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

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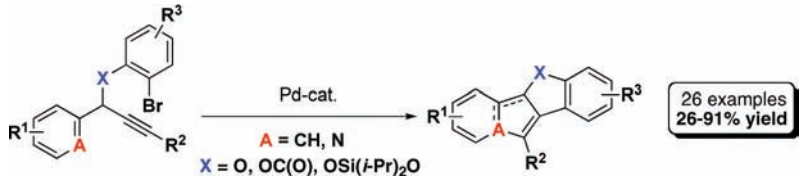
ABSTRACT



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 D[2] 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

(1) Fan, H.; Peng, J.; Hamann, M. T.; Hu, J.-F. *Chem. Rev.* **2008**, *108*, 264.

(2) Facompre, M.; Tardy, C.; Bal-Mahieu, C.; Colson, P.; Perez, C.; Manzanares, I.; Cuevas, C.; Bailly, C. *Cancer Res.* **2003**, *63*, 7392.

(3) (a) Bailly, C. *Curr. Med. Chem. Anti-Cancer Agents* **2004**, *4*, 363. (b) Pla, D.; Francesch, A.; Calvo, P.; Cuevas, C.; Aligue, R.; Albericio, F.; Alvarez, M. *Bioconjugate Chem.* **2009**, *20*, 1100.

(4) Marco, E.; Laine, W.; Tardy, C.; Lansiaux, A.; Iwao, M.; Ishibashi, F.; Bailly, C.; Gago, F. *J. Med. Chem.* **2005**, *48*, 3796.

(5) (a) Chittchang, M.; Batsomboon, P.; Ruchirawat, S.; Ploypradith, P. *ChemMedChem* **2009**, *4*, 457. (b) Pla, D.; Marchal, A.; Olsen, C. A.; Francesch, A.; Cuevas, C.; Albericio, F.; Alvarez, M. *J. Med. Chem.* **2006**, *49*, 3257.

(6) (a) Ballot, C.; Kluza, J.; Lancel, S.; Martoriati, A.; Hassoun, S. M.; Mortier, L.; Vienne, J. C.; Briand, G.; Formstecher, P.; Bailly, C.; Neviere, R.; Marchetti, P. *Apoptosis* **2010**, *15*, 769. (b) Ballot, C.; Kluza, J.; Martoriati, A.; Nyman, U.; Formstecher, P.; Joseph, B.; Bailly, C.; Marchetti, P. *Mol. Cancer Ther.* **2009**, *8*, 3307.

(7) See for example: (a) Ohta, T.; Fukuda, T.; Ishibashi, F.; Iwao, M. *J. Org. Chem.* **2009**, *74*, 8143. (c) Pla, D.; Marchal, A.; Olsen, C. A.; Albericio, F.; Alvarez, M. *J. Org. Chem.* **2005**, *70*, 8231.

(8) For recent synthetic approches toward novel hybrids, see: (a) Ploypradith, P.; Petchmanee, T.; Sahakitpichan, P.; Litvinas, N. D.; Ruchirawat, S. *J. Org. Chem.* **2006**, *71*, 9440. (b) Shen, L.; Yang, X.; Yang, B.; He, Q.; Hu, Y. *Eur. J. Med. Chem.* **2010**, *45*, 11.

(9) For silyl ether tether approach in Pd-catalyzed biaryl coupling, see: (a) Huang, C.; Gevorgyan, V. *Am. Chem. Soc.* **2009**, *131*, 10844. (b) Huang, C.; Gevorgyan, V. *Org. Lett.* **2010**, *12*, 2442.

(10) Chernyak, D.; Skontos, C.; Gevorgyan, V. *Org. Lett.* **2010**, *12*, 3242.

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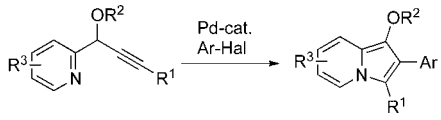
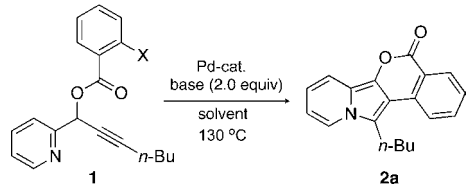
approach is limited to the synthesis of bicyclic and tricyclic heteroaromatic molecules only (eq 1). Herein, we report a novel Pd-catalyzed arylation cyclization cascade that allows for easy assembly of various tetra- and penta-cyclic isochromanone-annelated and other heterocycles.



