Palladium-Catalyzed Formal (4+2) Cycloaddition between Alkyl Amides and Dienes Initiated by the Activation of C(sp3)–H Bonds

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Palladium-catalyzed formal (4+2) cycloaddition between alkyl amides and dienes initiated by the activation of C(sp^3)–H bonds

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ABSTRACT: *We report a formal (4+2) cycloaddition between alkyl-nosylamides and dienes enabled by a palladium-catalyzed activation of C(sp^3)−H bonds beta to the amide group. This atom economical reaction which proceeds under operationally simple conditions, is compatible with a wide variety of dienes, and provides a straightforward method to assemble different types of saturated lactams. The annulation is favored over alternative pathways in part because of the key role of the extra double bond of the diene partner. The use of suitable nitrogen-based additives as palladium ligands, which enable the C(sp^3)−H activation without interfering in subsequent steps of the catalytic cycle, is also critical for the success of the reaction.*

KEYWORDS: *C(sp^3)−H activation, palladium, dienes, formal cycloaddition, alkyl amides, palladacycle*

These last decades have witnessed great progress in the field of transition metal-catalyzed activation (and functionalization) of C−H bonds.[1] While the activation of aromatic C(sp^2)−H bonds has become relatively routine (Figure 1a), the functionalization of more challenging aliphatic C(sp^3)−H bonds has been successfully addressed only recently, especially using palladium (II) catalysts (Figure 1b).[2] Despite mechanistic studies are yet scarce, these reactions involve the cleavage of the C−H bond, usually via CMD processes, to give five or six-membered metallacycles, which can be elaborated into different products depending on the coupling partners and reaction conditions. Most of reported examples consist of arylation reactions, but there have been also reports on acetoxylation, halogenation, borylation, or alkenylations processes, among others.[3]

In the case of the activation of C(sp^2)−H bonds, there have also been many contributions on the development of formal metal-catalyzed cycloadditions of heteroatom-containing precursors with unsaturated partners (Figure 1c). These transformations are of great constructive value because they provide a direct, atom economical entry to heterocyclic skeletons.[4] In these reactions, the metallacyclic intermediates generated after the C−H activation step evolve via migratory insertion of the unsaturated reaction partner, followed by reductive elimination, to yield the desired cycloadducts. Curiously, mechanistically related cycloadditions involving the cleavage of C(sp^3)−H instead of C(sp^2)−H bonds (Figure 1d), have not been described. There are some examples of carbonylation reactions of bulky alkyl amines or selected amides (formal n+1 annulations);[5] but we are not aware of formal (n+2) heteroannulations with standard two-carbon unsaturated partners such as alkenes, alkynes or similar.[6]

In order to fill this void, we report, for the first time, a formal (4+2) oxidative cycloaddition reaction involving a palladium-promoted activation and cleavage of C(sp^3)−H bonds. The reaction, which engages alkyl-nosylamides and dienes, is catalyzed by palladium (II) and provides a straightforward, unconventional entry to saturated lactam heterocycles (Scheme 1). The use of dienes is instrumental for the success of the reaction, likely because of the formation of key π-allyl intermediates like **B** (Scheme 1). We also provide mechanistic data, including the isolation of enlightening palladacycle intermediates.

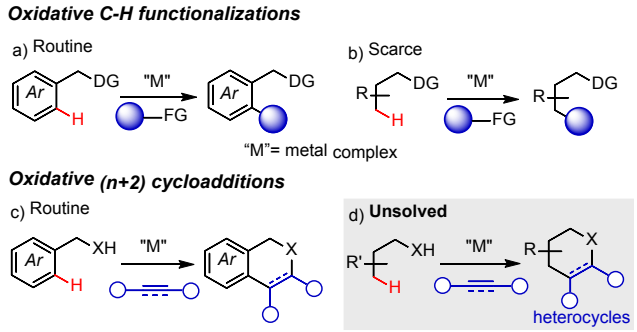
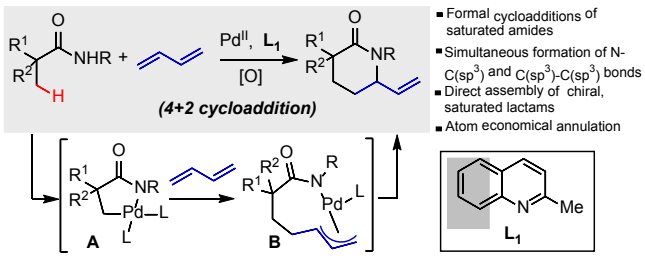


Figure 1. Metal-catalyzed C−H activations.

