

Understanding the Relative Easiness of Oxidative Addition of Aryl and Alkyl Halides to Palladium(0)

Alireza Ariaafard^{†,‡} and Zhenyang Lin^{*,†}

Department of Chemistry and Open Laboratory of Chirotechnology of the Institute of Molecular Technology for Drug Discovery and Synthesis, The Hong Kong University of Science and Technology, Clear Water Bay, Kowloon, Hong Kong, and Department of Chemistry, Faculty of Science, Central Tehran Branch, Islamic Azad University, Felestin Square, Tehran, Iran

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Summary: Density functional theory calculations were carried out to study the relative easiness of oxidative addition of aryl and alkyl halides to Pd(0). Kinetic but not thermodynamic factors were found to contribute to the better reactivity of aryl versus alkyl halides.

Oxidative addition of organic electrophiles (RX) to Pd(0) is an important step in many Pd-catalyzed cross-coupling reactions.^{1,2} Aryl, vinyl, benzyl, and alkyl halides, for example, are the common organic electrophiles used in these reactions. Among the organic electrophiles, the substrates having C(sp³)–X bonds, especially alkyl halides, have been much less used in the cross-coupling reactions.^{3–5} The main reason for the limitation is that oxidative addition of alkyl halides to the Pd(0) complexes is much slower than that of other commonly used substrates, which in turn leads to the difficulty of achieving coupling reactions.

To date, there are numerous experimental^{3,6} and theoretical⁷ studies concerning the oxidative addition of organic electrophiles (RX) to Pd(0). However, an in-depth understanding of the better reactivity of the aryl or vinyl halides versus alkyl halides is still lacking. In the literature, a few tentative explanations can be found. For example, one viewpoint is that the difference in reactivity could be related to the less electron rich C(sp²)–X bond in aryl or vinyl halides in comparison with the C(sp³)–X bond in alkyl halides.⁴ Another belief is that the difference may

be related to the fact that the Pd–C(aryl) or Pd–C(vinyl) bond formed in the product after oxidative addition is much stronger than the Pd–C(alkyl) bond.⁵

In this note, we attempt to provide a better understanding of what is responsible for the better reactivity of aryl versus alkyl halides with the aid of B3LYP density functional theory (DFT) calculations.⁸ The effective core potentials of Hay and Wadt with double- ζ valance basis sets (LanL2DZ) were chosen to describe Pd, Br, and P.⁹ The 6-31G basis set was used for the other atoms. Polarization functions were also added for P ($\zeta_d = 0.340$), C ($\zeta_d = 0.6$), and Br ($\zeta_d = 0.389$).¹⁰ Larger basis sets with more accurate core potentials were used to confirm the accuracy of the medium-size basis set (BSI) used.¹¹ In the DFT calculations, we investigated the model reactions (PH₃)₂-Pd + RX \rightarrow (PH₃)₂Pd(R)(X) (R = methyl, phenyl, vinyl, benzyl; X = bromide).¹² As in many other theoretical studies, a bis-phosphine Pd(0) model complex was used in our calculations for the purpose of comparing the reactivity of aryl and alkyl halides. We are aware that oxidative addition of organic electrophiles to Pd(0) may involve species other than PdL₂ (L = phosphine), such as PdL in a dissociative mechanism and [PdL₂(X)][–] (X = halides or acetate) in an anionic mechanism.^{6,7} The choice of PdL₂ is for the convenience of comparison. The qualitative conclusion made here should also be valid even when other species are considered because we mainly focus on the comparison of different substrates.

* To whom correspondence should be addressed. E-mail: chzlin@ust.hk.

[†] The Hong Kong University of Science and Technology.

[‡] Islamic Azad University.

(1) See for example: (a) Espinet, P.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4704. (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (c) Meijere, A. de; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379. (d) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. (e) Stille, J. K.; Lau, K. S. Y. *Acc. Chem. Res.* **1977**, *10*, 434.

