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Palladacycle catalysis: an innovation to the Suzuki–Miyaura cross-coupling reaction†

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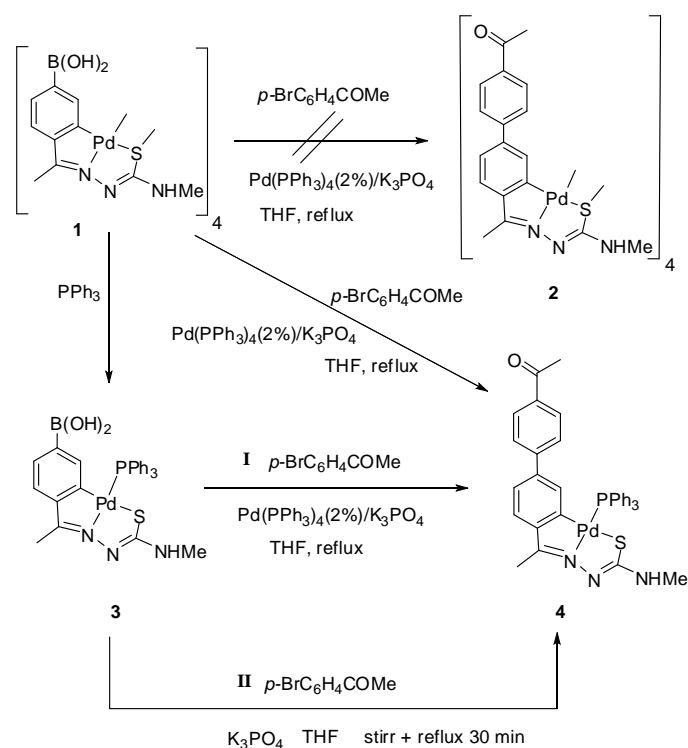
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Herein we report a Suzuki–Miyaura type cross-coupling between an aryl halide and a functionalized boronic acid palladacycle in the absence of an external catalyst. This reaction is an unprecedented case of catalysis in palladium metallacycle chemistry.

Palladium-catalyzed reactions represent one of the most valuable tools in organic synthesis over the last decades.[1] One of the most important and amply used processes for making carbon–carbon bonds is the Suzuki–Miyaura cross-coupling reaction.[2] Although there are commercially available reagents such as [Pd(OAc)₂] and [Pd(PPh₃)₄] that are more than acceptable catalysts, in view that many palladium-mediated coupling reactions involve palladacycle intermediates, the palladacycles[3] have emerged as a paramount group of catalysts owing, in part, to their stability towards air and moisture, and since the first phosphapalladacycles were emphasized by Herrmann *et al.*[4] literally scores of new species have arisen. Although Suzuki initially proposed a Pd(0)/Pd(II) mechanism, in cases in which the precatalyst is a Pd(II) complex a Pd(II)/Pd(IV) catalytic cycle has been suggested, in spite that the Pd(IV) intermediate [5–7] has only been detected in few cases. [7e] Inspired by the growing interest in the field of palladacycle catalysts, and also by the results from this laboratory related to thiosemicarbazone palladacycles [8–11], we sought to investigate the behavior of tetranuclear thiosemicarbazone palladacycles bearing a boronic function on the metallated ring. The purpose of which was to test the viability of the coupling reaction performed on the palladacycle itself thus opening new ground in palladacycle chemistry, with selection of the appropriate coupling substrate enabling one to modulate the properties of the new compounds; to the best of our knowledge there are yet no references to this process. Likewise, the required ligand **a** and compounds **1** and **3** are the first examples of a functionalized thiosemicarbazone ligand and of palladium metallacycles bearing a boronic acid functionality, and they themselves constitute a preminent part of the novel findings reported herein. Furthermore, this should enhance the solubility of the more often than not sparingly soluble tetranuclear clusters, which then could be useful as well, as palladium catalysts themselves. However, the outcome of our research has provided altogether new findings.

We began our investigation pursuing new cyclometallated compounds by way of Suzuki couplings and we sought to react boronic acid bearing palladacycles with aryl halides for which palladium thiosemicarbazone metallacycles were chosen; the

reason being that the tetranuclear thiosemicarbazone palladacycles are quite insoluble compounds in the more general organic solvents and in water. We aimed to devise a method to solubilize these species by appending non-aqueous solvent or water friendly groups. A means to achieve this would be preparing the tetranuclear boronic derivative first and then performing a cross-coupling reaction to attach the appropriate group on the metallated phenyl ring. Thus, reaction of 4-B(OH)₂C₆H₄C(Me)=NN(H)C(=S)NHMe (**a**) with K₂[PdCl₄] in ethanol or with Na₂[PdCl₄]/NaAcO in methanol gave **1**, which was treated under the Suzuki–Miyaura catalytic conditions (using 2 % Pd(PPh₃)₄) in the hope of making product **2** (Scheme 1).



