Digging into the mechanism of oxidative Pd(II)-catalyzed aminations

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Abstract
Although the Pd(II)-catalyzed alkene aminopalladation and allylic C-H activation have been much described in literature, the in-depth mechanism of such type of process is far from being a simple matter. This account focuses on the oxidative intramolecular Pd(II)-catalyzed amination of unsaturated N-sulfonyl carbamates and carboxamides, revealing that different mechanistic paths can be operative. In particular, after activation of the unsaturation by Pd(II) catalyst, aminopalladation can take place, affording the corresponding high-energy cyclic (5- or 6-membered) aminopalladated intermediate (AmPI). This latter can evolve along different pathways, such as: distocyclic β-H elimination, oxidation by a strong terminal oxidant, or carbopalladation. Otherwise, the cyclic AmPI can lay dormant, in equilibrium with the initial substrate. In this case, alternative reactivities may take place, such as allylic C-H activation of the olefinic substrate, [3,3]-sigmatropic rearrangement, or decomposition.
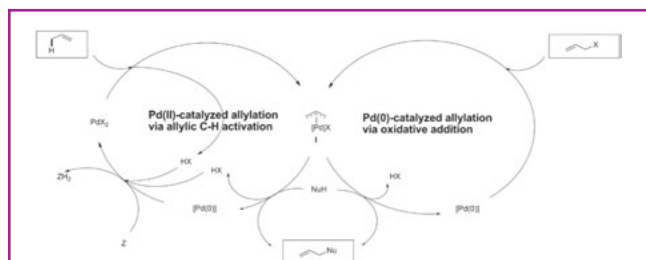
INTRODUCTION

The two interlaced Pd-catalyzed allylation paths

Pd(0)-catalyzed allylation is a powerful transformation discovered in the sixties by Tsuji.(1) In 1970, the first catalytic version of this reactivity appeared in publications or patents (2, 3) and, a few years later, Trost reported the first asymmetric version(4), confirming the synthetic potential of this method. In this transformation, a Pd(0) complex undergoes oxidative addition by an allylic system, to generate an electrophilic η^3-allyl-palladium intermediate **I**, which is finally trapped by a nucleophile to lead to the allylated product (Scheme 1, right). During the following decades, this Pd(0)-catalyzed allylation protocol gained a huge success. Many asymmetric variants,(5) as well as implementations as key steps in total and/or multistep syntheses of therapeutically relevant compounds have been reported. (6)
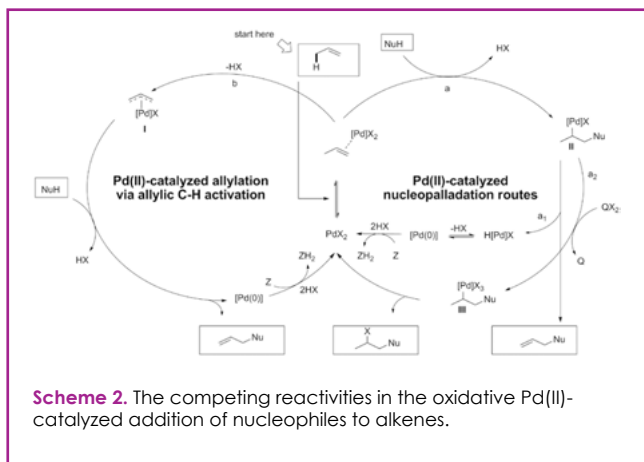
The same η^3-allyl-palladium complex **I** can also be reached by the interaction between a Pd(II) complex and an alkene bearing an allylic hydrogen atom (Scheme 1, left). As above, trapping by a nucleophilic reagent gives the final allylated compound and a Pd(0) complex. In this case, the presence of an external oxidizing agent (Z) is required to bring zerovalent Pd back to an active Pd(II) complex. This variant, also called "direct Pd-catalyzed allylation", involves the direct functionalization of an allylic C-H bond, and received considerable attention in recent years.(7) Indeed, these allylic, as well as the complementary aryl or alkyl C-H activations, provide the synthetic chemist with ever more selective and efficient methods to activate otherwise non reactive C-H bonds.

