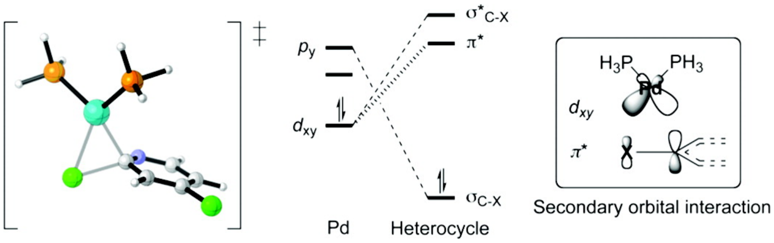
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

Origin of Regioselectivity in Palladium-Catalyzed Cross-Coupling Reactions of Polyhalogenated Heterocycles

Claude Y. Legault, Yeimy Garcia, Craig A. Merlic, and K. N. Houk

J. Am. Chem. Soc., **2007**, 129 (42), 12664-12665• DOI: 10.1021/ja075785o • Publication Date (Web): 03 October 2007



Journal of the American Chemical Society is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

J|A|C|S
COMMUNICATIONS

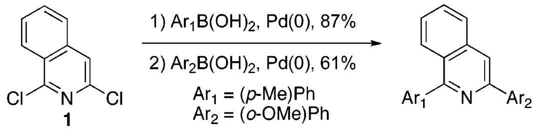
Origin of Regioselectivity in Palladium-Catalyzed Cross-Coupling Reactions of Polyhalogenated Heterocycles

Claude Y. Legault, Yeimy Garcia, Craig A. Merlic,* and K. N. Houk*

Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095

Received August 2, 2007; E-mail: merlic@chem.ucla.edu; houk@chem.ucla.edu

Polysubstituted heterocycles are important compounds widely used in the pharmaceutical industry.[1] Among the numerous synthetic methodologies that have been developed to access them, palladium-catalyzed cross-couplings have proven to be one of the most important synthetic techniques for C−C and C−heteroatom bond formation.[2] Sequential cross-coupling on multihalogenated heterocycles is a particularly attractive strategy for the divergent synthesis of libraries of compounds, as exemplified by eq 1.[3]



(1)

However, selective displacement of the halogens is critical to achieve synthetic utility.[4] In cases where the halogens are different, the observed selectivity is obviously related to the relative bond dissociation energies (BDEs) of the respective carbon−halogen bonds, the reactivity following the trend C−I > C−Br > C−Cl > C−F. However, the situation is complicated in the case of cross-coupling reactions of heterocycles bearing multiple identical halogens. Although in such cases some success was achieved in predicting the preferred position of coupling using NMR spectroscopy,[5] the factors that govern the regioselectivity are not well understood.

For example, the compounds illustrated in Figure 1 show exclusive regioselectivity at the specific position shown in boldface under classical cross-coupling conditions.[2] The BDEs shown of the different carbon−halogen bonds of these compounds were calculated using B3LYP/6-31G(d), which was found to give reliable relative BDEs when compared to a benchmark[6] done using G3B3.[7] The factors that control the relative BDEs will be discussed in future publications; an α-aza clearly facilitates CX cleavage.

The differences in BDE at different positions of the heterocycles cannot account for all observed reaction selectivities (Figure 1). For example, for 2,3-dibromofuran (**5**), the BDEs are identical, but exclusive reactivity of the 2-position is observed. Moreover, in the case of 2,5-dibromo-7-methoxybenzofuran (**4**) and 3,5-dichloro-4-cyanoisothiazole (**6**), the BDE differences are opposite to that of the experimental selectivities.

