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DFT Study of Pd(0)-Promoted Intermolecular C−H Amination with *O*-Benzoyl Hydroxylamines

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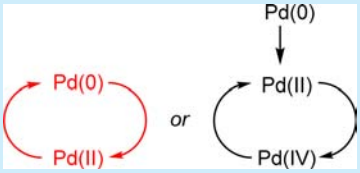
Supporting Information

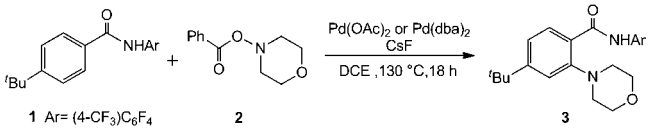
ABSTRACT: Computational studies were carried out to explore the mechanism of Pd-catalyzed intermolecular C−H amination with *O*-benzoyl hydroxylamines in which both Pd(0) and Pd(II) catalysts are effective. For the Pd(0)-catalyzed reaction, the generally assumed Pd(0)/Pd(II) catalytic cycle might not be feasible. Instead, Pd(0), being essentially a catalyst precursor, could be oxidized to Pd(II), and the C−H amination proceeds through the Pd(II)/Pd(IV) catalytic cycle.



Transition-metal-catalyzed direct amination of C−H bonds has attracted significant attention during the past decade,[1] since it offers a complementary method for C−N bond construction without the need of prefunctionalized substrates. To date, reported strategies for realizing C−H bond amination can be generally classified into three types. The first is the insertion of an active nitrene moiety into C−H bond.[2,3] The second is to take advantage of oxidative amination of C−H bond with amine derivatives in the presence of external oxidants.[4] The third approach employs N−O bond-containing compounds (such as hydroxylamine derivatives or oxime esters) as the nitrogen source to carry out the direct amination of C−H bond in a redox-neutral manner. A diverse range of palladium-,[5] rhodium-,[6] copper-,[7] or ruthenium-catalyzed[8] C−H direct amination reactions without the need of additional oxidant have emerged in recent years.

In particular, Yu's group reported a Pd-catalyzed intermolecular C−H amination of *N*-arylbenzamides with *O*-benzoyl hydroxylamines (R^1R^2NOBz) in 2011 (Scheme 1).[5c] It is noteworthy that both Pd(0) and Pd(II) catalysts are effective in promoting the C−H amination reaction. For the Pd(II)-catalyzed C−H amination, the cyclopalladium(II) intermediate **B** was proposed to be the key intermediate after the C−H bond activation by the coordinated acetate group (Scheme 2).

Scheme 1. Pd(II)- and Pd(0)-Catalyzed Intermolecular C−H Amination of *N*-Arylbenzamides with *O*-Benzoyl Hydroxylamines Reported by Yu[5c]

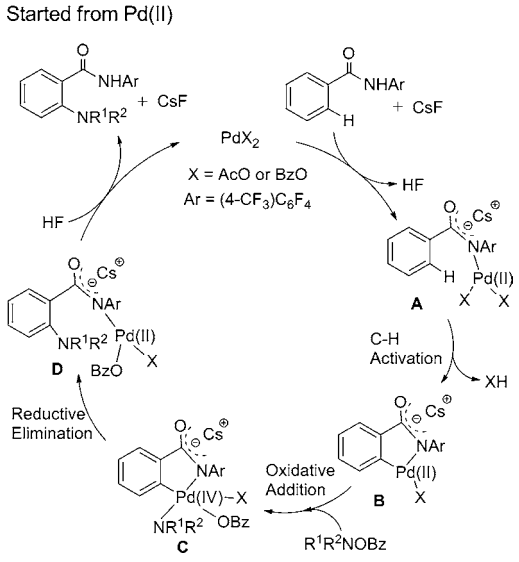


1 Ar= (4-CF_3)C_6F_4 2 3

cat. [Pd]	yield
$Pd(OAc)_2$	74 (98%)[a]
$Pd(dba)_2$	70 (96%)[a]

[a]The yields in parentheses were obtained with AgOAc.

Scheme 2. Proposed Mechanistic Pathway for the Pd(II)-Catalyzed Intermolecular C−H Amination with *O*-Benzoyl Hydroxylamines



