Note

Palladium-Catalyzed Nucleophilic Substitution/C-H Activation/Aromatization Cascade Reaction: One Approach to Construct 6-Unsubstituted Phenanthridines

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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.5b02145 • Publication Date (Web): 29 Oct 2015

Palladium-Catalyzed Nucleophilic Substitution/C-H Activation/Aromatization Cascade Reaction: One Approach to Construct 6-Unsubstituted Phenanthridines

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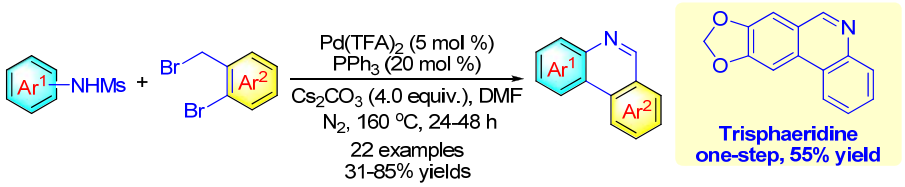


ABSTRACT:

A facile and practical palladium-catalyzed nucleophilic substitution/C-H activation/aromatization cascade reaction has been developed. A range of 6-unsubstituted phenanthridines could be obtained in moderate to good yields (31–85%) with readily prepared *N*-Ms arylamines and commercially available 2-bromobenzyl bromide derivatives as starting materials. The potential application of the protocol was also demonstrated by the expeditious synthesis of the natural alkaloid trisphaeridine.

The development of efficient methods to construct polycyclic aromatic hydrocarbons (PAHs) has been attracting considerable interest due to the potential applications of this kind of

compounds in organic materials[1] and medicinal chemistry.[2] In particular, phenanthridine has emerged as an attractive synthetic motif since it is not only frequently found in natural products (Figure 1) but also compounds incorporating such a motif possess several types of bioactivities such as antimalarial, cytotoxicity, antimycobacterial, and anticancer et al.[3,4] Thus, numerous methodologies for the construction of phenanthridine scaffold have been established.[5,6] And therein, relatively few methods for the preparation of 6-unsubstituted phenanthridines were reported. On the basis of an inspection into the literature data, it was found that the common strategies for the generation of 6-unsubstituted phenanthridines include the photochemical method,[7] oxidation of 5,6-dihydrophenanthridine,[8] microwave-assisted cyclization,[9] intramolecular condensation,[10] intramolecular biaryl-coupling,[11] and hydride-induced anionic cyclization.[12] Some selected approaches to 6-unsubstituted phenanthridines were summarized in Scheme 1. However, most of the approaches are mainly limited to the use of complex starting materials, such as *ortho*-functionalized biaryls. Accordingly, the development of facile and practical methods with easily accessible precursors for the construction of 6-unsubstituted phenanthridine compounds is still desirable and valuable.

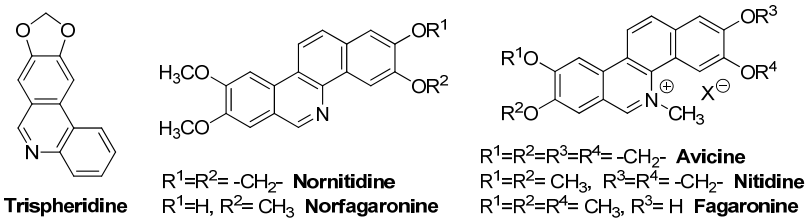
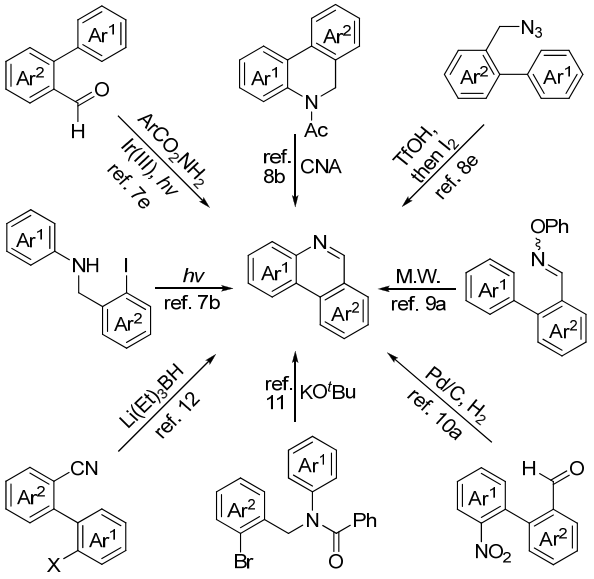


Figure 1. Biologically active phenanthridines.

