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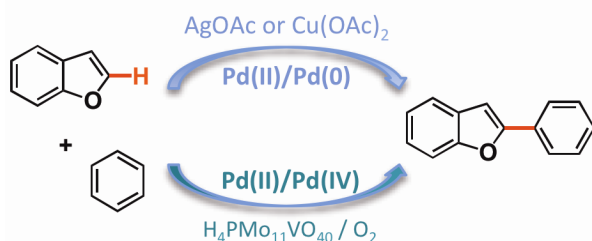
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## Graphical Abstract

**Mechanistic insight into the palladium  
catalyzed oxidative arylation of benzofuran:  
Heteropoly acid oxidants evoke a  
Pd(II)/Pd(IV) mechanism**

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# Insight into the palladium catalyzed oxidative arylation of benzofuran: Heteropoly acid oxidants evoke a Pd(II)/Pd(IV) mechanism

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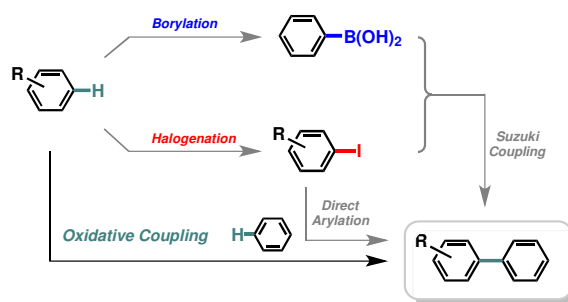
## ABSTRACT

The effects of oxidant and organic acid additives on the oxidative cross-coupling reactions of electron rich heterocycles such as benzofuran with benzene were studied. Both regioselectivity and reaction rate could be controlled by varying the condition parameters. Furthermore, mechanistic insight was achieved via kinetic studies which indicate that reactions that are oxidized by the heteropoly acid  $H_4PMo_{11}VO_{40}$  operate via a Pd(II)/Pd(IV) mechanisms, while reactions oxidized by either  $AgOAc$  or  $Cu(OAc)_2$  operate by a Pd(II)/Pd(0) mechanism.

## 1. Introduction

A consortium of process chemists from major pharmaceutical companies recently indicated that green coupling reactions involving carbon-hydrogen (C-H) bond activation for the formation of carbon-carbon (C-C) bonds were the highest-priority “aspirational” research area for new reaction development.<sup>1</sup> The current best methods for forming biaryl C-C bonds are well known and widely used, namely the Suzuki, Kumada and Negishi coupling reactions. Each of these processes are catalyzed by palladium and involve one arene substrate that contains a halogen or pseudohalogen; the second substrate has been metalated or borylated. The metal and halogen atoms of the substrates only serve to activate the substrates for the palladium catalyzed coupling, as they are removed during the course of the reaction and become part of the waste stream. Particularly when heavy halogens are employed, such as iodine, the waste associated with these coupling reactions can become problematic. Numerous groups have disclosed methods for direct arylation reactions that employ one unfunctionalized arene, formally activating the C-H bond of one of the substrates.<sup>2</sup> Unfortunately, the other substrate for the majority of these reactions is an aryl iodide or bromide, and more than one equivalent of this pre-functionalized arene is often required.

The ideal process for synthesizing biaryls would be the oxidative coupling of two unfunctionalized substrates (Scheme 1). We and others have recently disclosed that such oxidative couplings are possible, and are often regioselective.<sup>3</sup> While it is tempting to view these reactions as nearly ideal, in terms of atom economy, the stoichiometric oxidants that are often required contribute to the waste of the cross-coupling reaction. The best aspect of these reactions, in terms of green chemistry, is the fact that they do not require pre-functionalized substrates, so oxidative couplings reduce the total number of synthetic steps required to form a C-C bond. This process economy has the potential to significantly streamline the synthesis of biaryls both in terms of cost and E-factor.



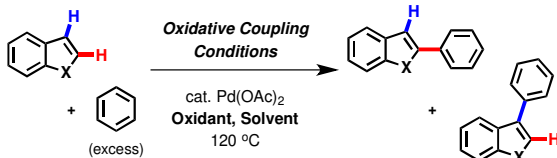
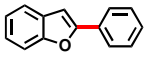
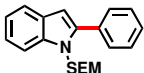
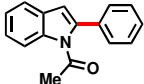
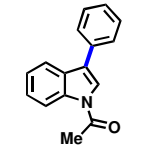
**Scheme 1.** Process economy of oxidative coupling

### 1.1. Classification of Oxidative Coupling Conditions

Our preliminary work in the field of palladium catalyzed oxidative cross couplings was fruitful, but also perplexing, in that we discovered four different reaction conditions, each optimized for the regioselective production of a different arylated heterocycle. Fagnou, Dong, Zhang and others have also discovered a variety of other palladium catalyzed oxidative coupling reactions; however, the catalysts for the processes are often similar to those shown in Table 1.<sup>4</sup>

We hypothesized that the variety of conditions shown in Table 1 can be classified into three categories based on their relative activity with our standard substrate, benzofuran (Table 2). We proposed that benzofuran was an excellent choice for comparing these reactions because of its reactivity in all of the reaction conditions and because it, unlike its indole counterparts, was not prone to decomposition.