Scheme 1 Preparation of compound **4**. Cross-coupling reaction between **3** and *p*-BrC₆H₄COMe: using Pd(PPh₃)₄ (**I**); in the absence of an external catalyst (**II**).

The initial suspension gave a light–yellow solution with formation of a solid plus a small amount of a black powder. No significant changes occurred after further stirring and/or heating the mixture. After filtration a thorough analysis of the solution and of the solid revealed that the solution contained: a) compound **4** from a one–pot process where the tetranuclear structure is cleaved and

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the carbon–carbon cross–coupling of the aryl bromide takes place in accordance only with the amount of catalyst used; b) the excess un–reacted aryl bromide. The solid consisted of the remaining Pd₄ starting material **1** and the resulting Pd(0) from the catalyst. Alternatively, treatment of **1** with triphenylphosphine gave **3** in good yield, which was quite soluble in the more common organic solvents, a typical feature of tetranuclear thiosemicarbazone palladacycles that are readily made soluble upon treatment with tertiary phosphines. [8–10] Reaction of **3** with *p*-BrC₆H₅COMe under the appropriate catalytic approach gave **4** (Scheme 1, path I). To our surprise, however, monitoring the latter process by TLC brought to light that prior to addition of the catalyst, there was an additional component to the starting materials.

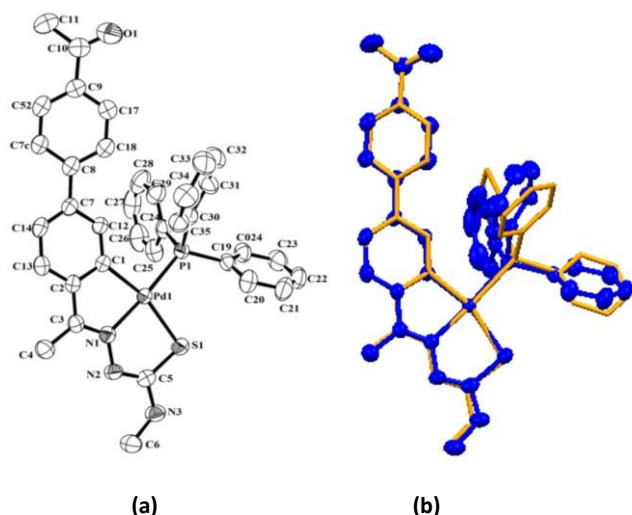
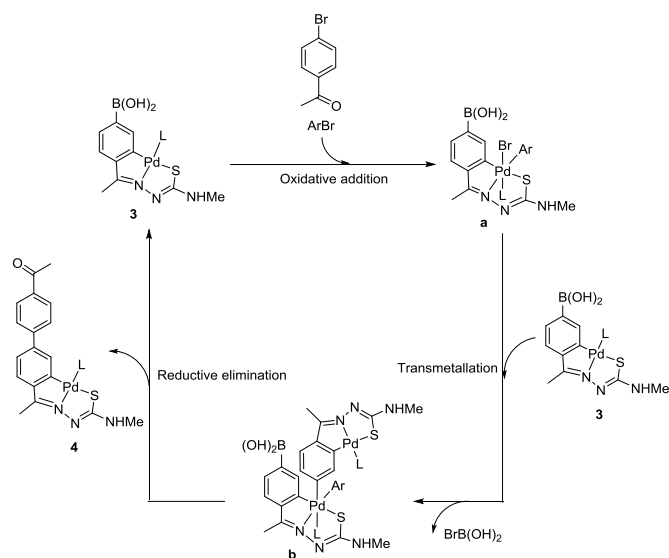


Fig. 1 (a) ORTEP view of the solid structure of **4** with ellipsoids drawn at the 30% probability level. (b) Comparison of the DFT optimized (orange) and crystal (blue) structures.

We next stirred the mixture further, without adding the catalyst, then refluxed for 30 minutes and left it to slowly cool to room temperature, whereupon yellow crystals appeared which were filtered off. An X-ray crystallographic analysis showed them to be compound **4** (Scheme 1, path II). A further batch of **4** could be obtained from the remaining solution as well as negligible amounts of **3** and of the aryl bromide. The NMR of **4** revealed the presence of the coupled *p*-substituted aromatic ring to the palladated phenyl, as a result of the cross–coupling reaction, as determined by the spectroscopy data. Characterization of the coupled moiety by ¹H NMR showed a resonance at 2.55 ppm which was assigned to the C(=O)Me group; also, resonances at 8.06 and 6.82 ppm (*N* = 8.3 Hz) were assigned to the four phenyl protons of the AA'XX' spin system, the latter strongly up–field shifted by the shielding effect of the phosphine phenyl rings; also, the IR spectrum showed a band at 1685 cm⁻¹ assigned to the ν(CO) stretch. The structure of **4** was confirmed by X-ray diffraction study providing to the best of our knowledge the first unequivocal evidence of the cross–coupling reaction performed on the metallated ring, of which to date there are no reported examples. Fig. 1(a) shows the ORTEP view of the molecule of **4** and selected bond distances and angles can be found in Tables 1–2 (see ESI). To keep the discussion to a minimum, the added cross–coupled aromatic ring is at 26.27° to the palladated ring; the latter and the metal coordination plane are nearly coplanar at 5.29°. The bond distances and angles are within the

