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A Modular Approach for the Palladium-Catalyzed Synthesis of Bis-heterocyclic Spirocycles

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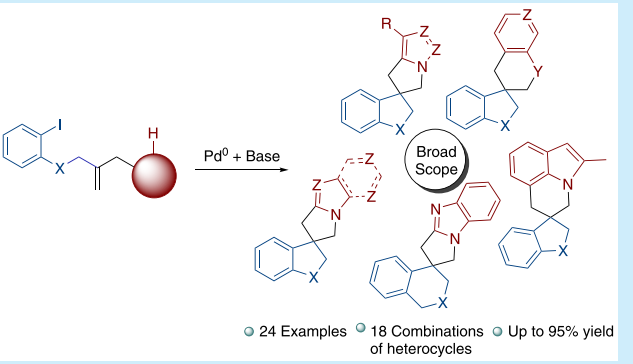
ABSTRACT: A simple and modular approach toward bis-heterocyclic spirocycles using palladium catalysis is reported. The enclosed methodology leverages a Mizoroki−Heck-type reaction to generate a neopentylpalladium species. This species can undergo intramolecular C−H activation on a wide array of (hetero)aryl C−H bonds, generating a variety of [4.4] and [4.5] bis-heterocyclic spirocycles in up to 95% yield. A diverse range of bis-heterocyclic spirocycles were possible, with 24 examples and 18 different combinations of heterocycles were synthesized. Biologically relevant aza-heterocycles such as purine, pyrazole, (benz)imidazole, (aza)indole, and pyridine were readily incorporated into the spirocyclic core. The reaction was readily scalable to 1 mmol using a lower catalyst loading and number of base equivalents, and the product was purified without the use flash column chromatography.



Bis-heterocyclic spirocycles are highly coveted motifs in medicinal chemistry, but their synthesis remains challenging. Conventionally, methods to access this molecular architecture tend to be highly specific toward one scaffold. Consequently, general strategies to access diverse spirocycles are underdeveloped compared with those targeting fused- or bridged-ring systems. We envisioned developing a modular palladium domino C−H activation approach to selectively access a diverse range of bis-heterocyclic spirocycles comprised of various different heteroatoms and ring sizes.

Our group has had a long-standing interest in utilizing palladium domino Mizoroki−Heck reactions to obtain spirocyclic compounds (Scheme 1a). The vast majority of recent methodologies have been applied to the generation of carbocyclic spirocycles via C−H activation to generate a five-membered palladacycle (Scheme 1a).[1−5] This species can undergo migratory insertion across a π system, such as an alkyne or benzyne, and subsequent reductive elimination furnishes the carbocyclic spirocycle (Scheme 1). Additionally, the palladacycle can perform a 1,1-insertion across a carbene or carbene equivalent,[6−8] react with a diaziridinone,[9] or undergo a ligand-dependent reductive elimination, generating spirocyclobutanes.[10,11] Although these strategies have been leveraged to incorporate a variety of functional groups, they are typically not amenable to accessing bis-heterocyclic frameworks.

Seminal work from the Grigg group in the mid-1990s demonstrated the ability to generate bis-heterocyclic compounds via an intramolecular Stille-type coupling[12] or using reactive π systems of heteroaromatic molecules or Michael systems. In the case of the latter, the authors proposed a sequential dearomative migratory insertion process.[13] These methodologies were limited to a few sulfonamide-derived indolines and specific activated π systems.

Likewise, the Zhu group used a similar approach to access spirodihydroquinolin-2-ones in 2012.[14] Given the plethora of modern domino C−H activation methodologies,[15−23] we aimed to build a range of bis-heterocyclic spirocycles via a simple and modular approach.

