Direct Oxidative Heck Cyclizations: Intramolecular Fujiwara-Moritani Arylations for the Synthesis of Functionalized Benzofurans and Dihydrobenzofurans

by Zhang, H.; Ferreira, E. M.; Stoltz, B. M.

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2004, *43*, 6144-6148

Erick B. Iezzi
Current Literature
November 27, 2004

Why is this Article Significant?

- Heck reaction is ubiquitous for the forming C-C bonds in synthetic molecules
  - uses halogenated arenes which requires an additional synthetic step
  - a base is needed to remove the generated hydrohalic acid

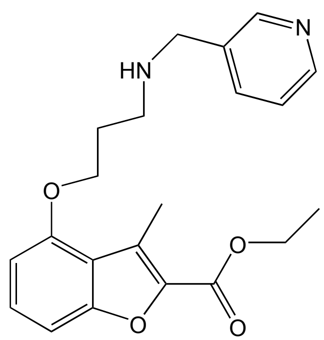
- C-H activation of arenes eliminates the need for halogens

- Demonstrates the first use of catalytic Pd for oxidative intramolecular C-H activation of arenes and the addition into unactivated olefins (Heck reaction)

- Illustrates that mechanism of cyclization follows the pathway of a Fujiwara-Moritani/oxidative Heck cyclization

- Synthesize benzofuran and dihydrobenzofuran structures, which are important components of numerous biologically active compounds

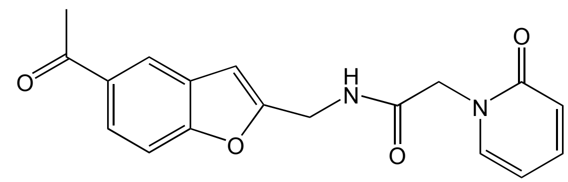
Examples of Biologically Active Benzofurans



RO-09-4609

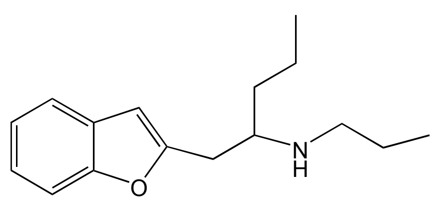
- Antifungal activity against *Candida albicans* (a pathogenic fungi)

Masubuchi, et al. *Bioorg. Med. Chem.* **2003**, *11*, 4463



- An oxytocin antagonist

Wyatt, et al. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1405

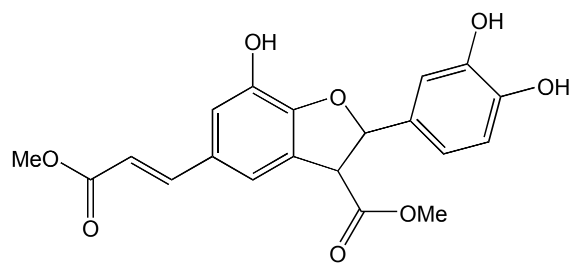


(-) BPAP

- A serotonin release enhancer

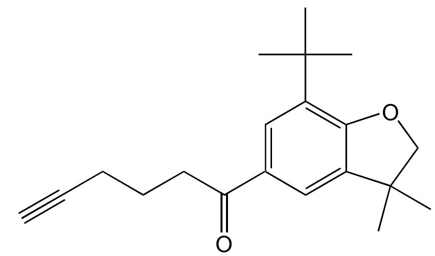
Yoneda, et al. *Bioorg. Med. Chem.* **2001**, *9*, 1197

Examples of Biologically Active Dihydrobenzofurans



- A tubulin polymerization inhibitor
  (GI_{50} of <10 nM against some breast cancer cell lines)

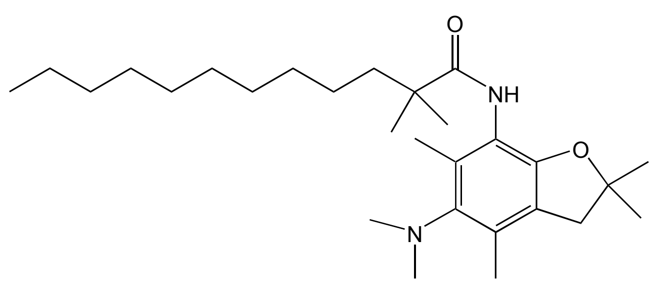
Pieters, et al. *J. Med. Chem.* **1999**, *42*, 5475