**Table 1.** Comparison of conditions for oxidative cross coupling of arenes<sup>4a-c</sup>

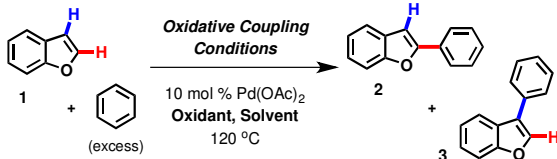
				
Entry	Solvent	Oxidant	Major Product	Regio-selectivity
1	AcOH	10 mol % H <sub>4</sub> PMo <sub>11</sub> VO <sub>40</sub> (HPMV), O <sub>2</sub>		>99:1 (ref 4a)
2	PivOH	AgOAc (3 equiv)		3:1 (ref 4c)
3	Dioxane	AgOAc (4 equiv)		3.6:1 (ref 4b)
4	Dioxane	Cu(OAc) <sub>2</sub> (4 equiv)		4:1 (ref 4b)

The most active conditions for the oxidative arylation of benzofuran (Table 2, Class I) involve the use of a catalytic polyoxometalate oxidant, H<sub>4</sub>Mo<sub>11</sub>VO<sub>40</sub> (HPMV), in an acidic medium. We hypothesized that this high catalytic activity was correlated to the acidic environment (no metal acetate oxidants).

Acidic reactions that are buffered by superstoichiometric amounts of AgOAc or Cu(OAc)<sub>2</sub> (Class II) perform oxidative couplings well, but are often complicated by the formation of by-products, such as dimers and acetoxyated species. The use of the same organometallic oxidants in a neutral solvent (dioxane) produces a relatively mild reaction medium (Class III). However, the lack of a Brønsted acid in this system is accompanied by a significant loss of catalytic activity. Higher catalyst loadings are often required, and both longer reaction times and incomplete conversions are often observed.

In addition to the activity of the catalyst varying, the selectivity of the reaction also varies from Class I to III, with 2-phenylbenzofuran **2** being favored at high acid concentrations (Class I) and 3-phenylbenzofuran **3** being favored in non-acidic conditions (Class III). With this rubric in hand, we set out to determine the exact role of the acidity of the solvent and the oxidant in the oxidative cross coupling reactions. The studies described below indicate that the mechanism by which the reaction proceeds is directly correlated to both the acidity of the reaction media and the nature of the oxidant.

**Table 2.** Classification of oxidative coupling conditions

			
Class	I (acidic)	II (buffered)	III (basic)
Oxidant	HPMV + O <sub>2</sub>	AgOAc or	AgOAc or

← Increasing Activity →

Solvent	Cu(OAc) <sub>2</sub>	
	AcOH or PivOH	AcOH or PivOH
% Yield ( <b>2</b> : <b>3</b> )	81% (>99:1) <sup>a</sup>	84% (1:1) <sup>a,b</sup>
Reaction Time	25 min.	3 hrs.

a) AcOH solvent. b) AgOAc (4 equiv)

## 2. Results and Discussion

### 2.1. The relationship between acid additive and both activity and regioselectivity

Our initial studies focused on the role of the acid in Class I and Class II reactions. It should be noted that the HPMV oxidized reactions (Class I conditions) presumably operate by an oxidative relay, as the vanadium-based oxidant, which is only present in catalytic quantities, is constantly regenerated by the O<sub>2</sub> atmosphere.<sup>5</sup> The 3 atm pressure that is used in these reactions is not necessary; we have observed that reactions containing only 1 atm of O<sub>2</sub> proceed well, but they stall because under these conditions, O<sub>2</sub> becomes the limiting reagent. Consequently, we have found it to be convenient to simply run the reactions at moderate pressures of O<sub>2</sub> to provide a sufficient supply of the terminal oxidant.

**Table 3.** Percent conversion as a function of organic acid

Entry	Organic Acid <sup>a</sup>	% Conversion, Ratio 2:3 (Time) with AgOAc <sup>b</sup>	% Conversion, Ratio 2:3 (Time) with HPMV <sup>c</sup>
1	AcOH (3 equiv)	44%, 1.6:1 (40 min)	42%, 69:1 (3 h)
2	EtCO <sub>2</sub> H (3 equiv)	77%, 1.7:1 (40 min)	43%, >99:1 (3 h)
3	<i>i</i> -BuCO <sub>2</sub> H (3 equiv)	85%, 1.6:1 (40 min)	25%, >99:1 (3 h)
4	PivOH (3 equiv)	50%, 1.2:1 (40 min)	30%, >99:1 (3 h)
5	PivOH (10 equiv)	97%, 1.8:1 (40 min)	
6	PivOH (10 equiv)	98%, 1.2:1 (120 min) <sup>d</sup>	
7	PivOH (20 equiv)		77%, >99:1 (6.5 h)

a) 1 equiv. b) 3 equiv AgOAc, 120 °C (MW). c) 10 mol% HPMV, 3 atm O<sub>2</sub>, 120 °C (oil bath). d) 3 equiv AgOAc, 3 atm O<sub>2</sub>, 120 °C (oil bath).

