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Palladium-Catalyzed Domino Intramolecular N-Arylation/Intermolecular C–C Bond Formation for the Synthesis of Functionalized Benzodiazepinediones

Angela Salcedo, Luc Neuville,* Christophe Rondot, Pascal Retailleau, and Jieping Zhu*

Institut de Chimie des Substances Naturelles, CNRS, 91198 Gif-sur-Yvette, France

zhu@icsn.cnrs-gif.fr; neuville@icsn.cnrs-gif.fr

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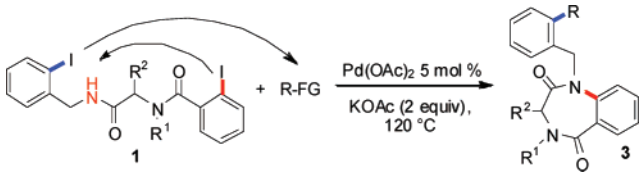
ABSTRACT



A divergent and regiocontrolled Pd-catalyzed domino sequence involving an intramolecular N-arylation and an intermolecular Heck reaction has been developed, providing rapid access to functionalized benzodiazepine-2,5-diones 3. The starting materials were synthesized by the Ugi four-component reaction. An unprecedented X-ray structure of bispalladacycle 6 was documented.

Direct C−H functionalization has attracted intensive research efforts recently, and a number of elegant approaches have been developed, allowing facile construction of the C−C/C−X bond from the ubiquitous C−H bond.[1] Whereas the ability to transform a variety of C−H bonds is changing the paradigm of synthetic chemistry and is opening new perspectives in complex organic synthesis,[2] it happens that C−H functionalization is, in some cases, not a desired process in a given transformation and needs to be suppressed. This could be a difficult task in certain circumstances wherein a C−H bond is in close proximity to the tethered organometallic species. Indeed, mechanistic studies indicated that cyclization via palladium-catalyzed C−H functionalization could be a kinetically fast process related to other elementary reactions.[3] In connection with our research program dealing with the transition-metal-catalyzed multicomponent[4,5] and domino processes,[6,7] we described a facile synthesis of tetracyclic compounds (**2**) from diamides (**1**) by a palladium-

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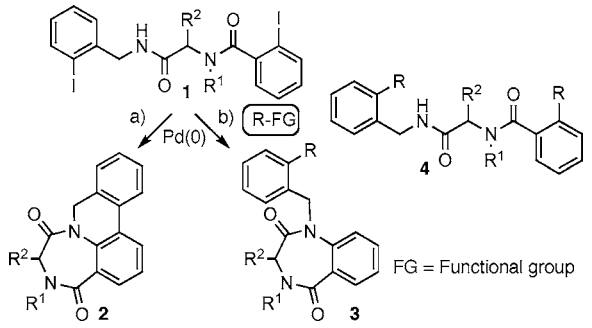
Scheme 1. Proposed Divergent Reaction Sequence

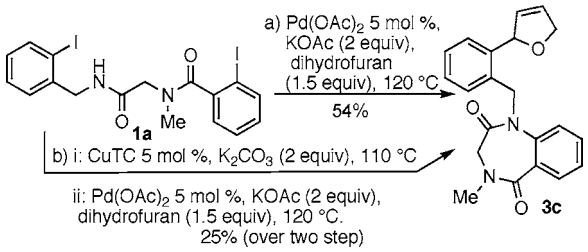


catalyzed domino intramolecular process (Scheme 1, eq 1).[8] Preliminary experiments demonstrated that (a) the presence of the two-diiodide functions was mandatory for the sequence and (b) once the reaction was initiated, it was impossible to interrupt the double cyclization, although the reaction went through the benzodiazepinedione intermediate. As a continuation of this research, we report herein that the direct C−H arylation could be effectively interrupted in the presence of a suitable trapping agent. Thus, starting from amide **1**, a domino sequence involving an intramolecular N-arylation[9] followed by an intermolecular Heck reaction afforded functionalized benzodiazepinedione (BZD) **3**, a privileged structure in medicinal chemistry (Scheme 1, eq 2).[10] We document also for the first time an X-ray structure of an unusual bimetallic macrocycle bridged by two dative Pd−I bonds.