The modularity of this approach is multifaceted. First, the use of a synthetic lynchpin such as 3-chloro-2-chloromethylpropene allows for a divergent substrate synthesis. Simple sequential S_N2 reactions using a variety of different nucleophiles, including an *o*-iodoarene or anaza-heterocycle, phenol, or aniline, provide rapid access to a myriad of scaffolds. This approach allows access to a multitude of heteroatom-rich substrates containing a wide range of (hetero)aryl C−H bonds (Scheme 1b). Moreover, on the basis of the mechanism of this reaction, this approach permits high selectivity for the bis-heterocyclic spirocycle that is formed. Classically the Mizoroki−Heck-type reaction is initiated via oxidative addition to an aryl halide followed by migratory insertion.[15,24,25] This strategy allows us to selectively generate each heterocycle, the

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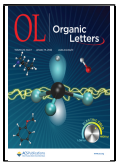

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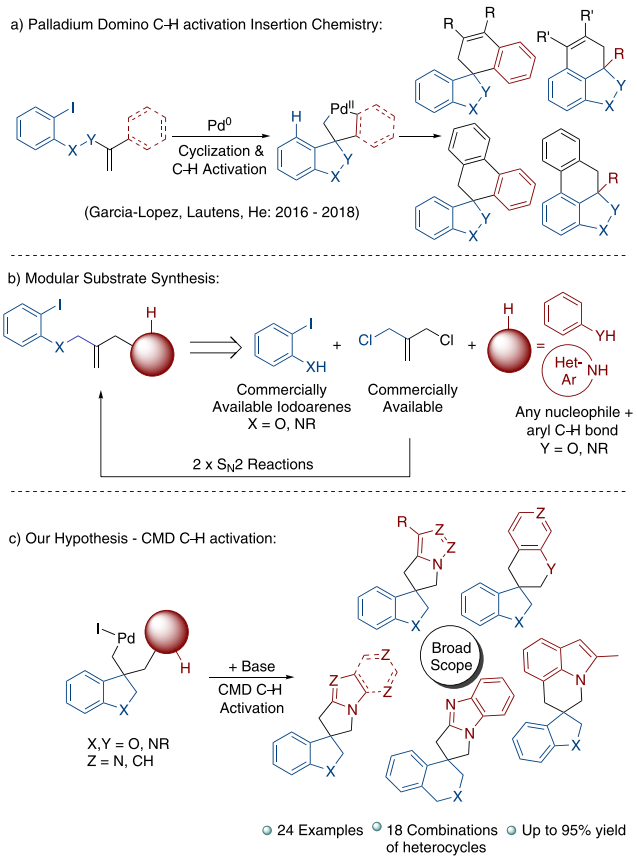
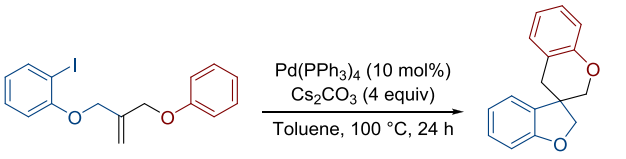
Scheme 1. Past Work and Our Objective



first of which previously contained the aryl iodide. The second step, consisting of base-mediated C−H activation, affords a six- or seven-membered palladacycle. Palladacycles of this size are prone to reductive elimination and thus form the second heterocyclic component. We prepared 24 different bis-heterocyclic spirocyles using this methodology, irrespective of the electronic environment or bond strength of the corresponding C−H bond (Scheme 1c).

$Pd(PPh_3)_4$ was identified as a simple Pd(0) source for the reaction. Cs_2CO_3 in toluene at 100 °C gave the optimal yield of spiro[benzofuran-3,3′-chromane] (**2a**) (88% NMR yield, 80% isolated yield). This strategy proved to be convenient to access spiro[benzofuran-3,3′-chromane]s, as previous methods to generate these compounds required sequential intramolecular C−O cross-couplings[26] or a multistep radical cyclization−reduction sequence.[27] It was essential to obtain >95% conversion of the starting material, as separation from the product proved to be extremely difficult. Using $Pd(OAc)_2$ with PPh_3 gave the product in a slightly reduced yield, while using dppf as the ligand severely diminished the yield (Table 1, entries 6 and 7). Surprisingly, other commonly employed bases for palladium concerted−metalation deprotonation (CMD) reactions such as K_2CO_3 and K_3PO_4 failed to yield any product (entries 4 and 5). The complete failure with K_2CO_3 is significant, as it was the base of choice in the Grigg report. In this case, only the protodemetalated product was observed (see the Supporting Information for more details). Moreover, employing an aryl bromide as the starting material or changing the solvent to DMF led to a reduced product yield (entries 8 and 9). Lowering the catalyst loading or the reaction time led