Reactions under both Class I and Class II conditions were performed in parallel and stopped after 3 hrs. Each of the reactions contained three equivalents of a carboxylic acid in the presence of gross excess of benzene (solvent). The AgOAc and HPMV oxidized reactions displayed opposite reactivity preferences with respect to the sterics of the carboxylic acid additive (Table 3). The conversion of the Class II reactions increased as the size of the carboxylic acid increased, though it appeared to reach a maximum at isobutyric acid (entry 3). Class I reactions, oxidized by HPMV, tended to be more active with smaller carboxylic acid additives (entries 1 and 2).

Interestingly, the observed rates for reactions containing AgOAc were 4.5 times faster than those containing HPMV, as they both reached ~40% conversion in 40 minutes and 3 hours, respectively (Table 3, entry 1). The rate enhancements for the

AgOAc reactions (Class II conditions) were not simply caused by the microwave heating, as comparable reactions in an oil bath took only twice as long to complete (Table 2, entries 5 and 6). When AgOAc was used with 10 equiv of PivOH, 40 min of microwave (MW) heating were required to achieve 97% conversion; whereas, HPMV with 20 equiv PivOH required 6.5 h (3 atm O<sub>2</sub>) in an oil bath to achieve 77% conversion (entries 6 and 7).

Though the activity of the catalysts was directly coupled to the sterics of the organic acid additive, the selectivity of the reactions was not. Reactions employing AgOAc as the oxidant provided approximately 1.5:1 ratios of the two regiomers, **2** and **3**, while reactions oxidized by HPMV produced the 2-phenyl product **2** nearly exclusively (Table 3).

The correlation between the concentration of the organic acid and the observed rate of the oxidative cross-couplings was confirmed for both Class I and Class II reaction conditions (Fig. 1 and 2). A series of identical reactions were performed where the only variable was the amount of organic acid that was added to the reaction. HPMV/O<sub>2</sub> oxidized reactions were accelerated by the presence of either acetic or pivalic acid. Only the 2-phenyl product **2** was observed for all of the data points with the Class I reactions.

As shown in Figure 3, the reactions that were oxidized by AgOAc yielded the 3-phenyl product **3** when no acid was present in the reaction, though very low conversions were observed (Class III conditions). A nearly equal mixture of **2** and **3** was produced when acid was introduced to the reaction (Class II conditions). As observed with the Class I reactions, the AgOAc oxidized conditions became more reactive as the organic acid concentration increased. Consequently, there is no advantage to using any amount of acidic additive beyond three equivalents, as the rate of the reaction will be comparable and the selectivity of the process is not affected by acidic additives. These data led us to optimize conditions for oxidatively arylating acid-sensitive substrates such as *N*-alkylindoles, the details of which were recently published.<sup>4c</sup>

## 2.2. Kinetic Studies

We next investigated the role of oxidant and catalyst loading on the rate of the reaction (Fig. 4). An “inverse-induction period” for the Class I conditions was observed. Induction periods are often observed in catalytic reactions, and they are marked by slow conversion at early reaction times while the active catalyst forms *in situ*; this period is then followed by an increase in the reaction rate. We observed the opposite trend: The first catalytic turnover was rapid and regeneration via oxidation was then rate-limiting (Figure 4). Doubling the catalyst loading caused the conversion during the inverse-induction period to also double. Furthermore, upon doubling the oxidant, the rate of the first catalyst turnover remained the same, however the rate of the reaction following the inverse induction period doubled. Following the inverse induction period, the HPMV catalyzed reaction displayed zeroth order kinetics, indicating that the rate-determining step of the overall process was the HPMV-mediated catalyst oxidation. If one of the two C-H palladations were rate-limiting, an increase in the overall rate of the reaction would be observed when the palladium loading was increased. These data indicate that the reaction is first order in both palladium and HPMV.

