Palladium catalyzed oxidative aminations and oxylations: where are we?

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Conference paper

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Abstract: Selective product formation in the Pd-catalyzed cyclization of unsaturated amide and carboxylic acid derivatives is an intriguing and challenging task. We recently discovered that the oxidative intramolecular Pd(II)-catalyzed amination or oxylation of unsaturated N-sulfonyl carbamates, N-sulfonyl carboxamides and carboxylic acids takes place through the involvement of cyclic (usually, 5- or 6-membered) aminopalladated (A*m*PIs) or oxypalladated (O*x*PI) intermediates. Such cyclic intermediates can undergo a variety of transformations such as distocyclic β-H elimination, oxidative acetoxylation or intramolecular carbopalladation, depending upon the substrate and/or the reaction conditions. In the absence of appropriate reaction pathways, the cyclic nucleopalladated intermediates (N*u*PIs) simply engage in an inconsequential equilibrium with the initial substrate and other transformations occur such as allylic C–H activation or, in the particular case of allyl carbamates, [3,3]-sigmatropic rearrangement.

Keywords: aminopalladation; C–H activation; C–H bond reactivity; ESOC-19; β-hydride elimination; nucleopalladation; oxypalladation; palladium (II); palladium catalysis; [3,3]-sigmatropic rearrangement.

Introduction

When an alkene coordinates to a PdX_2 complex, the electronic character of the olefin π-system changes enabling two main and mutually excluding reaction paths, namely nucleopalladation [1–6] or C–H allylic activation [7–12] to provide an electrophilic η^3-allylpalladium complex. Other reactions and intermediates are also accessible depending upon the nature of the starting alkene and/or the reaction conditions (Scheme 1) [13].

These transformations are normally oxidative and therefore require an oxidant to regenerate the active metal catalyst. The oxidant can intervene after the formation of product and convert Pd(0) back into Pd(II) (Scheme 2, left) or assist product formation through oxidation of an intermediate organometallic Pd(II) species to a more reactive Pd(IV) species (Scheme 2, right) [14–17].

Many studies on the role of the oxidant have been published. However, a complete understanding of the rules governing the path selection lacks. Accordingly, we decided to undertake a systematic investigation of the Pd(II)-catalyzed cyclization of unsaturated N-sulfonyl carboxamides (**1a**), carboxylic acids (**1b**), and N-sulfonyl carbamates (**1c**) in the presence of a variety of terminal oxidants (Scheme 3) [18]. This study has permitted a correlation of reaction pathway with substrate type and reaction conditions.

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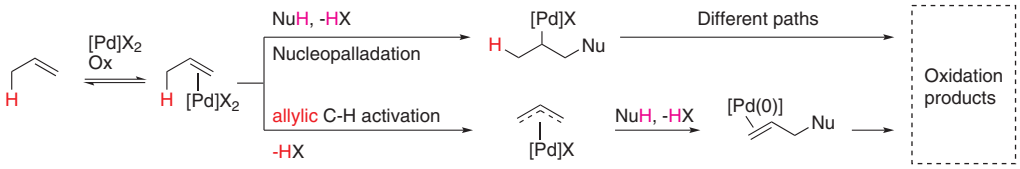
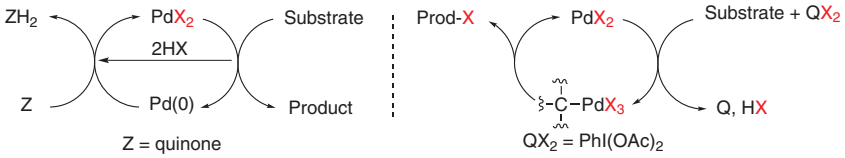
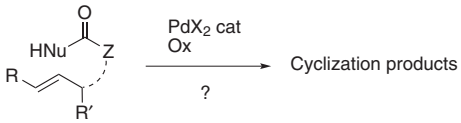


Scheme 1: Divergent paths in the Pd(II)-catalyzed addition of nucleophiles to alkenes.



Scheme 2: Left: a generic oxidative Pd(II)/Pd(0) catalytic system; right: a generic oxidative Pd(II)/Pd(IV) catalytic system.



