Organic LETTERS

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Opening the Way to Catalytic Aminopalladation/Proxicyclic Dehydropalladation: Access to Methylidene γ-Lactams

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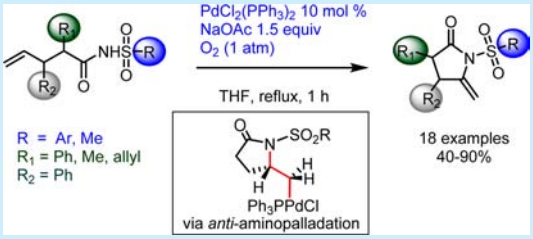
Supporting Information

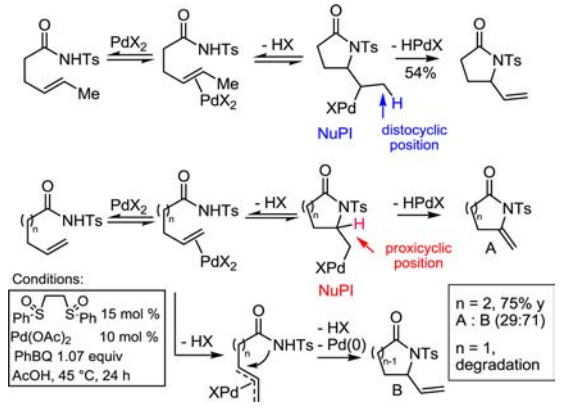
ABSTRACT: A new aerobic intramolecular palladium(II)-based catalytic system that triggers aminopalladation/dehydropalladation of *N*-sulfonyl-alkenylamides to give the corresponding methylidene γ-lactams has been identified. Use of triphenylphosphine and chloride anion as ligands is mandatory for optimal yields, and molecular oxygen can be used as the sole terminal oxidant. Scope and limitations of the methods are described. A mechanism is proposed on the basis of experimental results as well as density functional theory calculations.



Palladium-catalyzed oxidative alkene heterocyclization represents a widespread, atom-economical approach toward the synthesis of oxygen- or nitrogen-containing cyclic scaffolds.[1] However, starting from the same type of substrates and reaction conditions, two kinds of reactivities can be operative: allylic C−H activation[2] or nucleopalladation[3] (aminopalladation or oxypalladation).[4,5] We have recently investigated in detail the interplay of these mechanisms in intramolecular Pd(II)-catalyzed aminations[6] and oxylations[7] for various unsaturated *N*-sulfonyl carbamates, *N*-sulfonyl carboxamides, and carboxylic acids. The optimized reaction conditions found in these studies were as follows: 10 mol % of $Pd(OAc)_2$, 15 mol % of $PhS(O)(CH_2)_2S(O)Ph$ as the ligand, and 1.07 equiv of phenylbenzoquinone (PhBQ) as oxidant in AcOH for nitrogen-based nucleophiles and in CH_2Cl_2 with 1 equiv of NaOAc for oxygen-based nucleophiles. The results of these studies suggest the involvement of an initial rapid equilibrium between the PdX_2−substrate complex and a cyclic nucleopalladated intermediate (N*u*PI).[8] In particular, when the cyclic N*u*PI carries a H atom in a distocyclic[9] position (substrate with internal double bond), it can evolve via a rapid β-H elimination (Scheme 1, top, for *N*-Ts carboxamide). On the contrary, when the only β-H atom available in the cyclic N*u*PI is in a proxicyclic[9] position (substrate with terminal double bond), β-H elimination is totally or partially forbidden (Scheme 1, middle, product **A**), the cyclic N*u*PIs remaining in an unproductive equilibrium with the starting substrates.[10,11] In this case, alternative reactivities, such as the allylic C−H activation of the olefinic substrate, can take place (Scheme 1, bottom line, product **B**).