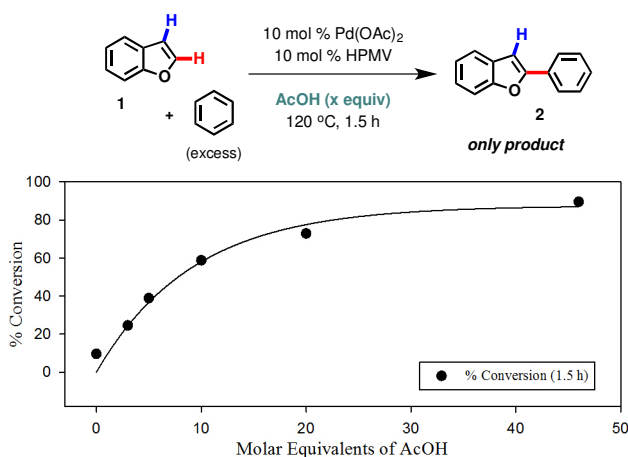


Fig. 1. Class I conditions: Effect of AcOH concentration

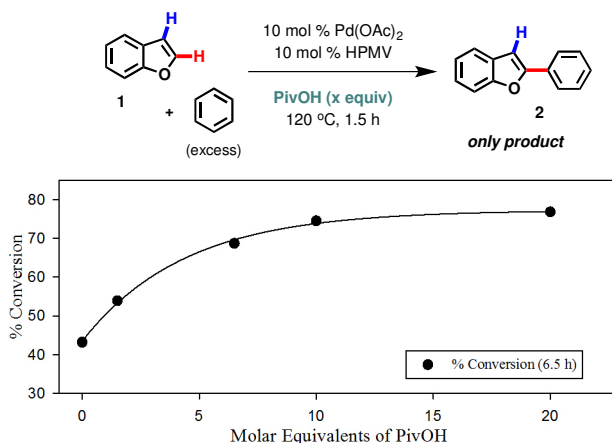


Fig. 2. Class I conditions: Effect of PivOH concentration

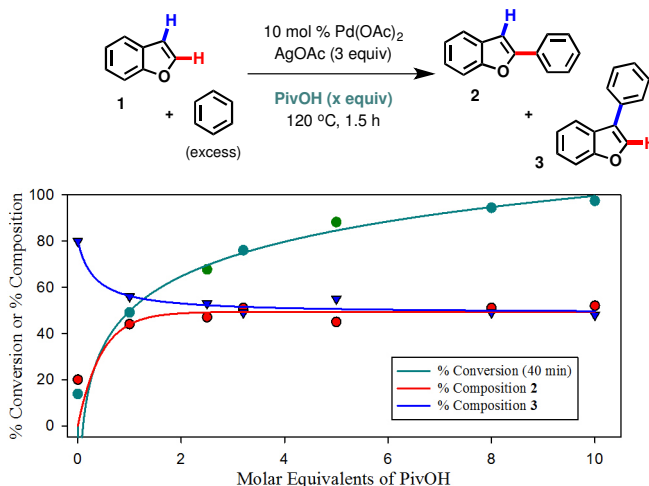
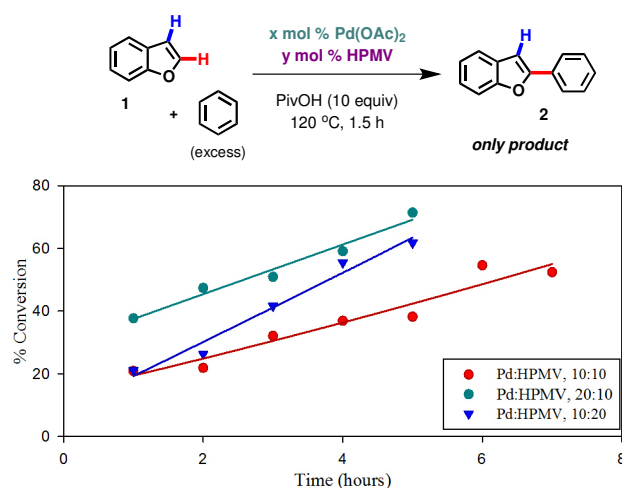


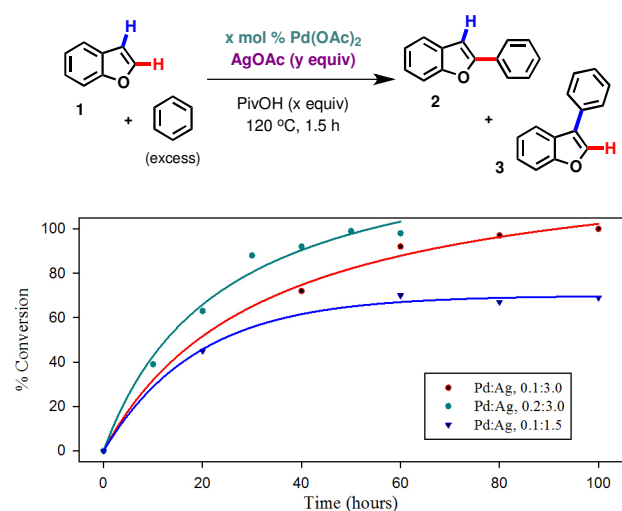
Fig. 3. Class II conditions: Effect of PivOH concentration<sup>4c</sup>

Quite different results were observed with AgOAc mediated reactions (Fig. 5). The rate-limiting step of the overall reaction was not catalyst regeneration. Unfortunately, it was difficult to perform kinetic studies to ascertain the orders of each of the reactants, as the AgOAc in these reactions is not completely dissolved. However, when the oxidant loading was reduced by 50%, the initial reaction rate remained nearly the same, indicating that the oxidant was likely not involved in the rate-determining step, as opposed to the HPMV-mediated reaction. Doubling of the palladium loading approximately doubled the initial reaction rate. These data lead us to postulate a first order dependence on the palladium catalyst concentration and zero order dependence for oxidant loading.





**Fig. 4.** Class I conditions: Kinetic studies



**Fig. 5.** Class II conditions: Kinetic studies

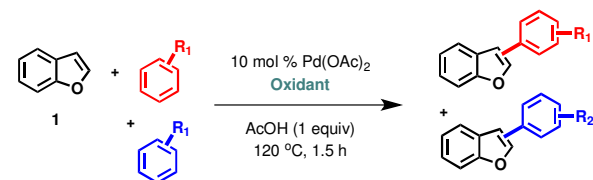
All of these data taken together indicate that reactions using Class I, Class II and Class III conditions are very different. Reactions oxidized by HPMV are better facilitated by AcOH, whereas, AgOAc performs better when used with sterically hindered organic acids, such as *i*-BuCO<sub>2</sub>H or PivOH. This provides evidence that AgOAc and HPMV likely oxidize palladium intermediates through orthogonal mechanisms.