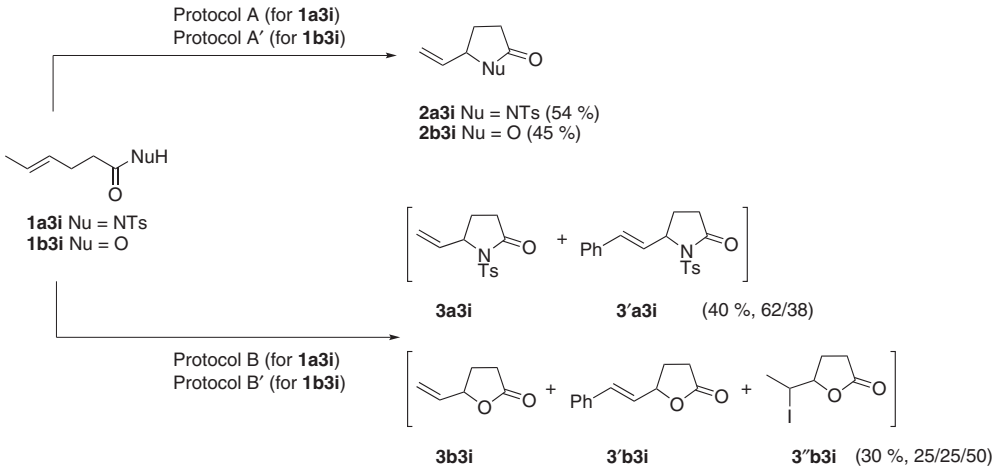
1a: Z = CH_2, Nu = NTs (N-tosyl carboxamides)
1b: Z = CH_2, Nu = O (carboxylic acids)
1c: Z = O, Nu = NTs (N-tosyl carbamates)

Scheme 3: Planned investigation of intramolecular oxidative Pd(II)-catalyzed alkene oxylation or amination.

Substrates with internal alkenes

Based on a series of preliminary experiments, optimal reaction conditions were defined for the nitrogen containing substrates [protocol A: $Pd(OAc)_2$ 10 mol %, $(PhSOCH_2)_2$ 15 mol %, phenylbenzoquinone (PhBQ) 1.07 equiv, AcOH (0.2 M), 45 °C, 24 h] and the unsaturated carboxylic acids [protocol A′: $Pd(OAc)_2$ 10 mol %, $(PhSOCH_2)_2$ 15 mol %, PhBQ 1.07 equiv, NaOAc 1 equiv, DCM (0.5 M), 45 °C, 24 h]. Submission of N-tosyl (*E*)-hex-4-enamide **1a3i** and of hex-4-enoic acid **1b3i** to these optimized reaction conditions gave 5-vinyl pyrrolidone **2a3i**, and 5-vinyl γ-butyrrolactone **2b3i** (Scheme 4, top), respectively [19].

On the other hand, the same reactions with $PhI(OAc)_2$ as oxidant [protocol B for **1a3i**: $Pd(OAc)_2$ 10 mol %, $(PhSOCH_2)_2$ 15 mol %, $PhI(OAc)_2$ 2.1 equiv, AcOH (0.2 M), 45 °C, 24 h; protocol B′ for **1b3i**: $Pd(OAc)_2$ 10 mol %, $(PhSOCH_2)_2$ 15 mol %, $PhI(OAc)_2$ 2.1 equiv, NaOAc 1 equiv, DCM (0.5 M), 45 °C, 24 h] gave rise to inseparable



Scheme 4: Reactivity of internal alkenes with two different terminal oxidizing agents.

mixtures; 5-vinyl- and β-styryl-pyrrolidones **3a3i** (same as **2a3i**) and **3′a3i** were obtained from **1a3i** and 5-vinyl-, 5-(β-styryl)- and 5-(1-iodo-ethyl)-γ-butyrrolactones **3b3i** (same as **2b3i**), **3′b3i**, and **3″b3i** were obtained from **1b3i** (Scheme 4, bottom).

