Ligand Effects of BrettPhos and RuPhos on Rate-Limiting Steps in Buchwald–Hartwig Amination Reaction Due to the Modulation of Steric Hindrance and Electronic Structure

Jiaqi Tian, Gaobo Wang, Zheng-Hang Qi, and Jing Ma*

Cite This: ACS Omega 2020, 5, 21385–21391

ABSTRACT: The differences in catalytic activity between two catalyst ligands of Buchwald–Hartwig amination reaction, BrettPhos versus RuPhos, were investigated using density functional theory (DFT) calculations. The reaction process consists of three consecutive steps: (1) oxidative addition, (2) deprotonation, and (3) reductive elimination. Among them, the rate-limiting step of Pd-BrettPhos catalytic system is oxidative addition but that of Pd-RuPhos catalytic system is reductive elimination due to their differences in steric hindrance and electronic structure. It was also revealed that amines with large-size substituents or halides with electron-withdrawing groups would reduce the activation energy barriers of the reactions. The insights gained from the calculations of the Buchwald–Hartwig amination reaction would be helpful for the rational designing of new catalysts and reactions.

1. INTRODUCTION

The C–N bond is one of the most common chemical bonds in nature. Cross-coupling reactions involving the formation of C–N bonds have been widely used in the fabrications of chemicals, materials, and medicines. The palladium-catalyzed C–N cross-coupling reactions discovered by Buchwald et al. and Hartwig et al. are the most representative reactions. Since the discovery of the reaction in 1995, there have been many reports in the field of experiments, mainly focusing on modification of the catalyst ligands, aiming to increase the reaction yield to improve the functional group tolerance of substrate and to realize the reaction under milder conditions. As shown in Figure 1a, some well-known ligands such as XPhos, SPPhos, RuPhos, and BrettPhos have been demonstrated to have high catalytic activities for specific substrates and have been branded and now put into practical use. In recent years, improvements in ligands have still been in progress.

Theoretical calculations have been carried out by several research groups to study the reaction pathways of Buchwald–Hartwig amination reactions, mainly focused on certain steps such as C–Br bond cleavage and C–N bond formation, influence of solvents and bases, and differences in structures of intermediates formed by different ligand catalysts. It is worth mentioning that Ke and Liu et al. calculated the potential energy curve of Buchwald–Hartwig amination reaction, which contained two key steps: ligand exchange and debromination.
However, the difference in catalytic activity between two kinds of widely used catalyst ligands, BrettPhos and RuPhos,\textsuperscript{17−20} has not been understood well. As shown in Figure 1b, the following question arises: why does BrettPhos have high catalytic activity for primary amines, while RuPhos has high catalytic activity for secondary amines?

Herein, we aim to answer these questions through theoretical studies on the Buchwald–Hartwig amination reaction pathway with different Pd\textsuperscript{0} ligand catalysts. It will be revealed that the catalytic systems of the two ligands, BrettPhos and RuPhos, have different rate-limiting steps. The effects of steric hindrance and electronic structure properties of substituents also play an important role in the reaction systems. Our research results would contribute to the knowledge of the Buchwald–Hartwig amination reaction mechanism, and hence, can provide useful information for the screening of catalysts or a rational design for new types of ligands.

2. COMPUTATIONAL DETAILS

All of the quantum chemical calculations were carried out with the Gaussian 16\textsuperscript{21} software package. The B3LYP functional\textsuperscript{22−24} of density functional theory (DFT) method was used in this work. We adopted two basis sets, i.e., basis set 1, B3LYP-D3 6-31G(d,p)//Lanl2dz,\textsuperscript{25} which was used for structural optimization, frequency analysis, and intrinsic reaction coordinate (IRC) analysis in SMD\textsuperscript{26} implicit solvation model and basis sets 2, B3LYP-D3 6-311++ G(d,p)\textsuperscript{27}//SDD,\textsuperscript{28} which was used to calculate the single point energy. The population analysis was performed using the natural bond orbital (NBO) method.\textsuperscript{29,30} The thermodynamic parameters were calculated at 298.15 K and 1.00 atm. The three-dimensional (3D) model was presented using CYLview\textsuperscript{31} software.

