

## Mechanism of Benzoquinone-Promoted Palladium-Catalyzed Oxidative Cross-Coupling Reactions

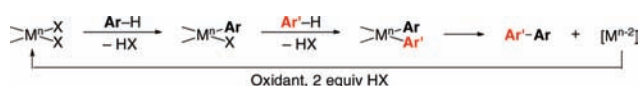
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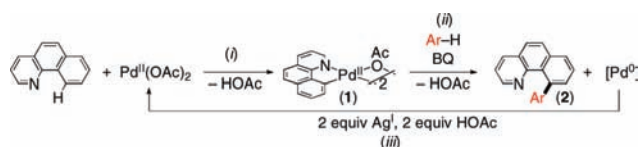
The development of mild, efficient, and selective transition-metal catalysts for the direct oxidative cross-coupling of simple arenes remains a significant challenge in organic synthesis.<sup>1–8</sup> Such transformations represent an atom-economical alternative to traditional Ar–X/Ar–M coupling reactions, which require the use of two prefunctionalized arene starting materials.<sup>1</sup> As shown in Scheme 1, a general mechanism for oxidative cross-coupling would involve sequential C–H activation of two different arene substrates followed by C–C bond-forming reductive elimination to release a biaryl product. A key challenge in these reactions is to control the selectivity of each C–H activation step.

**Scheme 1.** General Mechanism for Ar–H/Ar'–H Cross-Coupling



Several recent reports have described exciting progress in the development of Pd-catalyzed reactions for chemo- and regioselective Ar–H/Ar'–H cross-coupling.<sup>4–8</sup> For example, couplings between activated heteroarenes and arenes,<sup>5</sup> between cyclometalating substrates and arenes,<sup>6,7</sup> and between simple Ar–H derivatives<sup>8</sup> have been communicated over the past two years. These studies represent important advances in the field; however, the reactions remain limited by modest substrate scope, low turnover numbers, and the inability to rationally tune selectivity. These limitations are due, in large part, to a lack of fundamental mechanistic information about the factors controlling reactivity and selectivity in these systems. This communication describes the first detailed mechanistic investigation of a Pd-mediated oxidative cross-coupling reaction. The work provides key insights into the selectivity-determining step(s) of this transformation.

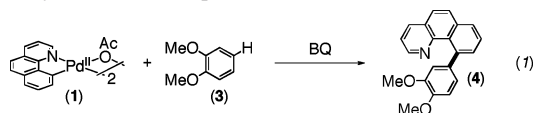
**Scheme 2.** General Pathway for Pd-Catalyzed Cross-Coupling



Our investigations focused on the Pd-catalyzed coupling of benzo[*h*]quinoline with simple arenes (Ar–H) (Scheme 2).<sup>6</sup> These transformations proceed with very high chemoselectivity for the formation of cross-coupled (vs homocoupled) products. Furthermore, like many related reactions, they afford modest to excellent selectivity for coupling at the least sterically hindered site of 1,2- and 1,3-disubstituted arenes.<sup>6,7</sup> However, this system is unique in that a substoichiometric quantity of a 1,4-benzoquinone (BQ) derivative is required to promote the oxidative coupling reaction. Furthermore, the structure of this quinone has a profound influence on the regioselectivity of coupling with certain arenes, suggesting

that the quinone acts as a ligand during the selectivity-determining step.<sup>6</sup> Thus, a key goal of these mechanistic studies was to more clearly elucidate the role of the quinone in these transformations.

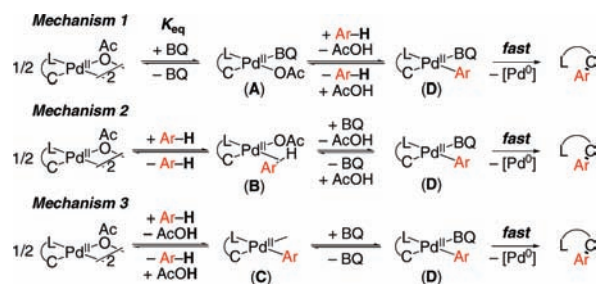
A general reaction pathway for the Pd-catalyzed oxidative coupling between benzo[*h*]quinoline and Ar–H involves (i) cyclometalation of benzo[*h*]quinoline to afford intermediate **1**, (ii) BQ-promoted Ar–H activation/Ar–Ar' coupling to liberate **2** and Pd<sup>0</sup>, and finally (iii) oxidation of Pd<sup>0</sup> to Pd<sup>II</sup> with Ag<sup>I</sup> (Scheme 2). On the basis of this pathway, we focused our mechanistic studies on the stoichiometric reaction between palladacycle **1** and 1,2-dimethoxybenzene (**3**) (eq 1):



This stoichiometric reaction was chosen because it allows for direct kinetic interrogation of the key Ar–H activation and C–C bond-forming steps [(ii) in Scheme 2], while eliminating complications from cyclometalation and oxidation processes. Arene **3** was selected for these studies because it reacts cleanly under both stoichiometric and catalytic conditions to afford a single biaryl product, **4**, in high yield.