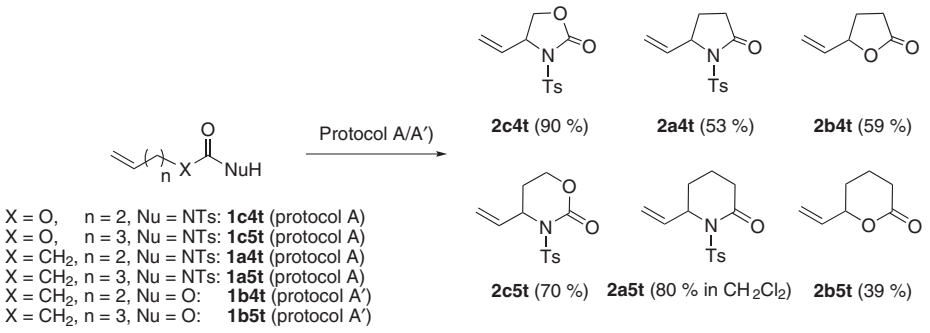
Substrates with terminal alkenes

N-sulfonyl carbamates [20], N-sulfonyl carboxamides [21], and carboxylic acids [22, 23] bearing terminal double bonds were also considered and gave similar results. In particular, reaction of N-tosyl but-3-en-1-yl carbamate **1c4t** and its homolog N-tosyl pent-4-en-1-yl carbamate **1c5t** according to protocol A provided 4-vinyl-1-tosyl-1,3-oxazolidin-2-one **2c4t** and 1-tosyl-4-vinyl-1,3-oxazinan-2-one **2c5t**, respectively. The expected products were also obtained from N-tosyl hex-5-en-amide **1a4t**, and N-tosyl hept-6-en-amide **1a5t**. Similarly, cyclization of the unsaturated carboxylic acids hex-5-enoic acid **1b4t** and hept-6-enoic acid **1b5t** furnished 5-vinyl γ-lactone **2b4t** (same as **2b3i**) and 6-vinyl δ-lactone **2b5t** (Scheme 5).

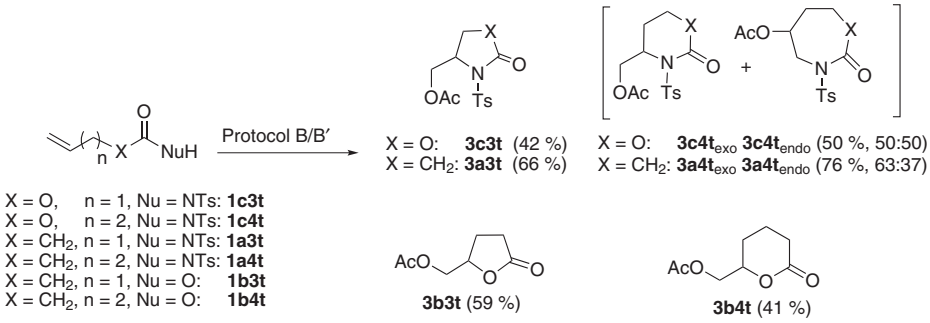
A very different outcome was observed when $PhI(OAc)_2$ was the oxidant (protocol B). Here, heterocycles resulting from a formal alkene 1,2-aminoacetoxylation were obtained (Scheme 6). In the case of the carbamates and the carboxamides with a three atom bridge between the nucleophile and the double bond, random mixtures of 6-exo and 7-endo products were detected.

Rationalization of the results

Although confusing at first glance, all the results obtained can be explained through an initial equilibration between the substrate and the nucleopalladated intermediate (N*u*PI). The fate of the N*u*PI depends upon the substrate and the reaction conditions, particularly the nature of the oxidizing agent. For substrates



Scheme 5: Reactivity of terminal alkenes with PhBQ as terminal oxidizing agent.

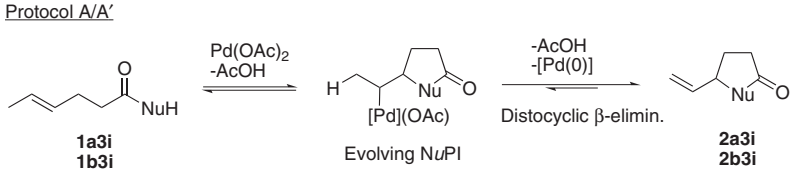


Scheme 6: Reactivity of terminal alkenes with $PhI(OAc)_2$ as terminal oxidizing agent.