(2) (a) Tsuji, J. *Palladium Reagents and Catalysts*: John Wiley & Sons, Ltd.: New York, 2004. (b) Diederich, F.; Stang, P. J. *Metal-Catalyzed Cross-Coupling Reactions*; Wiley-VCH: Weinheim, 1998.

(3) (a) Bedford, R. B.; Betham, M.; Coles, S. J.; Frost, R. M.; Hursthouse, M. B. *Tetrahedron* **2005**, *61*, 9663. (b) Cárdenas, D. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 384. (c) Hills, I. D.; Netherton, M. R.; Fu, G. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 5749. (d) Cárdenas, D. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 3018.

(4) Frisch, A. C.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 674.

(5) Luh, T.-Y.; Leung, M.-K.; Wong, K.-T. *Chem. Rev.* **2000**, *100*, 3187.

(6) (a) Barrios-Landeros F. Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 6944. (b) Espinet, P.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4704. (c) Roy, A. H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 13944. (d) Amatore, C.; Jutand, A. *Acc. Chem. Res.* **2000**, *33*, 314. (e) Amatore, C.; Jutand, A. *J. Organomet. Chem.* **1999**, *576*, 254. (f) Casado, A. L.; Espinet, P. *Organometallics* **1998**, *17*, 954. (g) Jutand, A.; Mosleh, A. *Organometallics* **1995**, *14*, 1810. (h) Hartwig, J. F.; Paul, F. *J. Am. Chem. Soc.* **1995**, *117*, 5373. (i) Paul, F.; Patt, J.; Hartwig, J. F. *Organometallics* **1995**, *14*, 3030. (j) Amatore, C.; Jutand, A.; Suarez, A. *J. Am. Chem. Soc.* **1993**, *115*, 9531. (k) Portnoy, M.; Milstein, D. *Organometallics* **1993**, *12*, 1665. (l) Amatore, C.; Pflüger, F. *Organometallics* **1990**, *9*, 2276.

(7) (a) Kozuch, S.; Amatore, C.; Jutand, A.; Shaik, S. *Organometallics* **2005**, *24*, 2319. (b) Goossen, L. J.; Koley, D.; Hermann, H. L.; Thiel, W. *Organometallics* **2005**, *24*, 2398. (c) Diefenbach, A.; Jong, G. T. de; Bickelhaupt, F. M. *J. Chem. Theory Comput.* **2005**, *1*, 286. (d) Senn, H. M.; Ziegler, T. *Organometallics* **2004**, *23*, 2980. (e) Goossen, L. J.; Koley, D.; Hermann, H. L.; Thiel, W. *Chem. Commun.* **2004**, 2141. (f) Jakt, M.; Johannissen, L.; Rzepa, H. S.; Widdowson, D. A.; Wilhelm, A. *J. Chem. Soc., Perkin Trans. 2* **2002**, 576. (g) Sundermann, A.; Uzan, O.; Martin J. M. L. *Chem. Eur. J.* **2001**, *7*, 1703. (h) Albert, K.; Gisdakis, P.; Rösch, N. *Organometallics* **1998**, *17*, 1608. (i) Bickelhaupt, F. M.; Ziegler, T.; Schleyer, P. v. R. *Organometallics* **1995**, *14*, 2288.

(8) See the Supporting Information for more computational details.

(9) (a) Wadt, W. R.; Hay, P. J. *J. Chem. Phys.* **1985**, *82*, 284. (b) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 299.

(10) Huzinaga, S. *Gaussian Basis Sets for Molecular Calculations*; Elsevier Science Pub. Co.: Amsterdam, 1984.

