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Mechanistic Study of Palladium-Catalyzed Oxidative C–H/C–H Coupling of Polyfluoroarenes with Simple Arenes

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Pd-catalyzed oxidative C–H/C–H coupling reaction is an emerging type of C–H activation reaction, which attracts great interests because both reaction partners do not require pre-functionalization. In the present study, we employed DFT methods to investigate the mechanism of Pd(OAc)₂-catalyzed oxidative C–H/C–H coupling of pentafluorobenzene with benzene. Four possible pathways were examined in the C–H activation part: path A benzene-pentafluorobenzene mechanism (C–H activation of benzene occurs before the C–H activation of pentafluorobenzene), path B pentafluorobenzene-benzene mechanism (C–H activation of benzene occurs after the C–H activation of pentafluorobenzene), path C benzene-pentafluorophenylsilver mechanism (C–H activation of benzene and subsequent transmetalation with pentafluorophenyl silver complex), path D pentafluorophenylsilver-benzene mechanism (transmetalation with pentafluorophenyl silver complex and subsequent C–H activation of benzene). Based on the calculations, the sequences of two C–H activation steps are found to be different in the oxidative couplings of same substrates (*i.e.* pentafluorobenzene and benzene) in different catalytic systems, where the additive Ag salts played a determinant role. In the absence of Ag salts, the energetically favored pathway is path B (*i.e.* the C–H activation of pentafluorobenzene takes place before the C–H cleavage of benzene). In contrast, with the aid of Ag salts, the coordination of pentafluorophenylsilver to Pd center could occur easily with a subsequent C–H activation of benzene in the second step, and the second step significantly raises the whole reaction barrier. Alternatively, in the presence of Ag salts, the kinetically preferred mechanism is path C (*i.e.* the C–H activation of benzene takes place in the first step followed by transmetalation with pentafluorophenylsilver complex), which is similar to path A. The calculations are consistent with the H/D exchange experiment and kinetic isotope effects. Thus the present study not only offers a deeper understanding of oxidative C–H/C–H coupling reaction, but also provides helpful insights to further development of more efficient and selective oxidative C–H/C–H coupling reactions.

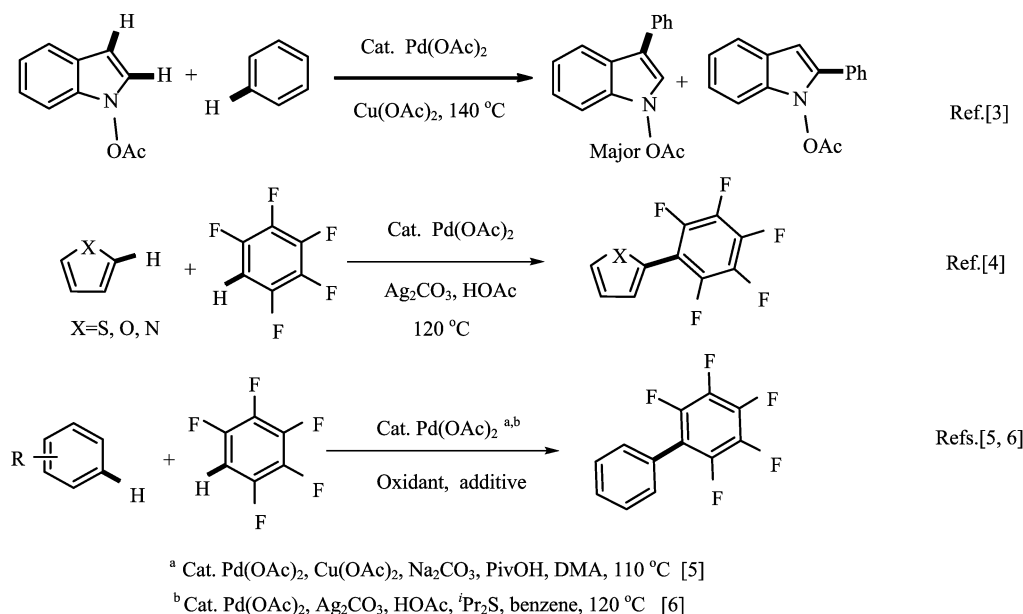
Key words: Pd catalysis, Oxidative coupling, C–H activation, Mechanism, Pentafluorobenzene