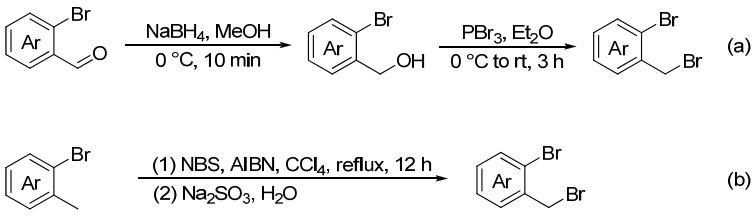
In recent years, transition-metal-catalyzed reactions have been well developed and used as a powerful method for the construction of complex structural moleculars.[13] Among them,

palladium-catalyzed cascade reactions involving C-H activation, which provide a straightforward and atom-economic approach to fused heterocyclic compounds, have also received increasing attention.[14,15] However, it should be noted that the synthetic methodology to access 6-unsubstituted phenanthridines through palladium-catalyzed cascade reaction is rare,[8c,16] especially starting from readily accessible substrates.

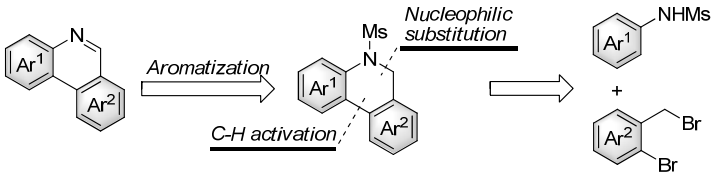
Scheme 1. Synthesis of 6-Unsubstituted Phenanthridines



Scheme 2. Synthesis of 2-Bromobenzyl Bromide Derivatives



Scheme 3. The Strategy of Our Proposed Methodology

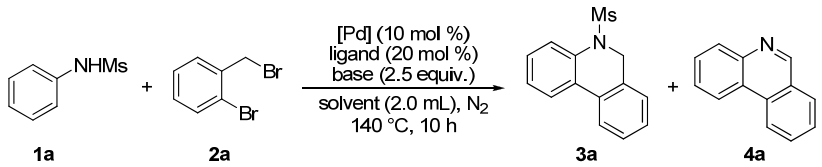


N-Ms arylamines[17] and 2-bromobenzyl bromide derivatives,[18] two kinds of readily accessible precursors, have been broadly applied in organic synthesis, respectively. Generally, there were two common methods for the synthesis of 2-bromobenzyl bromide derivatives: i) reduction of *ortho*-bromoarylaldehydes followed by substitution using tribromophosphine gave 2-bromobenzyl bromide derivatives [Scheme 2, Eq. (a)], and ii) substitution of *ortho*-bromomethylarenes with *N*-bromosuccinimide using azobisisobutyronitrile as radical initiator gave 2-bromobenzyl bromide derivatives [Scheme 2, Eq. (b)].[19] Therefore, promoted by the importance of this phenanthridine motif, and as our ongoing interest in the development of a facile and practical methodologies, we report herein an unconventional strategy for the construction of 6-unsubstituted phenanthridines from easily accessible precursors. Notably, this method is characterized by its easy accessibility of the starting materials, as well as the high efficacy which is inherent to a palladium-catalyzed cascade reaction sequence, involving the nucleophilic substitution/C-H activation/aromatization (Scheme 3).

