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Controlling Site Selectivity in Pd-Catalyzed Oxidative Cross-Coupling Reactions

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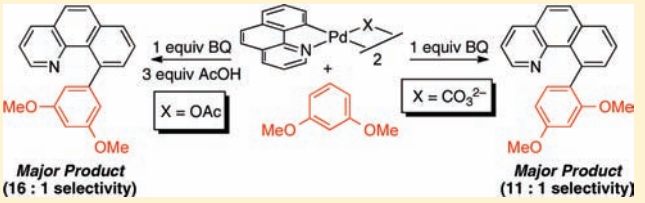
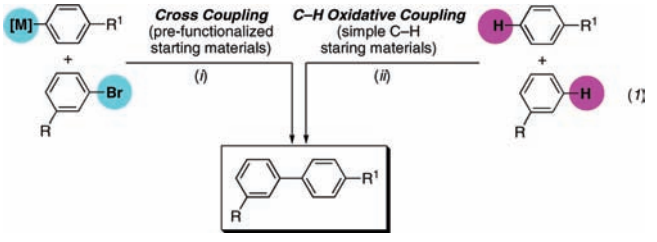
Supporting Information

ABSTRACT: This paper presents a detailed investigation of the factors controlling site selectivity in the Pd-mediated oxidative coupling of 1,3-disubstituted and 1,2,3-trisubstituted arenes (aryl−H) with cyclometalating substrates (L∼C−H). The influence of both the concentration and the steric/electronic properties of the quinone promoter are studied in detail. In addition, the effect of steric/electronic modulation of the carboxylate ligand is discussed. Finally, we demonstrate that substitution of the carboxylate for a carbonate X-type ligand leads to a complete reversal in site selectivity for many arene substrates. The origins of these trends in site selectivity are discussed in the context of the mechanism of Pd-catalyzed oxidative cross-coupling.

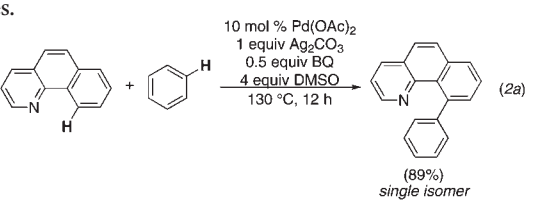


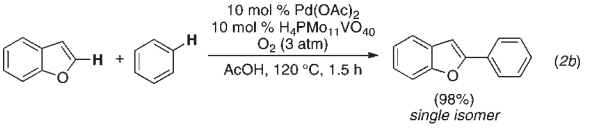
INTRODUCTION

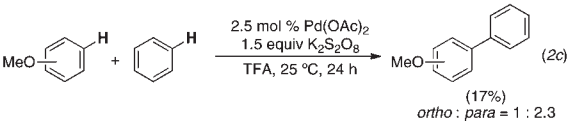
The biaryl linkage is an important structural motif that is prevalent in numerous organic compounds, including natural products,[1a−1e] pharmaceuticals,[1f,1g] agrochemicals,[1h] and conjugated materials.[1j] Aryl−aryl bonds are most commonly formed via Pd-, Ni-, or Cu-catalyzed cross-coupling between aryl halide electrophiles and [M]−aryl nucleophiles (eq 1, i).[2] While such reactions are extremely important and widely used synthetic methods, they remain fundamentally limited by the requirement for two prefunctionalized coupling partners.[3] C−H oxidative coupling reactions represent a highly attractive alternative strategy for constructing aryl−aryl bonds (eq 1, ii).[3m,3n,4] In these transformations, the biaryl linkage is generated via sequential C−H activation of two aromatic substrates (aryl−H and aryl′−H) followed by C−C bond formation. As such, this approach precludes the need for prefunctionalization of either aromatic starting material.



Several recent reports have described exciting progress in the development of Pd-catalyzed oxidative coupling reactions.[5−8] For example, our group[8b] and others[5,6,8] have demonstrated the cross-coupling of benzene with arenes, such as benzo[*h*]quinoline (eq 2a),[8b] benzofuran (eq 2b),[6c] and anisole (eq 2c).[5a] Despite these important advances, many challenges remain before these transformations can be widely practiced in organic synthesis. Currently, the most significant limitation is the inability to predictably control and modify site selectivity. This paper describes studies that address this crucial issue in the oxidative cross-coupling between cyclometalating substrates (L∼C−H) and aryl−H derivatives.







Our group has recently communicated a Pd-catalyzed reaction for the oxidative cross-coupling of benzo[*h*]quinoline (bzq) with arenes (aryl−H) promoted by benzoquinone (BQ) in the presence of a Ag^I oxidant (eq 2a).[8b] Extensive studies implicated a mechanism involving cyclopalladation of bzq to generate $[(bzq)Pd(OAc)]_2$, reversible activation of aryl−H, BQ-binding/BQ-promoted C−C bond-forming reductive elimination,[9]

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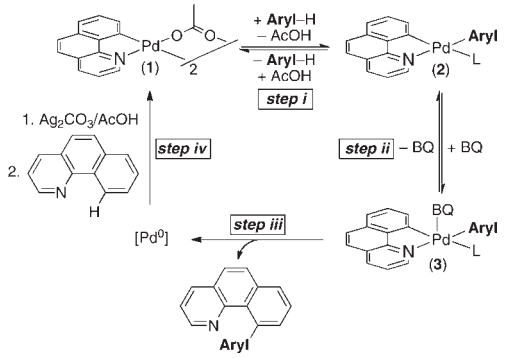
Scheme 1. Proposed Mechanism for Oxidative Coupling Between bzq and aryl−H



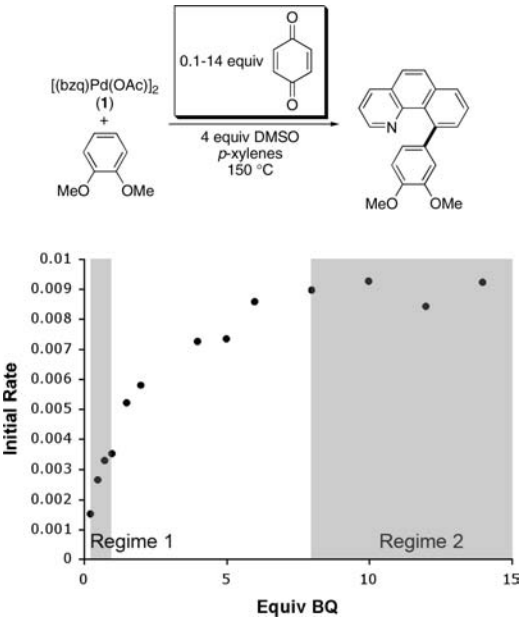


Figure 1. Initial rate versus equivalents of BQ in the coupling of compound **1** with 1,2-dimethoxybenzene.

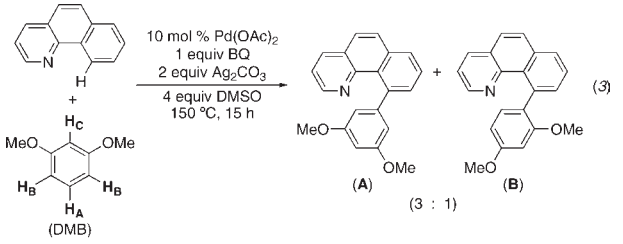
and finally, reoxidation of Pd^0 by Ag^I to regenerate the Pd^{II} catalyst (Scheme 1).[10]

Intriguingly, the rate-determining step of this sequence is dependent upon the concentration of the quinone promoter. For example, in the reaction of $[(bzq)Pd(OAc)]_2$ with 1,2-dimethoxybenzene, a first-order dependence upon [BQ] was observed at low concentrations of BQ, suggesting that quinone complexation (step ii) is rate-determining.[9,10] In contrast, saturation was observed at high [BQ], implicating rate-limiting C−H activation (step i) under these conditions (Figure 1).[10] These two kinetic regimes will be referred to as regime 1 (low [BQ], 1 equiv) and regime 2 (high [BQ], 20 equiv) throughout this paper.