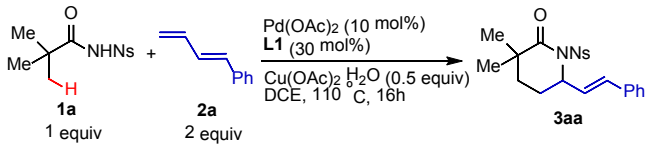
Our initial experiments were stimulated by previous reports on the palladium-promoted olefination of *N*-arylpivalamides with activated alkenes like acrylates.[7,8] These reactions are initiated by an amide-directed C−H insertion of Pd(II) to generate alkylpalladium intermediates, which undergo the migratory insertion of the alkene. However, the resulting palladacycles evolve by β-hydride elimination instead of by reductive elimination, which precludes the formation of 6-membered cycloadducts. To avoid this last mechanistic step, we considered the use of allenes instead of alkenes as reaction partners.[9] However, after an intense screening of reaction conditions, the desired formal (4+2) cycloadduct was obtained in yields lower than 30%.

Scheme 1. This work: Pd-catalyzed formal (4+2) cycloaddition with cleavage of a C(sp^3)−H bond



At this point, we thought that dienes might be more suitable reaction partners, owing to the "diene effect".[10] The presence of the extra double bond provides an additional binding ligand for the metal, which should favor the desired reductive elimination paths. Therefore, we made an extensive screening of conditions for the annulation between pivalamides and (*E*)-buta-1,3-dien-1-ylbenzene (**2a**), with parallel testing of different parameters (Table 1). We were pleased to find that the desired (4+2) annulation reaction can be achieved by using 10 mol% of $Pd(OAc)_2$ and 30 mol% of quinaldine (**L1**, inexpensive and commercially available), in DCE at 110 ºC, and in presence of 0.5 equiv of $Cu(OAc)_2$ as oxidant. The lactam product **3aa**, which exhibits a *trans* configuration in the remaining double bond, was obtained in 99% yield and with complete chemoselectivity.

Table 1. Optimization of the reaction conditions



Entry	Deviation from above conditions[a]	Yield[b]
1	none	99%
2	Tf instead of Ns	0%
3	4-$CF_3C_6F_4$ instead of Ns	16%
4	Aminoquinoline instead of Ns	0%
5	Ag_2CO_3 (2.5 equiv) as oxidant	46%[c]
6	Ag_3PO_4 (1 equiv) as oxidant	38%
7	Toluene instead of DCE	28%
8	TFT instead of DCE	39%
9	HFIP instead of DCE	0%
10	Dioxane instead of DCE	39%
11	Without **L1**	<5%

[a] Reactions conducted in 0.20 mmol scale. [b] Isolated yields. [c] NaOAc (4 equiv) added.

This screening revealed that the substituent at the amide nitrogen plays a key role in the efficiency of the reaction. Therefore, changing the nosyl for triflate is detrimental, and does not lead to the cyclic product (entry 2).[11] Furthermore, in contrast with previously described palladium-promoted arylations or alkenylations of pivalic amides, a secondary amide featuring a polyfluorinated aromatic substituent also gave poor results.[7a,8] Importantly, amides with a bidentate aminoquinoline auxiliary, widely used in C−H functionalization reactions,[12] were completely ineffective (entry 4), with the starting materials being recovered. Regarding oxidants, copper acetate was the most effective, while silver acetate or silver phosphate were less efficient even when used in stoichiometric quantitites (entries 5, 6). We also tested several solvents (entries 7-10), but DCE was found to be optimal.

