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Expeditious Synthesis of Highly Substituted Indolizinones via a Palladium-Catalyzed Domino Sequence†

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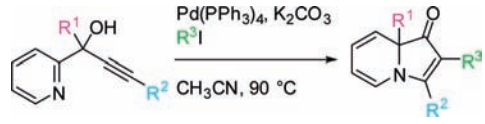
ABSTRACT

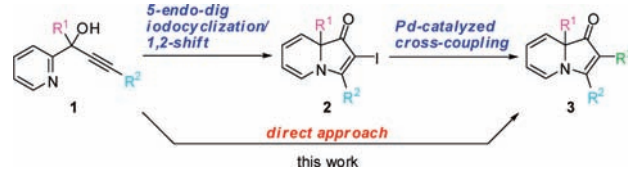


A direct one-pot approach to polysubstituted indolizinones from tertiary propargylic alcohols using a palladium-catalyzed domino process involving aminopalladation, reductive elimination, and 1,2-shift is described.

In recent years, alkyne activation by electrophilic reagents has represented a highly valuable means for many subsequent synthetic transformations such as cyclization.[1] For example, intramolecular attack of activated alkyne(s) by internal nucleophile(s) with a suitable length of tether allows access to a wide variety of carbo- and heterocycles. Among many alkynophilic reagents, palladium has been extensively employed as a reliable catalyst for a number of reactions involving alkynes.[2] In particular, exploitation of the organopalladium species formed before or after cyclization for further elaboration in a one-pot fashion renders a domino process possible.[3]

As part of our medicinal research program, we recently developed a facile combinatorial approach to an indolizinone[4] core-based library with three diversity points (Scheme 1).[5,6]

Scheme 1. One-Pot Approach to Polysubstituted Indolizinones



Although this procedure was easy to perform and provided good overall yields, we decided to pursue a more direct synthetic method of **3** from **1** without isolating **2**. As shown in Scheme 2, we reasoned that arylpalladium species formed in situ by oxidative addition of Pd(0) to R^3X could activate

† Dedicated to Professor George A. Kraus on the occasion of his 60th birthday.

(1) (a) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079. (b) Kirsch, S. F. *Synthesis* **2008**, 3183. (c) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266. (d) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351. (e) Lee, S. I.; Chatani, N. *Chem. Commun.* **2009**, 371. (f) Yamamoto, Y.; Gridnev, I. D.; Patil, N. T.; Jin, T. *Chem. Commun.* **2009**, 5075.

(2) (a) Negishi, E. *Handbook of Organopalladium Chemistry for Organic Synthesis*; Wiley and Sons: New York, 2002; Vols. 1 and *2*. (b) *Palladium Reagents and Catalysts: New Perspectives for the 21st Century*; Tsuji, J., Ed.; John Wiley & Sons, Ltd.: Chichester, 2004. (c) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285.

(3) Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644.

(4) Sarpong and Liu independently reported the synthesis of indolizinones with no substituent at C2 position by using Pt(II) and Cu(I) catalysts, respectively: (a) Smith, C. R.; Bunnelle, E. M.; Rhodes, A. J.; Sarpong, R. *Org. Lett.* **2007**, *9*, 1169. (b) Yan, B.; Zhou, Y.; Zhang, H.; Chen, J.; Liu, Y. *J. Org. Chem.* **2007**, *72*, 7783. For a catalyst-free approach to indolizinones, see: (c) Kim, I.; Choi, J.; Lee, S.; Lee, G. H. *Synlett* **2008**, 2334.

(5) Kim, K.; Kim, I. *J. Comb. Chem.* **2010**, published ASAP March 31, 2010. DOI: 10.1021/cc100015k.

(6) For our contribution in the area of fused azacycles, see also: (a) Kim, I.; Choi, J.; Won, H. K.; Lee, G. H. *Tetrahedron Lett.* **2007**, *48*, 6863. (b) Kim, I.; Won, H. K.; Choi, J.; Lee, G. H. *Tetrahedron* **2007**, *63*, 12954. (c) Kim, I.; Kim, S. G.; Kim, J. Y.; Lee, G. H. *Tetrahedron Lett.* **2007**, *48*, 8976. (d) Choi, J.; Lee, G. H.; Kim, I. *Synlett* **2008**, 1243.

