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Experimental and computational studies on the mechanism of the Pd-catalyzed C(sp^3)–H γ-arylation of amino acid derivatives assisted by the 2-pyridylsulfonyl group†

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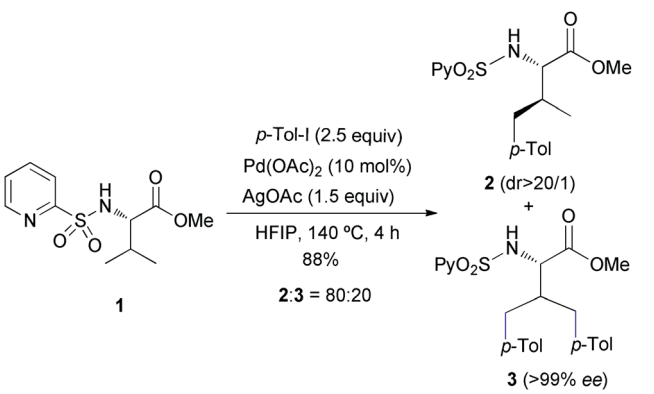
The $Pd(OAc)_2$-catalyzed γ-arylation of amino acid esters bearing a removable *N*-(2-pyridyl)sulfonyl directing group *via* C(sp^3)–H activation provides a direct method to form functionalized amino acids without racemization at the α-C and with a high degree of stereoselectivity. The present mechanistic studies suggest that the reaction proceeds *via* a catalytically active monomeric species, and that the C–H activation is reversible and is not always the turnover limiting step. Moreover, theoretical calculations explain the observed stereoselectivity and suggest 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 direct C(sp^3)–H functionalization are still limited.[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 has 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 α-C 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).

In addition, a bimetallic Pd(II) γ-metalated intermediate **5** was isolated and characterized from 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 °C in HFIP (hexafluoroisopropanol)] leading to a nearly equimolecular mixture of the monoarylated and bisarylated products **6** and **7**, respectively.



Scheme 1 Pd-catalyzed γ-arylation of L-valine derivative **1**.

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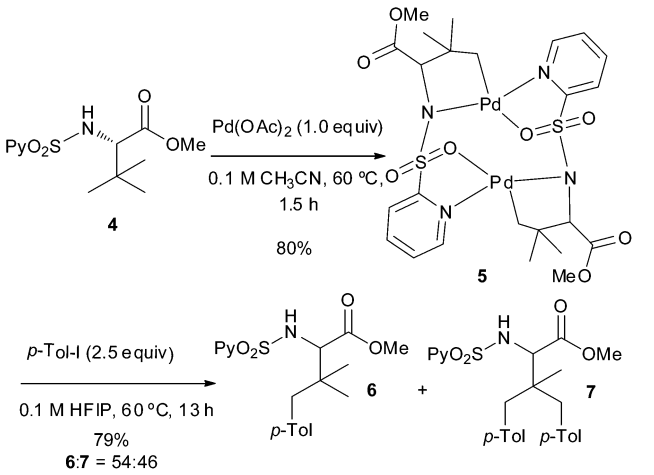


Scheme 2 Synthesis and reactivity of the bimetallic complex **5**.

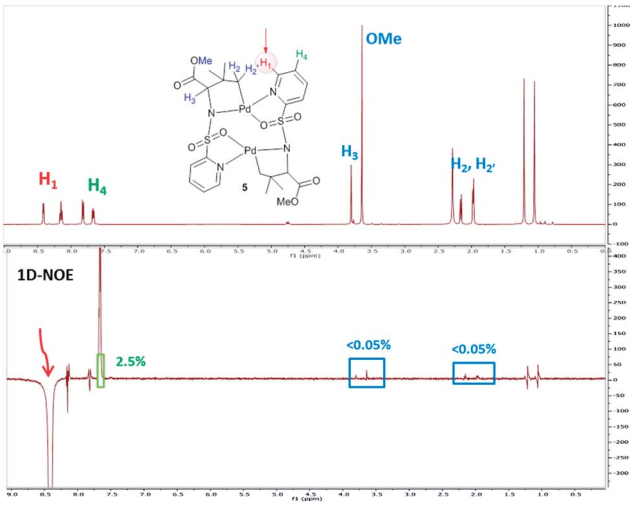


Fig. 1 1D-selective NOE spectrum of **5** (CD_3CN, 5 °C).