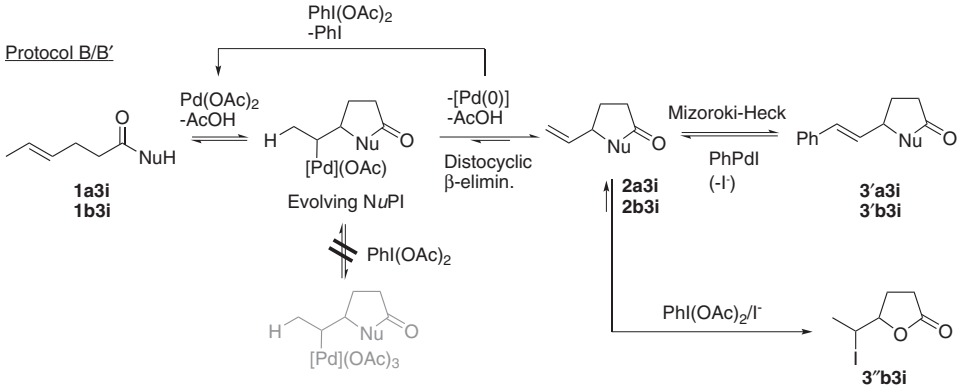
having a three atom bridge between the nucleophile and the unsaturation (Scheme 4, top), the intermediate 5-membered-ring N*u*PI [24] can easily undergo distocyclic dehydropalladation [25] in the presence of PhBQ (protocols A/A′) to provide vinylpyrrolidones or lactones (Scheme 7). Such a β-elimination is favored by the presence of three easily accessible equivalent hydrogen atoms.

The fact that these same products were generated in the presence of $PhI(OAc)_2$ (protocol B/B′) indicates that the oxidation of N*u*PI does not compete with this very facile β-H elimination. However, further reactions occurred to furnish the styryl heterocycles **3′a3i** and **3′b3i**, as a result of a Mizoroki–Heck process and, in the case of the carboxylic acids, the iodolactone **3″b3i** via a potential $PhI(OAc)_2$ promoted iodolactonisation (Scheme 8).

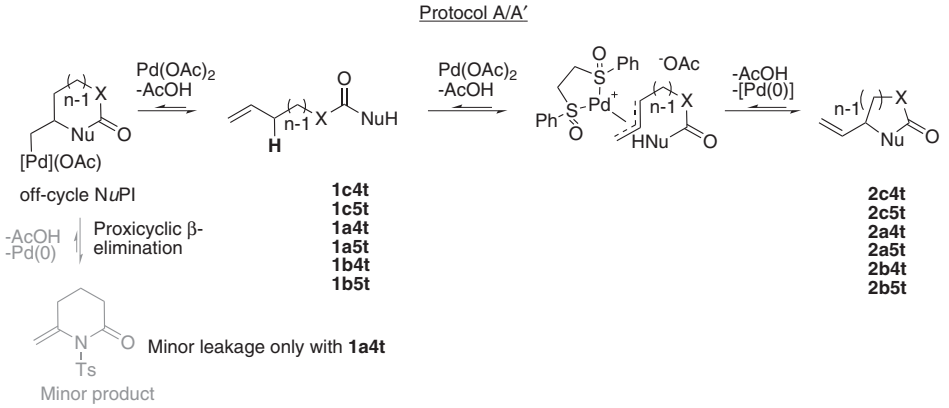
For substrates bearing a terminal unsaturation, we believe that the N*u*PI intermediate still forms in a rapid and reversible equilibrium [26–31] but that β-H elimination, only possible through a proxicyclic path, is disfavored [32]. Therefore, protocol A/A′ leads predominately to irreversible C–H activation before nucleophilic attack, to provide the product [33] (Scheme 9).



Scheme 7: Generation of a cyclic N*u*PI from an internal alkene and its evolution in the presence of PhBQ.



Scheme 8: Generation of a cyclic N*u*PI from an internal alkene and its evolution in the presence of $PhI(OAc)_2$.



Scheme 9: Allylic C–H activation from dormant N*u*PIs.

