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Two-Component Approach Toward a Fully Substituted N-Fused Pyrrole Ring

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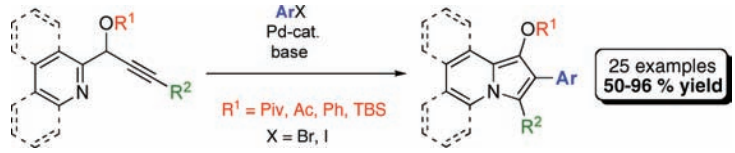
ABSTRACT



An efficient two-component palladium-catalyzed arylation/cyclization cascade approach toward a variety of N-fused pyrroloheterocycles has been developed. This transformation proceeds via the palladium-catalyzed coupling of aryl halides with propargylic esters or ethers followed by the 5-*endo-dig* cyclization leading to highly functionalized pyrroloheterocycles in good to excellent yield.

Nitrogen-containing heteroaromatic molecules and their analogues are pharmaceutically important scaffolds, broadly present in naturally occurring and synthetic biologically active molecules.[1] For example, molecules containing indolizine and other closely related cores exhibit a wide array of biological activities, including cytotoxicity,[2] multidrug resistance (MDR) reversal in some cancer cell lines,[3] and immunomodulation.[4]

In this regard, transformations that utilize readily available substrates to provide access to densely substituted pyrroloheterocycles are in high demand.[5] Previously, our group reported silver-catalyzed cycloisomerization of propargyl heterocycles as a route to 1,3-disubstituted N-fused heterocycles (Scheme 1, eq 1).[6] An alternative protocol is based on the gold-catalyzed migratory cycloisomerization of propargyl ethers into various types of 1,2-disubstituted N-fused heterocycles (eq 2).[7] Although these methods are general with respect to the heterocyclic core, these approaches are limited to the synthesis of 1,3- or 1,2-disubstituted indolizines, while either the C-2 or C-3 position remains unfunctionalized. This problem was recently mitigated by employing stoichiometric amounts of iodine,[5f−h] followed by cross-

Scheme 1. Approaches Toward Indolizines with Different Substitution Patterns

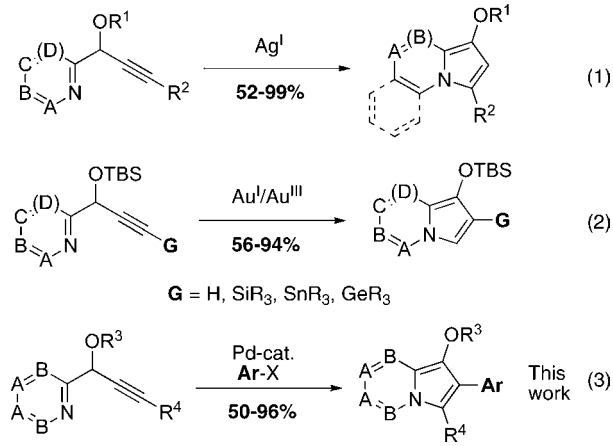


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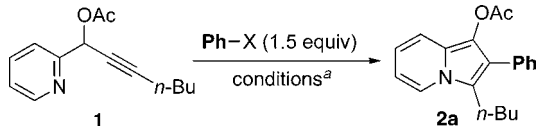
Table 1. Optimization of Cascade Approach



entry	X	Pd	base	solvent	additive	yield, %[b]
1	I	$PdCl_2(PPh_3)_2$	NEt_3	DMF	–	49
2	I	$PdCl_2(PPh_3)_2$	NEt_3	DMA	–	46
3	I	$PdCl_2(PPh_3)_2$	NEt_3	NMP	–	47
4	I	$PdCl_2(PPh_3)_2$	NEt_3	MeCN	–	34[c]
5	I	$PdCl_2(PPh_3)_2$	NEt_3	DMF	LiCl	54
6	I	$PdCl_2(PPh_3)_2$	NEt_3	DMF	TBAC	57
7	I	$PdCl_2(PPh_3)_2$	NEt_3	DMF	TBAB	60
8	I	$PdCl_2(PPh_3)_2$	NEt_3	DMF	TBAI	62
9	I	$PdCl_2(PPh_3)_2$	K_2CO_3	DMF	TBAI	69
10	**I**	**$PdCl_2(PPh_3)_2$**	**K_2CO_3**	**DMF**	**TBAI[d]**	**72**
11	Br	$PdCl_2(PPh_3)_2$	K_2CO_3	DMF	TBAI[d]	26

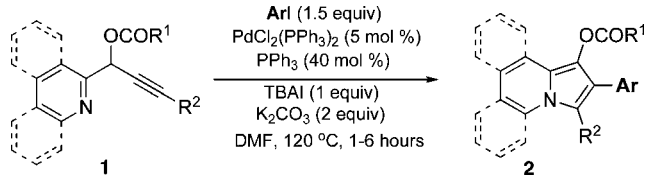
[a] Reactions were run in the precence of 5 mol % of catalyst in appropriate solvent (0.33 M) at 120 °C for 4 h. [b] GC/MS yields. [c] Reaction was performed at 90 °C. [d] Reaction was run with additional 40 mol % of PPh_3.

