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

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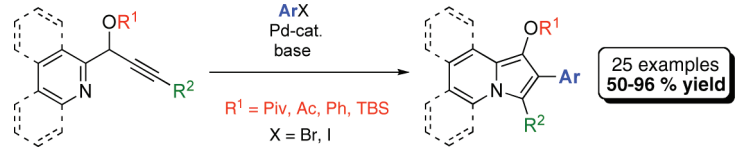
## ABSTRACT

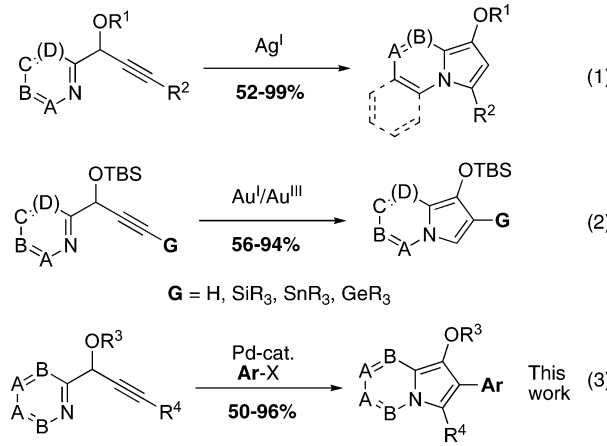



**An efficient two-component palladium-catalyzed arylation/cyclization cascade approach toward a variety of N-fused pyrroloheterocycles has been developed. This transformation proceeds via the palladium-catalyzed coupling of aryl halides with propargylic esters or ethers followed by the 5-*endo-dig*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




(1) (a) Bailly, C. *Curr. Med. Chem. Anti-Cancer Agents* **2004**, *4*, 363. (b) Fan, H.; Peng, J.; Hamann, M. T.; Hu, J.-F. *Chem. Rev.* **2008**, *108*, 264.

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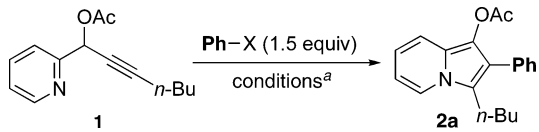
**Table 1.** Optimization of Cascade Approach




| 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 |

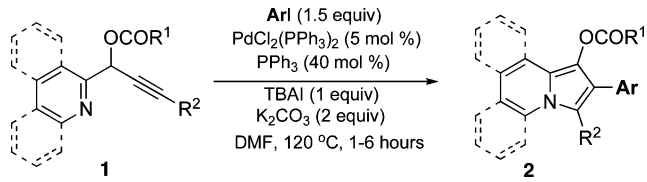
[a] Reactions were run in the precence of 5 mol % of catalyst in appropriate solvent (0.33 M) at 120 °C for 4 h. [b] GC/MS yields. [c] Reaction was performed at 90 °C. [d] Reaction was run with additional 40 mol % of $PPh_3$.

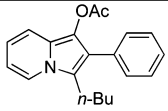
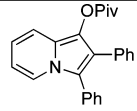
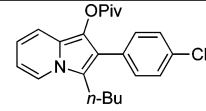
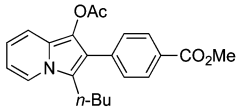
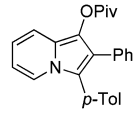
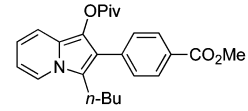
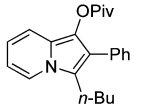
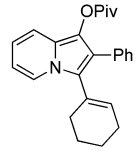
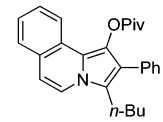
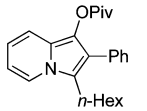
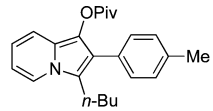
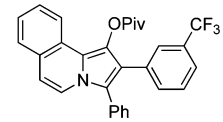
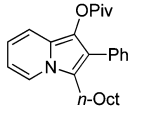
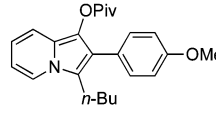
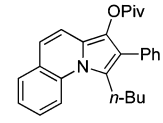
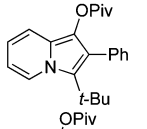
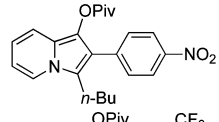
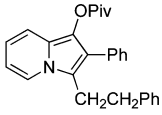
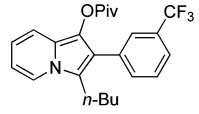
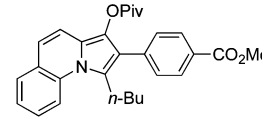
coupling steps. Herein, we report a Pd-catalyzed two-component arylation/cyclization cascade approach toward 1,2,3-trisubstituted N-fused heterocycles in good to excellent yields (eq 3).[8]

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).

