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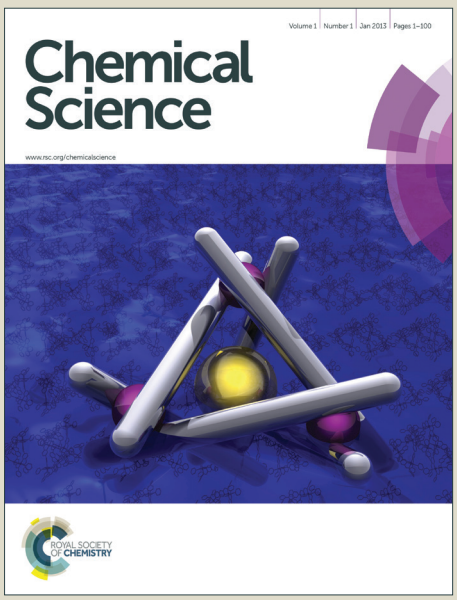

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ARTICLE

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

Cite this: DOI: 10.1039/xoxxoooooox

Received ooth January 2012,
Accepted ooth January 2012

DOI: 10.1039/xoxxoooooox

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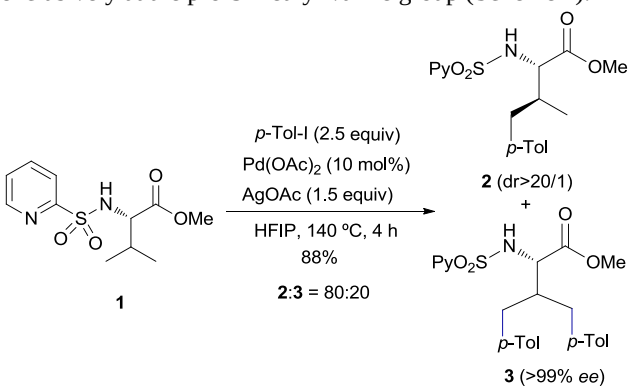
The $Pd(OAc)_2$-catalyzed γ-arylation of amino acid esters bearing a removable *N*-(2-pyridyl)sulfonyl directing group via C(sp^3)–H activation provides a direct method to functionalized amino acids without racemization at the αC and high degree of stereoselectivity. The present mechanistic studies suggest 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

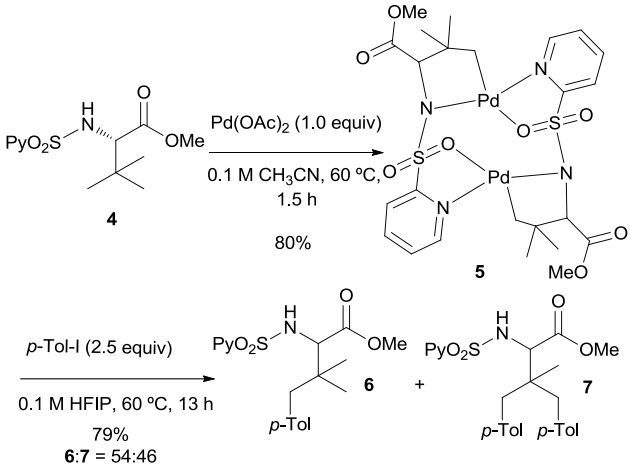
Transition metal-catalyzed activation of C–H bonds has become a powerful method to functionalize organic molecules.[1] Great progress has been made in the direct and selective metal-catalyzed functionalization of C(sp^2)–H bonds.[2] However, protocols for the direct C(sp^3)–H functionalization are still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

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^2)–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-metalated 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_3CN at 60 ˚C (Scheme 2). We observed that palladacycle **5** was able to react with 4-iodotoluene [60 ºC in HFIP (hexafluoroisopropanol)] leading to a nearly equimolecular mixture of the monoarylated and bisarylated products **6** and **7**.



Scheme 2 Synthesis and reactivity of the bimetallic complex **5**

Few mechanistic studies on palladium-catalyzed C–H arylation reaction have been reported,[8-15] 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 γ-arylation of amino acid derivatives with aryl iodides.

