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Formation of CC-type palladacycles with assistance from an apparently innocent NH(CO) functional group†

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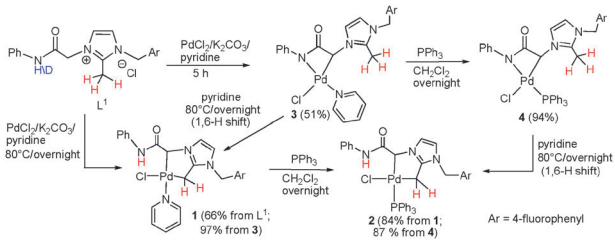
A novel cyclometalation pathway to form CC-type palladacycles is reported. Unlike common donor-assisted cyclometalation, the NH(CO) auxiliary group undergoes a deprotonation step to form a palladalactam intermediate. The coordinating nitrogen atom functions as an intramolecular base promoting selective C–H bond cleavage. Without the NH proton, the *ortho*-*N*-phenyl C–H is activated instead.

Palladacycles have recently received considerable attention because they are key intermediates in palladium-catalyzed ligand-directed C–H functionalization.[1–14] The most popular way to construct palladacycles is cyclometalation involving donor-assisted C–H bond activation.[15,16] Typical donor groups contain N, O, P, S, Se, or As. Carbon-assisted bond activation is also known to form CC-type palladacycles, but it is much rarer. Other synthetic routes, sometimes complementary to the donor-assisted approach,[17] have also been developed. Understanding the fundamental aspects of cyclometalation processes can provide useful insights into the mechanistic features of palladium-catalyzed C–H functionalization reactions.[18–20] Herein, we reveal a unique cyclometalation pathway that leads to the formation of CC-type palladacycles. Unlike common donor-assisted approaches, the NH(CO) functionality on these ligands serves as more than just a donor for a palladium atom to provide chelation-assisted C–H bond activation. An intermediate palladalactam actually involves a coordinating nitrogen atom, which then functions as an intramolecular base, promoting selective C–H bond cleavage. This mechanism could provide new pathways to create novel stoichiometric and catalytic transformations.

Preparation began by reaction of ligand L^1 with $PdCl_2$ in pyridine, employing K_2CO_3 as a base. Heating at 80 °C overnight afforded a five-membered palladacycle (**1**) in 66% yield (Scheme 1). Deprotonation of L^1 by pyridine led to double C–H bond activation of the methyl and methylene protons. Two groups of methylene protons were present in L^1,



Scheme 1 Formation of palladacycle *via* sp^3 C–H activation.

and the more acidic protons next to the carbonyl group were selectively activated. Complex **1** was identified by ^{1}H NMR spectroscopy, exhibiting a characteristic singlet methine signal at 5.32 ppm. The singlet for the methyl group was replaced by the diastereotopic signals of the metal-bound methylene group at 1.97 and 2.44 ppm. The NH proton (9.89 ppm) appears to be intact after the reaction. The pyridine ligand in **1** can easily be substituted with PPh_3 to afford **2** in 84% yield. In the $^{13}C\{^1H\}$ NMR spectrum of **2**, the methylene carbon *cis* to the PPh_3 was observed as a doublet at 7.6 ppm, with a $^2J_{PC}$ = 7.4 Hz. The large coupling constant ($^2J_{PC}$ = 97.6 Hz) for the doublet at 60.2 ppm was consistent with a *trans* relationship between the methine carbon and phosphorous atoms. X-ray diffraction analyses confirmed the formation of **1** and **2** (Fig. 1 and ESI†). The *cis* relationship between the methine carbon and chlorine atoms in **2** allowed the NH···Cl intra-molecular hydrogen bonds to stabilize the structures.