expected values with allowance for lengthening of the Pd(1)–N(1) bond distance consequent on the *trans* influence of the phosphine ligand,



Scheme 2 Plausible Pd(II)/Pd(IV) mechanism for the autocatalytic cycle. L = PPh₃

shortening of the C(7)–C(8) bond distance, 1.477(4) Å, in accordance with charge delocalization between the two phenyl rings, and for deviations from the ideal 90° angles at palladium owing to the strain imposed on the organic ligand by CNS coordination to the metal.

The reaction may involve a Pd(0)/Pd(II) or a Pd(II)/Pd(IV) catalytic cycle, and although we feel that the former is the most probable case, the latter one should not in principle be completely ruled out for a number of reasons. It is the suggested cycle in cases where the precatalyst is a Pd(II) complex; a Pd(IV) intermediate has recently been detected; [7e and references therein] no trace of Pd(0) was observed in the reaction in path II. Accordingly, in view of the recent advances related to the Pd(II)/Pd(IV) catalytic cycle [7b, 7e] we tentatively propose a plausible mechanism which could be consistent with our findings, Scheme 2, should the latter mechanism for the palladacycle described herein be the operational one. It should be noted that the proposed catalyst, or precatalyst, bears the metal as well as the boronic functionality, in what we cautiously term as a process of autocatalysis. Autocatalysis has been invoked earlier in phenyl to methyl group transfer from tin to iridium, [12a] σ–bond metathesis reactions [12b] and the hydrogenation of acetophenone, [12c] albeit involving differing pathways and metal species from those portrayed herein. In any case, regardless of the mechanism, the palladacycle itself catalyses the reaction as it is the sole source of palladium in path II. To further analyse the viability and energetics of the proposed mechanism DFT calculations using Gaussian 09 [13] were performed on the compounds named labeled as **3**, **4**, **a**, ArBr and BrB(OH)₂. In the case of **3**, **4**, and **a**, all the possible conformers were studied. The reported geometry and frequency calculations were carried out at the M06/ ECP28MDF_GUESS [14]/6-31G(d) level of theory and no imaginary frequencies were found, confirming the stationary points. The ΔG value for the overall reaction to produce **4** is ca. -40 Kcal /mol, in support of its favorable formation, as was

corroborated by the X-ray crystal analysis of the cross-coupling compound **4**. The DFT minimum energy structure for compound **4** contrasted against the crystal structure is depicted in Fig. 1(b).

Moreover, the calculations showed that the aryl halide addition compound, **a**, presents two sets of four isoenergetic conformers for the *cis* and *trans* arrangements of the bromine ligand and the aryl moiety (see ESI). The results put forward that the *cis* conformer, as depicted in Scheme 2, is in all cases the favored one by 9.65 Kcal/mol.

It also seems noteworthy to point out that because the palladium substrate itself plays the role of the catalyst, allocating on its coordination sphere the aryl feedstock to produce the coupling and eliminating the final product, the process is self-consuming without the need to recover the catalyst. These results have prompted us to extend our investigations towards boronic substrates other than 4-acetylphenylboronic acid and further investigations are currently being undertaken with the aim of developing this new feature of palladacycle chemistry.

In order to shed more light upon this findings we then tested compound **3** as a catalyst for the Suzuki-Miyaura reaction between *p*-BrC₆H₅COMe and phenylboronic acid, with **3** competing with the boronic acid substrate. It seemed reasonable that the metallated ring should be less prone to cross-coupling than the boronic acid phenyl, having the thiosemicarbazone functionality as well as the bond to palladium. Also, the steric hindrance of the boronic acid in the transmetallation step is much less than that of the boronic palladacycle in the same transition. When compound **3** was used as a catalyst the cross-coupling reaction proceeded smoothly and the biphenyl species was the major product, nevertheless a negligible amount of **4** was detected.

In conclusion, we have shown that in the absence of a conventional palladium catalyst the reaction of a boronic acid functionalized palladacycle with a convenient substrate evolves to the corresponding cross-coupling product, at least to a certain extent, suggesting the metallacycle is the palladium catalyst which self-transfers the aryl ketone substrate hereby giving an autocatalytic procedure, an unprecedented performance in palladacycle chemistry.

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