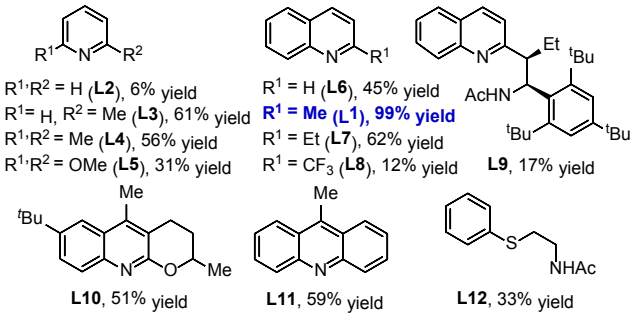
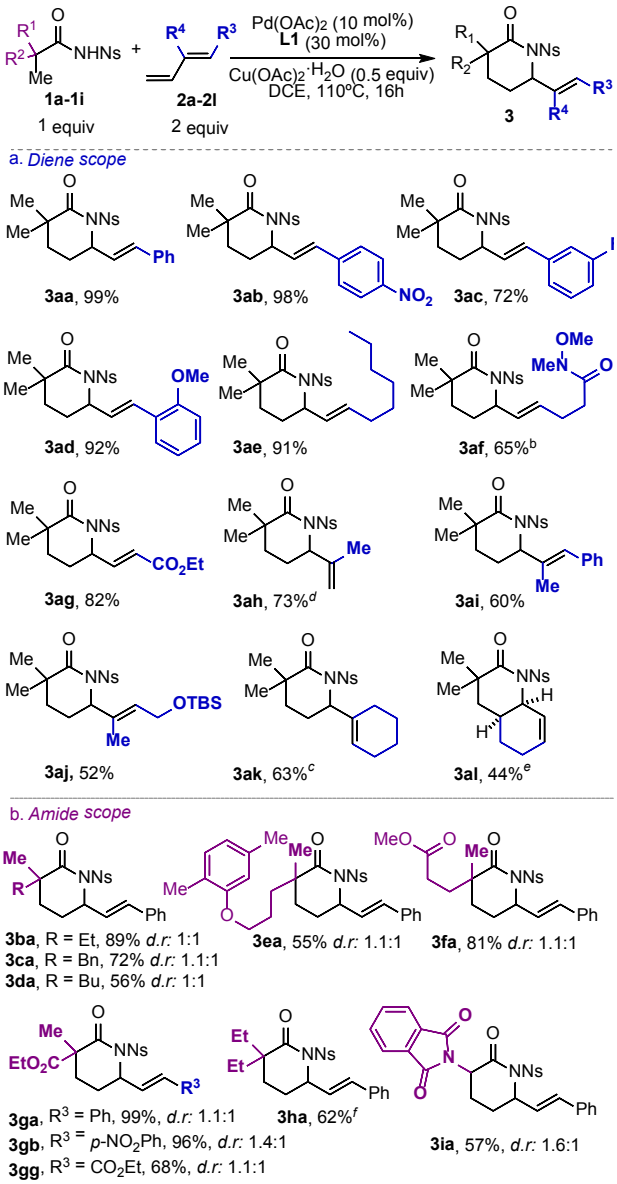


Figure 2. Screening of ligands under optimized conditions

The discovery of **L1** as the optimal ligand came after screening many other possibilities. As indicated in the Figure 2, pyridines or quinolines with *ortho* methyl groups (**L3**, **L4**, and **L1**) or *ortho* ethyl groups (**L7**) were the most effective, while those with an additional ring (**L10**, **L11**) led to lower yields. Bidentate ligands like **L9** and **L12**, previously used in C−H activation processes, provided low yields.[13,7a] Pyridine (**L2**) was also a poor ligand; and importantly, in the absence of ligands, the reaction does not proceed

With the optimized conditions in hand, we investigated the reaction scope using a variety of commercial and non-commercial dienes (Table 2). Dienes bearing aromatic groups presenting different electronic properties in the terminal position worked nicely, leading to high reaction yields (**3ab-3ad**, 72-99% yield). Alkyl substituents are also well tolerated (**3ae**, 91%, **3af**, 65%). Noticeably, a diene equipped with a strongly electron-withdrawing group reacts through the terminal double bond with complete chemoselectivity (**3ag**, 82% yield).