Few mechanistic studies on palladium-catalyzed C–H arylation reactions 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 reaction with these reagents remains elusive and speculative at this time. To cast some light on the subject, and taking advantage of the fact 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 the $Pd(OAc)_2$-catalyzed $C(sp^3)$–H γ-arylation of amino acid derivatives with aryl iodides.

Results and discussion

Identification of the catalytically active species

In our attempt to understand the mechanism of the C–H arylation reaction, we first sought to identify the catalytically active species. Thus, the nuclearity of the bimetallic complex **5** in solution was investigated. The 1D-selective NOE spectrum obtained by inversion of the signal corresponding to the proton (H_1, 8.38 ppm) *ortho* to the nitrogen of the pyridine ring 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) (Fig. 1). From the X-ray geometry of bimetallic complex **5**,[7] the measured distance between H_1 and H_2/$H_{2'}$ was between 2.1 and 3.2 Å (an average of 2.48 Å). For this short distance, a clear NOE interaction should be expected. However, the observed NOE was 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, the X-ray structure shows that 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 diffusion-ordered spectroscopy (DOSY) experiments for the bimetallic complex **5** and the monoarylated product **6**. The obtained D values are very similar (1.44×10^{-9} m^2 s^{-1} for bimetallic complex **5** and 1.43×10^{-9} m^2 s^{-1} 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 that of the expected weight for complex **5** (see ESI†). This experimental evidence strongly suggests that the bimetallic complex **5** is mainly present as a monomer in solution.[17]

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** and 4-iodotoluene in HFIP at 60 °C was monitored by ^1H NMR analysis after quenching the reaction at −78 °C. We established the product conversion from the total concentration of **6** and **7**.[18] Fig. 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 a slope of 1.0, revealing that the reaction is first order in complex **5** (see ESI†). 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]

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 (Fig. 3).[20] The monomer **8** was found to be unstable in the solid state and a new monomeric palladium complex **9**, with one fewer *tert*-butyl isocyanide ligand, 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 of 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.

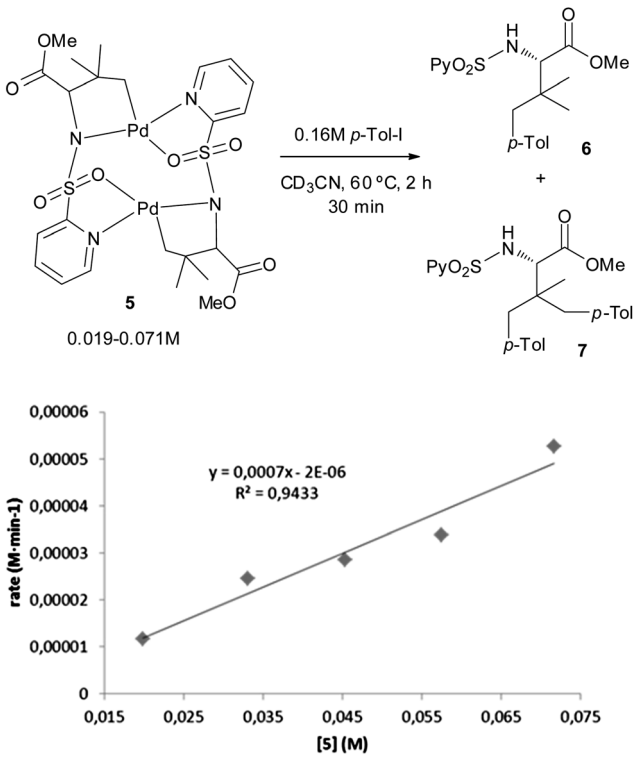
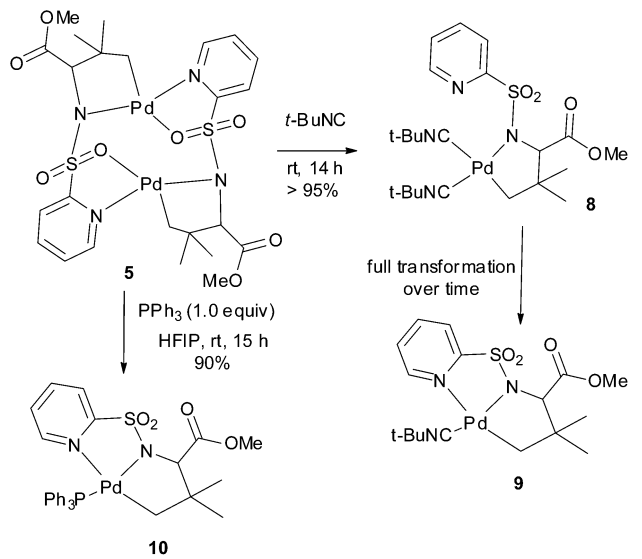


Fig. 2 Plot of the initial rate *vs.* [5] in HFIP at 60 °C.