(1)

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 idea was tested on cyclization of easily available propargyl-containing pyridine **1**[11] in the presence of $PdCl_2(PPh_3)_2$ catalyst. However, only trace amounts of desired product **2** were observed (Table 1, entries 1−3). Switching to $PdCl_2(MeCN)_2$ 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).

Table 1. Optimization of Reaction Conditions[a]

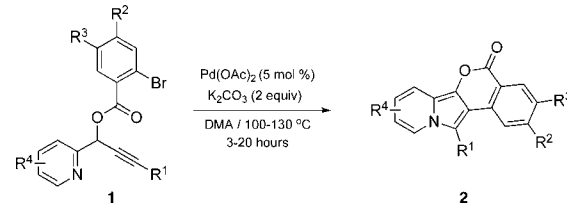


1 2a

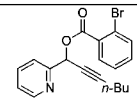
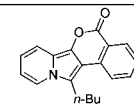
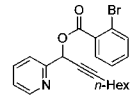
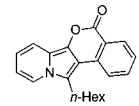
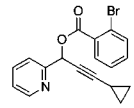
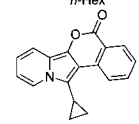
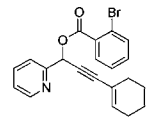
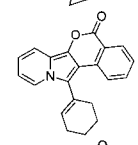
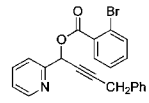
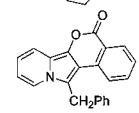
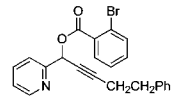
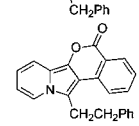
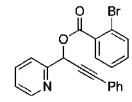
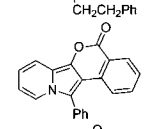
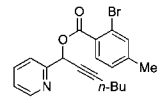
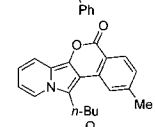
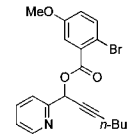
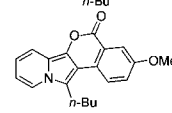
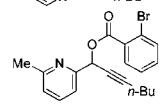
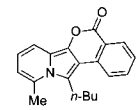
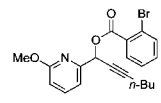
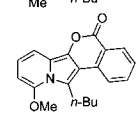
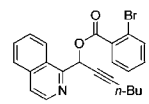
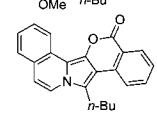
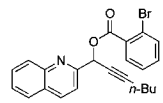
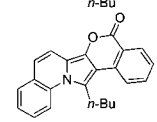
entry	X	Pd	base	solvent	yield, %[b]
1	Br	$PdCl_2(PPh_3)_2$	Cs_2CO_3	NMP	–
2	Br	$PdCl_2(PPh_3)_2$	K_3PO_4	NMP	–
3	Br	$PdCl_2(PPh_3)_2$	K_2CO_3	NMP	traces
4	Br	$PdCl_2(MeCN)_2$	Cs_2CO_3	NMP	–
5	Br	$PdCl_2(MeCN)_2$	K_3PO_4	NMP	–
6	Br	$PdCl_2(MeCN)_2$	K_2CO_3	NMP	traces
7	Br	$Pd(OAc)_2$	Cs_2CO_3	NMP	25
8	Br	$Pd(OAc)_2$	K_3PO_4	NMP	32
9	Br	$Pd(OAc)_2$	K_2CO_3	NMP	37
10	$Pd(OAc)_2$	K_2CO_3		DMF	72[c,d]
11[c]	Br	$Pd(OAc)_2$	K_2CO_3	NMP	68[c,d]
12	**Br**	**$Pd(OAc)_2$**	**K_2CO_3**	**DMA**	**80**[c,d]
13	I	$Pd(OAc)_2$	K_2CO_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.

