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Pd-Catalyzed Spirocyclization via C−H Activation and Benzyne Insertion

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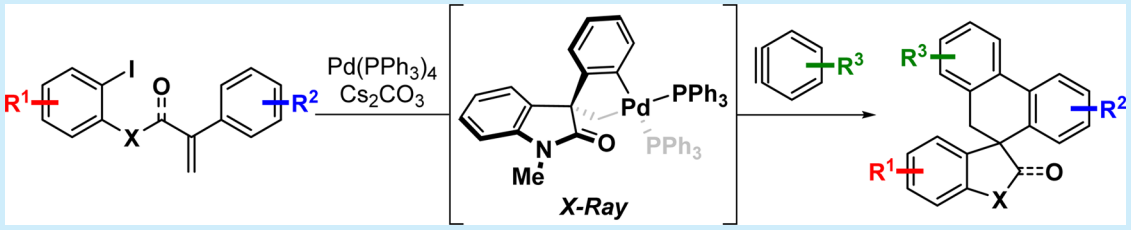
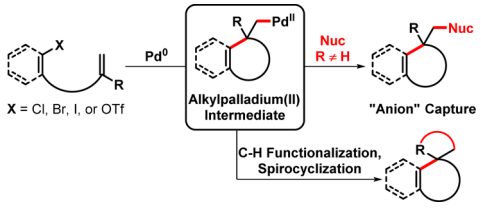
Supporting Information



ABSTRACT: A palladium-catalyzed spirocyclization forming spirooxindoles and spirodihydrobenzofurans has been achieved. Mechanistic studies suggest that the transformation proceeds through sequential carbopalladation, C−H activation, and benzyne insertion. Both classes of spirocycles have been synthesized in good to excellent yields, and the procedure is readily scalable.

Palladium-catalyzed C−H functionalization has attracted considerable interest as it provides an efficient and atom-economical process to forge novel bond connections.[1] Although a wide array of intermolecular transformations have been reported, the utility of this approach in an intramolecular cascade reaction has been underdeveloped. The combination of C−H functionalization with the intramolecular Heck reaction has provided a new venue in generating polyheterocyclic cores.[2] In addition, various groups have expanded the intramolecular process to the formation of biologically relevant spirocycles (Scheme 1).[3−5] Alternatively, the Pd-catalyzed domino-Heck

Scheme 1. Pd-Catalyzed Intramolecular C−H Activation and Domino Heck Anion Capture Cascade

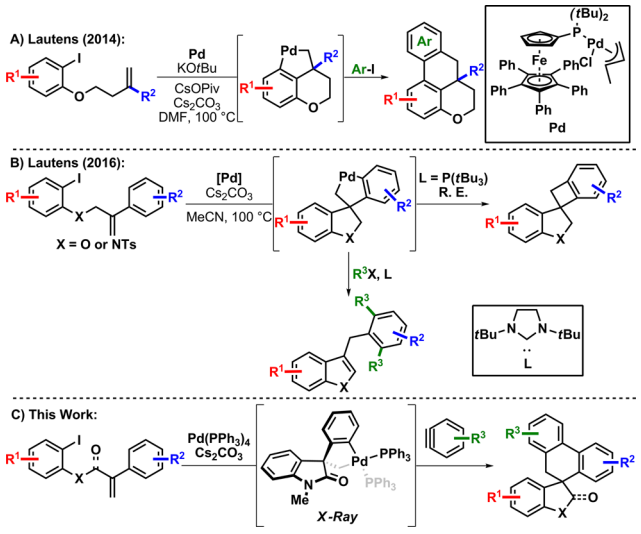


anion capture cascade pioneered by Grigg[6] has become a valuable methodology to synthesize useful heterocyclic scaffolds that map onto pharmaceutical agents and natural products (Scheme 1).[7,8]

Recently, our group has made contributions in the fields of intramolecular C−H functionalization[9] and domino-Heck anion capture cascade.[10] In 2014, both methodologies were applied in a single transformation by intercepting the palladacycle generated by an intramolecular C−H functionalization with an aryl iodide to provide polycyclic cores (Scheme 2A).[9a]

Following this work, a divergent Pd-catalyzed cascade reaction in which two classes of compounds originate from a single

Scheme 2. Pd-Catalyzed Cascade Reactions



spirocyclic palladacycle was reported[9b] (Scheme 2B). Reductive elimination yielded the benzocyclobutene derivatives, while in the presence of alkyl halides, a Catellani-like reaction furnished benzofurans. Interested in the reactivity of the described palladacycle (Scheme 2B), we sought to insert highly reactive benzynes[11] into this intermediate to access various classes of spirocycles.[12]

In addition to determining the generality of this process, we provide mechanistic insight on the Pd-catalyzed domino-Heck spirocyclization via C−H activation and benzyne insertion sequence. The described transformation showcases the synthesis

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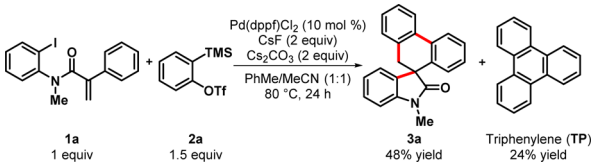
of spirooxindoles and spirodihydrobenzofurans in good to excellent yields (Scheme 2C).