DHDMBF

- An anti-inflammatory and analgesic drug

Janusz, et al. *J. Med. Chem.* **1998**, *41*, 1124

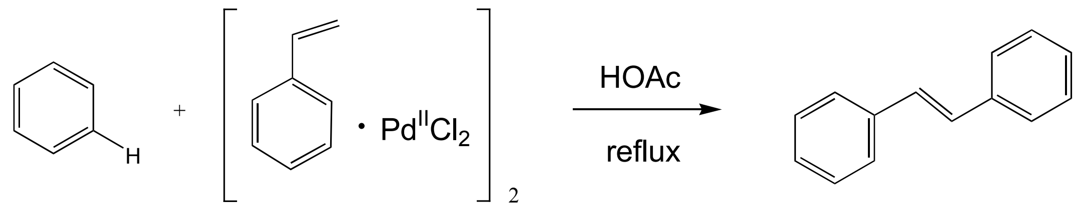


- An acyl-Co A: cholesterol acyltransferase inhibitor

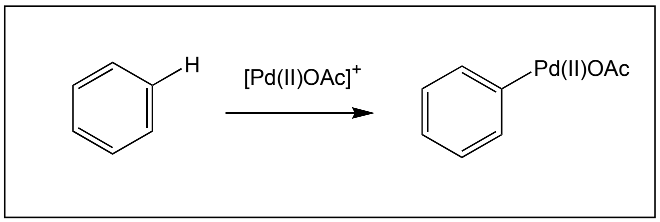
Kataoka, et al. *J. Med. Chem.* **1996**, *39*, 1262

Pd-Catalyzed Oxidative Heck Reaction

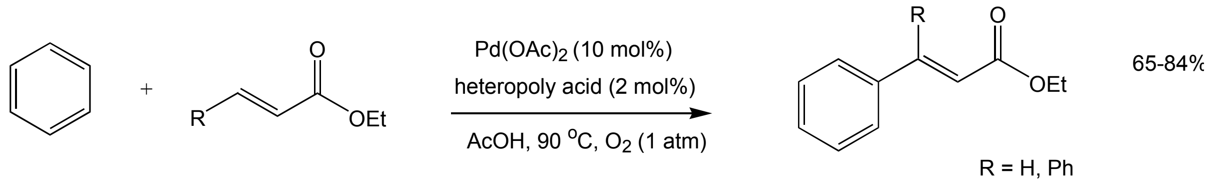
Fujiwara-Moritani arylation (1967)