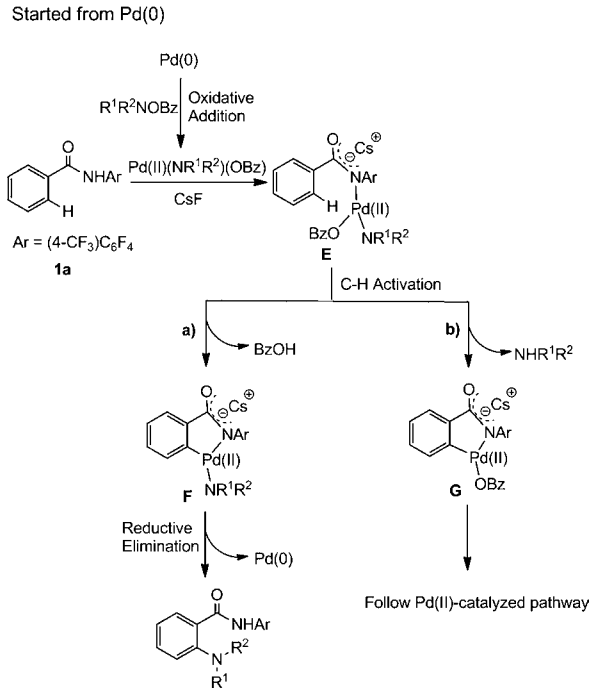
Computational studies suggested that the amination proceeded via the Pd(II)/Pd(IV) catalytic cycle, in which the aminating reagent (R^1R^2NOBz) could undergo oxidative addition (OA) onto the Pd(II) center to afford the Pd(IV) intermediate **C** and subsequently undergo reductive elimination (RE) to furnish the desired product.[9] In addition, the role of the silver salt additive was elegantly revealed.[9]

For the reaction mechanism that started with Pd(0) complex, the Pd(0)/Pd(II) catalytic cycle has been proposed (Scheme 3a).[5c] Initially, the OA of aminating reagent onto the Pd(0) might take place to yield Pd(II) species.[5b] After the coordination with the substrate, in which the acidic amide

Received: July 17, 2016
Published: August 30, 2016

DOI: 10.1021/acs.orglett.6b02093
Org. Lett. 2016, 18, 4506−4509

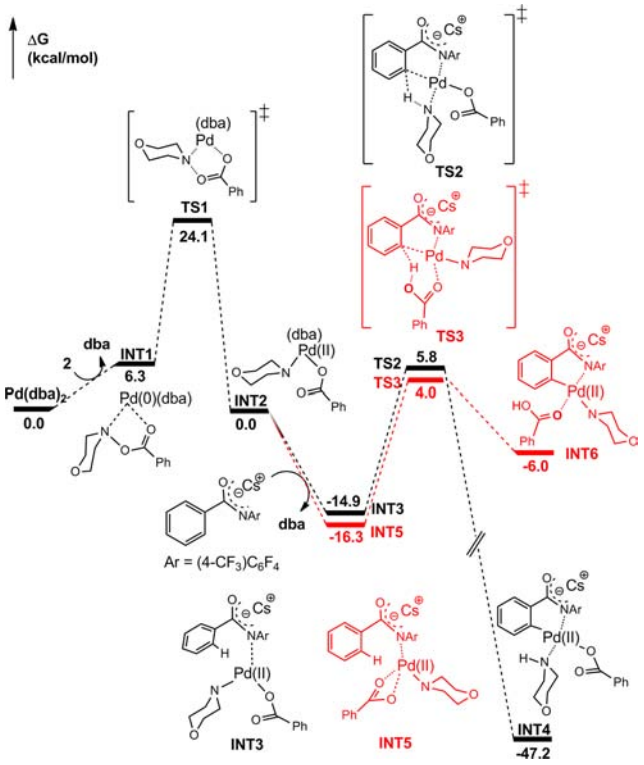
Scheme 3. Possible Mechanistic Pathways for the Pd(0)-Catalyzed Intermolecular C−H Amination with *O*-Benzoyl Hydroxylamines



could be deprotonated by CsF base, the key intermediate **E** might be formed. It is conceivable that the C−H bond might be activated by the ligand of benzoate to afford the cyclopalladium(II) intermediate **F**. This is followed by a RE step, and the desired amination product could be formed via a typical Pd(0)/Pd(II) catalytic cycle. However, little attention has been paid to an alternative pathway (Scheme 3b) in which the activation of the C−H bond is performed by the amino group to form intermediate **G**. The obtained key intermediate **G** is essentially the same as that in the Pd(II)-catalyzed mechanism, and the subsequent route leading to the desired amination product could follow the Pd(II)-catalyzed mechanism proposed previously.[9] In this work, the detailed mechanism of the intermolecular C−H amination of *N*-arylbenzamides with *O*-benzoyl hydroxylamines promoted by Pd(o) complex was explored computationally (see Supporting Information for computational details).