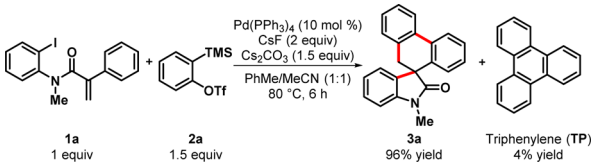
We envisioned the cyclization of **1a** and insertion of a benzyne (generated in situ from precursor **2a**) to afford **3a**. The desired spirooxindole **3a** was obtained in 48% yield and was accompanied by triphenylene (TP) (Scheme 3). The spirocyclic

Scheme 3. Initial Hit



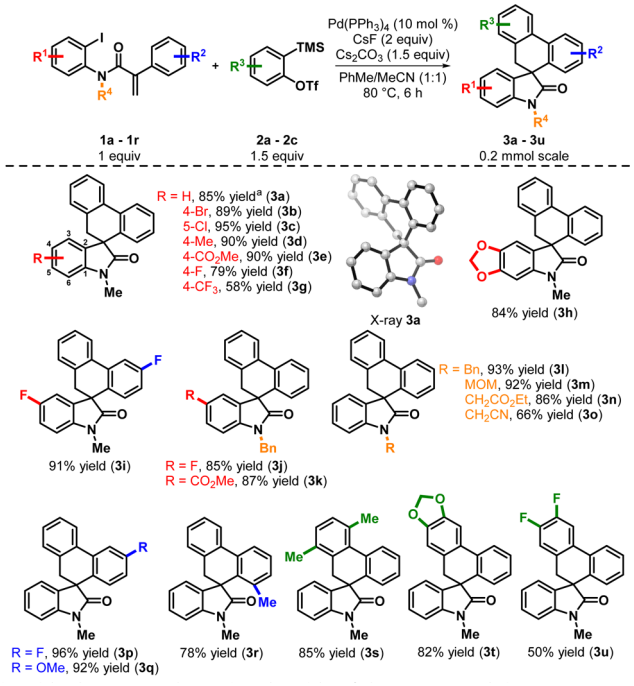
structure of **3a** was confirmed by spectroscopic data and X-ray crystallography. Encouraged by the initial hit, the reaction conditions were optimized to yield **3a** and minimize the formation of TP in 96% and 4% yield, respectively (Scheme 4).[13]

Scheme 4. Optimized Conditions



With the optimized conditions, we investigated the substrate scope (Scheme 5). Acrylamides bearing halogens and electron-neutral substituents at the 4- and 5-positions were well-tolerated (**1b**–**d**, 89–95% yield). A methyl ester at the 4-position cyclized

Scheme 5. Pd-Catalyzed Domino Heck Spirocyclization Forming Spirooxindoles: Reaction Scope[b]

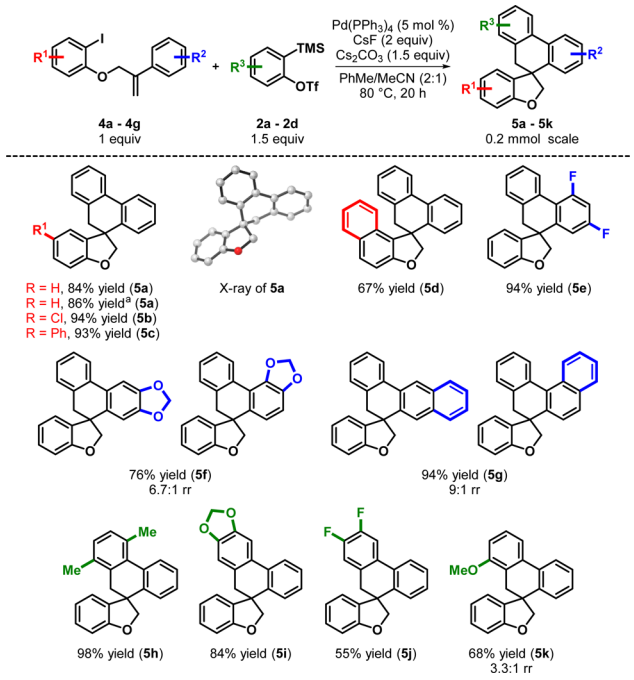


[a]The reaction was run on a 2.75 mmol scale. [b]Isolated yields of the spirooxindoles are shown.

