

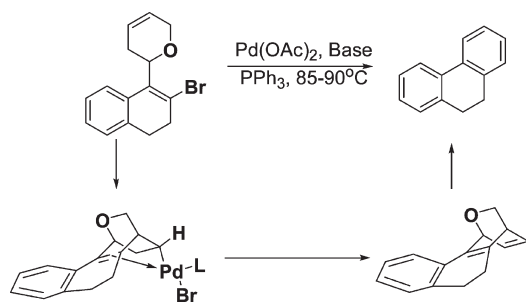
A Theoretical Investigation on the Mechanism of a Palladium-Mediated Formal 6π Electrocyclic Synthesis of 9,10-Dihydrophenanthrenes

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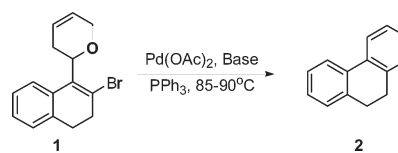
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Recently, a new method for the palladium-catalyzed synthesis of 9,10-dihydrophenanthrenes was published. A proposed mechanism indicated that the reaction proceeds via a disrotatory 6π electrocyclic ring closing reaction. Although the synthetic methodology is excellent for the preparation of 9,10-phenanthrenes, we propose an alternative mechanism that occurs through an intramolecular Heck reaction. Using theoretical calculations, we have investigated both mechanisms and find that the intramolecular Heck mechanism is lower in energy by 21.3 kcal/mol than the electrocyclic pathway.

The synthesis of polycyclic aromatic hydrocarbons is an attractive topic in both methodology and synthetic chemistry because it includes the formation of new C–C bonds.¹ Palladium is a powerful tool in the generation of a C–C bond, thus, palladium is widely used in the synthesis of 9,

SCHEME 1. The Reported Palladium-Catalyzed Intramolecular Cyclization⁴



10-dihydrophenanthrenes.² However, in most previous reports, palladium catalysts are used to generate the middle non-aromatic ring by C–H bond activation.³ Recently, a new synthesis for 9,10-dihydrophenanthrene by building one of the outer aromatic rings was reported (Scheme 1).⁴

In the reported synthesis,⁴ **1** was treated with Pd(OAc)₂ (10 mol %), base (2 equiv), PPh₃ (0.5 equiv), and *n*-Bu₄NCl (1 equiv) in DMF solvent, followed by heating at 85–90 °C for 1.5–2 h. The product 9,10-dihydrophenanthrene (**2**) was obtained in 70% yield. The methodology was extended to nine additional derivatives in yields of 58–80%, demonstrating broad applicability. A mechanism was proposed involving a 6π electrocyclic ring closing reaction of a putative 9-membered palladacycle (Scheme 2, pathway A). In the proposed mechanism, Pd(0) is initially oxidized by **1**, generating Pd(II) intermediate **3**. The base promotes an E2-type elimination reaction via transition state **4-ts**, which forms the nine-membered cyclic Pd–O complex **5**. The authors then proposed a disrotatory 6π electrocyclic ring closing reaction to form intermediate **6**. The product 9,10-dihydrophenanthrene is generated after the extrusion of a molecule of formaldehyde.

However, there are a few aspects in question in this mechanism: (1) E2-type elimination reactions require anti-coplanar geometry and a good leaving group, which was not specified in the mechanism; (2) we suspect that formation of intermediate **5** will be disfavored because a strong C–H bond and C–O bond are broken resulting in mild compensation of a weak Pd–O coordination and protonation of the base (in addition, the nine-membered ring should be entropically disfavored); (3) a disrotatory electrocyclic ring closure of a nine-membered ring to a six-membered ring is rare and unusual; and (4) after the E2 elimination, a trans C=C bond is generated, and it is likely difficult to isomerize to cis.