Dichotomic paths for the oxidative Pd(II)-catalyzed nucleophilic additions to alkenes

This Pd(II)-catalyzed direct allylic functionalization (Left cycle in Schemes 1 and 2) is not the only pathway that can occur when an alkene and a nucleophilic species are brought together in presence of a Pd(II) catalyst. Indeed, after activation of the unsaturation by a Pd(II) catalyst, a nucleopalladation reaction can also take place (Scheme 2, right cycle, path a), leading to an σ-alkyl-palladium complex **II**.(8) On the one hand, this latter can evolve via dehydropalladation (path a_1), affording the final unsaturated product with the concomitant reduction of Pd(II) to Pd(0). Oxidation of this zerovalent Pd by a terminal oxidizing agent closes the catalytic cycle. A number of amino- and oxy-(9) palladation processes, including the very popular Wacker process, follow this path. On the other hand, dehydropalladation can be avoided by treatment with appropriate oxidizing agent (QX_2) that oxidatively cleaves the Pd-C bond via a Pd(IV) intermediate **III** (Scheme 2, right cycle, path a_2).(10, 11)

Scheme 1. Right cycle: classical Pd(0)-catalyzed allylation. Left cycle: direct Pd(II)-catalyzed allylation.

Scheme 2. The competing reactivities in the oxidative Pd(II)-catalyzed addition of nucleophiles to alkenes.

Scheme 3. Quinazolinones *via* Pd(II)-catalyzed intramolecular direct allylic amination and benzodiazepinones *via* aminopalladation.

Despite the amount of data about both these alternative reactivity patterns, a study aimed at understanding the rules governing selection of one over the other path was until now unknown.(12) Therefore, we undertook a study aiming at discovering a unifying theory accounting for these two mutually excluding mechanisms. With this idea in mind, we undertook an in-depth investigation of the Pd(II)-catalyzed cyclization of unsaturated *N*-sulfonyl carbamates and carboxamides bearing different tethers between the nitrogen atom and the unsaturation, and by using different terminal oxidants.
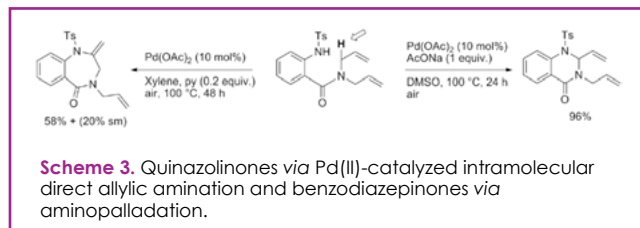
ABOUT THE TERMINAL OXIDANT

As stated, the above transformations are oxidative processes (Left cycle and right cycle, path a_1 in Scheme 2). Consequently, a terminal oxidant "Z" has to be present in the medium in stoichiometric amounts to sustain the oxidation state of Pd(II), so as to close the catalytic cycle. Several terminal oxidants can be used to efficiently oxidize Pd(0) to Pd(II), such as Cu(II), 1,4-benzoquinones, Ag(I) salts, etc. In particular, in the case where the terminal oxidant is dioxygen, the process is defined as "aerobic".(13)
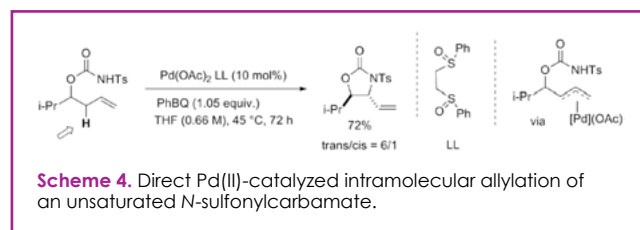Alternatively, when nucleopalladation is operative, stronger oxidants such as hypervalent iodine compounds (QX_2) can oxidize the intermediate alkyl-palladium(II) complex into the corresponding alkyl-palladium(IV) (or dimeric Pd(III)) complex (Right cycle, path a_2 in Scheme 2). This latter path is followed by the incorporation of a nucleophilic fragment on the substrate *via* reductive elimination, or S_N2 type substitution, which also induces the regeneration of the Pd(II) complex.

