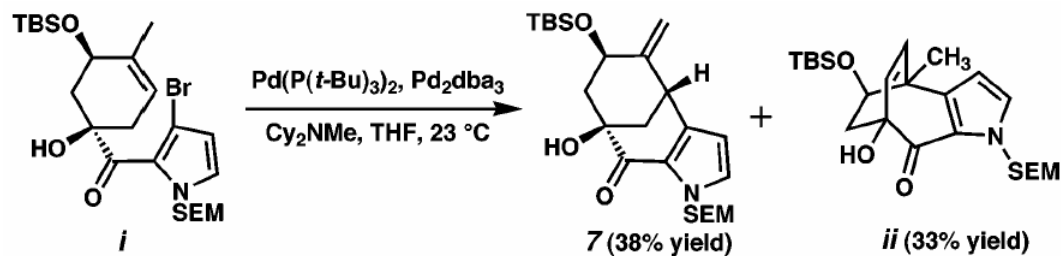
-- Observed stereochemistry of **4** supports palladation-syn insertion-syn β -elimination sequence.

Application of Pd(II)-mediated Aerobic Indole Annulation.

-- Optimized condition gave **7** as single isomer in good yield.

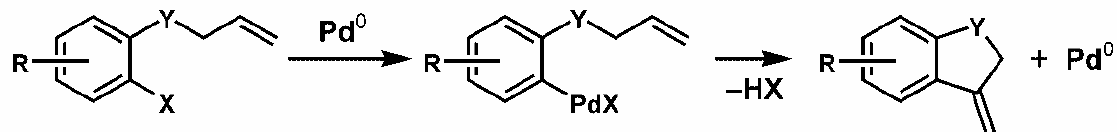


-- Intramolecular Heck cyclization resulted in competitive production of undesired product:

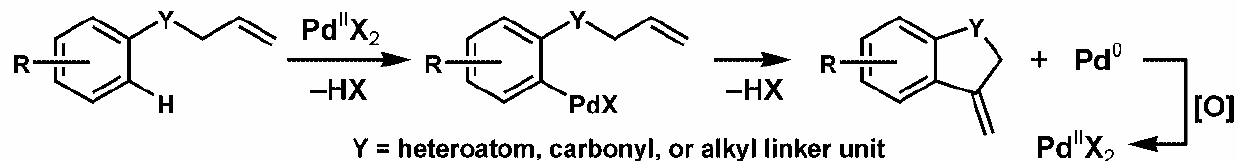


Intramolecular Pd(II)-mediated Oxidative Heck Cyclization

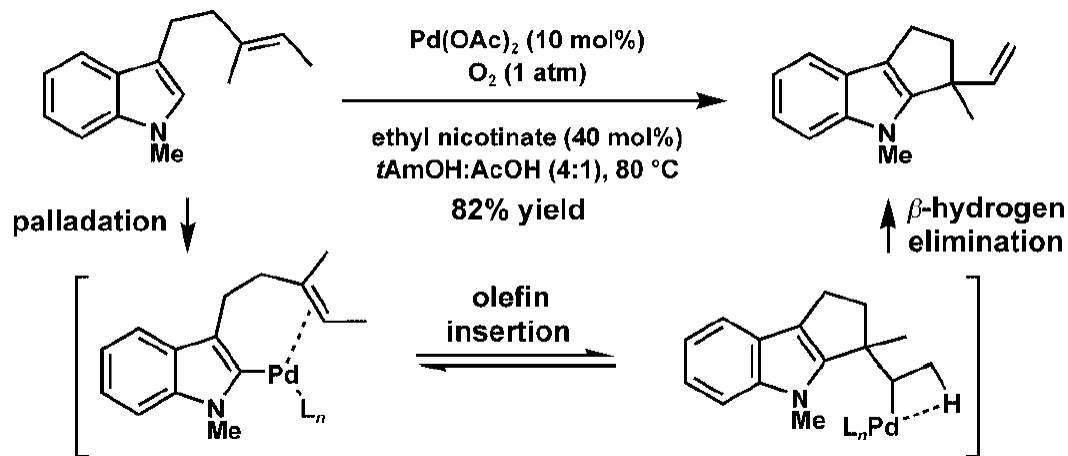
a) Heck Cyclization



b) Fujiwara-Moritani/Oxidative Heck Cyclization



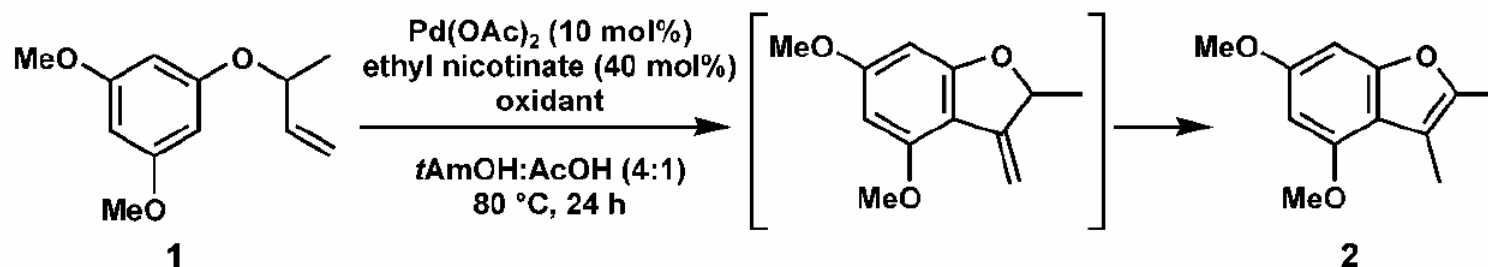
c) Indole Annulation



- $\text{Pd}(0)$ mediated oxidative addition of electron-rich aryl halides is typically slower than that to electron-poor arenes.
- Direct $\text{Pd}(\text{II})$ mediated oxidative process would be complementary.

Pd(II)-mediated Oxidative Cyclization – Benzofuran Synthesis

Table 1: Screening of oxidants for the intramolecular oxidative Heck cyclization.^[a]

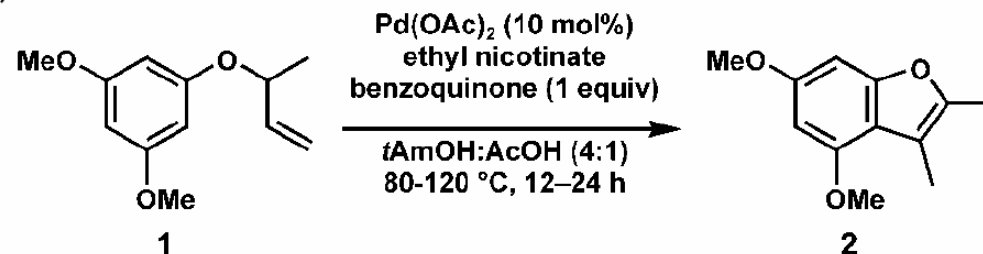


Entry	Oxidant [1 equiv]	Yield [%] ^[b]	Entry	Oxidant [1 equiv]	Yield [%] ^[b]
1	O ₂ (1 atm)	56	5	Tl(OCOCF ₃) ₃	< 10
2	benzoquinone	62	6	K ₂ S ₂ O ₈	30
3	Cu(OAc) ₂	31	7	H ₂ NC(S)NH ₂	< 10
4	AgOAc	29	8	PhCO ₃ <i>t</i> Bu	42

[a] All reactions were carried out with 0.10 mmol **1**, 10 mol% Pd(OAc)₂ (0.01 mmol), 40 mol% ethyl nicotinate (0.04 mmol), and 0.10 mmol or 1 atm oxidant in 1.0 mL 4:1 *t*AmOH:AcOH (0.1 M in substrate). [b] Yield determined by gas chromatography.

Pd(II)-mediated Oxidative Cyclization – Benzofuran Synthesis

Table 2: Optimization studies for the intramolecular oxidative Heck cyclization.^[a]



Entry	Ethyl nicotinate [mol %]	NaOAc [mol %]	T [°C]	t [h]	Yield [%] ^[b]
1	40	—	80	24	62
2	20	—	80	24	66
3	10	—	80	24	59
4	0	—	80	24	55
5	20	100	80	24	70
6	20	20	80	24	74
7	20	20	100	12	80 (77) ^[c]
8	20	20	120	12	67

[a] All reactions were carried out with 0.10 mmol **1**, 10 mol% $\text{Pd}(\text{OAc})_2$ (0.01 mmol), 0–40 mol% ethyl nicotinate (0–0.04 mmol), 0–0.10 mmol NaOAc, and 0.10 mmol benzoquinone in 1.0 mL 4:1 $t\text{AmOH}:\text{AcOH}$ (0.1 M in substrate). [b] Yield determined by gas chromatography. [c] Yield of isolated product in parentheses.