The investigation began with the optimization of several reaction conditions for the synthesis of 5-(methylsulfonyl)-5,6-dihydrophenanthridine (**3a**) using *N*-phenylmethanesulfonamide (**1a**) and 1-bromo-2-(bromomethyl)benzene (**2a**) as model substrates (Table 1). After an initial screen of palladium catalysts in the presence of PPh_3 using Cs_2CO_3 as base in DMF at 140 °C for 10 h (Table 1, entries 1–4), the annulated product **3a** could be obtained in 66% yield by using $Pd(TFA)_2$ as a catalyst (Table 1, entry 4). Several other ligands were also screened (Table 1, entries 5–7), it revealed that DPPB, BINAP, and Xantphos were inferior to PPh_3 for the reaction

(Table 1, entry 4). Using other inorganic bases led to no improvement in the reaction performance (Table 1, entries 8–11). A survey of solvents revealed that DMF was the best solvent (Table 1, entry 4 vs entries 12–14). Furthermore, we investigated the effect of the loading of $Pd(TFA)_2$ and PPh_3 (Table 1, entries 15–16), and 5 mol % of $Pd(TFA)_2$ and 20 mol % of PPh_3 were proven to be a good choice for the cascade process (Table 1, entry 16 vs entries 4 and 15). To our delight, the fused heterocyclic compound **4a** was obtained in 16% yield performing at 160 °C, suggesting that the aromatization process would readily proceed in high temperature (Table 1, entry 17). Surprisingly, extending the reaction time from 10 to 24 h led to **4a** in an improved yield (40%) (Table 1, entry 18). Afterward, increasing the equivalent of Cs_2CO_3 from 2.5 to 4.0, substrates **1a** and **2a** were completely converted into **4a** in 80% yield (Table 1, entry 19).

Table 1. Optimization of Reaction Conditions[a]