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

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

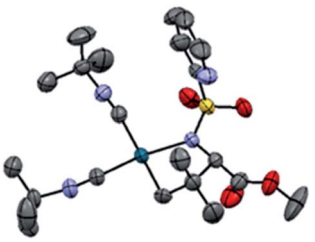


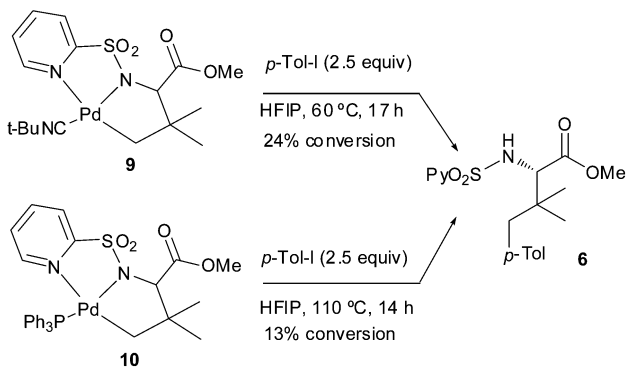
Fig. 3 ORTEP diagram of compound **8** determined by X-ray analysis. Hydrogen atoms have been removed for clarity.

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 °C 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 °C after 14 h. The reaction of the bimetallic complex **5** under similar reaction conditions (60 °C for 17 h or 110 °C for 14 h) resulted in 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 bimetallic complex **5**, and at the same time that complex **9** is more reactive than complex **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 (Fig. 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**, originating from 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 catalytically active species of the reaction.

The C–H activation step: reversibility and stereoselectivity

The reversibility of the C–H activation step was investigated for the reaction of bimetallic complex **5** with 40 equiv. of acetic



Scheme 4 Reactivity of the monomeric complexes **9** and **10**.

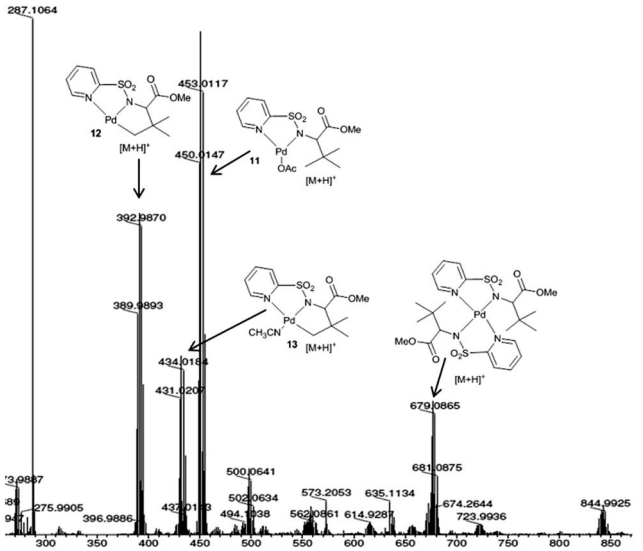


Fig. 4 ESI(+)-MS spectrum of the stoichiometric reaction between *tert*-leucine derivative **1** and $Pd(OAc)_2$ in CH_3CN at room temperature after 20 min.