(11) We carried out single-point energy calculations for several selected structures by using a larger basis set: SDDALL for Pd and 6-311G** for all other atoms. These additional calculations show that the basis set dependence is small. With the BSI basis set, the relative electronic energies of Pd(PH₃)₂ + **1**, **1_TS**, and **1_Prod** are 0.0, 14.2, and –11.3 kcal/mol, respectively, while with the larger basis set, the relative electronic energies are 0.0, 15.1, and –13.8 kcal/mol, respectively. Similarly, using the BSI basis set, the relative electronic energies of Pd(PH₃)₂ + **2**, **2_TS**, and **2_Prod** are 0.0, 24.6, and –10.7 kcal/mol, respectively, while using the larger basis set, the relative electronic energies are 0.0, 25.4, and –13.2 kcal/mol, respectively. For SDDALL, see: (a) Dolg, M.; Wedig, U.; Stoll, H.; Preuss, H. *J. Chem. Phys.* **1987**, *86*, 866. (b) Bergner, A.; Dolg, M.; Kuechle, W.; Stoll, H.; Preuss, H. *Mol. Phys.* **1993**, *80*, 1431.

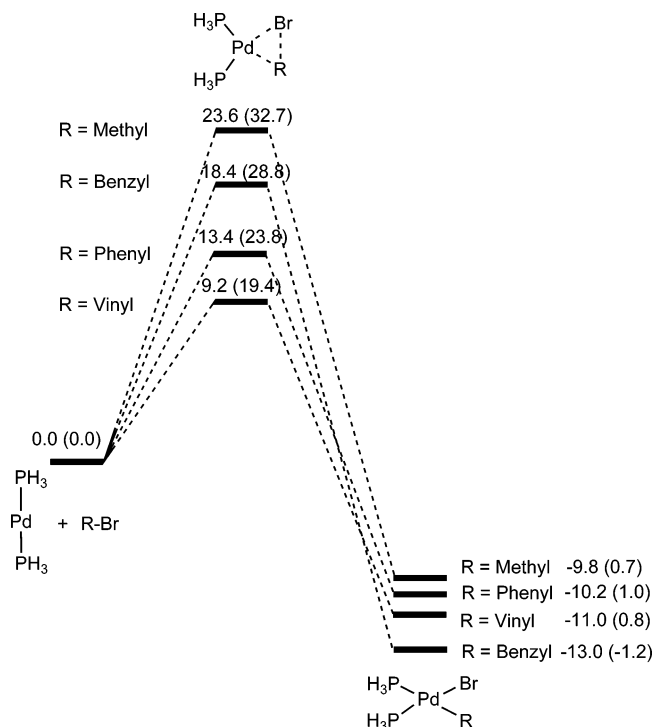


Figure 1. Potential energy profiles calculated for the oxidative addition of different organic electrophiles to Pd(0). Relative electronic energies with zero-point energy corrections and Gibbs free energies (in parentheses) at 1 atm, 298.15 K relative to the Pd(PH₃)₂ and RBr fragments are given in kcal/mol.

Our calculations show that oxidative addition of C(sp²)-Br bonds is much more facile than that of C(sp³)-Br bonds (Figure 1). The calculated activation energies for the oxidative addition of RBr decrease in the order of R = methyl > benzyl > phenyl > vinyl and span from 9.2 to 23.6 kcal/mol. These results agree well with the experimental findings that oxidative addition of vinyl-Br to [Pd(PPh₃)₄] is more favored than that of PhBr;¹³ benzyl-Br is less reactive than PhBr;¹⁴ and C(sp³)-Br bonds that are instantly next to a C(sp²) atom are oxidatively added to Pd(0) much easier than other C(sp³)-Br bonds.⁵

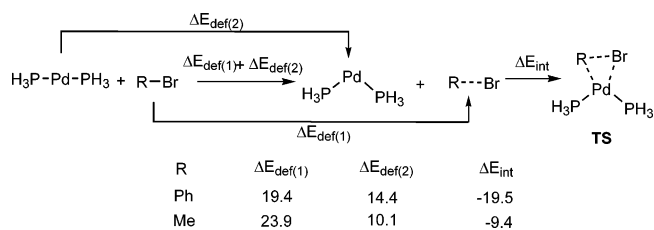
From Figure 1, one can easily find that the oxidative addition reaction energies do not follow the trend found in the reaction barriers. The reaction energies among the four reactions are comparable, indicating that the stronger Pd-C(phenyl) and Pd-C(vinyl) bonds in the products do not give greater exothermicities for the oxidative addition reactions of the PhBr and vinyl-Br substrates. Thus, the difference in reactivity of the C(sp²)-Br and C(sp³)-Br bonds cannot be explained from a thermodynamic point of view.