The molecular dynamics (MD) simulations of intermediates in toluene solvent molecules were also carried out with the Materials Studio 8.0 software. The atomic charges were obtained by the CHelpG\textsuperscript{32} method with Multiwfn\textsuperscript{33} software. All of the other parameters were generated from the consistent valence force field (CVFF).\textsuperscript{34}

3. RESULTS AND DISCUSSION

We start from the study of Group 1, in which bromobenzene (A\textsubscript{1}) reacts with aniline (B\textsubscript{1}) to form diphenylamine (C\textsubscript{1}) via catalyst Pd-BrettPhos or Pd-RuPhos, respectively. The whole reaction pathway can be divided into three parts: oxidative addition, deprotonation, and reductive elimination (Figure 2a). Configurations of intermediates in the reaction pathway are shown in Figure S1a. Considering the associations of sodium ions in intermediates 1 and 5, we run molecular dynamics simulations for the two intermediates in toluene. The MD snapshots in Figure 2b indicate that intermediates 1 and 5 have sufficient stabilities in toluene (detailed data are shown in Figure S4).

3.1. Oxidative Addition. Initially, the active Pd-BrettPhos/Pd-RuPhos is combined with the base sodium tert-butoxide to form intermediate 1, i.e., G\textsubscript{1}-Brett-1/G\textsubscript{1}-Ru-1 (G\textsubscript{1} refers to Group 1 system; “Brett” and “Ru” represent BrettPhos and RuPhos, respectively); then, intermediate 1, G\textsubscript{1}-Brett-1/G\textsubscript{1}-Ru-1, would coordinate with substrate A\textsubscript{1} by ligand exchange, and the base is removed to form intermediate 2, G\textsubscript{1}-Brett-2/G\textsubscript{1}-Ru-2. In the following step, the cleavage of C–Br bond of intermediate 2, G\textsubscript{1}-Brett-2/G\textsubscript{1}-Ru-2, occurs via the transition state TS\textsubscript{p}, G\textsubscript{1}-Brett-TS\textsubscript{p}/G\textsubscript{1}-Ru-TS\textsubscript{p}, to form intermediate 3, G\textsubscript{2}-Brett-3/G\textsubscript{2}-Ru-3. Among them, the combination of Pd-BrettPhos/Pd-RuPhos and base in the first step is indispensable because it lies in the energy basin on the potential energy surface (Figure 2b). The activation energy

Figure 2. (a) Illustration of the reaction pathway. (b) Potential energy surfaces. Snapshots of molecular dynamics simulations for intermediates 1 and 5 at 50 ps are shown in the insets.

Figure 3. (a) Group 1−5 reactions. (b) Differences in rate-limiting steps between Pd-BrettPhos and Pd-RuPhos catalytic systems.
barrier of oxidative addition is 23.3 kcal/mol (BrettPhos) or 13.3 kcal/mol (RuPhos).

3.2. Deprotonation. Substrate B1 further coordinated with intermediate 3, G1-Brett-3/G1-Ru-3, to form a four-coordinated intermediate 4, G1-Brett-4/G1-Ru-4; then, sodium tert-butoxide would grab the proton of aniline in intermediate 4, G1-Brett-4/G1-Ru-4, to form the deprotonated intermediate 5, G1-Brett-5/G1-Ru-5, which is another local minimum on the potential energy surface (Figure 2b). With the presence of bromine and palladium atoms, the sodium ion would form a complex instead of detaching from the intermediate.