1a **2a** **3a** **4a**

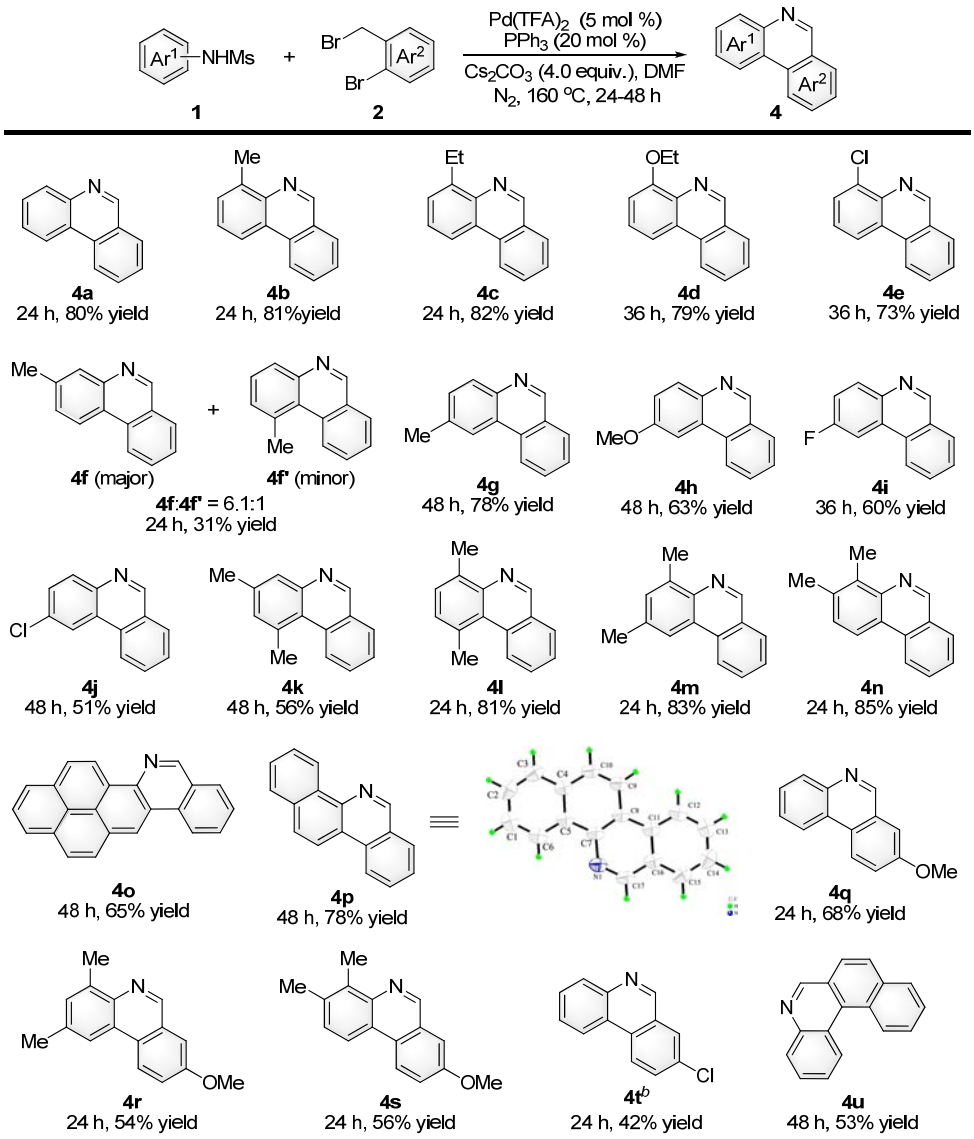
entry	[Pd]/ligand	base	solvent	yield (%)[b]	
				3a	**4a**
1	$Pd(PPh_3)_4/PPh_3$	Cs_2CO_3	DMF	16	<5
2	$Pd_2(dba)_3/PPh_3$	Cs_2CO_3	DMF	34	<5
3	$Pd(OAc)_2/PPh_3$	Cs_2CO_3	DMF	35	<5
4	$Pd(TFA)_2/PPh_3$	Cs_2CO_3	DMF	66	<5
5	$Pd(TFA)_2$/DPPB	Cs_2CO_3	DMF	36	<5
6	$Pd(TFA)_2$/BINAP	Cs_2CO_3	DMF	18	<5
7	$Pd(TFA)_2$/Xantphos	Cs_2CO_3	DMF	13	<5
8	$Pd(TFA)_2/PPh_3$	K_2CO_3	DMF	48	<5
9	$Pd(TFA)_2/PPh_3$	Na_2CO_3	DMF	10	0
10	$Pd(TFA)_2/PPh_3$	K_3PO_4	DMF	50	<5

11	$Pd(TFA)_2/PPh_3$	NaOPiv	DMF	11	0
12	$Pd(TFA)_2/PPh_3$	Cs_2CO_3	DMSO	15	<5
13	$Pd(TFA)_2/PPh_3$	Cs_2CO_3	mesitylene	39	<5
14	$Pd(TFA)_2/PPh_3$	Cs_2CO_3	*t*-Amylol	41	<5
15[c]	$Pd(TFA)_2/PPh_3$	Cs_2CO_3	DMF	26	<5
16[d]	$Pd(TFA)_2/PPh_3$	Cs_2CO_3	DMF	65	<5
17[de]	$Pd(TFA)_2/PPh_3$	Cs_2CO_3	DMF	69	16
18[def]	$Pd(TFA)_2/PPh_3$	Cs_2CO_3	DMF	44	40
19[defg]	$Pd(TFA)_2/PPh_3$	Cs_2CO_3	DMF	0	80

[a] Unless otherwise noted, all reactions were carried out with **1a** (0.3 mmol), **2a** (0.3 mmol) and base (2.5 equiv.) in 2.0 mL of solvent with 10 mol % Pd-catalyst and 20 mol % ligand under N_2 atmosphere at 140 °C for 10 h. [b] Isolated yield. [c] 5 mol % $Pd(TFA)_2$ and 10 mol % PPh_3 were used. [d] 5 mol % $Pd(TFA)_2$ and 20 mol % PPh_3 were used. [e] The reaction was performed at 160 °C. [f] The reaction was performed for 24 h. [g] 4.0 equiv. Cs_2CO_3 was used.