Puzzled by the forbidden (or strongly inhibited)[12] elimination of the cyclic N*u*PI proxicyclic β-H atoms, we decided to undertake further studies on this issue.[13] In the particular case of *N*-Ts carbamates and *N*-Ts carboxamides, we thought that under the acidic reaction conditions the nitrogen atom of the cyclic A*m*PI[8] is likely to be protonated which would, in turn, inhibit dehydropalladation, the proxicyclic hydrogen atom being too electron-depleted to interact with the palladium atom. Moreover, an intramolecular interaction between the Pd atom and an oxygen atom of the sulfonyl moiety could prevent the synperiplanar H−C−C−Pd arrangement needed for the dehydropalladation process (Figure 1, left). In this paper, we disclose new conditions that allow evolution of the A*m*PI (Figure 1, right).

Scheme 1. Possible Pathways for Pd(II)-Catalyzed Cyclization of *N*-Ts-carboxamides



We decided to search for new reaction conditions able to unlock the proxicyclic β-H elimination step, expected to give rise to alkylidene lactams (see product **A**, Scheme 1).[14] In line with the above reasoning, we surmised that the presence of a base and a coordinating ligand such as a phosphine[15] could remove the constraints, thereby allowing the β-H elimination process to take

Received: January 15, 2016
Published: February 23, 2016

DOI: 10.1021/acs.orglett.6b00143
Org. Lett. 2016, 18, 1020−1023

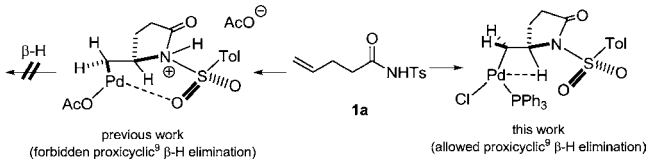
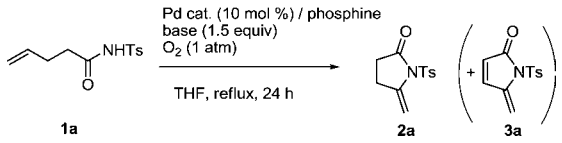


Figure 1. Dormant vs evolving A*m*PIs from *N*-Ts carboxamide **1a**.

place. Furthermore, in order to develop a green process, the use of molecular oxygen as the sole oxidant was considered.[16]

We chose as model substrate pent-4-enoic acid *N*-tosyl amide **1a**,[17] which gave rise only to degradation under the previously used acidic conditions (see Scheme 1). The influence of palladium catalyst, and the base, as well as of the ligand, was investigated, and the results are presented in Table 1.

Table 1. Optimization of the Pd(II)-Catalyzed Aerobic Amination[a]



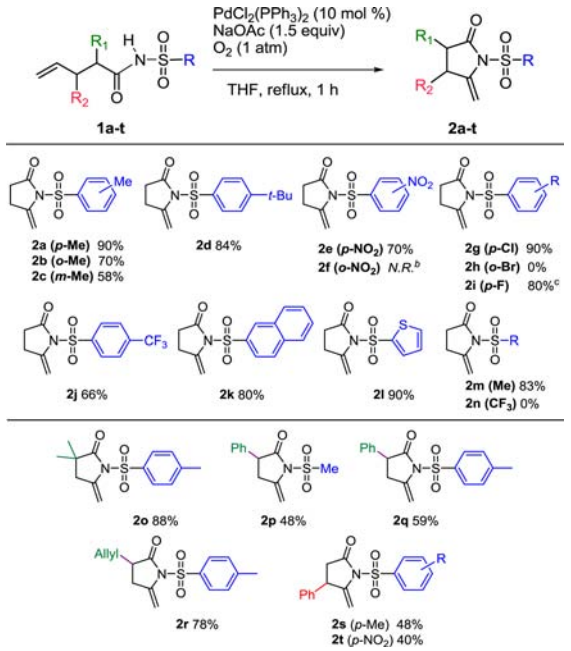
entry	Pd cat	phosphine (mol %)	base	yield[b] (%)
1	$Pd(OAc)_2$	PPh_3 (20)	NaOAc	65[c]
2	$Pd(OAc)_2$	XPhos (20)	NaOAc	20
3	$Pd(OAc)_2$	Binap (10)	NaOAc	30[c]
4	$Pd(OAc)_2$	dppe (10)	NaOAc	0
5	$Pd(OAc)_2$	PPh_3 (10)	NaOAc	41
6	$Pd(OAc)_2$	PPh_3 (30)	NaOAc	5[c]
7	$Pd(OAc)_2$	PPh_3 (20)	K_2CO_3	0
8	$Pd(OAc)_2$	PPh_3 (20)	NEt_3	20[c]
9	$PdCl_2(PPh_3)_2$		NaOAc	92
10	**$PdCl_2(PPh_3)_2$**		**NaOAc**	**92**[d]
11	$Pd(OAc)_2$	PPh_3 (20)	NaOAc	92[d,e]
12	$PdCl_2(PPh_3)_2$		NaOAc	12[d,f]
13	$PdCl_2(PPh_3)_2$			26[d]
14			NaOAc	0[d]