The realization of our projected sequence implied the differentiation of two aryl iodides[11] allowing their site-selective functionalization that must satisfy the following criteria: (a) The intramolecular N-arylation should precede any intermolecular bond-forming process to avoid the formation of linear adduct **4** (Scheme 1). (b) After the formation of benzodiazepinedione, the subsequent intermolecular bond formation must be kinetically faster than the alternative intramolecular C−H functionalization. Only a few examples were known wherein the interruption of the intramolecular C−H functionalization has been accomplished by an intermolecular process.[1h,12,3b]

An initial experiment using phenylboronic acid (**5**) as an intercepting agent met with failure. In fact, reaction of **1a** with **5** [$Pd(OAc)_2$, 5 mol %, KOAc, DMSO, 120 °C] furnished tetracyclic compound **2a** (R^1 = Me, R^2 = H) as the only isolable product in 90% yield. This result indicated that the intramolecular N-arylation and the subsequent C−H functionalization were much faster than the alternative intermolecular Suzuki−Miyaura coupling.[13] The whole reaction sequence was completely inhibited in the presence of morpholine or 4-benzyloxazolidinone under identical conditions. Copper-free Sonagashira coupling[14] was also incompatible with the projected sequence resulting a complex reaction mixture. On the other hand, using potassium ferro(II)-cyanide[6,15] as an anion-capturing agent, the desired benzodiazepinedione **3a** (R = CN, R^1 = Me, R^2 = H) was isolated in 22% yield together with the double cyclization product (**2a**, 35%). When a more reactive vinyltributylstannane was used as a nucleophile,[16] the desired benzodiazepinedione **3b** (R = vinyl, R^1 = Me, R^2 = H, 33%) was produced together with the linear double-vinylated product **4b** (R = vinyl, R^1 = Me, R^2 = H, 23%). Gratefully, reaction of **1a** in the presence of dihydrofuran afforded the expected benzodiazepinedione **3c** resulting from the N-arylation/Heck reaction in 54% yield (Scheme 2, a). This yield is quite remarkable,

Scheme 2. Proposed Mechanism for the Divergent Pathway



as only 25% of product **3c** was isolated using a two-step procedure based on our previous work,[8] involving a copper-catalyzed benzodiazepinedione synthesis, followed by a Heck reaction (Scheme 2, b).

In an attempt to optimize the reaction conditions, we observed that the ligandless conditions are essential for the present tandem process since in the presence of triphenylphosphine and other biarylphosphine ligands under otherwise identical conditions the intramolecular C−H functionalization prevails over the intermolecular Heck reaction, leading to the tetracyclic compound **2a** in excellent yield. While the Heck reaction did take place smoothly under diverse set of

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conditions,[17] it is interesting to note that the present transformation represented a rare example wherein an intramolecular N-arylation occurred under ligandless conditions leading to the formation of a seven-membered ring.[18] Even more surprisingly, this cyclization took place faster than most of the cross-coupling reactions that we examined.

The generality of this domino process was next examined by varying systematically the R^1 and R^2 residues. The cyclization precursors were prepared by the Ugi four-component (Ugi-4CR) reaction[19] using an *o*-iodobenzyl isonitrile, *o*-iodobenzoic acid, an amine, and an aldehyde as inputs (MeOH, rt). The benzodiazepinediones synthesized by this two-step sequence (Ugi 4CR/N-arylation−Heck reaction) are summarized in Figure 1. As is seen, both alkyl and aryl