(12) To study the steric effect missed from the small model calculations, we performed two-layer ONIOM (B3LYP/BSI: HF/Lanl2MB) calculations on (PPh₃)₂Pd + RBr → (PPh₃)₂Pd(R)(Br) (R = Me, Ph). In the ONIOM calculations, the six phenyl groups on the two phosphine ligands were treated as the second layer, while the rest were treated as the first layer. The calculation results (see the Supporting Information for the detailed results) show that the steric bulkiness of the two PPh₃ ligands does not affect the addition barriers. The geometry around the metal center in each of the transition states also does not change much. The results are understandable because these oxidative addition reactions have early transition states. For references of the ONIOM method, see: (a) Dapprich, S.; Komáromi, I.; Byun, K. S.; Morokuma, K.; Frisch, M. J. *J. Mol. Struct. (THEOCHEM)* **1999**, *462*, 1. (b) Vreven, T.; Morokuma, K. *J. Comput. Chem.* **2000**, *21*, 1419. For a similar two-layer ONIOM calculation, see: (c) Ananikov, V. P.; Szilagy, R.; Morokuma, K.; Musaev, D. G. *Organometallics*, **2005**, *24*, 1938.

(13) Jutand, A.; Négri, S. *Organometallics* **2003**, *22*, 4229.

(14) Crawforth, C. M.; Burling, S.; Fairlamb, I. J. S.; Kapdi, A. R.; Taylor, R. J. K.; Whitwood, A. C. *Tetrahedron* **2005**, *61*, 9736.

Scheme 1



To probe the reason that a C(sp²)-Br bond is more reactive than a C(sp³)-Br bond, we here compare the oxidative addition reactions of PhBr and MeBr. Figure 2 shows the calculated structural parameters for PhBr (**1**) and MeBr (**2**), their oxidative addition transition states (**1**_TS and **2**_TS), and products (**1**_Prod and **2**_Prod). The Pd-Br (2.641 Å) and Pd-C(1) (2.159 Å) bond distances in **1**_TS are shorter when compared with the Pd-Br (2.859 Å) and Pd-C(1) (2.382 Å) bond distances in **2**_TS, suggesting that interaction of C(1) and Br with Pd in **1**_TS is stronger than that in **2**_TS. The Pd-Br and Pd-C(1) bond distances on going from **1**_TS to **1**_Prod are shortened by 0.117 and 0.116 Å, respectively. The shortening, by 0.323 and 0.298 Å, respectively, is much larger from **2**_TS to **2**_Prod. These results indicate that **1**_TS is more product-like than **2**_TS. However, the C(1)-Br bond distance in **1**_TS is longer by 0.301 Å than that in the free aryl bromide (**1**), while the C(1)-Br bond in **2**_TS is longer by 0.383 Å than that in the free methyl bromide (**2**), indicating that in the PhBr transition state, the C(1)-Br bond is less broken. **1**_TS is relatively more stable when compared with **2**_TS, suggesting that interaction of PhBr with Pd in the transition state is considerably greater than that of MeBr with Pd.

An energy decomposition analysis, on the basis of the activation strain model,¹⁵ of the oxidative addition reaction barriers, shown in Scheme 1, was carried out to further support the notion that the interaction of PhBr with Pd in the transition state is considerably greater than that of MeBr with Pd. In the scheme, the deformation energy (ΔE_{def}) is defined as the energy associated with deforming the reactants from their equilibrium structures to the geometry they acquire in the transition state and the interaction energy (ΔE_{int}) represents the interaction energy between the deformed R-Br and Pd(PH₃)₂ fragments in the transition state.¹⁵ Interestingly, the sum of the deformation energies for the addition of PhBr does not differ much from that for the addition of MeBr. The larger ΔE_{def(2)} value for Ph when compared to that for Me can be related to the smaller P-Pd-P angle in **1**_TS (Figure 2). The difference between the two reaction barriers can be traced to the significant difference between the two interaction energies (ΔE_{int}), supporting the conclusion made above.

