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Transition-State Metal Aryl Bond Stability Determines Regioselectivity in Palladium Acetate Mediated C−H Bond Activation of Heteroarenes

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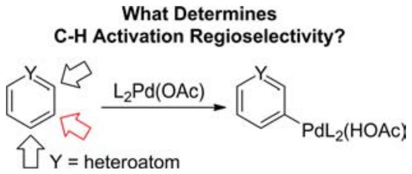
ABSTRACT



Density functional calculations reveal that the stability of developing metal aryl bonds in Pd(II)-acetate C−H activation transition states determines regioselectivity in arene and heteroarene compounds. This kinetic−thermodynamic connection explains the general preference for activation of the strongest C−H bond and provides the possibility for regioselectivity prediction.

Functionalized arenes and heteroarenes are found in biologically active compounds and are often targets for drug candidates.[1,2] Catalytic C−H bond activation provides a strategy for direct functionalization of arenes and heteroarenes. C−H activation and functionalization have been used in complex synthesis.[3−6] Regioselectivity in arene and heteroarene C−H activation/functionalization is often controlled by a substrate directing group (Scheme 1a).[7] Alternatively, regioselectivity can be dictated by the

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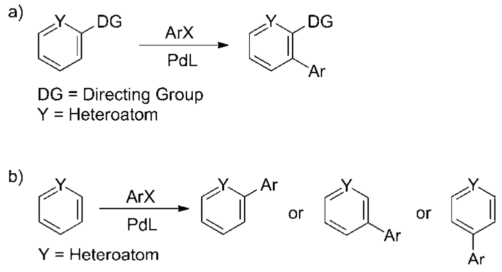
intrinsic positional reactivity of C−H bonds in substrates (Scheme 1b).

Scheme 1. C−H Activation/Functionalization Regioselectivity



Sanford,[8] Sames,[9,10] and others[11,12] have experimentally examined the regioselectivity of C−H bond functionalization in arenes and heteroarenes catalyzed by palladium acetate,[13,14] which has emerged as the most popular type of C−H functionalization catalyst.[15−18] Regioselectivity has been attributed to a variety of effects such as C−H bond acidity and carbon center nucleophilicity. Zhang et al.[19] have proposed that regioselectivity in cross-coupling reactions is the result of steric as well as stereoelectronic effects in the C−H bond cleavage step. Recently, Gorelsky[20] et al. have utilized an activation−strain analysis to investigate the regioselectivity of C−H bond activation in arene and heteroarene substrates. Based on their analysis arenes and heteroarenes were separated into three classes depending on whether the regioselective controlling feature was the distortion energy, the interaction energy, or both. This analysis provided details about subtle factors determining activation barriers, but there is no clear chemical or functional group connection between molecules of the same class. In addition, there was no consideration of thermodynamic influences on regioselectivity.

Here we use density functional theory to examine whether or not the thermodynamic stability of the metal aryl intermediate formed from C−H bond cleavage can be used as a predictor for C−H activation regioselectivity of arenes and heteroarenes. We have analyzed the (Ph)(PMe_3)Pd(OAc) complex, which was also studied by Gorelsky et al.[20] Figure 1 shows the substrates that were analyzed, which includes benzene and pyridine-type arene and heteroarenes **1**−**5**, five-membered heteroarenes **6**−**11**, and polycyclic arene and heteroarenes **12**−**14**.[21]

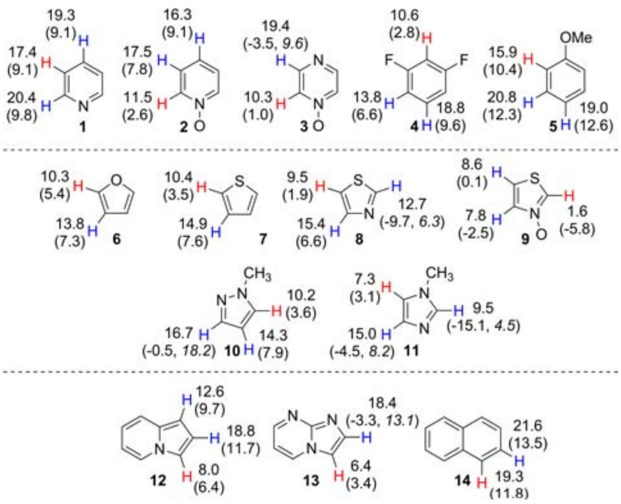


Figure 1. Activation energies for arene and heteroarene C−H bond cleavage by (Ph)(PMe_3)Pd(OAc) and palladium aryl thermodynamics (in parentheses). Values in italics are for palladium aryl intermediates with hydrogen bonding removed. Energy values given in kcal/mol.