Moritani, I.; Fujiwara, Y. *Tetrahedron Lett.* **1967**, 1119-1122

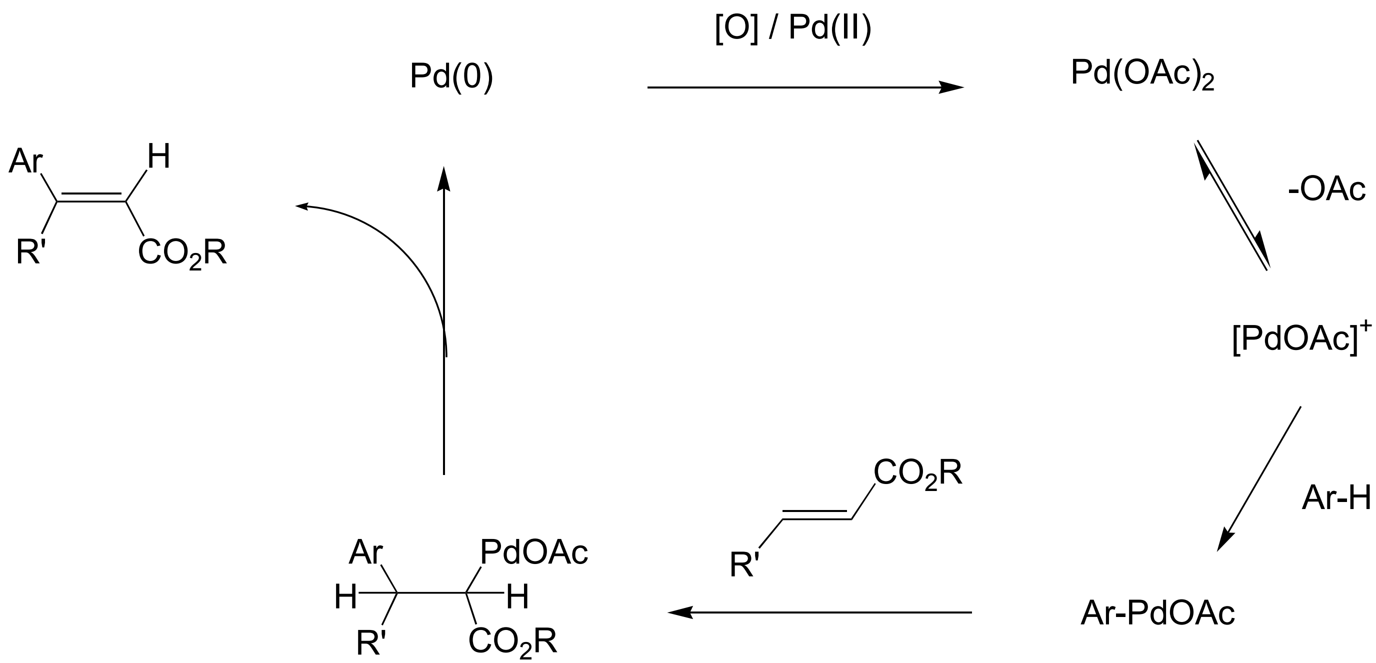


Catalytic intermolecular reaction with activated olefins

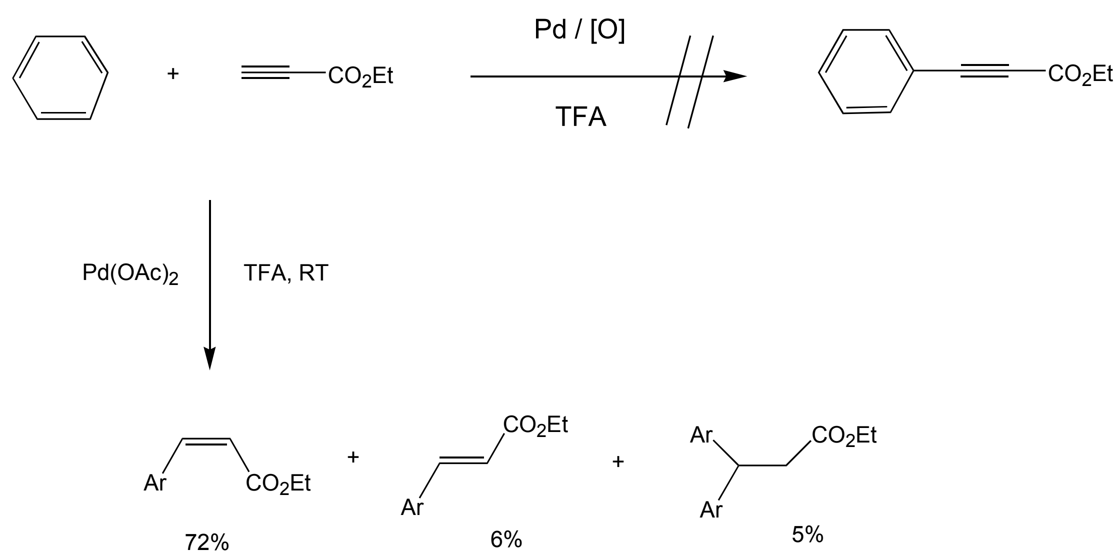


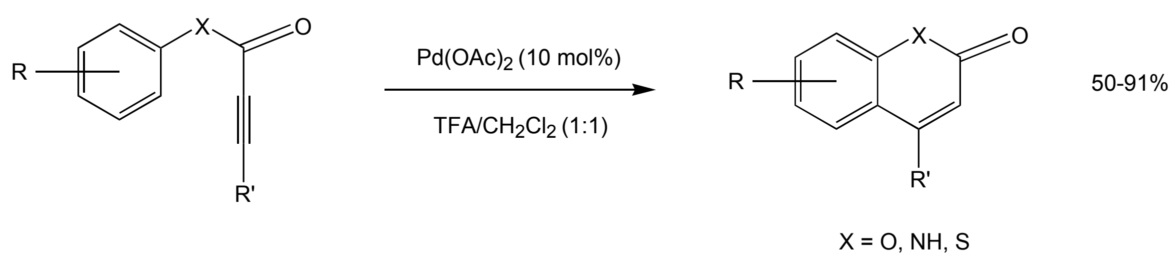
Ishii, et al. *J. Am. Chem. Soc.* **2003**, *125*, 1476-1477

Mechanism of Arene Insertion into Activated Esters and Reoxidation of Catalyst



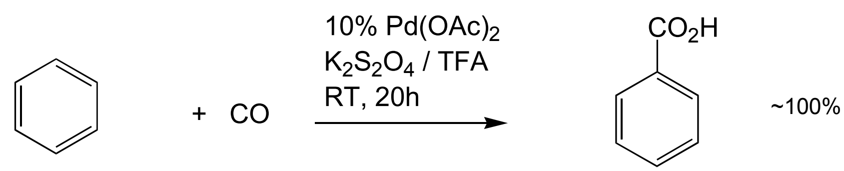
Pd-Catalyzed Reactions of Arenes with Alkynes