STATE OF THE ART

In 2004, Broggini *et al.* reported the first hints of this dichotomy for the oxidative Pd(II)-catalyzed cyclization involving a nitrogen nucleophile. Indeed, treatment of *N*-allyl-anthranilamides with catalytic amounts of Pd(OAc)$_2$ under aerobic conditions afforded either quinazolinones or benzodiazepinones, as a function of the reaction conditions (Scheme 3).(14) Specifically, the quinazolinones were obtained using DMSO as solvent in the presence of AcONa, while the formation of benzodiazepinones required the use of a non-coordinating solvent such as xylene. While the former cyclization was rationalized according to a C-H activation mechanism, the latter one clearly results from a Wacker-type reactivity (aminopalladation/dehydropalladation).
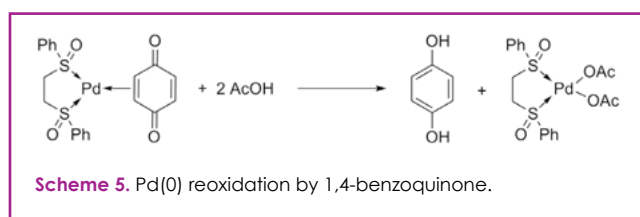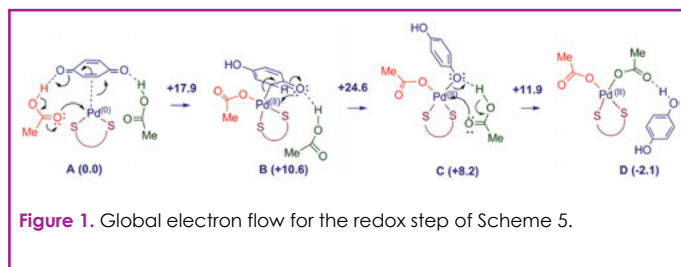
A few years later, White showed that the direct allylic amination of a terminal alkene can be performed in the presence of a specific disulfoxide ligand and a 1,4-quinone derivative as the terminal oxidizing agent (Scheme 4).(15) Stoichiometric experiments and tests on isomeric substrates bearing an internal (*E* or *Z*) alkene, pointed towards a mechanism involving an allylic C-H activation mechanism.

Scheme 4. Direct Pd(II)-catalyzed intramolecular allylation of an unsaturated *N*-sulfonylcarbamate.

