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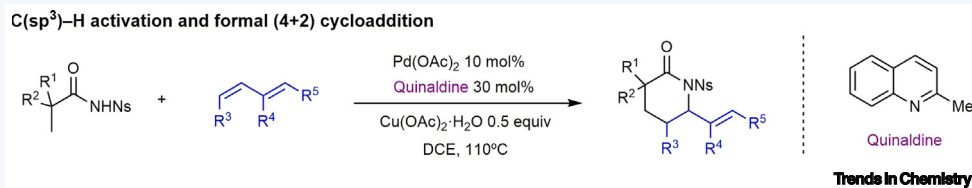
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(4 + 2) Cycloadditions via Pd C(sp³)-H activationXandro Vidal,¹ Marc Font,¹ Borja Cendón,¹ José Luis Mascareñas,¹ and Moisés Gulías^{1,*}¹Centro Singular de Investigación en Química Biolóxica e Materiais Moleculares (CiQUS), Departamento de Química Orgánica, Universidade de Santiago de Compostela, 15782 Santiago de Compostela, Spain

ORIGIN

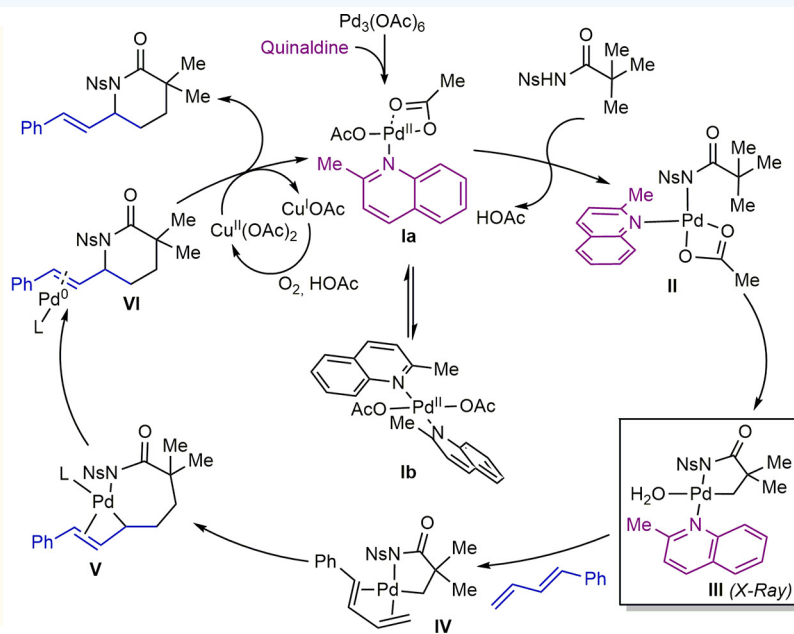
The functionalization of aliphatic C(sp³)-H bonds using Pd catalysis has emerged as a powerful, step economical methodology for the construction of C-C and C-X bonds. Despite the progress in this field, examples of formal cycloadditions entailing this type of activation have been essentially limited to carbonylation processes. This work describes a formal (4 + 2) cycloaddition between alkylamides and dienes, a reaction that provides a direct, simple, and unconventional access to saturated lactams.

REACTION MECHANISM

The proposed mechanism for the (4 + 2) cycloaddition starts with the formation of an active monomeric catalyst (**Ia**), with the quinaldine acting as a monodentate ligand. Because of the steric bulk of this ligand, the formation of unreactive complexes with two units of quinaldine (**Ib**) is disfavored. Then, facilitated by the relatively high acidity of the amide, the substrate displaces one of the acetate ligands to give the amidopalladium complex **II**. This complex evolves by activation of the C(sp³)-H bond of the methyl group, likely based on a concerted metalation deprotonation process, to form palladacycle **III**. This complex has been experimentally isolated and fully characterized and, not surprisingly, it can engage in the formal (4 + 2) cycloaddition with dienes by itself, which supports its participation as intermediate in this reaction. After the C-H activation step, the diene coordinates to the palladacycle and undergoes migratory insertion to give palladium π -allyl intermediate **V**, perhaps via intermediate **IV**. The π -allyl type of coordination may have a key role in stabilizing intermediate **V** and favoring a reductive elimination pathway over undesired β -hydride eliminations. This is supported by the fact that alkynes or alkenes do not engage in this kind of (4 + 2) cycloaddition. Finally, the resulting palladium (0) is reoxidized by copper(II) acetate to restart the catalytic cycle.

Key mechanistic findings:

- 1) The **quinaldine ligand** plays an essential role, facilitating the formation of **III**
- 2) The presence of a **nosyl group** in the amide is key for the success of the reaction
- 3) **Intermediate III** was isolated and demonstrated to work as substrate in the reaction.
- 4) **Cis dienes** show poor reactivity, suggesting the migratory insertion as plausible rate limiting step
- 5) Reaction favored by the "**diene effect**" (stabilization of intermediates by extra coordination). Alkynes, alkenes do not undergo the (4+2) annulation.



IMPORTANCE

This reaction represents the first palladium-catalyzed formal (4 + 2) cycloaddition enabled by the cleavage of nonactivated C(sp³)-H bonds, thereby proposing new avenues for the construction of heterocycles. Key for the success of the reaction is the use of a tailored quinoline as palladium ligand and dienes as cycloaddition partners.

Declaration of interests

No interests are declared.

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