Table 1. Deoptimization Table



1a **2a**

entry	variation from the standard conditions	% yield of product[a] (% SM)
1	none	88 [80] (<5)
2	3 equiv of base instead of 4 equiv	84 (<5)
3	90 °C instead of 100 °C, (3 equiv of base)	73 (27)
4	K_2CO_3 instead of Cs_2CO_3	n.p. (87)
5	K_3PO_4 instead of Cs_2CO_3	13 (<5)
6	$Pd(OAc)_2$, PPh_3 (30 mol %)	79 (<5)
7	$Pd(OAc)_2$, dppf (20 mol %)	39 (n.d.)
8	aryl bromide instead of iodide	35 (n.d.)
9	DMF instead of toluene, 3 equiv of base	75 (<5)
10	5 mol % catalyst	72 (27)
11	4 h instead of 24 h	25 (60)

[a]Yields were determined via ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene (TMB) as an internal standard. The yield in square brackets is an isolated yield. n.p. = no product. n.d. = not determined. All reactions were run at 0.1 M.

to lower yields and incomplete conversion of the starting material (entries 10 and 11).

We next explored the scope of the reaction, with the goal of identifying straightforward conditions applicable to a broad range of (hetero)aryl C−H bonds (Scheme 2). Bis-ether substrates afforded the spiro[benzofuran-3,3′-chromane] scaffolds **2a−c** in good yields. Interestingly, electron-neutral or electron-rich aromatic systems slightly outperformed an electron-deficient system. Next, we applied this method to the synthesis of aza- and oxo-containing [4.5] spirocycles. Using aniline- and phenol-derived nucleophiles, various combination of spirocycles including dihydrobenzofurans, indolines, chromanes, and tetrahydroquinolines with various protecting groups on the nitrogen (**2d−g**) were accessed in moderate to good yields. Notably, with product **2g** we were able to obtain the spiro-indoline−tetrahydroquinoline product with different protecting groups on each nitrogens.

When one of the nucleophiles was changed to an aza-heterocycle, [4.4] bis-spirocyclic heterocycles were readily prepared. A variety of pentacyclic spirocycles incorporating both the 2-iodoaniline and phenol derivatives, containing both electron-donating and -withdrawing groups, and benzimidazoles (**2h−k**), indole (**2l**), and azaindoles (**2m** and **2n**) were attainable, as well as a product bearing a chlorinated purine (**2o**). The yields were generally high, with the exception of the purine-containing molecule. Although the yield of **2o** was only 31%, the inclusion of a halogenated core of a nucleotide base was noteworthy. Furthermore, tetracyclic [4.4] spirocycles were also accessible using the methodology. Indoline and dihydrobenzofuran cores were successfully coupled with imidazoles (**2p** and **2q**), pyrazoles (**2r** and **2s**), and a triazole (**2t**). Of note, only one regioisomer of the imidazole-containing molecules was observed, with the C−H activation occurring at the more activated 2-position.[28]

Next, we investigated the synthesis of [4.5] bis-heteroyclic spirocycles wherein the C−H bond was itself part of another