The NH proton on L^1 was expected to be easier to deprotonate than the methyl and methylene protons. We were, however, rather surprised not to obtain a palladacycle containing an amidate moiety. To determine if any plausible palladium amidate complex could be isolated, we carried out the same reaction at ambient temperature for 5 h; palladalactam (**3**), an isomer of **1**, was afforded in 51% yield. ^{1}H NMR spectroscopy confirmed the formation of **3**, showing a methyl signal at 2.80 ppm and a methine singlet at 4.56 ppm. A downfield signal attributable to the NH proton was absent; however, signals from a coordinating pyridine were observed. The pyridine ligand was substituted with PPh_3, to afford **4**. The ^{1}H NMR spectrum of **4** also showed the characteristic methine and methyl signals. An X-ray structure determination revealed a highly distorted square planar coordination environment around the palladium atom due to the very small bite of

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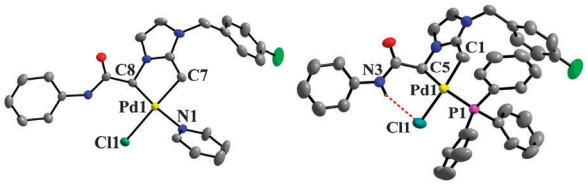


Fig. 1 Molecular structures of **1** (left) and **2** (right) with 50% probability ellipsoids for non-H atoms.

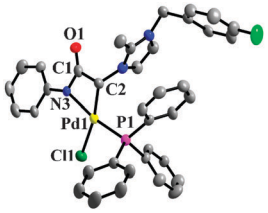
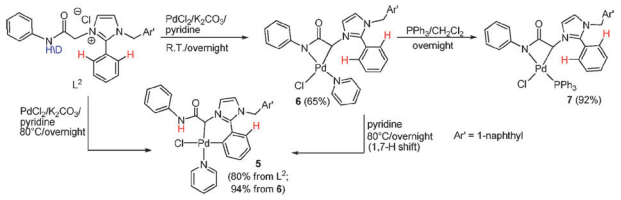


Fig. 2 Molecular structures of **4** with 50% probability ellipsoids. Only one of the two independent molecules is shown.

the organic ligand (Fig. 2 and ESI†). The N–Pd–C angle of 67.0(2)° was comparable to that of a similar palladalactam compound reported previously.[21] To test whether **3** was a kinetic product, pyridine or DMF solution of **3** was allowed to stir at 80 °C overnight. Pure **1** was cleanly obtained in almost quantitative yield after workup. Similarly, **4** could be isomerized to **2** in 87% yield.

Although, in general, sp^3 C–H bonds are much less reactive than sp^2 C–H bonds,[22] the methyl group in **1** was activated owing to its direct connection to the positively charged imidazolium ring.[23] To test whether similar reactivity occurs with an sp^2 C–H bond distant from the imidazolium ring, we synthesized L^2 in which a phenyl ring was attached to the C2 position of the imidazolium salt. For ease of synthesis, L^2 contained an *N*-1-naphthylmethyl instead of a 4-fluorobenzyl group (Scheme 2). The reactivity pattern was indeed similar to that of L^1 and $PdCl_2$, affording a four-membered palladacycle (**6**) and a six-membered palladacycle (**5**) as kinetic and thermodynamic products, respectively. Complex **7**, derived from **6** by substituting a pyridine with a PPh_3 ligand, was also obtained. The structures of **5** and **7** were confirmed by X-ray crystallographic analysis (Fig. 3 and ESI†).



Scheme 2 Formation of palladacycle *via* sp^2 C–H activation.

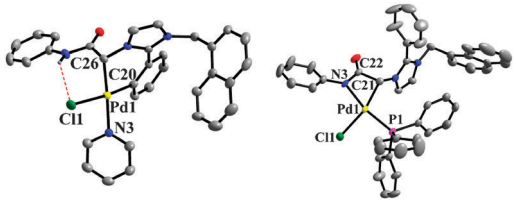
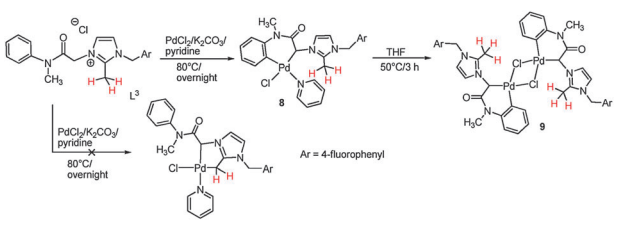


Fig. 3 Molecular structures of **5** (left) and **7** (right) with 50% probability ellipsoids for non-H atoms.