Results and Discusion

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_3CN 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**,[7] 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 ºC, suggesting that the dimer is not the predominant species in solution. On the other hand, in the X-Ray structure the H_1-H_3 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 (1.44×10^{-9} m^2/s for bimetallic complex **5** and 1.43×10^{-9} m^2/s for the monoarylated **6**), and the calculated molecular weight[16] 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.[17]

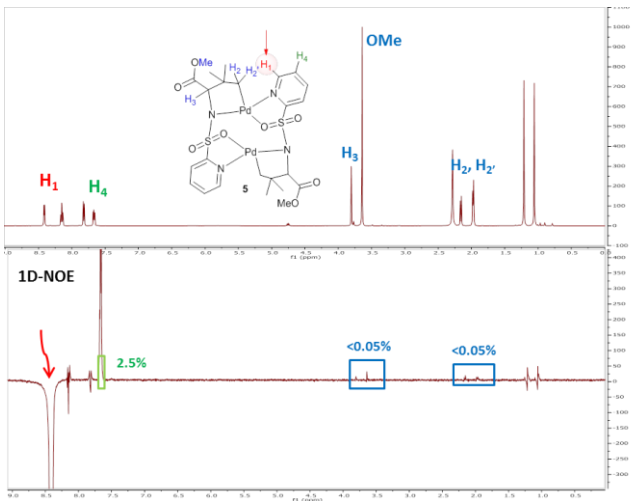
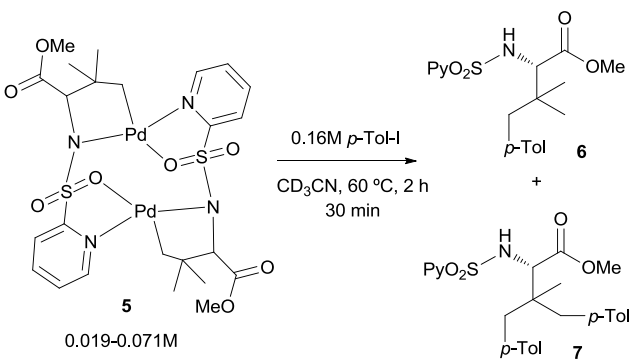


Fig. 1 1D-Selective NOE spectrum of **5** (CD_3CN, 5 ºC)

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 ºC was monitored by ^1H NMR analysis after quenching the reaction at -78 ºC. We established the product concentration from the mixture of **6** and **7**.[18] Figure 2 shows a linear fit of the reaction rate versus the concentration of complex **5** from 0.019-0.071 M.[17] 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.[19]



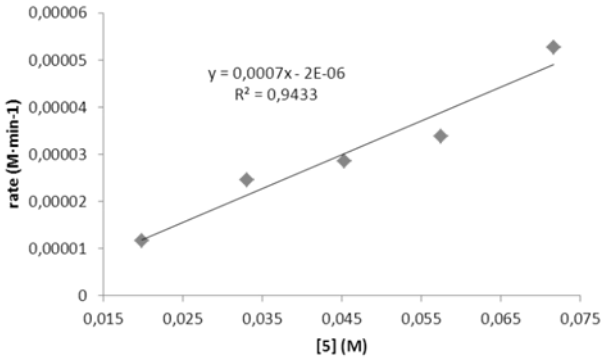
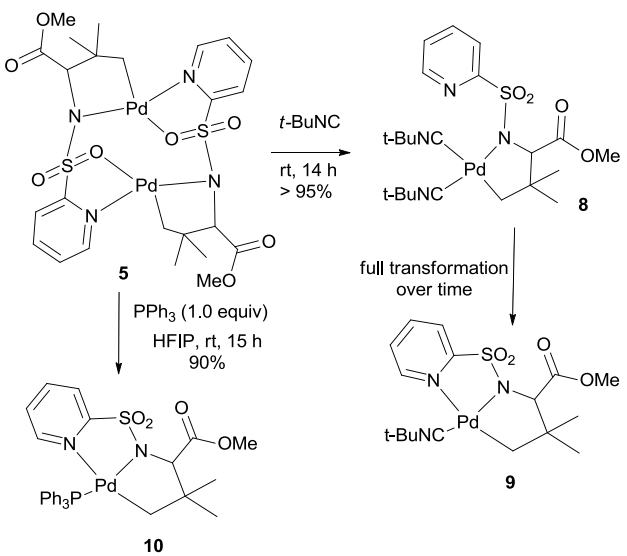