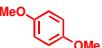

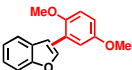



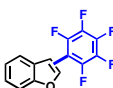
### 2.3. Competition studies indicate Pd(II)/Pd(IV) mechanism.

Both we and Fagnou have proposed mechanisms for the oxidative arylations of indole and benzofuran substrates.<sup>4c,e</sup> We have both assumed that these reactions proceed by two sequential C-H palladation steps forming Ar-Pd-Ar intermediates which undergo reductive elimination to form the biaryl products, and it is now generally accepted that these palladation steps occur via a concerted metalation-deprotonation (CMD) mechanism. The data presented herein indicate that the regioselectivity of the palladation of the benzofuran substrate is primarily controlled by the oxidant, but the absence of a Brønsted acid also influences the regioselectivity. As shown in Tables 1 and 2, the various reaction classes produce different regioisomers of phenylbenzofuran, with the acidic conditions favoring **2**, the buffered conditions producing a mixture of regiomers and the basic conditions favoring **3**. Interestingly, the buffered Class II conditions employing AgOAc produced a near equal mixture of **2** and **3**, while Class II conditions employing Cu(OAc)<sub>2</sub> yielded **3**.

as the major product. These data led us to speculate that the oxidant was associated with or was influencing the structure of the palladium catalyst during the benzofuran metalation step.<sup>4b,e,6</sup>

To assess whether the oxidant could also be influencing the palladation of the benzene substrate, we performed two competition studies. Equimolar amounts of *p*-dimethoxybenzene and *p*-xylene were reacted with benzofuran in reactions oxidized by HPMV, AgOAc and Cu(OAc)<sub>2</sub> (Class I and II conditions). Class III conditions were not screened because HPMV is insoluble in non-polar solvents like dioxane (Table 4).

**Table 4.** Competition Reactions

	Oxidant			Major Product	Prod. Ratio
1	10 mol % HPMV, O <sub>2</sub>				3.5:1
2	AgOAc (3 equiv)	“	“	“	2.9:1
3	Cu(OAc) <sub>2</sub> (3 equiv)	“	“	“	9:1
4	10 mol % HPMV, O <sub>2</sub>				3.5:1
5	AgOAc (3 equiv)	“	“		2.4:1
6	Cu(OAc) <sub>2</sub> (3 equiv)	“	“	“	1.2:1

For competitions between the two electron-rich arenes (entries 1-3), all three of the oxidants favored the formation of the *p*-dimethoxybenzene adduct, despite the fact that this was the more electron-rich, but more sterically hindered, substrate. When the reaction was allowed to choose between benzene and the deactivated arene, pentafluorobenzene, the Class II conditions preferred to arylate the fluorinated substrate despite the fact that the benzene substrate contained six times more C-H bonds. This chemoselectivity is consistent with a CMD palladation mechanism involving a Pd(II) intermediate.<sup>4c,7</sup> The Class I conditions, however, selectively arylated the benzene (entries 4-6). This implies that the Class I conditions may be evoking a unique mechanism. To date, all proposed mechanisms for these oxidative couplings assume that the intermediates are palladium complexes existing in either the 0 or +2 oxidation state. Based on the data shown in Table 4 and on the inverted preference for small carboxylic acid additives (Table 3), we hypothesize that the Class I reaction conditions (HPMV in acid) may promote a Pd(II)/Pd(IV) mechanism.<sup>8</sup> This possibility is also consistent with the fact that HPMV oxidized couplings do not precipitate palladium black—even after 100% conversion of the substrates—while the formation of palladium black is often evident in reactions that employ Ag(I) and Cu(II) oxidants.

HPMV, and other heteropoly acids having Keggin structures, have been classified as superacids and are strong oxidants.<sup>9a</sup>

HPMV has even been shown to efficiently oxidize methane in the presence of  $\text{H}_2\text{O}_2$ . Previously reported redox potentials of HPMV,  $\text{Ag}^+$  and  $\text{Cu}^{2+}$  (0.65 V,<sup>9b</sup> 0.41 V<sup>10</sup> and 0.40 V,<sup>11</sup> respectively) also indicate that HPMV has the potential to evoke a Pd(II)/Pd(IV) mechanism in oxidative reactions like the one described herein.

### 3. Conclusion

The classification system of reactions conditions of palladium-catalyzed oxidative coupling reactions that is presented herein explains the activity of reactions well, but does not necessarily predict the regioselectivity of the reactions. The evidence suggests that acid concentration plays a rather low role in mediating regioselective C2 vs. C3-arylation (**2**, **3**). Conversely, oxidant choice greatly affects regioselectivity. This is in line with our previous observations using *N*-acetylindole substrates, and both we and Fagnou have hypothesized that this oxidant-controlled selectivity is a consequence of the formation of heterometallic catalytic clusters.<sup>4b,e,6</sup> Furthermore, we have demonstrated that the rate-limiting step for our HPMV/ $\text{O}_2$  conditions is regeneration of the palladium catalyst, but for  $\text{AgOAc}$  oxidized reactions, it is likely one of the C-H palladations.

Furthermore, both the kinetic studies and the competition studies presented herein indicate that reactions oxidized by HPMV (Class I conditions) likely proceed by a different mechanism than those oxidized by either  $\text{AgOAc}$  or  $\text{Cu}(\text{OAc})_2$ . We propose that this unique mechanism involves Pd(IV) intermediates, while Class II and Class III conditions operate by a more conventional Pd(II)/Pd(0) mechanism.

