Synthetic Methods

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Trapping σ-Alkyl–Palladium(II) Intermediates with Arynes Encompassing Intramolecular C−H Activation: Spirobiaryls through Pd-Catalyzed Cascade Reactions

*Marta Pérez-Gómez and José-Antonio García-López**

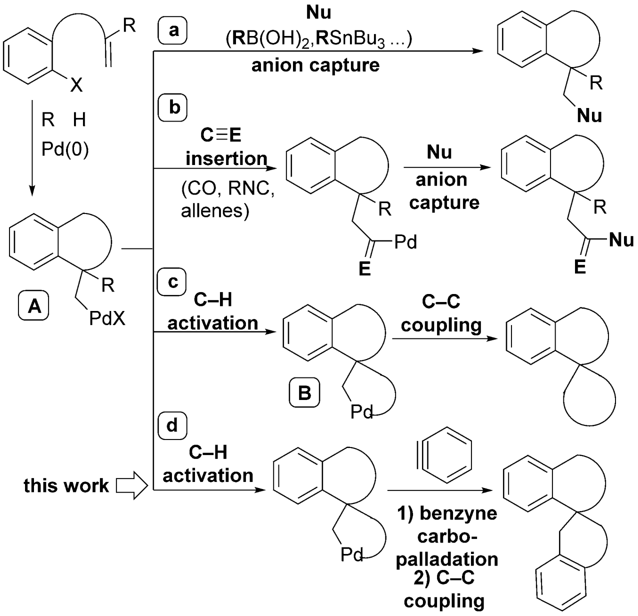
Abstract: *A palladium-catalyzed cascade reaction based on the trapping of transient alkyl–Pd^{II} intermediates with arynes encompassing a C−H activation step has been developed. This synthetic pathway gives rise to hetero-spirocyclic scaffolds containing a biaryl motif, and opens up new synthetic strategies in the design of cascade reactions since it gathers several aspects of Pd chemistry, i.e., intra- and intermolecular carbopalladation of unsaturated species, C−H activation and C−C coupling processes.*

The use of aryl halides or pseudohalides bearing a tethered alkene in the Heck–Mizoroki reaction[1] has proven particularly well suited for the synthesis of five- and six-membered carbo- and heterocyclic scaffolds such as indole, benzofuran and oxoindole derivatives, among others.[2] Furthermore, the design of substrates where β-hydride elimination (upon the initial carbopalladation step) is blocked has promoted the development of both intra- and intermolecular palladium-catalyzed cascade reactions, a topic of extraordinary interest since these reactions allow the construction of complex molecular structures from simple substrates in a straightforward and efficient manner, especially when they involve C−H activation processes in some of their steps.[3]

Pioneering work from Grigg in the trapping of transient σ-alkyl Pd^{II} intermediates arising from intramolecular Heck reactions opened up a wide range of organic transformations according to the terminating step of the cascade.[4] For instance, the intermediate complex **A** (Scheme 1) can be trapped with different nucleophilic coupling partners such as hydride,[4,5] boron derivatives,[6] organotin reagents,[7] hydrazones,[8] or cyanides among others[9,10] (path a, Scheme 1).

The presence of unsaturated molecules like CO,[11] allenes,[12] and also recently isocyanides[13] in the reaction mixture can serve to extend the cascade process by their insertion into the Pd−C bond present in the intermediate **A** (path b, Scheme 1).

A different strategy to quench the σ-alkyl Pd^{II} intermediate relays on the ability of this metal to activate C−H bonds (path c, Scheme 1).[14–18] Noteworthy, the reaction leads to spirocyclic compounds when the C−H activation event is performed intramolecularly.



Scheme 1. Cascade routes involving intramolecular Heck arylation.

The reactivity of type **B** intermediates (Scheme 1) remains underexplored. Shi et al. reported recently the intramolecular carbopalladation of alkenes followed by C−H activation/amination sequence using a diaziridinone reagent to access indoline derivatives.[19] To our knowledge, the behavior of type **B** intermediates toward unsaturated species has not yet been studied.

Inspired by the findings discussed above, and in connection with our interest in the C−H activation and carbopalladation fields,[20] we envisioned that three basic transformations in palladium chemistry such as the intramolecular Heck arylation of an olefin, the intermolecular carbopalladation of an unsaturated species and a C−H activation step could all be implemented in a single reaction through both the appropriate design of the substrate and the use of an adequate unsaturated coupling partner (path d, Scheme 1).