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Ground-state and transition-state (TS) geometries were optimized in Gaussian 09.[22] The M06/LANL2DZ-[6-31G(d,p)] method was chosen due to its excellent performance for transition metal complexes.[23]

Figure 1 gives the M06 activation energies ($\Delta E^{\ddagger}$) for C−H bond cleavage of heteroarenes **1**−**14** with (Ph)(PMe_3)-Pd(OAc) and the reaction energies (ΔE_{rxn}) for the resulting palladium aryl intermediate. The C−H bond cleavage TSs correspond to six-membered structures where the acetate ligand accepts the hydrogen with simultaneous formation of a Pd−C bond.[24] Figure 2 shows representative TSs and palladium aryl intermediates for heteroarene **3**. Our TSs computed at the M06 level of theory are highly similar to those computed by Gorelsky with B3LYP.[20]

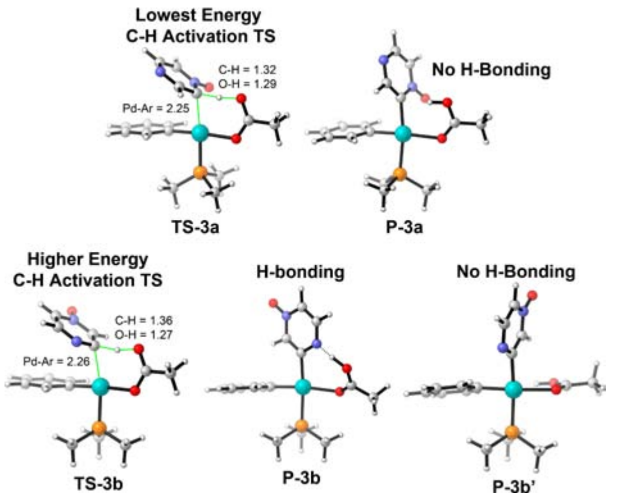

Figure 2. C−H activation transition states and palladium aryl intermediates for heteroarene **3**.

Inspection of Figure 1 reveals that for 9 out of 14 reactions considered the lowest energy C−H activation TS corresponds to the most stable metal aryl intermediate. Also evident is that almost all metal aryl intermediates are endothermic, which implies that the TS structures can be considered "late". Inspection of the palladium aryl intermediates generated from C−H bond cleavage of heteroarenes **3**, **8**, **11**, and **13**, the four reactions where the lowest $\Delta E^{\ddagger}$ value did not correspond with the most stable palladium aryl intermediate, shows that the most stable intermediate is the result of a H-bonding interaction between the newly formed HOAc group and a heteroarene N-atom. For example, Figure 2 shows the TSs and intermediates for the reaction between (Ph)(PMe_3)Pd(OAc) and pyrazine *N*-oxide (**3**). The $\Delta E^{\ddagger}$ values for **TS-3a** and **TS-3b** are 10.3 and 19.4 kcal/mol. The ΔE_{rxn} values for **P-3a** and **P-3b** are 1.0 and −3.5 kcal/mol, respectively. However, **P-3b** showcases a H-bonding interaction between the N4 nitrogen of the pyrazine *N*-oxide with the HOAc ligand, which makes it more stable than **P-3a**. Removal of this H-bonding interaction by rotation of the HOAc group by ~90° gives the metal aryl intermediate **P-3b′** that has a geometry similar to that of **P-2a** with a ΔE_{rxn} value of 9.6 kcal/mol. Now the relative thermodynamic stability of **P-3a** and **P-3b′**, which provides an approximate equal thermodynamic comparison, correctly corresponds to the relative ordering of the activation energies for **TS-3a** and **TS-3b**. A similar situation also applies for heteroarenes **8**, **11**, and **13**. Therefore, after consideration of H-bonding interactions the relative thermodynamics of the palladium aryl intermediates correctly predicts the regioselectivity for all arenes and heteroarenes investigated.