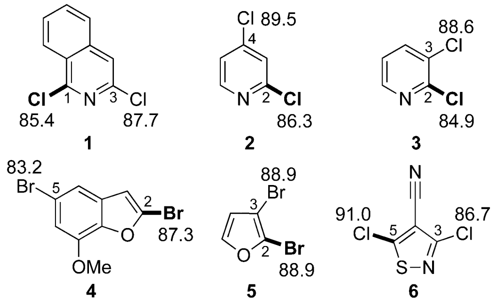
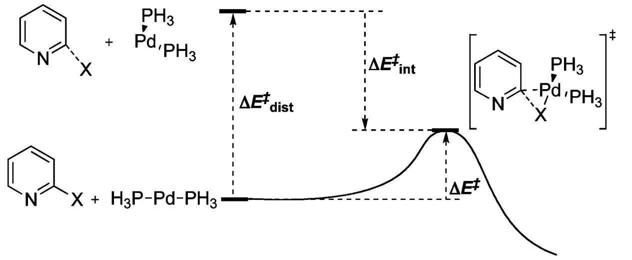


Figure 1. Regioselectivity patterns and BDEs of various heterocycles. (Bonds in bold represent the position of the first insertion.)

Scheme 1



In the overall cross-coupling process, the oxidative addition step is generally considered to be the selectivity-determining step. However, recent studies have also noted the possible reversibility of the oxidative addition step and importance of the transmetallation step in the regioselectivity outcome.[8] We have calculated the oxidative addition transition structures for many heterocycles, including those shown in Figure 1. Studies have reported the active Pd(0) species in the cross-coupling process to be either monoligated (PdL) or bisligated (PdL_2).[9] A simple Pd−bisphosphine model ($Pd(PH_3)_2$) was used for our calculations.[10] The computed relative activation energies are in excellent agreement with experimentally observed selectivities (see Table 1).[11,12]

In order to understand the factors controlling the oxidative addition, the energies to distort isolated reactants to the transition-state geometry (the distortion energy) and the energy of interaction between these distorted reactants (the interaction energy) were analyzed. This type of analysis, known as an activation strain model, has been applied by Bickelhaupt et al. to Pd(0) oxidative additions.[13] It is related to the deformation/interaction method developed by Morokuma et al.,[14] which has been elaborated and applied to other systems.[15] Distortion energies are also discussed by Guthrie.[16] The decomposition of the activation energy into distortion ($\Delta E^{\ddagger}_{\text{dist}}$) and interaction energies ($\Delta E^{\ddagger}_{\text{int}}$) is shown schematically in Scheme 1.

The analysis was carried out on compounds shown in Figure 1, and the results are summarized in Table 1. **1**−**3** have regioselectivity as expected on the basis of BDEs. Indeed, the relative distortion energies parallel the relative BDEs. The interaction energies follow the same trend or are nearly identical (e.g., 1,3-dichloroisoquinoline (**1**)). For most of the compounds, decomposition of the distortion energies into their bending and stretching components confirmed that the origin of their difference is due to the stretching of the C−X bond.[17] As noted above, the reaction selectivities observed with compounds **4**, **5**, and **6** do not parallel the BDEs; similarly the distortion energies are in the opposite order as activation energies or are nearly the same (**5**). These compounds have large differences in interaction energies, favoring the regioisomeric transition state that leads to the observed product. Thus, their

10.1021/ja075785o CCC: $37.00

Table 1. Distortion/Interaction Analysis for Oxidative Addition TS

cmpd	insertion position[a]	BDE_{298} (kcal/mol)	$\Delta E^{\ddagger}$	$\Delta E^{\ddagger}_{dist}$ (Pd)	$\Delta E^{\ddagger}_{dist}$ (Het)	$\Delta E^{\ddagger}_{int}$
1	**1**	85.4	12.8	14.0	23.5	−24.7
	3	87.7	16.3	14.6	27.3	−25.5
2	**2**	86.3	15.3	13.4	24.7	−22.8
	4	89.5	17.2	14.9	23.3	−21.0
3	**2**	84.9	14.4	13.4	24.6	−23.6
	3	88.6	17.4	14.4	23.9	−20.9
4	**2**	87.3	7.6	14.0	21.3	−27.7
	5	83.2	13.7	14.1	20.8	−21.2
5	**2**	88.9	9.8	12.7	18.7	−21.6
	3	88.9	14.0	12.9	19.8	−18.7
6	3	86.7	12.5	13.9	23.4	−24.8
	5	91.0	9.1	15.4	19.8	−26.1

[a] Observed reaction position indicated in **bold**.

