Theoretical study on the mechanism of palladium-catalyzed sp^2 C—H bond activation using cyano as a directing group

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ABSTRACT

A systematic theoretical study has been carried out on the mechanism for the Pd-catalyzed aromatic C—H activation reaction of aryl nitrile and aryl halide using cyano as the directing group. The entire catalytic cycle divides into four main processes involving C—H activation, CF$_3$COOH dissociation, oxidative addition, and reductive elimination and catalyst regeneration. The calculations indicate that the ortho carbon of the directing group cyano in aryl nitrile is activated by Pd(II) resulting in the activation of C—H bond. In CF$_3$COOH dissociation, it is found that the **5b** is an essential intermediate, which facilitates the dissociation of CF$_3$COOH ligand leading to the intermediate (η^2-CF$_3$COO$^-$)(η^2-aryl nitrile)Pd(II) (**6**). The Pd(II) intermediate further undergoes oxidative addition with PhI to form Pd(IV) intermediate, which proceeds by reductive elimination and catalyst regeneration to give the final product. And the reductive elimination and catalyst regeneration process can determine the reaction rate. Furthermore, the roles of additive Ag$_2$O, directing group cyano, and solvent Trifluoroacetic acid have also been examined.

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1. Introduction

Biphenyls are important structures that serve as key components in a large number of organic molecules. For example, biphenyls can be used in pharmaceuticals, agrochemicals, dyes, chiral ligands for metal catalysts, liquid crystals, organic semiconductors, and materials for molecular recognition devices [1]. Considering the importance of the molecules with the structural units, it is necessary to develop an effective method for the synthesis of biphenyl moieties. Recently, transition metal-catalyzed C—H bond activation has received increasing attention as a powerful method to construct C—C, C—N, C—O, and C—S bonds in organic synthesis [2]. In particular, C—H arylation has become an ideal choice to conventional C—C cross-coupling reactions owing to the minimization of stoichiometric metallic squander and the costs related with the preparation of starting materials. Furthermore, many C—H arylation reactions involving directing-group-assisted activation of sp^2 C—H bonds of ortho aromatic C—H bonds have been developed. A lot of coordination groups, such as acetamino [3], carboxylic acid [4], carbonyl [5], pyridyl [6], hydroxyl [7], and nitro [8] have been commonly used as the directing group for C—H bond activation.

In 2010, Li and co-workers reported a novel and efficient method for the synthesis of biphenyl-2-carbonitrile derivatives from aryl nitriles and aryl halides via a palladium-catalyzed C—H bond activation using cyano as the directing group (Scheme 1) [9]. The reaction is interesting and unusual because palladium-catalyzed C—H bond activation, in which cyano is used as a directing group, directly gives the product biphenyl nitriles. The cyano group has a linear configuration, which is different from the n-electron coordination in some other coordinating group directed C—H bond activation such as acetamino, acetyl, and carboxylic acid [10,11]. So the coordination of a π-electron between carbon and nitrogen to Pd is possible. The weak coordination interaction of the formed cyclopalladated intermediates might make them have higher reactivity. To better understand the present catalytic reaction of palladium-catalyzed C—H bond activation, Li and co-workers proposed an uncommon Pd(II)/Pd(IV) mechanism, shown in Scheme 2, which involves C—H activation, oxidative addition, and reductive elimination as found in other aromatic C—H activation reactions. The key feature of the proposed reaction mechanism is the formation of the cyclopalladated(II) intermediate A, which is not a general five-membered metallacycle. Then Pd(II) activates the sp^2 C—H bond to form the intermediate B, followed by an oxidative addition of aryl iodide to intermediate B to give a Pd(IV) intermediate C. Finally, reductive elimination affords the final products.

However, the details of the reaction mechanism are still ambiguous. Furthermore, there are several significant questions in the reaction of aryl nitrile with aryl iodide. How does each of the catalytic steps occur in Pd(II)/Pd(IV) mechanism? How does the cyano group assist in activation of C−H bond? What is the role of Ag_2O in catalytic cycle? Answers to these questions are of obvious value to the continuing study of the mechanism of the aromatic C−H activation reactions and, therefore, constitute the focal points of our present work. It is worth noting that there were some theoretical studies using Pd complexes as catalysts for C−H activation reactions. For example, the mechanism of the amino acid ligand-assisted Pd-catalyzed C−H activation reaction was studied by means of the B3LYP level of density functional theory (DFT) [12]. Morokuma et al. [13] reported the DFT methods to study the mechanism and stereoselectivity of directed C(sp^3)−H activation and arylation catalyzed by Pd(II).

To the best of our knowledge, no theoretical study has been reported to investigate the mechanism of the palladium-catalyzed sp^2 C−H bond activation using cyano as a directing group. In this article, a computational study based on DFT calculations was performed in order to determine the mechanisms of biphenyl-2-carbonitrile from aryl nitrile and aryl halide via a palladium-catalyzed aromatic C−H activation. Through the study, we have obtained detailed structural and energetic informations about each step of the aromatic C−H activation reaction. These results may have valuable implications for the development of new, more effective catalyst systems for the aromatic C−H activation reaction.