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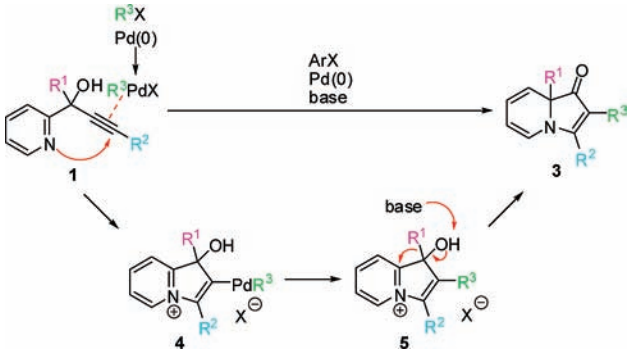
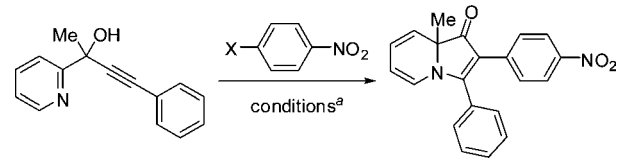
Scheme 2. Proposed Mechanism



the alkyne moiety, inducing 5-*endo-dig* cyclization by the neighboring pyridine group. The resulting indolizinium salt **4** would undergo reductive elimination to give **5**.[7,8] Finally, 1,2-migration[9] would occur to furnish the desired indolizinone **3**.

With this hypothesis in mind, we planned to explore the feasibility of this strategy.[10,11] Herein we report a facile and efficient approach to highly substituted indolizinones **3** using a Pd-catalyzed cascade reaction of tertiary propargylic alcohols **1**. To find the optimal conditions, we screened several reaction parameters with **1a** and 1-iodo-4-nitrobenzene as substrates. As shown in Table 1, K_2CO_3 was found to give the best result among the bases examined (entries 1−4). The desired product was obtained in excellent yield even with 5 mol % catalyst loading, although the yield was diminished with 1 mol % of Pd(0) (entries 5 and 6). While THF can be used as solvent, providing an excellent yield of **3a**, dioxane or DMF gave inferior results (entries 7−9). Other Pd(0) sources were tested to furnish the similar yield (entry 10). 1-Bromo-4-nitrobenzene, however, was not suitable for this transformation, leaving room for further optimization (entry 11). It should be mentioned that aryl halides were used as precursor for introduction of the functional group at the C2 position in this protocol, whereas our previous method utilized α,β-unsaturated esters, terminal acetylenes, or boronic acids,[5] which indicates both approaches are complementary.

Table 1. Reaction Optimization



1a **3a**

entry	X	Pd(0)	base	solvent	yield (%)[e]
1	I	$Pd(PPh_3)_4$	Et_3N	CH_3CN	69
2	I	$Pd(PPh_3)_4$	Na_2CO_3	CH_3CN	50
3	I	$Pd(PPh_3)_4$	K_2CO_3	CH_3CN	96
4	I	$Pd(PPh_3)_4$	Cs_2CO_3	CH_3CN	56
5	I	$Pd(PPh_3)_4$[b]	K_2CO_3	CH_3CN	99
6	I	$Pd(PPh_3)_4$[c]	K_2CO_3	CH_3CN	80
7	I	$Pd(PPh_3)_4$	K_2CO_3	dioxane	85
8	I	$Pd(PPh_3)_4$	K_2CO_3	THF	98
9	I	$Pd(PPh_3)_4$	K_2CO_3	DMF	52
10	I	$Pd_2(dba)_3 + PPh_3$[d]	K_2CO_3	CH_3CN	91
11	Br	$Pd(PPh_3)_4$	K_2CO_3	CH_3CN	trace

[a] A mixture of **1a** (0.13 mmol), aryl halide (1.5 equiv), Pd(0) (10 mol %), and base (2.5 equiv) in solvent (1 mL) was heated at 90 °C for 13 h unless otherwise noted. [b] 5 mol % $Pd(PPh_3)_4$ was used. [c] 1 mol % $Pd(PPh_3)_4$ was used. [d] 5 mol % $Pd_2(dba)_3$ and 10 mol % PPh_3 were used. [e] Isolated yield.

