Communication

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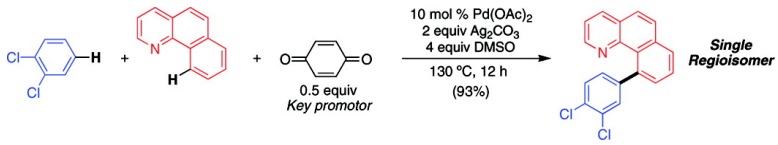

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Catalytic and Highly Regioselective Cross-Coupling of Aromatic C−H Substrates

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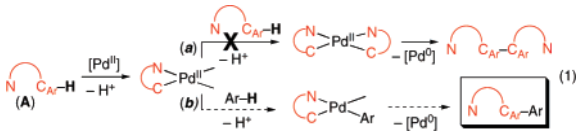
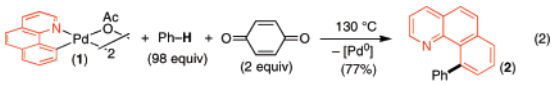
Aryl−aryl bonds are a key structural feature of diverse natural products, medicinal agents, and organic materials. Currently, the vast majority of biaryl linkages are constructed via the metal-mediated cross-coupling of two prefunctionalized arene building blocks.[1] However, a far more efficient approach to these bonds would involve direct oxidative coupling of two arene C−H substrates. Recent work has shown that Pd^{II} salts can catalyze the oxidative dimerization (homocoupling) of benzene,[2] thiophene,[3] and arylpyridine derivatives[4] under mild conditions. In contrast, very few reports have described the more synthetically useful catalytic oxidative cross-coupling of arenes.[5,6] Such reactions are particularly challenging because both the chemo- and regioselectivity of arene C−H activation and C−C coupling must be well-controlled to avoid formation of intractable mixtures of regioisomeric homo- and heterocoupled biaryls.



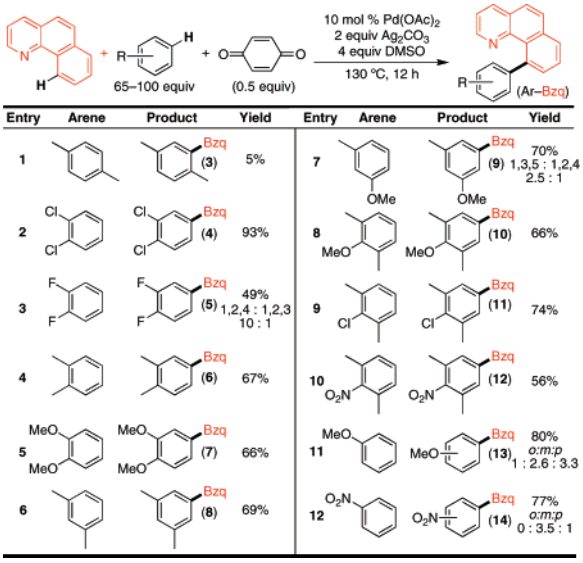
In order to develop selective arene C−H cross-coupling reactions, we sought to exploit ligand-directed C−H activation at Pd^{II}. It is well-known that the stoichiometric cyclopalladation of diverse substrates L∼C_{Ar}−H (**A**, eq 1) is facile and highly regioselective.[7] Furthermore, the mono-cyclometalated Pd^{II} products are typically unreactive toward a second ligand-directed C−H activation event under $Pd^{0/II}$ conditions,[4,8] which should limit competitive homocoupling of L∼C_{Ar}−H (eq 1, path a). As such, we hypothesized that the desired cross-coupling between L∼C_{Ar}−H and a simple arene (Ar−H) would be possible if the cyclopalladated complex could participate in a second, nondirected C−H activation reaction with Ar−H (eq 1, path b). *We demonstrate herein the application of this strategy to the Pd-catalyzed oxidative cross-coupling of diverse L∼C_{Ar}−H and Ar−H substrates. This novel transformation proceeds with extremely high chemoselectivity for cross-coupling; further, the two discrete C−H activation steps can both proceed with excellent (and in some cases tunable) levels of regiocontrol.*