The reaction conditions for the oxidative arylation of benzofuran are highly tunable in terms of overall starting material conversion and product regioselectivity. This shows much promise toward the extension of the scope of these conditions to other similar substrates.

## 4. Experimental section

### 4.1. General Considerations

Substrates, including benzofuran, propionic acid, isobutyric acid, trimethylacetic acid and dodecane were purchased from Acros Chemicals. All the oxidants used, with the exception of  $\text{H}_4\text{PMo}_{11}\text{VO}_{40}$ , were purchased from Acros Chemicals. Benzene was purchased from Sigma Aldrich. All reagents were stored under an inert atmosphere before use.  $\text{Pd}(\text{OAc})_2$  was obtained from Precious Metals Online (<http://www.precmet.com.au/>). Upon receipt, it was then dried under vacuum at 100 °C for approximately 2 h.  $\text{H}_4\text{PMo}_{11}\text{VO}_{40}$  was synthesized via a slight modification of the published procedure.<sup>9a</sup> This modification involved further drying by heating under vacuum at 135 °C for approximately 16 h, producing a golden brown powder. Vanadium(V) oxide and phosphoric acid were purchased from Acros Chemicals. Molybdc trioxide was purchased from Wayne Pigment Corp.  $\text{AcOH}$  was purchased from Alfa Aesar. Upon receipt, the  $\text{AcOH}$  was distilled over acetic anhydride (2:3 v/v) at 145 °C using a short path distillation apparatus.

Reactions that were heated in conventional oil baths were performed in Schlenk vacuum tubes that were purchased from Kontes (218710-0025). Microwave reactions were performed using either a CEM Explorer or Discover microwave synthesizer. Reactions containing  $\text{AgOAc}$  were prone to explosions when a Biotage Initiator microwave synthesizer was used because the silver mirror, which inevitably formed on the sides of the reaction vessel, interfered with the infrared sensor that was

positioned perpendicular to the reaction tube. CEM microwaves have an infrared sensor that is placed directly under the reaction vessel. Serendipitously, the action of the stir bar kept the bottom of the reaction tube clean, thus allowing for accurate temperature control.

GC/MS analysis was performed using an Agilent Technologies 6890 GC System fixed with a 5973 Mass Selective Detector. Dodecane was used as an internal standard. The GC method employed a 25 m x 0.200 mm, 0.33 micron, DB-1 column. The temperature program started at 40 °C for 0.50 min, which was followed by a ramp at a rate of 20 °C/min to 300 °C. The flow rate of the UHP He carrier gas was held constant at 0.8 mL/min. Retention times for benzofuran (**1**), dodecane, 3-phenylbenzofuran (**3**) and 2-phenylbenzofuran (**2**) were 4.88, 6.66, 9.93 and 10.33 min, respectively.

### 4.2. Class I Conditions: Representative Procedure

A magnetically stirred solution of benzofuran (0.080 g, 0.677 mmol), palladium acetate (0.015 g, 0.068 mmol),  $\text{H}_4\text{PMo}_{11}\text{VO}_{40}$  (0.121 g, 0.068 mmol) and  $\text{PivOH}$  (0.690 g, 6.77 mmol) in 4 mL of benzene was heated at 120 °C in a Schlenk tube under 3 atm  $\text{O}_2$ . An aliquot was subjected to GC/MS analysis before the reaction and at 60 min intervals (Schlenk tube is recharged with 3 atm  $\text{O}_2$  after each aliquot) to determine percent conversion with respect to dodecane as the internal standard. Purification was achieved by flash chromatography using 100% hexanes to yield pure **2** (106 mg, 81%). Spectral data was consistent with that which was previously reported.<sup>4a</sup>

### 4.3. Class II Conditions: Representative Procedure

A magnetically stirred solution of benzofuran (0.080 g, 0.677 mmol), palladium acetate (0.015 g, 0.068 mmol),  $\text{AgOAc}$  (0.339 g, 2.03 mmol) and  $\text{PivOH}$  (0.690 g, 6.77 mmol) in 4 mL of benzene and was heated at 120 °C in a closed vial. An aliquot was subjected to GC/MS analysis before the reaction and at 20 min intervals to determine percent conversion with respect to dodecane as the internal standard. Purification was achieved by flash chromatography using 100% hexanes to yield a 1:1 mixture of **2** and **3** (110 mg, 84%). Spectral data was consistent with that which was previously reported.<sup>4a</sup>

### 4.4. Class III Conditions: Representative Procedure

A magnetically stirred solution of benzofuran (0.080 g, 0.677 mmol), palladium acetate (0.015 g, 0.068 mmol),  $\text{AgOAc}$  (0.339 g, 2.03 mmol) and  $\text{PivOH}$  (0.690 g, 6.77 mmol) in 4 mL of benzene and was heated at 120 °C in a closed vial. An aliquot was subjected to GC/MS analysis before the reaction and at 2 h intervals to determine percent conversion with respect to dodecane as the internal standard. Purification was achieved by flash chromatography using 100% hexanes to yield a 1:6 mixture of **2** and **3** (110 mg, 84%). Spectral data was consistent with that which was previously reported.<sup>4a</sup>

### 4.5. Effect of Acid Sterics (Table 3)

A magnetically stirred solution of benzofuran (0.080 g, 0.677 mmol), palladium acetate (0.015 g, 0.068 mmol),  $\text{AgOAc}$  (0.318 g, 1.91 mmol) and 3 equiv. of varying organic acids in 4 mL of benzene was heated at 120 °C for 40 min (MW). An aliquot was subjected to GC/MS analysis before and after the reaction to determine percent conversion with respect to dodecane as the internal standard.

