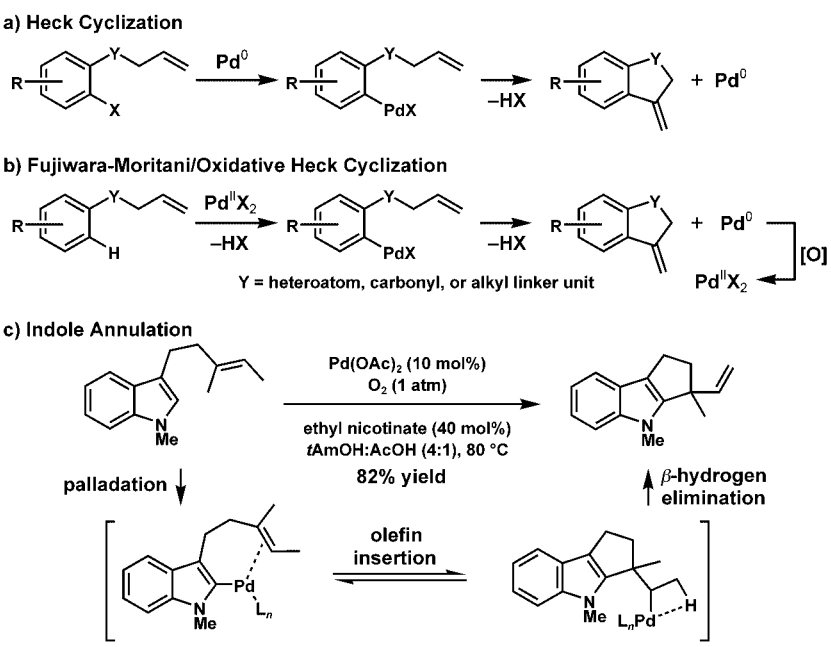
Pd-Catalyzed Cyclizations

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

*Haiming Zhang, Eric M. Ferreira, and Brian M. Stoltz**

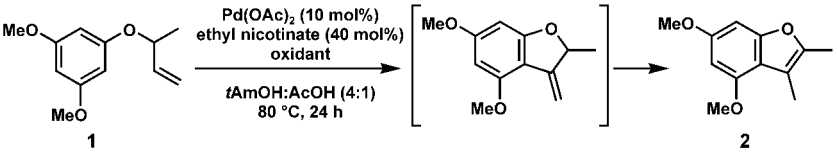
Over the past two and a half decades, the intramolecular Heck reaction has proven to be an integral process for the formation of C–C linkages in the synthesis of complex molecules.[1] While the reaction provides desirable products by the coupling of an aryl or vinyl halide with an olefin by extrusion of the hydrohalic acid, the overall process involves two discrete functionalization events: 1) halogenation of an aryl or vinyl precursor and 2) palladium(0)-catalyzed C–C bond formation (Scheme 1a). A potentially more efficient process would involve oxidative coupling of an unfunctionalized arene directly with an olefin, thus obviating the necessity for prehalogenation of the substrate (Scheme 1b). Although the intermolecular version of this reaction was discovered in 1967 by Fujiwara and Moritani,[2] subsequent studies have largely focused on couplings of benzene with activated olefins (e.g., acrylate esters).[3] In fact, the direct intramolecular oxidative arene/olefin coupling (i.e., oxidative Heck cyclization[4]) has not been studied thoroughly.[5]

In the course of our efforts to develop palladium(II)-catalyzed dehydrogenation as a general oxidation method,[6,7] we recently described the catalytic oxidative cyclization of unsaturated indoles to give annulated derivatives (Scheme 1c).[8] Our studies determined that the indole cyclization mechanism most likely involves initial arene palladation with subsequent olefin insertion and β-hydrogen elimination.[9] Importantly, this mechanism is analogous to that of the Heck cyclization, since a similar aryl–Pd^{II} species is believed to be the key intermediate in both processes; however, the new process is oxidative due to the initial C–H bond functionalization event and net dehydrogenation of the substrate. Furthermore, since Pd^0-mediated oxidative addition to electron-rich aryl halides is typically slower than that to electron-poor arenes,[10] this direct oxidative process (initiated by electrophilic palladation by Pd^{II}) is complementary to the Heck technology. We envisioned that electron-rich arenes other than indoles could participate in such oxidative cyclizations with unactivated olefins under similar catalysis.



