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Mechanistic Evidence for a Ring-Opening Pathway in the Pd-Catalyzed Direct Arylation of Benzoxazoles

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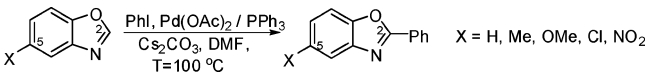
Azole represents an important structural motif commonly present in pharmaceuticals, organic dyes, and natural products. During the past decade, elaboration of azoles and particularly 1,3-azoles has largely focused on C−C functionalization.[1] Traditional transition-metal-mediated cross-coupling approaches have been particularly effective, allowing for regioselective arylation.[2] Despite this success, the availability of the azole coupling partner as either haloazole or metalated azole remains a scope-limiting factor. Direct arylation has emerged as an alternative method that does not require prefunctionalization,[3] and a wide variety of substrates including oxazoles,[3,4] thiazoles,[3,5,6] imidazoles,[3,5,7] indoles,[8−12] pyrroles,[8] indolizines,[13] imidazo[1,2-*a*]pyrimidines,[6,14] and imidazo[1,2-*b*]-[1,2,4]triazines[15] can be arylated using Pd catalysis. Although mechanistic details are sketchy, the direct Pd-catalyzed arylation is currently believed to involve electrophilic palladation of the azole ring.[3,7,10,13] Herein we present a line of mechanistic evidence supporting the involvement of a ring-opening mechanism in the Pd-catalyzed direct arylation of benzoxazoles.

Recently, we have reported that electron-poor oxazolo[4,5-*b*]-pyridine can be arylated at room temperature, in contrast to the strenuous reaction conditions typically required by the conventional electron-richer azoles.[16] To investigate the viability of nonelectrophilic pathways in the direct arylation, we performed a set of kinetic experiments on a series of 5-substituted benzoxazoles.

Hammett studies offer the opportunity to probe the electronic demand of Pd-catalyzed arylation by introducing substituents at the C-5 position of the benzoxazole ring. The studies were performed under standard conditions (2.5 mol % of $Pd(OAc)_2/PPh_3$, Cs_2CO_3, 100 °C, DMF) using 20 equiv of PhI.



Recognizing that the concentration of Cs_2CO_3 is quasi-constant due to its limited solubility in DMF, and assuming constant concentrations of PhI and the catalyst, one can write the pseudo-first-order approximation to the rate law as

$$-\mathrm{d[azole]}/\mathrm{d}t = k[\mathrm{azole}] \times [\mathrm{PhI}] \times [\mathrm{Cs_2CO_3}] \times [\mathrm{catalyst}] = k_{\mathrm{obs}}[\mathrm{azole}]$$

Good linearity was observed for the integrated form of this equation for all analyzed substrates over a wide range of conversions.[17] A consistent and significant increase in the rate of arylation was noted on going from 5-methoxy- to 5-nitrobenzoxazole, with the latter undergoing arylation already at room temperature. The Hammett plot (Figure 1) revealed an excellent correlation with σ^- ($r^2 = 0.99$), a poorer correlation with σ_p ($r^2 = 0.96$), and no correlation with σ^+, $\sigma^\bullet$, and σ_m set of constants.

Earlier work has shown that imidazoles, thiazoles, and oxazoles are appreciably C−H acidic and can form ring-opened isomers upon

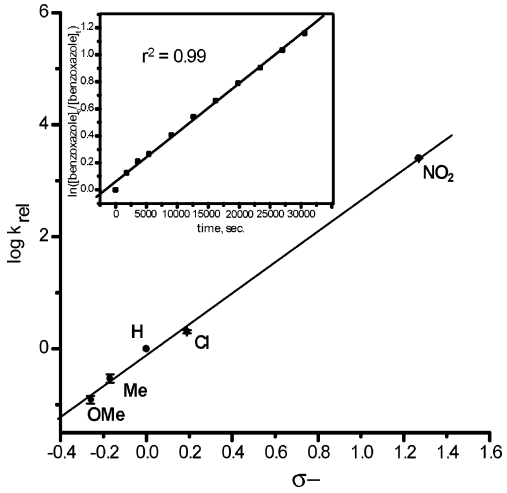
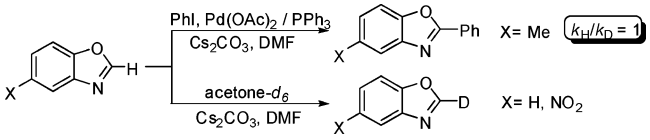


Figure 1. Hammett plot for direct Pd-catalyzed arylation of 5-substituted benzoxazoles, and (inset) the related pseudo-first-order kinetics for benzoxazole.

deprotonation.[18] Benzoxazole is particularly acidic ($pK_a < 16$), and its conjugate base exists predominantly as 2-isocyanophenolate. A control experiment confirmed that the deprotonation of benzoxazole under the arylation conditions is facile and is not assisted by Pd. When acetone-d_6 was used as cosolvent and a source of deuteron, a complete H/D exchange at the C-2 position occurred within 45 min at 70 °C in the absence of the catalyst. 5-Nitrobenzoxazole readily exchanges H for D at room temperature.