With the optimal reaction conditions in hand (Table 1, entry 19), the generality of this palladium-catalyzed cascade reaction was subsequently investigated. As shown in Scheme 4, all substrates could be smoothly transformed into the corresponding 6-unsubstituted phenanthridines in moderate to good yields. Whether substituent group is an electron–donating or –withdrawing at the *ortho* position on the *N*-Ms arylamines, the reactions proceeded smoothly and gave the corresponding products **4b**-**4e** in good yields (73–82%). However, *meta*-substituted *N*-Ms arylamine, such as *N*-*meta*-tolylmethanesulfonamide, gave two unseparated isomers in a 6.1:1 ratio and 31% overall yield (**4f**/**4f'**). For the *para* position, *N*-Ms arylamines bearing the electron-rich substitutes provided good yields (**4g** and **4h**), whereas the electron-deficient groups led to a slightly lower yields (**4i** and **4j**). Moreover, this cascade process can be extended to disubstituted *N*-Ms arylamines at different positions on the phenyl ring, giving the corresponding compounds in 56–85% yields (**4k**–**4n**). To our delight, the method was compatible with polycyclic

Scheme 4. Substrate Scope.[a]

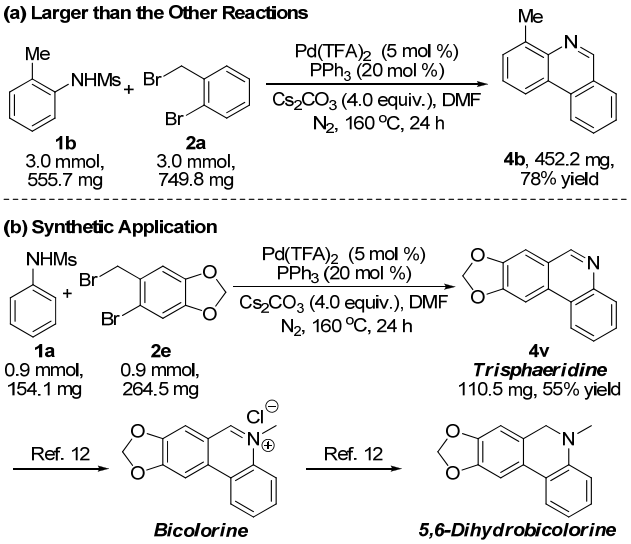


[a] The reactions were carried out with **1** (0.3 mmol), **2** (0.3 mmol), Cs_2CO_3 (4.0 equiv.), $Pd(TFA)_2$ (5 mol %), and PPh_3 (20 mol %) in 2.0 mL of DMF under N_2 atmosphere at 160 °C for specified reaction time. Isolated yields were given. [b] Using $PdCl_2$ instead of $Pd(TFA)_2$ at 120 °C.

arylamine, such as *N*-(pyren-1-yl)methanesulfonamide and *N*-(naphthalen-1-yl)methanesulfonamide, affording the corresponding fused heterocyclic compounds **4o** and **4p** in 65% and 78% yields, respectively.[20] For 2-bromobenzyl bromide derivatives **2**, the substrates bearing electron-donating or –withdrawing group at the C4 position

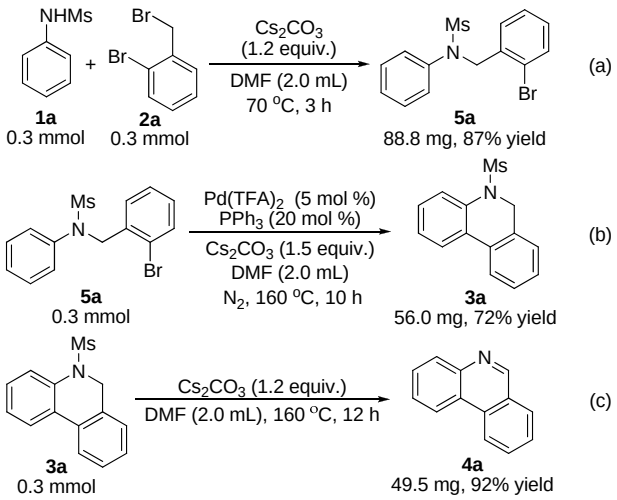
on the phenyl ring, the desired products **4q–t** were obtained in 42–68% yields. Ultimately, 1-bromo-2-(bromomethyl)naphthalene was also proved to be good candidate for this transformation, the expected product **4u** could be obtained in 53% yield.