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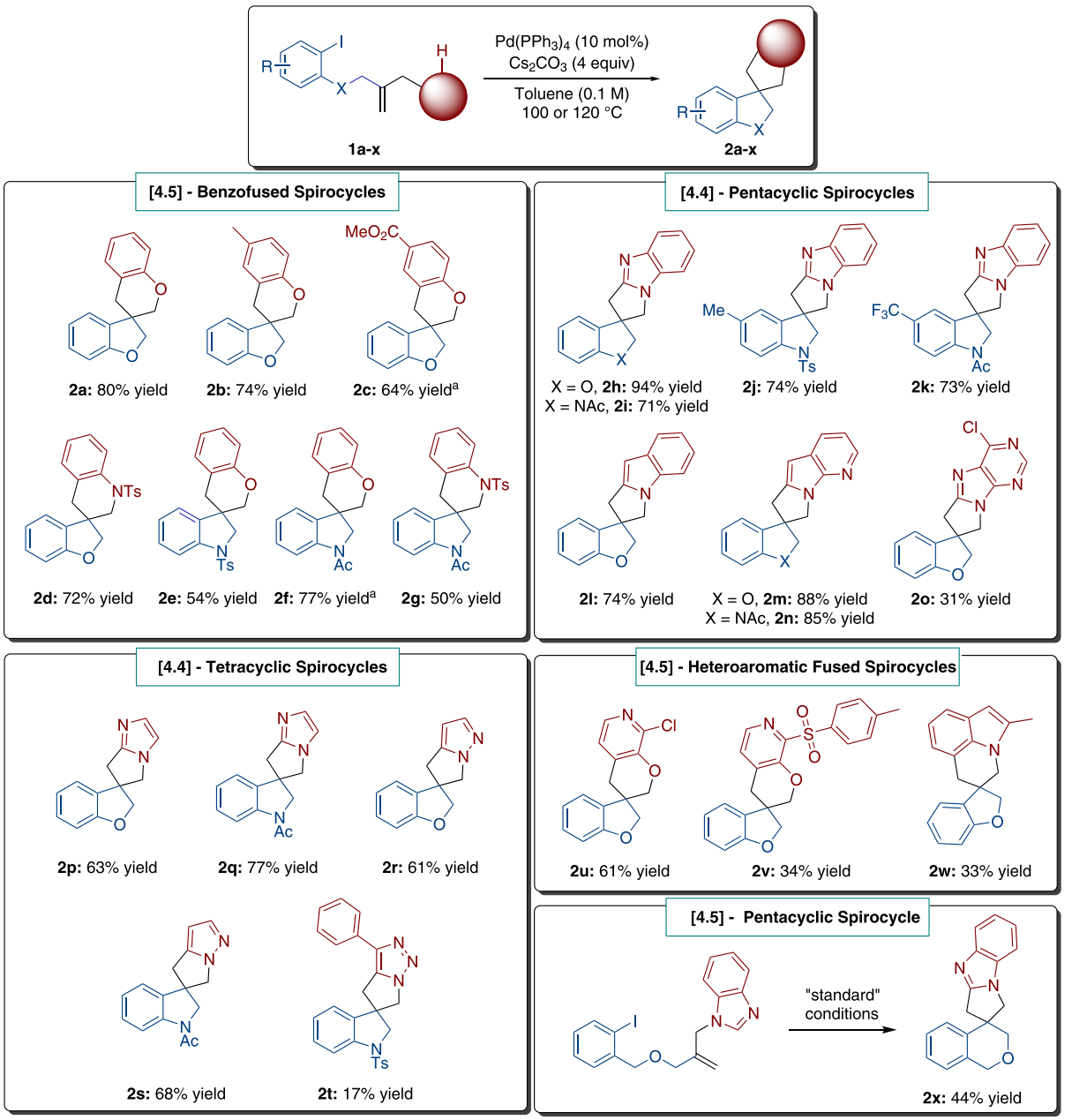
Scheme 2. Substrate Scope



[a]The yield was determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard, added to an inseparable mixture of the product and protodemetalation side product.

heterocycle. Substrates containing reactive chloro (**2u**) and tosyl (**2v**) groups at the 2-position of 3-hydroxypyridines gave the desired products in moderate yields. 3-Hydroxypyridine was reactive, but an inseparable mixture of regioisomers was obtained (see the SI for details). Furthermore, when the 2-position of an indole was blocked, C−H activation was forced to occur at the 7-position, forming [4.5] spirocycle **2w** in 33% yield. Moreover, [4.5] spirocycle **2x** containing an isochroman and a benzimidazole could also be obtained using the 2-iodobenzyl alcohol-derived starting material. Generally, reactions generating the six-membered ring of the spirocycle first gave lower yields, and the products were exceptionally difficult to isolate (see the SI for more details).

