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Formal Synthesis of Nitidine and NK109 via Palladium-Catalyzed Domino Direct Arylation/*N*-Arylation of Aryl Triflates

Mathieu Blanchot, David A. Candito, Florent Larnaud, and Mark Lautens*

Davenport Research Laboratories, Department of Chemistry, University of Toronto, Toronto, Ontario, Canada, M5S 3H6

mlautens@chem.utoronto.ca

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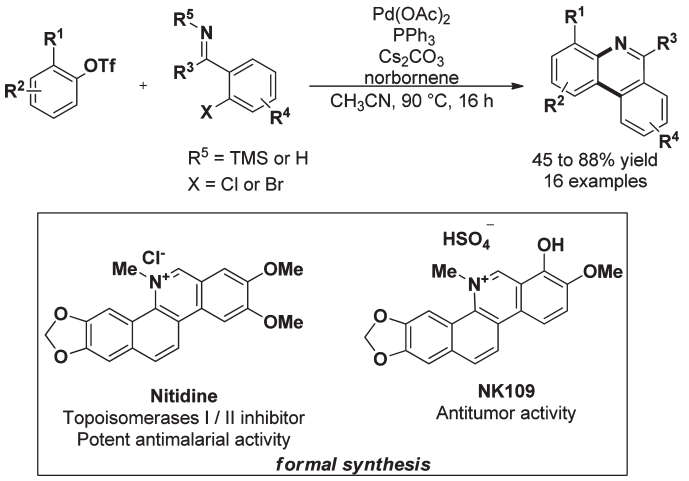
ABSTRACT



The use of aryl triflates as reaction partners in a palladium-catalyzed domino direct arylation/*N*-arylation provides a great advantage due to the availability of starting materials. Furthermore, it allows expedient access to biologically interesting benzo[*c*]phenanthridine alkaloids.

The phenanthridine core is an important substructure that is often found in natural products, particularly, the benzo[*c*]phenanthridine alkaloids. Members of this family have demonstrated antitumor, antimicrobial, and antiviral properties (Figure 1).[1]

The synthesis of these compounds is not trivial, and many studies have been directed toward their preparation and the synthesis of derivatives. Traditional syntheses often suffer from long synthetic pathways or are limited because of their lack of generality and functional group tolerance.[2] Other alternatives using palladium-catalyzed approaches have shown increasing popularity in recent

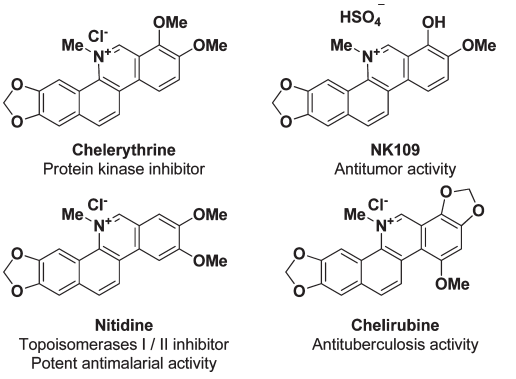


Figure 1. Biologically relevant benzo[*c*]phenanthridinium alkaloids.

(1) (a) Makhey, D.; Gatto, B.; Yu, C.; Liu, L.; Liu, F.; LaVoie, E. J. *Bioorg. Med. Chem.* **1996**, *4*, 781. (b) Lynch, M. A.; Duval, O.; Sukhanova, A.; Devy, J.; MacKay, S. P.; Waigh, R. D.; Nabiev, I. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2643. (c) Fang, S. D.; Wang, L. K.; Hecht, S. M. *J. Org. Chem.* **1993**, *58*, 5025. (d) Janin, Y. L.; Croisy, A.; Riou, J. F.; Bisagni, E. *J. Med. Chem.* **1993**, *36*, 3686.

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years since they offer the advantages of relatively mild reaction conditions and high functional group tolerance.[3] Methods employing direct arylation allow the use of simplified starting materials and offer a more atom economical approach relative to traditional metal-catalyzed cross-coupling reactions.[4]

Our group and that of Catellani have been engaged in studying a reaction manifold involving a sequence of domino *ortho*-functionalization followed by terminal cross-coupling processes for the synthesis of diversely substituted aromatic compounds.[5] Recently, we disclosed the first example of palladium-catalyzed synthesis of phenanthridine derivatives employing *N*-unsubstituted or *N*-silylimines and aryl iodides as coupling partners. Using this method, a number of diversely substituted phenanthridine derivatives were synthesized in good to excellent yields.[6]

We sought to validate the utility of our method by applying it to the synthesis of members of the benzo[*c*]phenanthridine alkaloid family of natural products. However, the synthesis of the requisite aryl iodide reaction partners proved to be inefficient. We recognized that the use of readily available aryl triflates could provide a potential solution to this problem. Significantly, aryl triflates were found to be unsuitable reaction partners in previous studies involving norbornene mediated C−H functionalization. Herein we report that aryl triflates can be utilized instead of aryl halides for the rapid construction of diversely substituted phenanthridines and outline the formal synthesis of the natural product Nitidine and NK109.