3.3. Reductive Elimination. Further, intermediate 5, G1-Brett-5/G1-Ru-5, is debrominated to form intermediate 6, G1-Brett-6/G1-Ru-6, followed by the detachment of Pd-BrettPhos/Pd-RuPhos via the transition state TS2, G1-Brett-TS2/G1-Ru-TS2, and the C–N bond formation to form product C1. Pd-BrettPhos/Pd-RuPhos continues to participate in the new reaction cycle. The activation energy barrier of reductive elimination is 19.8 kcal/mol (BrettPhos) or 32.0 kcal/mol (RuPhos).

3.4. Rate-Limiting Step of Pd-BrettPhos and Pd-RuPhos Catalytic Systems. Moreover, the rate-limiting step of Pd-BrettPhos catalytic system is oxidative addition and that of Pd-RuPhos catalytic system is reductive elimination, and it is the most significant difference between the two ligands. To further study the influence of different substrates, a series of Group 1–5 reactions with different steric hindrances in substrates were selected. As shown in Figure 3a, bromobenzene A1 reacting with five different anilines with increasingly large alkyl substitutions were introduced, and named B1–B5.

The calculation results in Figure 3b clearly show that for Pd-BrettPhos catalytic systems, all of the energy barriers of oxidative addition are higher than those of reductive elimination, while for Pd-RuPhos, the trend is just the opposite (detailed data are shown in Figure S2a–e). It is meaningful to recall that Buchwald et al.20 carried out kinetic studies of Buchwald–Hartwig amination of 3-bromoanisole and diphenylamine catalyzed by several kinds of ligand catalysts. It was found that the rate law of Pd-RuPhos catalytic system is consistent with the conclusion drawn from our computational results that reductive elimination is the rate-limiting step, while the rate law of Pd-BrettPhos catalytic system is different from that of Pd-RuPhos.

Figure 4. (a) Differences in steric hindrance between Pd-BrettPhos and Pd-RuPhos. (b) Differences in the electronic structures between Pd-BrettPhos and Pd-RuPhos.

Figure 5. (a) Energy barriers of reductive elimination. (b) Length and Wiberg bond index (WBI) of Pd-Br bonds of intermediates G1-Ru-5–G5-Ru-5. C–H bonds are hidden.
Comparing the differences in steric hindrance between the two ligand catalysts (Figure 4a), it can be seen that for Pd-BrettPhos, due to the presence of two methoxy groups in the “upper” benzene ring and isopropyl at the fourth position of the “lower” benzene ring, the hindrance around palladium atom is large, so the substrate tends to leave and the energy barrier of oxidative addition is higher than that of reductive elimination; but for Pd-RuPhos, the hindrance around palladium atom is relatively small, so the substrate tends to approach each other and the energy barrier of the reductive elimination is relatively higher.

In addition, from the viewpoint of the electronic structure (Figure 4b), we found that Pd-BrettPhos is an electron-rich system compared with Pd-RuPhos. Combining the previous conclusions, we can infer that the electron-rich Pd⁰ ligand catalyst tends to be more conducive to the elimination of substrates, while the relatively electron-deficient one tends to be more feasible for the addition of substrates. It was also demonstrated in experiments that an electron-rich lower aryl ring would lower the rate of reductive elimination.

3.5. Substituent Effects. It would be shown that amines with substituents of large steric hindrance would reduce the energy barriers of reductive elimination. From Group 1–5 reactions, it can be seen from Figure 5a that as the steric hindrance of amine increases, the energy barrier of reductive elimination gradually decreases. It is beneficial for the Pd-RuPhos catalytic system, of which the rate-limiting step is reductive elimination. As for Pd-BrettPhos, the energy barrier of oxidative addition is almost unchanged and lower than that of reductive elimination, so the rate-limiting step of Pd-BrettPhos catalytic system is still unchanged. As for primary amines or secondary amines with small steric hindrance, BrettPhos is more suitable than RuPhos (Figure 3b). Our following work will show that only when the steric hindrance...
of amine is large enough will RuPhos be more suitable than BrettPhos.