[a]Reaction conditions: **1a** (1 equiv), THF (0.2 M). [b]Spectroscopic (^{1}H NMR) yields using an internal standard (butadiene sulfone). [c]Traces of oxidation product **3a** were observed. [d]Reaction time: 1 h. [e]LiCl (20 mol %) was added. [f]Without oxidant.

A preliminary experiment using $Pd(OAc)_2$ as the Pd source, PPh_3 as the ligand, and NaOAc as the base, in THF at reflux, under O_2 (1 atm) afforded over 24 h the desired alkylidene γ-lactam **2a** in 65% yield along with traces of the Saegusa overoxidation product **3a**[18] (Table 1, entry 1). Replacement of PPh_3 for another monophosphine such as XPhos (entry 2) or a diphosphine such as Binap or dppe (entries 3 and 4), as well as changing of the phosphine loading, did not improve the outcome (entries 5 and 6).[19] The use of K_2CO_3 or NEt_3 as base completely or severely inhibited the reaction (entries 7 and 8). Other oxidants such as PhBQ and 2,6-dimethylbenzoquinone (2,6-DMBQ) did not lead to better results (see the Supporting Information). Gratifyingly, use of $[PdCl_2(PPh_3)_2]$ as the Pd source afforded **2a** as the sole product in 92% NMR yield (entry 9). Furthermore, with this palladium catalyst the reaction time could be reduced to 1 h (entry 10). The same result could be obtained using $Pd(OAc)_2$, PPh_3, and NaOAc and by addition of 20 mol % of LiCl, which confirmed the crucial role of the chloride anion (entry 11). Furthermore, one by one omission of the palladium source, the oxidant, or the base resulted in drastic yield drops (entries 12 and 13) or in the total recovery of the unreacted substrate (entry 14).

With our optimal conditions in hand $[PdCl_2(PPh_3)_2]$ (10 mol %), NaOAc (1.5 equiv), O_2 (1 atm), THF, reflux, 1 h, we proceeded to explore the scope of the reaction (Scheme 2).[17] The

Scheme 2. Scope of the Pd(II)-Catalyzed Aerobic Amination[a]



[a]Reaction conditions: **1a−t** (1 equiv), $[PdCl_2(PPh_3)_2]$ (10 mol %), NaOAc (1.5 equiv) O_2 (1 atm), THF (0.2 M), isolated yields. [b]Nonreproducible result. [c]Structure was confirmed by single-crystal X-ray diffraction analysis.