A magnetically stirred solution of benzofuran (0.080 g, 0.677 mmol), palladium acetate (0.015 g, 0.068 mmol),  $\text{H}_4\text{PMo}_{11}\text{VO}_{40}$  (0.121 g, 0.068 mmol) and 3 equiv. of varying organic acids in



4 mL of benzene was heated at 120 °C for 3 h in a Schlenk vacuum tube under 3 atm O<sub>2</sub>. An aliquot was subjected to GC/MS analysis before and after the reaction to determine percent conversion with respect to dodecane as the internal standard.

#### 4.6. Kinetic Studies: Effect of Acid Concentration (Figures 1,2 and 3)

A magnetically stirred solution of benzofuran (0.075 g, 0.635 mmol), palladium acetate (0.014 g, 0.064 mmol), AgOAc (0.318 g, 1.91 mmol) and varying amounts of PivOH in 3 mL of benzene was heated at 120 °C for 40 min (MW). An aliquot was subjected to GC/MS analysis before and after the reaction to determine percent conversion with respect to dodecane as the internal standard.

A magnetically stirred solution of benzofuran (0.080 g, 0.677 mmol), palladium acetate (0.015 g, 0.068 mmol), H<sub>4</sub>PMo<sub>11</sub>VO<sub>40</sub> (0.121 g, 0.068 mmol) and varying amounts of PivOH in 3 mL of benzene was heated at 120 °C for 6.5 h in a Schlenk vacuum tube under 3 atm O<sub>2</sub>. An aliquot was subjected to GC/MS analysis before and after the reaction to determine percent conversion with respect to dodecane as the internal standard.

A magnetically stirred solution of benzofuran (0.080 g, 0.677 mmol), palladium acetate (0.015 g, 0.068 mmol), H<sub>4</sub>PMo<sub>11</sub>VO<sub>40</sub> (0.121 g, 0.068 mmol) and varying amounts of AcOH in 3 mL of benzene was heated at 120 °C for 1.5 h in a Schlenk vacuum tube under 3 atm O<sub>2</sub>. An aliquot was subjected to GC/MS analysis before and after the reaction to determine percent conversion with respect to dodecane as the internal standard.

#### 4.7. Kinetic Studies: Effect of Catalyst and Oxidant Concentration (Figure 4 and 5)

*10 mol% Pd(OAc)<sub>2</sub>, 10 mol% H<sub>4</sub>PMo<sub>11</sub>VO<sub>40</sub>*: A magnetically stirred solution of benzofuran (0.080 g, 0.677 mmol), palladium acetate (0.015 g, 0.068 mmol), H<sub>4</sub>PMo<sub>11</sub>VO<sub>40</sub> (0.121 g, 0.068 mmol) and PivOH (0.690 g, 6.77 mmol) in 4 mL of benzene was heated at 120 °C in a Schlenk vacuum tube under 3 atm O<sub>2</sub>. An aliquot was subjected to GC/MS analysis before the reaction and at 60 min intervals (Schlenk tube was recharged with 3 atm O<sub>2</sub> after each aliquot) to determine percent conversion with respect to dodecane as the internal standard.

*20 mol% Pd(OAc)<sub>2</sub>, 10 mol% H<sub>4</sub>PMo<sub>11</sub>VO<sub>40</sub>*: A magnetically stirred solution of benzofuran (0.080 g, 0.677 mmol), palladium acetate (0.030 g, 0.134 mmol), H<sub>4</sub>PMo<sub>11</sub>VO<sub>40</sub> (0.121 g, 0.068 mmol) and PivOH (0.690 g, 6.77 mmol) in 4 mL of benzene was heated at 120 °C in a Schlenk vacuum tube under 3 atm O<sub>2</sub>. An aliquot was subjected to GC/MS analysis before the reaction and at 60 min intervals (Schlenk tube was recharged with 3 atm O<sub>2</sub> each time) to determine percent conversion with respect to dodecane as the internal standard.

*10 mol% Pd(OAc)<sub>2</sub>, 20 mol% H<sub>4</sub>PMo<sub>11</sub>VO<sub>40</sub>*: A magnetically stirred solution of benzofuran (0.080 g, 0.677 mmol), palladium acetate (0.015 g, 0.068 mmol), H<sub>4</sub>PMo<sub>11</sub>VO<sub>40</sub> (0.242 g, 0.134 mmol) and PivOH (0.690 g, 6.77 mmol) in 4 mL of benzene was heated at 120 °C in a Schlenk vacuum tube under 3 atm O<sub>2</sub>. An aliquot was subjected to GC/MS analysis before the reaction and at 60 min intervals (Schlenk tube was recharged with 3 atm O<sub>2</sub> each time) to determine percent conversion with respect to dodecane as the internal standard.