ROLE OF THE pH

Our studies in this domain took initial inspiration from the above results by M. C. White, judged on the high synthetic interest. In particular, we speculated that a specific step in the catalytic cycle was likely to be responsible of slowing down the kinetics of the process. Indeed, we reasoned that under the above reaction conditions, the only protons available to generate hydroquinone from benzoquinone (and thus to carry on the Pd reoxidation) are the allylic hydrogen and the one on the nitrogen atom. As protic activation of benzoquinone is needed for Pd(0) reoxidation,(16) we suspected that the long reaction times (72 h) might be due to a turnover limiting Pd reoxidation step. Accordingly, we settled to monitor the detailed events of this redox process in terms of free energies in the presence of AcOH (Scheme 5).(17)
Computational studies showed that the conjugate addition of Pd(0) to BQ in the LLPd(0)(η^2-BQ) complex (LL = PhSOCH$_2$CH$_2$SOPh) activated by two H-bonded AcOH molecules occurs *via* an energy barrier (**TS$_{A-B}$**) of +17.9 kcal/mol. This process leads to transient intermediate **B** (+10.6 kcal/mol) (Figure 1), where the Pd atom is coordinated by LL, AcO$^-$ and BQ ligands. The C atom which lies a to the carbonyl of the BQ, interacts with the metal (Pd-C = 2.19 Å) which results in an about 10° bending off the C6 ring. A crucial H-bonding between BQ and a second AcOH molecule decreases the barrier of this step, which would rise up by about 50 percent in its absence. Moreover, the concerted incoming of the acetate ligand activates the protonated BQ, dihapto coordinated to Pd(0). In the conversion from **A** to **B**, this entering AcO$^-$ ligand assists the transfer of the originally back-
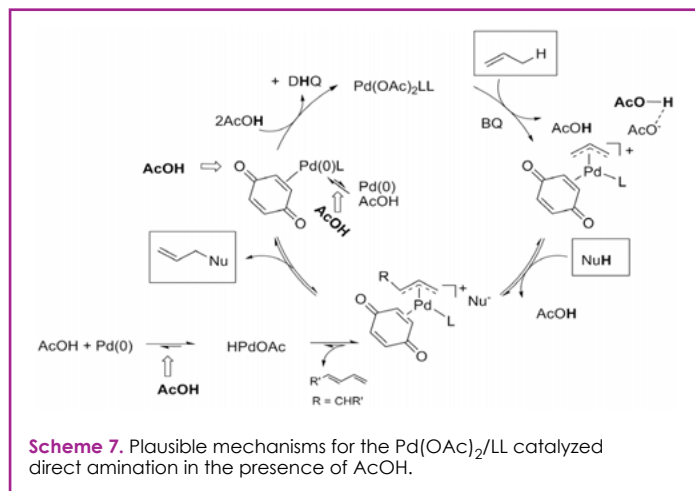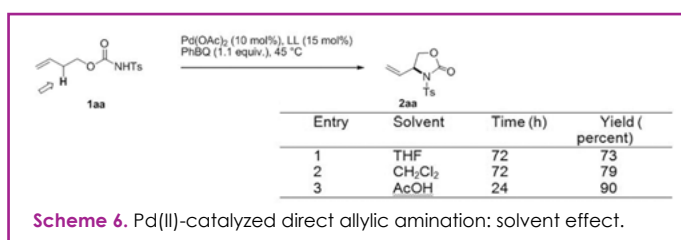

Scheme 5. Pd(0) reoxidation by 1,4-benzoquinone.

Figure 1. Global electron flow for the redox step of Scheme 5.

donated metal electron pair to the carbon atom, which formally becomes an s-alkyl donor toward the already oxidized d^8 metal. The η^1-coordination to Pd(II) *via* its quasi aromatic ring, underlines the pronounced phenoxide nature of **B**. Then, the BQ carbonyl oxygen atom acts as the $2e^-$ donor, generating a full phenol structure in **C**. Such a structural rearrangement, although requiring a major barrier (**TS$_{B-C}$** = +14.0 kcal/ mol), is thermodynamically favored by -2.4 kcal/mol with respect to **B**. The strong H-bonding of the second AcOH molecule (O···H is only 1.47 Å in **TS$_{B-C}$**), once more assists this step, which barrier would also be increased by 50 percent without it. Reaching the global minimum **D** (-2.1 kcal/mol lower than **A**), involves coordination of the second AcO$^-$ ligand concomitantly with BQ protonation, which allow this final step to proceed quite smoothly (**TS$_{C-D}$** +3.7 kcal/mol). Overall, the role of the two AcOH molecules is not limited to releasing protons and providing acetate ligands, but that they also control the redox and coordination properties of the metal. These computations thus corroborate the expectation that acetic acid exerts a beneficial kinetic effect in the intramolecular Pd(OAc)$_2$/LL catalyzed direct aminations

Subsequent tests on unsaturated *N*-sulfonyl carbamate **1aa** (Scheme 6) confirmed the above hypothesis. The yields and kinetics of the reactions in AcOH proved to be higher than in non protic solvents and diastereoselection was usually better when substituted unsaturated *N*-sulfonyl carbamates were used.