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



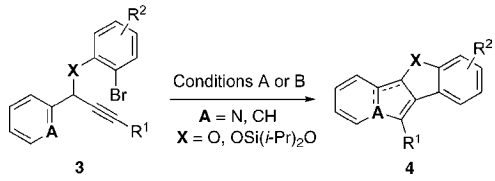
1 2

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

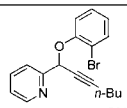
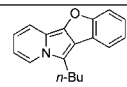
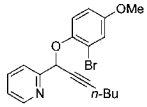
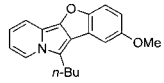
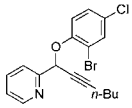
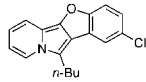
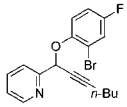
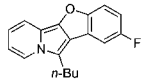
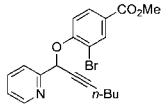
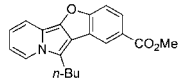
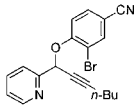
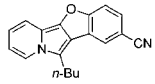
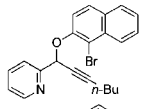
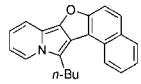
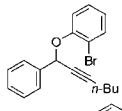
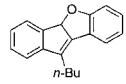
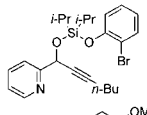
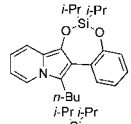
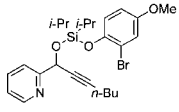
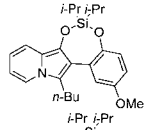
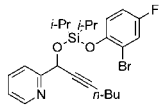
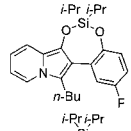
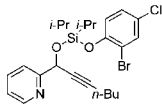
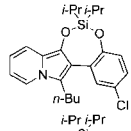
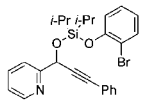
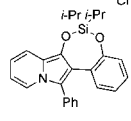
[a] All reactions were performed on 0.15 mmol scale in DMA (0.33 M) at 100 to 130 °C for time specified in the Supporting Information. [b] Yield of the isolated product after flash chromatography on silica gel.

(11) For transition-metal catalyzed cycloisomerization approaches toward N-fused pyrroloheterocycles, see: (a) Seregin, I. V.; Gevorgyan, V. *J. Am. Chem. Soc.* **2006**, *128*, 12050. (b) Seregin, I. V.; Schammel, A. W.; Gevorgyan, V. *Org. Lett.* **2007**, *9*, 3433. (c) Smith, C. R.; Bunnelle, E. M.; Rhodes, A. J.; Sarpong, R. *Org. Lett.* **2007**, *9*, 1169. (d) Hardin, A. R.; Sarpong, R. *Org. Lett.* **2007**, *9*, 4547. (e) Yan, B.; Zhou, Y.; Zhang, H.; Chen, J.; Liu, Y. *J. Org. Chem.* **2007**, *72*, 7783.

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



3 **4**

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 %), K_2CO_3 (2.0 equiv), *n*-Bu_4NCl (1.0 equiv), DMF, 120 °C. [d] Reaction conditions **B**: $Pd(OAc)_2$ (5 mol %), K_2CO_3 (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 conditions[13] (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.

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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.

OL102447S

(12) See Supporting Information for the detailed preparative procedures.
(13) Jeffery, T. *Tetrahedron Lett.* **1985**, *26*, 2667.
(14) (a) Kel'in, A. V.; Sromek, A. W.; Gevorgyan, V. *J. Am. Chem. Soc.* **2001**, *123*, 2074. (b) Schwier, T.; Sromek, A. W.; Yap, D. M. L.; Chernyak, D.; Gevorgyan, V. *J. Am. Chem. Soc.* **2007**, *129*, 9868. (c) Seregin, I. V.; Schammel, A. W.; Gevorgyan, V. *Tetrahedron* **2008**, *64*, 6876. For a catalyst-free approach toward indolizines, see: (d) Chernyak, D.; Gadamsetty, S. B.; Gevorgyan, V. *Org. Lett.* **2008**, *10*, 2307.