Fig. 2 Plot of the initial rate vs [**5**] in HFIP at 60 ºC

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).[20] The monomer **8** was found to be unstable in solid state and a new monomeric 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 PPh_3 in HFIP at room temperature furnished directly the monomeric complex **10**. Unfortunately, all our attempts to characterized 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**

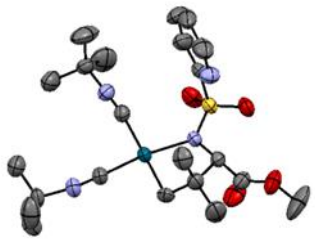
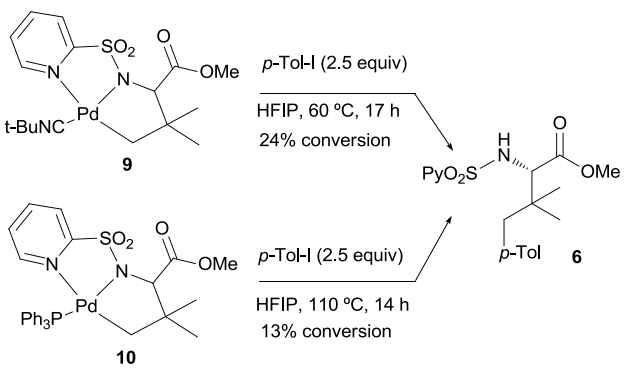


Fig. 3 ORTEP diagram of compound **8** determined by X-ray analysis. Hydrogen atoms have been removed for clarity

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 spectroscopy (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

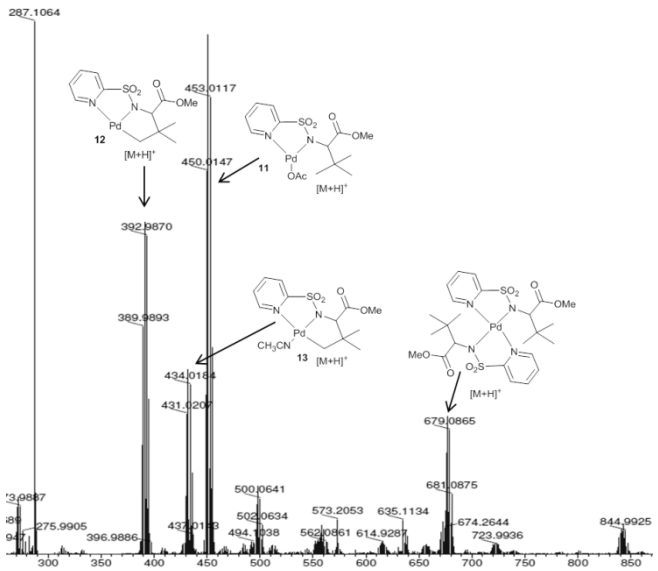
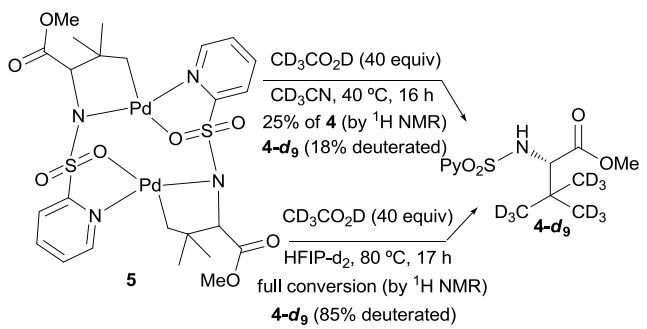


Fig. 4 ESI(+)-MS of the stoichiometric reaction between *tert*-leucine derivative **1** and $Pd(OAc)_2$ in CH_3CN at room temperature after 20 min