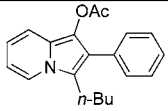
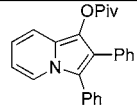
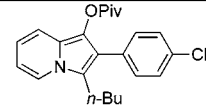
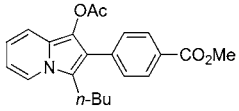
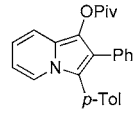
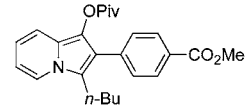
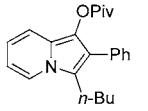
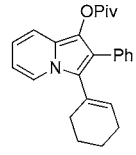
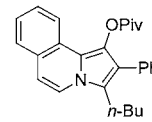
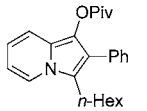
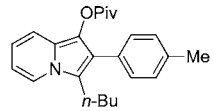
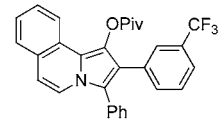
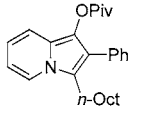
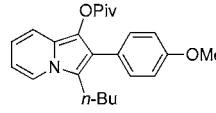
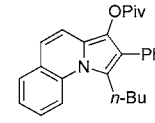
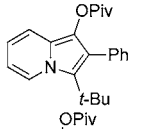
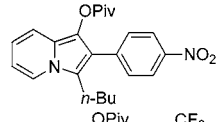
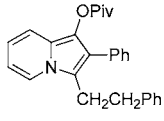
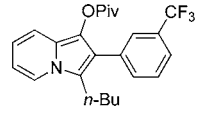
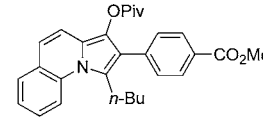
coupling steps. Herein, we report a Pd-catalyzed two-component arylation/cyclization cascade approach toward 1,2,3-trisubstituted N-fused heterocycles in good to excellent yields (eq 3).[8]

We hypothesized that Ar−Pd−X species would undergo carbopalladation of the propargylic moiety of **1** with subsequent 5-*endo-dig* cyclization to produce **2** (eq 3).

To test this idea, the easily accessible propargyl-containing pyridine **1**[9] was first subjected to the palladium-catalyzed arylation/cyclization reaction. Employing iodobenzene as the electrophilic component led to formation of the desired indolizine **2a** in 49% yield (Table 1, entry 1). Attempts to substitute DMF with other solvents were not particularly successful (entries 2−4). Utilizing different lithium and ammonium salts led to a significant improvement in the reaction yields (entries 5−8). Switching the base from NEt_3 to K_2CO_3 was also beneficial (entry 9).

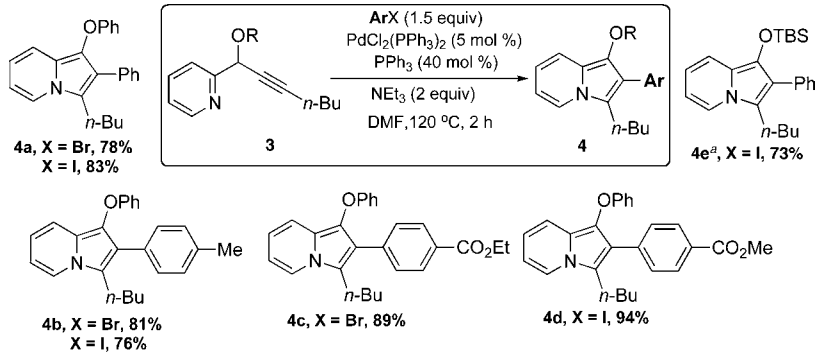
Table 2. Arylation/Cyclization Cascade Reactions of Propargylic Esters **1**[a]



entry	2		yield, %[b]	entry	2		yield, %[b]	entry	2		yield, %[b]
1		**2a**	72	8		**2h**	69	15		**2o**	93
2		**2b**	76	9		**2i**	68	16		**2p**	88
3		**2c**	94	10		**2j**	96	17		**2q**	71
4		**2d**	77	11		**2k**	87	18		**2r**	74
5		**2e**	94	12		**2l**	53	19		**2s**	78
6		**2f**	50	13		**2m**	70				
7		**2g**	94	14		**2n**	90	20		**2t**	88

[a] All reactions were performed on 0.5 mmol scale in DMF (0.33 M) at 120 °C. [b] Yield of the isolated product after flash chromatography on silica gel.