With optimized conditions in hand, we first examined the scope of aryl iodides with **1a** (Table 2). Excellent yields of the desired products were obtained with aryl iodides bearing electron-withdrawing groups, whereas the reactions with aryl iodides having electron-donating groups gave the corresponding products in modest yields (entries 5−7 and 10). Heterocycles were also incorporated successfully at the C2 position of indolizinones by using the corresponding iodides (entries 8 and 12).

To expand the generality of this process, we also reacted other tertiary propargylic alcohols bearing different substituents at R^1 and R^2 sites with several aryl iodides under identical reaction conditions (Table 3). To our delight, a diverse array of densely functionalized indolizinones was readily constructed in good to excellent yields. Due to the difference in reactivity under these conditions, reactions of **1b** and **1c** with 2-bromo-5-iodopyridine only produced 2-bromopyridine-containing indolizinones **3o** and **3t**, providing a functional handle for further coupling reactions (entries 2 and 7).

In conclusion, we have shown that polysubstituted indolizinones could be constructed from readily available tertiary propargylic alcohols in a one-pot manner employing a Pd-catalyzed domino procedure where aminopalladation and reductive elimination were successfully coupled with 1,2-rearrangement for the first time. Mild reaction conditions, ease of operation, high yields, and a wide

(7) For reviews, see: (a) Battistuzzi, G.; Cacchi, S.; Fabrizi, G. *Eur. J. Org. Chem.* **2002**, 2671. (b) Balme, G.; Bouyssi, D.; Lomberget, T.; Monteiro, N. *Synthesis* **2003**, 2115. (c) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873. (d) Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644.

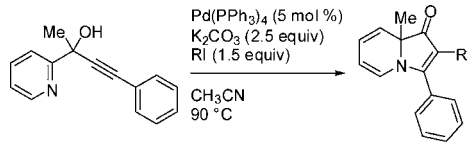
(8) (a) Tsuda, T.; Ohashi, Y.; Nagahama, N.; Sumiya, R.; Saegusa, T. *J. Org. Chem.* **1988**, *53*, 2650. (b) Arcadi, A.; Cacchi, S.; Del Rosario, M.; Fabrizi, G.; Marinelli, F. *J. Org. Chem.* **1996**, *61*, 9280. (c) Rossi, R.; Bellina, F.; Biagetti, M.; Mannina, L. *Tetrahedron Lett.* **1998**, *39*, 7599. (d) Jacobi, P. A.; Liu, H. *Org. Lett.* **1999**, *1*, 341. (e) Flynn, B. L.; Hamel, E.; Yung, M. K. *J. Med. Chem.* **2002**, *45*, 2670. (f) Dai, G.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 920. (g) Bossharth, E.; Desbordes, P.; Monteiro, N.; Balme, G. *Org. Lett.* **2003**, *5*, 2441. (h) Hu, Y.; Nawoschik, K. J.; Liao, Y.; Ma, J.; Fathi, R.; Yang, Z. *J. Org. Chem.* **2004**, *69*, 2235. (i) Cacchi, S.; Fabrizi, G.; Goggiamani, A. *Adv. Synth. Catal.* **2006**, *348*, 1301.

(9) (a) Paquette, L. A.; Lanter, J. C.; Johnston, J. N. *J. Org. Chem.* **1997**, *62*, 1702. (b) Paquette, L. A.; Kinney, M. J.; Dullweber, U. *J. Org. Chem.* **1997**, *62*, 1713. (c) Fenster, M. D. B.; Patrick, B. O.; Dake, G. R. *Org. Lett.* **2001**, *3*, 2109. (d) Overman, L. E.; Pennington, L. D. *J. Org. Chem.* **2003**, *68*, 7143. (e) Kirsch, S. F.; Binder, J. T.; Liébert, C.; Menz, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 5878.