The reaction was successfully run on a 1 mmol scale with a reduced loading of the catalyst and base (Scheme 3, top) We sought to develop a simplified purification procedure for the scaled-up reaction. Filtration of the crude reaction mixture through a small (3 cm) pad of silica followed by three rounds of trituration with Et_2O gave spectroscopically pure **2h** in a comparable yield (95%; see the SI for a detailed procedure). Although this purification method may be limited to specific substrates, when it is possible it offers an efficient and simple strategy for product isolation.

On the basis of our previous work[29] and related reports,[15] we hypothesize a mechanism that follows a typical domino Mizoroki−Heck-type pathway (Scheme 3, bottom). The reaction is initiated via oxidative addition to the aryl iodide

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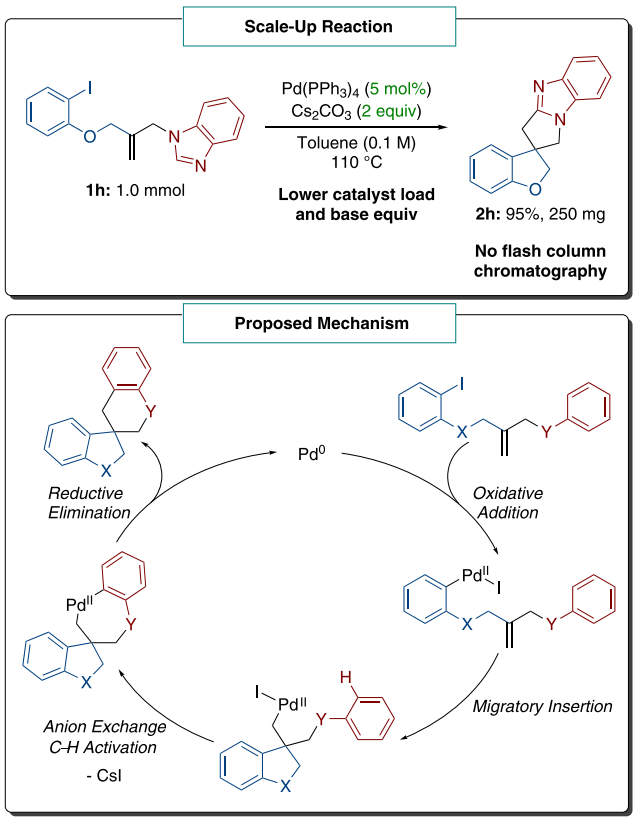
Scheme 3. Scale-Up Reaction and Proposed Mechanism



starting material. Migratory insertion onto the tethered olefin generates the neopentylpalladium^{II} species. Given the broad range of aryl C−H bonds that were amenable to this reaction and the necessity for Cs_2CO_3 as the base, we propose that the resulting neopentylpalladium^{II} species performs a CMD-type C−H activation of the (hetero)aryl ring. The resulting palladacycle undergoes reductive elimination, thereby forming the spirocyclic core and regenerating the palladium^{0} catalyst.

In conclusion, we report a general method for the synthesis of bis-heterocyclic spirocycles using a palladium domino C−H activation sequence. By the use of 3-chloro-2-chloromethylpropene as a synthetic lynchpin for starting material synthesis, a myriad of substrates were easily transformed into novel bis-heterocyclic spirocycles. We obtained 18 novel combinations of spirocyclic cores incorporating a variety of nitrogen and oxygen-based heterocycles. The methodology proved to be readily scalable, with lower catalyst and base loadings leading to comparable product yields.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c03682.

General procedures and compound characterization (PDF)

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Notes

The authors declare no competing financial interest.

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