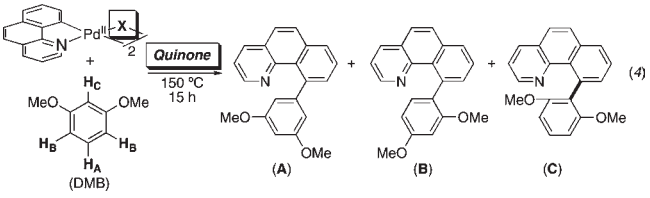
With this mechanistic framework in hand, we turned our attention toward understanding and controlling the site selectivity of aryl−H functionalization. We hypothesized that the change in rate-determining step between regimes 1 and 2 might also lead to a change in site selectivity. Furthermore, we reasoned that systematic modification of the ancillary ligands at Pd intermediates **1**−**3** might enable catalyst control. This paper describes a detailed investigation of the factors dictating site selectivity in these oxidative coupling reactions. We demonstrate that the X-type ligands have a particularly dramatic influence on selectivity and discuss the origin of these ligand effects in the context of the mechanistic framework in Scheme 1.

RESULTS AND DISCUSSION

Selection of the Arene Substrate for Initial Studies. 1,3-Dimethoxybenzene (DMB) was selected as a test substrate for probing site selectivity. DMB contains three different aromatic hydrogens (H_A, H_B, and H_C) with dramatically different steric and electronic properties. H_B and H_C are attached to the most nucleophilic carbons in the molecule. H_A is located at the most sterically accessible position. H_C is at the most sterically crowded site on the arene. Under our original conditions [10 mol % of $Pd(OAc)_2$, 2 equiv of Ag_2CO_3, 4 equiv of DMSO], DMB underwent oxidative coupling with benzo[*h*]quinoline to afford a 3:1 mixture of isomers **A**/**B** (derived from replacing H_A and H_B, respectively) (eq 3).[11] This result suggests that there is relatively little inherent selectivity in this system, which renders it an ideal case for studying catalyst control.



Selection of the Reaction to Investigate Site Selectivity. The studies described throughout this paper involve the reaction of DMB with $[(bzq)PdX]_2$ to afford mixtures of isomers **A**, **B**, and **C** (eq 4). This stoichiometric transformation allows us to directly probe DMB functionalization without interference from the cyclometalation or oxidation steps of the catalytic cycle. Most importantly, this approach excludes any influence of oxidant-derived X/L-type ligands on reactivity or selectivity. The results obtained in regime 1 (1 equiv of quinone relative to [Pd]) and regime 2 (20 equiv of quinone relative to [Pd])[12] are discussed below as a function of three variables: (1) quinone, (2) carboxylate, and (3) other X-type ligands.[13]



Role of Quinone. The reaction of DMB with $[(bzq)Pd(OAc)]_2$ was first studied as a function of the concentration of BQ. The site selectivity showed a clear dependence upon [BQ], with the ratio of isomers **A**/**B** ranging from 11:1 at 0.005 M (0.2 equiv) to 1.1:1 at 0.5 M (20 equiv). (Less than 5% of isomer **C** was observed in any of these reactions.) A plot of **A**/**B** versus equiv of BQ (Figure 2) showed that the ratio levels out at approximately 1:1 at 0.20 M (8 equiv). This is the same concentration at which saturation is observed in Figure 1, consistent with a change in both rate- and selectivity-determining steps between regimes 1 and 2.

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This reaction was next studied using a series of alkyl-substituted quinone promoters. In regime 1 (0.025 M, 1 equiv of quinone),[12] quinone substitution had a dramatic effect on selectivity, with **A**/**B** increasing from 5:1 with BQ to 14:1 with 2,3,5,6-tetramethylbenzoquinone (Table 1).[14] Notably, the improved selectivity was generally accompanied by a decrease in the overall yield. In regime 2 (0.5 M, 20 equiv of quinone),[12] the **A**/**B** ratio was significantly lower with all of the quinone derivatives. This ratio dropped even further as [quinone] was increased to 1.0 M (40 equiv).

Selectivity was also investigated with a series of *para*-substituted 2,5-diarylquinones. This study was conducted in regime 1, because this is where the largest effect was expected. In general, the **A**/**B** ratio was higher with more electron-donating X substituents (Table 2). A Hammett plot of ($\log[\mathbf{A}/(\mathbf{A}+\mathbf{B})_X/\mathbf{A}/(\mathbf{A}+\mathbf{B})]_H$) versus σ_{para} (Figure S1 in the Supporting Information) showed a reasonable correlation ($R^2 = 0.86$), with a ρ value of -0.8 ± 0.2.

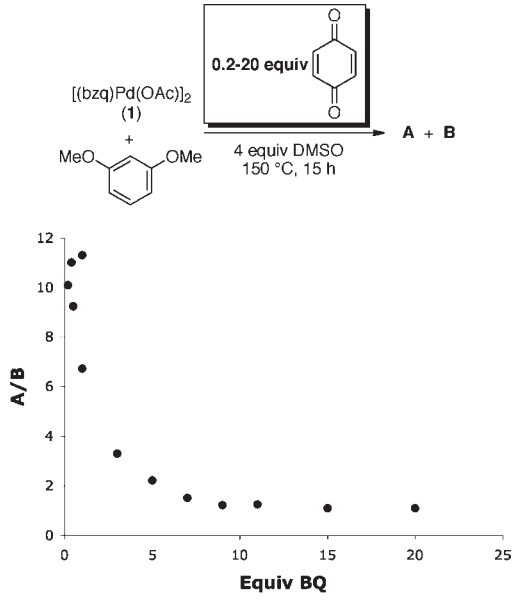


Figure 2. **A**/**B** versus equiv of BQ for the reaction of compound **1** with DMB.

Role of Carboxylate. The reaction of DMB with $[(bzq)Pd(O_2CR)]_2$ was next studied using carboxylate ligands with R = Me, Et, ^{i}Pr, or ^{t}Bu. In regime 2, larger R groups provided enhanced preference for isomer **A**; for example, **A**/**B** increased from 1:1.5 to 1.8:1 upon moving from R = CH_3 to ^{t}Bu (entries 5−8 in Table 3). Interestingly, a similar trend was observed in regime 1, with **A**/**B** changing from 5:1 to 9:1 for R = CH_3 and ^{t}Bu, respectively (entries 1−4 in Table 3).

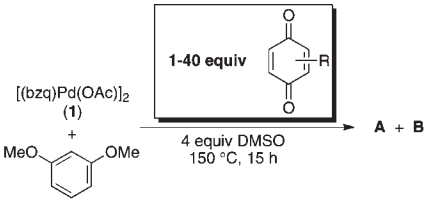
We also added 3 equiv of RCO_2H to the reactions in regime 1 to facilitate complete equilibration of the C−H activation step (step i in Scheme 1). Under these conditions, **A**/**B** increased from 5:1 to 16:1. Furthermore, this ratio remained constant over the entire range of carboxylate derivatives (Table 4).