I. INTRODUCTION

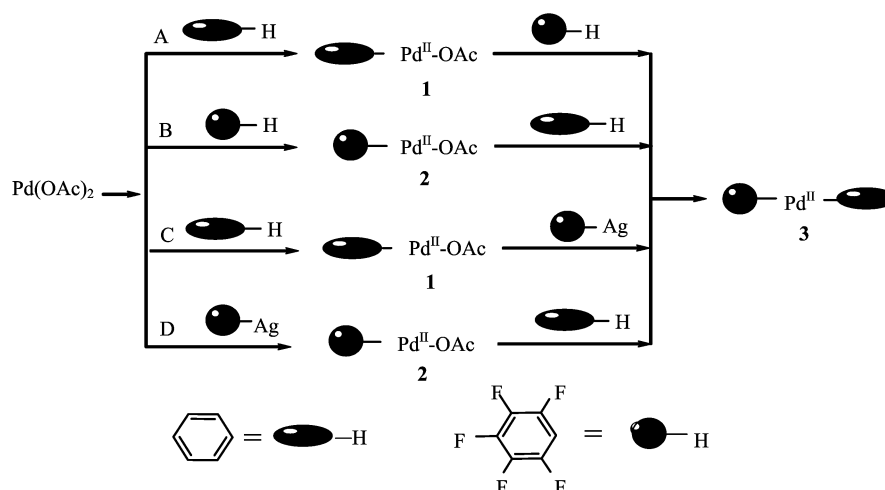
During the past decades, palladium mediated C–H activation reaction has attracted considerable interest because of its high atom economy [1]. Owing to the high regioselectivity and excellent functional group tolerance, such reactions have become one of the most powerful methods for direct C–C bond formation, which have been widely applied in natural products synthesis and material science [2]. The most common types of Pd-catalyzed C–H activation reactions are the coupling of C–H substrates with electrophiles R–X (X=halides, OTf, *etc.*) or nucleophiles R–M (M=metal, B, Si, *etc.*).

Another important type of C–H activation reaction is the coupling between two C–H substrates (called oxidative C–H/C–H coupling). This new type of C–H activation reaction has drawn great attention because both the reaction partners do not require prefunctionalization. Nonetheless, the main challenge of oxidative C–H/C–H coupling reactions is the selectivity control (homocoupling versus heterocoupling). An available solution to this problem is to use substrates with different inherent electronic bias. As elegant examples of this strategy, Fagnou *et al.* in 2007 described that the Pd(OAc)₂ together with Cu(OAc)₂ catalyzed oxidative coupling of electron-rich heterocycles (*i.e.* indole) and benzene affording heterocoupling product in high yield and regioselectivity [3]. Zhang *et al.* in 2010 demonstrated the efficient coupling of electron-rich heterocycles and electron-deficient aromatics in the presence of

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Scheme 1 Examples for Pd-catalyzed C–H/C–H oxidative cross-coupling reactions.



Scheme 2 Different sequences of the two C–H activation steps.

Pd(OAc)₂ catalyst and Ag₂CO₃ [4]. Moreover, Su *et al.* [5] and Shi *et al.* [6] independently reported the Pd-catalyzed selective coupling of simple aromatics (*i.e.* substituted benzene) with electron-deficient aromatics (*e.g.* polyfluorobenzene) (see Scheme 1).

Although the selective cross-coupling could be achieved successfully by using substrates with distinct electronic properties, the sequence of two C–H activation steps on different substrates in the catalytic cycle remains unclear. Take the reaction between pentafluorobenzene and benzene as an example, there are four possible pathways to obtain the Pd^{II}(Ph)(C₆F₅) complex **3** (Scheme 2), from which the heterocoupling products can be finally formed through reductive elimina-

tion. In pathway A, the cleavage of C–H bond of benzene takes place in the first step. This step produces Pd^{II}-Ph intermediate **1**, which then ruptures the C–H bond of pentafluorobenzene. Pathway B is opposite to pathway A. Pentafluorobenzene (instead of benzene) is first transformed into intermediate **2** with the help of Pd(OAc)₂. Different from pathways A and B, pentafluorobenzene was not directly involved in the C–H activation step in pathways C and D. As shown in Scheme 2, the deprotonation of pentafluorobenzene could occur, resulting in organo-silver complex (Ag-C₆F₅) in the presence of Ag₂CO₃ in pathways C and D. As to pathway C, after the Pd(OAc)₂ mediated C–H bond (of benzene) breaking, the Pd^{II}-Ph intermediate **1** could re-

act with organo-silver complex $\text{Ag-C}_6\text{F}_5$ through transmetalation to generate complex **3**. In pathway D, the transmetalation initially takes place between $\text{Ag-C}_6\text{F}_5$ and $\text{Pd}(\text{OAc})_2$ and then the C–H of benzene is broken by intermediate **2**. Su *et al.* suggested that the breaking of C–H bond of benzene would take place in the first step (*i.e.* pathway A) due to the stronger interaction between the relative electron-rich benzene and Pd catalyst compared with the electron-poor pentafluorobenzene [5]. In contrast, Shi *et al.* suggested that pathway D could be plausible based on the deuterated pentafluorobenzene formation via the H/D exchange experiment between pentafluorobenzene and CD_3OD in the presence of Ag_2CO_3 [6]. However, the H/D exchange experiment was carried out in the absence of $\text{Pd}(\text{OAc})_2$. Therefore, Shi's observations could not rule out the other possible pathways involving $\text{Pd}(\text{OAc})_2$.