Scheme 1. a) A generalized Heck cyclization (note that the halide must be installed in a discrete step). b) A generalized Fujiwara–Moritani/oxidative Heck cyclization. c) An example of an indole annulation by oxidative arene–olefin cyclization.[8]

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



1 2

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	$K_2S_2O_8$	30
3	$Cu(OAc)_2$	31	7	$H_2NC(S)NH_2$	<10
4	AgOAc	29	8	$PhCO_3tBu$	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.

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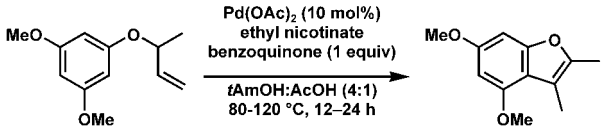
Herein, we report a direct method for the synthesis of benzofurans and dihydrobenzofurans by palladium-catalyzed intramolecular Fujiwara–Moritani/oxidative Heck reactions.[11,12]

In order to test the viability of applying the intramolecular oxidative Heck cyclization to a nonindolic system, we prepared allyl phenyl ether **1** by alkylation of the corresponding phenol. Ether **1** was subjected to our optimized conditions for the aforementioned indole cyclization in the presence of a variety of stoichiometric oxidants (Table 1). We were gratified to observe that in the presence of a range of oxidants, ether **1** cyclized to give benzofuran **2** at 80 °C, presumably by palladium-catalyzed C–C bond formation and β-hydride elimination, followed by isomerization of the olefinic product to the thermodynamically more stable benzofuran. As we observed for indole cyclization, it was found that molecular oxygen was a competent stoichiometric oxidant for the cyclization **1**→**2**. However, in the case at hand, benzoquinone provided the highest yield of **2** (62% yield by GC) and thus was used for further optimization.

Having found benzoquinone to be the optimal oxidant in the cyclization **1**→**2**, we examined the other parameters in the process (Table 2).[13] It was found that a 1:2 ratio of Pd:ethyl nicotinate was ideal (entries 1–4) and that inclusion of a substoichiometric amount of NaOAc (20 mol%) provided increased yields (entries 5 and 6). Finally, increasing the temperature to 100 °C led to optimal results, providing benzofuran **2** in 77% yield after 12 h (entry 7).

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

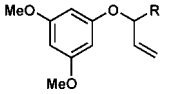
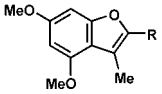
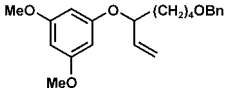
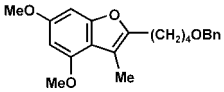
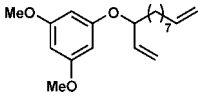
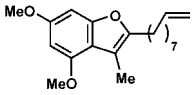
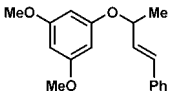
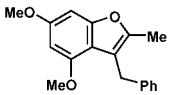
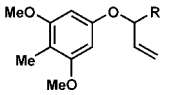
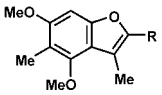
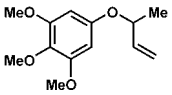
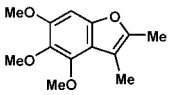
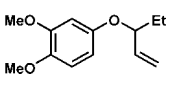
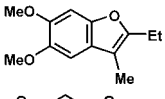
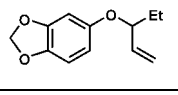
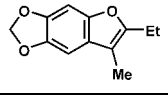


1 **2**

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% $Pd(OAc)_2$ (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*AmOH:AcOH (0.1 M in substrate). [b] Yield determined by gas chromatography. [c] Yield of isolated product in parentheses.

Table 3: Oxidative benzofuran synthesis.[a]

Entry	Substrate	Product		*t* [h]	Yield [%][b]
1			R = Me	12	77
2			R = Et	12	74
3			R = *n*-C_5H_{11}	13	72
4				12	62
5				14	54
6				12	61
7			R = Me	14	75
8			R = Et	12	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.