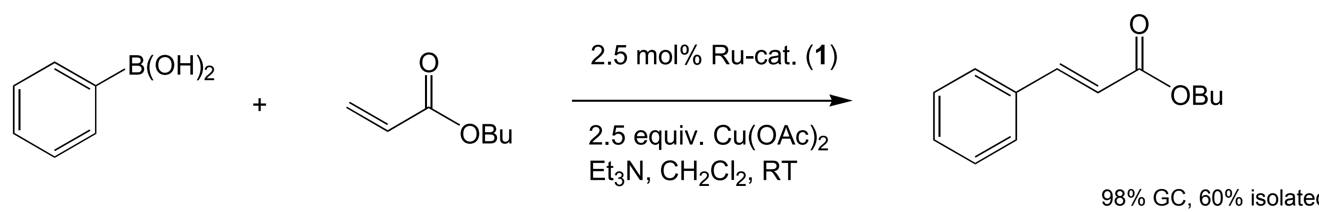


Fujiwara, et al. *Acc. Chem. Res.* **2001**, *34*, 633-639

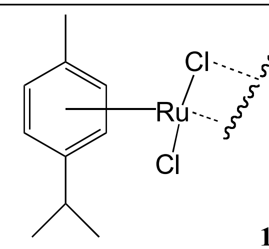
Carboxylation of Arenes and Ru-Catalyzed Oxidative Heck Reactions



Fujiwara, et al. *Acc. Chem. Res.* **2001**, *34*, 633-639



* need prefunctionalized arene to facilitate reaction



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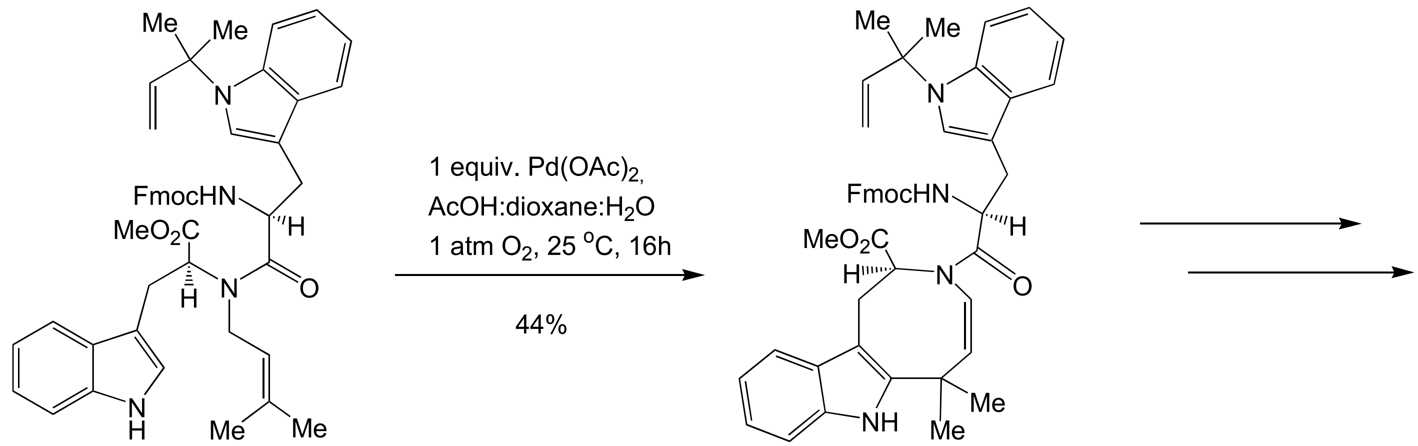
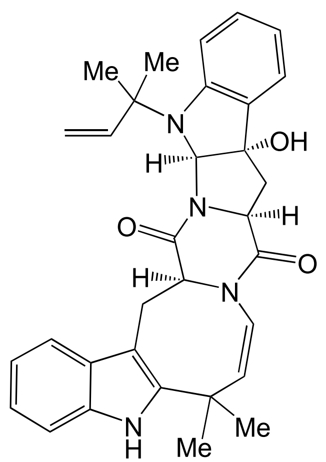
Brown, et al. *Angew. Chem. Int. Ed.* **2002**, *41*, 169-171

