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Experimental and Computational Studies on the Mechanism of Pd-Catalyzed C(sp\(^3\))–H γ-Arylation of Amino Acid Derivatives assisted by the 2-Pyridylsulfonyl Group

Ana Poveda\(^{a}\), Inés Alonso*\(^{a,b}\) and M. Ángeles Fernández-Ibáñez*\(^{a,b}\)

The Pd(OAc)_2-catalyzed γ-arylation of amino acid esters bearing a removable N-(2-pyridyl)sulfonyl directing group via C(sp\(^3\))–H activation provides a direct method to functionalized amino acids without racemization at the aC and high degree of stereoselectivity. The present mechanistic studies suggest that the reaction proceeds via catalytic active monomeric species, the C–H activation is reversible and is not always the turnover limiting step. Moreover, theoretical calculations explained the observed stereoselectivity and suggested that the reaction proceeds through a Pd(II)/Pd(IV) mechanism.

Introduction

Transition metal-catalyzed activation of C–H bonds has become a powerful method to functionalize organic molecules.\(^1\) Great progress has been made in the direct and selective metal-catalyzed functionalization of C(sp\(^3\))–H bonds.\(^2\) However, protocols for the direct C(sp\(^3\))–H functionalization are still limited to date.\(^3\) Among these transformations, the use of catalytic amounts of palladium is by far the most employed approach.\(^4\)

In the area of C-C bond forming reactions that proceed via a C–H activation mechanism, direct C–H arylation has been achieved with aryl halides, diaryliodonium salts, potassium aryltrifluoroborates, boronic acids or esters, arylsilanes as well as without prefunctionalized arylating agents.\(^2,4\) In particular, the combination of catalytic amounts of Pd(OAc)_2 with aryl iodides in conjunction with Ag(I) salts have been employed for the C(sp\(^3\))–H arylation of a wide range of substrates.\(^5\) The same catalytic system has been used for the arylation of unactivated C(sp\(^3\))–H bonds using pyridines, aminoquinolines, picolinamides and carboxylic acids as directing groups.\(^6\) In this context, we recently reported an efficient Pd(OAc)_2-catalyzed γ-arylation of amino acid esters bearing a removable N-(2-pyridyl)sulfonyl directing group.\(^7\) The reaction of the N-(2-pyridyl)sulfonyl valine derivative 1 under optimal reaction conditions, provided a mixture of the mono- and bisarylated products 2 and 3 without racemization at the Cα center. Moreover, the monoarylated product 2 was obtained with very high diastereoselectivity (dr>20/1), with the arylation occurring exclusively at the pro-S methyl valine group (Scheme 1).

Scheme 1 Pd-Catalyzed γ-arylation of L-valine derivative 1

In addition, a bimetallic Pd(II) γ-metalted intermediate 5 was isolated and characterized by the stoichiometric reaction of the N-(2-pyridyl)sulfonyl tert-leucine derivative 4 with Pd(OAc)_2 in CH\(_2\)CN at 60 °C (Scheme 2). We observed that palladacycle 5 was able to react with 4-iodotoluene [60 °C in HFIP (hexafluoroisopropanol)] leading to a nearly equimolecular mixture of the monoarylated and bisarylated products 6 and 7.

![Chemical structure of compounds](image-url)
Few mechanistic studies on palladium-catalyzed C–H arylation reaction have been reported, none of which include the combination of Ag(I) salts and aryl iodides. Thus, the mechanism for the Pd(OAc)$_2$-catalyzed C–H arylation with these reagents remains elusive and speculative at this time. To bring some light into the subject, and taking the advantage that we had isolated the bimetallic Pd(II) intermediate 5, we decided to embark on a mechanistic study of the reaction. Herein, we report experimental and computational studies on the mechanism of Pd(OAc)$_2$-catalyzed C(sp$^3$)–H arylation of amino acid derivatives with aryl iodides.

Results and Discussion

Identification of the catalytic active species.