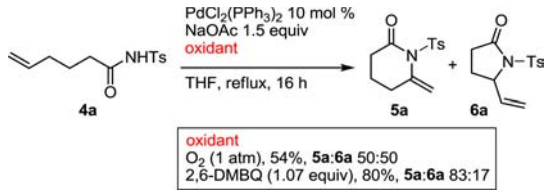
effect of the substitution on the sulfonyl moiety was investigated first. Electron-donating substituents (**1a−d**) on the aryl ring were well tolerated. Electron-withdrawing *para*-substitution, such as nitro (**1e**) or trifluoromethyl groups (**1j**), chlorine atoms (**1g**), or fluorine atoms (**1i**) also led to the corresponding alkylidene γ-lactams in good yields. On the other hand, electron-withdrawing *ortho*-substitution (*o*-NO_2, *o*-Br) (**1f**, **1h**) was not compatible. The bicyclic and heterocyclic naphthyl- (**1k**) and thiophene-yl-substituted (**1l**) amides performed well. A mesyl substitution led to the target alkylidene γ-lactams (**2m**) with a good yield too, indicating that the scope is not limited to aromatic sulfonyl derivatives. However, the triflyl derivative (**1n**) did not afford the desired product. Nonsulfonyl groups such as benzyl, aryl, benzoyl, *tert*-butoxycarbonyl (BOC), or *tert*-butylsulfinyl substituents were found to be unpromising (see the Supporting Information). The acidity of the N−H in the *N*-protected carboxamides seems to be crucial. Indeed, the lack of reactivity of the triflyl, alkyl, and acyl derivatives suggests that the ideal pK_a for the substrates is around 4−5. Substituents on the tether were then tested (Scheme 2). Alkyl and allyl substituents (**1o**, **1r**) afforded the desired products with good yields. Phenyl substitution (**1p−q,s−t**) did also work, albeit with a slight yield erosion.

Finally, this method was extended to the more challenging hex-5-enoic acid *N*-tosylamide **4a**, which in the previously developed acidic conditions led to an inseparable mixture (71:29) of the vinylpyrrolidone **6a** (from the C−H activation path, product **B**, *n*

DOI: 10.1021/acs.orglett.6b00143
Org. Lett. 2016, 18, 1020−1023

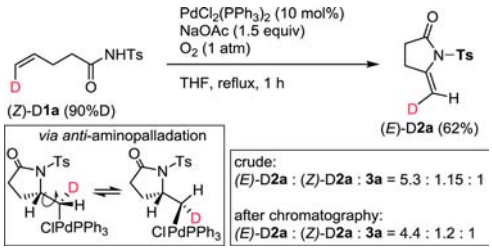
= 2, Scheme 1) and the methylidene piperidone **5a** (from an aminopalladation/dehydropalladation sequence, product **A**, n = 2, Scheme 1). In the event, treatment of carboxamide **4a** with the new reaction conditions again gave a mixture of **6a** and **5a**, though in a modified 1:1 ratio. However, replacing molecular oxygen for 2,6-DMBQ increased both the yield and, more importantly, the amount of alkylidene lactam **5a** (83:17) (Scheme 3).

Scheme 3. Pd(II)-Catalyzed Amination 5-Enoic Acid *N*-Tosylamide



Finally, to unveil the stereochemistry of the process, the selectively deuterium-labeled *N*-tosylamide (*Z*)-D**1** was synthesized and tested for cyclization. Indeed, assuming that the dehydropalladation is a stereospecific *syn* process,[20] a *syn*-aminopalladation should afford a (*Z*)-lactam, while an *anti*-aminopalladation is expected to lead to the (*E*)-isomer. Submission of (*Z*)-D**1a** to our reaction conditions provided the γ-lactam (*E*)-D**2a**, which unequivocally disclosed an *anti*-aminopalladation process (Scheme 4). A small amount of (*Z*)-D**2a** was also observed, which could come from a competitive *syn*-aminopalladation or from an *anti*-aminopalladation followed by an *anti*-dehydropalladation.