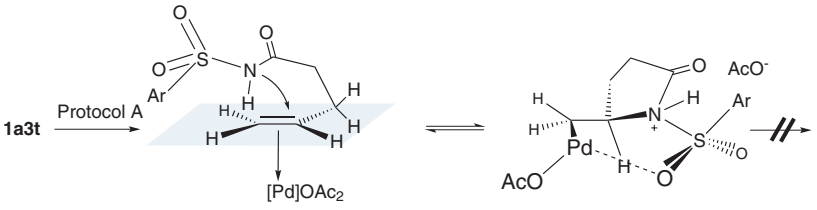
We believe that the proxicyclic dehydropalladation of carbamates and carboxamides is disfavored by electronic effects as well as geometric constraints. Indeed, in AcOH solvent, the nitrogen atom of A*m*PI can be protonated, thereby rendering β-H elimination more difficult. Furthermore, interaction between the Pd atom and one of the two oxygen atoms of the sulfonyl moiety may impede the synperiplanar H-C-C-Pd arrangement, required in the β-H elimination step (Scheme 10).

However, in the presence of $PhI(OAc)_2$ (protocol B/B′), oxidation of the N*u*PI intermediate can occur, opening up a new product manifold. The oxidation to either a Pd(IV) [34, 35] or a dimeric Pd(III) intermediate apparently occurs, followed by reductive elimination [14–17]. This process is much faster than the C–H activation observed in the presence of PhBQ (Scheme 11).

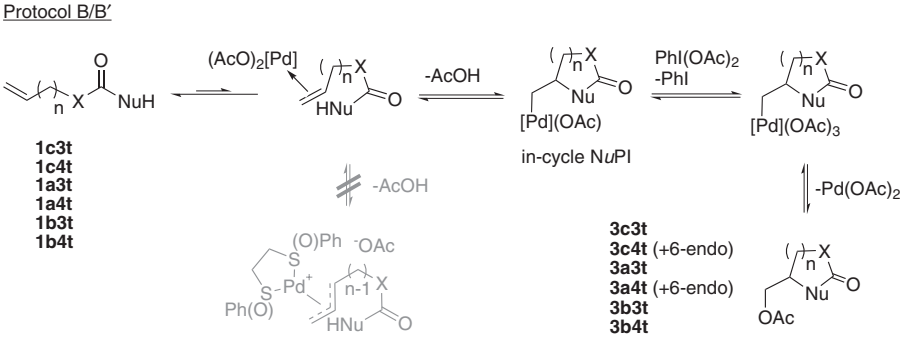
Carbopalladation as a means to trap the elusive *Nu*PIs

According to this proposed mechanism, substrates possessing a terminal unsaturation are expected to reversibly form an off-cycle N*u*PI under reaction conditions A/A′ as a result of a forbidden proxicyclic β-H elimination (Scheme 12, left). One clever way to demonstrate the existence of such elusive intermediate would be to incorporate an additional unsaturation into the substrate, so as to enable an easy intramolecular carbopalladation/dehydropalladation sequence, according to a domino process [36, 37] (Scheme 12, right).

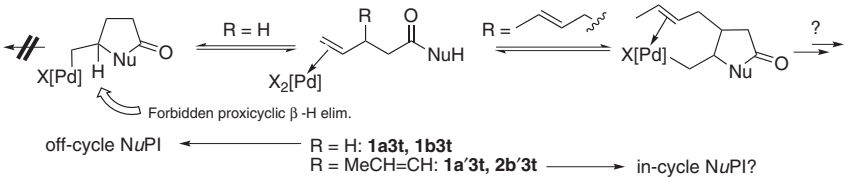
Indeed, submission of N-tosyl 3-vinylhept-5-enamide **1a′3t** to cyclization protocol A afforded the fused pyrrolidin-2-one **2a′3t** as a single diastereoisomer in 10 % yield (40 % when using 26 mol % of $Pd(OAc)_2$)



Scheme 10: Reversible generation of a cyclic N*u*PI from a terminal alkene and its hampered β-elimination when using PhBQ as oxidizing agent.



Scheme 11: Generation of a cyclic N*u*PI from a terminal alkene and its evolution when using $PhI(OAc)_2$ as oxidizing agent.