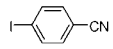
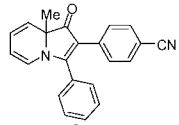
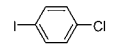
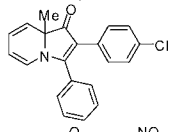
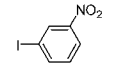
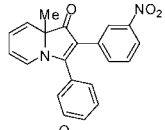
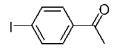
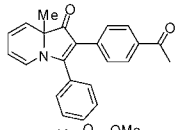
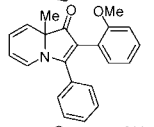
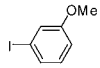
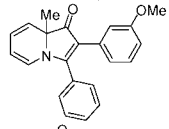
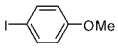
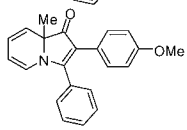
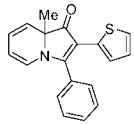
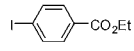
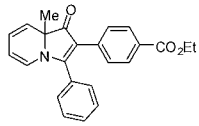
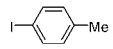
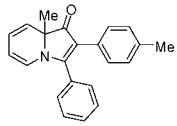
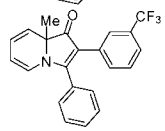
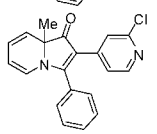
(10) To the best of our knowledge, strategic applications of this combination (aminopalladation, reductive elimination, and 1,2-migration) in a cascade manner have never been reported in the literature.

(11) Pd-catalyzed ring expansion of 1-(1-alkynyl)cycloalkanols is a related process. (a) Larock, R. C.; Reddy, C. K. *Org. Lett.* **2000**, *2*, 3325. (b) Larock, R. C.; Reddy, C. K. *J. Org. Chem.* **2002**, *67*, 2027. (c) Wei, L.-M.; Wei, L.-L.; Pan, W.-B.; Wu, M.-J. *Tetrahedron Lett.* **2003**, *44*, 595.

Table 2. Synthesis of Indolizinones from the Reaction of **1a** with Various (Hetero)aryl Iodides

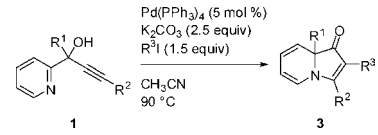


1a **3**

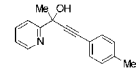
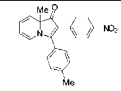
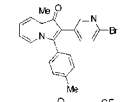
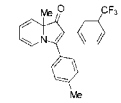
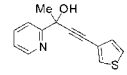
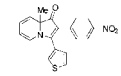
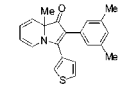
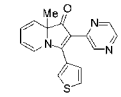
entry	RI	3	yield[a]
1		 **3b**	100
2		 **3c**	86
3		 **3d**	82
4		 **3e**	95
5		 **3f**	47
6		 **3g**	55
7		 **3h**	53
8		 **3i**	77
9		 **3j**	78
10		 **3k**	45
11		 **3l**	92
12		 **3m**	95

[a] Isolated yield (%).

Table 3. Synthesis of Indolizinones from the Reaction of Diverse Propargylic Alcohols with Various (Hetero)aryl Iodides



1 **3**

entry	1	R^3I	3	yield[a]
1	 **1b**		 **3n**	90
2	**1b**		 **3o**	77
3	**1b**		 **3p**	89
4	 **1c**		 **3q**	95
5	**1c**		 **3r**	63
6	**1c**		 **3s**	72
7	**1c**		**3t**	78
8	**1d**		**3u**	98
9	**1d**		**3v**	89
10	**1d**		**3w**	100
11	**1e**		**3x**	100
12	**1e**		**3y**	77
13	**1e**		**3z**	71
14	**1f**		**3aa**	81
15	**1f**		**3bb**	96
16	**1f**		**3cc**	85
17	**1g**		**3dd**	99
18	**1g**		**3ee**	100
19	**1g**		**3ff**	78

[a] Isolated yield (%).

functional-group tolerance are several merits of this highly efficient protocol. Given the importance of this scaffold as a pharmacophore, the chemistry described here should be useful for the rapid assembly of diverse indolizinone derivatives. Further investigation to extend the scope of this reaction as well as biological evaluation of these compounds is currently underway and will be reported in the near future.

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Supporting Information Available: Experimental procedure, characterization data, and copies of ^{1}H and ^{13}C NMR spectra of **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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