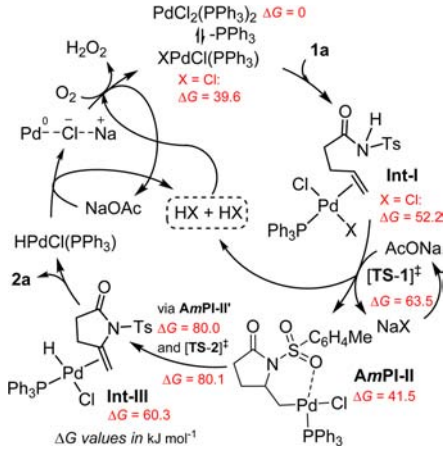
Scheme 4. Assessment of the Stereochemistry of the Aminopalladation



The mechanism of this transformation was studied using DFT calculations,[21] leading to the proposal of a catalytic cycle (Scheme 5). The substrate **1a** coordinates to Pd(II) by dissociative substitution of one phosphine from the [$PdCl_2(PPh_3)_2$] precatalyst, affording **Int-I**. This substitution is endergonic by 52.2 kJ mol^{-1}. **Int-I** undergoes acetate anion assisted *anti*-aminopalladation, which brings about chloride release with an energy barrier of 11.3 kJ mol^{-1} (**TS-1**, 63.5 kJ mol^{-1}),[22] leading to the corresponding **AmPI II** (41.5 kJ/mol). The subsequent proxicyclic β-H elimination involves a high energy intermediate (**AmPI-II′**, ΔG = 80 kJ mol^{-1}), followed by the highest energy transition state (**TS-2**, 80.1 kJ mol^{-1}), and generates **Int-III**. Alkene decoordination releases product **2a** and [PdCl(H)-(PPh_3)], which undergoes acetate anion assisted reductive elimination to give an anionic Pd(0) species.[23] Finally, reoxidation by O_2 regenerates the competent catalyst (see also section IX in the SI).

In this catalytic cycle, triphenylphosphine is expected to prevent coordination between a sulfonyl oxygen and palladium,

Scheme 5. Proposed Mechanism of the Catalytic Cycle



favoring the anti-aminopalladation process and allowing the synperiplanar H−C−C−Pd arrangement needed for the subsequent dehydropalladation step. On the other hand, k^2 PP (chelating) diphosphines such as Binap or dppe (see Table 1, entries 3 and 4), which do not change easily to monocoordination with palladium, halt, or strongly inhibit, dehydropalladation. Worthy of note, too, this protocol calls for the presence of chloride anions (compare Table 1, entries 1 and 11). This fact may be rationalized on the basis of the higher electron-withdrawing power of chlorine, as compared to bromine, iodine,[24] or acetate, which maximizes the electrophilic character of the coordinated alkene.[25] Furthermore, according to Jutand's studies,[23] we can predict that one chloride ligand is likely to stay bound to palladium throughout the catalytic cycle, which implies the involvement of an anionic Pd(II)−peroxo intermediate during the reoxidation step. Finally, acetate anion behaves as proton shuttle in two points of the catalytic cycle: the aminopalladation and the reductive elimination step.

In conclusion, in the framework of our ongoing long-term research program dedicated to the mechanistic study of transition-metal-catalyzed nucleophilic additions to alkenes, we have now developed a new aerobic Pd-catalyzed protocol providing access to a diverse array of alkylidene γ-lactams from *N*-sulfonylalkenylamides. From a mechanistic viewpoint, this new procedure opens the way to aminopalladation/proxicyclic β-dehydropalladation, a sequence hitherto regarded as forbidden for these substrates. A thorough optimization established that triphenylphosphine and chloride anions are central to promote the cyclization, and ad hoc experiments unequivocally demonstrated that the aminopalladation step occurs via *anti* stereochemistry. Finally, with the help of DFT calculations, a plausible catalytic cycle is put forward. Studies are in progress to intercept the transient A*m*PI through alternative ways.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00143.

