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New seven membered palladacycles: C–Br bond activation of 2-bromo-pyridine derivative by Pd(II)†

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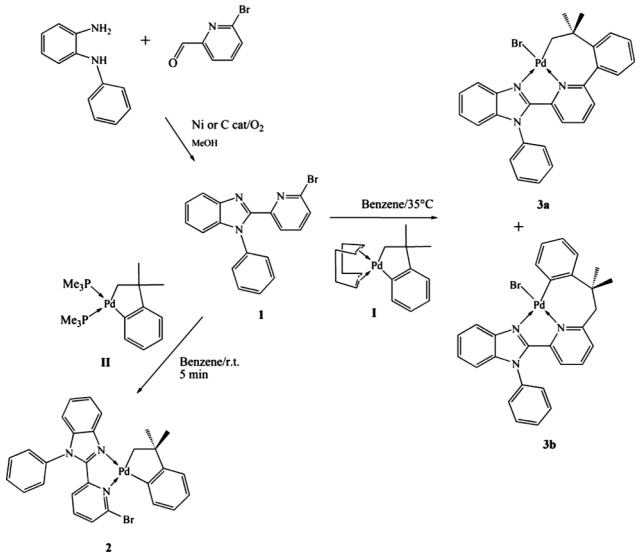
C–Br bond activation followed by a C–C coupling reaction of the *2-bromo-pyridyl* unit of [1-phenyl-2-(6-bromopyridin-2-yl)-benzoimidazole] was performed by $\overline{Pd(CH_2CMe_2\text{-}o\text{-}C_6H_4)}(\eta^4\text{-COD})$. Two new seven membered palladacycles were obtained. A combined experimental and theoretical DFT study elucidates the mechanism for this reaction.

Some twenty years ago, the chemistry of neophyl-derived metallacycles (neophyl = CH_2CMe_2Ph) of group 10 elements of the type $M(CH_2CMe_2\text{-}o\text{-}C_6H_4)(L_2)$, where L_2 represents a diolefin like 1,4-cyclooctadiene (COD) or two PMe_3 (or other tertiary phosphine ligands), and M = Ni, Pd, Pt, experienced a remarkable growth due to their facile synthesis and rich chemical properties.[1] A number of synthetically useful transformations of these molecules were discovered particularly during investigation of their migratory insertion chemistry toward unsaturated inorganic and organic molecules (*e.g.* CO, CS_2, SO_4, alkynes, etc).[1,2] Furthermore, the palladacycle $\overline{Pd(CH_2CMe_2\text{-}o\text{-}C_6H_4)}(\eta^4\text{-COD})$ has been used as a precursor of cationic κ^2-hydrotrispirazolylborate (Tp) palladacycles utilized in the Pd(IV) complexes synthesis either through electrochemical or aliphatic C–X bond activation.[3] Interestingly, in the latter case, it has been reported that the reaction of CH_2X_2 (X = Br or I) with the cationic palladacycle gives rise to relatively stable six membered metallacycles, as a result of the formal insertion of CH_2 into the Pd–C_{aryl} bond. However, the synthesis of palladacycles larger than six members has proven to be difficult since this type of derivative undergoes facile reductive elimination. Thus, as a consequence, examples of well-characterized compounds of this kind are rare.[4] Additionally, to the best of our knowledge, no reports on the use of palladacycles for activation of halo-heterocyclic (*e.g.* halo-pyridine) species are found.

Is it possible to use palladacycles to activate a halo-pyridine? In general, pyridine derivative synthesis involves classic Stille, Suzuki, Negishi, Kumada, and Hiyama cross couplings.[5–12] However, these reactions show important challenges in (1) the pre-activation conditions and (2) the coupling reactions. Although arylation of N-oxide pyridines has been considered as an alternative to overcome the previous cited cross-coupling problems, and the coupling of halo-pyridines with aryl boronic acids is known,[13–14] the use of non-activated pyridine compounds in coupling reactions is of great interest given that the pyridine moiety is an important heterocycle which is present in several natural products and pharmaceutical agents.

Herein we describe an unexpected C–Br bond activation of a 2-bromopyridine derivative by Pd(II) in the palladacycle $\overline{Pd(CH_2CMe_2\text{-}o\text{-}C_6H_4)}(\eta^4\text{-COD})$. Overall, this transformation provides a new strategy for pyridyl transfer between Pd(II) centers to form stable seven-membered palladacycles.

We first prepared Br-PBI **1** through activated carbon promoted cyclization/oxidation of *N*-phenyl-1,2-phenylene-diamine and 6-bromo-2-pyridine-carboxaldehyde (Scheme 1).[15] In order to obtain the target complex **2**, the subsequent reaction of **1** with



Scheme 1 Synthesis of compounds **1**, **2** and **3a–b**.