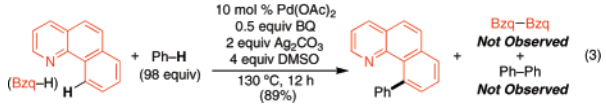
Our initial studies focused on stoichiometric reactions between cyclopalladated benzo[*h*]quinoline (Bzq) complex **1** and C_6H_6. Heating **1** to 150 °C in C_6H_6 did not afford any of the cross-coupled product **2**, indicating that this complex does not directly effect arene C−H activation. However, gratifyingly, the addition of 2 equiv of benzoquinone (an additive previously shown to promote C−H activation reactions at Pd^{II} centers)[9] to a C_6H_6 solution of **1** at 130 °C produced **2** in 77% yield along with a black/silver precipitate believed to be Pd^0 aggregates (eq 2).

With this encouraging result in hand, we turned our efforts to rendering this reaction catalytic in Pd. A variety of catalytic

Table 1. Scope and Selectivity of Bzq/Arene Cross-Coupling



conditions were examined with benzoquinone (BQ) as the stoichiometric oxidant; however, despite the utility of BQ as an oxidant in other $Pd^{II/0}$ reactions,[9] only a single turnover to form **2** was observed. We next explored Ag^I salts, which are known to be effective oxidants in the Pd-catalyzed oxidative dimerization of thiophenes.[3] We were pleased to discover that the use of 2 equiv of Ag_2CO_3 in the presence of 0.5 equiv of BQ, 98 equiv of C_6H_6, and 10 mol % of $Pd(OAc)_2$ afforded **2** *catalytically* in 74% yield. The addition of 4 equiv of DMSO further enhanced the yield to 89%, possibly by slowing catalyst decomposition/Pd^0 aggregation.[10] Importantly, under these optimized conditions, *none* of the homocoupled products (Ph−Ph or bzq−bzq) were observed (eq 3).



The scope of this reaction with respect to the arene coupling partner was next explored. Initial studies revealed that *p*-xylene (which is electronically similar to C_6H_6 but has significantly more sterically hindered arene C−H bonds) exhibited low reactivity under our conditions (Table 1, entry 1). This observation was surprising because *p*-xylene was reported to be a good substrate for other Pd^{II}-catalyzed oxidative cross-couplings.[5] This result suggested that steric factors might be uniquely critical for controlling reactivity (and also potentially selectivity) during the C−H activation of Ar−H in our system. To probe this possibility, we examined a series of 1,2-disubstituted arenes, in which the two different aromatic C−H bonds are electronically similar but have very different steric environments. In all cases, oxidative coupling proceeded in good yield and with high (≥10:1) selectivity for coupling at the less hindered 4-position of Ar−H (entries 2−5).[11]

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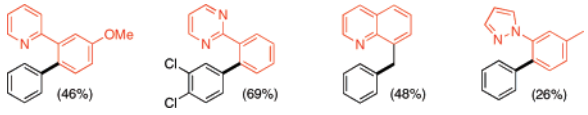

Figure 1. Cross-coupling products with other directing groups.

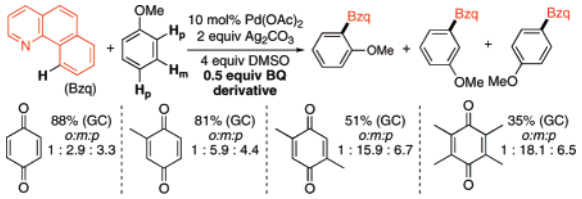

Figure 2. Effect of benzoquinone structure on selectivity.