A charge analysis also shows that PhBr gains 0.304e from the Pd(PH₃)₂ fragment in the transition state, while MeBr gains only 0.190e. The charge transfer in the transition state of the addition of PhBr is much more significant than that in the transition state of the addition of MeBr. To better understand the difference in the charge transfer, we compared the occupied molecular orbitals for **1**_TS and **2**_TS having the metal-to-ligand back-bonding interactions (Figure 3). From Figure 3, one can easily find that involvement of the Ph-Br π* orbital in the HOMO of **1**_TS is very significant. The bending of the C(1)-Br bond of PhBr away from the phenyl plane in the transition

(15) (a) Bickelhaupt, F. M. *J. Comput. Chem.* **1999**, *20*, 114. (b) Diefenbach, A.; Bickelhaupt, F. M. *J. Phys. Chem. A* **2004**, *108*, 8640. (c) Diefenbach, A.; de Jong, G. T.; Bickelhaupt, F. M. *J. Chem. Theory Comput.* **2005**, *1*, 286.

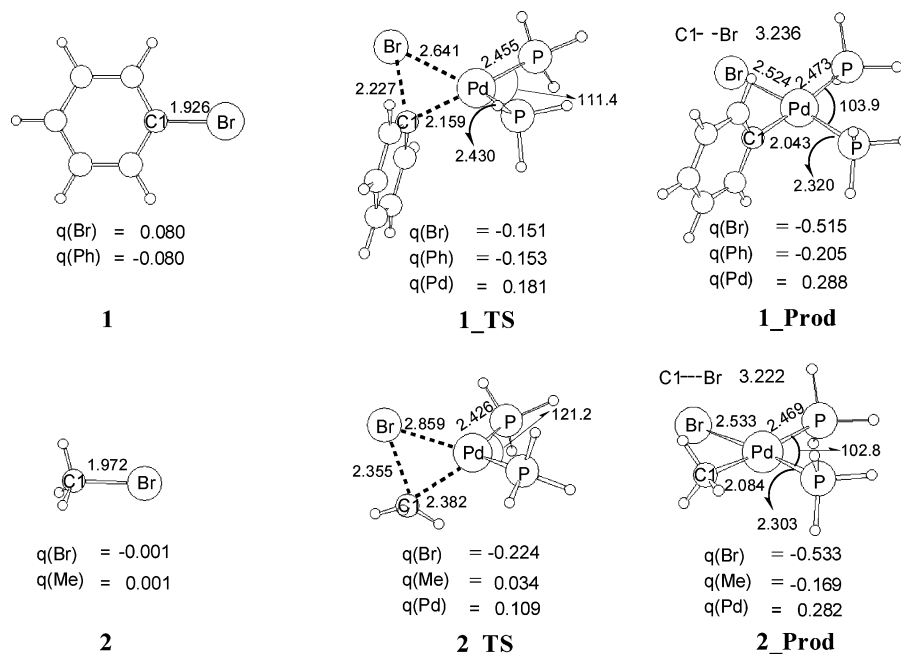


Figure 2. Calculated structures for species involved in the oxidative addition of PhBr and MeBr. Bond distances are given in Å and bond angles in deg.