To prove the feasibility of the cascade process under study we chose the substrate *N*-(2-phenylallyl)sulfonamide **1a**, a type of structure where selective 5-*exo-trig* cyclization under Pd^0 catalysis is well documented.[11a–c] Benzyne was selected as the coupling partner for several reasons: first, it bears two reactive positions which leads to 1,2-difunctionalized arenes,[21,22] and second, it is a highly reactive species that

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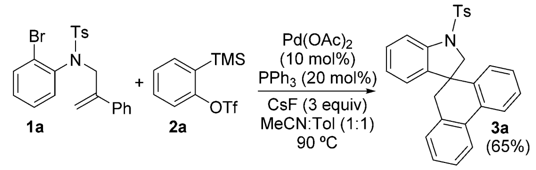
could trap the intermediates **A** or **B** (Scheme 1) fast enough to avoid the undesired and well-documented [1,4]-Pd shift-induced intramolecular termination of the cascade reaction (see below, Scheme 7).[23] Furthermore, the carbopalladation of benzyne and subsequent C–C coupling would lead to a biaryl scaffold, a structural motif present in a widespread number of functional materials, natural products, pharmaceuticals and ligands used in catalysis.[24]

A small amount of the expected product **3a** (Scheme 2) was formed when the substrate **1a** was reacted with the benzyne precursor **2a** (2 equiv) in MeCN at 90°C in the presence of CsF (3 equiv) and a catalytic amount of Pd-$(OAc)_2/PPh_3$. Under these conditions, a substantial quantity of triphenylene arising from the Pd-catalyzed cyclotrimerization of the aryne was generated,[25,26] plus other by-products (see below). In order to conciliate the generation rates of the desired σ-alkyl Pd^{II} intermediate and benzyne, we screened other solvents to modulate the formation of benzyne, and found that a 1:1 mixture of toluene and MeCN gave the best results (Scheme 2). Lower catalyst loadings (5 mol%) or other phosphine ligands were less effective (see the Supporting Information (SI)).



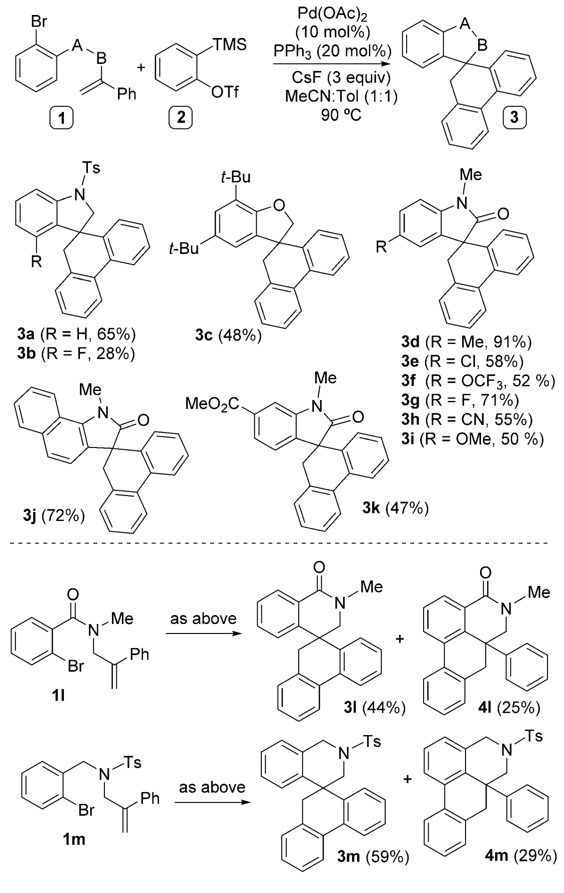
Scheme 2. Optimized conditions for the cascade reaction.

We studied the scope of the reaction by varying the nature and length of the tethering chain bearing the alkene moiety, the substituents on the aryl or heteroaryl rings, and the aryne coupling partner (Schemes 3 and 4). The substrates **1a–k**, undergoing an initial 5-*exo-trig* cyclization, generated selectively the corresponding [4,5]-spirocycles **3a–k** in moderate to good yields in spite of the existence of two possible C–H moieties susceptible to be activated and later functionalized.