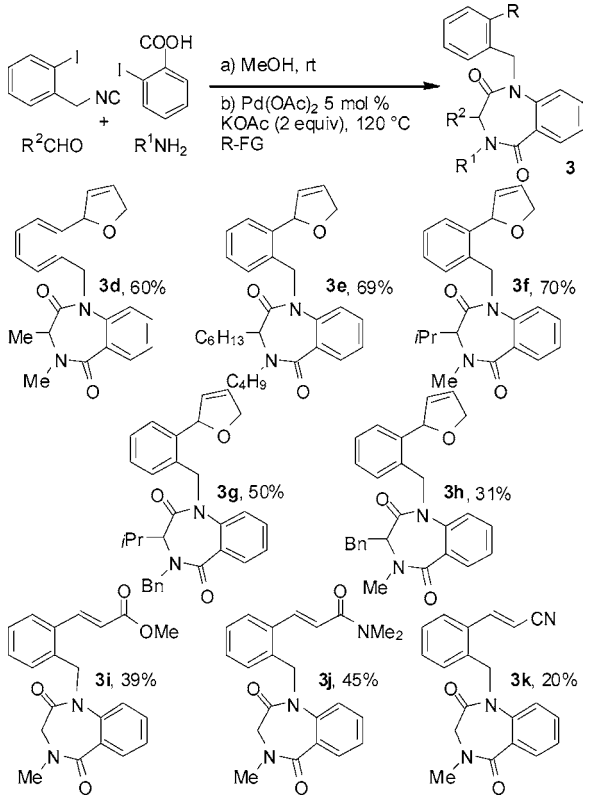
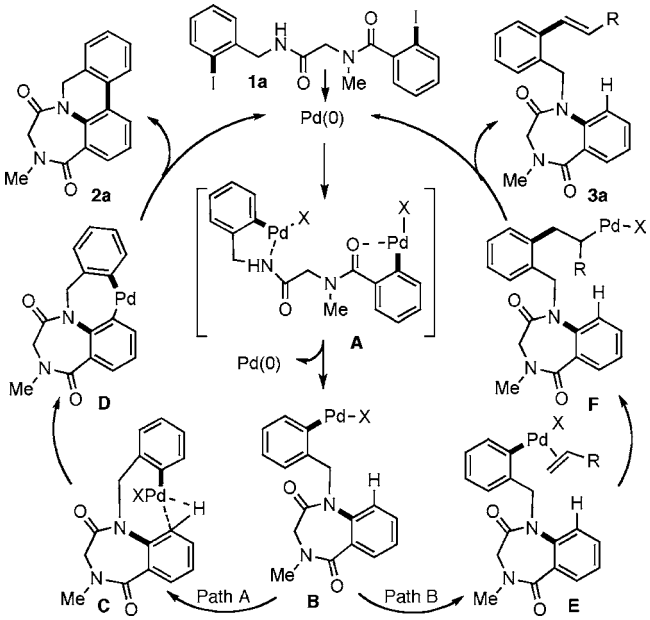


Figure 1. Two-step synthesis of benzodiazepinediones. (Yields refer to the palladium-catalyzed domino sequence.)

groups in the amide backbone are tolerated, and among the precursors evaluated, linear amide bearing a substituent at the C-3 position gave a generally higher yield of the corresponding dihydrofuranyl-BZD except for compound **3h**. In the case of compounds **3d**−**h**, two inseparable diastereomers were produced together with the conformers inherent to benzodiazepinedione. The NMR spectra of these compounds were therefore rather complex.[20] Methyl acrylate and dimethylacrylamide are also viable substrates to interrupt the C−H activation process providing **3i** and **3j** in yields of 39% and 45% respectively, whereas acrylonitrile gave substantially lower yield of the desired product (**3k**, 20%).

A possible reaction scenario that accounts for the formation of both benzodiazepinediones **2** and **3** is illustrated in Scheme 3.

Scheme 3. Synthesis of Dihydrofuranylbenzodiazepinedione **3c**



We have demonstrated in previous studies the importance of the bis-aryl halide function in the formation of benzodiazepinedione. Therefore, the regioselective process cannot rely on simple selectivity during oxidative addition on one aryl iodide. We proposed that the two aryl halides were not differentiated in the oxidative addition step leading to the bis-arylpalladium halide intermediate (**A**).[21] This intermediate might adopt a conformation that is conducive to the cyclization, making the intramolecular N-arylation kinetically competitive relative to other coupling process. An intramolecular N-arylation would generate a second Pd^{II} intermediate (**B**), from which two divergent pathways were possible. The intramolecular C−H activation followed by reductive elimination would produce compound **2a** (path A). On the other hand, in the presence of an external nucleophile that is susceptible to react with the Pd^{II} species, a cross coupling, or carbopalladation (via, for example, intermediates **E** and