Palladium-Promoted Oxidative Heck Cyclization in Total Synthesis

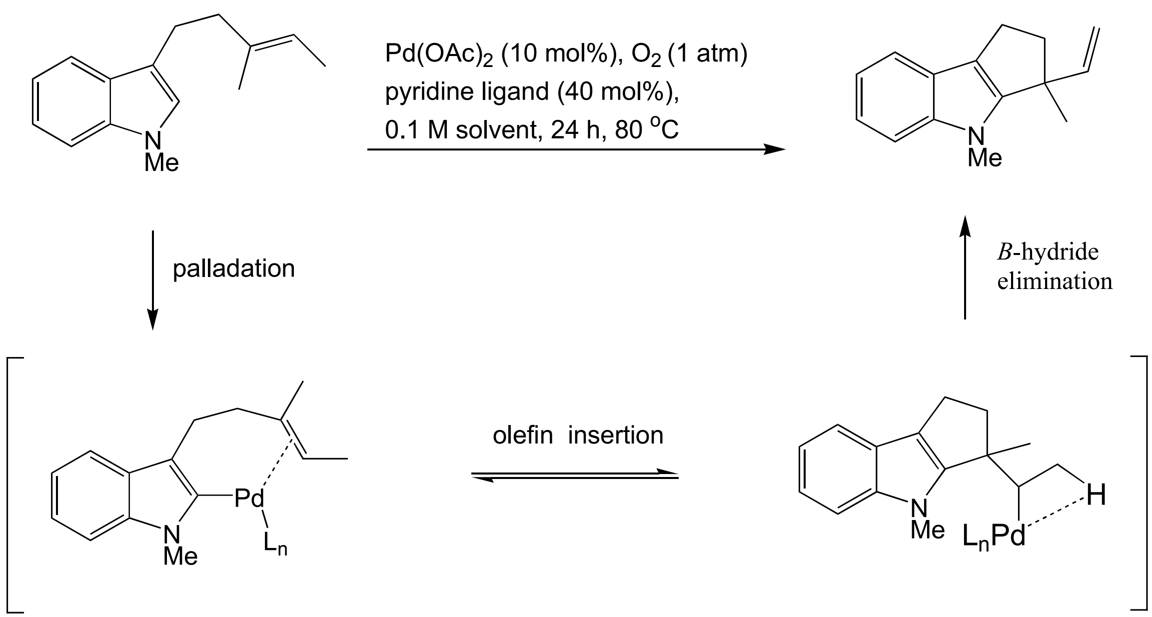




Okaramine N

Corey, et al. *J. Am. Chem. Soc.* **2003**, *125*, 5628-5629

First Example of Pd-Catalyzed Oxidative Annulations of Indoles

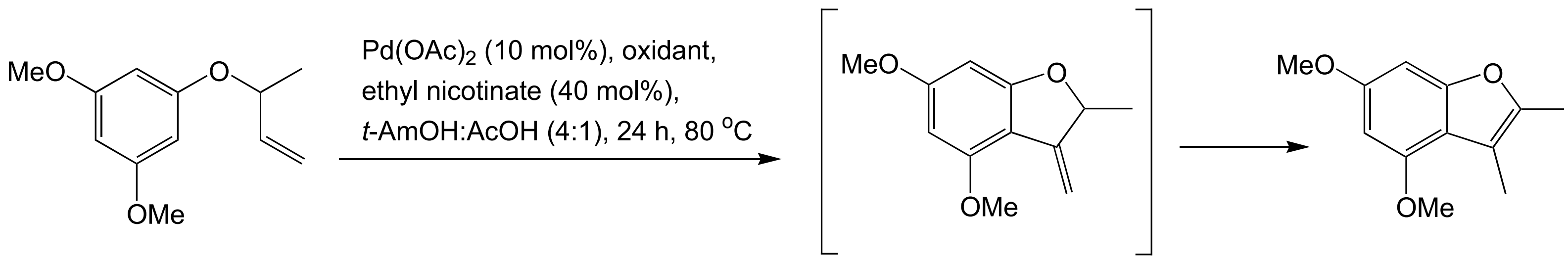


Entry	Pyridine ligand	$pKa(pyrH^+)$	conversion (%)
1	4-OMe	6.47	3
2	4-*t*-Bu	5.99	1
3	unsub.	5.25	23
4	4-CO_2Et	3.45	52
*** 5**	**3-CO_2Et**	**3.35**	**76**
6	3-$COCH_3$	3.18	58
7	3-F	2.97	64
8	3-CN	1.39	55
9	3,5-di-Cl	0.90	22

Best result:
40 mol% ethyl nicotinate*,
0.1M *tert*-amyl alcohol/AcOH (4:1),
99% conversion, 82% isolated yield