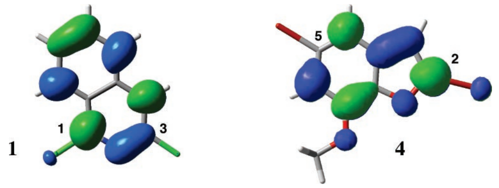


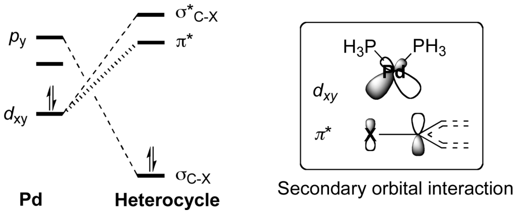
Figure 2. LUMO of **1** and **4**.

activation energies are strongly linked to the different interaction energies.

Both distortion energies and interaction energies may control regioselectivities. Clearly, the distortion energies are related to the BDEs, but what controls the interaction energies? We have found that the heterocycle π^* LUMO-Pd d_{xy} HOMO interaction controls the relative interaction energies. **1** and **4** are representative examples of substrates that participate in strain (BDE)- and interaction (FMO)-controlled reactions, respectively. A closer look at the molecular orbitals of the heterocycles points to a pattern of reactivity. The LUMOs for **1** and **4** are represented in Figure 2.[17] The MO coefficients at the 1- and 3-positions for **1** are roughly similar, which is reflected in the nearly identical interaction energies. Conversely, the LUMO of **4** shows a sharp difference in the coefficients at the 2- and 5-positions, being virtually nonexistent at the 5-position. The interaction energy at C-2 is nearly 7 kcal/mol larger than that at C-5 (Table 1).

Analysis of the frontier molecular orbitals (FMO) of the Pd species leads to a rationalization of the results obtained. Pd(0) is an electron-rich d^{10} metal. The oxidative addition TS will thus be stabilized if back-donation is possible. Morever, this back-donation should be more pronounced as the $HOMO_{Pd}-LUMO_{Heterocycle}$ gap becomes smaller. Not surprisingly, a strong correlation is found between the HOMO−LUMO gap and the charge transfer to the heterocycle in the transition structures. The major MO interactions in the oxidative addition process are shown in Scheme 2. The $p_y-\sigma_{C-X}$ and $d_{xy}-\sigma^*_{C-X}$ interactions, responsible for the bond-forming/-breaking processes, are present in all oxidative additions. In contrast, the magnitude of a stabilizing $d_{xy}-\pi^*$ secondary orbital interaction is dependent on the π^* LUMO coefficient at the insertion position. In cases such as **4**, **5**, and **6**, variations in this stabilizing back-donation at the different positions are such that they control the oxidative addition process. These results are in accord with the study of Lin et al. concerning the relative ease of oxidative addition to aryl vs alkyl halides.[9b] The latter lack the π^* orbital that strongly increases the interaction energy stabilization. They have also reported a correlation between relative oxidative addition barriers and the LUMO energies of different aryl substrates.[9a]

Scheme 2



The selectivity in palladium-catalyzed cross-coupling reactions of heterocycles bearing multiple identical halogens is determined by both the strength of the carbon−halogen bond (related to BDE) and the LUMO of the heterocycle (related to FMO interactions). We will report on a predictive model that will enable easy assessment of the relative BDE and LUMO coefficients in order to rapidly predict experimental reactivity.

Acknowledgment. We are grateful to the National Institutes of General Medical Sciences, National Institutes of Health for financial support of this research. C.Y.L. is grateful to NSERC for a postdoctoral fellowship. We thank Paul Ha-Yeon Cheong for insightful comments.