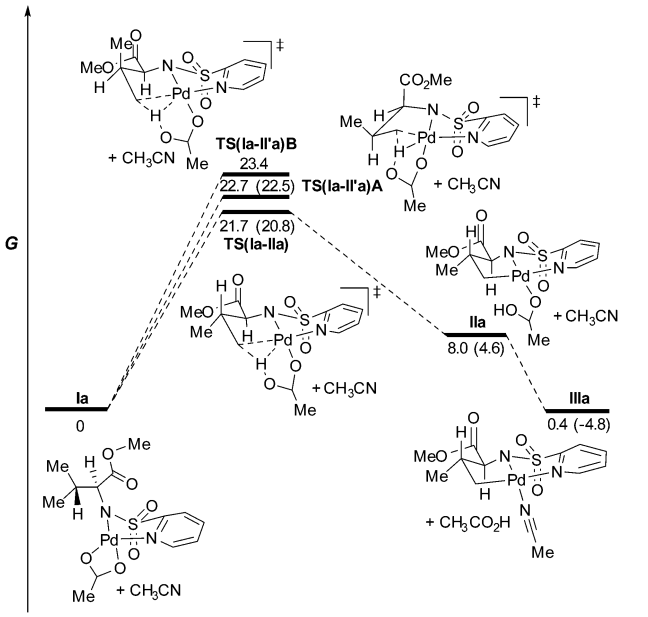
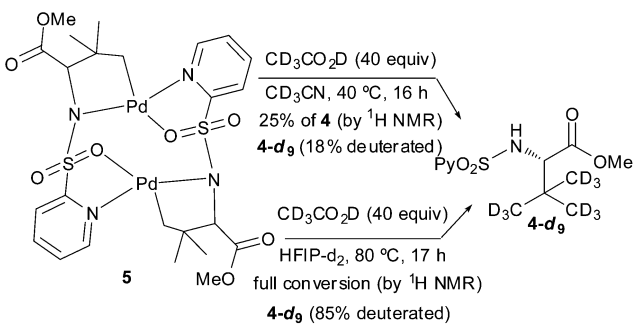


Fig. 5 Energy profile for the C–H activation step of the *N*-(2-pyridyl) sulfonyl valine derivative **1** in the gas phase (M06/6-311 + G(2df, 2p) (C, H, N, O, S), SDD (Pd)//B3LYP/6-31G(d) (C, H, N, O, S), SDD (Pd)). Relative *G* values are reported at 298 K (kcal mol^{-1}). Single point solvation energy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

acid-d_4 (Scheme 5). It was found that the reaction at 40 °C in CD_3CN provided partially deuterated (*ca.* 18%) *tert*-leucine derivative **4-d_9** in 25%[21] conversion after 16 h, while the reaction in HFIP-d_2 at 80 °C afforded almost completely deuterated (*ca.* 85%) *tert*-leucine derivative **4-d_9** after 17 h. This interconversion implies that the C–H activation step 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 °C in HFIP-d_2, temperatures at which the forward reaction can take place.

The stereoselectivity of the C–H activation step was studied by DFT calculations (see ESI† for details) (Fig. 5). Among the several potential mechanisms by which this reaction may occur, and that have been studied by theoretical methods – 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 which has also been evaluated in the case of $C(sp^3)$–H bonds – a concerted metalation–deprotonation (CMD) pathway has often been found to be the most favourable.[22,9b] Moreover, taking into account the early findings of Houk and Yu[19] using this type of mechanism to explain the stereoselectivity in other Pd(II)-catalyzed $C(sp^3)$–H activation reactions, 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 a *N*-(2-pyridyl)sulfonyl valine derivative (**Ia**) was used as starting material in the model. This study revealed that the C–H activation of both diastereotopic methyl groups affords several diastereomeric transition states showing different conformations of the tricyclic palladacycle that is being formed.[23] The most stable and representative examples are shown in Fig. 5. Among them, the most stable transition state, **TS(Ia–IIa)**, arises from C–H activation at the pro-*S* methyl group, and this could account for the experimental selectivity observed. By contrast, **TS(Ia–II'a)A** and **TS(Ia–II'a)B**, that come from C–H activation at the pro-*R* methyl group and would afford the diastereomeric product, were found 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.



Scheme 5 H/D exchange studies.