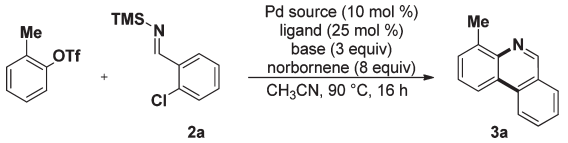
As a starting point we chose to study the reaction shown in Table 1. Combinations of several palladium precursors with phosphine ligands in acetonitrile at 90 °C gave low conversion (entries 1−4). Cleavage of the triflate to the phenol competed with the main reaction; organic bases such as DABCO or DMAP were found to eliminate this side reaction, but conversions were low (entries 5 and 6). Reducing the amount of cesium carbonate and increasing the amount of the imine employed proved to be effective at increasing the yield (entry 7). With these conditions product **3a** could be obtained in 85% yield.

We next tested the generality of this protocol by applying it to the synthesis of diversely substituted phenanthridines and benzo[*c*]phenanthridines. A wide range of aryl triflates, easily generated from the corresponding commercially available phenols, could be successfully employed (Table 2).

Aryl triflates bearing chloro, methoxy, and alkyl substituents reacted smoothly with the *N*-silylaldimine **2a** (entries 1−4) to form the corresponding phenanthridine. The only apparent requirement is that aryl triflate must be *ortho*-substituted. On the other hand, a range of imines, including *N*-silylaldimines, and unsubstituted ketimines reacted in good to moderate yields (entries 5−13).

Finally, based on the promising results of this investigation, we decided to test its applicability to the synthesis of more complicated structures (Scheme 1). Triflate **1a** was easily prepared in three steps from commercially available dibromide **4**. Slow addition of *n*-BuLi to dibromide **4** at −78 °C generated an aryne intermediate, which underwent

Table 1. Optimization[a]



	Pd source	ligand	base	yield (%)[b]
1	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	48
2	$PdCl_2$	PPh_3	Cs_2CO_3	14
3	$Pd(OAc)_2$	TFP	Cs_2CO_3	≤5
4	$Pd(OAc)_2$	P(*t*-Bu)3	Cs_2CO_3	0
5	$Pd(OAc)_2$	PPh_3	DMAP	0
6	$Pd(OAc)_2$	PPh_3	DABCO	11
7	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	85[c]

[a] Reaction conditions: aryl triflate (0.2 mmol, 1.0 equiv), imine (1.1 equiv), Pd source (10 mol %), Ligand (25 mol %), Base (3 equiv), and norbornene (8.0 equiv) in MeCN (0.05 M) were heated in a sealed tube at 90 °C for 16 h. [b] NMR yield using mesitylene as an internal standard. [c] Imine (2.0 equiv), Cs_2CO_3 (1.5 equiv).

(2) Recent synthetic studies aimed at benzo[*c*]phenanthridines, see: (a) Korivi, R. P.; Cheng, C.-H. *Chem.—Eur. J.* **2010**, *16*, 282. (b) Abe, H.; Kobayashi, N.; Takeuchi, Y.; Harayama, T. *Heterocycles* **2010**, *80*, 873. (c) Kohno, K.; Azuma, S.; Choshi, T.; Nobuhiro, J.; Hibino, S. *Tetrahedron Lett.* **2009**, *50*, 590. (d) Ramani, P.; Fontana, G. *Tetrahedron Lett.* **2008**, *49*, 5262. (e) Sanz, R.; Fernandez, Y.; Castroviejo, M. P.; Perez, A.; Fananas, F. J. *Eur. J. Org. Chem.* **2007**, 62. (f) Luo, Y.; Mei, Y.; Zhang, J.; Lu, W.; Tang, J. *Tetrahedron* **2006**, *62*, 9131. (g) Le, T. N.; Gang, S. G.; Cho, W.-J. *J. Org. Chem.* **2004**, *69*, 2768. (h) Harayama, T.; Sato, T.; Nakano, Y.; Abe, H.; Takeuchi, Y. *Heterocycles* **2003**, *59*, 293. (i) Watanabe, T.; Ohashi, Y.; Yoshino, R.; Komano, N.; Eguchi, M.; Sakiko, M.; Ishikawa, T. *Org. Biomol. Chem.* **2003**, *1*, 3024. (j) Harayama, T.; Akiyama, T.; Akamatsu, H.; Kawano, K.; Abe, H.; Takeuchi, Y. *Synthesis* **2001**, 444. (k) Nakanishi, T.; Suzuki, M. *Org. Lett.* **1999**, *1*, 985. (l) Geen, G. R.; Mann, I. S.; Mullane, M. V.; McKillop, A. *Tetrahedron* **1998**, *54*, 9875. (m) Sotomayor, N.; Dominguez, E.; Lete, E. *J. Org. Chem.* **1996**, *61*, 4062. (n) Seraphin, D.; Lynch, M. A.; Duval, O. *Tetrahedron Lett.* **1995**, *36*, 5731. (o) Maestri, G.; Larraufie, M.-H.; Derat, E.; Ollivier, Fensterbank, L.; Lacôte, E.; Malacria, M. *Org. Lett.* **2010**, *12*, 5692.