Pd(II)-mediated Oxidative Cyclization – Benzofuran Synthesis

Table 3: Oxidative benzofuran synthesis.^[a]

Entry	Substrate	Product	<i>t</i> [h]	Yield [%] ^[b]
1			R = Me	77
2			R = Et	74
3			R = <i>n</i> -C ₅ H ₁₁	72
4			12	62
5			14	54
6			12	61
7			R = Me	75
8			R = Et	79
9			12	61
10			16	56 ^[c]
11			16	52 ^[c]

[a] All reactions were carried out with 0.50 mmol substrate, 10 mol% Pd(OAc)₂ (0.05 mmol), 20 mol% ethyl nicotinate (0.10 mmol), 0.10 mmol NaOAc, and 0.50 mmol benzoquinone in 5.0 mL 4:1 *t*AmOH:AcOH (0.1 M in substrate) at 100 °C. [b] Yield of isolated product. [c] Produced as a single regioisomer.

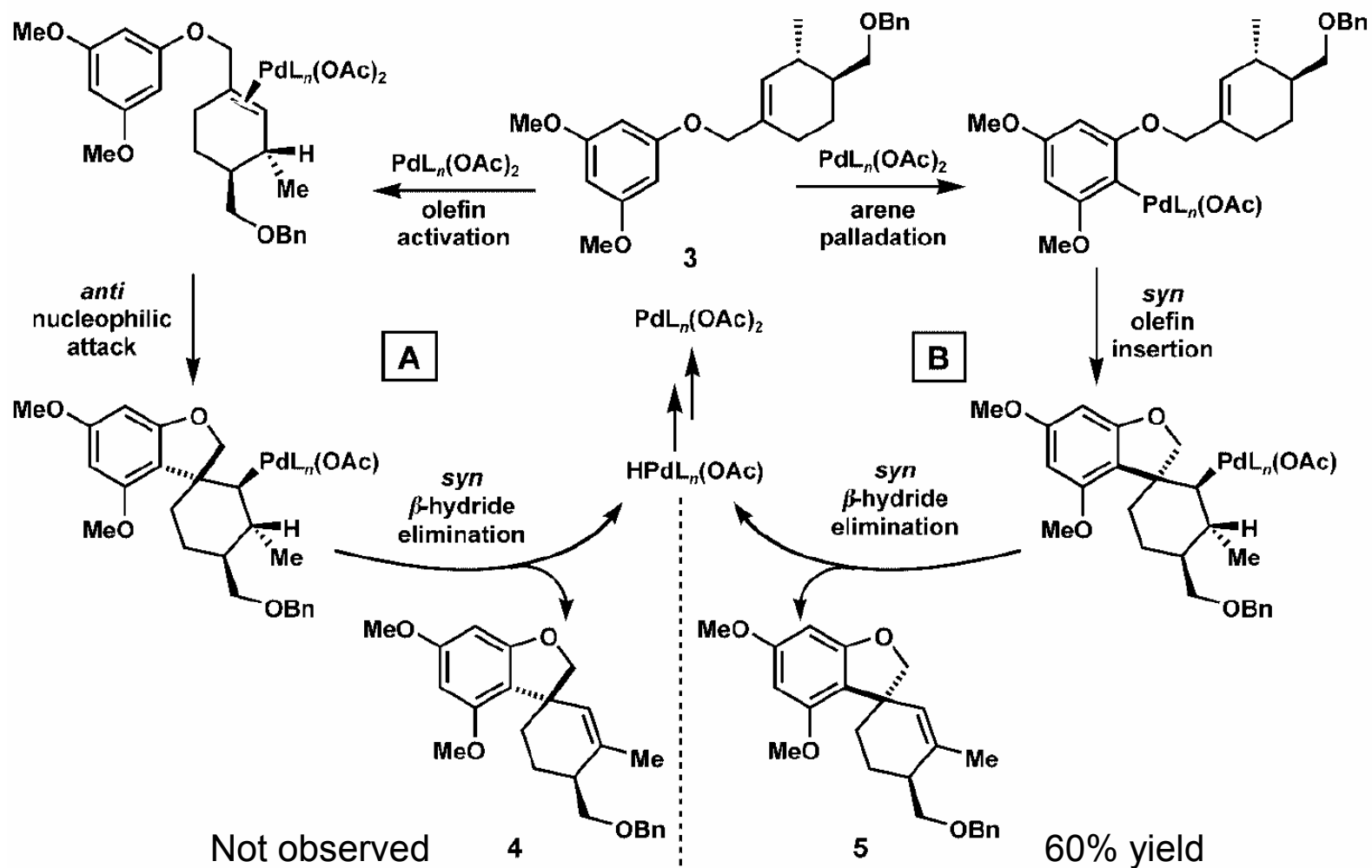
Pd(II)-mediated Oxidative Cyclization – Dihydroenzofuran Synthesis