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 (Fig. 6). The six-membered cycle formed by Pd, N and the rest of the 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**

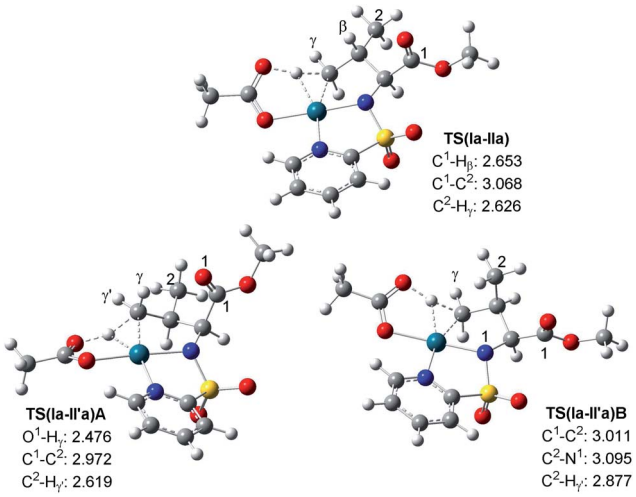


Fig. 6 Optimized geometries of transition states **TS(Ia–IIa)**, **TS(Ia–II'a)A** and **TS(Ia–II'a)B**. Distances are given in Å.

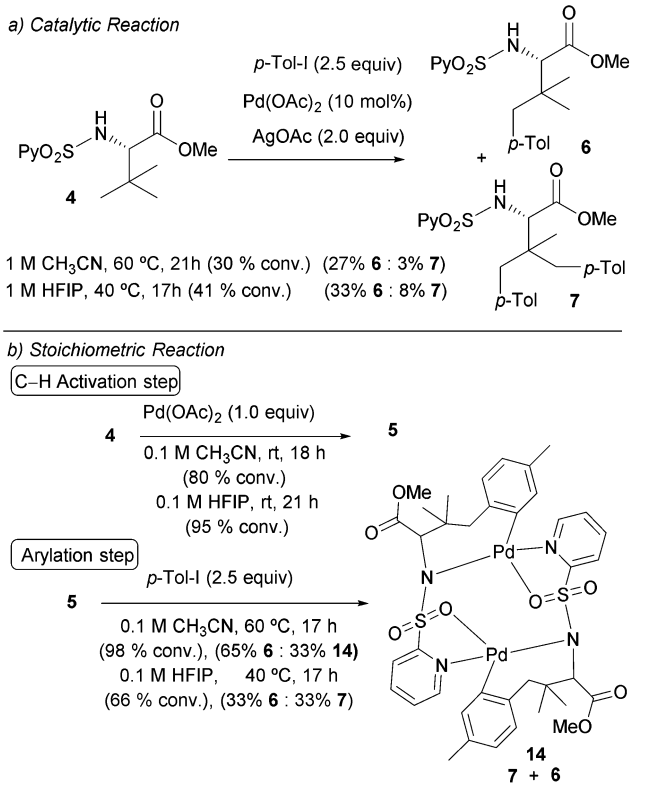
shows, in addition to *gauche* repulsions (CH_3/H–C_γ and O=C/CH_3), an important 1,3-*syn*-diaxial interaction between the methoxy carbonyl group and H–C_γ bond. With respect to **TS(Ia–II'a)B**, the axial methyl group exhibits important *gauche* interactions with all of the surrounding groups.

Insights into the turnover-limiting step

To gain insight 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_3CN or 40 °C in HFIP, which are the same temperatures necessary for bimetallic complex **5** to react with 4-iodotoluene. However, the formation of complex **5** from the 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 step 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 spectrometry, from a mixture of the γ-monoarylated product **6** and palladacycle **14** (see ESI†). According to its structure it should be formed by the *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**, seems to be a monomer in solution on the basis of DOSY analysis (D 1.32 × 10^{-9} m^2 s^{-1}) (see ESI†).

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 (complexes **5**, **14**, **15** and **16**) in about 9–10 mol% (with respect to total amounts of **4**, **6** and **7**), with **5** being the predominant resting state. After 5 min of reaction the bimetallic complexes **5** and **14** were observed in a 4.9 : 1 ratio, respectively. By increasing the reaction time, new