We have carried out a theoretical study on the proposed mechanism. We find that it is less likely than an alternative mechanism that involves an intramolecular Heck reaction⁵ followed by aromatization through formaldehyde elimination (Scheme 2, pathway B). In our alternative mechanism, after the oxidative addition of Pd(0), intermediate **7** is

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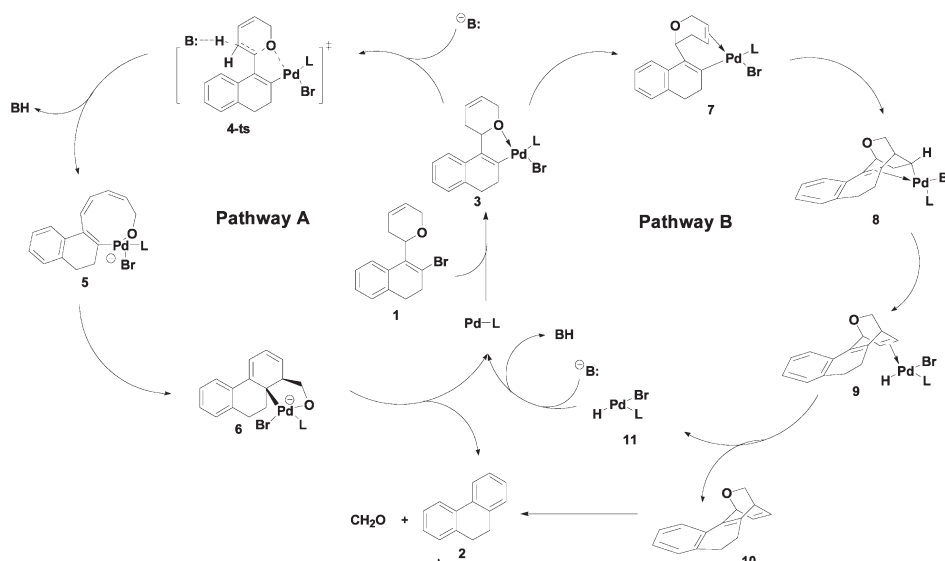
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SCHEME 2. Comparison of the Proposed Mechanism Involving the 6π Electrocyclic Ring Closing Reaction (A)⁴ and an Alternative Intramolecular Heck Mechanism (B)



formed. The vinyl group inserts into the Pd–C bond, forming the oxa-bicyclic intermediate **8**. Next, β -hydrogen elimination leads to intermediate **9** and the olefin moiety in **10** dissociates from the palladium center to generate intermediate **11**. The intermediate **11** then reacts with the base to generate the Pd(0) complex for the next catalytic cycle. A molecule of formaldehyde is released from complex **10**, producing 9,10-dihydrophenanthrene (**2**). Here, we report these results. The density functional theory method was used to study the mechanism of the synthesis of 9,10-dihydrophenanthrene. In our calculations, complex **1** was used as the substrate and PPh₃ was used as the ligand. As in previous studies,^{6,7} Pd(PPh₃)₂ (**12**) was taken as the energy reference. All calculations were carried out with the GAUSSIAN 03 package of programs⁸ employing the B3LYP⁹ density functionals. Each structure was fully optimized with the SDD basis set¹⁰ for Pd and Br, and the 6-31G(d) basis set for all other atoms in the gas phase. Harmonic frequency calculations were performed for every structure to confirm it as a local minimum or transition structure and to derive the thermochemical corrections for enthalpy and free energy. The solvent effect of DMF ($\epsilon = 36.71$, $R(\text{Solv}) = 2.647 \text{ \AA}$, $\text{density}(\text{Solv}) = 0.00778$, $V_{\text{mol}}(\text{Solv}) = 77.442$) was evaluated by single point calculations, using the Polarizable Continuum Model (PCM) with simple united atom¹¹ topological model radii. All enthalpies and the Gibbs free energies in the text are in kilocalories/mole and are calculated for standard conditions (298 K, 1 atm) and corrected for solvation effect as described above. All distances are given in angstroms.

Results and Discussion. As shown in Scheme 2, both mechanisms contain the same oxidative addition step. The oxidative addition of monodentate coordinated palladium has been fully studied by experimental¹² and theoretical¹³ methods. A free energy profile of this initial oxidative addition step is shown in Figure 1.

As shown in Figure 1, the relative energies of complexes **1** and **12** are set to zero in the free energy profile. After the dissociation of one PPh₃ ligand, the relative free energy increases to 18.9 kcal/mol. However, when the vinyl of complex **1** binds to **13** to form intermediate **14** the free energy decreases to 13.9 kcal/mol. From intermediate **14**, the activation free energy of oxidative addition is only 5.1 kcal/mol via transition state **15-ts** and the stable intermediate **16** is generated. Up to this point, the two proposed mechanisms are the same.