In addition to its action on Pd-reoxidation, AcOH may have a beneficial kinetic effect for other reasons. Indeed, due to its protic acidity, it can protonate the acetate ligand bound to Pd, thereby facilitating the formation of a reactive cationic complex.(18) Additionally, due to the Le Chatelier-Braun principle, it can prevent dehydropalladation from the η^3-allyl-palladium complex intermediate bearing a hydrogen in β-position.(19) Scheme 7 exemplifies the generic mechanisms of this transformation and highlights the sites in the catalytic cycle where AcOH can have a pertinent role.(17)
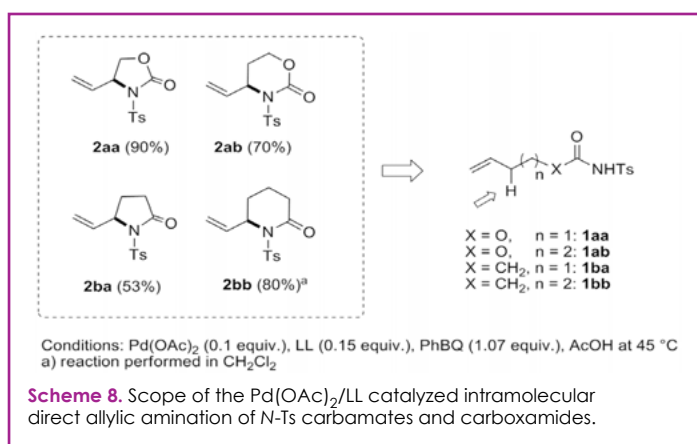
CASES ASSOCIATED TO A DORMANT CYCLIC AMINOPALLADATED INTERMEDIATE (AmPI)
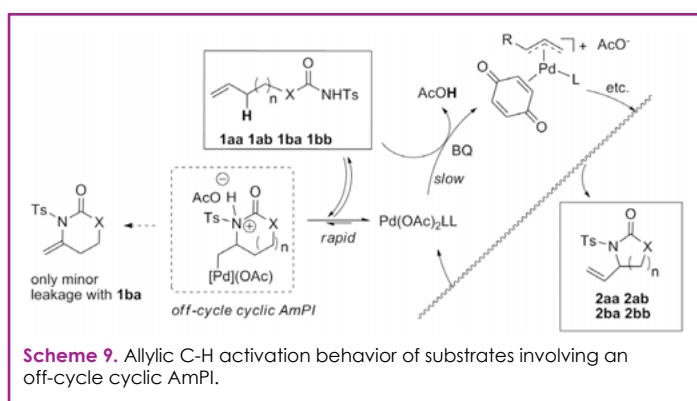
Allylic C-H activation
We subsequently decided to start a systematic study to rationalize the behavior of these substrates under oxidative catalytic Pd(II) conditions.(20) In the event, the same cyclization *via* allylic C-H activation was also observed on *N*-tosyl 5-hexenamide (**1ba**) and

Scheme 6. Pd(II)-catalyzed direct allylic amination: solvent effect.

Scheme 7. Plausible mechanisms for the Pd(OAc)$_2$/LL catalyzed direct amination in the presence of AcOH.

the corresponding C1 homologated substrates (**1ab** and **1bb**), giving respectively 5-vinyl pyrrolidone (**2ba**),(21) 4-vinyl oxazinone (**2ab**) and 6-vinyl piperidone (**2bb**) (Scheme 8).