Although the formation of **1** through intermediate **3** involves deprotonation of the NH proton, in its subsequent conversion to **1**, the NH proton was replaced. This NH proton could have come from either the solvent or a proton transfer from the methyl C–H bond. To gain mechanistic insight into the proton source, we labeled the NH proton in L^1 with deuterium by employing the readily available $PhND_2$ as a starting material. First, we verified the inclusion of deuterium into the amide group of L^1. The ^1H NMR spectrum of deuterated L^1 did not show a downfield signal corresponding to the NH proton between 9 and 10 ppm. The ^2H NMR spectrum duly shows the deuterium signal at 10.21 ppm, confirming the successful formation of the deuterated compound. Next, deuterated L^1 was carried forward to prepare **1**. The synthetic procedure was slightly modified to avoid aqueous washing, thus eliminating the possibility of deuterium exchange with water solvent. After workup, the ^1H NMR spectrum of the product clearly showed the downfield NH proton integrating with one proton at 9.89 ppm. The possibility of deuterium exchange with pyridine solvent was ruled out by carrying out the reaction between non-deuterated L^1 and $PdCl_2$ in pyridine-d_5. The results indicated that there was no deuterium incorporation into the amide group. Thus, we confirmed that the amide proton in **1** comes from the methyl proton exclusively. A similar deuterium labeling experiment also confirmed that a similar hydrogen migration occurred in the conversion of **6** to **5**.

To further illustrate the importance of the NH proton in the selective cyclometalation that formed **1**, we prepared the *N*-methyl ligand precursor L^3 and investigated its cyclometalation with $PdCl_2$. Since the NH proton was replaced by a methyl group, the formation of four-membered palladacycles such as **3** and **6** was prohibited. The reaction thus took a different course, affording a six-membered palladacycle (**8**) in which the *ortho*-C–H bond of the *N*-phenyl ring was activated (Scheme 3). Such C–H bond activation is commonly observed in palladium-catalyzed C–H functionalization reactions involving amides as directing groups.[3,8,24] The ^1H NMR spectrum of **8** shows the characteristic peaks of the methyl and methine signals at 3.38 and 5.61 ppm, respectively. Further heating a THF solution of **8** for 3 h produces dimeric compound **9** (Fig. S1, ESI†). The pyridine ligand in **8** is more labile than those in **1** and **5**. Our results indicate that the amide α-methylene on L^3 was initially deprotonated and coordinated to the palladium centre. Because no amide proton was available for activation, chelation-assisted sp^2 C–H cleavage was preferred over the sp^3 C–H bond, forming **8** as the product. The possibility of palladalactam was thus blocked and a five-membered palladacycle such as **1** could not form. A preliminary study revealed a similar reactivity pattern for the reaction between $PdCl_2$ and a



Scheme 3 Formation of palladacycle *via* *o*-*N*-phenyl C–H activation.

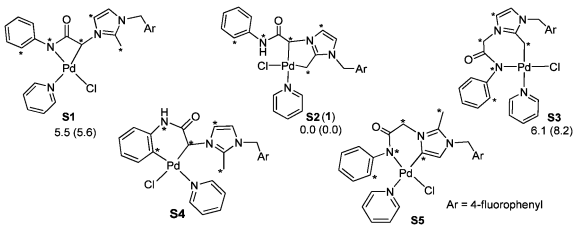


Chart 1 Five possible Pd isomers from L^1. Relative energies (in kcal mol^{-1}) for the three most stable isomers are shown (relative free energies are in parentheses; possible coordination sites of ligand are marked by asterisks).

derivative of L^3 containing an *N*-methyl group and a phenyl ring on the C2 position of the imidazolium ring.