Scheme 5. Larger than the Other Reactions and the Synthetic Application



To evaluate the practicability of the established methodology, the palladium-catalyzed cascade process was conducted on a larger than the other reactions. As shown in Scheme 5, the reaction proceeded well to afford the corresponding product **4b** in a slightly downward isolated yield (78% yield) [Scheme 5, Eq. (a)]. This method was also successfully applied to the synthesis of natural alkaloid trisphaeridine in 55% yield, which represented the shortest route for trisphaeridine starting from commercially available materials to date.[7a,7c,7e,10a,11,12,21] In addition, it was worth emphasizing that trisphaeridine can be converted into two other alkaloids bicolorine and 5,6-dihydrobicolorine in light of the reported procedures [Scheme 5, Eq. (b)].[12]

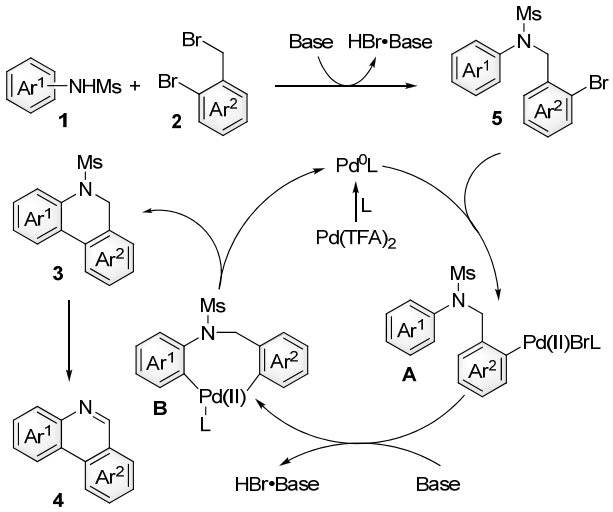
Scheme 6. Preliminary Mechanism Studies



In order to understand the reaction mechanism of this sequential nucleophilic substitution, C-H activation and aromatization process, some control experiments were carried out. When the reaction of **1a** and **2a** was carried out in the absence of $Pd(TFA)_2$ and PPh_3, substituted product **5a** was obtained in 87% yield [Scheme 6, Eq. (a)]. Starting from **5a**, palladium-catalyzed intramolecular C-H arylation could take place, giving the corresponding annulated product **3a** in 72% yield [Scheme 6, Eq. (b)]. And then, treatment of **3a** with 1.2 equiv. of Cs_2CO_3 in DMF at 160 °C for 12 h led to aromatized product **4a** in 92% yield [Scheme 6, Eq. (c)]. These results suggest that compound **5a** and **3a** are possible reaction intermediates for the formation of **4a**.

While a precise mechanism awaits further study, a possible catalytic cycle for the cascade reaction is proposed in Scheme 7. Firstly, the base promoted the nucleophilic substitution between *N*-Ms arylamines (**1**) and 2-bromobenzyl bromide derivatives (**2**) producing compound **5**. Then the oxidative addition of **5** to in-situ generated Pd^0 species, followed by the intramolecular C-H activation to form the intermediate **B**. Subsequent reductive elimination occurred to afford the annulated product **3**, while Pd^0 species were regenerated to complete the catalytic cycle. Further aromatization of **3** occurred to deliver the fused heterocycles **4** at high temperature in the presence of base.

Scheme 7. Proposed Catalytic Cycle



In summary, we have developed an efficient palladium-catalyzed sequential nucleophilic substitution/C-H activation/aromatization process, providing a variety of 6-unsubstituted phenanthridine compounds in moderate to good yields (31–85%). Moreover, natural alkaloid trisphaeridine could be efficiently synthesized in only one step using the present methodology. Notably, this work represents a facile and practical protocol leading to 6-unsubstituted phenanthridines from readily prepared *N*-Ms arylamines and commercially available 2-bromobenzyl bromide derivatives. Additionally, the developed protocol will open up a straightforward way to access 6-unsubstituted phenanthridines.