Scheme 12: Envisaged proof of concept: intramolecular cabopalladation to activate the intrinsically dormant cyclic N*u*PI.

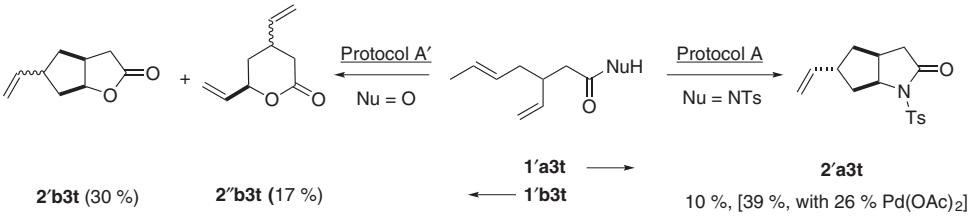
(Scheme 13, right). Under the same conditions, 3-vinylhept-5-enoic acid **1b′3t** gave a mixture of the expected bicyclic γ-lactone **2b′3t** and the dienic δ-lactone **2b″3t**. We surmised that the poor Pd turnover for carboxamide **1a′3t** was due to an unfavorable equilibrium in the reductive elimination step, AcO[Pd]H ⇆ [Pd(0)] + AcOH, due to the acidic conditions. Repeating the reaction under basic aerobic conditions [protocol A″: $Pd(OAc)_2$ (0.1 equiv), NaOAc (2 equiv), DMSO, O_2, 80 °C, 24 h] provided the desired product **2a′3t** in an improved yield of 40 %.

Interestingly, whereas the reaction cascade consisting of 5-exo aminopalladation and carbopalladation was stereo- and regio-selective for the carboxamide, transformation of the carboxylic acid substrate was characterized by two unselective and competing reactions: 5-exo oxypalladation/carbopalladation and 6-exo oxypalladation/distocyclic dehydropalladation sequence (Scheme 14). Despite the moderate Pd turnover, these catalytic domino sequences are of synthetic interest and unequivocally confirm the involvement of the postulated cyclic N*u*PIs.

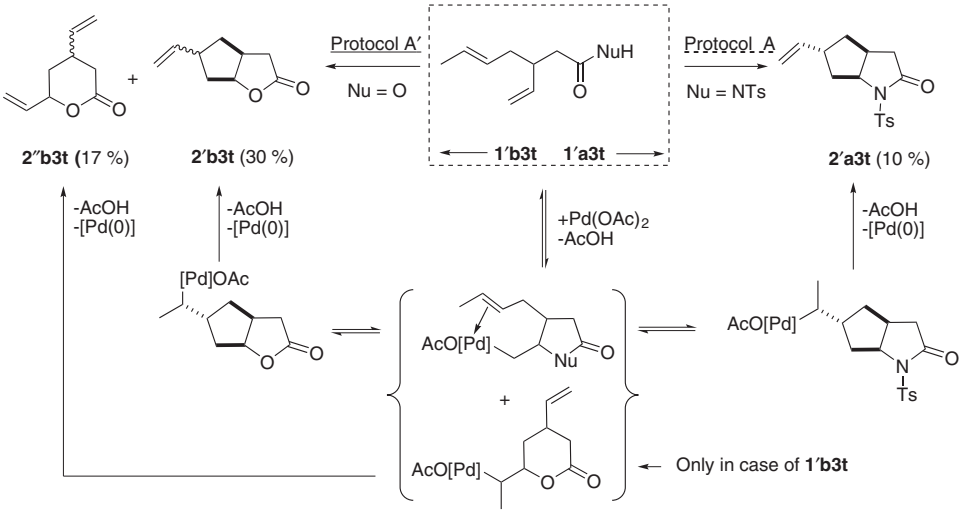
The special case of allylic carbamates

Reaction of prop-3-enyl N-tosylcarbamate **1c3t** according to protocol A (but using CH_2Cl_2 instead of AcOH), gave only the allyl-N-tosyl amine **2c′3t** in 54 % yield. Here again, a rapid and reversible equilibrium with an off-cycle cyclic A*m*PI could be present but, in this particular case, the substrate undergoes a facile [3,3]-sigmatropic rearrangement [38–43] followed by decarboxylation [44] (Scheme 15).