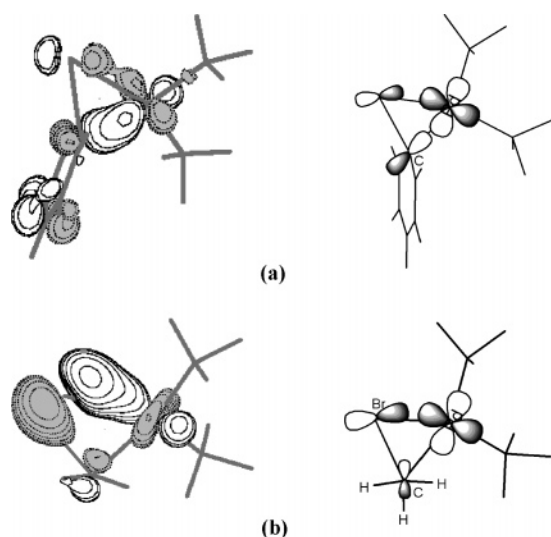


Figure 3. Occupied frontier molecular orbitals showing the metal-(d)-to-ligand(σ^*/π^*) back-bonding interactions in the transition states of oxidative addition of PhBr (a) and MeBr (b).

state allows mixing of the Ph–Br π^* and σ^* orbitals, giving a new hybrid orbital that can effectively overlap and interact with the occupied Pd 4d atomic orbital (Figure 4a) and thus increasing the donor–acceptor orbital interactions in the transition state between the occupied Pd 4d atomic orbital and the empty hybrid acceptor orbital. Owing to the strong directionality of the sp^3 hybrid orbital on Me, the overlap between the Me–Br σ^* orbital and the Pd 4d atomic orbital in the transition state **2_TS** is poor (Figure 4b). To confirm this claim, we analyzed the Laplacian of the electron density ($-\nabla^2 r$) on the plane defined by Pd, C(1), and Br for the transition states **1_TS** and **2_TS** using the AIM theory (Figure 5).¹⁶ Although some of the concepts in the AIM theory have been questioned,¹⁷ the concept of the Laplacian plots (Figure 5) is still useful in understanding the electron density features in the transition states. For **1_TS** (Figure 5a), the electron density around C(1) is significantly polarized toward the Pd metal center, indicating the back-

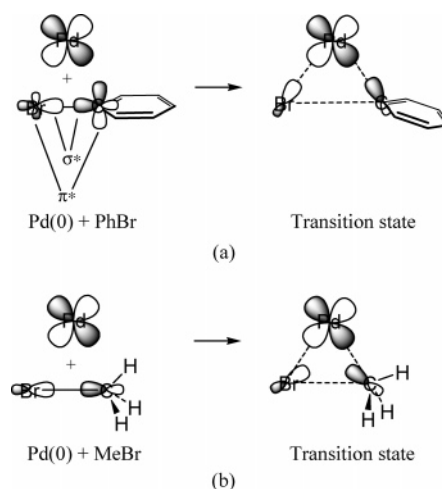


Figure 4. Schematic illustration showing how the occupied Pd 4d orbital interacts with the Ph–Br σ^*/π^* orbitals (a) and with the Me–Br σ^* orbital (b) in the transition states.

bonding interaction from the occupied Pd 4d orbital to the hybrid derived from the mixing of the C(1)–Br π^* and σ^* orbitals. For **2_TS** (Figure 5b), the polarization is much less significant because of the strong directionality of the Me sp^3 hybrid orbital.

One of the reviewers was concerned that possible agostic interactions between the C–H bonds on the substrate and Pd might stabilize **1_TS** more when compared with **2_TS**. Examining the structure of **1_TS**, we do not find the possible agostic interactions. The shortest Pd–H distance is 2.933 Å. In other words, agostic interactions do not play a role in stabilizing **1_TS**. However, in **2_TS**, we did find that there is a weak agostic interaction, with a Pd–H distance of 2.212 Å, between one of the C–H bonds from the methyl group (see the C–H bond shown on the right-hand side of C(1) in **2_TS** or

(16) Bader, R. F. W. *Atoms in Molecules: A Quantum Theory*; Oxford University Press: Oxford, UK, 1990.

(17) (a) Nguyen, M. H.; Hajnal, M. R.; Ha, T.-K.; Vanquickenborne, L. G.; Wentrup, C. *J. Am. Chem. Soc.* **1992**, *114*, 4382. (b) Haaland, A.; Shorokhov, D. J.; Tverdova, N. V. *Chem. Eur. J.* **2004**, *10*, 4416.