In our attempt to understand the mechanism of the C–H arylation, we first sought to identify the catalytic active species. Thus, the nuclearity of the bimetallic complex 5 in solution was investigated. A 1D-selective NOE spectrum obtained by inversion of the signal corresponding to the ortho-proton to the nitrogen of the pyridine (H$_1$, 8.38 ppm) of 5 in CD$_3$CN showed a weak NOE interaction (<0.05%) with the methylene protons (H$_2$ and H$_2'$, 2.12 and 1.94 ppm, respectively) as well as with the OMe group (3.61 ppm) and the CH proton (H$_3$, 3.77 ppm) (Figure 1). From the X-Ray geometry of bimetallic complex 5, the measured distance between H$_1$ and H$_2$/H$_2'$ is between 2.1-3.2 Å (averaged 2.48 Å). For this short distance, a clear NOE interaction should be expected. However, the observed NOE is very weak. Indeed, it could only be observed after lowering the temperature to 5 °C, suggesting that the dimer is not the predominant species in solution. On the other hand, in the X-Ray structure the H$_1$–H$_1'$ and H$_1$–OMe distances are longer than 5.5 Å, much longer than those expected for the observed NOEs. This fact evidences the presence of a different species in solution. Additionally, diffusion coefficients ($D$) were estimated from the diffusion-ordered spectroscopy DOSY experiment for the bimetallic complex 5 and the monoarylated product 6. The obtained $D$ values are very similar (1.44 x 10$^{-9}$ m$^2$/s for bimetallic complex 5 and 1.43 x 10$^{-9}$ m$^2$/s for the monoarylated 6), and the calculated molecular weight from this value for the bimetallic complex 5 is 381.4, which is almost half of the expected weight for complex 5 (see Supporting Information). These experimental evidences strongly suggest that the bimetallic complex 5 in solution is mainly present as a monomer.

With the nuclearity of the complex 5 in solution established, we determined the order of the reaction for the complex 5 in the γ-arylation process by the initial rate method. The progress of the reaction between the complex 5 with 4-iodotoluene in HFIP at 60 °C was monitored by $^1$H NMR analysis after quenching the reaction at -78 °C. We established the product concentration from the mixture of 6 and 7. Figure 2 shows a linear fit of the reaction rate versus the concentration of complex 5 from 0.019-0.071 M. The plot of the logarithms of the reaction rate against the concentration provides a straight line with slope of 1.0, revealing that the reaction is first order in the complex 5 (see Supporting Information). Thus, the first order dependence on the concentration of complex 5, which in solution is mainly present as a monomer, implies that the reaction occurs via a catalytically active monomeric species.
Fig. 2 Plot of the initial rate vs [5] in HFIP at 60 ºC

Synthesis and reactivity of monomeric complexes.

Although the active monomeric species could not be isolated, the reaction of the dinuclear complex 5 in tert-butyl isocyanide at room temperature afforded cleanly a mononuclear complex 8 (Scheme 3), whose structure was confirmed by single-crystal X-ray analysis (Figure 3). The monomer 8 was found to be unstable in solid state and a new mononuclear palladium complex 9, with one tert-butyl isocyanide ligand less, could be isolated. In addition, the reaction of the dinuclear complex 5 with 1 equiv of PPh₃ in HFIP at room temperature furnished directly the monomeric complex 10. Unfortunately, all our attempts to characterize complexes 9 and 10 by single-crystal X-ray analysis were unsuccessful. However, these monomeric complexes were fully characterized by NMR analysis as well as by mass spectroscopy.

Scheme 3 Synthesis of the monomeric complexes 8, 9 and 10

The structure of complex 8 points out towards a mechanism whereby the dinuclear complex 5 is transformed into the mononuclear species. Direct ligand substitution between two molecules of tert-butyl isocyanide (or any other ligand/solvent) replacing the bidentate sulfonylpyridyl ligand results in the formation of 8, which undergoes an intramolecular ligand substitution by the pyridyl moiety to afford 9.