Stoltz, et al. *J. Am. Chem. Soc.* **2003**, *125*, 9578-9579

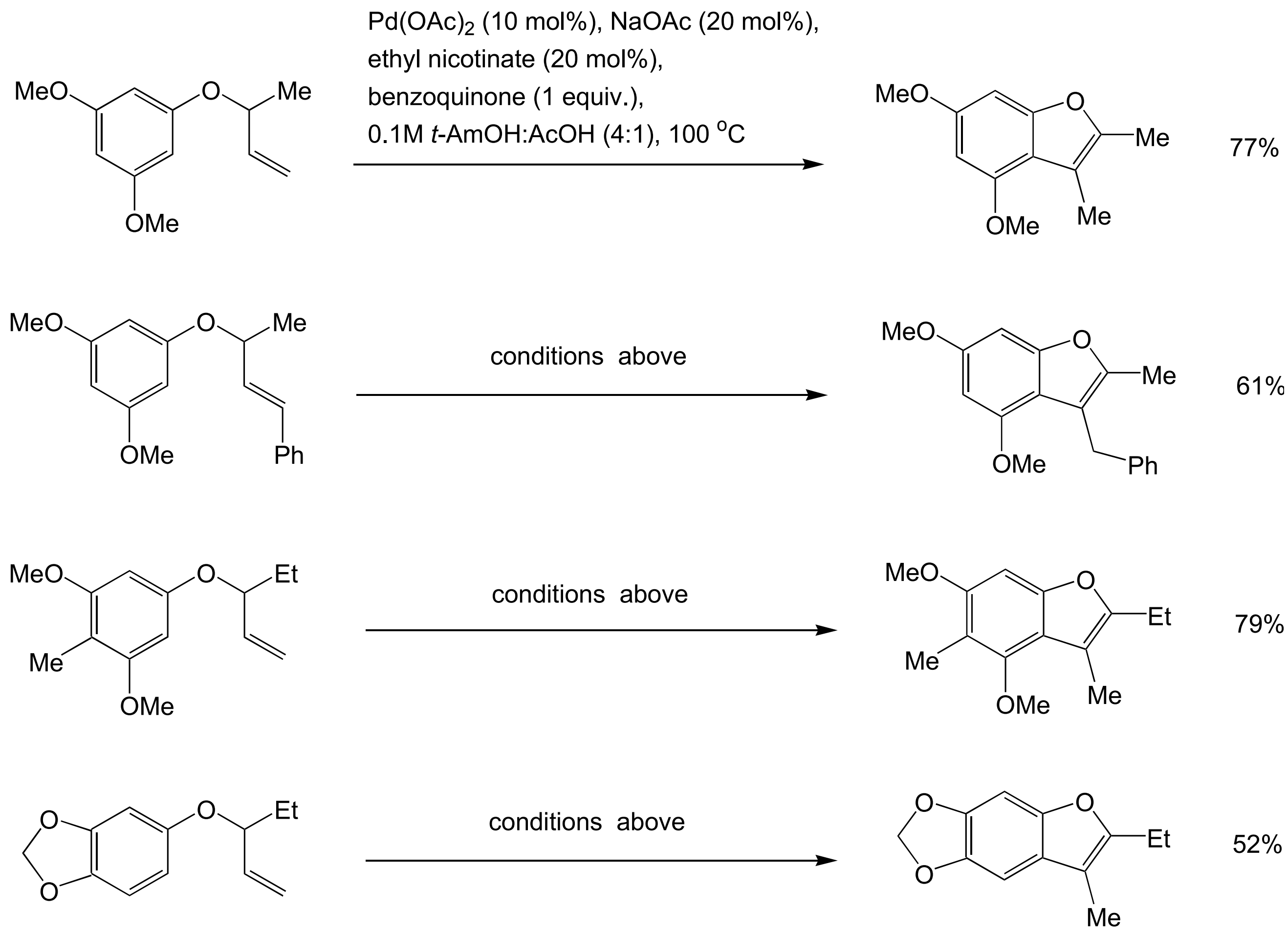
Screening of Oxidants for the Catalytic Intramolecular Oxidative Heck Cyclization



Entry	Oxidant [1 equiv.]	Yield [%] by GC
1	O_2	56
2	benzoquinone	62
3	$Cu(OAc)_2$	31
4	AgOAc	29
5	$Tl(OCOCF_3)_3$	<10
6	$K_2S_2O_8$	30
7	$H_2NC(S)NH_2$	<10
8	$PhCO_3tBu$	42