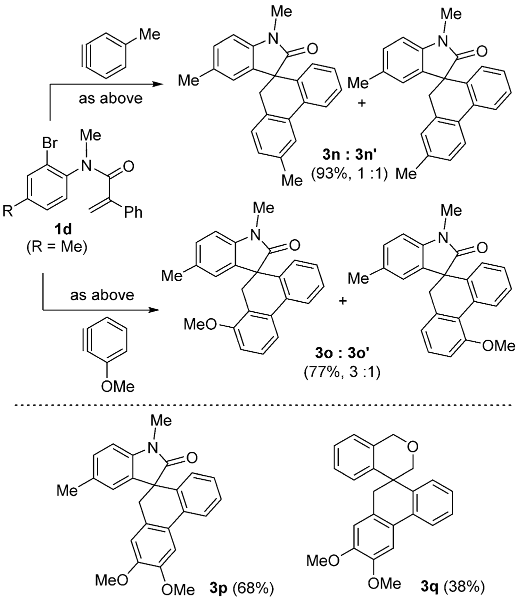
Interestingly, the substrates **1l** and **1m**, where the Heck carbopalladation occurs via 6-*exo-trig* cyclization, gave mixtures of isomers arising from the two possible C–H activation sites (**3l**, **4l** and **3m**, **4m**, respectively). The influence of the nature of the tethering chain in the regioselectivity of the cascade process might be related to the relative tension of the quaternary spiro-carbon in the former palladacycle intermediate, leading to the structures **3** or **4** (see below, Scheme 7). Other substrates such as *N*-(2-bromopyridin-3-yl)-*N*-(2-phenylallyl)benzenesulfonamide or 2-bromophenyl 2-phenylacrylate were unproductive under the standard conditions of the cascade reaction.

We performed the cascade reaction of substrate **1d** replacing PPh_3 for (*R*)-BINAP as ligand, obtaining a slightly enantioenriched product **3d** (ratio 54:46) in a 42% yield.

It is widely proven that *meta*-substituted arynes do not undergo regioselective attack to their strained triple bond.[22,28a] We tested the reaction of substrate **1d** and the *m*-methyl-substituted substrate **2b**. As expected, the reaction afforded a 1:1 mixture of the spirocycles **3n** and **3n′** in good yield (Scheme 4). The 3-OMe-substituted aryne, however,



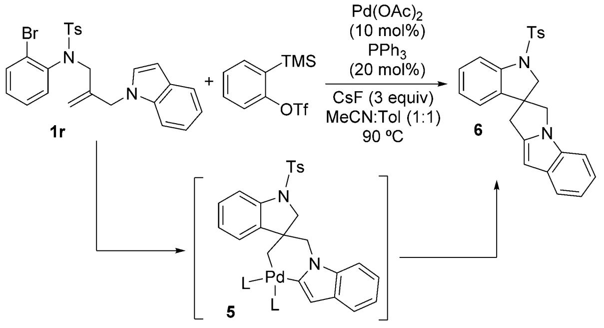
Scheme 3. Scope of the cascade reaction.



Scheme 4. Scope of the cascade reaction with different arynes.

gave a 3:1 mixture of isomers **3o** and **3o′**, with **3o** as the major component, which arises from the carbopalladation where the Pd atom occupies the closer position to the OMe group, resulting from both the higher electrophilicity of the remote carbon of the aryne and the suitable coordination of the OMe group to Pd. This is the behavior observed in other transition metal-catalyzed transformations where this type of aryne has been used.[27,28] The symmetrically substituted aryne **2d** reacted smoothly to give the compounds **3p** and **3q** in moderate yield.

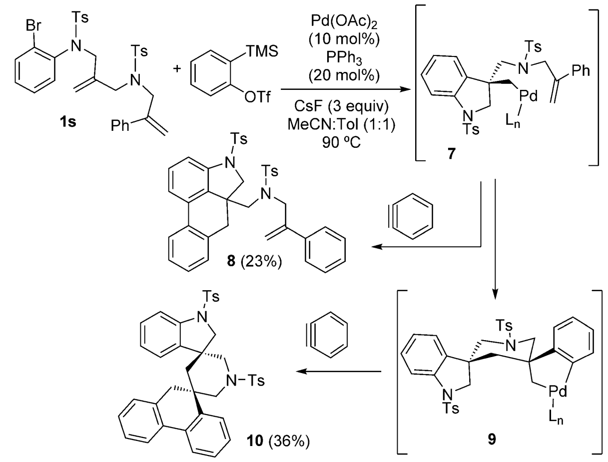
We attempted the cascade reaction with the substrate **1r** bearing an *N*-substituted indole moiety (Scheme 5). While only traces of the expected arylated product were detected, the main component of the mixture was the spirocyclic compound **6**, formerly reported by Grigg et al.[14a]