We considered three mechanisms for the Ar–H activation/Ar–Ar' coupling steps of this Pd-mediated oxidative coupling (Scheme 3). Mechanism 1, which was proposed in our initial paper,<sup>6</sup> involves reversible coordination of  $\pi$ -acidic BQ to Pd followed by Ar–H activation and then reductive elimination to form the new Ar–Ar' bond. Mechanism 2 proceeds by reversible formation of an agostic Ar–H/Pd adduct (intermediate **B**), then BQ-promoted Ar–H activation, and finally reductive elimination. Mechanism 3 involves reversible Ar–H activation to form intermediate **C** followed by coordination of BQ and then reductive elimination to release the biaryl product. Notably, in each case, we assume that C–C coupling from intermediate **D** is fast and that the slow step is either Ar–H activation or BQ coordination.<sup>9</sup>

**Scheme 3.** Possible Detailed Mechanisms for Ar–H Activation/C–C Bond Formation from **1** Promoted by BQ



A variety of experiments were conducted to distinguish between mechanisms 1, 2, and 3.<sup>10</sup> Initial kinetic investigations revealed

that the oxidative coupling between **1** and **3** is half-order with respect to **1** and first-order with respect to **3** and exhibits saturation kinetics with respect to BQ (Figure 1). This data could potentially be consistent with all of the mechanisms in Scheme 3.

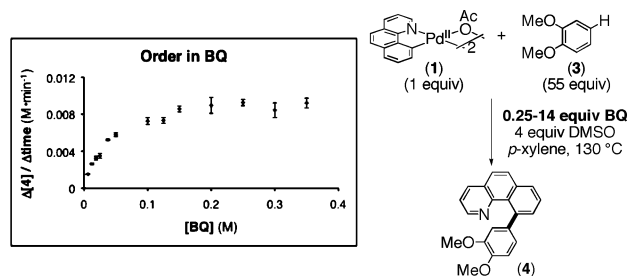


Figure 1. Saturation kinetics in benzoquinone.

The order of 0.5 with respect to **1** indicates cleavage of the native dimer to a kinetically competent monomeric species prior to the rate-determining step. The saturation kinetics with respect to BQ could result from two possible scenarios. For mechanism 1, saturation could be observed if equilibration between **1** + BQ and **A** were much faster than the subsequent Ar–H activation. At saturation ( $\sim 0.2$  M in BQ),  $K_{eq}$  would be expected to be significantly greater than 1 (see the Supporting Information); therefore, the Pd–BQ adduct **A** should be detectable. However,  $^1\text{H}$  NMR spectroscopic analysis of the reaction in the presence of up to 0.5 M BQ did not show formation of a new Pd<sup>II</sup> complex or the diagnostic signals associated with a coordinated quinone.<sup>12c</sup> These results suggest that mechanism 1 is unlikely.

Instead, we propose that the saturation kinetics are due to the formation of a steady-state (SS) intermediate that undergoes subsequent reaction with BQ. Such a scenario is consistent with either mechanism 2 (with the SS intermediate being agostic complex **B**) or mechanism 3 (with the SS intermediate being bisaryl complex **C**).

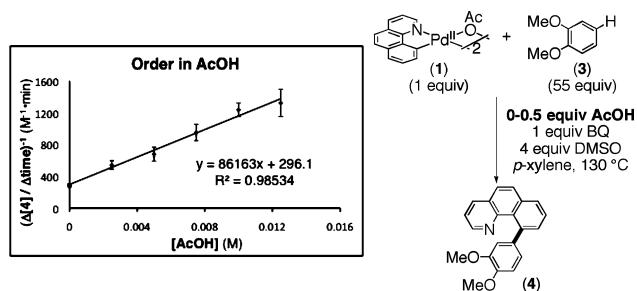
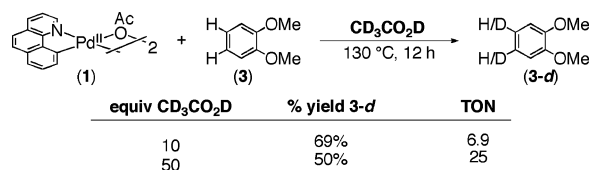


Figure 2. Inverse-first-order kinetics with respect to AcOH.