In the present study, we used computational methods to investigate the mechanism of $\text{Pd}(\text{OAc})_2$ -catalyzed oxidative C–H/C–H coupling of pentafluorobenzene with benzene. All the mechanistic possibilities shown in Scheme 2 were carefully examined. Based on the calculations, we found the sequence of the C–H activation steps on pentafluorobenzene and benzene in the catalytic cycle is different depending on the additive Ag salts. In the absence of Ag salts, the energetically favored pathway is path B (*i.e.* the C–H activation of pentafluorobenzene takes place before the C–H cleavage of benzene), because the second step determines the reaction barrier and the coordination between the benzene and Pd center in the second step of path B requires less energy than that of path A. In contrast, with the help of Ag salts, the coordination in the second step between pentafluorophenylsilver ($\text{Ag-C}_6\text{F}_5$) and Pd center could easily occur after the C–H activation of benzene. Therefore, in the presence of Ag salts, the kinetically preferred mechanism is path C (*i.e.* the C–H activation of benzene takes place in the first step followed by transmetalation with pentafluorophenylsilver complex). The calculation is consistent with the experimental kinetic isotope effects. The results obtained in the present study not only offer a more detailed understanding on the effect of additives (*e.g.* silver salts) in the oxidative C–H/C–H coupling mechanism, but also provide helpful insights to further development of more efficient and selective oxidative C–H/C–H coupling reactions.

II. COMPUTATIONAL METHODOLOGY

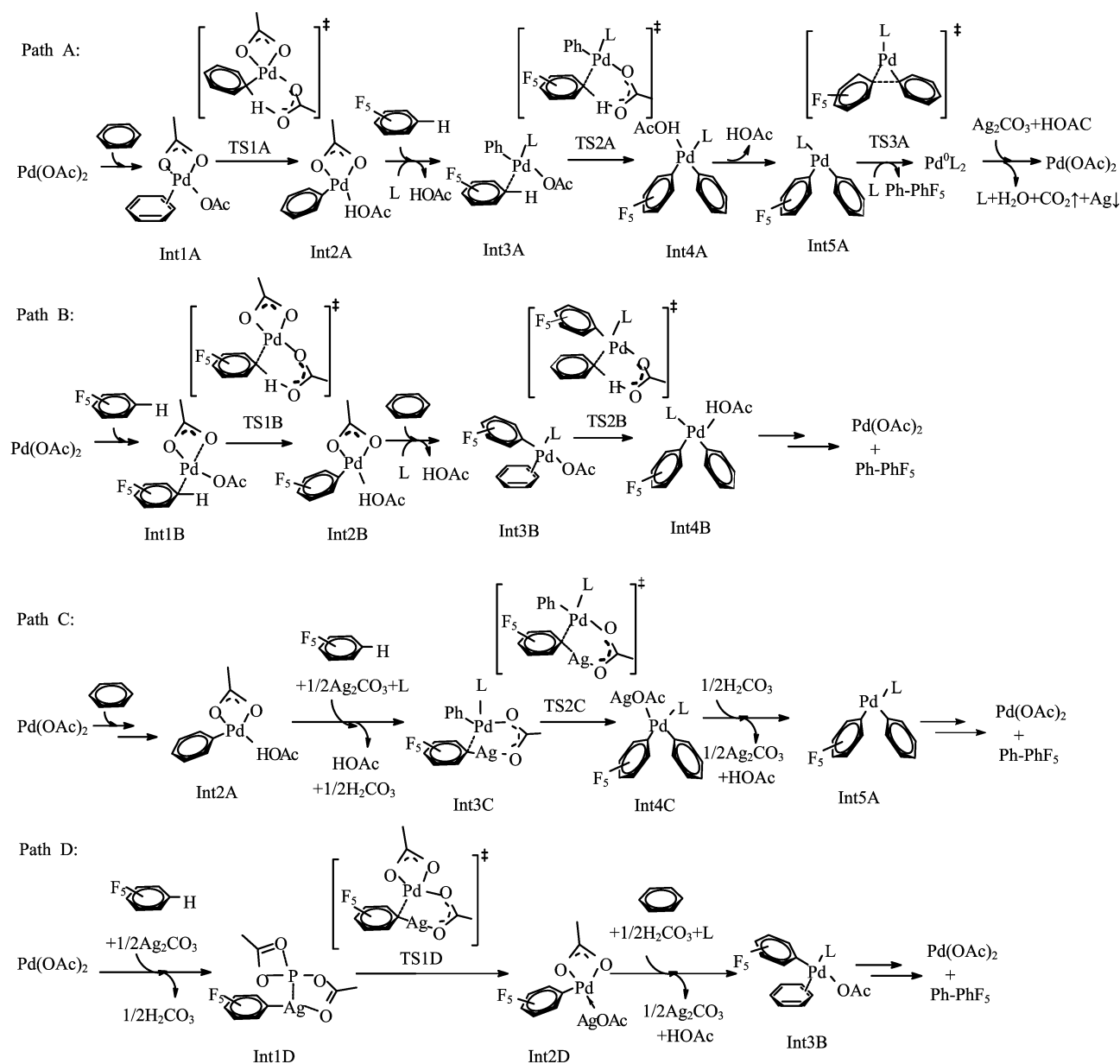
Geometry optimization of all compounds in gas-phase was optimized without any constraint by the density functional theory method (B3LYP) [7] with a combined basis set, *i.e.*, LANL2DZ [8] for Pd, I atoms and 6-31+G(d) for the rest atoms. Frequency calculation was performed at the same level of theory with geometry optimization, to confirm the stationary points to be minima or saddle points. For saddle points, intrinsic re-