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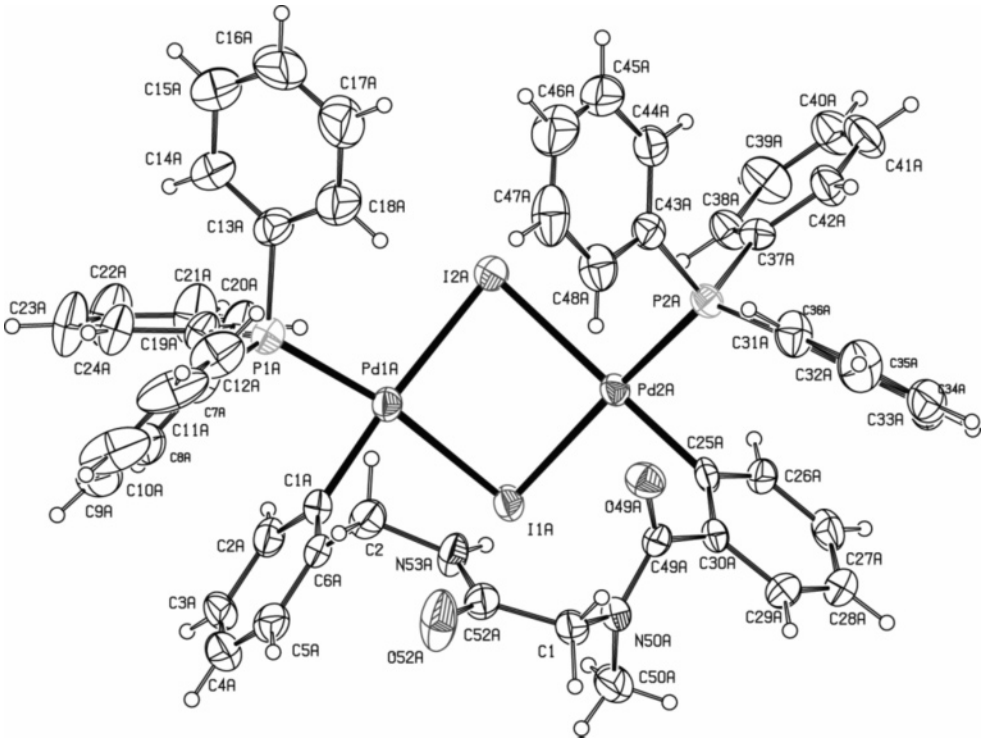

Figure 2. ORTEP view of the X-ray crystal structure of one conformer of compound **6**.[24]

F, via path B) could occur to produce bicyclic compound **3**. Partition between these two pathways depended on the structure of the nucleophile, and from our experimental results, we speculated that the latter process became competitive when the external nucleophile was able to coordinate to the palladium(II) intermediate. The observation that phosphine ligand completely suppressed the Heck pathway could be explained by the fact that its presence disfavored the coordination of olefin to palladium, thereby favoring the alternative direct arylation pathway.

To support this mechanistic view, palladium complex **6** was prepared by a reaction of **1a** with 2 equiv of tetrakis-triphenylphosphine Pd(0) and was characterized by X-ray analysis (Figure 2). The tertiary amide oxygen possibly coordinated to the proximal palladium as indicated by the short interatomic bond distance ($d \approx 3.25$ Å),[22] whereas the long distance between the nitrogen atom of the secondary amide and the proximal palladium Pd_1 ($d \approx 4.57-4.83$ Å) indicated the lack of coordination between these two atoms.[23] To the best of our knowledge, such a bimetallic macrocycle bridged by two dative Pd−I bonds has not been characterized before.

The easy formation of this 13-membered palladacycle **6** is intriguing and may be facilitated by conformational properties of the linear amide.[25] By an obvious entropic factor, the formation of **6** might in turn facilitate the coordination of the secondary amide to the remote palladium, leading consequently to the intramolecular N-arylation.[26]

In summary, a palladium-catalyzed domino process allowing the site-selective functionalization of two tethered aryl iodides has been developed for the synthesis of functionalized benzodiazepine-2,5-diones (**3**). Key to the success was the formation of 7-membered ring via a facile intramolecular N-arylation and the suppression of the entropically favored C−H functionalization process. An X-ray structure of unprecedented bimetallic macrocycle bridged by two dative Pd−I bonds brings an interesting mechanistic insight on the unusual facile N-arylation step. By combining the Ugi-4CR with the present catalytic domino process, the medicinally relevant bicyclic compound **3** is readily synthesized in only two steps from simple starting materials.

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Supporting Information Available: Experimental procedures, product characterization, NMR spectra of compounds **3a**−**k**, and CIF files for **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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