The reactivity of the monomeric complexes 9 and 10 in the arylation reaction was investigated (Scheme 4). Thus, the reaction of complex 9 with 4-iodotoluene at 60 ºC after 17 h afforded the monoarylated product 6 in 24% conversion while no reaction was observed under the same conditions with complex 10. Complex 10 reacted with 4-iodotoluene to provide 6 in 13% conversion at 110 ºC after 14 h. The reaction of the bimetallic complex 5 under similar reaction conditions (60 ºC/17 h or 110 ºC/14 h) gave full conversion to the mono- and diarylated products 6 and 7. These results showed that monomeric complexes 9 and 10 are less reactive in the arylation reaction with 4-iodotoluene than the bimetallic complex 5 and at the same time that complex 9 is more reactive than complex 10.

Scheme 4 Reactivity of the monomeric complexes 9 and 10

In addition, the analysis of the stoichiometric reaction between the tert-leucine derivative 4 and Pd(OAc)₂ by positive electrospray ionization mass spectrometry (ESI-MS) after 20 min showed some monomeric Pd(II) intermediates (Figure 4): i) the monomer 11 (m/z 451.01 [M+H]+) which corresponds to an intermediate before the C–H activation step and ii) the monomeric species 12 and 13 originated after the C–H activation step (m/z 390.99 [M+H]+ and 432.02 [M+H]+, respectively). At this point and taking into account the
structures of the monomeric complexes 9 and 10 (see Scheme 3), it seems reasonable to consider the monomeric species 13 as the catalytic active species of the reaction.

\[ \text{C(sp^3)\text{-}H oxidative addition also evaluated in the case of C(sp^3)\text{-}H bonds, concerted metalation-deprotonation (CMD) pathway has often been found as the most favourable one.} \]

Moreover, taking into account the early finding by Houk and Yu, using this type of mechanism to explain the stereoselectivity in certain Pd(II)-catalyzed C(sp^3)\text{-}H activation, we envisaged that a similar model could be applied in our case. For this purpose a complex similar to 11 (see Figure 4) but resulting from the N-(2-pyridyl)sulfonyl valine derivative (Ia) was used as starting material model. This study revealed that the C\text{-}H activation of both diastereotopic methyl groups would afford several diastereomeric transition states showing different conformations of the tricyclic palladacycle that is being formed. The most stable and representative ones are shown in the Figure 5. Among them, the most stable TS(Ia-IIa) arises from the C\text{-}H activation at the pro-S methyl group and could account for the experimental selectivity observed. By contrast, TS(Ia-IIaA) and TS(Ia-II\text{a}B), that come from the C\text{-}H activation at the pro-R methyl group and would afford diastereomeric product, resulted to be less stable (1 and 1.7 kcal\text{·}mol\textsuperscript{-1} respectively). In addition, the energy profile also agrees with the reversibility of the C\text{-}H activation step.

![Fig. 4](image)

**Fig. 4** ESI(+)-MS of the stoichiometric reaction between tert-leucine derivative 1 and Pd(OAc)\textsubscript{2} in CH\textsubscript{3}CN at room temperature after 20 min

**The C\text{-}H activation step: reversibility and stereoselectivity**

The reversibility of the C\text{-}H activation step was investigated in the reaction of the bimetallic complex 5 with 40 equiv of acetic acid-d\textsubscript{t} (Scheme 5). It was found that the reaction at 40 °C in CD\textsubscript{3}CN provided 25%\textsuperscript{21} of tert-leucine derivative 4-d\textsubscript{t} partially deuterated (c.a. 18%) after 16 h, while the reaction in HFIP-d\textsubscript{2} at 80 °C afforded the tert-leucine derivative 4-d\textsubscript{0} almost completely deuterated (c.a. 85%) after 17 h. This interconversion implies that the C\text{-}H activation is reversible but the reverse reaction (formation of 4 from 5) is slower than the forward reaction since the tert-leucine derivative 4-d\textsubscript{t} was not formed at room temperature in CD\textsubscript{3}CN or at 60 °C in HFIP-d\textsubscript{2}, temperatures at which the forward reaction can take place.