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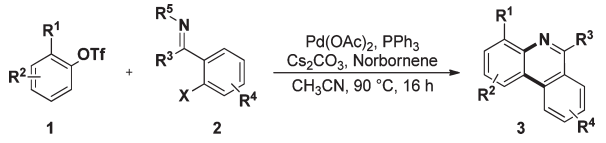
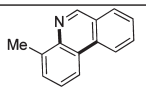
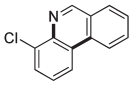
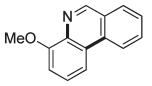
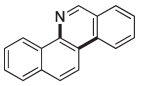
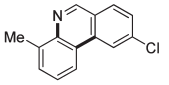
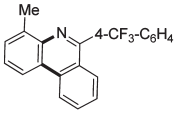
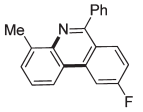
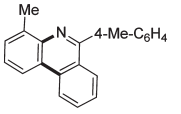
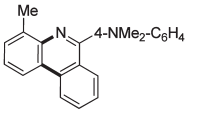
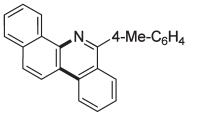
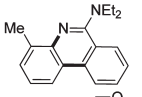
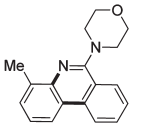
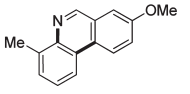
(5) Reviews: (a) Tietze, L. F.; Brasche, G. ; Gericke, K. M. *Domino Reaction in Organic Synthesis*; Wiley-VCH: Weinheim, 2006. (b) Chiusoli, G. P.; Catellani, M.; Costa, M.; Motti, E.; Della Ca', N.; Maestri, G. *Coord. Chem. Rev.* **2010**, *254*, 456. (c) Lautens, M.; Alberico, D.; Bressy, C.; Fang, Y.-Q.; Mariampillai, B.; Wilhelm, T. *Pure Appl. Chem.* **2006**, *78*, 351.

(6) Candito, D. A.; Lautens, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 6713.

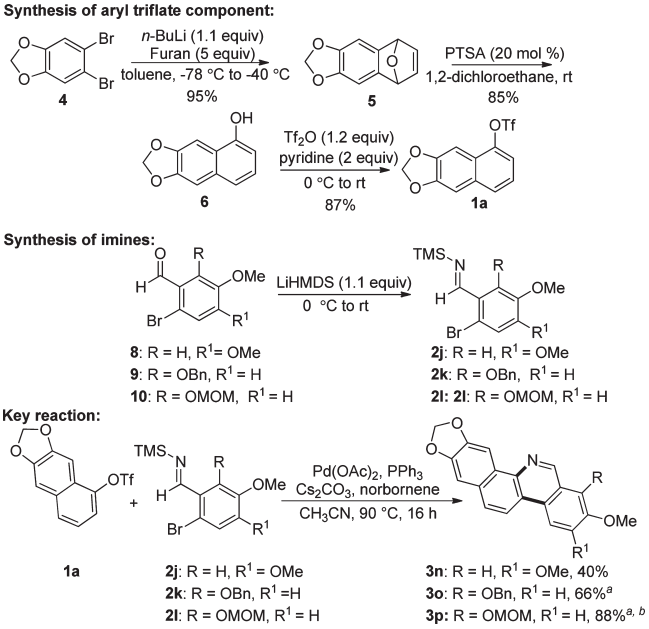
Table 2. Substrate Scope of the Palladium-Catalyzed Domino Direct Arylation/*N*-Arylation[a]



	imine			product		yield (%)[b]
	X	R^5				
1	Cl	TMS	**2a**		**3a**	85
2	Cl	TMS	**2a**		**3b**	51
3	Cl	TMS	**2a**		**3c**	45
4	Cl	TMS	**2a**		**3d**	62
5	Cl	TMS	**2b**		**3e**	51
6	Cl	H	**2c**		**3f**	85
7	Cl	H	**2d**		**3g**	57
8	Cl	H	**2e**		**3h**	85
9	Cl	H	**2f**		**3i**	38
10	Cl	H	**2e**		**3j**	75
11	Cl	H	**2g**		**3k**	75
12	Cl	H	**2h**		**3l**	73
13	Br	TMS	**2i**		**3m**	69