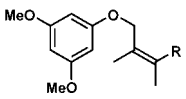
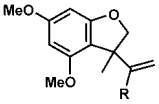
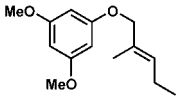
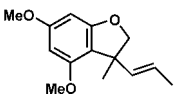
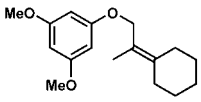
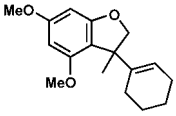
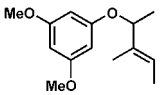
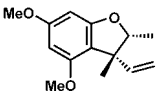
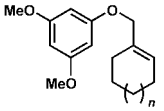
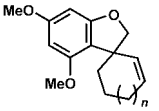
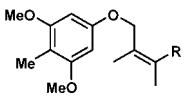
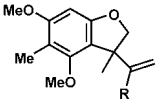
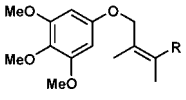
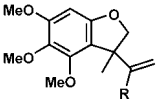
With a viable oxidative cyclization to produce benzofuran **2** in hand, we set out to explore the generality of the transformation. As shown in Table 3, the scope of the oxidative benzofuran synthesis is quite broad, leading to highly substituted products by selective *ortho* reactivity. The methodology is currently limited to the use of electron-rich arenes; however, the aryl subunit tolerates several alkoxy and alkyl groups and substitution patterns. Likewise, the allylic portion may be functionalized at both the proximal and distal positions relative to the ether linkage with a variety of groups (e.g. alkyl, aryl, functionalized alkyl).

We next investigated the feasibility of synthesizing quaternary carbon-containing dihydrobenzofurans by employing tri- and tetrasubstituted olefins in the process to avoid olefin isomerization after the cyclization step. As shown in Table 4, an array of highly functionalized dihydrobenzofuran derivatives can be synthesized in good yields with as little as 5 mol% $Pd(OAc)_2$ (Table 4, entry 2).[14]

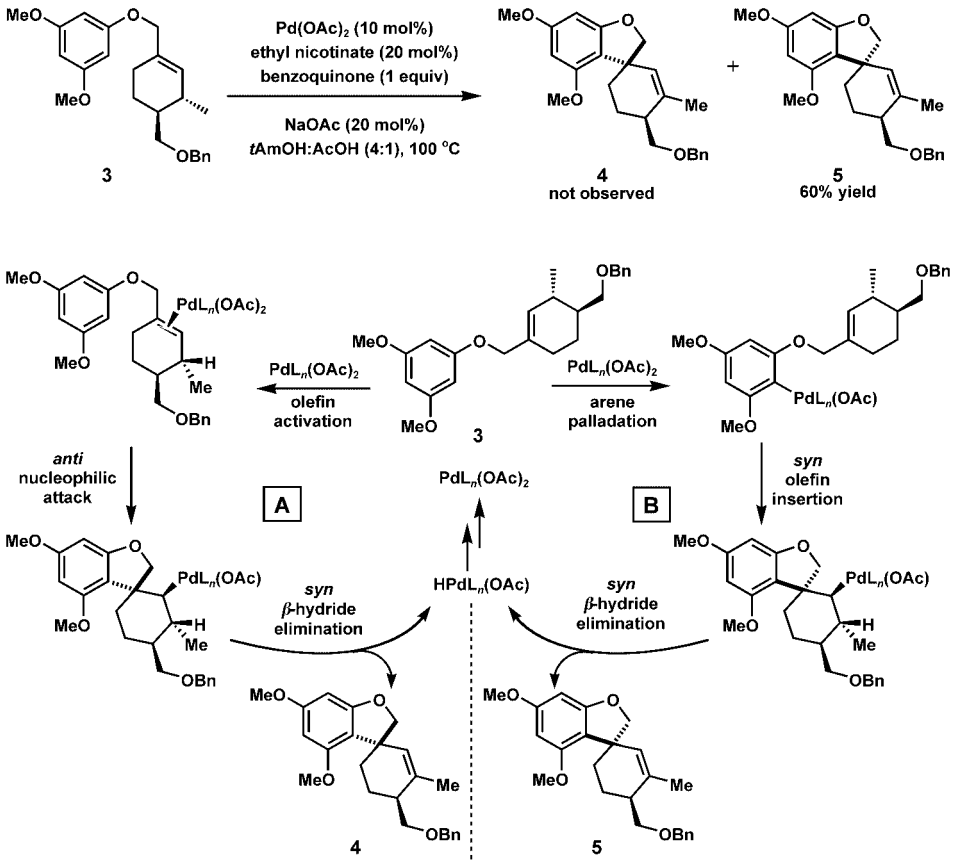
In order to probe the mechanism of these carbocyclizations, we prepared substrate **3** and subjected it to the oxidative cyclization conditions (Scheme 2). Cyclization of this substrate can distinguish between two mechanistically distinct pathways (Scheme 2, A and B) by formation of diastereomeric products (i.e., either **4** or **5**). Specifically, a mechanism proceeding by means of olefin activation, *anti* nucleophilic attack of the arene on the Pd π complex, and *syn* β-hydride elimination (Scheme 2, pathway A) can be differentiated from one involving aryl-palladation, *syn* olefin insertion, and *syn* β-hydride elimination (Scheme 2, pathway B). Under our standard reaction conditions, ether **3** cyclized to produce a diastereomerically pure product in 60% yield, which was determined to be dihydrobenzofuran **5** by ^{1}H NMR NOE experiments.[15] The outcome of this mechanistic study suggests that pathway B is operative and that C–H bond functionalization precedes olefin insertion and β-hydride elimination.[16] Additionally, this reaction demonstrates that quaternary carbon stereocenters can be generated diastereoselectively, by chirality transfer, from a tertiary carbon center.