Table 2. Scope of the reaction[a]



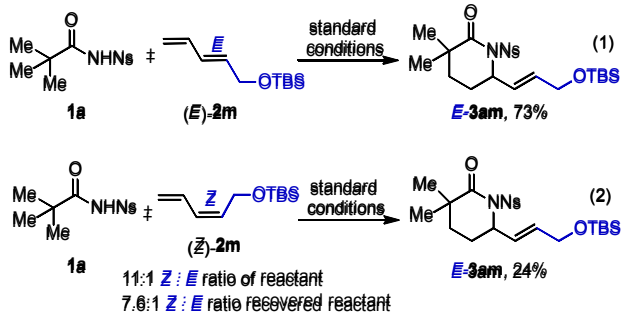
[a] Reactions conducted in 0.20 mmol scale. [b] 1 equiv $Cu(OAc)_2 \cdot H_2O$. [c] 10 equiv of diene. [d] 3 equiv of diene [e] 60 mol% **L1**, 1 equiv $Cu(OAc)_2 \cdot H_2O$. [f] Another 10 mol% of $Pd(OAc)_2$ was added after 7h.

The reaction also works with dienes featuring substituents in other positions. Thus, commercially available isoprene led to 73% of the expected product (**3ah**), although we had to use 10 equivalents of the reactant because of its high volatility. More elaborated 1,2-disubstituted dienes were also effective (**3ai-3ak**, 52-63% yields). Notably challenging cyclohexa-1,3-dienes led to the formation of relevant bicyclic structures, although in moderate yield (**3al**, 44% yield).

We also investigated the scope with regard to the aliphatic amides, using diene **2a** as model reacting partner. As shown in table 2b, in general, α,α-disubstituted propanamides gave the expected cycloadducts in good yields (**3ba-3ga**), which was particularly high in the case of substrates with an *alpha*-ester group (product **3ga**, 99% yield). These annulations are extensible to other dienes (e.g **3gb** and **3gg**, 96% and 68% yield respectively). α-Tertiary amides, like isobutyramide also work, albeit with lower yields, and produce a chromatographically inseparable mixture of lactams and α,β-unsaturated lactams (1:2 ratio). However, the alanine-derived amide **1i** was an effective partner, as exemplified by the formation of products **3ia** (57% yield).[14]

Mechanistically relevant, the reaction of diastereoisomeric dienes (*E*)-**2m** and (*Z*)-**2m** with **1a** gave the same lactam product (**3am**), with *E* stereochemistry in the remaining alkene, although in different yield [73% for (*E*)-**2m** and 24% for (*Z*)-**2m**, Scheme 2]. This is consistent with the presence of a π-allyl intermediate (**B**, Scheme 1), while the differences in yield suggest that the migratory insertion of the *cis*-diene presents a higher activation barrier.

Scheme 2. Comparison of reactivity between *cis* and *trans* dienes

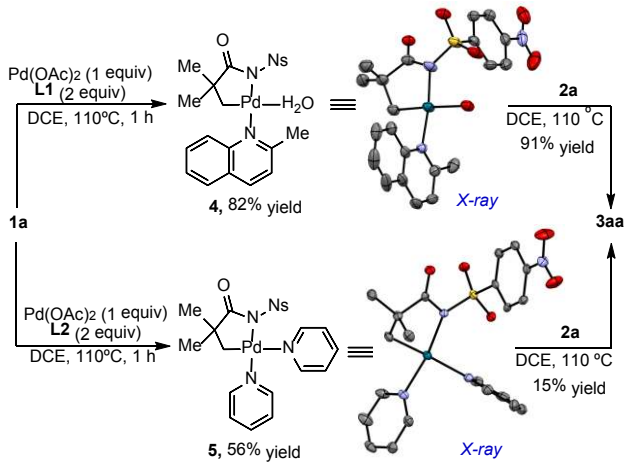


The "diene effect" not only favors the cycloaddition pathway but also the overall reactivity. Thus, when we used 1-octene as reaction partner for the nosylamide **1a**, we observed mixtures of olefination products in less than 10% yield.