X-ray crystallographic data for compound **2i** (CIF)
Experimental procedures, compound characterization, computational details, coordinates, structures and energies of all intermediates and transition states, and reaction energy profile (PDF)

DOI: 10.1021/acs.orglett.6b00143
Org. Lett. 2016, 18, 1020−1023

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank Camille Huynh (UPMC) for her contribution in preliminary experiments, Geoffrey Gontard (UPMC) for X-ray crystallographic analyses, and Omar Khaled (UPMC) for HRMS analyses. CNRS, UPMC, and Labex Michem are acknowledged for financial support. Support through CMST COST Action, CM1205 (CARISMA), is also gratefully acknowledged. M.J.C. and F.J.S.D. thank the Fundação para Ciência e Tecnologia for financial support (UID/MULTI/00612/2013) and a fellowship (SFRH/BPD/76878/2011, to F.J.S.D.).

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(8) We propose the acronym N*u*PI for a generic nucleopalladated intermediate and A*m*PI and O*x*PI for the specific aminopalladated or oxypalladated intermediates, respectively.

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(11) When only a proxicyclic H position is available, activation of the cyclic NuPI by a strong oxidant like $PhI(OAc)_2$ allows the formation of acetoxylated products. This oxidation turns out to be much faster than the C−H activation reactivity; see: (a) Chen, S.; Wu, T.; Liu, G.; Zhen, X. *Synlett* **2011**, *2011*, 891. (b) Hovelmann, C. H.; Streuff, J.; Brelot, L.; Muñiz, K. *Chem. Commun.* **2008**, 2334. (c) Li, Y.; Song, D.; Dong, V. M. *J. Am. Chem. Soc.* **2008**, *130*, 2962. (d) Alexanian, E. J.; Lee, C.; Sorensen, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 7690.

(12) Under these acidic conditions, a small extent of proxicyclic β-H elimination was observed only when starting from hex-5-enoic acid *N*-tosylamide.

(13) For an example of a blocked proxicyclic dehydropalladation process from a cyclic A*m*PI, see: Balázs, A.; HeténYi, A.; Szakonyi, Z.; Sillanpää, R.; Fülöp, F. *Chem. - Eur. J.* **2009**, *15*, 7376.

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(17) For synthesis and characterizations of all starting materials, see the Supporting Information.

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(19) Use of triphenylphosphine oxide as the ligand provided **2a** in 10% NMR yield (see the Supporting Information) This suggests that under our conditions triphenylphosphine is not oxidized by dioxygen (^{1}H and ^{31}P NMR analyses).

(20) For very rare examples of *anti*-β-H elimination with particular substrates and/or conditions, see: (a) Takacs, J. M.; Lawson, E. C.; Clement, F. *J. Am. Chem. Soc.* **1997**, *119*, 5956. (b) Maeda, K.; Farrington, E. J.; Galardon, E.; John, B. D.; Brown, J. M. *Adv. Synth. Catal.* **2002**, *344*, 104. (c) Farina, V.; Azad Hossain, M. *Tetrahedron Lett.* **1996**, *37*, 6997−7000. (d) Lautens, M.; Fang, Y.-Q. *Org. Lett.* **2003**, *5*, 3679. (e) Glover, B.; Harvey, K. A.; Liu, B.; Sharp, M. J.; Tymoschenko, M. *Org. Lett.* **2003**, *5*, 301.

(21) All calculations were carried out with Gaussian09 at the PBE1PBE/6-311+G(2d,2p)//PBE1PBE/6-31G(d,p) level in THF. Details are given in the SI.

(22) The deprotonation step might take place on the iminol tautomer. Furthermore, the alternative allylic CH-activation is calculated to proceed via a 161.1 kJ/mol TS. See the Supporting Information.

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(24) Use of 20 mol % of LiBr, or LiI, in the presence of $Pd(OAc)_2$, PPh_3, and NaOAc led to **2a** in about 40% NMR yield, which confirmed the crucial role of the chloride anion (Table 1, entry 11).

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NOTE ADDED AFTER ASAP PUBLICATION

Paragraph discussing Scheme 5 was corrected February 23, 2016.

DOI: 10.1021/acs.orglett.6b00143
Org. Lett. 2016, 18, 1020−1023