action coordinate analysis (IRC) [9] was carried out to verify that they connect the right reactant and product on the potential energy surface. Single-point energy calculation was performed by using B3LYP method with a more flexible basis set, *i.e.*, SDD [10] for Pd, Ag, and 6-311+G(d,p) for the rest elements. The solvent effect was calculated with self-consistent reaction field (SCRF) method using CPCM model and UAHF radii [11]. Benzene ($\epsilon=2.247$) in Shi's experiments [6] were used as the solvent in the calculations. Acetonitrile ($\epsilon=36.64$) was used as solvent in calculations to replace the experimentally used N,N-dimethylacetamide (DMA, $\epsilon=37.781$) [12], because the solvation parameters for N,N-dimethylacetamide are not available in Gaussian 03 suite of program, with which all the calculations were performed [13]. Single-point energy corrected by the Gibbs free energy correction from frequency calculation was added to the solvation free energy to describe the reaction energetics throughout the study. Note that the reference state of calculated free energies in gas phase is 1 atm. However, the calculated solvation free energies use a reference state of 1 mol/L. To convert the reference state, the equation ($G_{\text{gas}}=G_{\text{gas}}+RT\ln(\Delta V)$) is used [14]. The correction term is 1.90 kcal/mol when $\Delta V=24.46$ L at 298 K.

III. RESULTS AND DISCUSSION

A. Possible mechanisms

Su group and Shi group independently reported the oxidative C–H/C–H coupling of pentafluorobenzene with benzene. The mechanism of the oxidative C–H/C–H coupling of pentafluorobenzene with benzene can be divided into two main parts: C–H activations of substrates and reductive elimination. In the case of C–H activation part, four possible pathways would be examined: path A, C–H activation of benzene and then pentafluorobenzene; path B, C–H activation of pentafluorobenzene and then benzene; path C, C–H activation of benzene and subsequent transmetalation with the pentafluorophenylsilver complex; path D, transmetalation with pentafluorophenyl silver complex and subsequent C–H activation of benzene (Scheme 2 and 3). According to previous studies on Pd-catalyzed C–H activation reactions [15], concerted metalation-deprotonation (CMD) [16] would be taken into account in the C–H activation step. Note that, according to Shi's experiments, the additive Ag salt might directly participate in the cleavage of C–H bonds. Therefore, four possible mechanisms mentioned above are all examined for Shi's catalytic system. Differently, Ag salt was not employed in Su's reactions. As a result, only two routes (*i.e.* path A and B) could be considered with respect to Su's reactions.



Scheme 3 Detailed reaction processes for path A, B, C, and D.

B. Path A and B under Su's conditions

1. Path A

In the case of path A, Pd(OAc)₂ catalyst is first coordinated with the double bond of benzene to give η^2 - π complex Int1A (Fig.1). Int1A then undergoes concerted metalation-deprotonation via the six-membered-ring transition state TS1A to generate the HOAc coordinated phenylpalladium intermediate Int2A. The free energy barrier for C–H activation of benzene is +11.3 kcal/mol (from Int1A to TS1A). After ligand exchange, pentafluorobenzene is bound to Pd moiety in an η^2 -fashion, resulting in the intermediate Int3A. In

Int3A, an agostic interaction is found between the C–H bond and Pd center (the bond lengths of Pd–C and Pd–H are 2.32 Å and 2.51 Å shown in Fig.2). Subsequently, C–H activation of pentafluorobenzene could easily occur through the CMD transition state TS2A with a small free energy barrier of +1.8 kcal/mol (from Int3A to TS2A). The barrier for C–H activation of pentafluorobenzene is much lower than that of benzene, which was also demonstrated by Fagnou group [17]. This step produces Pd(Ph)(C₆F₅) intermediate Int4A, HOAc and the ligand (*i.e.* DMA, the solvent molecular). After removal of the HOAc ligand, Int5A could proceed through reductive elimination via a typical triangular transition state TS3A to form the heterocou-

