

Palladium-Catalyzed Intramolecular Carbopalladation/Cyclization Cascade: Access to Polycyclic N-Fused Heterocycles

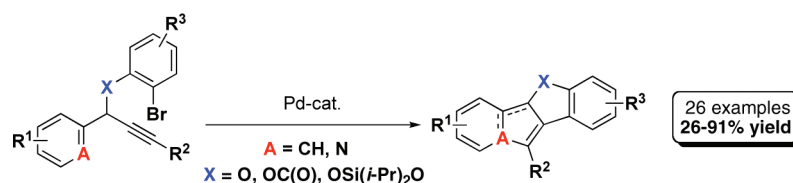
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Received October 9, 2010

ABSTRACT



An efficient palladium-catalyzed intramolecular carbopalladation/cyclization cascade toward tetra- and pentacyclic N-fused heterocycles has been developed. This transformation proceeds via the palladium-catalyzed coupling of aryl halides with internal propargylic esters or ethers followed by the 5-*endo-dig* cyclization leading to polycyclic pyrroloheterocycles in moderate to excellent yields.

Nitrogen-containing heteroaromatic molecules and their analogues are pharmaceutically significant scaffolds, widely present in naturally occurring and synthetic biologically active molecules.¹ For example, molecules containing an indolizine motif, such as Lamellarin D² and other closely related cores,³ exhibit a wide array of biological activities, including human DNA topoisomerase I inhibition,⁴ the ability to reverse multidrug resistance,⁵ and the ability to induce apoptosis through a mitochondria-mediated pathway toward a broad range of cancer cell

lines.⁶ These significant biological activities brought substantial attention to the synthesis of Lamellarins and their analogues.^{7,8} Although several routes toward their core exist, new methods allowing for the efficient construction of heterocycles, particularly those with modified core and different substitution patterns, are in high demand. We have recently reported a two-component coupling methodology toward fully substituted N-fused heterocycles.^{9,10} Although quite general with respect to the heterocyclic core, this

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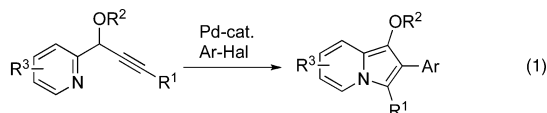
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approach is limited to the synthesis of bicyclic and tricyclic heteroaromatic molecules only (eq 1). Herein, we report a novel Pd-catalyzed arylation cyclization cascade that allows for easy assembly of various tetra- and penta-cyclic isochromanone-annulated and other heterocycles.



We envisioned, that internal Ar–Pd–X species would undergo carbopalladation of the propargylic moiety of **1** with subsequent 5-endodig cyclization to produce **2** (Table 1). This

Table 1. Optimization of Reaction Conditions^a

entry	X	Pd	base	solvent	yield, % ^b
1	Br	PdCl ₂ (PPh ₃) ₂	Cs ₂ CO ₃	NMP	—
2	Br	PdCl ₂ (PPh ₃) ₂	K ₃ PO ₄	NMP	—
3	Br	PdCl ₂ (PPh ₃) ₂	K ₂ CO ₃	NMP	traces
4	Br	PdCl ₂ (MeCN) ₂	Cs ₂ CO ₃	NMP	—
5	Br	PdCl ₂ (MeCN) ₂	K ₃ PO ₄	NMP	—
6	Br	PdCl ₂ (MeCN) ₂	K ₂ CO ₃	NMP	traces
7	Br	Pd(OAc) ₂	Cs ₂ CO ₃	NMP	25
8	Br	Pd(OAc) ₂	K ₃ PO ₄	NMP	32
9	Br	Pd(OAc) ₂	K ₂ CO ₃	NMP	37
10	Pd(OAc) ₂	K ₂ CO ₃	DMF	72 ^{c,d}	
11 ^c	Br	Pd(OAc) ₂	K ₂ CO ₃	NMP	68 ^{c,d}
12	Br	Pd(OAc)₂	K₂CO₃	DMA	80^{c,d}
13	I	Pd(OAc) ₂	K ₂ CO ₃	DMA	21 ^{c,d}

^a Reactions were run in the presence of 5 mol % of Pd-catalyst in appropriate solvent (0.5M) at 130 °C for 8 h unless otherwise noted. ^b GC/MS yields. ^c Reactions was performed in appropriate solvent (0.33M) at 130 °C for 8 h. ^d Isolated yield.

idea was tested on cyclization of easily available propargyl-containing pyridine **1**¹¹ in the presence of PdCl₂(PPh₃)₂ catalyst. However, only trace amounts of desired product **2** were observed (Table 1, entries 1–3). Switching to PdCl₂(MeCN)₂ catalyst did not provide any improvement of reaction outcome (entries 4–6). However, employment of the ligand-free catalyst Pd(OAc)₂ led to considerable enhancement of the reaction yields (entries 7–9). Solvent and concentration screening revealed the optimal conditions (entry 12).