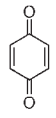
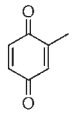
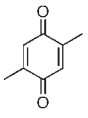
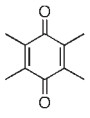
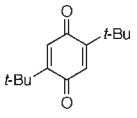
The electronic influence of the carboxylate ligand was assessed using $[(bzq)Pd(O_2C(p\text{-}XC_6H_4))]_2$. In regime 1, the *para* substituent X had a relatively minimal impact on selectivity, particularly upon the addition of 3 equiv of $ArCO_2H$ (entries 1−8 in Table 5). In regime 2, small electronic effects were observed, with **A**/**B** ranging from 1:1.7 to 1:2.9. However, there was no clear correlation between **A**/**B** and Hammett σ values in this system.

Discussion of Ligand Effects with $[(bzq)Pd(O_2CR)]_2$. The results described above provide a comprehensive picture of the influence of the quinone promoter and carboxylate ligand on selectivity. A detailed mechanism that is consistent with all of this data is shown in Scheme 2, and it implicates two limiting mechanistic scenarios. In the first (limit 1), intermediates $\mathbf{Pd_A}$ and $\mathbf{Pd_B}$ are in a fast and reversible equilibrium, where $k_1[\mathbf{1}][DMB]$ and $k_{-1}^{A/B}[\mathbf{Pd_{A/B}}][RCO_2H] \gg k_2^{A/B}[\mathbf{Pd_{A/B}}][quinone]$. This is a classic Curtin−Hammett situation, where the rate and selectivity will be dictated by the relative magnitudes of $\Delta G^{\ddagger}$ for quinone complexation with $\mathbf{Pd_A}$ versus $\mathbf{Pd_B}$, respectively. In the second limiting possibility (limit 2), $k_2^{A/B}[\mathbf{Pd_{A/B}}][quinone] \gg k_1[\mathbf{1}][DMB]$. Under these conditions, the rate and selectivity will be determined by the relative magnitude of $\Delta G^{\ddagger}$ for C−H activation to form $\mathbf{Pd_A}$ versus $\mathbf{Pd_B}$, respectively.

The experiments described above use 1 equiv of quinone (regime 1) and 20 equiv of quinone (regime 2) to approximate

Table 1. Site Selectivity as a Function of Quinone Substitution[a]



	Equiv of quinone (Regime)					
A/B	1 (Regime 1)	5 : 1	6 : 1	11 : 1	14 : 1	11 : 1
Yield		100%	100%	74%	54%	56%
A/B	20 (Regime 2)	1 : 1	1.5 : 1	4 : 1	8 : 1	5 : 1
Yield		65%	64%	94%	97%	100%
A/B	40 (Regime 2)	1 : 1.7	1 : 1	3 : 1	7 : 1	4 : 1
Yield		61%	59%	82%	66%	99%

[a] Yields were determined by gas chromatography (GC) analysis of the crude reaction mixtures versus an internal standard and represent an average of 2 runs.

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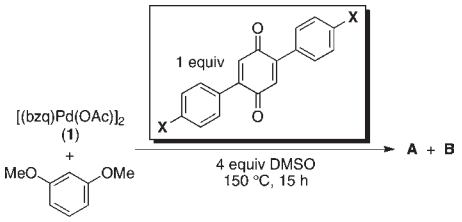
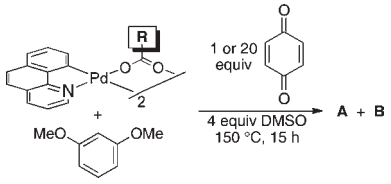
Table 2. Site Selectivity as a Function of Quinone Substitution (Electronic Effects)



entry	X	yield (%)[a]	A/B
1	CF_3	62	1.1:1
2	F	59	2.1:1
3	H	65	3:1
4	Me	49	2.6:1
5	OMe	68	5.7:1

[a] Yields were determined by GC analysis of the crude reaction mixtures versus an internal standard and represent an average of two runs.

Table 3. Site Selectivity as a Function of Carboxylate Substitution



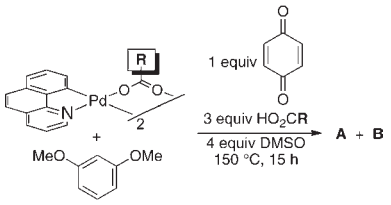
entry	conditions	R	yield (%)[a]	A/B
1	1 equiv of BQ	Me	76	5:1
2	1 equiv of BQ	Et	78	6:1
3	1 equiv of BQ	^{i}Pr	79	7:1
4	1 equiv of BQ	^{t}Bu	84	9:1
5	20 equiv of BQ	Me	61	1:1.5
6	20 equiv of BQ	Et	62	1:1.2
7	20 equiv of BQ	^{i}Pr	82	1.5:1
8	20 equiv of BQ	^{t}Bu	65	1.8:1

[a] Yields were determined by GC analysis of the crude reaction mixtures versus an internal standard and represent an average of 2 runs.

these two limiting scenarios. However, changes to the quinone and the carboxylate ligands can clearly influence both the relative and absolute values of the six key rate constants in this system (k_1^A, k_1^B, k_{-1}^A, k_{-1}^B, k_2^A, and k_2^B). As such, the experimental results in regimes 1 and 2 approach but do not necessarily reach the limiting scenarios outlined above. In other words, while quinone complexation always dominates the selectivity in regime 1, the C−H activation step can also provide a small contribution under some conditions. Similarly, the C−H activation step always dominates the selectivity in regime 2, but quinone complexation can also have some influence depending upon the ligands present and relative rate constants. A detailed discussion of the effects of quinone and carboxylate on regimes 1 and 2 is outlined below.

Discussion of the Quinone Promoter. In regime 1, we propose that the rate and selectivity are primarily dictated by quinone complexation through the d_{z^2} orbital of one of two interconverting σ-aryl Pd intermediates (**Pd$_A$** and **Pd$_B$**). The d_{z^2} orbital of **Pd$_B$** is significantly more sterically congested than that of

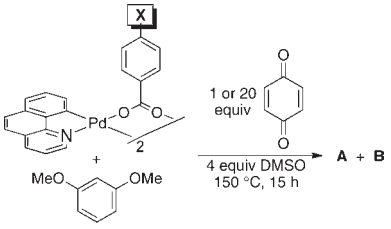
Table 4. Site Selectivity as a Function of Carboxylate Substitution in the Presence of Exogenous Acid



entry	conditions	R	yield (%)[a]	A/B
1	1 equiv of BQ, 3 equiv of $MeCO_2H$	Me	94	16:1
2	1 equiv of BQ, 3 equiv of $EtCO_2H$	Et	95	16:1
3	1 equiv of BQ, 3 of equiv $^iPrCO_2H$	^{i}Pr	91	16:1
4	1 equiv of BQ, 3 equiv of $^tBuCO_2H$	^{t}Bu	64	16:1

[a] Yields were determined by GC analysis of the crude reaction mixtures versus an internal standard and represent an average of 2 runs.