However, if we consider the intramolecular Heck reaction as an alternate pathway, then the point of entry is intermediate **17**, which is an isomer of **16** where the vinyl group binds to palladium (Figure 2). Calculations indicate a barrier of 18.4 kcal/mol from **16** to **17**, indicating an easy isomerization. In **17**, the bond lengths of Pd–C5 and Pd–C6 are 2.24 and 2.34 Å, respectively, which are consistent with known intermolecular vinyl–Pd bond lengths,^{6a,13} indicating that the binding of vinyl has minimal impact on strain.

The free energy profile of the proposed electrocyclic mechanism is shown in Figure 2. After the formation of intermediate **16**, an E2-type reaction occurs via transition state **18-ts**. However, the calculated activation barrier of this elimination step is remarkably high, 43.6 kcal/mol in DMF solvent (from **16** to **18-ts**). Note that when this step is complete, the nine-membered ring intermediate (**19**) contains a trans C=C and the relative free energy of complex **19** is 24.9 kcal/mol higher than the stable intermediate **16**. Attempts to locate the transition state for the C=C bond

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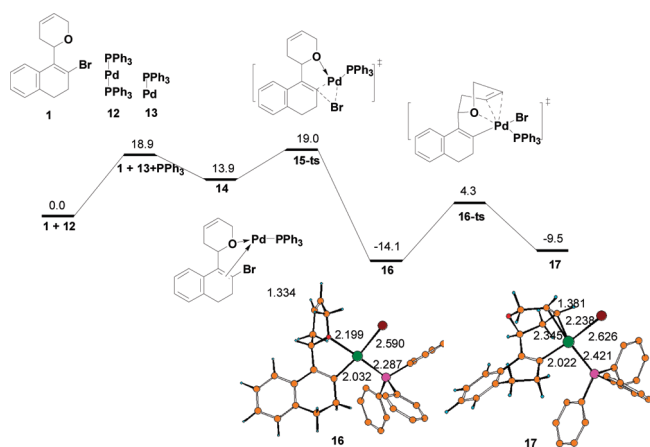


FIGURE 1. The initial oxidative addition step of two alternative mechanisms.

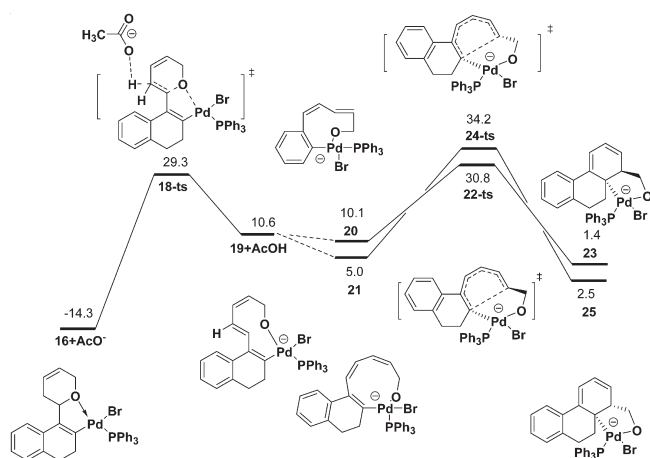


FIGURE 2. The calculated free energy profile of the proposed electrocyclic mechanism.⁴

rotation failed, but constraint of the dihedral angle $D_{C2-C3-C4-C5}$ of **22** to 90° indicated a destabilization of 25.0 kcal/mol.

The stereochemical details of the geometry of **19** are further illustrated in Figure 3. Clearly, the $C3=C4$ is trans and $C1$ and $C6$ must eventually cyclize on opposing sides. Therefore, the 6π electrocyclic ring close reaction can hardly occur directly. If we consider the possibility of rotation of the $C3=C4$ and $C5=C6$ double bonds, then **19** might isomerize to **20** (with trans $C5=C6$) and subsequent isomerization to **21** will give the intermediate with correct stereochemistry (Figure 3). However, it is likely that these isomerizations are not facile.