In order to further understand the critical role of the ligands, we pursued the isolation of palladium complexes resulting from the C−H activation step. Heating a mixture of amide **1a** with equimolar amounts of $Pd(OAc)_2$ and 2 equiv of **L1** (1h in DCE under reflux), allowed for the isolation of the 5-membered palladacycle **4** in 82% yield (Scheme 3, hydrogens of X-Ray structures omitted for clarity). The crystal structure shows a distorted square-planar geometry with only one quinoline ligand coordinated to palladium and in *trans* position to the amide group.[15] One molecule of water (adventitious) occupies one of the fourth coordination positions. The Pd−O bond is very long (2.21 Å), because of the *trans effect* of the alkyl group, highlighting the lability of the aquo ligand. Treatment of complex **4** with 2 equiv of diene **1a** for 3 hours leads to an almost quantitative formation of the cycloadduct **3aa**, indicating that this palladacycle is part of the catalytic cycle, and that the oxidant is not involved in the cycloaddition mechanism. Not surprisingly, complex **4** is also a competent catalyst for the reaction.

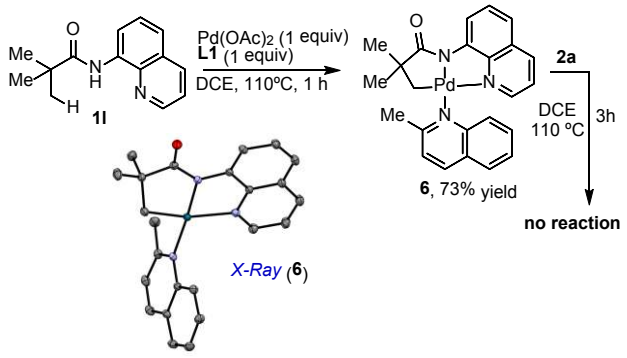
Remarkably, heating substrate **1a** with stoichiometric amounts of $Pd(OAc)_2$, but in the absence of **L1**, failed to give any product, thereby indicating the critical role of the nitrogenated ligand. Moreover, when the stoichiometric experiment was carried out with pyridine (**L2**) instead of quinaldine (**L1**), we isolated a palladacycle similar to **4**, but with two pyridine ligands attached to the palladium (**5**). This result could be explained in terms of the smaller size of pyridine compared to quinaldine. Again, the pyridine *trans* to the alkyl group has an elongated Pd−N bond, suggesting that this is the most labile position (2.17 Å vs 2.05 Å). Complex **5**, when treated with the diene under standard conditions, led to the corresponding product **3aa** in only 15% yield. This much lower reactivity with respect to complex **4**, might be associated to the difficulties in releasing the pyridine compared to the aquo ligand. The higher reactivity achieved with ligand **L1** might be related with obtaining an appropriate steric balance around the metal center.

Scheme 3. Isolation of key intermediates



We have also been able to isolate a palladacycle resulting from the substrate containing a bidentate aminoquinoline ligand (**6**). Importantly, this complex didn't react with the diene when submitted to standard annulation conditions (Scheme 4). This result confirms that the bidentate ligand is suitable for the C−H activation, but compromises the subsequent steps of the cycloaddition, likely by hampering a suitable coordination of the diene.