Conditions: Pd(OAc)$_2$ (0.1 equiv.), LL (0.15 equiv.), PhBQ (1.07 equiv.), AcOH at 45 °C
a) reaction performed in CH$_2$Cl$_2$

Scheme 8. Scope of the Pd(OAc)$_2$/LL catalyzed intramolecular direct allylic amination of *N*-Ts carbamates and carboxamides.
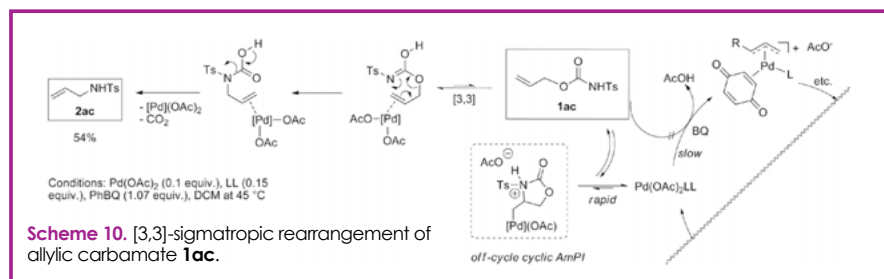
We presume that under the reaction conditions with quinone as oxidant, a rapid equilibrium occurs between the substrate and the corresponding cyclic aminopalladated intermediate (AmPI),(22) whose proxicyclic(23) β-H elimination is totally or partially forbidden. Indeed, in the absence of a β-H eliminative evolution, and due to the reversibility of the aminopalladation step,(24) the substrate is slowly but irreversibly consumed by a C-H activation path.(25) Hence, in this case, the cyclic aminopalladated intermediate (AmPI) is just an off-cycle intermediate, gradually depleted and injected into the catalytic cycle of the direct allylic C-H activation (Scheme 9).

Scheme 9. Allylic C-H activation behavior of substrates involving an off-cycle cyclic AmPI.
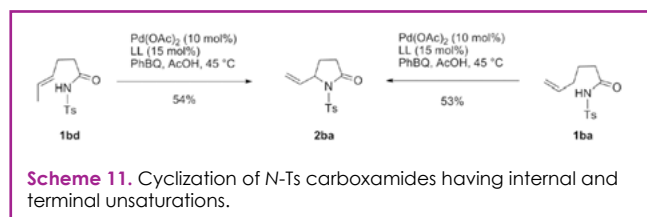
[3,3]-sigmatropic regarrangement

The treatment of prop-3-enyl *N*-tosylcarbamate **1ac** in the same conditions (except that in CH$_2$Cl$_2$ instead of AcOH), gave only the allyl-*N*-tosyl amine **2ac** in a moderate 54 percent yield (Scheme 10). Here again, the involvement of a rapid and reversible equilibrium with a dormant (off-cycle) cyclic AmPI, in which the proxicyclic β-H elimination is inhibited, can also be postulated. However, in this case **1ac** is poised to undergo a [3,3]-sigmatropic rearrangement(26) / decarboxylation(27) sequence, affording the observed allyl *N*-tosyl amine **2ac**.
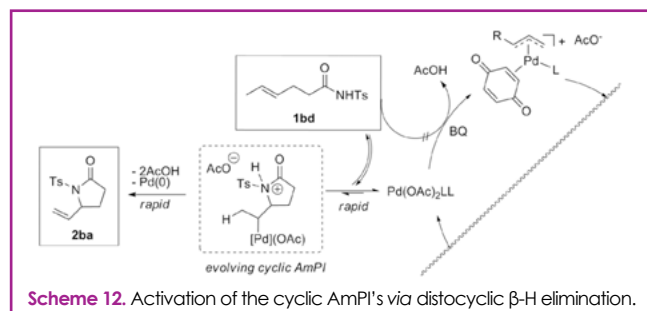

Scheme 10. [3,3]-sigmatropic rearrangement of allylic carbamate **1ac**.

CASES ASSOCIATED TO AN EVOLVING AmPI

Distocyclic dehydropalladation: internal olefin

Applying the above reactions conditions to *N*-tosyl (*E*)-hex-4-enamide (**1bd**) gave cleanly the same vinyl pyrrolidone (**2ba**), as obtained from the isomer **1ba** having a terminal unsaturation (Scheme 11).(28) It has to be noted that White's ligand is not expected to bring about C-H activation on linear alkenes with internal unsaturation.