The pivotal role of C−H acidity in the direct arylation of activated arenes was recently demonstrated by Fagnou[19] and Echavarren and Maseras.[20] Both studies reported significant primary deuterium kinetic isotope effect interpreted in terms of a rate-limiting proton abstraction. We found no deuterium kinetic isotope effect at C-2 of 5-methylbenzoxazole as measured by the competition kinetics and, independently, by the ^{1}H NMR-detected isotope fractionation.[21]

Several conclusions can be drawn from the kinetic experiments. The absence of a primary kinetic isotope effect allows one to exclude from consideration the concerted metalation[19] and C−H insertion mechanisms. Furthermore, the positive ρ rules out electrophilic arylation. Importantly, the linearity of the Hammett plot implies a single-pathway mechanism featuring a direct resonance of the aromatic ring and electron density developing at the O atom of the substrate. The excellent Hammett correlation

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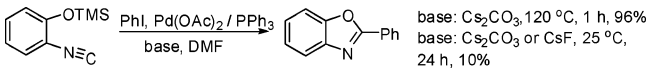
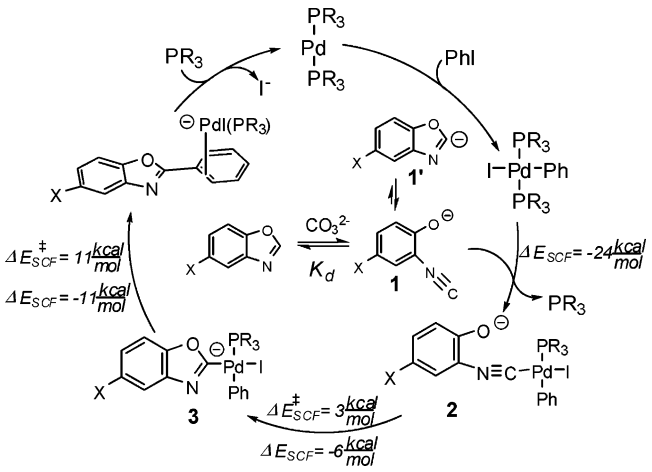
with σ^- set of constants is further consistent with a phenolate-type intermediate and suggests that the formation and reactivity of 2-isocyanophenolate is kinetically significant.

The direct support for the ring-opening pathway was obtained when 2-trimethylsiloxyphenyl isocyanide[22] was subjected to direct arylation conditions. At 120 °C, the reaction was completed in less than 1 h, giving 2-phenylbenzoxazole in 96% yield. We found that the arylation also proceeds at room temperature, although significantly slower (24 h, 10% yield). CsF is also effective, suggesting that both cesium salts act as desilating agents liberating the reactive isocyanophenolate.



The mechanistic picture that emerges from the experimental data was further analyzed by DFT calculations (BP86/TZVP; R,X = H).[23] We propose that the first step of the reaction includes a reversible deprotonation of the substrate, which enters the catalytic cycle as 2-isocyanophenolate **1**. From the literature, it is known that 2-isocyanophenolate derivatives are excellent ligands for Pd(II).[24] Accordingly, we calculated that the reaction between PhPd(PH$_3$)$_2$I and **1**, resulting in the substitution of phosphine and generation of Pd-isocyanide **2**, is exothermic by 24 kcal/mol. The intramolecular nucleophilic attack of the phenolate oxygen on the activated isocyanide carbon[24] of **2** gives palladate **3**. The calculations indicate that this cyclization proceeds with an activation barrier as low as 3 kcal/mol. In the final, rate-determining step, **3** reductively eliminates 2-phenylbenzoxazole and regenerates the Pd(0) catalyst via a transition state lying only 11 kcal/mol above **3**.



The pre-equilibria involving phenolate derivatives **1** and **2**, followed by the rate-limiting reductive elimination of two electronically dissimilar aryl groups[25] from **3**, provide a ready rationale for the σ^- correlation seen in the Hammett plot. The large ρ value (2.8) is also consistent with the cumulative effect these steps are expected to have on the overall kinetics.[26] Although one cannot rigorously rule out a direct attack of **1′** on PhPd(PH$_3$)$_2$I, this alternative pathway would be inconsistent with the observed Hammett plot. The rate constant, analytically derived for the proposed catalytic cycle and written as a product $k_{Ar}K_d$,[27] indicates that the overall kinetics is co-determined by the C−H acidity of the substrate (K_d). This is in agreement with the observed kinetic and H/D exchange data in the present and the previous work.[16] The DFT calculations and the room-temperature arylation of 2-trimethylsiloxyphenyl isocyanide also suggest that given the availability of isocyanophenolate all steps in the catalytic cycle are accessible at ambient temperatures. Indeed, we found that benzoxazole does undergo slow arylation at 30 °C (5 days, 26% yield).

This study is limited to the benzoxazole system. However, an analogous ring-opening chemistry has been demonstrated for 2-metalated thiazoles and imidazoles,[18] lending more support to the generality of the proposed mechanism and warranting further investigations on these systems.

In conclusion, our results show that the direct Pd-catalyzed arylation of benzoxazoles is inconsistent with the electrophilic mechanism implicated by earlier studies. A new mechanism, proposed on the basis of experimental and computational studies, includes generation of isocyanophenolate as the key step. The DFT analysis indicates that the direct arylation of benzoxazoles is an inherently facile process and that the control of substrate C−H acidity is the key element in developing a mild arylation protocol with the potential to accommodate a wide variety of electron-deficient substrates.

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Supporting Information Available: Experimental procedures, kinetic data, and details of the computational study (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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