The C–H activation step: reversibility and stereoselectivity

The reversibility of the C–H activation step was investigated in the reaction of the bimetallic complex **5** with 40 equiv of acetic acid-d_4 (Scheme 5). It was found that the reaction at 40 ºC in CD_3CN provided 25%[21] of *tert*-leucine derivative **4-*d*$_9$** partially deuterated (c.a. 18%) after 16 h, while the reaction in HFIP-d_2 at 80 ºC afforded the *tert*-leucine derivative **4-*d*$_9$** almost completely deuterated (c.a. 85%) after 17 h. This interconversion implies that the C–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*$_9$** was not formed at room temperature in CD_3CN or at 60 ºC in HFIP-d_2, temperatures at which the forward reaction can take place.



Scheme 5. H/D Exchange studies

The stereoselectivity of the C–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 $C(sp^2)$–H bonds, or classic C-H oxidative addition also evaluated in the case of $C(sp^3)$–H bonds, concerted metalation-deprotonation (CMD) pathway has often been found as the most favourable one.[22,9b] Moreover, taking into account the early finding by Houk and Yu,[18] using this type of mechanism to explain the stereoselectivity in certain Pd(II)-catalyzed $C(sp^3)$–H activation, we envisaged that a similar model could be applied in our case. For this purpose a complex similar to **11** (see Fig. 4) but resulting from the *N*-(2-pyridyl)sulfonyl valine derivative (**Ia**) was used as starting material model. This study revealed that the C–H activation of both diastereotopic methyl groups would afford several diastereomeric transition states showing different conformations of the tricyclic palladacycle that is being formed.[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–H activation at the pro-*S* methyl group and could account for the experimental selectivity observed. By contrast, **TS(Ia-II'a)A** and **TS(Ia-II'a)B**, that come from the C–H activation at the pro-*R* methyl group and would afford diastereomeric product, resulted to be less stable (1 and 1.7 kcal·mol^{-1} respectively).[24] In addition, the energy profile also agrees with the reversibility of the C–H activation step.

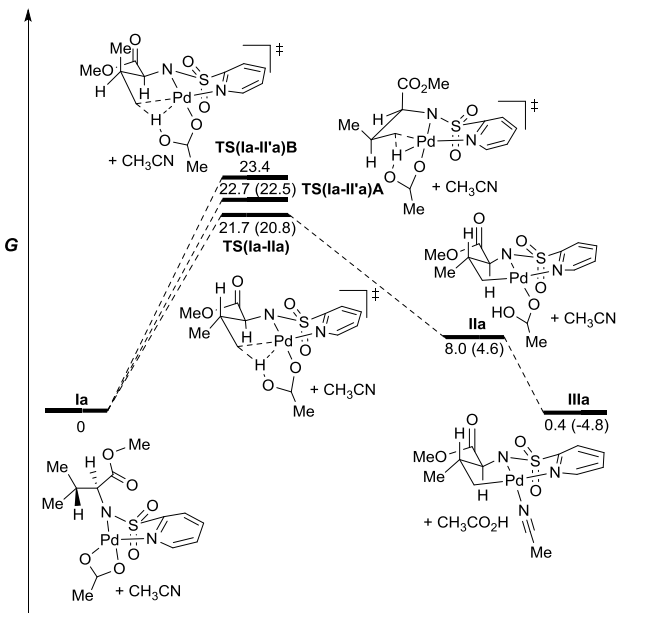


Fig. 5 Energy profile for the C–H activation step of the *N*-(2-pyridyl)sulfonyl valine derivative **1** in the gas phase (M06 / 6-311+G(2df,2p) (C,H,N,O,S), SDD (Pd) // B3LYP / 6-31G(d) (C,H,N,O,S), SDD (Pd)). Relative G values at 298 K (kcal mol^{-1}) Single point solvation energy corrections (CH_3CN, CPCM model) are indicated in parentheses