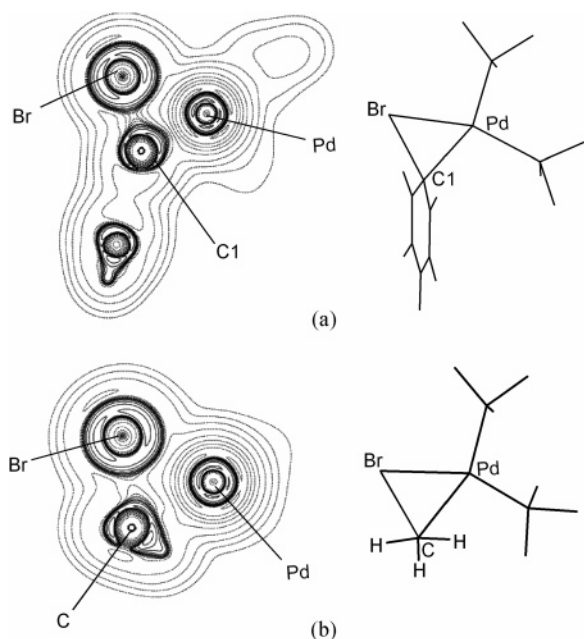


Figure 5. Plots of the Laplacian of electron density for **1_TS** (a) and **2_TS** (b) on the C(1)–Pd–Br plane.

Figure 2) and the Pd metal center. The C–H bond for the weak agostic interaction is longer by 0.015 Å than the other two C–H bonds. The existence of such an agostic interaction in **2_TS** can be explained as follows. As mentioned above, there is a relatively poor overlap between the Me–Br σ^* and the Pd 4d orbital in the transition state (**2_TS**) owing to the strong directionality of the sp^3 hybrid orbital on Me. Therefore, the direct bonding interaction between Pd and C1 is weak. To gain stability, the Pd metal center instead interacts strongly with the nearest C–H bond of the methyl group.

It is interesting to note from Figure 1 that the oxidative addition of vinyl–Br has the smallest barrier. This result is unusual in view of the fact that due to its smaller conjugation system the vinyl–Br π^* orbital is expected to be higher in

energy than the Ph–Br π^* orbital. It is because of its smaller conjugation that gives the Br-bonded carbon in vinyl–Br a greater percentage contribution to the vinyl–Br π^* orbital, enhancing the donor(Pd 4d)–acceptor(vinyl–Br π^*) orbital interactions in the transition state and therefore lowering the oxidative addition barrier. Benzyl–Br has a smaller oxidative addition barrier than MeBr, reflecting the weaker benzyl–Br bond when compared with the Me–Br bond. Benzyl–Br has a greater oxidative addition barrier than both PhBr and vinyl–Br, again due to the lack of low-lying C–Br π^* orbitals.

In summary, the better reactivity of aryl versus alkyl halides is related to the availability of Ar–X π^* orbitals in the aryl halides. In a given oxidative addition of RX to Pd(0), the transition state involves breaking of the R–X bond and formation of the Pd–X and Pd–R bonds. Therefore, the back-bonding interaction from Pd(d) to the R–X antibonding orbital(s) dominates in the transition state. The availability of Ar–X π^* orbitals in the aryl halides allows an efficient back-bonding interaction in the transition state with less involvement of the Ar–X σ^* orbital, lowering significantly the addition barrier. Clearly, kinetic but not thermodynamic factors contribute to the reactivity difference among the different types of organic halides.

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Supporting Information Available: The calculated structures for species involved in the oxidative addition of vinyl–Br and BnBr to $(\text{PH}_3)_2\text{Pd}(0)$, and the ONIOM-calculated structures for species involved in the oxidative addition of MeBr and PhBr to $(\text{PPh}_3)_2\text{Pd}(0)$. Tables giving Cartesian coordinates, electronic energies, electronic energies corrected by zero-point energies, and Gibbs free energies for all the calculated structures. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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