It has been previously mentioned that reductive elimination involves two steps: debromination and C−N bond formation. As the steric hindrance of the amine increases, the major contribution of the reduced energy barrier to reductive elimination is derived from debromination (Figure 5a). We compared the configurations of intermediates G1-Ru-5−G2-Ru-5 in the five groups, and it can be seen that the Pd-Br bond length gradually increases (Figure 5b), while the Wiberg bond index of Pd-Br bond gradually decreases. So Pd-Br bond is more likely to cleave if the amine has large steric groups, leading to a decrease in the energy barrier of the rate-limiting step of the entire Pd-RuPhos catalytic system.

In addition, halides with electron-withdrawing groups would reduce the energy barriers. Here, we designed Group 6 (G6) and Group 7 (G7) reactions (Figure 6a), which includes methoxy-substituted A1 and nitro-substituted A2, representative of electron-donating groups and electron-withdrawing groups, respectively. As shown in Figure 6b, compared with Group 1, the energy barriers of oxidative addition and reductive elimination of Group 6 are both increased, while those of Group 7 are decreased (detailed data are shown in Figure S2f and S2g). Therefore, halides with electron-withdrawing groups are advantageous for both Pd-BrettPhos and Pd-RuPhos catalytic systems. This conclusion has been demonstrated by relevant kinetic studies in experiments.36,37

The main contribution of the increase or decrease of the energy barrier of oxidative addition comes from ligand exchange (Figure 6b). Herein, we calculated the Wiberg bond index of the Pd−C bond of intermediates G1-Brett-2, G1-Ru-2, and G2-Brett-2 from Groups 1, 6, and 7 reactions, respectively. Results in Figure 6c indicate that the Pd−C bond of G1-Brett-2 is stronger than the other two.

Similarly, the main contribution of the increase or decrease of the energy barrier of reductive elimination comes from C−N bond formation (Figure 6b). Focusing on the final step of the reaction path, in which the products detach from Pd-RuPhos, we calculated the frontier orbital energy of Pd-RuPhos and products C1, C2, and C3 as shown in Figure 6d. It is interesting that products with lower highest occupied molecular orbital (HOMO) energies tend to have lower C−N bond formation energy barriers.

To further survey the differences in catalytic activity between BrettPhos and RuPhos, we carried out DFT calculations on the reaction of p-methoxybromobenzene with aniline and morpholine, which was reported by Buchwald et al.17 From their work, we knew that in the reaction of p-methoxybromobenzene and aniline (Group 6), BrettPhos has higher catalytic activity and enables the reaction in 10 min, while in the reaction of p-methoxybromobenzene and morpholine (Group 8), RuPhos has the higher catalytic activity and enables the reaction in 3 min (Figure 7a). We focused on the rate-limiting steps of reactions and compared the energy barriers of the two ligands. The calculation results of these two reactions are also shown in Figure 7b. For Group 6, Pd-BrettPhos catalytic system has a lower energy barrier, while for Group 8, Pd-RuPhos catalytic system has a lower energy barrier (detailed data are shown in Figure S2f and h), which is consistent with the experimental results of gas chromatography (GC) yield. Compared with Group 6, morpholine selected in Group 8 is a secondary amine and has a large steric hindrance, resulting in a reduction in the energy barrier of reductive elimination.

4. CONCLUSIONS

We carried out systematic calculations to understand the difference in catalytic activity between BrettPhos and RuPhos. Due to differences in steric hindrance and electronic structures of the two ligand catalysts, the rate-limiting step of Pd-BrettPhos catalytic system is oxidative addition but that of Pd-RuPhos is reductive elimination. We also found that amines with substituents of large steric hindrance or halides with electron-withdrawing groups would reduce the energy barriers of reactions. Our results would provide useful information for the screening of catalysts of the Buchwald−Hartwig amination reaction and make it useful for a rational design of new types of ligands.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.0c01528. Details of DFT calculations of optimized structures of intermediates and transition states; potential energy surfaces; intrinsic reaction coordinate (IRC) analyses for the transition states; molecular dynamics simulations for
the intermediates $G_1$-Brett-1 and $G_2$-Brett-5; Cartesian coordinates and energies of all species (PDF)