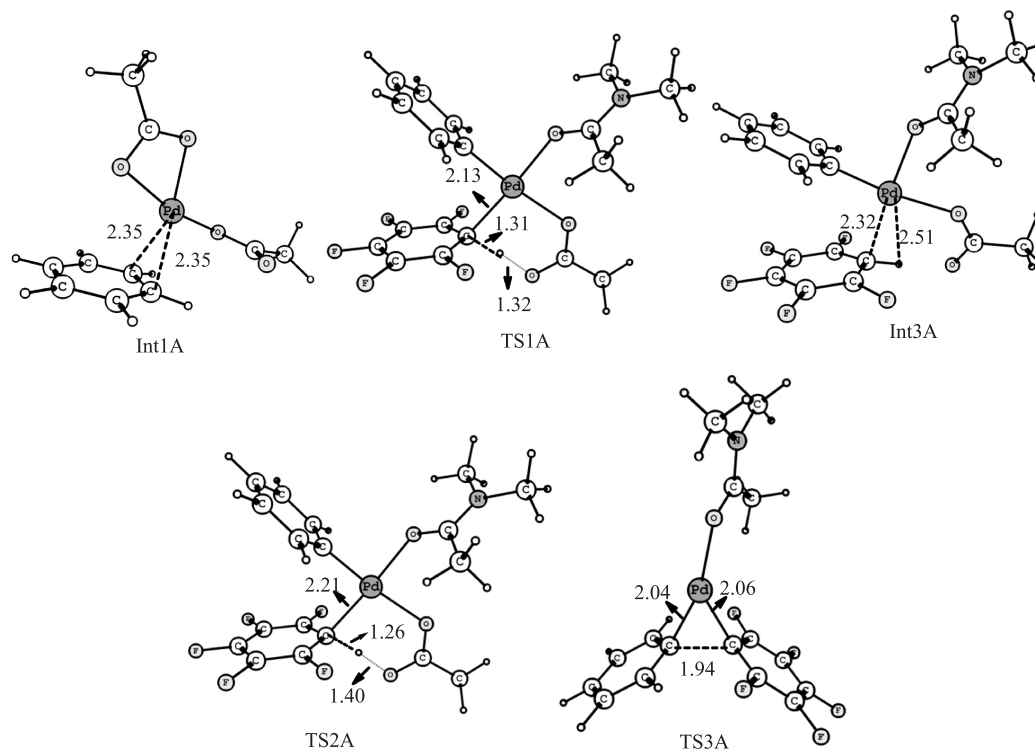


FIG. 1 Key intermediates and transition states in path A under Su's conditions. All bond lengths are in Å.

pling product 2,3,4,5,6-pentafluorobiphenyl. The whole free energy barrier is +37.6 kcal/mol (from $\text{Pd}(\text{OAc})_2$ to TS2A) and the rate-limiting step is the CMD C–H process of pentafluorobenzene.

2. Path B

Different from path A, pentafluorobenzene is initially coordinated with the catalyst $\text{Pd}(\text{OAc})_2$ (Fig.2). The CMD C–H activation process then takes place to generate arylpalladium intermediate Int2B with a very low barrier of +0.2 kcal/mol (from Int1B to TS1B). The coordination process is endergonic (+23.8 kcal/mol, from $\text{Pd}(\text{OAc})_2$ to Int1B), which is much higher than that in path A (+13.7 kcal/mol, from $\text{Pd}(\text{OAc})_2$ to Int1A). The result agrees with Su's speculation that the interaction between the electron-poor pentafluorobenzene and Pd is weaker than that between benzene and Pd. Starting from Int2B, the second substrate benzene coordinates with the Pd center, followed by C–H activation and subsequent reductive elimination to obtain the heterocoupling product (Fig.3). The whole free energy barrier is +33.0 kcal/mol (from $\text{Pd}(\text{OAc})_2$ to TS2B) and the rate-limiting step is the CMD process of benzene.

Comparing path A with B, the whole free energy barrier of path B is +33.0 kcal/mol, which is lower than that of path A (+37.6 kcal/mol). It means that path B is kinetically more favored than path A. Moreover, our calculation indicates that the C–H activation of ben-

zene is the rate-determining step for path B and the Kinetic isotope effect (KIE) values were calculated to be 3.6 and 3.5 for benzene and 1,2-dichlorobenzene, respectively (Supplementary material). This is consistent with Su's intermolecular kinetic isotope effect experiments. In their experiments, primary KIEs were observed for benzene (KIE=6.5) and 1,2-dichlorobenzene (KIE=4.8). Based on the above results, path B (*i.e.* C–H activations of pentafluorobenzene and then benzene) is concluded to be favored under Su's conditions. This conclusion is different from Su's speculation. The interaction between the relative electron-rich benzene and Pd catalyst is indeed stronger than that of the electron-poor pentafluorobenzene, which is consistent with Su's proposal. However, the second C–H activation step limits the whole reaction barrier instead of the first C–H activation. Therefore, path B involving C–H activation of benzene as the second step is the favored mechanism.

C. Path A, B, C, and D under Shi's conditions

Shi *et al.* also investigated the mechanism of oxidative C–H/C–H coupling between pentafluorobenzene and benzene in presence of Ag_2CO_3 . They found that deuterated pentafluorobenzene was formed via the H/D exchange experiment between pentafluorobenzene and CD_3OD in the presence of Ag_2CO_3 (without $\text{Pd}(\text{OAc})_2$). It is suggested that the deprotonation of