Table 5. Site Selectivity as a Function of Benzoate Substitution (Electronic Effects)



entry	conditions	p-XC_6H_4 (Ar)	yield (%)[a]	A/B
1	1 equiv of BQ	p-$MeOC_6H_4$	58	14:1
2	1 equiv of BQ	C_6H_5	62	10:1
3	1 equiv of BQ	p-$CF_3C_6H_4$	45	11:1
4	1 equiv of BQ	p-$NO_2C_6H_4$	39	11:1
5	1 equiv of BQ/3 equiv of $ArCO_2H$	p-$MeOC_6H_4$	36	17:1
6	1 equiv of BQ/3 equiv of $ArCO_2H$	C_6H_5	35	16:1
7	1 equiv of BQ/3 equiv of $ArCO_2H$	p-$CF_3C_6H_4$	23	19:1
8	1 equiv of BQ/3 equiv of $ArCO_2H$	p-$NO_2C_6H_4$	9	20:1
9	20 (regime 2)	p-$MeOC_6H_4$	36	1:1.7
10	20 (regime 2)	C_6H_5	40	1:2
11	20 (regime 2)	p-$CF_3C_6H_4$	38	1:2.9
12	20 (regime 2)	p-$NO_2C_6H_4$	38	1:2.5

[a] Yields were determined by GC analysis of the crude reaction mixtures versus an internal standard and represent an average of two runs.

Pd$_A$ because of the *ortho*-substituted σ-aryl ligand. As a result, we hypothesize that quinone association (and subsequent irreversible bzq−DMB coupling) is slower at **Pd$_B$** than **Pd$_A$**, leading to selective formation of isomer **A**.[15]

In regime 1, more electron-deficient quinones provided lower **A**/**B** ratios (Table 2), and there are likely two factors that contribute to this effect. First, electron-deficient BQ derivatives are more reactive π-acids and are thus expected to be less selective in distinguishing between Pd_A and Pd_B. Second, the higher reactivity of electron-deficient quinones should increase k_2^A and k_2^B, leading to a larger contribution of the C−H activation step (which shows less kinetic preference for isomer **A**) to selectivity.[16]

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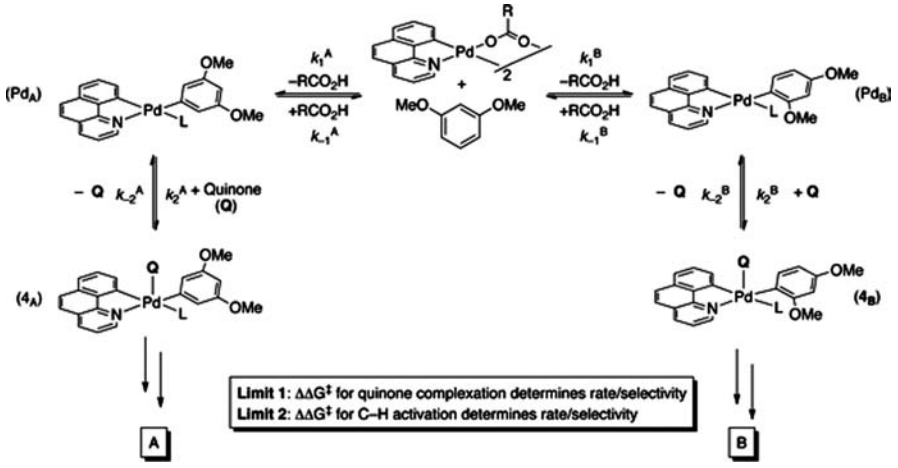
Scheme 2. Detailed Mechanism for Coupling between $[(bzq)Pd(O_2CR)]_2$ and DMB



In regime 1, alkyl substituents on the quinone resulted in enhanced selectivity for **A** (Table 1). This is likely due to a combination of electronic and steric effects. Alkyl groups are moderately electron-donating, which, as discussed above, favors the formation of **A**. Alkyl substitution also increases the size of the quinone, which should exacerbate unfavorable steric interactions in its reaction with $\mathbf{Pd_B}$.

In regime 2, the rate and selectivity are dominated by the C−H activation step. Interestingly, under these conditions, the reaction showed almost no selectivity for isomer **A**, providing an approximately 1:1 ratio of **A**/**B** (20 equiv of BQ). This result indicates that, as conditions approach limit 2, there is much less kinetic preference for activation of H_A versus H_B at this Pd^{II} center. Notably, most other C−H activation reactions at Pd^{II} are strongly affected by steric/electronic factors;[3,6,8,17] therefore, the apparently low inherent site selectivity of this step is an unusual feature of the current transformation, which remains the subject of detailed exploration.

In regime 2, changes to the quinone structure are expected to have minimal impact on selectivity, because quinone is not involved in the C−H activation step. As illustrated in Table 1, increasing the [quinone] resulted in a decrease of the **A**/**B** ratio in all cases. However, even at 1.0 M (40 equiv), the differentially substituted quinones provided somewhat different selectivities. These data suggest that many of these reactions have not completely reached limit 2, and thus, the quinone complexation step still provides some contribution to selectivity.

Discussion of the Effect of Carboxylate Ligands. In regime 1, sterically larger carboxylates provided enhanced selectivity for **A** (entries 1−4 in Table 3). We initially considered that the carboxylic acid might serve as the ligand L in $\mathbf{Pd_{A/B}}$ (Scheme 2). However, this proposal is inconsistent with the inverse first-order kinetics in AcOH observed during this transformation,[10] which implicate AcOH dissociation prior to the rate-determining step.

Instead, we propose that C−H activation is not fully reversible in the presence of 1 equiv of BQ. As a result, a Curtin−Hammett situation (involving fast pre-equilibration between $\mathbf{Pd_A}$ and $\mathbf{Pd_B}$ followed by rate- and selectivity-determining BQ complexation) is not fully established. The different relative rates of C−H activation/protonation (k_1^A/k_{-1}^A versus k_1^B/k_{-1}^B) for each carboxylate complex thus contribute to the observed selectivities.

Consistent with this proposal, the **A**/**B** selectivity became independent of R upon the addition of 3 equiv of RCO_2H to these reactions. The added acid should increase the relative rate of protonation of $\mathbf{Pd_A}/\mathbf{Pd_B}$ ($k_{-1}[RCO_2H][\mathbf{Pd_{A/B}}]$) compared to that of BQ complexation ($k_2[BQ][\mathbf{Pd_{A/B}}]$). As such, it should promote more complete equilibration of the C−H activation step, such that selectivity is dictated solely by $\Delta\Delta G^{\ddagger}$ for quinone complexation.

In regime 2, the carboxylate ligand is expected to be coordinated to Pd during the rate/selectivity-determining C−H activation step. Consistent with this, the **A**/**B** ratio in regime 2 was sensitive to both steric and electronic perturbation of R. Sterically large carboxylate ligands provided enhanced selectivity for functionalization at the least hindered site of DMB (to form **A**), implicating unfavorable steric interactions in the transition state for C−H activation. Small electronic effects were also observed with *p*-substituted benzoate derivatives; however, the modest magnitude and the lack of a clear trend preclude definitive interpretation of these results at this time.

Influence of Varying the X-Type Ligand. On the basis of the studies described above, we reasoned that substituting carboxylates with alternative X-type ligands might further modulate selectivity in these systems. Thus, we examined the reaction of DMB with $[(bzq)PdCl]_2$ (**5**) in the presence of a variety of AgX salts. Importantly, complex **5** is unreactive under these conditions without added AgX (entry 1 in Table 6), presumably because of its low solubility. Therefore, any observed reactivity implicates at least partial substitution of Cl with X.