## AUTHOR INFORMATION

**Corresponding Author**

Jing Ma — School of Chemistry and Chemical Engineering, Key Laboratory of Mesoscopic Chemistry of Ministry of Education, Institute of Theoretical and Computational Chemistry, Nanjing University, Nanjing 210093, People's Republic of China; orcid.org/0000-0001-5848-9775; Phone: +86-25-89681772; Email: majing@nju.edu.cn

**Authors**

Jiaqi Tian — School of Chemistry and Chemical Engineering, Key Laboratory of Mesoscopic Chemistry of Ministry of Education, Institute of Theoretical and Computational Chemistry, Nanjing University, Nanjing 210093, People’s Republic of China

Gaobo Wang — School of Chemistry and Chemical Engineering, Key Laboratory of Mesoscopic Chemistry of Ministry of Education, Institute of Theoretical and Computational Chemistry, Nanjing University, Nanjing 210093, People’s Republic of China

Zheng-Hang Qi — School of Chemistry and Chemical Engineering, Key Laboratory of Mesoscopic Chemistry of Ministry of Education, Institute of Theoretical and Computational Chemistry, Nanjing University, Nanjing 210093, People’s Republic of China

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.0c01528

**Notes**

The authors declare no competing financial interest.

## ACKNOWLEDGMENTS

This work was supported by the National Natural Science Foundation of China (grant nos. 21673111 and 21873045). We are grateful to the High Performance Computing Centre of Nanjing University for providing the IBM Blade cluster system.

## REFERENCES

(1) Ruiz-Castillo, P.; Buchwald, S. L. Applications of Palladium-Catalyzed C–N Cross-Coupling Reactions. Chem. Rev. 2016, 116, 12564–12649.

(2) Guram, A. S.; Rennels, R. A.; Buchwald, S. L. A Simple Catalytic Method for the Conversion of Aryl Bromides to Arylamines. Angew. Chem., Int. Ed. 1995, 34, 1348–1350.

(3) Louis, J.; Hartwig, J. F. Palladium-catalyzed synthesis of amines from aryl halides. Mechanistic studies lead to coupling in the absence of tin reagents. Tetrahedron Lett. 1995, 36, 3609–3612.

(4) Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. Expanding Pd-Catalyzed C–N Bond-Forming Processes: The First Amidation of Aryl Sulfonates, Aqueous Amination, and Complementarity with Cu-Catalyzed Reactions. J. Am. Chem. Soc. 2003, 125, 6653–6655.

(5) Walker, S. D.; Bader, T. E.; Martinelli, J. R.; Buchwald, S. L. A rationally designed universal catalyst for Suzuki-Miyaura coupling processes. Angew. Chem., Int. Ed. 2004, 43, 1871–1876.

(6) Charles, M. D.; Schultz, P.; Buchwald, S. L. Efficient Pd-Catalyzed Amidation of Hetaryl Halides. Org. Lett. 2005, 7, 3965–3968.

(7) Fors, B. P.; Watson, D. A.; Biscoe, M. R.; Buchwald, S. L. A Highly Active Catalyst for Pd-Catalyzed Amidation Reactions: Cross-Coupling Reactions Using Aryl Mesylates and the Highly Selective Monoarylation of Primary Amines Using Aryl Chlorides. J. Am. Chem. Soc. 2008, 130, 13552–13554.

(8) Kim, M.; Shin, T.; Lee, A.; Kim, H. Synergistic Ligand Effect between N-Heterocyclic Carbene (NHC) and Bicyclic Phosphoramide (Bphps) Ligands in Pd-Catalyzed Amination. Organometallics 2018, 37, 3253–3258.