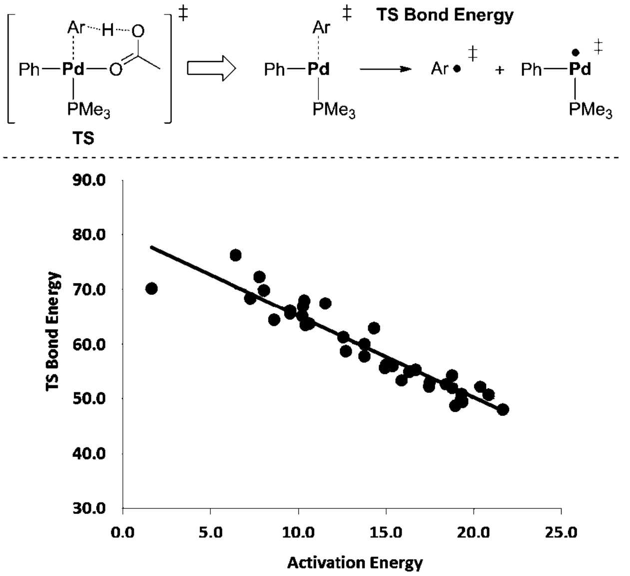

Figure 3. Definition of palladium aryl transition-state bond energies and correlation with $\Delta E^{\ddagger}$ values ($y = -1.5 + 80.1$; $R^2 = 0.89$) [kcal/mol].

The results in Figure 1 implicate a quantitative relationship between TS energies and metal aryl thermodynamics.

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Indeed, a plot of $\Delta E^{\ddagger}$ versus ΔE_{rxn} values gives a definitive linear correlation with a moderate R^2 value of ~0.8 (see Supporting Information, SI). The correlation between C–H bond activation barriers and the thermochemistry of the corresponding metal aryl intermediates is not unprecedented. Eisenstein, Perutz, and others have shown similar correlations for C–H bond activation reactions of fluorinated arenes and related compounds.[25]

To more directly quantify and understand how the thermodynamic stability of the palladium aryl intermediate influences the TS activation energy, we have computed the TS Pd–C bond energies. Figure 3 outlines how the TS palladium aryl bond energy was computed. This involved deletion of the HOAc group from the TS structure followed by calculation of the Pd–C bond energy without geometry relaxation ($[(\mathrm{Ph})(\mathrm{PMe_3})\mathrm{Pd}(\mathrm{Ar})]^{\ddagger} \rightarrow [(\mathrm{Ph})(\mathrm{PMe_3})\mathrm{Pd}\bullet]^{\ddagger} + [\mathrm{Ar}\bullet]^{\ddagger}$). This analysis provides a quantitative estimate of the relative strengths of developing Pd aryl bonding in the TS. Figure 3 also shows a plot of $\Delta E^{\ddagger}$ values versus TS bond energies for the activation of all C–H bonds in arenes and heteroarenes **1**–**14**. There is an excellent linear correlation (R^2 = 0.9) between these values, which reveals that the Pd–C bonding interaction that develops along the reaction coordinate for C–H bond activation contributes significantly to stabilizing the TS and dictates regioselectivity. This also suggests that the breaking of the C–H bond and the formation of the HOAc ligand OH bond are likely somewhat constant for the various C–H bond activation reactions.

Realization that the most favorable C–H activation TS corresponds to the most favorable metal aryl bond energy has more implications. This correlation suggests that the strongest C–H bond will be preferentially activated since it will lead to the most stable Pd–C bond. Indeed, for arenes and heteroarenes **1**–**14** the strongest C–H bond generally has the lowest activation energy. However, there is no linear correlation between computed C–H bond dissociation energies (BDEs) and $\Delta E^{\ddagger}$ values (see SI) since it is the developing metal aryl bond and not the breaking of the C–H bond that determines relative barrier heights.

In conclusion, we have demonstrated that the stability of developing palladium aryl bonds in C–H activation TSs, and the corresponding palladium aryl intermediates (with careful consideration of hydrogen bonding interactions), determines regioselectivity for a variety of arene and heteroarene substrates. The kinetic–thermodynamic connection explains the general preference for activation of the strongest C–H bond in a substrate, since it leads to the most stable Pd–C bond. From a valence bond perspective the stronger Pd–C bond is likely the result of more polar covalent bonding that results in larger covalent–ionic ($\mathrm{Pd^+C^-}$) resonance stability. Comprehensive thermodynamic analysis of palladium aryl bonding will be the subject of a future detailed study. Lastly, this breakthrough in understanding what determines regioselectivity in C–H bond functionalization[26] of arenes and heteroarenes provides the possibility for predicting regioselecitivty in new compounds without resorting to calculation of TSs.

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Supporting Information Available. M06 absolute energies, complete ref 22, and linear correlation plots. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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[26] In this study we examined only the C–H activation step, which is not always the selectivity-determining step in a reaction sequence or catalytic cycle. In cases where C–H activation is reversible the regioselectivity may be determined by the functionalization step.