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palladacycle **I** in benzene at 35 °C followed, resulting in a yellow precipitate after stirring for one day (Scheme 1). After filtration and work-up, the obtained product was isolated as a yellow solid in good yield. Surprisingly, ^{1}H NMR analysis revealed an unexpected and complex resonance pattern arising from the neophyl fragment, which did not correspond to compound **2**. So, two doublets series at δ 2.8/2.56 and 2.7/2.4 ppm were observed. These signals were assigned to the nonequivalent CH_2 group protons, suggesting the presence of two isomers **3a–b**. The same was observed for the methyl protons, giving two singlets for each isomer, which is in agreement with their non-equivalence. The above assignments were confirmed by a 2D ^{1}H NMR COSY experiment. Compounds **3a–b** were formed in an approximate ratio of 2 : 1. A pure sample of **3a** was successfully obtained when the reaction was carried out at 25 °C and this was further characterized by X-ray crystallography.‡

The X-ray structure indicated **3a** as a new unexpected seven membered palladacycle (Fig. 1). The formation of this species resulted from an unexpected cleavage of a C–Br bond in the pyridine derivative **1**, presumably *via* oxidative addition,[16] and concomitant C_{sp^2}–C_{sp^2} reductive coupling to give the seven membered palladacycle **3a**. As expected, the local geometry around the Pd atom in **3a** was square planar and bond lengths and angles were consistent with those reported for analogous complexes.[1,2,4,17] The X-ray structure confirmed that the non-equivalence of the methylene and methyl protons of the neophyl fragment was due to the nature of the seven-membered chelate ring.

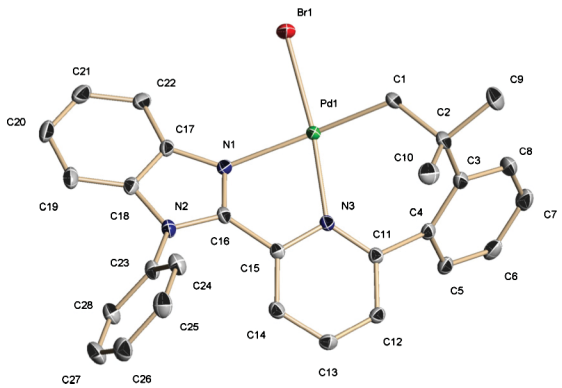

Fig. 1 ORTEP representation of **3a**; H-atoms are omitted for clarity. Selected bond lengths (Å) and angles (°): Pd(1)–C(1) 2.0217(16), Pd(1)–N(3) 2.0972(13), Pd(1)–N(1) 2.1692(13), Pd(1)–Br(1) 2.4392(2); C(1)–Pd(1)–N(3) 100.77(6), C(1)–Pd(1)–N(1) 168.93(7), N(3)–Pd(1)–N(1) 77.97(5), C(2)–C(1)–Pd(1) 121.80(11).

In an attempt to understand the mechanism of formation of **3a–b**, the reaction was monitored in a NMR tube charged with a freshly prepared mixture of **1** and **I** in $CDCl_3$ or C_6D_6, at 25 °C. ^{1}H NMR spectra were collected every 10 min. Initial proton spectra revealed resonance signals attributed to the formation of **3a**, with concomitant signals of unbound COD and unreacted **1** and **I** but no intermediate species was detected. The reaction was completed in one day and no significant differences were observed for both of the solvents used in the NMR experiments.

To gain further insight, a similar reaction was carried out between **1** and $\overline{Pd(CH_2CMe_2\text{-}o\text{-}C_6H_4)}(PMe_3)_2$ (**II**), in C_6D_6 at 25 °C. In this case, compound **2** was obtained after 5 min in quantitative yield (Scheme 1). The ^{1}H NMR spectra showed only one signal for the CH_2 and CH_3 groups at 1.39 and 1.12 ppm, respectively, confirming the formation of **2**.

These results indicated the bidentate COD ligand being important in the formation mechanism of **3**. Palladacycles reacting with aryl C_{sp^2}–X electrophiles to form C_{sp^2}–C_{sp^2} bonds present in the final product are found in the literature, but no example has been given using heteroaryl electrophiles and/or the palladacycle $\overline{Pd(CH_2CMe_2\text{-}o\text{-}C_6H_4)}(\eta^4\text{-COD})$.[18] In this area, norbornene derived palladacycles have been the most studied systems, providing most of the mechanistic clues found up to date for this type of reaction. However, a definite mechanistic path has not been elucidated yet. In general two mechanisms have been proposed: one involves the oxidative addition of the C_{sp^2}–X electrophile, forming a Pd(IV) palladacycle, followed by the reductive elimination and formation of the C_{sp^2}–C_{sp^2} and C_{sp^2}–C_{sp^3} cross coupling products. The second suggests a palladium(II) transmetalation,[19] involving the palladacycle. Given that $\overline{Pd(CH_2CMe_2\text{-}o\text{-}C_6H_4)}(\eta^4\text{-COD})$ features similarities with the reported norbornene palladacycles, it is reasonable to assume that a similar mechanism might be implicated for the reactions described herein. Moreover, it is important to highlight that for the norbornene palladacycles, the oxidative addition/reductive elimination/C–C coupling reactions usually proceed in coordinating solvents such as DMF and DMA, and in the absence of phosphines.