Experiments were next designed to differentiate between mechanisms 2 and 3. First, we measured the effect of 0.1–0.5 equiv of AcOH on the initial reaction rate in the presence of 1 equiv of BQ (nonsaturation conditions). This transformation showed an inverse-first-order dependence on AcOH (Figure 2), suggesting that AcOH is lost during formation of the SS intermediate. This is consistent with mechanism 3 (where AcOH is released in the generation of SS intermediate **C**) but not with mechanism 2 (where AcOH is formed only during the reaction of SS intermediate **B** with BQ).

Further support for mechanism 3 was obtained from the H/D exchange reaction between **1**, **3**, and  $\text{CD}_3\text{CO}_2\text{D}$  in the absence of BQ (Scheme 4).  $^2\text{H}$  NMR spectroscopic analysis of this transformation after 12 h at 130 °C showed significant D incorporation into **3**, presumably via reversible C–H activation/deuteration.<sup>11</sup> This

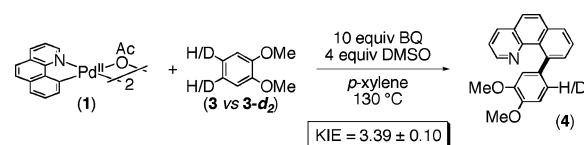
Scheme 4. H/D Exchange between **3** and  $\text{CD}_3\text{CO}_2\text{D}$  Catalyzed by **1**



result is consistent only with mechanism 3, since no H/D exchange would be expected if mechanisms 1 or 2 were operating.<sup>12,13</sup>

We next sought to take advantage of the observed saturation kinetics to directly probe the mechanism of Ar–H activation. These studies were all conducted under saturation conditions ( $[\text{BQ}] > 0.15$  M), ensuring that C–H activation is rate-limiting. We first determined the intermolecular kinetic isotope effect (KIE) for Ar–H activation by comparing the initial reaction rate for **3** to that for **3-d<sub>2</sub>** (Scheme 5). The KIE was found to be  $3.39 \pm 0.10$ , which indicates that the transition state involves significant Ar–H bond breaking.<sup>14</sup>

Scheme 5. Kinetic Isotope Effect Study



The effect of electronically varying the carboxylate ligand was studied next by examining the reaction of para-substituted benzoate complexes with **3** in the presence of 20 equiv of BQ. The Hammett plot obtained from this data showed a  $\rho$  value of  $-0.94 \pm 0.16$  (Figure 3). This indicates that the carboxylate ligand stabilizes positive-charge buildup in the transition state for C–H activation.

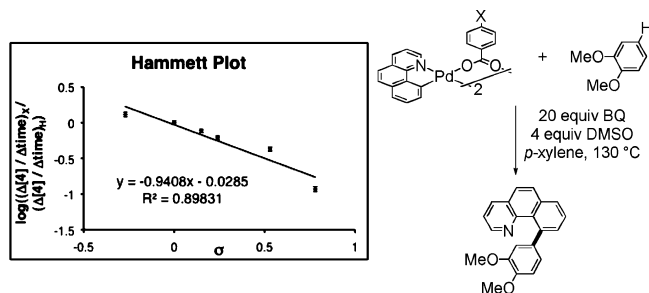
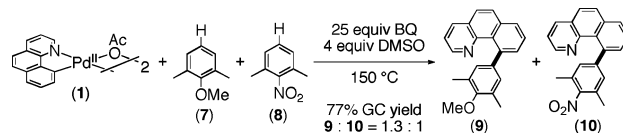


Figure 3. Hammett plot for variation of the carboxylate ligand.

Scheme 6. Arene Electronic Effects on the C–H Activation Step



Finally, the influence of Ar–H electronics was examined using the reaction depicted in Scheme 6. The competition between **7** and **8** afforded a 1.3:1 ratio of products **9** and **10**, demonstrating that the relative rate of C–H activation is slightly larger for the electron-rich arene **7**. The observed chemoselectivity provides evidence against a mechanism involving Ar–H deprotonation, since such reactions are typically much faster with more acidic C–H bonds.<sup>15</sup> Further, the modest magnitude of this electronic effect is inconsistent with an  $\text{S}_{\text{E}}\text{Ar}$  mechanism.<sup>16</sup> On the basis of this result, along with the KIE and Hammett data, we hypothesize that C–H

activation in this system proceeds by an intermediate mechanism that resembles  $\sigma$ -bond metathesis.<sup>17</sup> Computational studies to further assess the nature of this transition state are ongoing.