We first examined the reaction of compound **5** with AgOAc and AgOPiv. The **A**/**B** selectivity in these systems was nearly identical to that obtained using the preformed carboxylate-bridged dimers (compare entries 1 and 4 in Table 3 to entries 2 and 3 in Table 6). This suggests that the reaction between compound **5** and AgO_2CR generates $[(bzq)Pd(O_2CR)]$ *in situ*.

We next surveyed Ag salts containing weakly coordinating counterions (e.g., $CF_3CO_2^-$, NO_3^-, BF_4^-, and PF_6^-). In all cases, modest to poor yields and low levels of site selectivity were observed (entries 4−7 in Table 6). In striking contrast, Ag_2CO_3 provided an excellent chemical yield (92%) with a complete reversal of selectivity (1:6 ratio of **A**/**B**; entry 8 in Table 6).[18] In addition, for the first time, traces (~5%) of isomer **C** (derived from functionalization at the most hindered site on DMB) were observed.

Alkali metal carbonate salts provided similar results to Ag_2CO_3 (Table 7), and both reactivity and selectivity generally improved with increasing size of the cation. For example, 1 equiv of Na_2CO_3 afforded 51% yield of product as a 1:3 ratio of isomers

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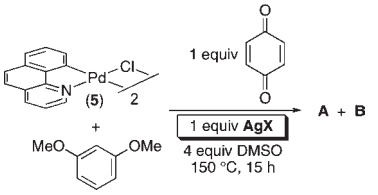
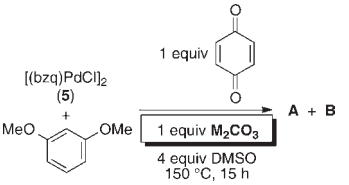
Table 6. Site Selectivity as a Function of AgX[a]



entry	AgX	A/B	yield (%)[b]
1	none		nr[c]
2	AgOAc	5:1	98
3	AgOPiv	9:1	79
4	AgO_2CCF_3	1:1	13
5	$AgNO_3$	2:1	38
6	Ag_2SO_4	nr[c]	nr[c]
7	$AgBF_4$	nr[c]	nr[c]
8	Ag_2CO_3	1:6[d]	92

[a] A total of 1 mol of Ag was used per mole of Pd (e.g., 1 mol of AgOAc/0.5 mol of compound **5**). [b] Yields were determined by GC analysis of the crude reaction mixtures versus an internal standard and represent an average of 2 runs. [c] nr = no reaction observed. [d] Trace amounts (~5%) of **C** were also observed.

Table 7. Selectivity, Yield, and Function of M_2CO_3



entry	M_2CO_3	A/B[a]	yield (%)[b]
1	Na_2CO_3	1:3	51
2	K_2CO_3	1:2	25
3	Rb_2CO_3	1:10	99
4	Cs_2CO_3	1:11	100

[a] Less than 5% of isomer **C** was observed in these reactions. [b] Yields were determined by GC analysis of the crude reaction mixtures versus an internal standard and represent an average of 2 runs.

A/B, while 1 equiv of Cs_2CO_3 provided quantitative yield of a 1:11 mixture of **A/B** (entries 1 and 4 in Table 7, respectively).

We also evaluated **A/B** selectivity in the carbonate system as a function of the quinone concentration (Figure 3). Intriguingly, the **A/B** ratio changed only a small amount from 0.1 to 20 equiv of BQ (**A/B** moved from 1:7 to 1:11). This is in marked contrast to the much larger effect observed in the acetate system (where **A/B** decreased from 11:1 to 1.1:1 over the same concentration range).

In summary, metal carbonate salts are uniquely effective in reversing the selectivity of oxidative coupling between compound **5** and DMB. The generality of this effect with respect to other aromatic substrates as well as preliminary investigations of its mechanistic origin are discussed below.

Application to Diverse Substrates. The reaction of 1,3-diisopropoxybenzene with [(bzq)PdX] in the presence of 1 equiv of BQ showed nearly identical trends in reactivity and

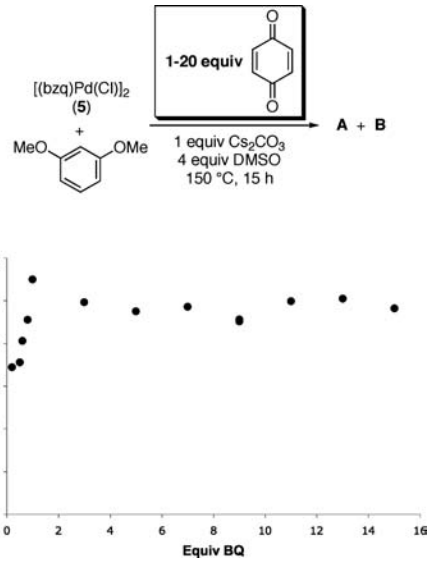


Figure 3. Site selectivity (**B**/**A**) as a function of the equivalent of BQ for the coupling of compound **5**/Cs_2CO_3 with DMB.

selectivity as with DMB. With X = AcO^-, **A/B** was 6:1, and this could be increased to 15:1 by adding 3 equiv of AcOH (entry 1 in Table 8). Moving from BQ to more electron-rich and sterically hindered quinones, such as 2,3,5,6-tetramethylbenzoquinone, also led to significant improvements in selectivity (**A/B** increased to 13:1); however, this was accompanied by a decrease in chemical yield (49%; Table S2 in the Supporting Information). Site selectivity could be reversed through the use of [(bzq)-$PdCl]_2$/Cs_2CO_3, which provided the C−C coupled product as a 1:6 ratio of **A/B** in excellent (85%) yield (entry 2).

1,2,3-Trisubstituted arenes also reacted with compound **1** in the presence of 1 equiv of BQ to afford high selectivity for isomer **A** (**A/B** was typically >50:1) (entries 3, 5, 7, and 9 in Table 8). With complex **5**/Cs_2CO_3, the site selectivity changed dramatically in all cases; however, the magnitude of this change was subject to the electronic character of the 2-substituent. For example, with a 2-nitro group, **A/B** = 1:5 (entry 4), while with a methoxy substituent at the 2 position, **A/B** = 1:1 (entry 8). Finally, 1,2-dimethoxybenzene (**11**) showed analogous trends in selectivity. This arene reacted with compound **1** to give high selectivity for isomer **A** (**A/B** = 41:1; entry 11 in Table 8). In contrast, with compound **5**/Cs_2CO_3, the **A/B** ratio was 1:1 (entry 12 in Table 8).

Similar trends were observed in complexes with other cyclometalated ligands (Table 9). For example, $[(phpy)PdX]_2$ (phpy = 2-phenylpyridine) reacted with DMB to afford an 8:1 ratio of **A/B** when X = AcO^- in the presence of AcOH and a 1:6 ratio of **A/B** when X = CO_3^{2-} (entries 3 and 4 in Table 9). Similarly, the 8-methylquinoline (mq) complex $[(mq)PdX]_2$ provided a 5:1 ratio of **A/B** when X = AcO^- in the presence of AcOH and a 1:4 ratio of **A/B** when X = CO_3^{2-} (entries 5 and 6 in Table 9). The results in Tables 8 and 9 clearly demonstrate that the selectivity trends derived for DMB are applicable across a range of different aromatic substrates and cyclometalating ligands.