The energy difference between **TS(Ia-IIa)**, **TS(Ia-II'a)A** and **TS(Ia-II'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–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_β, CH_3/H-C_γ and O=C/CH_3) can be observed. However, in the case of **TS(Ia-**

II'a)A and **TS(Ia-II'a)B** both structures show one of the groups, methoxy carbonyl and methyl respectively, in an axial arrangement. Thus, **TS(Ia-II'a)A** shows, in addition to *gauche* repulsions (CH_3/H-C_γ and O=C/CH_3), an important 1,3-*syn*-diaxial interaction between methoxy carbonyl group and H-C_γ. Respect to **TS(Ia-II'a)B**, the axial methyl group has important *gauche* interactions with all groups around.

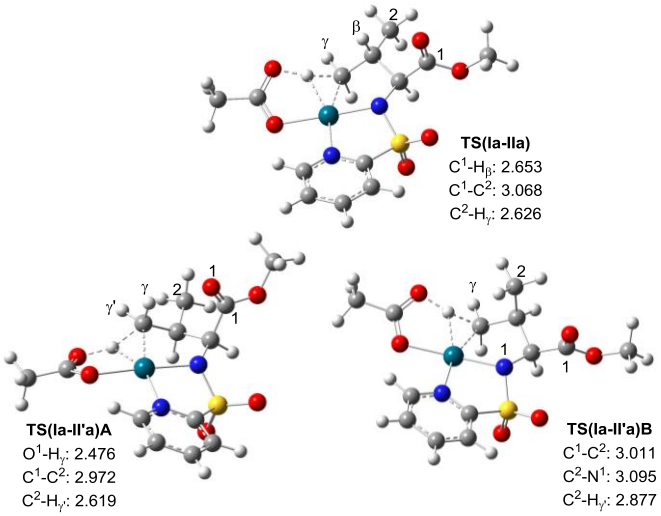
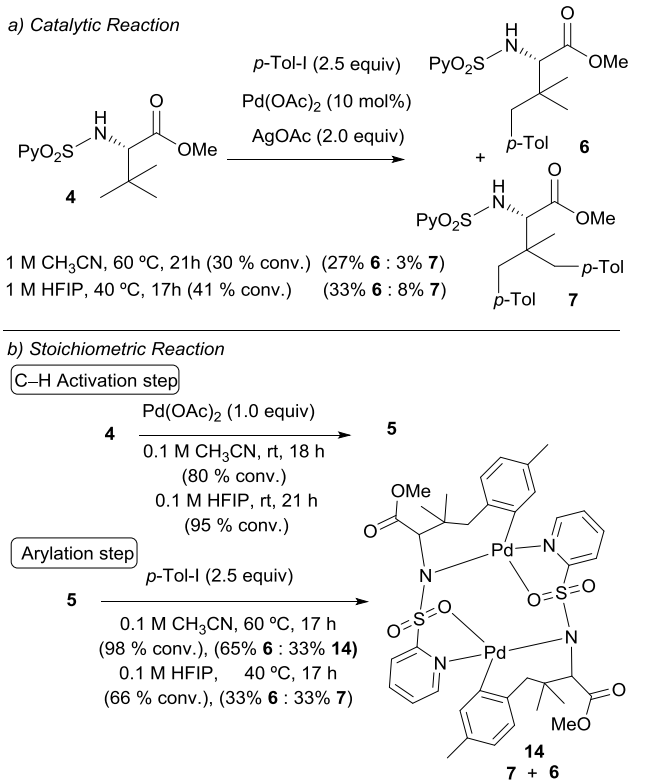


Fig. 6 Optimized geometries of transition states **TS(Ia-IIa)**, **TS(Ia-II'a)A** and **TS(Ia-II'a)B.** Distances are given in Å