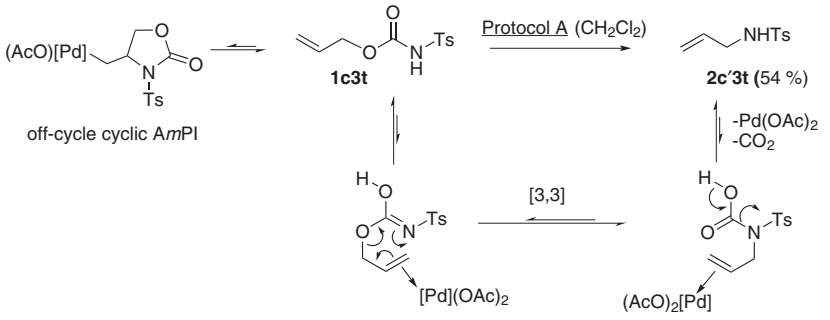
Substrate **1c3i** is an intriguing probe as it can undergo both aminopalladation as well as the [3,3]-sigmatropic rearrangement sequence. Using protocol A″ (protocol A was ineffective), a mixture of 4-vinyl



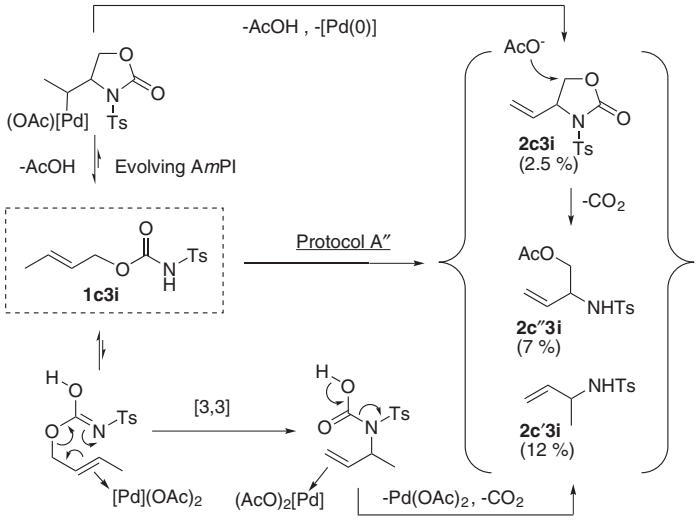
Scheme 13: Different behavior of carboxamide **1a′3t** and carboxylic acid **1b′3t** in the domino nucleopalladation/carbopalladation process.



Scheme 14: Proposed mechanisms associated to the different behavior of carboxamide **1a′3t** and carboxylic acid **1b′3t**.



Scheme 15: The [3,3]-sigmatropic rearrangement of the allylic carbamate **1c3t**.



Scheme 16: Case of the allylic carbamate **1c3i**: competition between [3,3]-sigmatropic rearrangement and distocyclic β-elimination.

oxazolidinone **2c3i** (2.5 %), N-tosyl 3-aminobutene **2c′3i** (7 %) and 4-acetoxy-3-tosylamino butene **2″c3i** (12 %) was obtained. This is not totally unexpected and reflects a balanced competition between the [3,3]-sigmatropic rearrangement and the distocyclic β-H elimination pathways. Worthy of note is the B_{AL}-type [45] cleavage of the oxazolidinone ring by the acetate anion at high temperature (protocol A″ @ 80 °C). This leads to the aminoacetoxy derivative **2c″3i** after decarboxylation (Scheme 16).

Conclusion

The present account provides the first unified mechanistic scheme for the Pd(II)-catalyzed oxidative cyclization of unsaturated carbamates, carboxamides and carboxylic acids. The formation of a cyclic N*u*PI appears always possible, although it may or may not lie on the path of product generation. In particular, these intermediates can occur along several reaction pathways such as distocyclic β-H elimination, oxidative acetoxylation, or carbopalladation. On the other hand, in the absence of the above transformations, the N*u*PI may participate in an equilibrium with the initial substrate, potentially leading to [3,3]-sigmatropic rearrangements or allylic C–H activation of olefinic substrates.

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