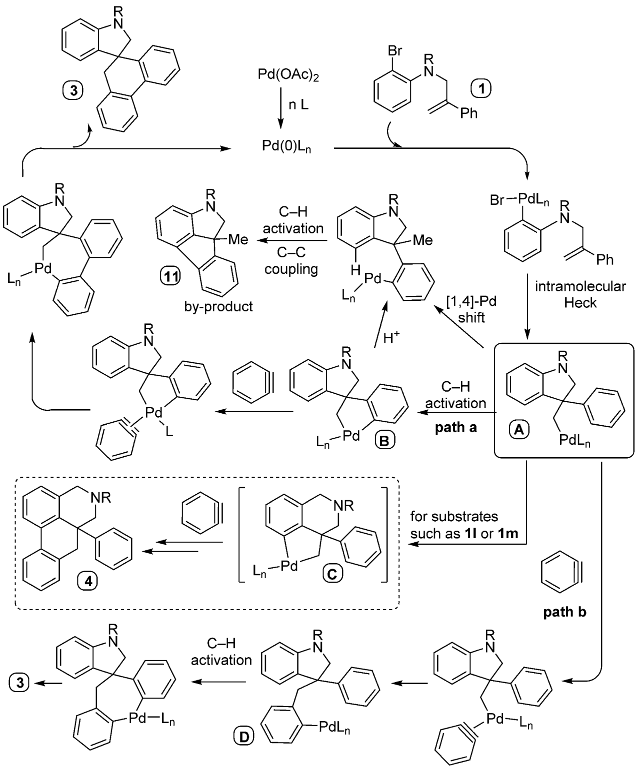
Scheme 5. Attempted cascade reaction from the indole derivative **1r**.

This result indicated that, first, the C–H activation event could take place prior to the aryne carbopalladation step, and second, the final oxidative C–C coupling process from the intermediate **5** could happen fast enough to prevent the aryne insertion if it leads to unstrained cyclic structures. In the case of the substrates **1a**–**k**, a similar process would lead to much more strained [4,3]-spirocycles.

The cascade reactions can be extended by including a relay moiety (such as a second unsaturation) in the tethering chain.[10b,29] Hence, when **1s** was submitted to the standard reaction conditions (Scheme 6), we could isolate the biaryl **8** (23 %), resulting from the premature quenching of intermediate **7** with benzyne, and the polyspirocycle **10** (36 %), produced when two sequential intramolecular carbopalladation steps occur prior to the insertion of the aryne into the Pd–C bond and final oxidative C–C coupling. Interestingly, in this domino process four C–C bonds are formed in a diastereoselective way, probably due to a chair-like pre-transition state of intermediate **7** where the Ph group occupies the equatorial position.[11a,29,30]



Scheme 6. Extended cascade reaction from substrate **1s**.



Scheme 7. Proposed mechanism for the cascade process. "L" represents a generic ligand or counterion (Br, OAc).

Two possible mechanisms are compatible with the cascade process reported herein (Scheme 7). In the first one, the intramolecular Heck arylation of the tethered alkene leads to the σ-alkyl Pd^{II} intermediate **A**, where the metal performs a C–H activation in any of the two nearby aryl rings to afford a five-membered palladacycle. In principle, while the substrates **1a**–**k** would selectively generate the palladacycle of type **B,** substrates with longer tethering chain, such as **1l** or **1m**, could also give rise to the palladacycle of type **C**. The regioselectivity of this step would be determined by the relative strain of the two possible structures. Related five-membered palladacycles containing a C(sp^3),C(sp^2)-chelating ligand have been isolated and characterized by Cámpora et al.[31] The desired cascade reaction can be quenched when the intermediate **B** undergoes a protonolysis of the C(sp^3)–Pd bond, which is formally a [1,4]-Pd shift from **A**, to further evolve giving **11**, which was detected in small amounts during the optimization of the conditions for the cascade reaction, and isolated in 60 % yield in the absence of the aryne precursor. The intermediates **B** and **C** could easily undergo the insertion of the aryne, to produce the structures **3** or **4**, respectively, upon the C–C coupling step.[32] Alternatively, the intermediate **A** could trap the aryne to afford intermediate **D**, which undergoes the C–H activation and C–C coupling to generate the spirocyclic compound **3**.

In conclusion, we have reported a new synthetic strategy which merges the fields of Heck arylation, C–H activation and aryne chemistry, showcasing the versatility of palladium catalysis in organic synthesis. This protocol leads to interesting hetero-spirocycles containing biaryl units, and opens up new ways to construct complex molecular architectures from simple substrates. Studies to extend this chemistry to other unsaturated species are currently underway in our laboratory.

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Keywords: aryne · carbopalladation · cascade reactions · C–H activation · spirocycles

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Communications

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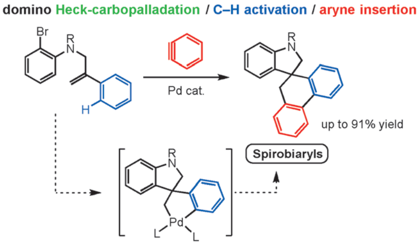

From simple to complex: A palladium-catalyzed cascade Heck carbopalladation/C—H activation/aryne insertion provides easy access to spirobiaryls. The process tales advantage of several aspects of Pd chemistry, i.e., intra- and intermolecular carbopalladation of unsaturated species, C—H activation and C—C coupling processes.