2. Computational details

Molecular geometries of all complexes were optimized without constraints via DFT level of theory with Becke3LYP(B3LYP) [14,15] functional. All calculations were performed with the Gaussian 09 software package [16]. The 6-311+G(d,p) [17] basis set was employed for C, H, O, N, and F atoms. The Pd, Ag, and I atoms were described using the LANL2DZ basis set including a double-ζ valence basis set with the Hay and Wadt effective core potential. Polarization functions were also added for Pd ($\zeta_f = 1.472$), Ag($\zeta_f = 1.611$), and I($\zeta_d = 0.266$) [18]. Frequency calculations were carried out at the same level of theory for all the stationary points to characterize the transition states (one imaginary frequency) and the equilibrium structures (no imaginary frequency). Calculations of intrinsic reaction coordinates (IRC) [19] were also performed on transition states to check that such structures are indeed connecting two minima. Numerous theoretical studies of Pd-catalyzed reactions at the B3LYP level were reported in the literature, which confirms that such exchange-correlation functional is a reasonable method for obtaining reliable geometries [20−22]. Gibbs free-energy corrections at 383.5 K were determined from harmonic frequencies and added to the total electronic energies to get the Gibbs free energies. Hirshfeld charges and inter- and intramolecular interactions were analyzed through the Multiwfn program on some structures in the process of the reaction [23−25]. To test the reliability of our computational scheme, all of optimized geometries have also been reoptimized and characterized with M06 [26−28] functional, in which the 6-311+G(d,p) basis set has been employed for C, H, O, N, and F atoms and the LANL2DZ has been used for the Pd, Ag, and I atoms (see Table S1 in the Supporting Information).

For evaluating the solvent effect, single-point solvation energies were calculated by using SMD solvation model (solvent = Trifluoroacetic acid) [29]. The solvation free energy was calculated at B3LYP/6-311+G(d,p) (LANL2DZ+p for Pd, Ag, and I atoms) level and added to the gas-phase free energy to obtain the Gibbs free energy in solution. The data are given in parentheses of the corresponding free energy profiles throughout the study.

3. Results and discussion

3.1. Reaction mechanisms

In this section, the potential energy surface of the Pd-catalyzed the C−H activation reaction of aryl nitrile with aryl halide is fully investigated. Our results shed light on that the title reaction should be considered to include four processes: C−H activation, CF_3COOH dissociation, oxidative addition, and reductive elimination and catalyst regeneration. The detailed mechanism of the title reaction is discussed in the following sections.
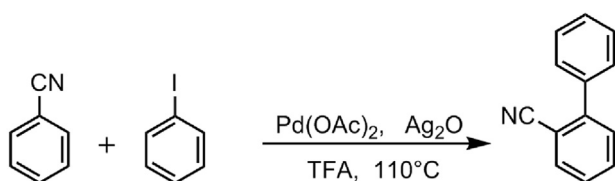
3.1.1. C−H activation

In light of Li and co-workers' proposed mechanism, they implied that the catalytic reaction starts with the coordination of aryl nitrile to Pd(II) species and the true catalyst in this reaction is Pd(TFA)$_2$, as outlined in Scheme 2. Thus, Pd(TFA)$_2$ is chose as the reference point of Gibbs free energies for convenience of comparison. The free energy profile for this process is reported in Fig. 1, while some key structures are shown in Fig. 2.

Starting with the complex Pd(TFA)$_2$, aryl nitrile coordination to the Pd(TFA)$_2$ via a five-coordinate transition state **TS(Pd(TFA)$_2$/1)** forms the four-coordinate intermediate **1**. Due to the planar C_{2h} Pd(TFA)$_2$ construction, the aryl nitrile enters the Pd coordination sphere by the N atom attacking the equatorial site. Thus, the coordination mode of one of the CF_3COO^- ligands to the Pd center in **1** changes from η^2-to η^1-coordination. In addition, it is found that **1** involves an intramolecular H-bonding interaction between H1 and O1 atoms, in which the C1−H1···O1 bond angle is 142° and the H1···O1 distance is 2.481 Å. The binding energy of H1···O1 is −6.59 kcal/mol with AIM analysis, which also indicates that the C1−H1···O1 bond exits H-bonding interaction. The profile in Fig. 1 shows that the process is predicted to be exergonic by 7.00 kcal/mol and has a small free energy barrier of 7.91 kcal/mol. Then, Pd atom attacks on the ortho carbon of the directing group cyano via transition state **TS(1/2)**. As shown by the Hirshfeld charges in Fig. S1, the C1 (−0.06e), H1 (0.14e), and O1 (−0.28e) atoms in **1** are increased to −0.80e (C1), 0.35e (H1), and −0.40e (OI) in **TS(1/2)**. It is implied that the Pd−C1 bond will be formed and the interaction between H1 and O1 atoms will be enhanced. Once intermediate **2** is generated, the cleavage of C1−H1 bond and the formation of H1−O1 bond occur easily, which is caused by the attraction of O1 in the η^1-CF_3COO^- ligand, thus giving rise to (η^2-CF_3COO^-)(η^1-CF_3COOH)(η^1-aryl nitrile)Pd intermediate (**3**) via the classical six-membered transition state **TS(2/3)** [12]. As depicted in Fig. 2, the H1−O1 and Pd−C1 bonds are formed in intermediate **3**, which is considered the result of the C−H activation of aryl nitrile by catalyst Pd(TFA)$_2$. From Fig. 1, this step has an activation energy of 11.92 kcal/mol while endergonic by 0.33 kal/mol.

3.1.2. CF_3COOH dissociation

Based on the generation of the intermediate **3**, two possible pathways of CF_3COOH dissociation for producing original metallacycle intermediates are proposed. To state the reaction mechanism

Scheme 1.