in high yield and did not undergo side reactions with the aryne (**3e**, 90% yield). Fluorine and trifluoromethyl substitution produced the desired products in 79% and 58% yield, respectively (**3f** and **3g**). Electron-rich substituents also cyclized to generate **3h** in 84% yield. Gratifyingly, substitution of the tethered aryl group with a fluorine improved the reactivity, giving **3i** in 91% yield. *N*-Benzylated acrylamides also participated in the reaction in excellent yields (**3j** and **3k**, 85% and 87% yield, respectively). *N*-MOM- and *N*-CH_2CO_2Et-protected acrylamides also cyclized in 92% and 86% yield, respectively (**3m** and **3n**). Electron-poor *N*-protected acrylamide **1o** reacted in slightly lower yield (66% yield). Electron-rich and -poor substituents on the tethered aryl group did not negatively impact the cyclization (**3p** and **3q**, 96% and 92% yield, respectively). An *ortho* substituent on the tethered aryl group produced the spirooxindole in good yield (**3r**, 78% yield). Sterically encumbered and electron-rich benzyne precursors **2a** and **2b** were reacted with **1a** to produce **3s** and **3t** in 85% and 82% yield, respectively. Electron-poor benzyne precursor **2c** cyclized to form **3u** in 50% yield. On a gram scale, **3a** was isolated in 85% yield. Alkynes and cyclohexynes did not undergo insertion to form the respective spirocycles.

In addition to the preparation of spirooxindoles, the synthesis of spirodihydrobenzofurans was also investigated (Scheme 6).

Scheme 6. Pd-Catalyzed Domino Heck Spirocyclization Forming Spirodihydrobenzofurans: Reaction Scope[b]



[a]The reaction was run on a 2.97 mmol scale. [b]Isolated yields of spirodihydrobenzofurans are shown. rr = ratio of regioisomers.

Lowering the catalyst loading to 5 mol % Pd and altering the solvent ratio to PhMe:MeCN = 2:1 allowed the cyclization to give **5a** in 84% yield. Sterically encumbered aryl iodide **4d** also reacted to give **5d** in 67% yield. Electron-poor tethered aryl groups enhanced the cyclization to give the spirobenzofurans (**5e**, 94% yield). It was found that unsymmetrical tethered aryl groups underwent the C–H activation regioselectively to minimize steric interaction on the palladacycle (**5f** and **5g**, 6.7:1 rr and 9:1 rr, respectively). In line with the findings on the

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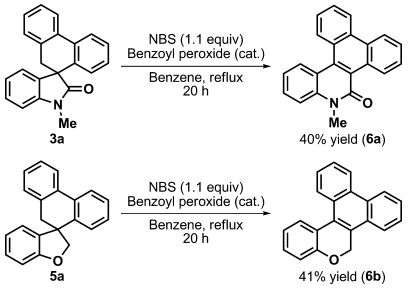
spirooxindoles, sterically encumbered and electron-rich benzynes **2b** and **2c** reacted to generate **5h** and **5i** in 98% and 84% yield, respectively. An electron-poor aryne generated **5j** in 55% yield. Interestingly, the unsymmetrical benzyne precursor **2d** reacted with 3.3:1 rr to give **5k**. A gram-scale reaction was performed to examine the scalability, and **5a** was generated in 86% yield.

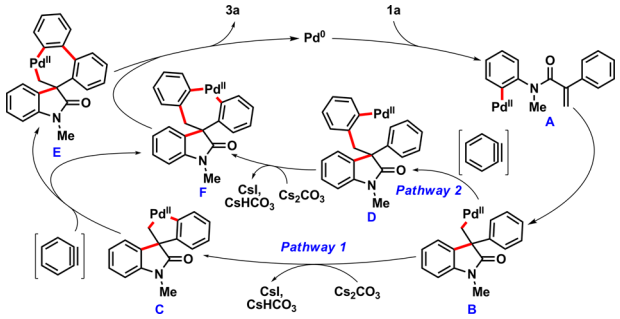
Derivatizations of the spirocycles were explored. A radical benzylic bromination gave ring expansion and aromatization of both the spirodihydrobenzofuran and spirooxindole in moderate yields (**6a** and **6b**, 40% and 41%, respectively; Scheme 7).