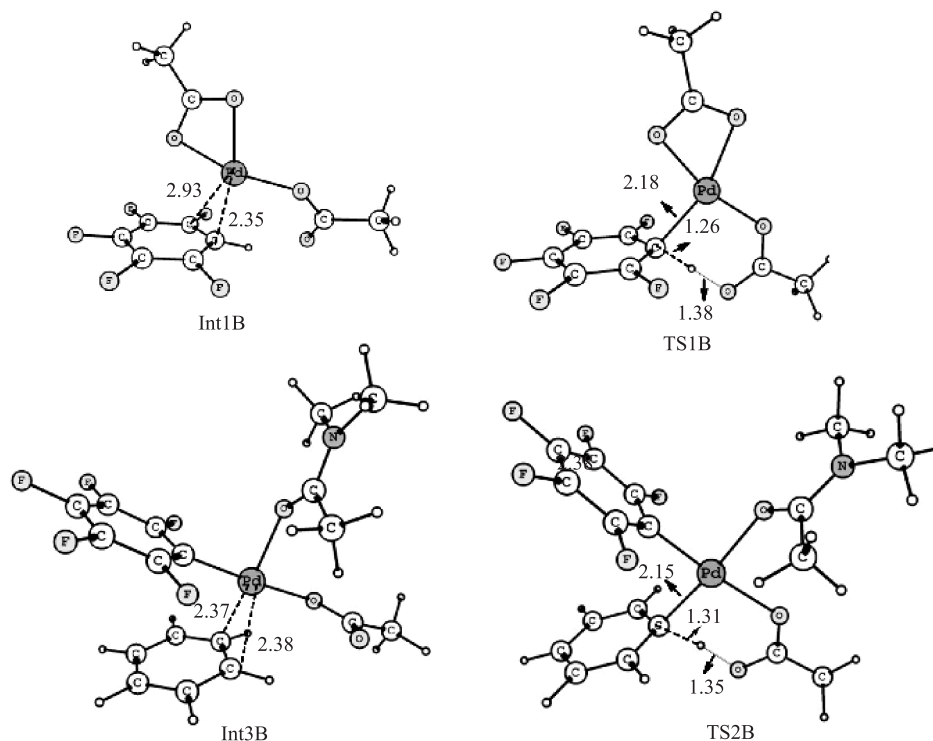


FIG. 2 Key intermediates and transition states in path B under Su's conditions.

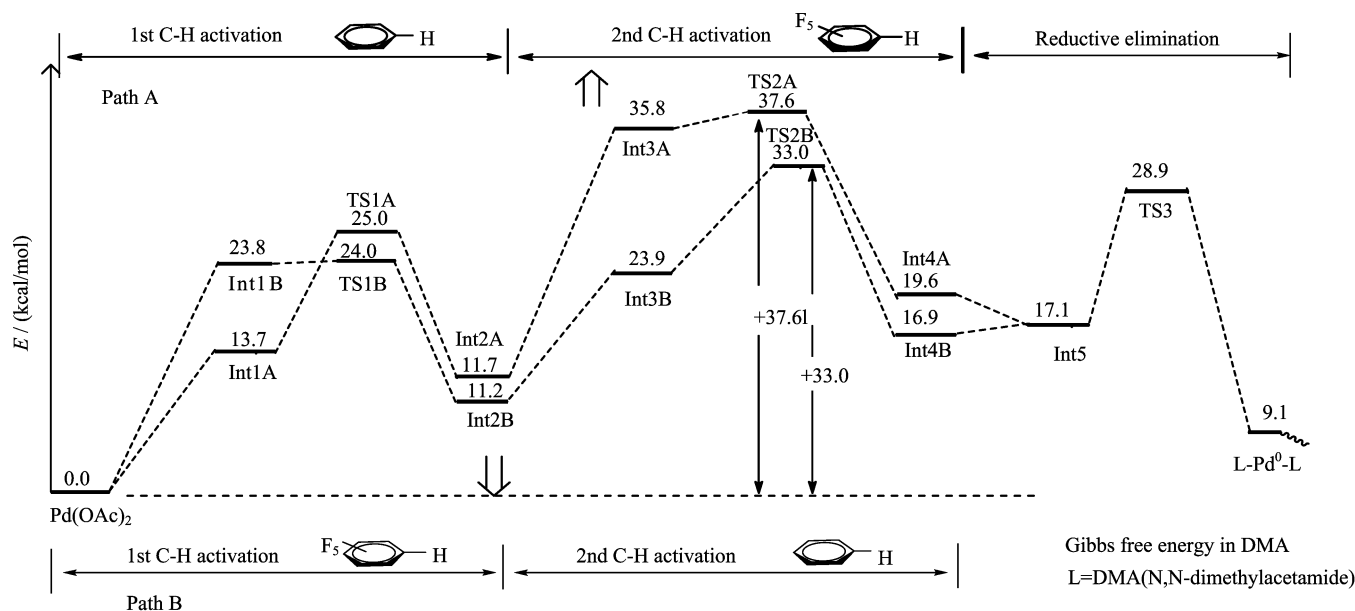


FIG. 3 Energy profiles for path A and B under Su's conditions.

acidic pentafluorobenzene could easily take place with the aid of Ag salts. We calculated the Ag-assisted deprotonation of pentafluorobenzene. The formation of pentafluorophenylsilver complex is calculated to be slightly endergonic by 6.3 kcal/mol from pentafluorobenzene. It means that pentafluorophenylsilver complex might be formed in this reaction system. Based

on this result, path A, B, C, and D were proposed in the oxidative C–H/C–H coupling reactions (Scheme 2 and 3). Details of path A and B are as the same as that involved in Su's reactions and the energy profiles are shown in Fig.4.

In the following, we mainly focus on the discussion of path C and D (Fig.4 and Fig.5).