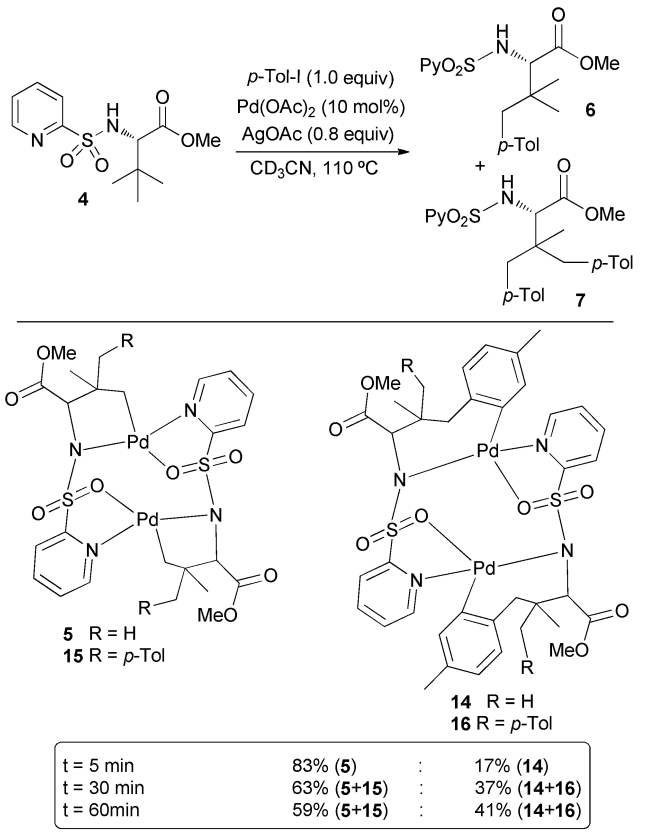
Scheme 6 Stoichiometric and catalytic reactivity of *tert*-leucine derivative **4**.

palladium complexes **15** and **16**, which are the monoarylated analogues of **5** and **14**, respectively, were also detected (see ESI†). The identification of **5** as the predominant resting state, which is located before the turnover-limiting step, indicates that, in this case, the C–H activation step could not be the turnover-limiting step, in contrast to the majority of Pd-catalyzed C–H functionalization reactions, where cyclopalladation is typically rate limiting.[5c,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 spectrometry, 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 °C after 16 h (see ESI†).

Transmetallation or oxidative addition mechanism?

After the C–H activation step two possible mechanisms might be considered (Fig. 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* the oxidative addition of an aryl iodide to a palladium(II) species followed by reductive elimination. Although no mechanistic investigations have been conducted for $Pd(OAc)_2$-catalyzed C–H arylation reactions 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 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



Scheme 7 Identification of the resting states in the catalytic reaction.

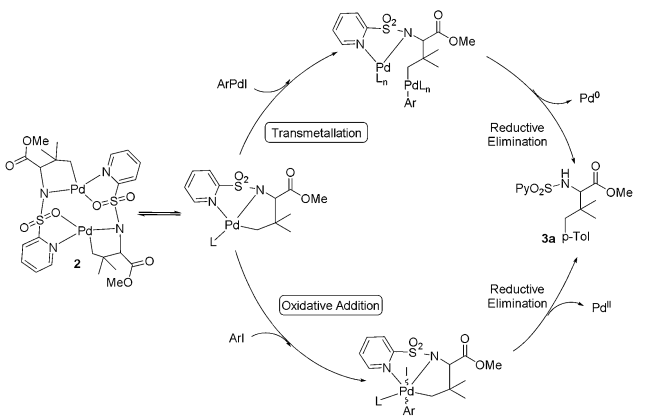


Fig. 7 Possible mechanisms after the C–H activation step.

that only one example of a Pd(IV) complex resulting from the oxidative addition of an aryl iodide to a Pd(II) species has been described to date.[28]

These possible mechanisms were studied by means of DFT calculations. The complete energy profile for the reaction of **4** is depicted in Fig. 8. The barrier for the C–H activation step for *tert*-leucine derivative **Ib** is lower than that of valine derivative **Ia** (for comparison see Fig. 5) being also slightly lower than the corresponding values for the following steps *via* oxidative addition or transmetallation (Fig. 8, profiles blue and red, respectively). This point is in agreement with the experimental results that suggest that, in the case of **4**, the C–H activation step could not be the turnover-limiting step.[29] From intermediate **IIIb**, possible mechanisms *via* the oxidative addition of an aryl iodide to a palladium(II) species followed by reductive elimination (intermediates **IVb**, **Vb**, **VIb**) and *via* transmetallation between two palladium(II) centers followed by reductive elimination (intermediates **VIIb**, **VIIIb**, **IXb**, **Xb**) were evaluated.