The Pd(0) complex, $Pd(dba)_2$, could undergo ligand exchange with the aminating reagent (**2**) to form **INT1**, being endothermic by 6.3 kcal/mol (Scheme 4). Subsequently, the OA of **2** onto the Pd(0) species via **TS1** might occur with an activation free energy barrier of 24.1 kcal/mol to afford the Pd(II) intermediate (**INT2**). Musaev and Yu have suggested that the presence of CsF could assist the deprotonation of amide,[10] converting the substrate, PhCONHAr (**1a**), to $[PhCONAr]^-Cs^+$.[11] Thus, after the formation of **INT2**, the deprotonated amide, $[PhCON\text{-}Ar]^-Cs^+$, might coordinate with the Pd(II) species by replacing the remaining dba ligand. The deprotonated amide directing group is more ready to coordinate with the Pd(II) catalyst via the N atom than the O atom.[9,10,12] Depending on the subsequent C−H activation via either amino or benzoate groups (concerted metalation−deprotonation step), the intermediates **INT3** and **INT5**, which are exergonic by 14.9 and 16.3 kcal/mol, respectively, could be formed (Scheme 4).

Scheme 4. Energy Profile for the OA of *O*-Benzoyl Hydroxylamines onto Pd(0) and Subsequent Pathways of C−H Activation



For the following C−H bond activation step, two possible routes are proposed as shown in Scheme 3, which are activated by either the amino ligand or by the benzoate ligand. For the benzoate activation route, the **TS3** was located, whereby the C···H distance is lengthened to 1.44 Å while the H···O distance is shortened to 1.26 Å (Figure 1). The free energy barrier was

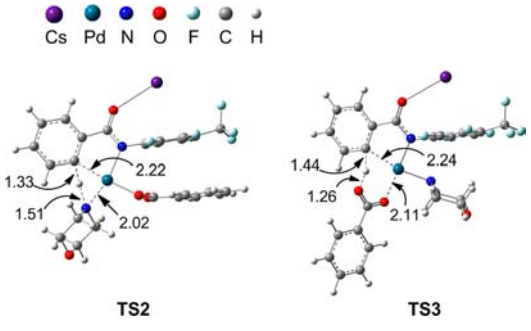


Figure 1. Optimized geometries of **TS2** and **TS3**. Bond lengths are given in angstroms.

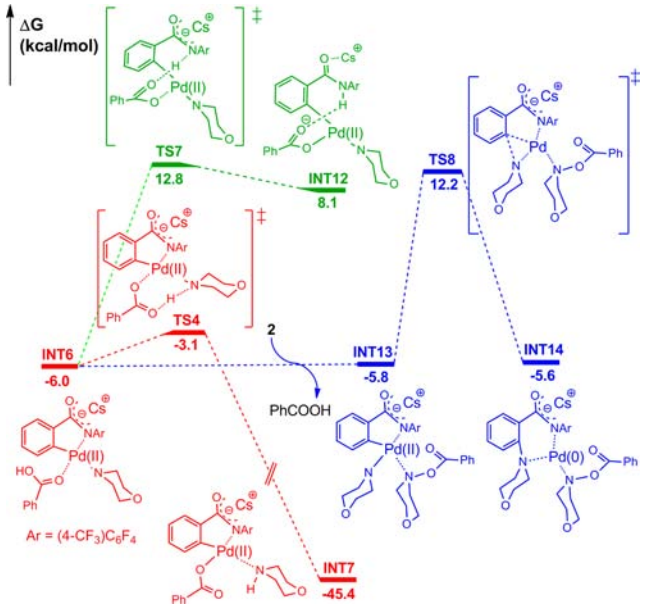
calculated to be 20.3 kcal/mol. For the C−H activation via the amino group route the **TS2** was optimized, in which the C···H distance is lengthened to 1.33 Å while the H···N distance is shortened to 1.51 Å (Figure 1). The predicted free energy barrier is 20.7 kcal/mol. Interestingly, the energy barriers of the two C−H activation modes were very close (20.3 and 20.7 kcal/mol). Nevertheless, it should be noted that the formed intermediate, **INT6**, via the benzoate ligand activation mode is thermodynamically unstable, being endothermic by 10.3 kcal/mol. In sharp contrast, the obtained intermediate (**INT4**) via the amino ligand activation path is thermodynamically very

DOI: 10.1021/acs.orglett.6b02093
Org. Lett. 2016, 18, 4506−4509

stable, being exothermic by 32.3 kcal/mol. Therefore, the activation via the amino group would be more favorable in terms of the thermodynamic point of view.