In summary, we have developed a method for intramolecular oxidative C–C bond formation that relies on Pd^{II} catalysis to access electron-rich, highly substituted benzofuran and dihydrobenzofuran derivatives. These oxidations produce important heterocyclic ring systems[11] by direct C–H bond functionalization of the aromatic ring and cyclization with unactivated olefins. Based on mechanistic insight (i.e. the proposed intermediacy of an aryl Pd^{II} species), we have illustrated the analogy of such oxidative carbocyclizations to the corresponding intramolecular Heck reaction, and we thus

Table 4: Oxidative dihydrobenzofuran synthesis.[a]

Entry	Substrate	Product		*t* [h]	Yield [%][b]
1			R = H	16	74
2[c]			R = Me	12	71
3				30	58[d]
4				28	55
5				15	74[e]
6			*n* = 1	24	80
7			*n* = 0	18	78
8			R = H	15	50
9			R = Me	15	63
10			R = H	15	60
11			R = Me	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.



Scheme 2. Mechanistic probe for the oxidative cyclization.

classify these transformations as Fujiwara–Moritani/oxidative Heck cyclizations. Furthermore, this methodology may be considered orthogonal to the traditional Heck reaction in that highly electron-rich arenes may be employed directly. In certain cases, halogenated derivatives of such arenes may be difficult to access selectively or may have undesirably low reactivity toward Pd^0 catalysts. While the method is currently limited to the synthesis of five-membered ring ethers, the utilization of the oxidative Heck cyclization for the synthesis of complex molecules and the demonstration of its orthogonality to the Heck reaction should help to further elucidate the scope; these remain primary goals of our laboratory.[17]

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Keywords: benzofurans · homogeneous catalysis · oxidation · palladium

[1] For outstanding reviews on Pd-catalyzed intramolecular Heck reactions, see: a) S. Braese, A. de Meijere, in *Handbook of Organopalladium Chemistry for Organic Synthesis, Vol. 1* (Ed.: E.-I. Negishi), Wiley, Hoboken, New Jersey, **2002**, pp. 1223–1254; b) J. Tsuji, *Palladium Reagents and Catalysts*, Wiley, Chichester, UK, **1995**, chap. 4; c) J. T. Link, *Org. React.* **2002**, *60*, 157–534.

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[15] In addition to **5**, a small amount of starting ether **3** was isolated. No other isomeric products were observed in the reaction.
[16] A similar observation was made in our studies directed toward the oxidative annulation of indoles.[8]
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