(9) Huang, F.; Xu, C.; Lu, D.; Shen, D.; Li, T.; Liu, F. Pd-PEPPSI-IIPent™ Promoted Deactivated Amination of Aryl Chlorides with Amines under Aerobic Conditions. J. Org. Chem. 2018, 83, 9144–9155.

(10) Chartoire, A.; Claver, C.; Corpet, M.; Krinsky, J.; Mayen, J.; Nelson, D.; Nolan, S. P.; Peaïfiet, I.; Woodward, R.; Meadows, R. E. Recyclable NHC Catalyst for the Development of a Generalized Approach to Continuous Buchwald–Hartwig Reaction and Workup. Org. Process Res. Dev. 2016, 20, 551–557.

(11) Peixoto, D.; Locati, A.; Marques, C. S.; Goth, A.; Ramalho, J. P. P.; Burke, A. J. A Catalytic Route to Dibenzoazepines involving Buchwald-Hartwig Coupling: Reaction Scope and Mechanistic Consideration. RSC Adv. 2015, 5, 99990–99999.

(12) Sunesson, Y.; Lime, E.; Lill, S. O. N.; Meadows, R. E.; Norrby, P. Role of the Base in Buchwald–Hartwig Amination. J. Org. Chem. 2014, 79, 11961–11969.

(13) Barder, T. E.; Buchwald, S. L. Insights into Amine Binding to Biaryl Phosphine Palladium Oxidative Addition Complexes and Reductive Elimination from Biaryl Phosphine Aryl palladium Amido Complexes via Density Functional Theory. J. Am. Chem. Soc. 2007, 129, 12003–12100.

(14) Kim, S.; Pudasaini, B.; Baik, M. Mechanism of Palladium-Catalyzed C–N Coupling with 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) as a Base. ACS Catal. 2019, 9, 6851–6856.

(15) Scharf, L. T.; Rodstein, I.; Schmidt, M.; Scherpf, T.; Gessner, V. H. Unraveling the High Activity of Ylide-Functionalized Phosphines in Palladium-Catalyzed Amination Reactions: A Comparative Study with 1,3,3,7,7-Hexamethylphosphinooxirane (HMPO). J. Am. Chem. Soc. 2020, 10, 999–1009.

(16) Lan, X.; Li, Y.; Li, Y.; Shen, D.; Ke, Z.; Liu, F. Flexible Steric Bulky Bis(Imino)acenaphthene (BIAN)-Supported N-Heterocyclic Carbene Palladium Precatalysts: Catalytic Application in Buchwald–Hartwig Amination in Air. J. Org. Chem. 2017, 82, 2914–2925.

(17) Fors, B. P.; Davis, N. R.; Buchwald, S. L. An Efficient Process for Pd-Catalyzed C–N Cross-Coupling Reactions of Aryl Iodides: Insight Into Controlling Factors. J. Am. Chem. Soc. 2009, 131, 5766–5768.

(18) Maiti, D.; Fors, B. P.; Henderson, J. L.; Nakamura, Y.; Buchwald, S. L. Palladium-catalyzed coupling of functionalized primary and secondary amines with aryl and heteroaryl halides: two ligands suffice in most cases. Chem. Soc. Rev. 2011, 2, 57–68.

(19) Perez, F.; Minnati, A. Palladium-Catalyzed C/N-Cross Coupling Reactions of 3-Halo-2-aminopyridines. Org. Lett. 2011, 13, 1984–1987.

(20) Arrechea, P. L.; Buchwald, S. L. Biaryl Phosphine Based Pd(II) Amidocomplexes: The Effect of Ligand Structure on Reductive Elimination. J. Am. Chem. Soc. 2016, 138, 12486–12493.