Scheme 2. Arylation/Cyclization Cascade Reactions of Propargylic Ethers **3**



[a] Reaction was performed under optimized conditions reported in Table 2.

Furthermore, using triphenylphosphine as an additive led to the formation of **2a** in 78% yield (entry 10). Employment of bromo-benzene under these conditions proved to be less efficient producing indolizine **2a** in 29% yield only (entry 11).

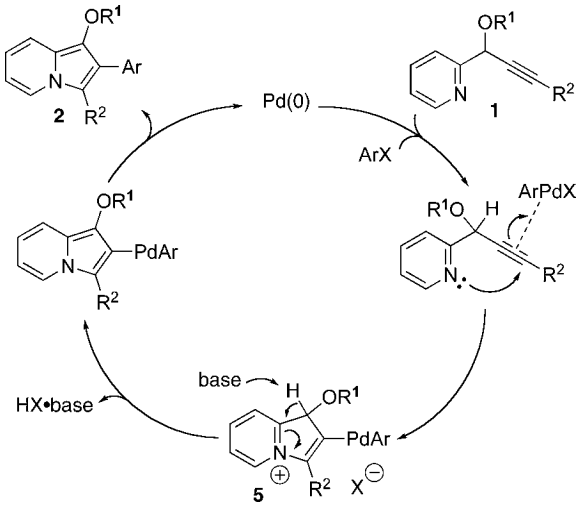
Next, under the optimized conditions, the scope of this cascade cyclization was examined (Table 2). Thus, acetyloxy and pivalyloxy-propargylic esters possessing alkyl (entries 1−7), aryl (entries 8 and 9), or alkenyl (entry 10) substituents at the triple bond underwent smooth conversion to give the corresponding heterocycles **2a**−**j** in good to excellent yields. To provide a handle for further functonalization, pivalates were chosen over acetates due to their greater potential to participate in Suzuki−Miyaura[10] and Kumada[5e] coupling reactions.

The generality of this process was expanded by utilization of a variety of functionalized iodobenzenes which uneventfully cyclized into the corresponding indolizines **2k**−**p** (entries 11−16). Notably, this reaction proceeded equally efficiently with other heterocyclic cores; quinoline and isoquinoline propargylic esters were successfully utilized in this transformation providing access to tricyclic cores **2q**−**t** in a highly efficient manner (entries 17−20).

It was also found that propargylic phenylethers **3** could be employed in this transformation (Scheme 2). Interestingly, bromobenzenes performed equally well in this process (**4a**−**c**). Similarly, the cascade cyclization of propargylic silylether **3** gave the corresponding indolizine **4e** in 73% yield.

Presumably, this palladium-catalyzed arylation/cyclization reaction proceeds through a coordination of the triple bond of an alkyne **1** with ArPdX, triggering the 5-*endo-dig* cyclization by the nucleophilic attack of the pyridyl nitrogen, leading to the formation of zwitterionic adduct **5** (Scheme 3). The latter, upon deprotonation/tautomerization and subsequent reductive elimination,[11] would give product **2**.

Scheme 3. Proposed Mechanism



In summary, we have developed a practical and efficient two-component coupling method toward fully substituted fused pyrroloheterocycles, including indolizines, pyrroloquinolines, and pyrroloisoquinolines. This method is comple-

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(7) Seregin, I. V.; Gevorgyan, V. *J. Am. Chem. Soc.* **2006**, *128*, 12050.

(8) When this manuscript was in preparation, a related report on synthesis of the indolizinone core appeared: Kim, I.; Kim, K. *Org. Lett.* **2010**, *12*, 2500.

(9) See Supporting Informationfor a detailed preparative procedure.

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mentary to the previously developed approaches[6,7,12] toward mono- and disubstituted N-fused pyrroloheterocycles.

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(12) Seregin, I. V.; Schammel, A. W.; Gevorgyan, V. *Tetrahedron* **2008**, *64*, 6876.

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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