Scheme 11. Cyclization of *N*-Ts carboxamides having internal and terminal unsaturations.

In the case of carboxamide **1bd**, the preferred mechanism changes because of two reasons: a) the 5-membered AmPI can now easily evolve *via* distocyclic β-H elimination, b) the C-H allylic activation process is disfavoured due to the internal position of the alkene. As a result, formation of 5-vinyl-pyrrolidin-2-one **2ba** *via* aminopalladation/dehydropalladation becomes the only favored pathway (Scheme 12).

Scheme 12. Activation of the cyclic AmPI's *via* distocyclic β-H elimination.

Quite interestingly, switch of the operating mechanism from C-H allylic activation to aminopalladation (compare generation of **2ba** from **1ba** (Schemes 8 and 11) and from

1bd (Scheme 12)) can be induced by a formal slippage of the unsaturation in the starting substrate.
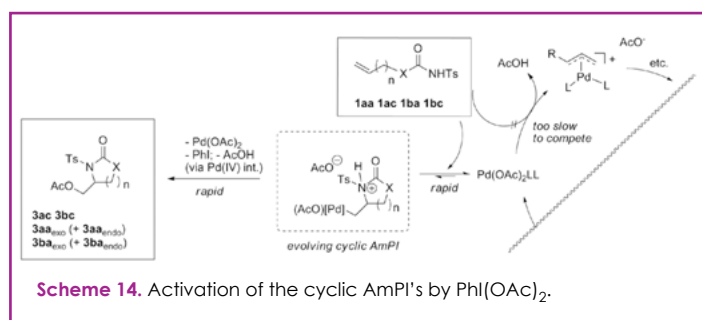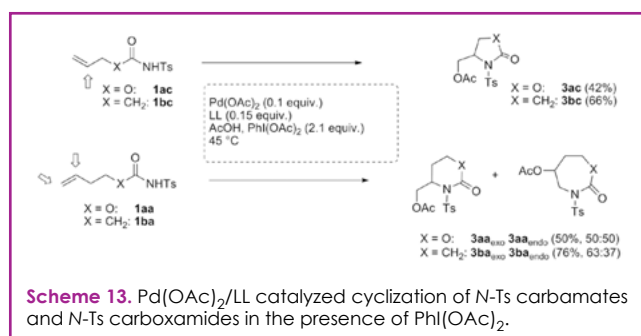
Oxidative cleavage

The same substrates as before were then submitted to the same reaction conditions, except for the replacement of PhBQ by PhI(OAc)$_2$ as the terminal oxidant. In these cases, the heterocycles obtained came from a net aminoacetoxylation of the double bond (Scheme 13). In this case, the previously "dormant" cyclic AmPI can be "awakened" by PhI(OAc)$_2$. Such activation, which is expected to transit through a Pd(IV) (or a dimeric Pd(III)) intermediate and subsequent reductive elimination,(29) turns out to be much faster than the previously observed C-H activation reactivity (Scheme 14).(30)
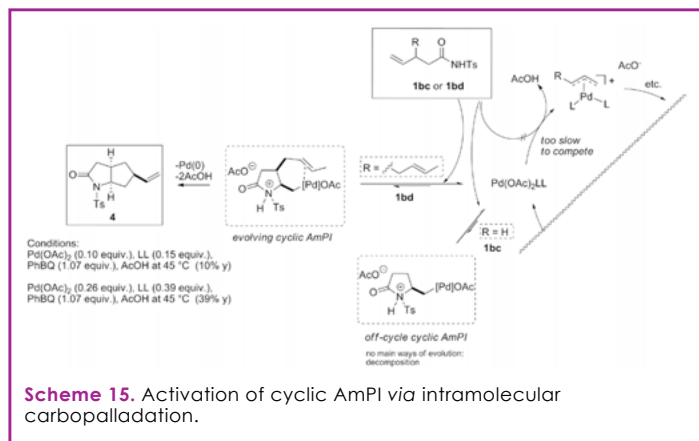
Carbopalladation