The Pd(IV) pathway begins by the exchange of the labile solvent ligand with iodobenzene to afford **IVb**, from which **TS(IVb–Vb)** is reached (Fig. 9). The free activation energy required for this oxidative addition step was found to be only slightly higher than that for the C–H activation step, and even lower when solvent corrections were considered. Thus, the pentacoordinated Pd(IV) complex **Vb** was formed.[30] From this point, reductive elimination takes place through a cyclic chair like transition state **TS(Vb–VIb)** (Fig. 9), incorporating a three-membered ring with bonds that are being formed and broken, similar in energy to that involved in the previous oxidative addition step **TS(IVb–Vb)**.[31]

With respect to the transmetallation pathway, the 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 atoms 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 metallacycle 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 enables the formation of the C–C bond through **TS(IXb–Xb)** (Fig. 9), which shows the three-membered 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 for **TS(IXb–Xb)** and **TS(Vb–VIb)**, respectively). 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* the oxidative addition of an 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 take 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 step to take place. Instead, the 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]

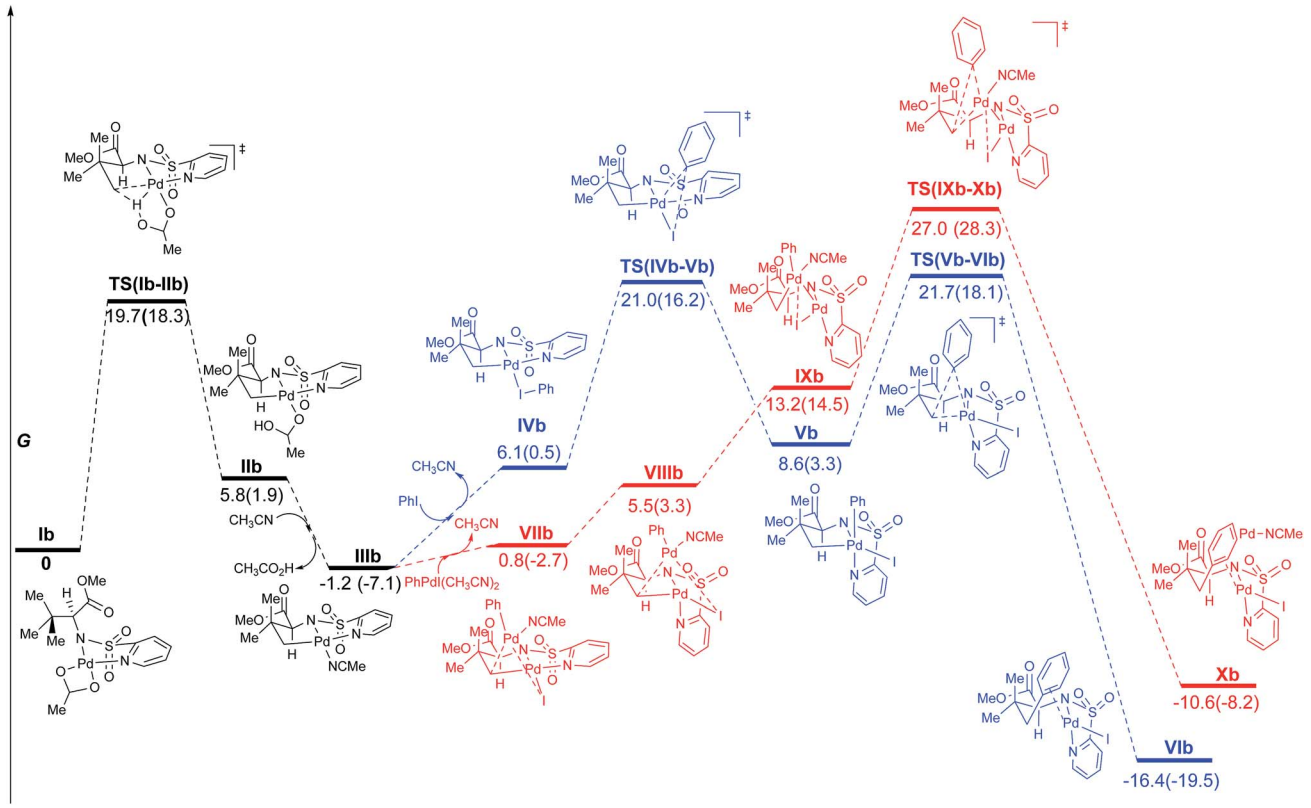


Fig. 8 A complete energy profile for the reaction of the *N*-(2-pyridyl)sulfonyl *tert*-leucine derivative in the gas phase (M06/6-311 + G(2df, 2p) (C, H, N, O, S), SDD (Pd)//B3LYP/6-31G(d) (C, H, N, O, S), SDD (Pd)). Relative *G* values are reported at 298 K (kcal mol^{-1}). Single point solvation energy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