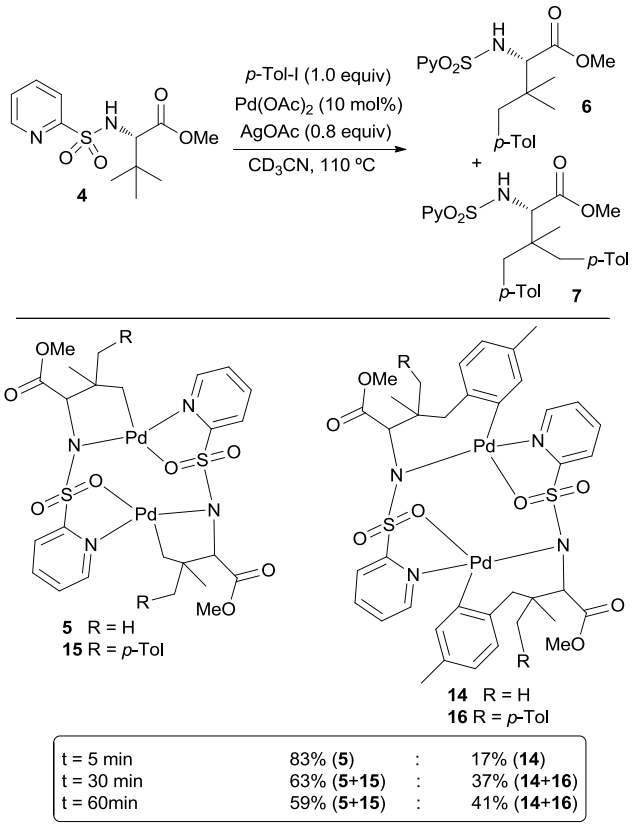
Scheme 6 Stoichiometric and catalytic reactivity of *tert*-leucine derivative **4**

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 ºC in CH_3CN or 40 ºC 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_3CN 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^2)–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) (see Supporting Information).

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 ^1H NMR spectra during the reaction at 110 ºC 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.[5c,25]



Scheme 7 Identification of the resting states in the catalytic reaction

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_3CN 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 and *ii*) a Pd(II)/Pd(IV) mechanism via oxidative addition of aryl iodide to a palladium(II) species 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]

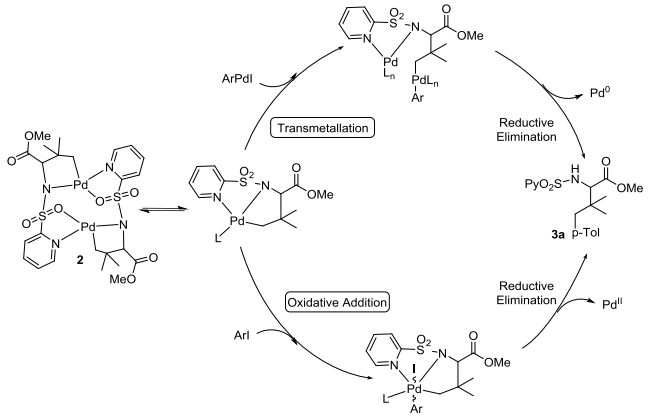


Fig. 7 Possible mechanisms after the C–H activation step

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**, **VIb**) or via transmetallation between two palladium(II) centers followed by reductive elimination (intermediates **VIIb**, **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-VIb)** (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).[30a] 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(IXb-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).