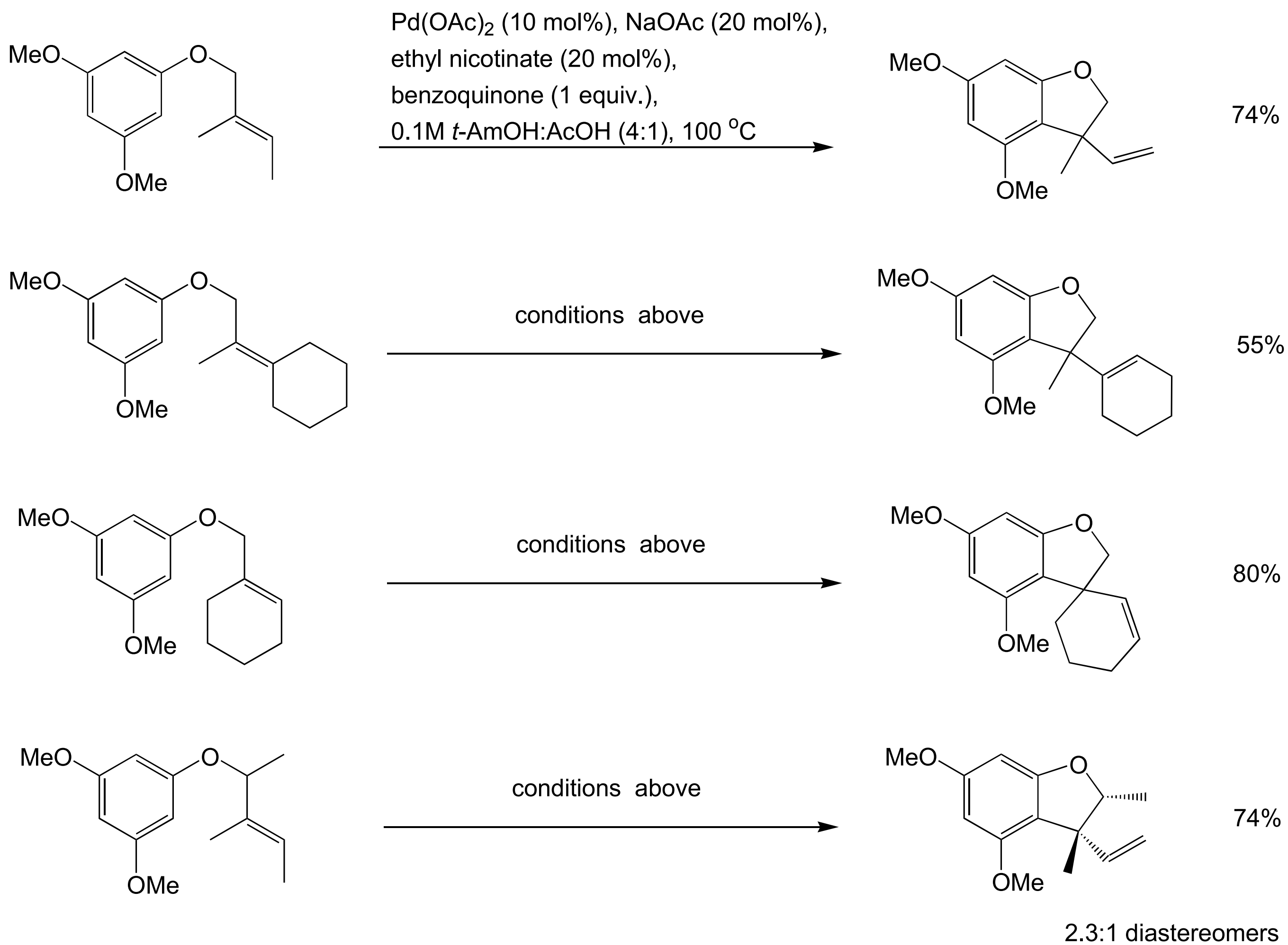
Stoltz, et al. *Angew. Chem. Int. Ed.* **2004**, *43*, 6144-6148