Studies To Understand Selectivity in Carbonate Systems. Finally, we sought mechanistic insight into the reversal of site selectivity between the carboxylate and carbonate systems. In the carboxylate case, steric effects appear to dominate selectivity. Particularly, in regime 1, the least sterically hindered site (C−H_A) was functionalized with >5:1 (and often much higher) selectivity in all

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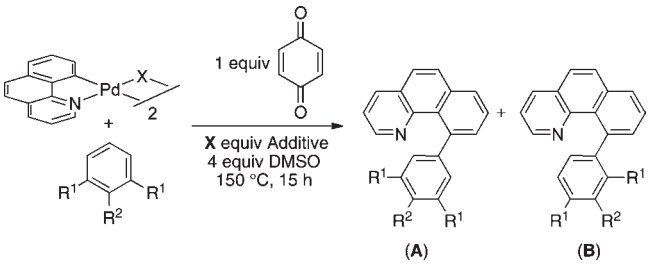
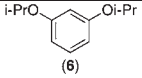
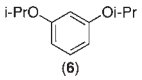
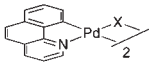
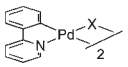
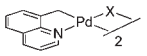
Table 8. Arene Scope with Bzq



Entry	Arene	X[a]	Additive	A/B	Yield[a]
1	 (6)	OAc	3 equiv AcOH	15 : 1	94 %
2	 (6)	CO_3	---	1 : 6	85%
3	 (7)	OAc	---	64 : 1	100%
4	 (7)	CO_3	---	1 : 5	69%
5	 (8)	OAc	---	60 : 1	95%
6	 (8)	CO_3	---	1 : 2	67%
7	 (9)	OAc	---	53 : 1	77%
8	 (9)	CO_3	---	1 : 1	67%
9	 (10)	OAc	---	55 : 1	84%
10	 (10)	CO_3	---	1 : 1	69%
11	 (11)	OAc	---	41 : 1	89%
12	 (11)	CO_3	---	1 : 1	91%

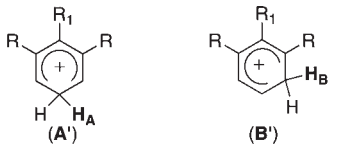
[a] X = CO_3^{2-} generated from $[(bzq)PdCl]_2$ (0.5 equiv) and Cs_2CO_3 (1 equiv). [b] Yields were determined by GC analysis of the crude reaction mixtures versus an internal standard and represent an average of 2 runs.

Table 9. Scope of Cyclometalated Ligands for Oxidative Coupling with DMB[a]

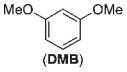
Entry	[Pd]	X[b]	Additive	A / B	Yield[c]
1		OAc	3 equiv AcOH	15 : 1	80%
2		CO_3	---	1 : 11[d]	100%
3		OAc	3 equiv AcOH	8 : 1	31%
4		CO_3	---	1 : 6[d]	64%
5		OAc	3 equiv AcOH	5 : 1	54%
6		CO_3	---	1 : 4[d]	72%

[a] Conditions: 1 equiv of [Pd], 1 equiv of BQ, 4 equiv of DMSO, 1 or 0 equiv of Cs_2CO_3, 0.8 mL of DMB, 150 °C, and 15 h. [b] X = CO_3^{2-} generated from $[(bzq)PdCl]_2$ (0.5 equiv) and Cs_2CO_3 (1 equiv). [c] Yields were determined by GC analysis of the crude reaction mixtures versus an internal standard and represent an average of 2 runs. [d] Traces of isomer **C** (<5%) were observed in these reactions.

Table 10. Calculated Values of $E_{A'} - E_{B'}$ for Different Arene Substrates



$E_{A'} - E_{B'}$ = *energetic preference for S_EAr at C_B–H_B versus C_A–H_A*

Arene	$[\Delta G_{form}$ (**A'**) $- \Delta G_{form}$ (**B'**)] (kcal/mol)[a]	Selectivity **B / A** with **5**/Cs_2CO_3
 (10)	8.27	1 : 1
 (9)	–0.23	1 : 1
 (8)	2.03	1.9 : 1
 (7)	5.20	5 : 1
 (DMB)	24.38	11 : 1

[a] DFT calculations performed using Spartan '08 using B3LYP 6-31G** basis set.

substrates examined. The dominance of steric effects is fully consistent with the mechanism outlined in Scheme 2.

In marked contrast, the combination of complex **5**/Cs_2CO_3 provided modest to high selectivity for functionalization of more sterically hindered C−H_B in DMB to afford **B**. Because C−H_B is more nucleophilic than C−H_A (by virtue of being *ortho* and *para* to MeO substituents), we first hypothesized that the observed selectivity might arise from an electrophilic aromatic substitution (S_EAr) type mechanism for C−H cleavage. To test this possibility, we conducted density functional theory (DFT) calculations to assess the relative energies of S_EAr intermediates **A′** and **B′**

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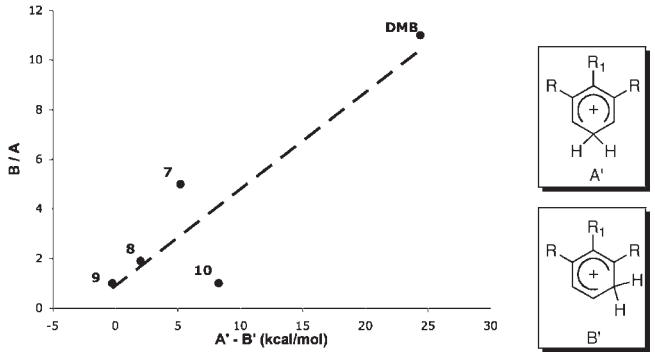

Figure 4. Plot of **B**/**A** ratio (experimental from reactions of compound **5**/Cs_2CO_3) versus $E_{A'} - E_{B'}$ (DFT).

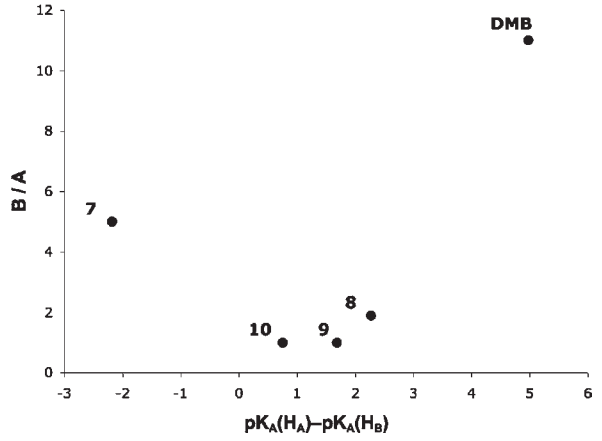

Figure 5. **B**/**A** ratio (experimental from reactions of compound **5**/Cs_2CO_3) versus $pK_a(H_A) - pK_A(H_B)$.

(Table 10) for a variety of 1,2- and 1,2,3-substituted aromatics. The difference in energy between these intermediates ($E_{A'} - E_{B'}$) was then used to approximate the energetic preference for S_EAr at C−H_B versus at C−H_A. As shown in Figure 4, the calculated $E_{A'} - E_{B'}$ values showed a poor correlation with the experimental **B**/**A** selectivities. Even in 1,3-dimethyl-substituted arenes **7**−**10** (where the C−H_B bonds are sterically identical), the experimental isomer ratios did not track well with those predicted for S_EAr.[19] As such, we conclude that **B**/**A** selectivity in the [(bzq)PdCl]/Cs_2CO_3 system is unlikely to be due to selectivity-determining electrophilic palladation.