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Table 2. Carbopalladation/Cyclization Reaction of Propargylic Esters **1**^a

entry	1	2	yield, % ^b
1	1a	2a	80
2	1b	2b	65
3	1c	2c	71
4	1d	2d	70
5	1e	2e	88
6	1f	2f	76
7	1g	2g	84
8	1h	2h	91
9	1i	2i	64
10	1j	2j	90
11	1k	2k	73
12	1l	2l	58
13	1m	2m	72

^a All reactions were performed on 0.15 mmol scale in DMA (0.33 M) at 100 to 130 °C for time specified in the Supporting Information. ^b Yield of the isolated product after flash chromatography on silica gel.

Table 3. Carbopalladation/Cyclization Reaction of Propargylic Ethers **3**^a

entry		3	4	yield, % ^b
1		3a		4a 63 ^c
2		3b		4b 26 ^c
3		3c		4c 38 ^c
4		3d		4d 35 ^c
5		3e		4e 64 ^c
6		3f		4f 47 ^c
7		3g		4g 70 ^c
8		3h		4h 83 ^c
9		3i		4i 71 ^d
10		3j		4j 64 ^d
11		3k		4k 68 ^d
12		3l		4l 48 ^d
13		3m		4m 83 ^d

^a All reactions were performed on 0.15 mmol scale in appropriate solvent (0.33 M) at 120 to 135 °C for time specified in the Supporting Information. ^b Isolated yield. ^c Reaction conditions A: Pd(OAc)₂ (5 mol %), K₂CO₃ (2.0 equiv), *n*-Bu₄NCl (1.0 equiv), DMF, 120 °C. ^d Reaction conditions B: Pd(OAc)₂ (5 mol %), K₂CO₃ (2.0 equiv), LiCl (1.0 equiv), *p*-xylene, 135 °C.

With these optimized conditions in hand, the scope of this cascade cyclization was examined (Table 2). Hence, benzyloxy-propargylic esters **1**, possessing different alkyl (entries 1–3), alkenyl (entry 4), aryl (entries 5–7) substituents at the triple bond underwent smooth conversion to give the corresponding polycyclic heterocycles **2a–g** in good yields. The generality of this transformation was further extended by employment of a number of functionalized benzyloxy-propargylic esters that smoothly were converted into the corresponding polycyclic N-fused heterocycles **2 h–k** (entries 8–11). Importantly, this transformation performed with comparable efficiency with other heterocyclic cores; isoquinoline and quinoline propargylic ester were effectively transformed to the pentacyclic N-fused heterocycles **2l** and **2m**, respectively (entries 12, 13).

Furthermore, we found that propargylic ethers **3**¹² could also be utilized in this transformation providing access to another polycyclic scaffold, employing slightly modified reaction conditions¹³ (Table 3). Interestingly, this reaction proved even more general with respect to the functional group compatibility (Table 3, entries 1–6). Pentacyclic heterocycle **4g** was also efficiently obtained using this methodology.

Notably, this transformation could also be successfully performed on the carbocyclic analog, giving access to the fused indenofuran derivative **4h** (entry 8). Propargylic silyl ethers **3i–m** also proved efficient to undergo the carbopalladation/cyclization sequence, thus affording access toward novel silacyclic scaffolds (entries 8–13).⁹

In summary, we have developed a new synthetic protocol for rapid and efficient assembly of three distinct tetra- and pentacyclic cores from easily accessible starting materials. This cascade carbopalladation/cyclization approach is complementary to the previously developed methods^{10,11,14} toward multisubstituted N-fused heterocycles.

Acknowledgment. We gratefully acknowledge the financial support of the National Institutes of Health (GM-64444).

Supporting Information Available: Experimental details and characterization data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(12) See Supporting Information for the detailed preparative procedures.

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