EXPERIMENTAL SECTION

General experimental information

All commercially available reagents were used without further purification. Column chromatography was performed on silica gel (200-400 mesh). ^{1}H NMR (400 MHz) chemical shifts were reported in ppm (δ) relative to tetramethylsilane (TMS) with the solvent resonance employed as the internal standard. Data were reported as follows: chemical shift, multiplicity (s = singlet, d

= doublet, t = triplet, q = quartet, td = triplet-doublet, m = multiplet), coupling constants (Hz) and integration. ^{13}C NMR (100 MHz) chemical shifts were reported in ppm (δ) from tetramethylsilane (TMS) with the solvent resonance as the internal standard. Melting points were uncorrected.

N-phenylmethanesulfonamide (**1a**), 1-bromo-2-(bromomethyl)benzene (**2a**), 1-bromo-2-(bromomethyl)-4-methoxybenzene (**2b**), 1-bromo-2-(bromomethyl)-4-chlorobenzene (**2c**), 1-bromo-2-(bromomethyl)naphthalene (**2d**) and 5-bromo-6-(bromomethyl)benzo[*d*][1,3]dioxole (**2e**) were purchased from commercial suppliers. Other *N*-Ms arylamines were prepared according to the reported procedures.[17]

General procedure for the synthesis of phenanthridines 4a-4u. A 4 mL flame-dried vial with a stir bar was charged with *N*-Ms arylamines (**1**) (0.3 mmol), 2-bromobenzyl bromide derivatives (**2**) (0.3 mmol), Cs_2CO_3 (391.0 mg, 1.2 mmol), $Pd(TFA)_2$ (5.0 mg, 0.015 mmol), and PPh_3 (15.7 mg, 0.06 mmol) in 2.0 mL of dry DMF under nitrogen atmosphere at 160 °C for 24-48 h. After the completion of the reaction detected by thin layer chromatography (TLC), brine (10.0 mL) was added, and the mixture was extracted with EtOAc (5 x 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated by rotary evaporation. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 5:1) to afford the desired product **4a-4u**.

Phenanthridine (4a). White solid, 43.0 mg, yield 80%, mp 106.8-108.2 °C (lit.[7b] mp 104-106 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.27 (s, 1H), 8.60-8.53 (m, 2H), 8.20 (d, J = 8.0 Hz, 1H), 8.01 (d, J = 8.0 Hz, 1H), 7.84-7.80 (m, 1H), 7.77-7.71 (m, 1H), 7.69-7.64 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.6, 144.5, 132.6, 131.1, 130.2, 128.8, 128.7, 127.5, 127.1, 126.4, 124.2, 122.3, 121.9; HRMS (ESI-TOF) Calcd. for $C_{13}H_{10}N$ $[M+H]^+$: 180.0808; found: 180.0803.

4-Methylphenanthridine (4b) Light yellow solid, 47.0 mg, 81% yield, mp 93.1-94.6 °C (lit.[7a] mp 94.2-95.4 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.30 (s, 1H), 8.56 (d, J = 8.0 Hz, 1H), 8.41 (d, J = 8.0 Hz, 1H), 8.02 (d, J = 8.0 Hz, 1H), 7.83-7.79 (m, 1H), 7.69-7.65 (m, 1H), 7.61-7.53 (m, 2H), 2.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2, 143.3, 137.8, 132.9, 131.0, 129.6, 128.7, 127.3, 126.7, 126.2, 124.0, 122.1, 120.2, 18.8; HRMS (ESI-TOF) Calcd. for $C_{14}H_{12}N$ $[M+H]^+$: 194.0964; found: 194.0958.