Elegant studies by Fagnou/Gorelsky and coworkers[20] as well as Echavarren and coworkers[21] have shown that C−H acidity can play a large role in both reactivity and selectivity in Pd-catalyzed C−H functionalization reactions. We hypothesized that, if an analogous effect were responsible for selectivity with compound **5**/Cs_2CO_3, then there should be a correlation between ΔpK_a [$pK_a(H_A) - pK_A(H_B)$] and experimental **B**/**A** ratios. DFT calculations were used to calculate the deprotonation energies of H_A and H_B in a series of 1,3- and 1,2,3-substiuted aromatics to approximate the relative pK_a of H_A and H_B, and the data are reported in Table S7 in the Supporting Information.[22] A plot of [$pK_a(H_A) - pK_A(H_B)$] versus experimental **B**/**A** ratios showed no clear relationship between these values (Figure 5). Even in the sterically similar arenes **7**−**10**, **B**/**A** ratios were poorly correlated with $pK_a(H_A) - pK_A(H_B)$. These data suggest that a thermodynamically controlled deprotonation is not the selectivity-determining step of this transformation.[23]

These studies provide evidence against two limiting possibilities for selectivity in the compound **5**/Cs_2CO_3 reactions: (i) selectivity-determining palladation via an S_EAr pathway and (ii) selectivity-determining thermodynamically controlled deprotonation. The origin of selectivity in this system remains the subject of ongoing investigations.[24] We are currently considering at least two alternative possibilities: (1) the selectivity-determining step changes as a function of the arene substrate (for example, involving C−H cleavage via electrophilic palladation with certain arenes and concerted metalation−deprotonation with others), and/or (2) this transformation involves a mechanistically unique selectivity-determining step that remains to be elucidated.

CONCLUSION

By examining the factors controlling site selectivity under the two regimes outlined above, we have gained insight into the mechanism of Pd-catalyzed aryl−aryl′ oxidative cross-coupling. We have shown that the steric and electronic environment at [Pd] can be tuned to control the site selectivity of arene C−H functionalization. In the process, we have also discovered new ways of altering the preferred regioisomer formed in these transformations. In general, isomer **A** is formed selectively with carboxylate X-type ligands in the presence of ≤1 equiv of quinone, with added RCO_2H and with alkyl-substituted quinones. Switching to carbonate as the X-type ligand at [Pd] reverses the selectivity to favor isomer **B**. The ability to achieve this type of catalyst-based control over site selectivity is a significant advance, and we anticipate that the observed effects may be more broadly applicable to other C−H arylation reactions. Efforts to investigate the origin of the reversal in site selectivity with X = CO_3^{2-} as well as to apply the principles derived herein to diverse catalytic transformations are ongoing and will be reported in due course.[25]

ASSOCIATED CONTENT

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

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REFERENCES

(1) (a) Torsell, K. B. G. *Natural Product Chemistry*; Wiley: Chichester, U.K., 1983. (b) Thomson, R. H. *The Chemistry of Natural Products*; Blackie and Son: Glasgow, U.K., 1985. (c) Baudoin, O.; Guéritte, F. *Stud. Nat. Prod. Chem.* **2003**, *29*, 335–417.(d) Herz, W.; Kirby, G. W.; Falk, H.; Moore, R. E. *Progress in the Chemistry of Organic Natural Products*; Springer-Verlag: Vienna, Austria, 2001; Vol 82.

(e) Kozlowski, M. C.; Morgan, B. J.; Linton, E. C. *Chem. Soc. Rev.* **2009**, *38*, 3193 and references therein. (f) Rao, A. V. R.; Gurjar, M. K.; Reddy, K. L.; Rao, A. S. *Chem. Rev.* **1995**, *95*, 2135. (g) Nicolaou, K. C.; Boddy, C. N. C.; Bräse, S.; Winssinger, N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2096. (h) Cepanec, I. *Synthesis of Biaryls*; Elsevier, Inc.: San Diego, CA, 2004. (i) Roncali, J. *Chem. Rev.* **1992**, *92*, 711. (j) Mei, X.; Wolf, C. *J. Am. Chem. Soc.* **2006**, *128*, 13326.

(2) (a) Stille, J. K. *Angew. Chem., Int. Ed.* **1986**, *25*, 508. (b) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1. (c) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (d) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147. (e) Beletskaya, I. P.; Cheprakov, A. *Chem. Rev.* **2000**, *100*, 3009. (f) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633. (g) Denmark, S. E.; Sweis, R. F. *Acc. Chem. Res.* **2002**, *35*, 835. (h) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131. (i) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359.(j) de Meijere, A.; Diederich, F. *Metal-Catalyzed Cross-Coupling Reactions*; Wiley-VCH; Weinheim, Germany, 2004. (k) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461.

(3) For reviews that discuss C−H arylation reactions, see: (a) Campeau, L. C.; Fagnou, K. *Chem. Commun.* **2006**, 1253. (b) Daugulis, O.; Zaitsev, V. G.; Shabashov, D.; Pham, Q. N.; Lazareva, A. *Synlett* **2006**, 3382. (c) Yu, J. Q.; Giri, R.; Chen, X. *Org. Biomol. Chem.* **2006**, *4*, 4041. (d) Godula, K.; Sames, D. *Science* **2006**, *312*, 67. (e) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (f) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**, *107*, 5318. (g) Ackermann, L. *Synlett* **2007**, 507. (h) Fairlamb, I. J. S. *Chem. Soc. Rev.* **2007**, *36*, 1036. (i) Campeau, L. C.; Fagnou, K. *Chem. Soc. Rev.* **2007**, *36*, 1058. (j) Catellani, M.; Motti, E.; Della Ca', N. *Acc. Chem. Res.* **2008**, *41*, 1512. (k) Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, 3013. (l) Li, B. J.; Yang, S. D.; Shi, Z. J. *Synlett* **2008**, 949. (m) McGlacken, G. P.; Bateman, L. M. *Chem. Soc. Rev.* **2009**, *38*, 2447. (n) Chen, X.; Engle, K. M.; Wang, D. H.; Yu, J. Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (o) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147.

(4) Ashenhurst, J. A. *Chem. Soc. Rev.* **2010**, *39*, 540.

(5) (a) Li, R.; Jiang, L.; Lu, W. *Organometallics* **2006**, *25*, 5973. (b) Rong, Y.; Li, R.; Lu, W. *Organometallics* **2007**, *26*, 4376. (c) You, S.; Xia, J. *Top. Curr. Chem.* **2010**, *292*, 165–195.

(6) (a) Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172. (b) Stuart, D. R.; Villemure, E.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 12072. (c) Dwight, T. A.; Rue, N. R.; Charyk, D.; Josselyn, R.; DeBoef, B. *Org. Lett.* **2007**, *9*, 3137. (d) Potavathri, S.; Dumas, A. S.; Dwight, T. A.; Naumiec, G. R.; Hammann, J. M.; DeBoef, B. *Tetrahedron Lett.* **2008**, *49*, 4050. (e) Xi, P.; Yang, F.; Qin, S.; Zhao, D.; Lan, J.; Gao, G.; Hu, C.; You, J. *J. Am. Chem. Soc.* **2010**, *132*, 1822. (f) Potavathri, S.; Pereira, K. C.; Gorelsky, S. I.; Pike, A.; LeBris, A. P.; DeBoef, B. *J. Am. Chem. Soc.* **2010**, *132*, 14676.