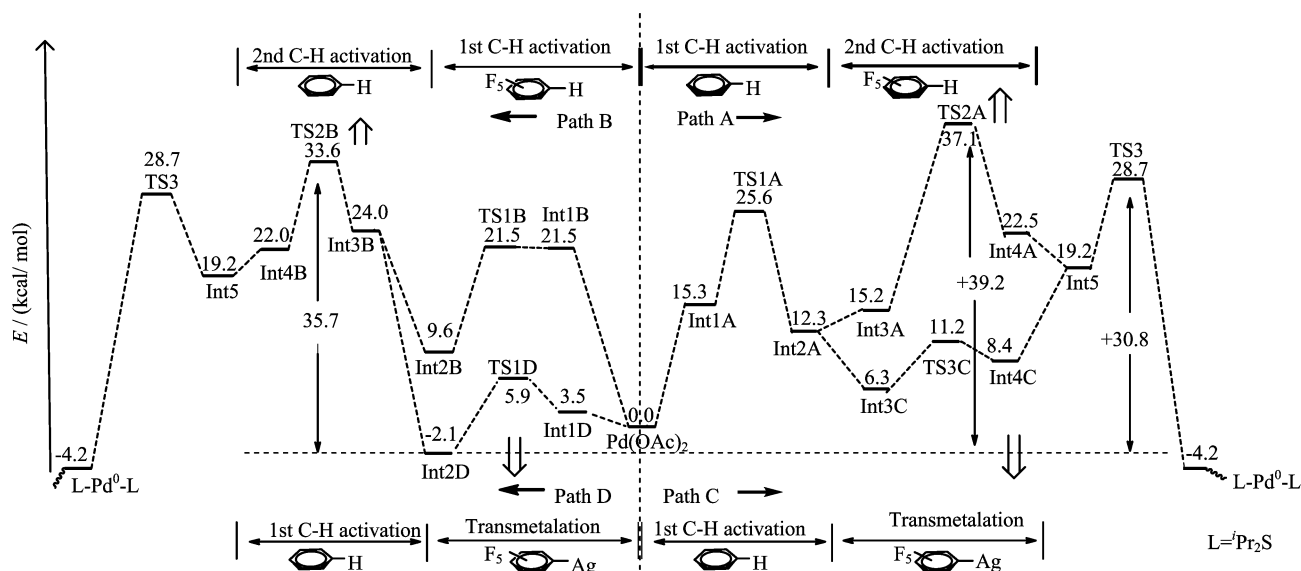


FIG. 4 Energy profiles for Path A, B, C and D in the presence of Ag_2CO_3 under Shi's conditions. Note that the solvent and ligand is different from that in Su's reactions in Fig.3.

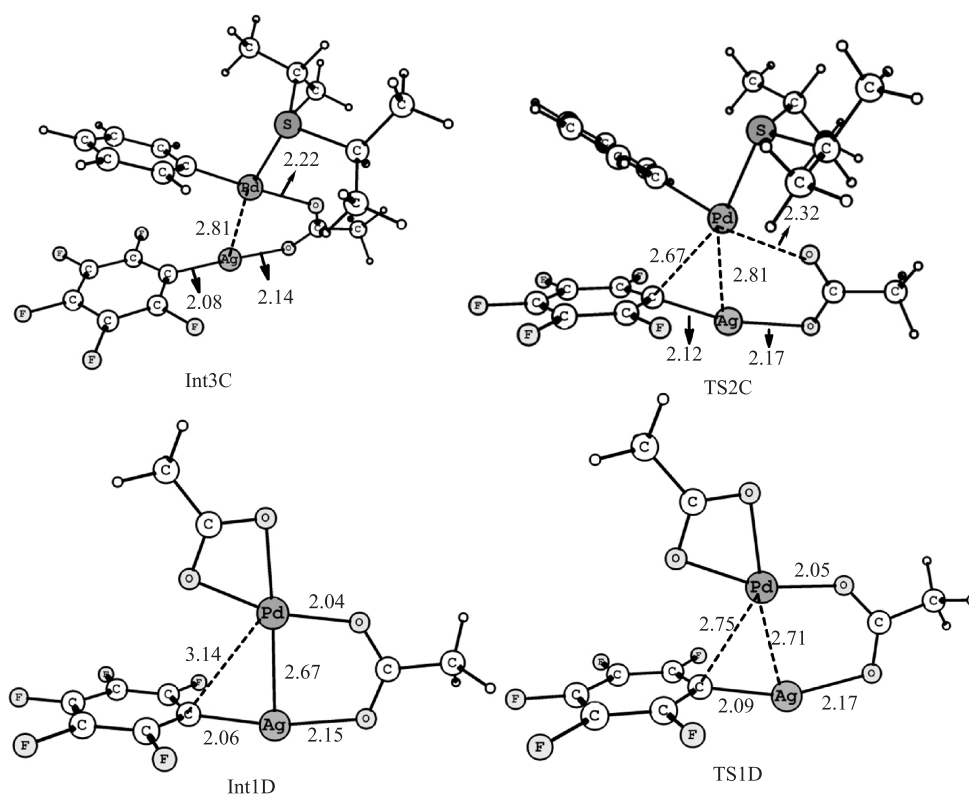


FIG. 5 Key intermediates and transition states in path C and D in the presence of Ag salts under Shi's conditions. The bond length is in Å.