![Scheme 5](image)

**Scheme 5.** H/D Exchange studies

The stereoselectivity of the C\text{-}H activation step was studied by DFT calculations (see Supporting Information for details) (Figure 5) Among the several potential mechanisms by which this reaction may occur, that have been studied by theoretical ways, such as electrophilic aromatic substitution or Heck type arylation, proposed in the case of C(sp\textsuperscript{3})\text{-}H bonds, or classic C-H oxidative addition also evaluated in the case of C(sp\textsuperscript{3})\text{-}H bonds, concerted metalation-deprotonation (CMD) pathway has often been found as the most favourable one.\textsuperscript{22,23}

Moreover, taking into account the early finding by Houk and Yu,\textsuperscript{18} using this type of mechanism to explain the stereoselectivity in certain Pd(II)-catalyzed C(sp\textsuperscript{3})\text{-}H activation, we envisaged that a similar model could be applied in our case. For this purpose a complex similar to 11 (see Figure 4) but resulting from the N-(2-pyridyl)sulfonyl valine derivative (Ia) was used as starting material model. This study revealed that the C\text{-}H activation of both diastereotopic methyl groups would afford several diastereomeric transition states showing different conformations of the tricyclic palladacycle that is being formed.\textsuperscript{23} The most stable and representative ones are shown in the Figure 5. Among them, the most stable TS(Ia-IIa) arises from the C\text{-}H activation at the pro-S methyl group and could account for the experimental selectivity observed. By contrast, TS(Ia-IIaA) and TS(Ia-II\text{a}B), that come from the C\text{-}H activation at the pro-R methyl group and would afford diastereomeric product, resulted to be less stable (1 and 1.7 kcal\text{·}mol\textsuperscript{-1} respectively).\textsuperscript{24} In addition, the energy profile also agrees with the reversibility of the C\text{-}H activation step.

![Fig. 5](image)

**Fig. 5** Energy profile for the C\text{-}H activation step of the N-(2-pyridyl)sulfonyl valine derivative 1 in the gas phase (M06 / 6-311+G(2df,2p) (C,H,N,O,S), SDD (Pd) / B3LYP / 6-31G(d) (C,H,N,O,S), SDD (Pd)). Relative G values at 298 K (kcal\text{·}mol\textsuperscript{-1}) Single point solvation energy corrections (CH\textsubscript{3}CN, CPCM model) are indicated in parentheses

The energy difference between TS(Ia-IIa), TS(Ia-II\text{a}A) and TS(Ia-II\text{a}B) can be attributed to different steric interactions (Figure 6). The six-membered cycle formed by Pd, N and the rest of amino acid moiety, including the C\text{-}H bond being cleaved, adopts a distorted chair-like conformation. In TS(Ia-IIa), this conformation locates both methyl and methoxy carbonyl groups in a pseudoequatorial arrangement and only weak gauche interactions (O=C/H-C\textsubscript{\beta}, CH\textsubscript{3}/H-C\textsubscript{\gamma} and O=C/CH\textsubscript{2}) can be observed. However, in the case of TS(Ia-
II’a)A and TS(II’a)B both structures show one of the groups, methoxy carbonyl and methyl respectively, in an axial arrangement. Thus, TS(II’a)A shows, in addition to gauche repulsions (CH$_3$/H-$C\gamma$ and $O=C$/CH$_3$), an important 1,3-syn-diaxial interaction between methoxy carbonyl group and H-$C\gamma$. Respect to TS(II’a)B, the axial methyl group has important gauche interactions with all groups around.