We next thought that a way to further confirm the involvement of such elusive cyclic AmPI's could consist of awakening an inherently dormant one *via* a juxtaposed built-in unsaturation, so as to engage it in a carbopalladation/ dehydropalladation sequence. Accordingly, we submitted *N*-tosyl 3-vinylhept-5-enamide **1bd** to the above reaction conditions. It has to be noted that **1bd** is an analog of the unreactive **1bc** analogue, but bearing a juxtaposed unsaturation. Much to our satisfaction, the planned domino reaction did take place, affording the fused pyrrolidin-2-one **4** in 10 percent or 39 percent yield as a single diastereoisomer when using 10 mol percent or 26 mol percent Pd(OAc)$_2$, respectively (Scheme 15). Despite an inefficient Pd turnover, this reactivity represents, on the one hand, a synthetically interesting catalytic pure domino sequence, and on the other hand unambiguously demonstrates the involvement of the postulated elusive cyclic AmPI.

CONCLUSION

The present brief account gathers our most recent studies on the Pd(II)-catalyzed oxidative cyclization of unsaturated *N*-tosyl carbamates and

Scheme 13. Pd(OAc)$_2$/LL catalyzed cyclization of *N*-Ts carbamates and *N*-Ts carboxamides in the presence of PhI(OAc)$_2$.

Scheme 14. Activation of the cyclic AmPI's by PhI(OAc)$_2$.

Scheme 15. Activation of cyclic AmPI *via* intramolecular carbopalladation.

carboxamides to try and provide a unified picture of their mechanistic behavior. In particular, we found that AcOH can dramatically speed up the intramolecular Pd(II)-catalyzed C-H direct amination of these substrates. Furthermore, the subtle intertwined relations existing between allylic C-H activation and nucleopalladation processes have been unveiled. Indeed, the initially and reversibly formed cyclic aminopalladated intermediate (AmPI) can either evolve along various pathways or stay dormant. Now, with a better understanding of the factors that forbid or allow its evolution, novel reactive pathways and synthetic applications remain to be explored.

ACKNOWLEDGEMENTS

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21. In this particular case dehydropalladation of the AmPI is observed to a small extent, which affects the isolated yield of the product.
22. For precedents of reversible aminopalladation, see ref 6 and: a) Hahn, C., Morvillo, P., Vitagliano, A. *Eur. J. Inorg. Chem.*, 419-429 (2001). b) Hahn, C., Morvillo, P., Herdtweck, E., Vitagliano, A. *Organometallics*, **21**, 1807-1818 (2002). c) Cucciolito, M. E., D'Amora, A., Vitagliano, A. *Organometallics*, **24**, 3359-3361 (2005). d) Michael, F. E., Cochran, B. M. *J. Am. Chem. Soc.*, **130**, 2786-2792 (2008). e) Timokhin, V. I., Stahl, S. S. *J. Am. Chem. Soc.*, **127**, 17888-17893 (2005). f) Bar, G. L. J., Lloyd-Jones, G. C., Booker-Milburn, K. I. *J. Am. Chem. Soc.*, **127**, 7308-7309 (2005).
23. We propose the adjectives *proxicyclic* and *distocyclic* to unambiguously distinguish between a β-H elimination involving a hydrogen atom in a cyclic structure (*proxicyclic*) with respect to an alternative elimination involving a hydrogen atom in a linear fragment (*distocyclic*).
24. For a previous proposal of an impeded β-H elimination from a cyclic AmPI, see: a) Balázs, A., Hetényi, A., Szakonyi, Z., Sillanpää, R., Fülöp, F. *Chem. Eur. J.*, **15**, 7376-7381 (2009). Unpublished experiments in our laboratory as well as literature precedents tend to indicate that the corresponding unsaturated *N*-tosylamines (Ts-NHCH₂R) do not experience such a difficult dehydropalladation.
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30. The absence of quinone in these experiments may further inhibit the alternative C-H activation pathway.