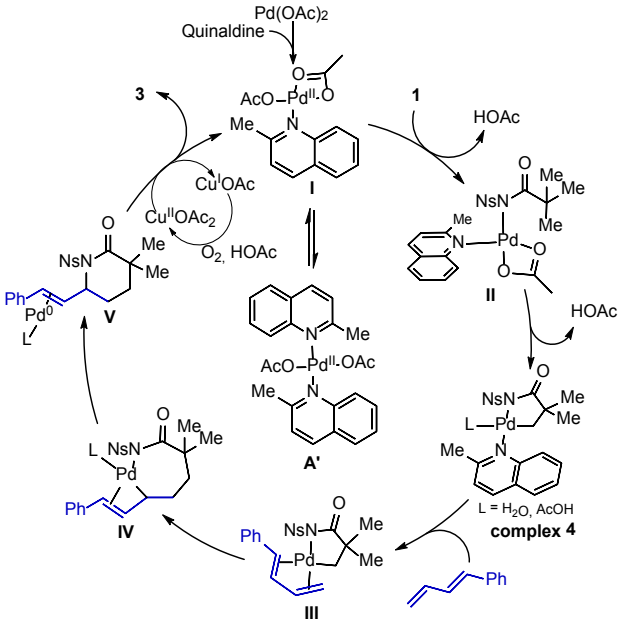
Scheme 4. Isolation of complex 6



All together, these results allow us to draw a plausible catalytic cycle (Scheme 5). Quinaldine (**L1**) likely plays a key initial role in promoting the formation of active monomeric species of type **I**,

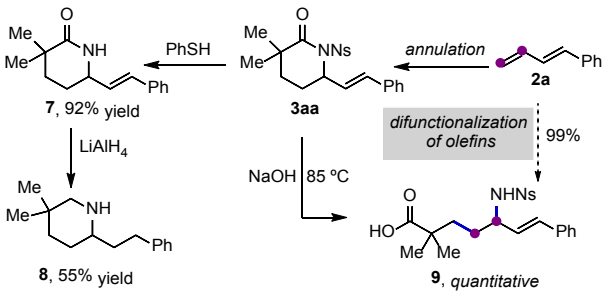
which might prevail over resting species like **A'** because of the steric properties of the ligand. The relatively high acidity of the amide facilitates the formation of amidopalladium complexes like **II**, responsible for the C−H activation step. The steric properties of the ligand not only avoid the coordination of two amide substrates, but could also favor the concerted metalation deprotonation process that yields palladacycles like **4**. The bidentate characteristics of the diene probably facilitates the release of labile ligands and the formation of complexes required for the migratory insertion step, to give palladium π-allyl intermediates of type **IV**. Importantly, the extra coordination site provided by the diene partner is instrumental in favoring a reductive elimination versus non-desired β-hydride elimination paths. The resulting palladium (0) species are reoxidized by copper (II) acetate to restart the catalytic cycle.

Scheme 5. Proposed mechanistic cycle



The lactam skeletons resulting from the above cycloadditions can be elaborated in divergent, synthetically appealing ways. The nosyl group is easily removed using tiophenol to form the free lactam product **7**, which can be reduced to the corresponding piperidine by treatment with LAH (**8**, Scheme 6). Moreover, hydrolysis of **3aa** with sodium hydroxide leads to the δ-amino acid **9**, a product that can be formally considered as the result of a chemo- and regioselective 1,2-carboamination of **2a**, an otherwise unfeasible transformation.[16]

Scheme 6. Manipulation of the cycloadducts



In summary, we have developed a palladium (II)-catalyzed formal (4+2) cycloaddition between readily available aliphatic amides and dienes to give a variety of saturated lactams. To the best of our knowledge, this represents the first demonstration of a (4+2) cycloaddition involving the activation and cleavage of non-activated C(sp^3)−H bonds, and which proceeds through standard migratory insertion/reductive elimination mechanisms. Our study has also demonstrated that the denticity of the directing groups and the structure of the ligands play a decisive role in the reactivity. Moreover, the presence of a conjugated double bond in the alkene partner is key for the success of the transformation. Considering the relevance that related annulations engaging C(sp^2)−H bonds have achieved, we foresee that our discovery will trigger the development of other type of formal cycloadditions that can further advance the field of synthetic chemistry.

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Notes

The authors declare no competing financial interests.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
Experimental procedures and spectroscopic data for new compounds (PDF)
CIF files for compounds **3aa**, **3af**, complex **4**, complex **5** and complex **6**

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