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Analysis of the Concerted Metalation-Deprotonation Mechanism in Palladium-Catalyzed Direct Arylation Across a Broad Range of Aromatic Substrates

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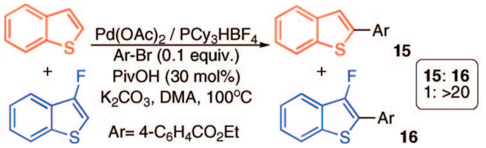
Palladium-catalyzed direct arylation is emerging as a valuable and efficient alternative to traditional metal-catalyzed cross-couplings in the construction of biaryl compounds (eq 1).[1–3] To predict substrate suitability and regioselectivity, however, will require a more complete understanding of the underlying physical parameters governing reactivity and selectivity across the broadest range of substrates possible. With palladium, several reaction pathways have been proposed including oxidative C−H insertion,[4] electrophilic aromatic substitution (S_EAr),[5] Heck-like,[6] anionic cross-coupling, and concerted metalation-deprotonation (CMD).[7] Two of these mechanisms have received the most support: S_EAr with electron-rich, π-nucleophilic heteroarenes and CMD with simple and electron-deficient benzenes. Herein we demonstrate that the CMD pathway not only predicts the reactivity and regioselectivity observed with some simple and electron-deficient benzenes but also does so for a diverse set of arenes spanning the entire spectrum of known direct arylation coupling partners, including those that have been proposed to react via S_EAr (Figure 1).

$$\text{Ar–H} + \text{Ar–X} \xrightarrow{\text{catalyst}} \text{Ar–Ar} \qquad (1)$$

The mechanism for reaction with arenes **1** to **14**[8] was evaluated by density functional theory (DFT) with the B3LYP[9] exchange-correlation functional (Figure 1). In each case, a relevant transition state (TS) corresponding to the CMD pathway was located (the TS for arene **8** is included in Figure 2). This pathway corresponds to the lowest energy pathway and predicts regioselectivity for all arenes, regardless of their electronic properties.[10] Furthermore, the calculated relative reactivity of substituted indolizines **8**, **9**, and **10** under the CMD pathway correlates well with the minimal impact of these substituents on experimental outcomes.[5c] Evaluation of the CMD TS as a potential deprotonation step in an S_EAr mechanism was performed by searching for relevant stationary points corresponding to Wheland intermediates. Intermediate complexes were identified with arenes **1** and **8** (Figure 2); however, these species are best described as η^1- and η^2-C−Pd coordination complexes, not Wheland intermediates. Very little charge is present on the aromatic ring (−0.005 au for **1-RC** and +0.145 au for **8-RC**), and retention of aromaticity is observed for all substrates at the CMD TS.[11]

Experimentally, 3-fluorobenzothiophene **14** reacts preferentially over the more nucleophilic benzothiophene **13** in a competition reaction (eq 2). While this outcome is incompatible with S_EAr reactivity,[12,13] it conforms with calculated CMD values (Figure 1). A kinetic isotope effect of 2.1 is obtained for a reaction run in the presence of **10** and 1,3- d_2-**10**.[11]



(2)

To cast light on how arenes such as **11** and **8** with such disparate physical properties might follow the same CMD pathway, an activation−strain analysis was performed (Scheme 1).[14] The energetic cost (distortion energy, E_{dist}) associated with distortion of the catalyst and arene from ground state **I** and **II** to TS geometries **III** and **IV**, as well as the energetic gain arising from bringing **III** and **IV** together to form TS **V** (electronic interaction energy, E_{int}), was determined. As could be anticipated, π-electron-rich arenes **4** to **10** benefit from the largest negative E_{int} values. This gain is offset, however, by large E_{dist} penalties. On the other hand, electron-deficient arenes **11** and **3** do not benefit from large E_{int} values, but the TS remains accessible due to favorably low E_{dist} arising from a more facile arene distortion. Thiazole *N*-oxides **1** and **2** represent special cases (as also observed experimentally) since they benefit from both a small E_{dist} penalty and a large E_{int} gain. Reaction with benzene **12** is not favored by either value, resulting in the highest $\Delta E^{\ddagger}$ of all the arenes evaluated.

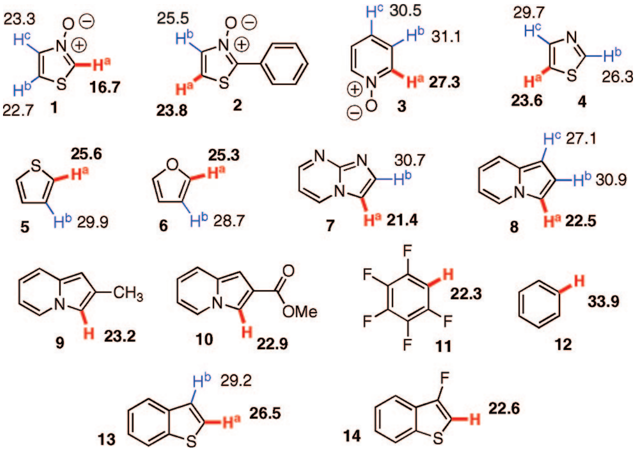


Figure 1. Free energy of activation ($\Delta G^{\ddagger}_{298\text{K}}$, kcal mol^{-1}) for direct arylation via the CMD pathway involving an acetate ligand. Red bonds indicate the experimentally observed sites of arylation.