Scheme 7. Ring Expansion of Spirocycles



The spirocyclization product can be explained through the postulated mechanism in Scheme 8. Aryl iodide **1a** undergoes

Scheme 8. Postulated Mechanism for the Spirocyclization

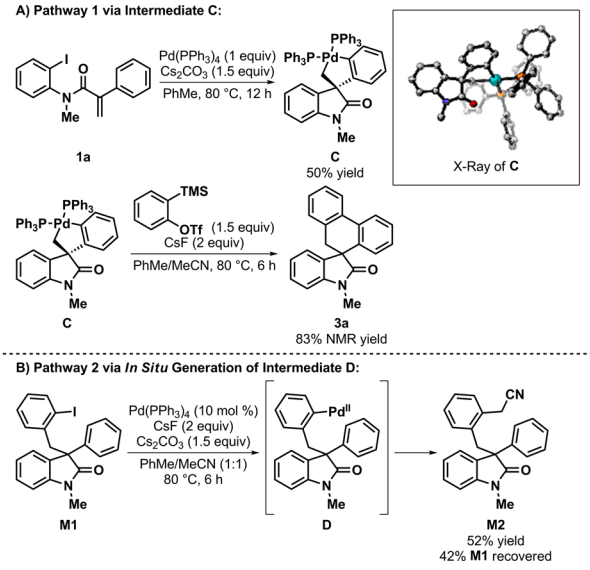


Pd-catalyzed oxidative addition followed by carbopalladation to generate alkylpalladium(II) intermediate **B**, from which two divergent pathways are possible. In pathway 1, intramolecular C−H activation of the pendant aryl group generates palladacycle **C.** Insertion of the aryne leads to intermediate **E** or **F**,[14] which undergoes reductive elimination to release **3a** and regenerate the catalyst. In constrast, pathway 2 involves intermolecular insertion of the aryne to form intermediate **D** followed by C−H activation to yield intermediate **E** and reductive elimination to form **3a**.

Intrigued by the two pathways and eager to gain insight into the C−H activation versus addition to the aryne, we performed a series of mechanistic experiments (Scheme 9). Pathway 1 involves an intramolecular C−H activation forming palladacycle **C**. To support its viability in the mechanism, **1a** was reacted with stoichiometric quantities of $Pd(PPh_3)_4$ and excess Cs_2CO_3 to generate **C** in 50% yield. The structure was confirmed by spectroscopic data and X-ray crystallography. Palladacycle **C** was then reacted with the in situ-generated benzyne to yield **3a** in 83% yield (Scheme 9A). The generation of **3a** from **C** suggests that **C** can be an intermediate in the catalytic cycle.

Pathway 2 was investigated by generating intermediate **D** via oxidative addition of the corresponding aryl halide **M1**. However,

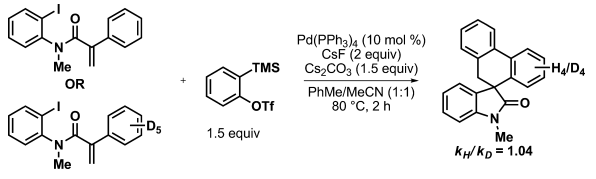
Scheme 9. Mechanistic Experiments



under the standard reaction conditions, the cyclization following the C−H activation did not occur, and instead, arylation of acetonitrile proceeded exclusively to generate **M2** (52% yield; Scheme 9).[15] The formation of **M2** suggests that generation of the seven-membered palladacycle after insertion of the benzyne is unfavorable under the reaction conditions. We propose that the reaction proceeds exclusively through pathway 1.

In order to determine whether the intramolecular C−H activation is the rate-determining step, a kinetic isotope effect was measured using parallel experiments. The initial rates of cyclization of acrylamide **1a** and the deuterated derivative were determined, and a k_H/k_D of 1.04 was determined. This result provides evidence that C−H activation is not the rate-limiting step in the catalytic cycle (Scheme 10).[16]

Scheme 10. Parallel KIE Experiment



In summary, we have developed a Pd-catalyzed domino Heck spirocyclization to provide a range of spirooxindoles and spirodihydrobenzofurans in good to excellent yields. A series of mechanistic experiments were performed to provide insight into the reaction, and some derivatization experiments showed the utility of these spirocycles. We are currently investigating the enantioselective variant.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03213.

X-ray data for **C** (CIF)
X-ray data for **3a** (CIF)
X-ray data for **5a** (CIF)
Experimental procedures, optimization, characterization, and X-ray data (PDF)

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Notes

The authors declare no competing financial interest.

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(13) Refer to the Supporting Information for the deoptimization table for spirooxindoles and spirodihydrobenofurans.

(14) The benzyne can insert into intermediate **C** to yield **E** or **F** depending on which bond undergoes insertion. We believe intermediate **E** is more likely based on analogous results from the Catellani reaction.

(15) Throughout the evaluation of the scope, byproducts similar to **M2** were not observed.

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