*10 mol% Pd(OAc)<sub>2</sub>, 3 equiv AgOAc*: A magnetically stirred solution of benzofuran (0.080 g, 0.677 mmol), palladium acetate (0.015 g, 0.068 mmol), AgOAc (0.339 g, 2.03 mmol) and PivOH

(0.690 g, 6.77 mmol) in 4 mL of benzene and was heated at 120 °C in a closed vial. An aliquot was subjected to GC/MS analysis before the reaction and at 20 min intervals to determine percent conversion with respect to dodecane as the internal standard.

*20 mol % Pd(OAc)<sub>2</sub>, 3 equiv AgOAc*: A solution of benzofuran (0.160 g, 1.354 mmol), palladium acetate (0.060 g, 0.272 mmol) and PivOH (1.38 g, 13.54 mmol) in 8 mL of benzene. Two magnetically stirred solutions were created from the reaction material. AgOAc (0.339 g, 2.03 mmol) was then added to each vial and heated at 120 °C in a closed vial. An aliquot was subjected to GC/MS analysis before the reaction (for each vial) and at 20 min intervals (offset by 10 min, i.e. A: 10 min, 30 min, etc.; B: 20 min, 40 min, etc.) to determine percent conversion with respect to dodecane as the internal standard.

*10 mol% Pd(OAc)<sub>2</sub>, 1.5 equiv AgOAc*: A magnetically stirred solution of benzofuran (0.080 g, 0.677 mmol), palladium acetate (0.015 g, 0.068 mmol), AgOAc (0.170 g, 1.01 mmol) and PivOH (0.690 g, 6.77 mmol) in 4 mL of benzene was heated at 120 °C in a closed vial. An aliquot was subjected to GC/MS analysis before the reaction and at 20 min intervals to determine percent conversion with respect to dodecane as the internal standard.

#### 4.8. Competition Studies (Table 4)

A magnetically stirred solution of benzofuran (0.050 g, 0.423 mmol), palladium acetate (0.010 g, 0.042 mmol), H<sub>4</sub>PMo<sub>11</sub>VO<sub>40</sub> (0.075 g, 0.085 mmol), benzene (1.33 mL, 14.9 mmol), pentafluorobenzene (1.66 mL, 14.9 mmol) and 2 mL acetic acid was heated at 120 °C for 1 h in a Schlenk vacuum tube under 3 atm O<sub>2</sub>. An aliquot was subjected to GC/MS analysis after the reaction to determine product ratios.

A magnetically stirred solution of benzofuran (0.050 g, 0.423 mmol), palladium acetate (0.010 g, 0.042 mmol), silver acetate (0.212 g, 1.27 mmol), benzene (1.33 mL, 14.9 mmol), 1.66 mL pentafluorobenzene (1.66 mL, 14.9 mmol) and 2 mL acetic acid was heated at 120 °C for 1 h in a Teflon capped vial. An aliquot was subjected to GC/MS analysis after the reaction to determine product ratios.

A magnetically stirred solution of benzofuran (0.050 g, 0.423 mmol), palladium acetate (0.010 g, 0.042 mmol), copper(II) acetate (0.230 g, 1.27 mmol), benzene (1.33 mL, 14.9 mmol), 1.66 mL pentafluorobenzene (1.66 mL, 14.9 mmol) and 2 mL acetic acid was heated at 120 °C for 1 h in a Teflon capped vial. An aliquot was subjected to GC/MS analysis after the reaction to determine product ratios.

A magnetically stirred solution of benzofuran (0.050 g, 0.423 mmol), palladium acetate (0.010 g, 0.042 mmol), H<sub>4</sub>PMo<sub>11</sub>VO<sub>40</sub> (0.075 g, 0.085 mmol), *p*-xylene (1.40 mL, 11.4 mmol), 1,4-dimethoxybenzene (1.57 g, 11.4 mmol) and 2 mL acetic acid was heated at 120 °C for 1 h in a Schlenk vacuum tube under 3 atm O<sub>2</sub>. An aliquot was subjected to GC/MS analysis after the reaction to determine product ratios.

A magnetically stirred solution of benzofuran (0.050 g, 0.423 mmol), palladium acetate (0.010 g, 0.042 mmol), silver acetate (0.212 g, 1.27 mmol), *p*-xylene (1.40 mL, 11.4 mmol), 1,4-dimethoxybenzene (1.57 g, 11.4 mmol) and 2 mL acetic acid was heated at 120 °C for 1 h in a Teflon capped vial. An aliquot was subjected to GC/MS analysis after the reaction to determine product ratios.

A magnetically stirred solution of benzofuran (0.050 g, 0.423 mmol), palladium acetate (0.010 g, 0.042 mmol), copper(II) acetate (0.230 g, 1.27 mmol), *p*-xylene (1.40 mL, 11.4 mmol), 1,4-dimethoxybenzene (1.57 g, 11.4 mmol) and 2 mL acetic acid

was heated at 120 °C for 1 h in a Teflon capped vial. An aliquot was subjected to GC/MS analysis after the reaction to determine product ratios.

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## Supplementary Material

Complete descriptions of all procedures for kinetic and competition experiments as well as analytical methods can be found online.