Examples of Oxidative Benzofuran Synthesis



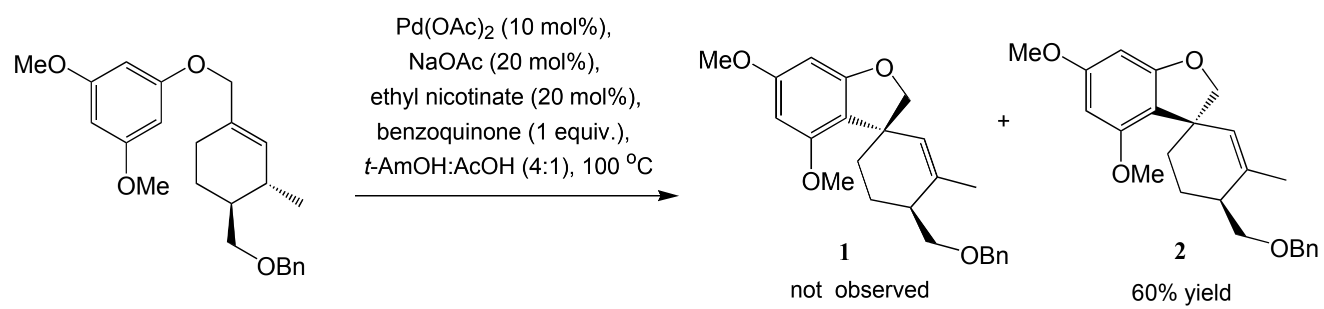
Stoltz, et al. *Angew. Chem. Int. Ed.* **2004**, *43*, 6144-6148

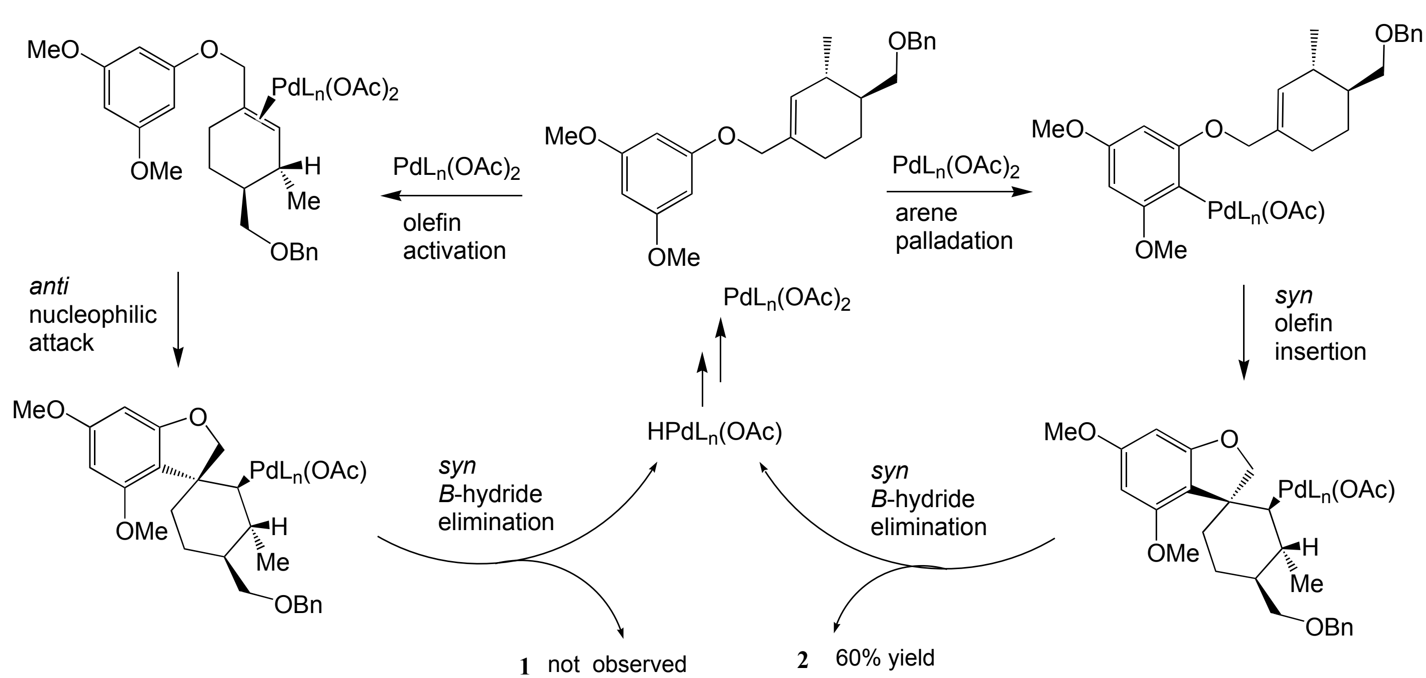
Synthesis of Quaternary Carbon-Containing Dihydrobenzofurans via Oxidative Cyclization



Stoltz, et al. *Angew. Chem. Int. Ed.* **2004**, *43*, 6144-6148

Mechanistic Probe for the Oxidative Heck Cyclization





Future Work

- Develop catalysts to facilitate oxidative C-H activation of electron-poor arenes

- Develop method of synthesizing ether rings of six-members and greater