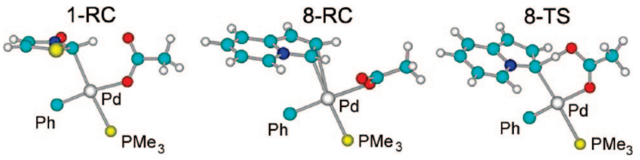


Figure 2. Structures corresponding to minima on the CMD reaction for **1** and **8** leading to the CMD TS (shown only for **8**).

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Scheme 1. Activation−Strain Analysis

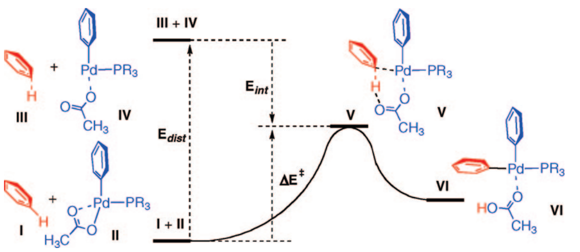

Table 1. Distortion/Interaction Analysis (kcal mol^{-1}) for the Lowest Free Energy CMD Transition States

Arene	ΔE‡	E_{dist} (ArH)	E_{dist} (PdL)[a]	E_{int}	q_{NPA} (ArH)[b]	$B_{Pd\text{-}C}$[c]
1	5.8	29.3	16.6	-40.1	-0.039	0.45
2	12.4	33.8	16.7	-38.1	-0.079	0.44
3	16.5	36.8	15.4	-35.7	-0.065	0.43
4	14.5	36.8	16.9	-39.2	-0.041	0.51
5	15.9	39.9	17.4	-41.4	-0.014	0.52
6	15.6	42.5	17.9	-44.8	+0.009	0.56
7	11.1	42.2	18.3	-49.4	+0.017	0.58
8	13.1	48.1	19.9	-54.9	+0.065	0.62
9	12.5	50.1	20.4	-58.0	+0.078	0.59
10	12.8	40.0	18.6	-45.8	+0.003	0.51
11	11.9	28.8	15.3	-32.2	-0.092	0.44
12	25.1	44.6	15.8	-35.3	-0.010	0.51
13	16.7	37.5	16.8	-37.6	-0.035	0.50
14	12.3	32.4	17.2	-37.3	-0.041	0.48

[a] Pd(Ph)(PMe$_3$)(OAc). [b] NPA-derived charge (a.u.) of arene. [c] Mayer bond order for Pd−C$_A$ interaction.

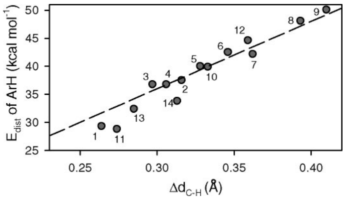

Figure 3. Changes in C−H bond lengths (Δd_{C-H}) and the distortion energies (E_{dist}) for arenes **1**−**14** for CMD TSs.

These studies also cast light on the superior reactivity of **14** over **13**. The presence of the fluorine atom has little impact on E_{int} but results in a pronounced decrease in E_{dist} resulting in a more facile arene palladation.

The E_{int} reflects the strength of the carboxylate−H_{Ar} and Pd−C_{Ar} interactions. The accessible electron density of arene defines the C_{Ar}−Pd covalent interaction[15] and can be quantified by the Pd−C_{Ar} bond order[16] at the TS (Table 1). The factors contributing to E_{dist} are a focus of ongoing study. Previously, a correlation between C−H acidity and reactivity with electron-deficient arenes such as **12** has been noted.[2e] A closer examination of C−H bond elongation (Δd_{C-H}) at the CMD TSs reveals that the largest Δd_{C-H} values are, in fact, not associated with the most acidic arenes (Figure 3). This indicates that simple Brönsted acidity may be a paralleling trend in some cases but not a governing influence.

These studies indicate that the involvement of the CMD mechanism, as described or as a related variant, may be much more broadly implicated than previously imagined in palladium-catalyzed direct arylation. Further critical mechanistic evaluation of this pathway should lead to a better understanding of the necessary substrate/catalyst parameters leading to successful coupling and facilitate the establishment of predictive rules for use with palladium-catalyzed direct arylation in biaryl synthesis.

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Supporting Information Available: Experimental procedures and computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Other pathways that were investigated include C−H oxidative insertion, outer sphere CMD, and Heck-like carbometalation.

(11) See Supporting Information for computational and experimental details.

(12) A competition Friedel−Crafts acylation reaction involving **13** and **14** results in the preferential reaction of **13** (6.7:1; **13/14**) and a 4.4:1 ratio of reaction at C3/C2 on **13**. See Supporting Information for experimental details.

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