As shown in Figure 2, the relative free energy of complex **20** is 0.5 kcal/mol lower than that of intermediate **19**. If the 6π electrocyclic ring closure proceeds via transition state **22-ts**, generating the trans product **23**, the barrier for the cyclization reaction is about 20.7 kcal/mol, smaller than that of cyclization of 1,3,5-hexatriene.¹⁴ The overall barrier with respect to **16** is 45.1 kcal/mol. The reaction can also take place from complex **21** via transition state **24-ts**. Then, the cis

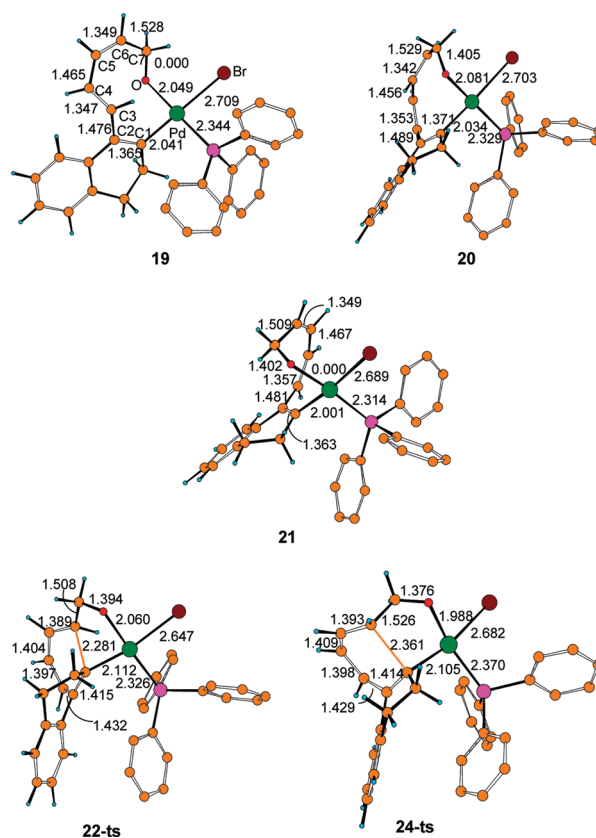


FIGURE 3. The calculated geometries of complexes **19**, **20**, and **21**, and transition states **22-ts** and **24-ts**.

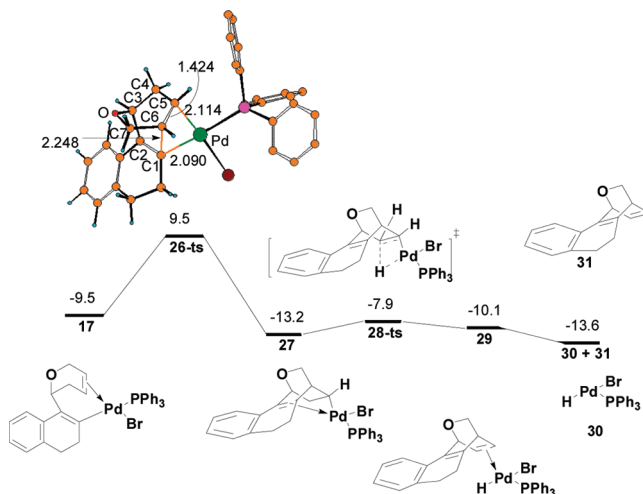


FIGURE 4. The calculated free energy profile of the intramolecular Heck-type mechanism.

product **25** is formed and the overall barrier is 48.5 kcal/mol (from **16** to **24-ts**). These high barriers clearly suggest that the mechanism is unfeasible especially at the experimental temperatures of $85-90^\circ\text{C}$.⁴

A major problem for the above mechanism is the high instability of intermediates **19-21**. These are less stable than **16** by over 19 kcal/mol. One important reason for this is the absence of a strong base such that the elimination reaction is unfavorable. A second reason is that there is a significant strain

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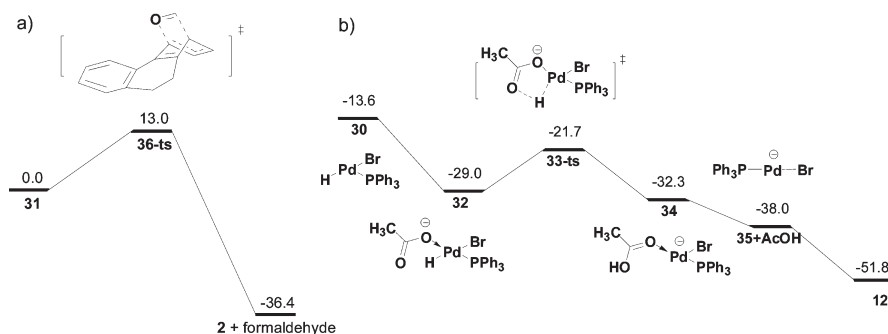


FIGURE 5. The generation of (a) final product and (b) the catalyst

in the 9-membered ring, especially in **19** and **20**, as indicated by a large distortion of the butadiene moiety from planarity.