![Fig. 6 Optimized geometries of transition states TS(IIa), TS(II’a)A and TS(II’a)B. Distances are given in Å](image)

**Insights into the turnover-limiting step**

To gain insights into the nature of the turnover-limiting step, we decided to study the temperatures at which the catalytic and stoichiometric reactions take place (Scheme 6). Thus, the lowest temperature at which the catalytic reaction occurs was determined to be 60 °C in CH$_3$CN or 40 °C in HFIP, that are the same temperatures required by bimetallic complex 5 to react with 4-iodotoluene. However, the formation of complex 5 by stoichiometric reaction of tert-leucine derivative 4 with Pd(OAc)$_2$ took place with good conversion at room temperature in CH$_3$CN or HFIP. These results suggest that, in the case of 4, the C–H activation could not be the turnover-limiting step.

Palladacycle 14 (see Scheme 6) could not be isolated, however, it was characterized by one- and two-dimensional NMR studies, as well as by high resolution mass analysis, from a mixture of the γ-monoarylated product 6 and palladacycle 14 (see Supporting Information). According to its structure it should be formed by an ortho C(sp$^3$)-H bond activation of the aryl ring introduced in the first C(sp$^3$)-H arylation reaction. This compound, as well as 5, in solution seems to be a monomer on the basis of DOSY spectroscopy analysis (D 1.32x 10$^{-9}$ m$^{-2}$s$^{-1}$) (see Supporting Information).

![Scheme 6 Stoichiometric and catalytic reactivity of tert-leucine derivative 4](image)

We next sought to identify the resting state of the Pd(OAc)$_2$-catalyzed C–H arylation of tert-leucine derivative 4 (Scheme 7). Examination of the $^1$H NMR spectra during the reaction at 110 °C after 5 min, 30 min, and 1 h showed the formation of different palladium species (complex 5, 14, 15 and 16) in a ratio of 9-10 mol% (respect to total amount of 4, 6 and 7) being 5 the predominant resting state. After 5 min of reaction the bimetallic complexes 5 and 14 were observed in a 4.9:1 ratio, respectively. Increasing the reaction time, new palladium complexes 15 and 16, which are the monoarylated analogous of 5 and 14, respectively, were also detected. (See Supporting Information). The identification of 5 as the predominant resting state, which is located before the turnover-limiting step, indicate that, in this case, the C–H activation could not be the turnover-limiting step, in contrast with the majority of Pd-catalyzed C–H functionalization reactions, where cyclopalladation is typically the rate limiting.$^{3c,25}$
Complexes 15 and 16 (see Scheme 7) were also characterized by one- and two-dimensional NMR studies, as well as by high resolution mass analysis, from the reaction mixture of the bimetallic complex 5 with 2.5 equiv of 4-iodotoluene and 2.0 equiv of AcOH in CD$_3$CN at 60 ºC after 16 h (see Supporting Information).

**Transmetallation or Oxidative Addition Mechanism?**

After the C–H activation step two possible mechanisms might be considered (Figure 7): i) a Pd(II)/Pd(0) mechanism via transmetallation between two palladium(II) centers followed by reductive elimination. Although no mechanistic investigations have been conducted for the Pd(OAc)$_2$-catalyzed C–H arylation with Ag(I) salts$^{26,27}$ and aryl iodides, it is believed that these reaction follow a Pd(II)/(IV) mechanism.$^{5,6}$ Alternatively, a mechanism involving the transmetallation between two Pd(II) centers could also be considered.$^{9a,14}$ This proposal has been supported by computational studies,$^{15}$ and by the fact that only one example of Pd(IV) complex resulting from the oxidative addition of aryl iodide to Pd(II) species has been described to date.$^{28}$

![Scheme 7 Identification of the resting states in the catalytic reaction](image)