[a] Reaction conditions: Aryl triflate (0.2 mmol, 1.0 equiv), imine (2 equiv), $Pd(OAc)_2$ (10 mol %), PPh_3 (25 mol %), Cs_2CO_3 (1.5 equiv), and norbornene (8.0 equiv) in MeCN (0.05 M) were heated in a sealed tube at 90 °C for 16 h. [b] Isolated.

Scheme 1. Formal Synthesis Nitidine and NK109



[a] $Pd(OAc)_2$ (20 mol %), PPh_3 (50 mol %), and Cs_2CO_3 (3 equiv) were used. [b] Aryl triflate (5.3 mmol, 1.0 equiv).

a Diels–Alder reaction with furan to furnish the oxabicycle **5** in 95% yield. Treatment of **5** with catalytic PTSA (4-methylbenzenesulfonic acid) led to the naphthol **6** which could be readily converted to triflate **1a** using triflic anhydride and pyridine. The imines were easily prepared by treatment of the corresponding aldehydes with LiHMDS. Aldehyde **8** is commercially available, and aldehyde **9** and **10** can be prepared in four straightforward steps from *o*-vanillin. Purification of the imines proved to be difficult, and thus the crude imines were used directly for the reaction. **1a** could be reacted with imines **2j–l** under our developed conditions to afford products **3n–p** in 40%, 66%, and 88% yield, respectively. Significantly, the synthesis of **3p** was performed on a gram scale. The outlined route constitutes a formal syntheses of Nitidine[7] and NK109,[8] respectively.

It is anticipated that this process follows a similar catalytic cycle to that of other norbornene mediated C–H functionalizations (Scheme 2).[9] Oxidative addition of the aryl triflate, carbopalladation of norbornene, and electrophilic metalation followed by deprotonation can yield palladacyclic intermediate **I**. Then the palladacycle

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(8) Nakanishi, T.; Suzuki, M.; Mashiba, A.; Ishikawa, K.; Yokotsuka, T. *J. Org. Chem.* **1998**, *63*, 4235.
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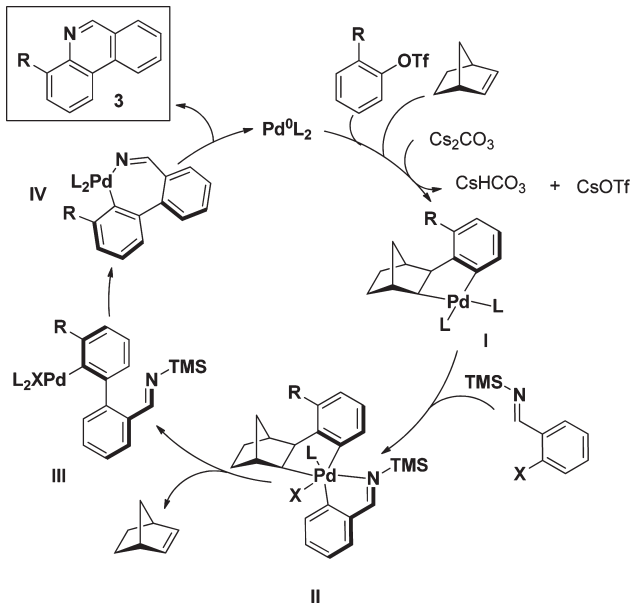
Scheme 2. Proposed Mechanism



can go on to react with the imine to yield Pd(IV) intermediate **II**. Chemoselective reductive elimination followed by decarbopalladation can yield intermediate **III**. This intermediate can then produce intermediate **IV** which reductively eliminates to yield the desired phenanthridines, **3**.

In conclusion, this new protocol for the palladium-catalyzed domino direct arylation/*N*-arylation using aryl triflates represents a powerful strategy for heterocycle synthesis. The ability to use aryl triflates has overcome previous limitations and made this reaction more practical. A concise synthesis of Nitidine and NK109 has been demonstrated, opening new opportunities for biological studies of this substrate class.

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