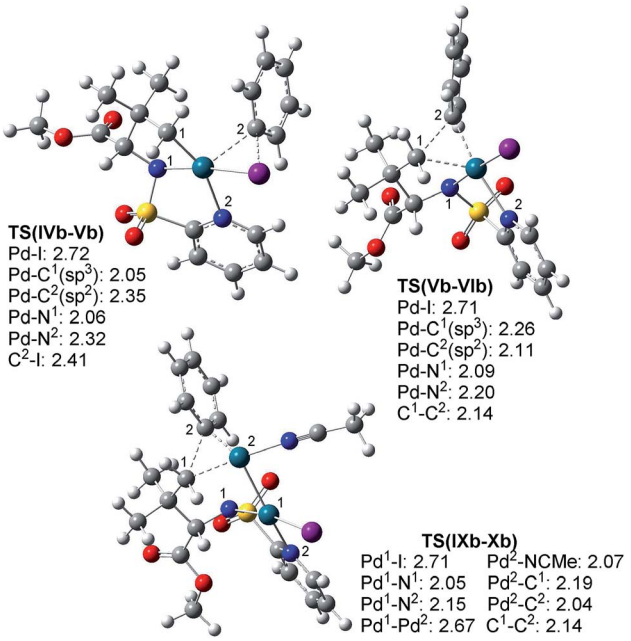


Fig. 9 Optimized geometries of the transition states for the arylation step *via* the Pd(IV) species [**TS(IVb–Vb)** and **TS(Vb–VIb)**] and reductive elimination step for the transmetallation pathway [**TS(IXb–Xb)**]. Bond lengths are given in Å.

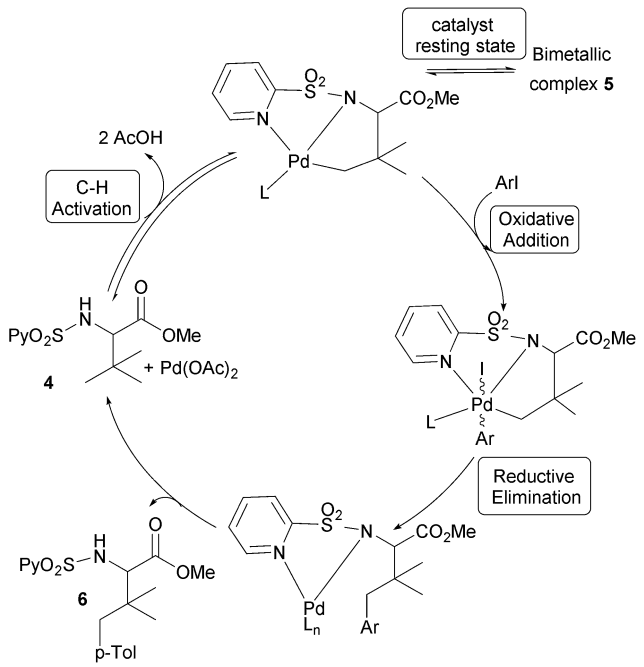


Fig. 10 Proposed catalytic cycle.

Conclusions

In summary, we carried out detailed mechanistic investigations of the $Pd(OAc)_2$-catalyzed $C(sp^3)$–H γ-arylation of amino acid derivatives with aryl iodides. The results obtained, summarized in Fig. 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, (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 step 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 the 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* the oxidative addition of an aryl iodide to a palladium(II) species followed by a reductive elimination rate determining step. We hope that a greater understanding of this transformation might contribute to the design and development of novel reactions in this field.

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18 In an independent reaction, we confirmed that **6** can be converted into **7** under the reaction conditions. Thus, we took the total concentration of **6** and **7** as product conversion.

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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 to 1.7 kcal mol^{-1} under these conditions. This value predicts a 19 : 1 diastereomeric ratio in excellent agreement with the experimental results (dr > 20 : 1, Scheme 1).

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

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