Table 4: Oxidative dihydrobenzofuran synthesis.^[a]

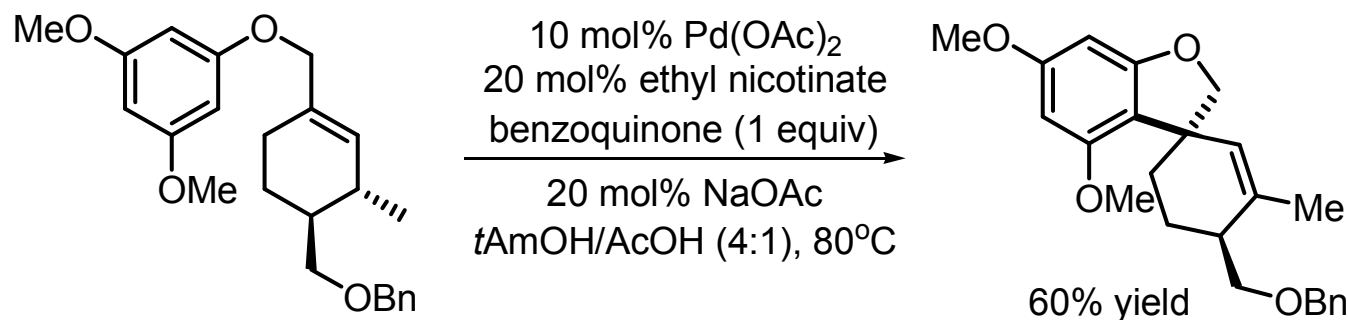
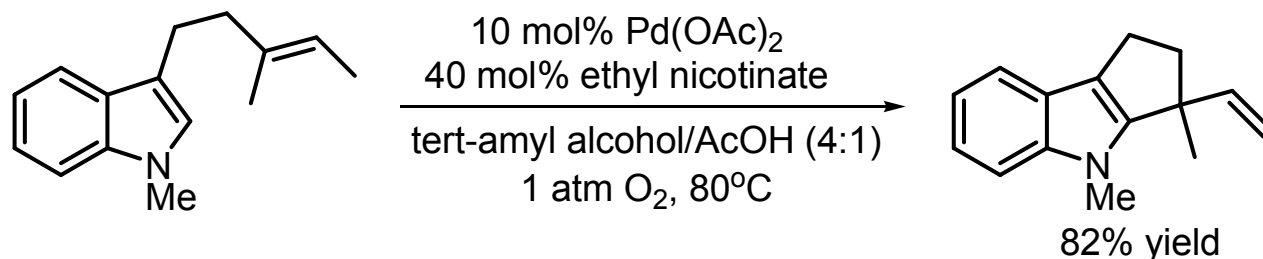
Entry	Substrate	Product	<i>t</i> [h]	Yield [%] ^[b]
1			16	74
2 ^[c]			12	71
3			30	58 ^[d]
4			28	55
5			15	74 ^[e]
6			24	80
7			18	78
8			15	50
9			15	63
10			15	60
11			15	66

[a] All reactions were carried out with 0.50 mmol substrate, 10 mol% Pd(OAc)₂ (0.05 mmol), 20 mol% ethyl nicotinate (0.10 mmol), 0.10 mmol NaOAc, and 0.50 mmol benzoquinone in 5.0 mL 4:1 *t*AmOH:AcOH (0.1 M in substrate) at 100 °C. [b] Yield of isolated product. [c] Performed with 5 mol% Pd(OAc)₂ and 10 mol% ethyl nicotinate. [d] An inseparable mixture of roughly 66% product (*E/Z* = 3:1) and 10% starting material was isolated after 18 h. This mixture was subjected to another reaction with 5 mol% Pd(OAc)₂, 10 mol% ethyl nicotinate, 20 mol% NaOAc, and 50 mol% benzoquinone in 4:1 *t*AmOH:AcOH (0.1 M) for 12 h after which only the *E* isomer was observed. The yield presented is the overall yield of isolated product. [e] A 2.3:1 mixture of diastereomers was isolated with the major isomer shown.

Pd(II)-mediated Oxidative Cyclization – Dihydroenzofuran Synthesis



Pd(II)-mediated Oxidative Cyclization - Summary



Summary:

- Mild oxidative C-C bond formation with unactivated olefin using catalytic Pd(II).
- Access to wide range of indoles, benzofurans, dihydrobenzofurans.

Drawback:

- Benzofuran methodology limited to five-membered ring.
- Only electron-rich arene would undergo cyclization.