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These possible mechanisms were studied by means of DFT calculations. The complete energy profile for the reaction of 4 is depicted in Figure 8. The barrier for the C–H activation step of tert-leucine derivative Ib decreases comparing to the case of valine derivative Ia (for comparison see Fig. 5) being slightly lower than the corresponding values for the rest of steps. This point is in agreement with the experimental results that suggest that, in the case of 4, the C–H activation could not be the turnover-limiting step.$^{29}$ From intermediate IIIb, the possible mechanisms via oxidative addition of aryl iodide to a palladium(II) species followed by reductive elimination (intermediates IVb, Vb, VIIb) or via transmetallation between two palladium(II) centers followed by reductive elimination (intermediates VIIIb, IXb, Xb) were evaluated. The Pd(IV) pathway begins by exchange of the labile solvent ligand with iodobenzene to afford IVb from which TS(IVb-Vb) is reached (Figure 9). The free activation energy required for this oxidative addition step resulted to be only slightly higher than that for the C–H activation step and even lower when solvent corrections are considered. Thus, the pentacoordinated Pd(IV) complex Vb is formed.$^{30}$ From this point, reductive elimination takes place through a cyclic chair like transition state TS(Vb-VIIb) (Fig. 9), in which the three membered ring with bonds that are being formed and broken is integrated, that lies close to that of the oxidative addition.$^{31}$ Respect to the transmetallation pathway, reaction of IIIb with a second Pd(II) center leads to VIIb in which both palladium atoms show a slightly distorted square planar coordination with the calculated distance between both of them being 2.69 Å, lower than the sum of their van der Waals radii (3.26 Å).$^{30}$ Changing the coordination mode of the palladium in the metalladacycle leads to complex VIIIb from which transfer of the alkyl group of the metallacycle to the second metal center affords complex IXb. Despite several attempts, we could not find a transition state for this step. Reductive elimination from this latter complex allows the formation of the C-C bond through TS(IIXb-Xb) (Fig. 9), that shows the three member ring with bonds that are being formed and broken integrated in a seven membered cycle, with a higher steric hindrance between
the aryl group that is transferred and the axial Me group than in the case of TS(Vb-VIb) (3.11 Å and 3.28 Å respectively).

![Fig. 8. Complete energy profile for the reaction of the N-(2-pyridyl)sulfonyl tert-leucine derivative in the gas phase (M06 / 6-311+G(2df,2p) (C,H,N,O,S), SDD (Pd) // B3LYP / 6-31G(d) (C,H,N,O,S), SDD (Pd)). Relative G values at 298 K (kcal mol\(^{-1}\)) Single point solvation energy corrections (CH\(_3\)CN, CPCM model) are indicated in parentheses.](image)

**Fig. 8.** Complete energy profile for the reaction of the N-(2-pyridyl)sulfonyl tert-leucine derivative in the gas phase (M06 / 6-311+G(2df,2p) (C,H,N,O,S), SDD (Pd) // B3LYP / 6-31G(d) (C,H,N,O,S), SDD (Pd)). Relative G values at 298 K (kcal mol\(^{-1}\)) Single point solvation energy corrections (CH\(_3\)CN, CPCM model) are indicated in parentheses.

![Fig. 9. Optimized geometries of transition states for the arylation steps via Pd(IV) species [TS(Vb-Vb) and TS(Vb-VIb)] and reductive elimination step for the transmetallation pathway [TS(Xb-Xb)]. Bond lengths are given in Å.](image)

**Fig. 9.** Optimized geometries of transition states for the arylation steps via Pd(IV) species [TS(Vb-Vb) and TS(Vb-VIb)] and reductive elimination step for the transmetallation pathway [TS(Xb-Xb)]. Bond lengths are given in Å.

This would be the most energy demanding step of the entire process.\(^{32}\) Thus, according to the energy profile, the preferred pathway would be the Pd(II)/Pd(IV) mechanism via oxidative addition of aryl iodide to a palladium(II) species followed by reductive elimination. Both transition states in this pathway are quite close in energy, however reductive elimination could be the rate determining step especially if solvent effects are considered.