(7) For examples of Pd-catalyzed oxidative Ar−H homocoupling, see: (a) Hull, K. L.; Lanni, E. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 14047. (b) Mori, A.; Sugie, A. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 548.(c) Ref 5b. (e) Liang, Z.; Zhao, J.; Zang, Y. *J. Org. Chem.* **2010**, *75*, 170.

(8) (a) Xia, J. B.; You, S. L. *Organometallics* **2007**, *26*, 4869. (b) Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 11904. (c) Tian, S. L.; Fang, Z.; Shi, Z. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1115. (d) Brasche, G.; García-Fortanet, J.; Buchwald, S. L. *Org. Lett.* **2008**, *47*, 2207. (e) Zhao, X.; Yeung, C. S.; Dong, V. M. *J. Am. Chem. Soc.* **2010**, *132*, 5837. (f) Yeung, C. S.; Zhao, X.; Borduas, N.; Dong, V. M. *Chem. Sci.* **2010**, *1*, 331. (g) Scheuermann, C. J. *Chem.—Asian J.* **2010**, *5*, 436.

(9) The exact mechanism of BQ complexation and BQ-promoted reductive elimination remains to be elucidated. For example, the initial BQ binding could occur via a 5-coordinate intermediate, such as compound **3** in Scheme 1, or via an associative ligand substitution reaction (where compound **3** is a transition state for the ligand substitution event).

(10) Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 9651.

(11) Functionalization at H_C (to form isomer **C**) was not detected under these conditions.

(12) The use of 1 and 20 equiv of BQ were examined as representative points in regimes 1 and 2. For consistency, we have compared all of the reactions presented herein under these conditions.

(13) The presence/absence of DMSO did not influence the selectivity in this system. It was used as an additive in our previously reported catalytic L∼C−H/aryl−H cross-coupling reactions and was maintained throughout the current investigations for consistency.

(14) The addition of 3 equiv of AcOH to regime 1 in this series of sterically differentiated quinones altered the magnitude of selectivity; however, the overall trend remained unchanged. See page S18 of the Supporting Information for details.

(15) For other examples of BQ-promoted reductive elimination, see: (a) Temple, J. S.; Riediker, M.; Schwartz, J. *J. Am. Chem. Soc.* **1982**, *104*, 1310. (b) Backvall, J. E.; Bystrom, S. E.; Nordberg, R. E. *J. Org. Chem.* **1984**, *49*, 4619. (c) Bäckvall, J. E.; Nordberg, R. E.; Wilhelm, D. *J. Am. Chem. Soc.* **1985**, *107*, 6892. (d) Szabó, K. *Organometallics* **1998**, *17*, 1677. (e) Albéniz, A. C.; Espinet, P.; Martn-Ruiz, B. *Chem.—Eur. J.* **2001**, *7*, 2481. (f) Chen, M. S.; Prabagaran, N.; Labenz, N. A.; White, M. C. *J. Am. Chem. Soc.* **2005**, *127*, 6970. (g) Chen, X.; Li, J. J.; Hao, X. S.; Goodhue, C. E.; Yu, J. Q. *J. Am. Chem. Soc.* **2006**, *128*, 78. (h) Pérez-Rodríguez, M.; Braga, A. A. C.; Garcia-Mechor, M.; Pèrez-Temprano, M. H.; Casares, J. A.; Ujaque, G.; de Lera, A. R.; lvarez, R.; Maseras, F.; Espinet, P. *J. Am. Chem. Soc.* **2009**, *131*, 3650. (i) Lanci, M. P.; Remy, M. S.; Kaminsky, W.; Mayer, J. M.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 15618. (j) Yin, G.; Wu, Y.; Liu, G. *J. Am. Chem. Soc.* **2010**, *132*, 11978. (k) Ishikawa, A.; Nakao, Y.; Sato, H.; Sakaki, S. *Dalton Trans.* **2010**, *39*, 3279.

(16) Experiments performed at lower than 1 equiv of quinone provided further support for this hypothesis. For example, the use of 0.1 equiv of 2,5-diarylquinone with X = CF_3 afforded a 7:1 ratio of **A**/**B**, consistent with a reduced contribution from $k_2^{A/B}[\mathbf{Pd_{A/B}}][\text{quinone}]$ to selectivity.

(17) Liégault, B.; Petrov, I.; Gorelsky, S. I.; Fagnou, K. *J. Org. Chem.* **2010**, *75*, 1047 and references therein.

(18) This reversal is consistent with the **A**/**B** selectivity of 3:1 in the catalytic reactions, where both AcO^- [from the $Pd(OAc)_2$ catalyst] and CO_3^{2-} (from the Ag_2CO_3 oxidant) are present. This is an intermediate to the **A**/**B** ratio, with X = AcO^- (5:1) and CO_3^{2-} (1:6).

(19) The lack of correlation is even more pronounced if transition-state theory (TST) is used to estimate the expected isomer distribution. Using the difference in intermediate energies ($E_{A'} - E_{B'}$) as a crude approximation for the relative transition-state energies, the expected **B**/**A** selectivities were calculated and are shown in Table S6 in the Supporting Information.

(20) (a) Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 8754. (b) Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 10848.

(21) Garcia-Cuadrado, D.; Braga, A. A. C.; Maseras, F.; Echaverren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 1066.

(22) Literature studies have shown that gas-phase calculations with diffuse basis sets are appropriate for calculating the deprotonation energies of simple molecules. For example, see: (a) Hehre, W. J.; Radom, L.; Schleyer, P. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; John Wiley and Sons: New York, 1986. (b) Maksic, Z. B.; Kovacek, D.; Eckert-Maksic, M.; Zrinski, I. *J. Org. Chem.* **1996**, *61*, 6717.

(23) A recent report by Potavathri et al.[6f] suggested that the relative reactivity of arene C−H bonds toward Pd-catalyzed C−H functionalization via a concerted metalation/deprotonaton mechanism can be predicted by their ground-state bond lengths. As shown in Table S9 in the Supporting Information, the C−H_A and C−H_B bond lengths for the 1,3- and 1,2,3-substituted arenes in Table 10 show no correlation with **B**/**A** isomer ratios from the compound **5**/Cs_2CO_3 reactions.

(24) Another possibility to account for the reversal in selectivity with compound **5**/Cs_2CO_3 is that the presence of a carbonate base renders the C−H activation step of Scheme 2 irreversible. In this scenario, equilibration between Pd_A and Pd_B would be inhibited and the reversal in selectivity would be due to a kinetic preference for C−H cleavage to form Pd_B over Pd_A (analogous to the situation in limiting regime 1). Several pieces of evidence suggest that this is not the complete explanation for the observed effect with complex **5**/Cs_2CO_3. First, Figure 2 shows that the **A**/**B** selectivity levels off at close to 1:1 in regime 1, which is considerably different from that obtained with complex **5**/Cs_2CO_3. Second, the reaction of acetate complex **1** with DMB in the presence of 1 equiv of BQ and 1 equiv of Cs_2CO_3 afforded

an **A**/**B** ratio of 1:1. This is much lower than the 1:11 ratio obtained with compound **5**/Cs_2CO_3, suggesting that the carbonate is doing more than simply serving as a base to push the reaction toward regime 1 (otherwise comparable selectivities would be expected in these two experiments).

(25) Our initial efforts to apply the findings with $[(bzq)PdCl]_2$/Cs_2CO_3 to a catalytic process have thus far failed to find a suitable oxidant to reoxidize Pd^0. Significant efforts are underway to address this challenge.