In order to clarify these initial findings, we carried out a series of DFT calculations[20] to give an insight into the mechanistic details of the reaction. According to the well accepted mechanistic proposal for cross-coupling Pd reactions,[21] and to the reported characterization of a Pd(IV) species for a phenanthroline norbornene palladacycle,[22] we considered an oxidative addition to be the initial step for activating the C–Br bond for the reaction presented herein. We tested several conformations looking first for an interaction of the substrate with the Pd center but due to the bulkiness of the COD ligand, either it reverted into a separated set of two molecules (*Reactants*) or Br-PBI displaced COD from the coordination sphere of the metal center. This ligand exchange, namely the (Br-PBI)neophylpalladacycle + COD, was found to be 1.9 kcal mol^{-1} higher in energy than $\overline{Pd(CH_2CMe_2\text{-}o\text{-}C_6H_4)}(\eta^4\text{-COD})$ + Br-PBI, but the consequent C–Br bond activation goes uphill 31.3 kcal mol^{-1} without COD (an analogous process **Int1′** → **Int2′** to that depicted in Fig. 2). So this reaction cannot proceed under mild conditions without the coordinative effect of COD in an earlier stage of the reaction mechanism. Then, another possibility was the η^2-coordination of a C–C double bond of COD.[23] We found that this process has an energy barrier of 19.1 kcal mol^{-1} for the isolated $\overline{Pd(CH_2CMe_2\text{-}o\text{-}C_6H_4)}(\eta^4\text{-COD})$ complex but the presence of Br-PBI decreases this barrier to 15.6 kcal mol^{-1} (see Fig. 2).

Formation of **Int1** is a prior condition that generates a coordination site which can then be occupied by Br-PBI even when an earlier interaction of this last with palladium is not achieved yet at this stage (Br–Pd bond distance was 5.343 Å and the nearest N–Pd bond was 4.681 Å). The reaction proceeds through the C–Br bond activation in **TS2** with an energy barrier of 9.3 kcal mol^{-1} where mono-coordinated COD ligand rotates around palladium into an equatorial position. A similar value of 11.6 kcal mol^{-1} was calculated for a bis-triphenyl phosphine Pd complex activating a C–Br bond.[24] This transition state structure is characterized by bond distances of C–Br, 2.239 Å; Pd–Br, 2.664 Å; and Pd–C, 2.222