Even though the formed **INT6** via the benzoate ligand activation mode is thermodynamically unstable, the subsequent RE step toward the desired product was explored computationally (Scheme 5). The **INT13** might be formed via a ligand-

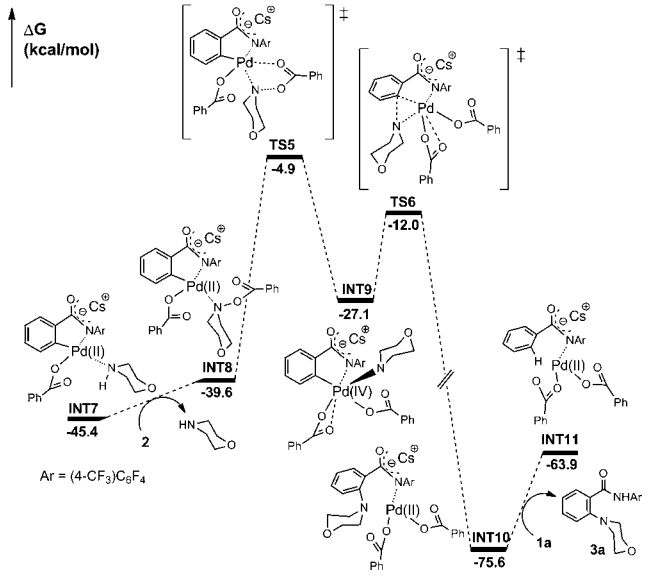
Scheme 5. Energy Profiles for the RE Pathway toward the Desired Amination Product and Possible Proton Transfer Routes from INT6



exchange step. The subsequent RE step leading to the desired product was predicted to have a free energy barrier of 18.0 kcal/mol. Alternatively, for **INT6**, the formed benzoic acid could undergo a proton-transfer step to the amino group to yield **INT7**. The predicted energy barrier for this proton transfer step is only 3 kcal/mol, which is much lower than the RE route. It should be noted that the formed **INT7** is thermodynamically stable and is essentially the conformational isomer when compared with **INT4**.[13] In addition, the proton-transfer step from the formed benzoic acid to the deprotonated amide was also investigated. The calculated energy barrier is much higher than the previous proton-transfer step (18.8 kcal/mol). Therefore, for the C−H bond activation driven by the benzoate ligand, the formed carboxylic acid readily undergoes proton-transfer step to the amino group, which essentially follows the same route as the direct C−H activation via the amino group. The proposed RE of the amino-containing Pd(II) intermediate leading to the desired amination product is unlikely to occur in the presence of carboxylic acid because the amino group is facile to be protonated. Thus, the proposed mechanism via the Pd(0)/Pd(II) catalytic cycle might not be feasible.

After the formation of the Pd(II) intermediate (**INT7**), replacing the labile morpholine ligand by the aminating reagent (**2**) to afford **INT8** may be followed.[14] Next, **2** could undergo OA into the Pd(II) center via **TS5** to form the Pd(IV) intermediate **INT9**. The free energy barrier was calculated to be 34.7 kcal/mol (Scheme 6). The obtained **INT9** could undergo RE to afford the desired amination product, and the predicted

Scheme 6. Energy Profile for the Pd(II)/Pd(IV) Catalytic Cycle Leading to the Desired Amination Product



free energy barrier for this step is 15.1 kcal/mol. The formed **INT10** is thermodynamically very stable, and the amination product could be completely released by the uptake of another molecule of the substrate **1a**. In fact, the Pd(0) complex, being a precatalyst, could be activated by hydroxylamines to form a Pd(II) catalyst, and the C−H amination proceeds through the Pd(II)/Pd(IV) mechanism.

In summary, for the Pd(0)-promoted intermolecular C−H amination of *N*-arylbenzamides with *O*-benzoyl hydroxylamines, after the oxidative addition of aminating reagent onto Pd(0), the formed amino group in the key Pd(II) intermediate is ready to undergo either C−H bond activation or acceptance of a proton from carboxylic acid, which could be formed by C−H bond activation driven by the benzoate ligand. Thus, the subsequent reductive elimination leading to the desired amination product is unlikely to occur, and the proposed Pd(0)/Pd(II) catalytic cycle might not be feasible. In fact, the Pd(0) complex could be oxidized to Pd(II), and the C−H amination proceeds through the Pd(II)/Pd(IV) catalytic cycle.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02093.

Computational methods, Scheme S1, Cartesian coordinates, and energies of the studied molecules (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The research was supported by grants from the Natural Science Foundation of China (NSFC 21302133) and the Priority

DOI: 10.1021/acs.orglett.6b02093
Org. Lett. 2016, 18, 4506−4509

Academic Program Development of Jiangsu Higher Education Institutions (PAPD).

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(13) The interconversion between **INT4** and **INT7** might be achieved via the dissociation of the labile morpholine ligand, reorientation of the benzoate group, and the recombination of the morpholine ligand.

(14) A similar process started with **INT4** was also explored. After the ligand-exchange step, the resulting **INT8a**, however, was more endothermic than the formation of **INT8**, suggesting that the subsequent reaction with **INT8** would be more likely (see Scheme S1 in the SI).

DOI: 10.1021/acs.orglett.6b02093
Org. Lett. 2016, 18, 4506−4509