(21) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; Li, X.; Caricato, M.; Marenich, A. V.; Bloino, J.; Janesko, B. G.; Gomperts, R.; Mennucci, B.; Hratchian, H. P.; Ortiz, J. V.; Izmaylov, A. F.; Sonnenberg, J. L.; Williams-Young, D.; Ding, F.; Lipparini, F.; Egidi, F.; Goings, J.; Peng, B.; Petrone, A.; Henderson, T.; Ranasinghe, D.; Zakrzewski, V. G.; Gao, J.; Rega, N.; Zheng, G.; Liang, W.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A.; Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E. N.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Morokuma, K.; Klene, M.; Adamo, C.; Cammi, R.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Farkas, O.; Foreman, J. B.; Fox, D. J. Gaussian 16, revision A02, Gaussian Inc.: Wallingford, CT, 2016.
(22) Vosko, S. H.; Wilk, L.; Nusair, M. Accurate spin-dependent electron liquid correlation energies for local spin density calculations: a critical analysis. *Can. J. Phys.* 1980, 58, 1200−1211.

(23) Lee, C.; Yang, W.; Parr, R. G. Development of the Colle-Salvetti correlation-energy formula into a functional of the electron density. *Phys. Rev. B: Condens. Matter Mater. Phys.* 1988, 37, 785−789.

(24) Becke, A. D. Density-functional thermochemistry. III. The role of exact exchange. *J. Chem. Phys.* 1993, 98, 5648−5652.

(25) Hay, P. J.; Wadt, W. R. Ab initio effective core potentials for molecular calculations. Potentials for K to Au including the outermost core orbitals. *J. Chem. Phys.* 1985, 82, 299−310.

(26) Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. Performance of SM6, SM8, and SMD on the SAMPL1 test set for the prediction of small-molecule solvation free energies. *J. Phys. Chem. B* 2009, 113, 4538−4543.

(27) Rassolov, V. A.; Pople, J. A.; Ratner, M. A.; Windus, T. L. 6-31G* basis set for atoms K through Zn. *J. Chem. Phys.* 1998, 109, 1223−1229.

(28) Hay, P. J.; Wadt, W. R. Ab initio effective core potentials for molecular calculations. Potentials for the transition metal atoms Sc to Hg. *J. Chem. Phys.* 1985, 82, 270−283.

(29) Reed, A. E.; Weinhold, F. Natural bond orbital analysis of near-Hartree−Fock water dimer. *J. Chem. Phys.* 1983, 78, 4066−4073.

(30) Foster, J. P.; Weinhold, F. Natural hybrid orbitals. *J. Am. Chem. Soc.* 1980, 102, 7211−7218.

(31) Legault, C. Y., CYLview, 1.0b; Universite’ de Sherbrooke: Sherbrooke, Quebec, Canada, 2009, [http://www.cylibview.org](http://www.cylibview.org).

(32) Lu, T.; Chen, F. Multiwfn: A multifunctional wavefunction analyzer. *J. Comput. Chem.* 2012, 33, 580−592.

(33) Hagler, A. T.; Huler, E.; Lifson, S. Energy functions for peptides and proteins. I. Derivation of a consistent force field including the hydrogen bond from amide crystals. *J. Am. Chem. Soc.* 1974, 96, 5319−5327.

(35) Tatsumi, K.; Hoffmann, R.; Yamamoto, A.; Stille, J. K. Reductive Elimination of d8-Organotransition Metal Complexes. *Bull. Chem. Soc. Jpn.* 1981, 54, 1857−1867.

(36) Mann, G.; Baranano, D.; Hartwig, J. F.; Rheingold, A. L.; Guzei, I. A. Carbon-Sulfur Bond-Forming Reductive Elimination Involving sp, sp2, and sp3-Hybridized Carbon. Mechanism, Steric Effects, and Electronic Effects on Sulfide Formation. *J. Am. Chem. Soc.* 1998, 120, 9205−9219.

(37) Hartwig, J. F. Electronic Effects on Reductive Elimination To Form Carbon−Carbon and Carbon−Heteroatom Bonds from Palladium(II) Complexes. *Inorg. Chem.* 2007, 46, 1936−1947.