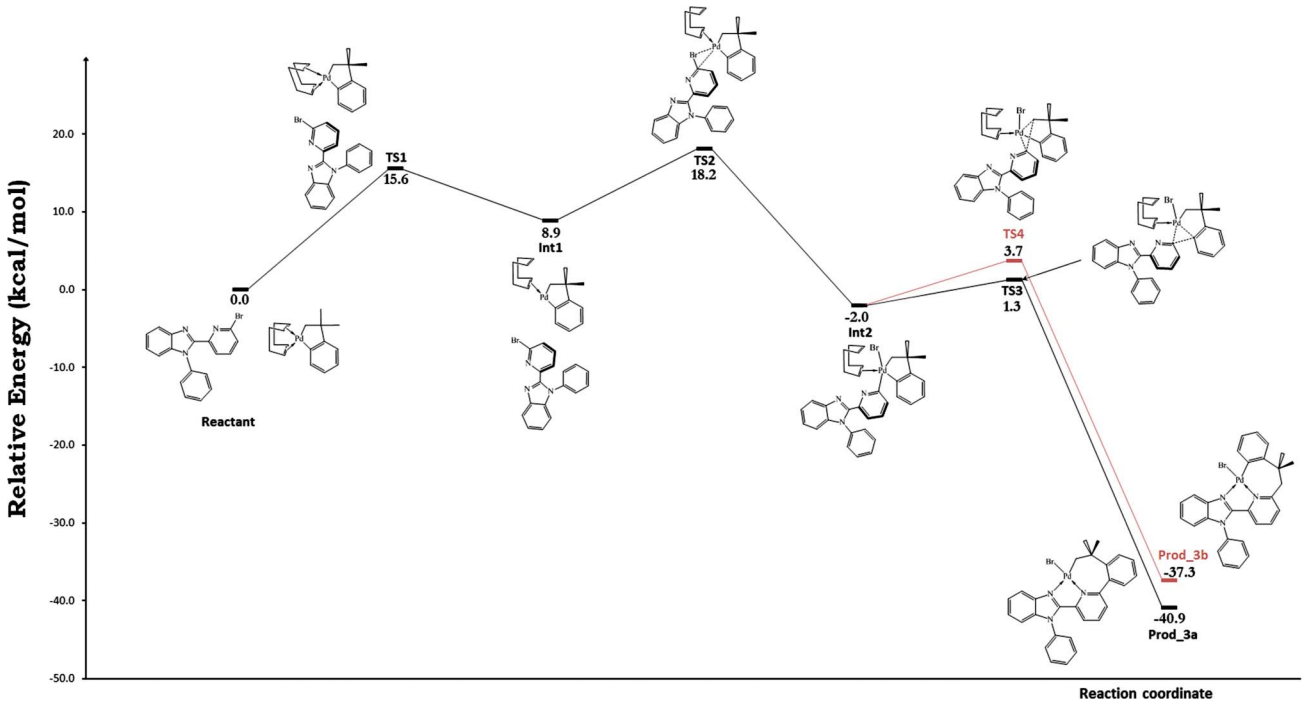

Fig. 2 Energy profile of the studied reaction mechanisms calculated at B3LYP/*mix-basis* level. Enthalpies are expressed as relatives energies with respect to the reactant.

Å. The role of COD is still crucial since considering it as a leaving group in this step raises the energy barrier up to 10.1 kcal mol^{-1}. This suggests that COD remains attached to the palladium center filling a coordination site and conferring stability to the complex when oxidative addition takes place leading to **Int2** species.

This intermediate turns out to be the structure where the two channels for reductive elimination diverge into both reaction products, **Prod_3a** and **Prod_3b**. The pyridine ring can then be coupled in two fashions: (1) C_{sp^2}–C_{sp^2} cross-coupling reaction goes through the **TS3** transition state, and (2) the C_{sp^2}–C_{sp^3} cross-coupling reaction proceeds *via* the **TS4** transition state, as shown in Fig. 2. Both reactions are quite exothermic.

Thus, **TS3** cross-coupling leading to **Prod_3a** was favored over **TS4** which was converted into **Prod_3b** and the energy difference of 2.4 kcal mol^{-1} is in excellent agreement with the experimental findings. The reason behind this preference can be attributed to the formation of a slightly more strained ring in **TS4** when compared to **TS3**. This might cause an elongation of Pd–C bonds to reach the transition state condition for cross-coupling. In fact, by inspecting the **Int2** structure, we found that Pd–C_{sp^2}(pyridine), Pd–C_{sp^2} and Pd–C_{sp^3} bond distances are 1.993, 2.034, and 2.070 Å, respectively. A comparison with the activated bonds in **TS3** (Pd–C_{sp^2}(pyridine), 2.093 Å, and Pd–C_{sp^2}, 2.108 Å) and **TS4** (Pd–C_{sp^2}(pyridine), 2.134 Å, and Pd–C_{sp^3}, 2.276 Å), shows that those bond distances are indeed longer in the latter structure.

In summary, we report an unusual C–Br bond activation of a 2-bromopyridine compound by the palladacycle Pd(CH_2CMe_2-*o*-C_6H_4)(η^4-COD) under soft conditions. Mechanistic studies were performed using both computational and experimental techniques in order to explain the experimental results. DFT calculations showed that the reaction reported herein follows a Pd(II)/Pd(IV) mechanism in which the key step was found to be the η^2-COD-coordination, followed by an oxidative reaction of the substrate through the C–Br bond giving a Pd(IV) species. Finally an energetically favored selective intramolecular C–C cross-coupling followed to give **3a–b**. Further investigations on the role of the substrate (2-halopyridines derivatives), the Pd(II) complexes and the catalytic activation are underway.

Acknowledgements

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Notes and references

‡ Crystal data for **3a**: $C_{28}H_{24}BrN_3Pd$; Monoclinic, $P\,2_1/c$, $F_w = 588.81$, $a = 13.3675(7)$; $b = 8.5040(4)$; $c = 21.0854(11)$, $\beta = 90.387(2)$, $V = 2396.9(2)$, $T = 100(2)$ K, $Z = 4$, $Dc = 1.632$ g cm^{-3}, $\mu = 2.463$ mm^{-1}, $F\,(000) = 1176$, $\theta_{max} = 30.48°$, ($-17 \le h \le 19$, $-12 \le k \le 12$, $-19 \le l \le 30$), reflections collected 49938, unique 7288 [$R_{int} = 0.0241$), final R indices [$I > 2\sigma(I)$] were $R_1 = 0.0229$, $wR_2 = 0.0516$, R indices (all data) $R_1 = 0.0294$, $wR_2 = 0.0536$, GOF = 1.078. Largest diff. peak and hole 0.875 and –0.632 e Å^{-3}.

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