The results of the mechanistic studies detailed herein have important implications for the future development of this oxidative coupling reaction. Most notably, they suggest that the chemo- and regioselectivity of these transformations can be tuned by rational modification of the reaction conditions. In the presence of a large excess of BQ, Ar–H activation should not be reversible; therefore, the observed selectivity should reflect that inherent to the C–H activation step. However, as the amount of BQ is decreased and/or as AcOH is added, the Ar–H activation step should become highly reversible. Under these Curtin–Hammett-type conditions, the selectivity should approach that intrinsic to the BQ-promoted reductive elimination step.

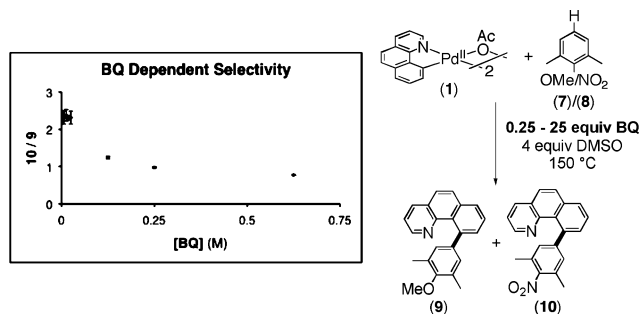


Figure 4. 10/9 ratio as a function of [BQ].

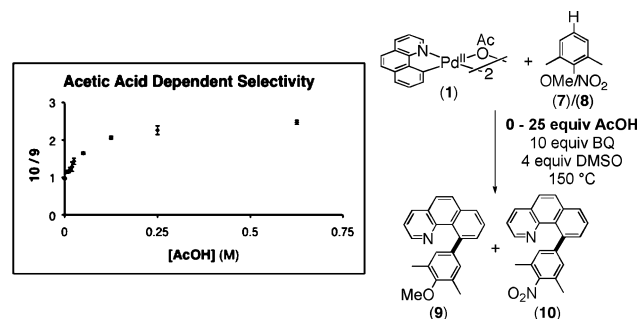


Figure 5. 10/9 ratio as a function of [AcOH].

For a preliminary demonstration of this powerful concept, we examined the chemoselectivity of the competition reaction between **1** and **7/8** under the two limiting scenarios. As shown in Figure 4, when [BQ] was increased from 0.00625 M (0.25 equiv) to 0.625 M (25 equiv), the chemoselectivity of the reaction was reversed from favoring product **10** ( $10/9 = 2.3:1$  with [BQ] = 0.00625 M) to favoring **9** ( $10/9 = 1:1.3$  with [BQ] = 0.625 M). The former selectivity reflects that of the BQ-promoted Ar–Ar' coupling reaction, while the latter represents that for Ar–H activation at **1**.<sup>18</sup> As expected, similar results were obtained when AcOH (0 to 0.625 M) was added to the reaction, with the  $10/9$  ratio changing from 1:1 at [AcOH] = 0 M to 2.5:1 at [AcOH] = 0.625 M (Figure 5).

In conclusion, this communication has described detailed mechanistic investigations of the Pd-mediated cross-coupling between benzo[*h*]quinoline and simple arenes (Ar–H). These studies all support a mechanism involving pre-equilibrium Ar–H activation followed by BQ-promoted Ar–Ar' reductive elimination to release the cross-coupled product. This work serves as a foundation for the rational design of reaction conditions and catalysts for the

systematic tuning of both reactivity and selectivity in these transformations.

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**Supporting Information Available:** Experimental details and spectroscopic data for new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- The assumption that C–C coupling from **D** is fast is based on (1) calculations and experiments showing that coordination of BQ to Pd<sup>II</sup>(R)<sub>2</sub> complexes dramatically lowers the barrier for C–C bond-forming reductive elimination and (2) the fact that observable Pd<sup>II</sup>(BQ) complexes are extremely rare in the literature (see ref 12c), presumably because they are highly reactive towards reductive elimination. See: (a) Pérez-Rodríguez, M.; Braga, A. A. C.; Garcia-Melchor, M.; Pérez-Temprano, M. H.; Casares, J. A.; Ujaque, G.; de Lera, A. R.; Alvarez, R.; Maseras, F.; Espinet, P. *J. Am. Chem. Soc.* **2009**, *131*, 3650. (b) Szabo, K. J. *Organometallics* **1998**, *17*, 1677.
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