Supporting Information Available: Cartesian coordinates, energies, thermal corrections, and full authorship of Gaussian (ref 6). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Pozharskii, A. F.; Soldatenkov, A. T.; Katritzky, A. R. *Heterocycles in Life and Society*; Wiley: New York, 1997.
(2) Schroter, S.; Stock, C.; Bach, T. *Tetrahedron* **2005**, *61*, 2245.
(3) Ford, A.; Sinn, E.; Woodward, S. *J. Chem. Soc., Perkin Trans. 1* **1997**, 927.
(4) Fairlamb, I. J. S. *Chem. Soc. Rev.* **2007**, *36*, 1036.
(5) Handy, S. T.; Zhang, Y. *Chem. Commun.* **2006**, 299.
(6) The benchmark was done on a set of 47 heterocycles and shows excellent correlation between G3B3 and B3LYP/6-31G(d) ($BDE_{G3B3} = 0.94{*}BDE_{B3LYP} + 12.0$, $R(2) = 0.951$). Calculations done using Gaussian 03: Frisch, M. J.; et al. *Gaussian 03*; Gaussian, Inc.: Pittsburgh, PA, 2004.
(7) Baboul, A. G.; Curtiss, L. A.; Redfern, P. C.; Raghavachari, K. *J. Chem. Phys.* **1999**, *110*, 7650.
(8) (a) Espino, G.; Kurbangalieva, A.; Brown, J. M. *Chem. Commun.* **2007**, 1742. (b) Ariafard, A.; Lin, Z.; Fairlamb, I. J. S. *Organometallics* **2006**, *25*, 5788.
(9) (a) Lam, K. C.; Marder, T. B.; Lin, Z. *Organometallics* **2007**, *26*, 758 and refs therein. (b) Ariafard, A.; Lin, Z. *Organometallics* **2006**, *25*, 4030.
(10) Monoligated palladium species ($PdP(t\text{-}Bu)_3$) and bisligated palladium species $Pd(PMe_3)_2$ gave similar results.
(11) The TSs of Pd insertion into the halo positions of the heterocycles were computed at B3LYP with 6-31G(d) and LANL2DZ+ECP (for Pd) basis sets. B3LYP was found to be an adequate method to study these reactions, see: de Jong, G. T.; Bickelhaupt, F. M. *J. Chem. Theory Comput.* **2006**, *2*, 322.
(12) Example of computed transition structures of oxidative addition to 4,6-dichloro-2-pyrone, see: Fairlamb, I. J. S.; O'Brien, C. T.; Lin, Z.; Lamb, K. C. *Org. Biomol. Chem.* **2006**, *4*, 1213.
(13) (a) de Jong, G. T.; Bickelhaupt, F. M. *ChemPhysChem* **2007**, *8*, 1170. (b) de Jong, G. T.; Bickelhaupt, F. M. *J. Chem. Theory Comput.* **2007**, *3*, 514. (c) Diefenbach, A.; de Jong, G. T.; Bickelhaupt, F. M. *J. Chem. Theory Comput.* **2005**, *1*, 286. (d) Diefenbach, A.; Bickelhaupt, F. M. *J. Phys. Chem. A* **2004**, *108*, 8640. (e) Bickelhaupt, F. M. *J. Comput. Chem.* **1999**, *20*, 114.
(14) (a) Kitaura, K.; Morokuma, K. *Int. J. Quantum Chem.* **1976**, *10*, 325. (b) Morokuma, K. *J. Chem. Phys.* **1971**, *55*, 1236.
(15) (a) Strozier, R. W.; Caramella, P.; Houk, K. N. *J. Am. Chem. Soc.* **1979**, *101*, 1340. (b) Ziegler, T.; Rauk, A. *Inorg. Chem.* **1979**, *18*, 1755. (c) Ziegler, T.; Rauk, A. *Inorg. Chem.* **1979**, *18*, 1558. (d) Ziegler, T.; Rauk, A. *Theor. Chim. Acta* **1977**, *46*, 1.
(16) Guthrie, J. P. *ChemPhysChem* **2003**, *4*, 809.
(17) See Supporting Information for more details.

JA075785O