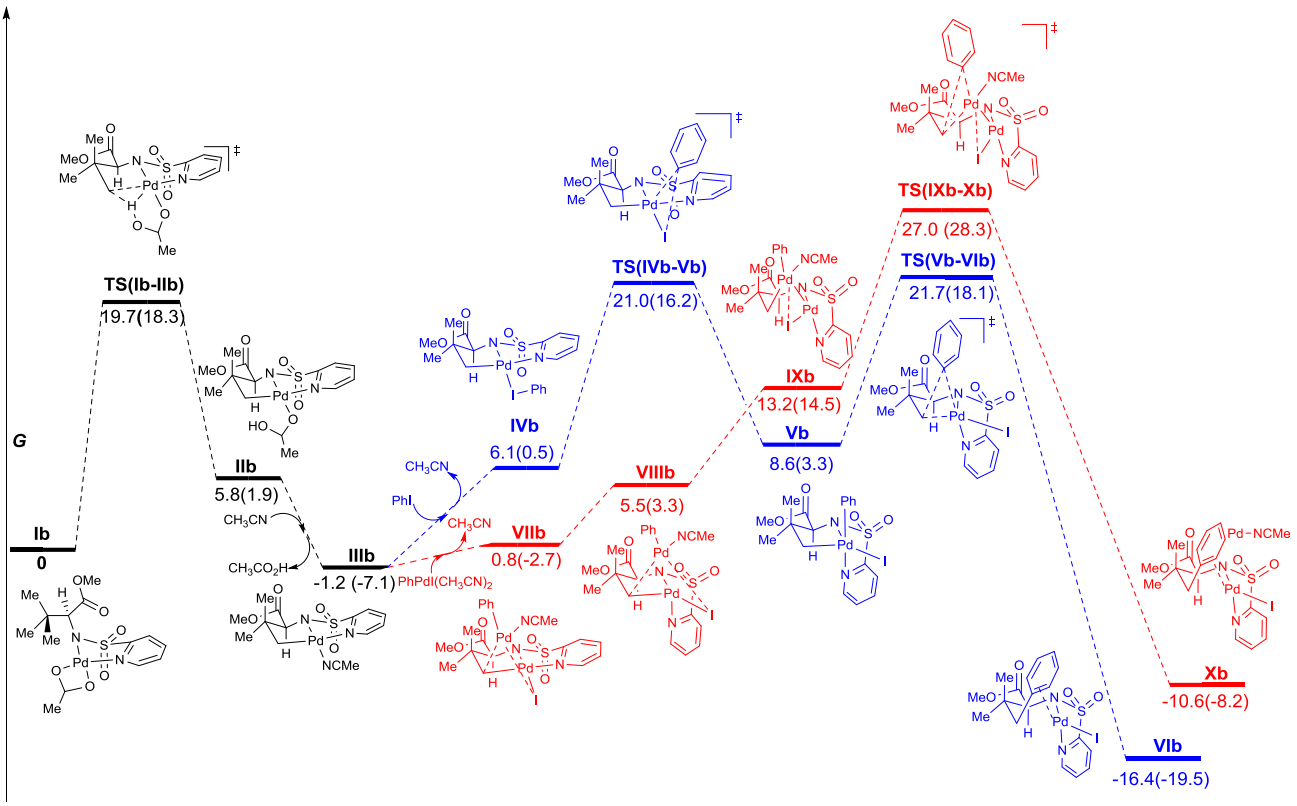


Fig. 8. Complete energy profile for the reaction of the *N*-(2-pyridyl)sulfonyl *tert*-leucine derivative in the gas phase (M06 / 6-311+G(2df,2p) (C,H,N,O,S), SDD (Pd) // B3LYP / 6-31G(d) (C,H,N,O,S), SDD (Pd)). Relative G values at 298 K (kcal mol^{-1}) Single point solvation energy corrections (CH_3CN, CPCM model) are indicated in parentheses

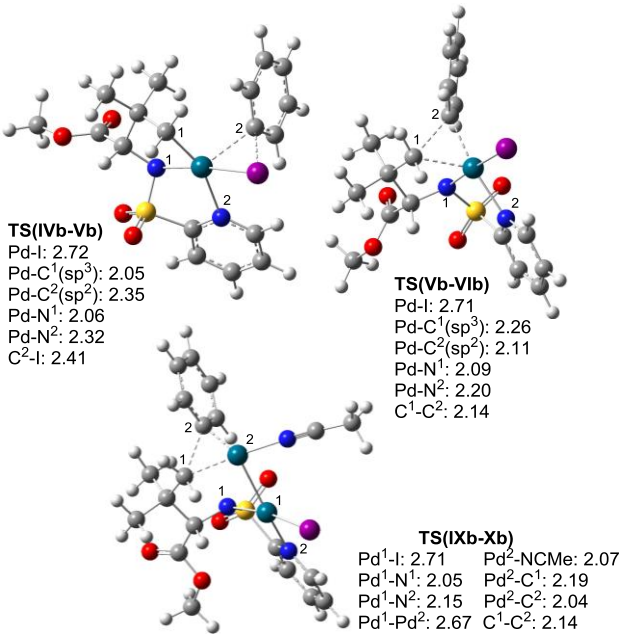


Fig. 9 Optimized geometries of transition states for the arylation steps via Pd(IV) species [**TS(IVb-Vb)** and **TS(Vb-VIb)**] and reductive elimination step for the transmetallation pathway [**TS(IXb-Xb)**]. Bond lengths are given in Å