(I) Path C. In this pathway, the first step is C–H activation of benzene, followed by transmetalation with pentafluorophenylsilver complex. The C–H activation process of benzene is the same as that in path A. Starting from phenylpalladium intermediate Int2A, pentaflu-

orophenylsilver complex easily coordinates with the Pd center of Int2A to produce a more stable intermediate Int3C. Subsequently, Int3C could readily proceed through a six-centered transmetalation transition state TS3C with a free energy barrier of +4.9 kcal/mol (from

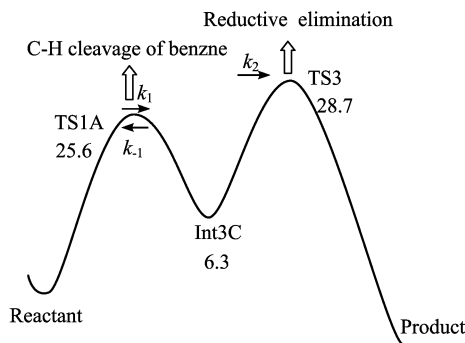


FIG. 6 Simple energy profile for path C.

Int3C to TS3C). This process generates Pd(Ph)(C₆F₅) intermediate Int4C, which could undergo reductive elimination to furnish the heterocoupling process.

(II) Path D. Different from path C, the coordination and subsequent transmetalation between Pd(OAc)₂ and pentafluorophenylsilver complex takes place as the first step. In detail, Pd(OAc)₂ could be coordinated with the Ag atom of pentafluorophenylsilver complex to give Int1D, which could facily undergo transmetalation via six-membered-ring transition state TS1D to generate a stable (C₆F₅)Pd intermediate Int2D. The following step (*i.e.* C–H activation of benzene by (C₆F₅)Pd intermediate) is the same as that in path B.

Note that Int2D is the most stable intermediate in this system and the transmetalation involving Int2D is a reversible transformation (Fig.4). As a result, the free energy barriers for path A, B, C and D are +39.2 (from Int2D to TS2A), +35.7 (from Int2D to TS2B), +30.8 (from Int2D to TS3), +35.7 (from Int2D to TS2B) kcal/mol, respectively. Path C is the kinetically favored pathway with the lowest barrier of +30.8 kcal/mol. Reductive elimination is the rate-determining step. Interestingly, although the C–H cleavage of benzene is not the rate-limiting step in the path C, the intermolecular kinetic isotope effect was observed in Shi's reaction. This is a special example described in Hartwig's report [18]: the simplified energy profile of path C and related parameters are shown in Fig.6. In this scenario, the breaking of C–H bond of benzene is reversible and takes place before the rate-determining step. Moreover, the reversible C–H activation process and the rate-determining step have similar rates. For such reaction, the following equation Eq.(1) could be obtained by considering the rate law. It reveals that the KIE value is connected with C–H cleavage of benzene in Shi's reaction, although the breaking of C–H bond is not the rate-determining step. According to the Arrhenius equation Eq.(2), our modeling reaction shows primary kinetic isotope effect (KIE=3.6), which is consistent with the experimental observed primary KIE

(KIE=6.81).

$$\frac{d[P]}{dt} = k_2[\text{Int3C}] = \frac{k_1 k_2 [R]}{k_{-1} + k_2} \quad (1)$$

$$k = A \exp\left(-\frac{\Delta G^\ddagger}{RT}\right) \quad (2)$$

Consequently, path C (*i.e.* C–H activation of benzene and subsequent transmetalation with pentafluorophenyl silver complex) is the kinetically favored pathway in the presence of Ag under Shi's conditions. The calculation is also consistent with the intermolecular kinetic isotope effect experiments.

IV. CONCLUSION

Pd-catalyzed oxidative C–H/C–H coupling reactions is a new type of C–H activation reaction, which draws great attention because both of the partners do not require prefunctionalization. In the present study, we investigated the mechanism of Pd(OAc)₂-catalyzed oxidative C–H/C–H coupling of pentafluorobenzene with benzene with the aid of DFT methods. Four possible mechanisms were carefully examined. Based on the calculations, we found sequences of the two C–H activation steps with the same substrates (pentafluorobenzene and benzene) are different, depending on the presence or absence of the additive Ag salts. In the absence of Ag salts, the energetically favored pathway is path B (*i.e.* the C–H activation of pentafluorobenzene takes place in the first step followed by C–H cleavage of benzene). The reason is that the second step strongly influences the reaction barrier and the energetic requirement of the coordination between the benzene and Pd on the second step in path B is lower than that in path A. On the contrary, with the help of Ag salts, the coordination between pentafluorophenylsilver complex and Pd center could easily occur following the C–H activation of benzene in the second step. Therefore, in the presence of Ag salts, the kinetically preferred mechanism is path C (*i.e.* the C–H activation of benzene takes place in the first step followed by transmetalation with pentafluorophenylsilver complex), which is similar to path A. The calculations are consistent with the H/D exchange experiment and kinetic isotope effects. These results can offer a more comprehensive understanding of oxidative C–H/C–H coupling reaction, and provide helpful insights to further development of more efficient and selective oxidative C–H/C–H coupling reactions.

V. ACKNOWLEDGMENTS

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carried out at the supercomputer center of Shanghai and University of Science and Technology of China.

Supplementary material: Cartesian coordinates of optimized structures and detailed thermodynamic data are shown.

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