A series of 1,3-di- and 1,2,3-trisubstituted arenes were also investigated (entries 6−10). Again, high selectivity was obtained for coupling at the less hindered 5-position, which can be particularly challenging to functionalize selectively using traditional organic reactions. The only substrate that afforded >5% of the 4-regioisomer was 1-methyl-3-methoxybenzene (entry 7, 2.5:1 isomer ratio). The minor product resulted from coupling adjacent to the OMe group, presumably due to the relatively small size of this substituent. Even with nitrobenzene and anisole, coupling at the *p*- and *m*-positions was significantly favored over the *o*-position (entries 11 and 12). Notably, similar steric-based selectivity has been reported for Ir- and Rh-catalyzed C−H activation/borylation;[11] however, to our knowledge, the observed selectivities are unprecedented in arene C−H activation at Pd^{II}.

With data on steric effects in hand, we next probed the influence of electronic factors on the C−H activation of Ar−H. The reaction of Bzq was conducted with a mixture of 40 equiv of 1,3-dimethyl-2-nitrobenzene and 40 equiv of 1,3-dimethyl-2-methoxybenzene, which contain sterically identical arene C−H bonds. Remarkably, this reaction afforded a 1:1.4 ratio of **10**/**12**, showing that the relative rates of C−H activation are barely affected by large electronic perturbations of the aromatic ring.

These transformations could also be applied to a variety of other L∼C−H coupling partners. Under identical conditions to the Bzq reactions, 2-arylpyridine, 1-arylpyrazole, and 2-arylpyrimidine derivatives afforded biaryl products in modest to good yields (Figure 1). 8-Methylquinoline was also an effective substrate and reacted to form a new sp^3−sp^2 C−C bond.

We next sought to gain insights into the role of benzoquinone in these reactions. We hypothesized that BQ could bind to an initially formed cyclometalated Pd^{II} complex and thereby promote C−H activation of Ar−H.[9,12] In this scenario, steric/electronic modification of the BQ ligand would be expected to influence the regioselectivity of arene C−H activation. To test this hypothesis, we examined coupling between Bzq and anisole in the presence of a series of methyl-substituted BQ derivatives. Intriguingly, increased methylation of the BQ led to a dramatic decrease in coupling at the *o*-position of the anisole and a concomitant increase in reaction at the *m*- and *p*-positions (Figure 2).[13] Mechanistically, this result strongly suggests that the BQ ligand is bound to the Pd center during arene C−H activation.[12] In addition, *these data provide promising precedent that the selectivity of C−H oxidative coupling at* Pd^{II} *can be tuned through steric and electronic modification of an ancillary ligand.*

On the basis of the data presented thus far, we propose that these transformations proceed via the mechanism depicted in Figure 3. The key steps involve: (*i*) ligand-directed C−H activation to afford a cyclometalated intermediate, (*ii*) BQ-assisted C−H activation of the arene, (*iii*) C−C bond forming reductive elimination, and (*iv*) oxidation of the Pd^0 to Pd^{II} by Ag_2CO_3. The nature of the second C−H activation event is particularly intriguing because the electronic and steric effects are very different from those previously observed at Pd^{II} centers. These effects are not consistent with either an electrophilic C−H activation mechanism (which should result in dramatically faster reaction rates with electron rich arenes)[7,14] or a C−H deprotonation mechanism (which should show preference for activation of the most acidic C_{Ar}−H bonds next to electron-withdrawing F/NO_2 substituents).[15]

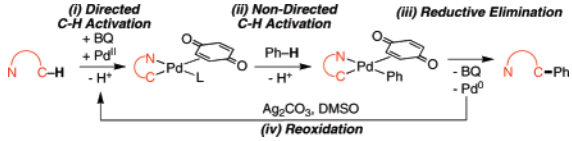

Figure 3. Preliminary proposed mechanism.

In summary, this communication describes a new Pd-catalyzed reaction for the highly chemo- and regioselective oxidative cross-coupling of aromatic C−H bonds. This transformation is proposed to proceed via two discrete C−H activation steps whose selectivities are predominantly controlled by proximity to a ligand (first C−H activation) or by the steric environment around the arene C−H bond (second C−H activation). Ongoing work seeks to exploit this mechanistic manifold for other synthetically useful cross-coupling reactions as well as to further probe the mechanism of these new transformations.

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Supporting Information Available: 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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