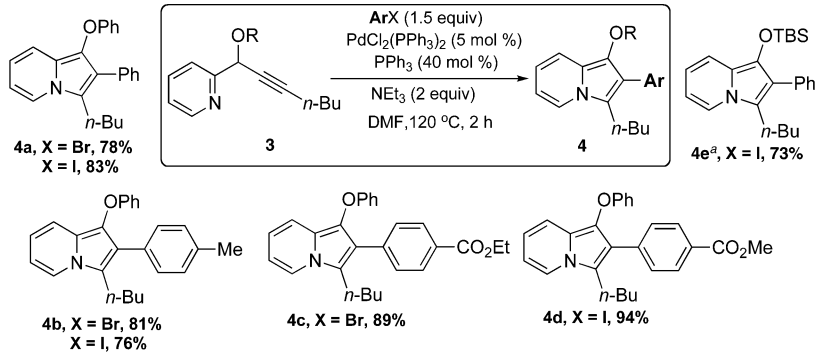
**Table 2.** Arylation/Cyclization Cascade Reactions of Propargylic Esters **1**[a]




| 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).

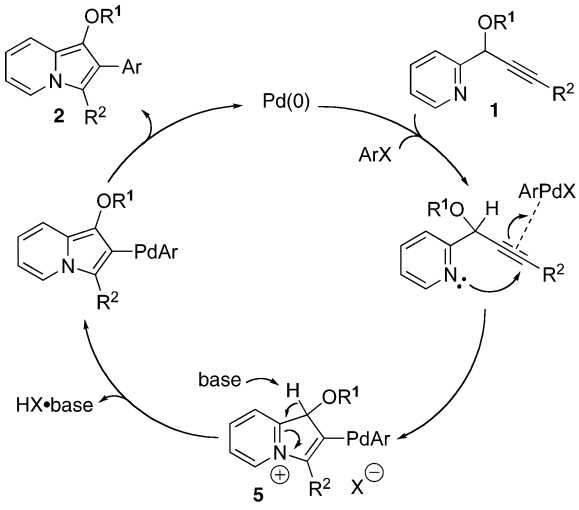
Next, under the optimized conditions, the scope of this cascade cyclization was examined (Table 2). Thus, acetyloxy and pivalyloxy-propargylic esters possessing alkyl (entries 1−7), aryl (entries 8 and 9), or alkenyl (entry 10) substituents at the triple bond underwent smooth conversion to give the corresponding 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-

(5) (a) Kel'in, A. V.; Sromek, A. W.; Gevorgyan, V. *J. Am. Chem. Soc.* **2001**, *123*, 2074. (b) Smith, C. R.; Bunnelle, E. M.; Rhodes, A. J.; Sarpong, R. *Org. Lett.* **2007**, *9*, 1169. (c) Hardin, A. R.; Sarpong, R. *Org. Lett.* **2007**, *9*, 4547. (d) Yan, B.; Zhou, Y.; Zhang, H.; Chen, J.; Liu, Y. *J. Org. Chem.* **2007**, *72*, 7783. (e) Schwier, T.; Sromek, A. W.; Yap, D. M. L.; Chernyak, D.; Gevorgyan, V. *J. Am. Chem. Soc.* **2007**, *129*, 9868. For a catalyst-free approach toward indolizines, see: (f) Chernyak, D.; Gadamsetty, S. B.; Gevorgyan, V. *Org. Lett.* **2008**, *10*, 2307. (g) Kim, I.; Choi, J.; Won, H. K.; Lee, G. H. *Tetrahedron Lett.* **2007**, *48*, 6863. (h) Kim, I.; Won, H. K.; Choi, J.; Lee, G. H. *Tetrahedron* **2007**, *63*, 12954. (i) Kim, I.; Kim, S. G.; Kim, J. Y.; Lee, G. H. *Tetrahedron Lett.* **2007**, *48*, 8976.

(6) Seregin, I. V.; Schammel, A. W.; Gevorgyan, V. *Org. Lett.* **2007**, *9*, 3433.

(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.

(10) Quasdorf, K. W.; Tian, X.; Garg, N. K. *J. Am. Chem. Soc.* **2008**, *130*, 14422.

(11) (a) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285. (b) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873. (c) Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644.

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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