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,

indicate that *i*) in solution, the bimetallic Pd(II) complex **5** is in equilibrium with an active monomeric species, which represents the main species in solution, *ii*) the C–H activation step is reversible, *iii*) the bimetallic Pd(II) γ-metalated complexes are the resting states of the catalytic reaction and *iv*) the C–H bond cleavage is likely not the rate determining step at least for the *tert*-leucine derivative **4**. In addition, the DFT calculations explained the observed stereoselectivity in the case of valine derivative, for which arylation occurs exclusively at the pro-*S* methyl group, and suggested that the reaction proceeds through a Pd(II)/Pd(IV) mechanism via oxidative addition of aryl iodide to a palladium(II) species followed by reductive elimination rate determining step. We hope that the understanding of this transformation might contribute in the design and development of novel reactions in the field.

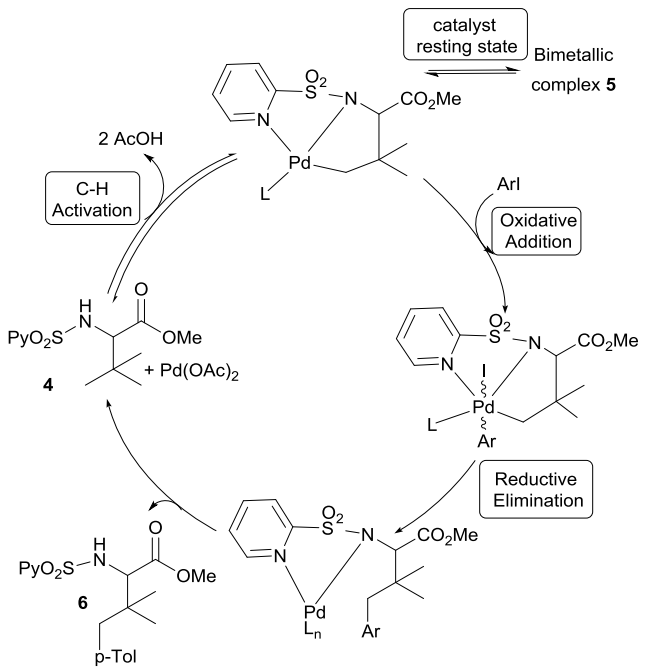


Fig. 10 Proposed catalytic cycle

Acknowledgements

Financial support from the Ministerio de Economía y Competitividad (MINECO, project CTQ2012-35790) and the Consejería de Educación de la Comunidad de Madrid (programme AVANCAT; S2009/PPQ-1634) are gratefully acknowledged. We thank Prof. Juan Carlos Carretero for helpful suggestions and for laboratory facilities. We also thank the Centro de Computación Científica (UAM) for generous allocation of computer time.

Notes and references

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† 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/

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21 Ratio calculated by ^{1}H NMR of the crude mixture by integration of the *ortho*-proton to the nitrogen of the pyridine moiety. Three products were detected: *i*) the bimetallic complex **5**, with a value of two protons for the corresponding signal of the *ortho*-proton, *ii*) the *tert*-leucine derivative **4** partially deuterated with a value of one proton for the corresponding signal of the *ortho*-proton and, *iii*) an unknown compound which value for the *ortho*-proton we assignment as one proton.

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24 The barrier for the C–H activation step slightly decreases when solvent effects are considered. Moreover, the relative free activation energy between **TS(Ia-IIa)** and **TS(Ia-II'a)A**, the most stable of the transition states that would afford the diastereomeric product, increases till 1.7 $kcalmol^{-1}$ in these conditions. This value predicts a 19/1 diastereomeric ratio in excellent agreement with experimental results (dr>20/1, Scheme 1).

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32 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.

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