L^1 offers five coordination sites for metal complexation: the *ortho*-*N*-phenyl carbon, the nitrogen atom, the methylene carbon, the methyl carbon, and the C4 site of the imidazolium ring (to form an abnormal NHC complex[25]). To understand the thermodynamic stabilities of different isomers of palladium complexes of L^1, we performed density functional theory (DFT) calculations at the B3LYP/LANL2DZ level of theory. The three most stable structural isomers are shown in Chart 1. The structural parameters of **S2** were in good agreement with the experimental structural data for **1**. The studies showed that **S2** is more stable than **S1** by 5.6 kcal mol^{-1}. Although there was a slight discrepancy between the calculations and experimental observations in the stereochemistry of **S1** and **S3** (chlorine and pyridine swapped coordination sites), the relative energies of **S2** and **S1** agreed with the experimental result that the five-membered palladacycle **1** is thermodynamically preferred over the four-membered palladacyclic product **3**. Also in accord with the experimental results, the seven-membered palladacycle (**S3**) with an amidate and alkyl donor was less stable, and it was not observed experimentally.

In the transformation of **3** to **1**, a concerted, direct hydrogen migration mechanism was postulated. The possibility of C–H oxidative addition through an octahedral palladium(IV) species is unlikely owing to the electron deficiency of **3**. The preliminary computational results for this transformation are shown in Fig. 4, where **TS1** has an imaginary frequency of -110 cm^{-1}. The transition state exhibited a markedly negligible methyl C–H bond agostic interaction with a Pd···C distance of 3.345 Å (the sum of the van der Waals radii of Pd and C equals 3.33 Å)[26] and a long Pd···H contact of 2.997 Å. On the other hand, the methyl C–H bond was in close contact with the nitrogen atom at a very short distance of 2.169 Å (the sum of the van der Waals radii of N and H equals 2.75 Å).[26] Agostic interactions have been commonly involved in many transition metal-mediated C–H bond activations.[18,27] However, since the methyl C–H bond was acidic enough owing to its attachment to the imidazolium ring,[23] no significant preactivation *via* agostic interactions was required. The energy

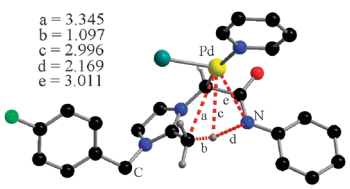


Fig. 4 **TS1** for the conversion of **3** to **1**. Selected H atoms have been removed for clarity. Distances are in Å.

barrier in the gas phase was calculated to be 38.1 kcal mol^{-1}. When solvent correction (pyridine as solvent) was applied, the barrier to the transformation was reduced to 35.3 kcal mol^{-1}.

We have demonstrated a novel cyclometalation process for the formation of CC-type palladacycles *via* a unique NH(CO)-assisted selective C–H bond activation pathway. Our results contrast literature examples of cyclometalation involving donor-assisted C–H bond activation. In the present case, the auxiliary functional group is non-coordinating and appears to be intact in the final product; however, a detailed investigation revealed a mechanistic pathway involving the formation of a palladalactam. After forming this kinetic product, the possibility of *ortho*-*N*-phenyl C–H activation was blocked. Subsequent facile sp^3 or sp^2 C–H bond activation assisted by the coordinated nitrogen as a base led to the formation of **1** and **5** while the amide moiety was regenerated. By blocking this pathway with an *N*-methyl group, we prevented access to the five-membered palladacycles. Instead an *ortho*-*N*-phenyl C–H activation pathway was favored, affording CC-type palladacycle **8**. Work to apply this mechanism to new modes of catalysis is in progress.

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