To evaluate the alternate intramolecular Heck-type mechanism, we obtained the entire potential free energy profile (Figure 4). Initially, the relative free energy of **17** is only 4.6 kcal/mol higher than the stable intermediate **16**. When the vinyl group inserts into the Pd–C bond via transition state **26-ts** to form intermediate **27**, the barrier is only 19.0 kcal/mol (from **16** to **26-ts**). At this point, we identified a transition state that involves an agostic C–H interaction with the Pd (**28-ts**) resulting in a β -hydrogen elimination. For this step the free energy barrier is 5.3 kcal/mol, which is very close to that of typical intermolecular Heck reactions.¹⁵

The rate-determining step to the intramolecular Heck reaction is the insertion of the olefin (**17** to **26-ts** to **27**) with an overall activation free energy of 23.8 kcal/mol with respect to **16**. Compared to the original electrocyclic mechanism, this step is about 19.8 kcal/mol lower than the barrier for the E2-type elimination step (**18-ts**), and 21.3 kcal/mol lower than that for the 6π electrocyclic ring closing transition state (**22-ts**). This comparison indicates that the overall intramolecular Heck pathway is much more favorable than the proposed electrocyclic mechanism.

It is known that the insertion step in typical intermolecular Heck reactions is more facile than intramolecular Heck reactions.¹⁵ In the geometry of **26-ts** (Figure 4), a new C–C bond is formed between C1 and C6 and the distance between C1 and C6 is 2.25 Å, slightly longer than the distance of the bond-forming carbons in a typical intermolecular Heck reaction (~ 2.05 Å).^{6a,13} When C6 is close to C1, the strain as indicated by the dihedral angle C5–C4–C6–C7 increases. However, when the C1–C6 bond is forming, the planar conformation of the C6 atom is transforming to a tetrahedron, resulting in a decrease in strain. Thus, the transition state occurs earlier than the former intermolecular olefin insertion, and the strain also leads to an increase in barrier to olefin insertion. On the other hand, because of the strain of the C3–C4–C5–C6–C7–O ring, the geometry

of the four-member ring Pd–C1–C6–C4 is far away from the stable planar conformation. The dihedral angle of Pd–C1–C1–C6 is only 117° indicating an increase in energy barrier.

Our calculations indicate that product **31** from the intramolecular Heck reaction is unstable. However, a simple retro-Diels–Alder will proceed via transition state **36-ts** (Figure 5a) to dissociate a molecule of formaldehyde, generating the final product 9,10-dihydrophenanthrene (**2**). Because a new aromatic ring is formed in this step, the reaction is very favorable (ΔG of -36.4 kcal/mol) with a low activation energy barrier of 13.0 kcal/mol.

To complete the mechanism, after the β -hydrogen elimination, vinyl-coordinated intermediate **29** is formed and the intramolecular Heck reaction product **31** dissociates in a nearly barrier-free sequence. We also show that when the protonated palladium intermediate **30** is generated it may be coordinated by AcO^- generating intermediate **32** (Figure 5b). Finally, reductive elimination of AcOH occurs via transition state **33-ts** to form **34** with only 7.3 kcal/mol, and after dissociation of AcOH, the palladium anion **35** is formed. After the ligand exchange, the original Pd(PPh₃)₂ (**12**) is formed (Figure 5b).

In conclusion, we propose an intramolecular Heck-type mechanism for the synthesis of 9,10-dihydrophenanthrene from 2-(2-bromo-3,4-dihydro-naphthalen-1-yl)-dihydro-2H-pyran, which includes (1) oxidative addition to Pd(0), (2) intramolecular olefin insertion, (3) β -hydrogen elimination, (4) and formaldehyde extrusion. We employed density functional theory calculations to validate the proposed mechanism. This mechanism is calculated to be much more favorable than the 6π electrocyclic mechanism; however, it has a reaction free energy profile similar to that previously reported for the Heck reaction.^{6,13}

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Supporting Information Available: The energetics and coordinates of the structures presented in the text. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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