For the catalytic cycle, the role of AgOAc is not entirely clear.\(^{33}\) Since, in the stoichiometric reaction, the formation of the bimetallic complex 5 and its reaction with 4-iodotoluene takes place without AgOAc, providing cleanly the arylated products 6 and 7 (see Scheme 2), we might intuitively rule out that AgOAc is acting as a promoter for the oxidative addition step or that it is necessary for the C–H activation to take place. Instead, Ag salts are likely acting as a halide scavenger, and/or an oxidant for the palladium center. However, silver salts could also be involved in the formation of hetero-bimetallic Pd–Ag species, which could participate in the C–H activation step.\(^{26,27}\)

**Conclusions**

In summary, we carried out detailed mechanistic investigations of Pd(OAc)\(_2\)-catalyzed C(sp\(^3\))–H γ-arylation of amino acid derivatives with aryl iodides. The results obtained, summarized in Figure 10,
Catalyst resting state

Bimetallic complex 5

2 AcOH

C-H Activation

Oxidative Addition

PyO2S

[Ar]

Pd(OCO)2

+ Pd[Ar]

OMe

OMe

Reductive Elimination

Fig. 10 Proposed catalytic cycle

Acknowledgements

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Notes and references

a. Servicio Interdepartamental de Investigación (SII), Facultad de Ciencias, Universidad Autónoma de Madrid, Cantoblanco 28049 Madrid (Spain).
b. Departamento de Química Orgánica, Facultad de Ciencias, Universidad Autónoma de Madrid, Cantoblanco 28049 Madrid (Spain). Fax: +34 914973966; Tel: +34 914972996; E-mail: rati.fernandez@uam.es and ines.alonso@uam.es

† Electronic Supplementary Information (ESI) available: experimental and computational details as well as spectroscopic, crystallographic and analytical data for new compounds. See DOI: 10.1039/b000000x/


For references on mechanistic studies of Pd(OAc)$_2$-catalyzed C(sp$^3$)–H arylation using diaryl iodonium salts, see: (a) N. R. Deprez and M. S. Sanford, J. Am. Chem. Soc. 2009, 131, 11234. (b) A. J. Canty, A. Ariaifar, M. S. Sanford and B. F. Yates, Organometallics 2013, 32, 544.


The mechanistic studies of ref. 26 indicated that the C–H activation occurs via a Pd-Ag heterodimeric transition state.


However, in the case of valine derivative theoretical calculations indicate that the C–H activation step is the rate-limiting one (see SI for the complete energy profile).

In the case of valine derivative 1, other possible Pd(IV) penta and hexacoordinated complexes (octahedral complex by association of a solvent molecule) resulted less stable. Equivalent coordinatively unsaturated complexes have been proposed as intermediates in analogous theoretical studies, see: (a) G. Maestri, E. Motti, N. Della Ca, M. Malacria, E. Derat and M. Catellani, J. Am. Chem. Soc. 2011, 133, 8574. (b) M. Malacria and G. Maestri, J. Org. Chem. 2013, 78, 1323.

Although it has been usually accepted that reductive elimination on a Pd(IV) center is faster than oxidative addition (see ref. 13), kinetic data do not provide direct evidence to support either step as rate-determining (see L. Jiao, E. Herdtweck, T. Bach. J. Am. Chem. Soc. 2012, 134, 14563). On the other hand, taking into account the presence of acetic acid in the reaction media and in order to study its possible effect to facilitate the reductive elimination step (see ref. 9b) protonated species VbH and TS(Xb-Xb)H were studied resulting to be much more unstable than the corresponding Vb and TS(Xb-Xb) (26.5 and 27.6 kcal mol⁻¹, respectively, in solution and even more in the gas phase) (see SI).

Transmetallation pathway calculated from Pd(0) and PhI (as in ref. 15) would give a free activation energy for the reductive elimination step lower than for the C–H activation step. This fact is not in agreement with the experimental observation that suggests the C–H activation step in this case could not be the rate limiting one.