4-Ethylphenanthridine (4c)[8c]. Light yellow oil, 51.0 mg, 82% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.31 (s, 1H), 8.57 (d, J = 8.0 Hz, 1H), 8.43-8.41 (m, 1H), 8.02 (d, J = 8.0 Hz, 1H), 7.82-7.78 (m, 1H), 7.68-7.64 (m, 1H), 7.63-7.59 (m, 2H), 3.40 (q, J = 7.6 Hz, 2H), 1.45 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2, 143.7, 142.7, 133.0, 130.8, 128.7, 127.9, 127.3, 126.9, 126.2, 124.1, 122.1, 120.1, 25.3, 15.6; HRMS (ESI-TOF) Calcd. for $C_{15}H_{14}N$ $[M+H]^+$: 208.1121; found: 208.1120.

4-Ethoxyphenanthridine (4d). White solid, 52.9 mg, 79% yield, mp 73.4-74.8 °C; IR (KBr) ν (cm^{-1}) 3414, 2927, 1620, 1528, 1352, 1258, 1092, 750; ^{1}H NMR (400 MHz, DMSO-d_6 + $CDCl_3$) δ 9.12 (s, 1H), 8.39 (d, J = 8.4 Hz, 1H), 7.95 (d, J = 8.4 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.67-7.63 (m, 1H), 7.51 (d, J = 7.2 Hz, 1H), 7.40 (t, J = 8.0 Hz, 1H), 6.97 (d, J = 8.0 Hz, 1H), 4.16 (q, J = 7.2 Hz, 2H), 1.44 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6 + $CDCl_3$) δ 154.9, 151.7, 135.1, 132.0, 130.6, 128.3, 127.3, 127.0, 126.0, 124.9, 122.0, 113.5, 109.0, 64.0, 14.5; HRMS (ESI-TOF) Calcd. for $C_{15}H_{14}NO$ $[M+H]^+$: 224.1070; found: 224.1070.

4-Chlorophenanthridine (4e). Light yellow solid, 46.7 mg, 73% yield, mp 101.1-102.4 °C (lit.[8c] mp 98-100 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.37 (s, 1H), 8.56 (d, J = 8.4 Hz, 1H), 8.46 (d, J =

8.4 Hz, 1H), 8.06 (d, *J* = 8.0 Hz, 1H), 7.89-7.82 (m, 2H), 7.73 (td, *J* = 0.8, 7.6 Hz, 1H), 7.57 (td, *J* = 1.6, 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2, 140.8, 134.4, 132.4, 131.6, 129.2, 129.1, 128.3, 127.1, 126.4, 126.0, 122.2, 121.3; HRMS (ESI-TOF) Calcd. for $C_{13}H_9ClN$ $[M+H]^+$: 214.0418; found: 214.0419.

3-Methylphenanthridine (4f, major)[22d] **and 1-Methylphenanthridine (4f', minor).** Light yellow oil, 18.0 mg, 31% yield; major : minor = 6.1 : 1; ^{1}H NMR (400 MHz, $CDCl_3$): δ (major + minor) 9.26 (s, 1H), 8.89 (d, *J* = 9.2 Hz, 0.14H), 8.57 (d, *J* = 8.0 Hz, 0.86H), 8.46 (d, *J* = 8.0 Hz, 0.86H), 8.12-8.07 (m, 0.28H), 8.03 (d, *J* = 8.0 Hz, 0.86H), 7.98 (s, 0.86H), 7.86-7.82 (m, 1H), 7.70-7.66 (m, 1.14H), 7.51 (d, *J* = 8.0 Hz, 1H), 3.13 (s, 0.42H), 2.60 (s, 2.58H); ^{13}C NMR (100 MHz, CDCl3): δ (major + minor) 153.6, 144.6, 139.1, 132.8, 131.4, 131.2, 130.6, 129.7, 129.3, 129.0, 128.9, 128.0, 127.2, 126.9, 126.6, 126.2, 122.2, 121.9, 121.8, 26.9, 21.7; HRMS (ESI-TOF) Calcd. for $C_{14}H_{12}N$ $[M+H]^+$: 194.0964; found: 194.0958

2-Methylphenanthridine (4g). Light yellow solid, 45.2 mg, 78% yield, mp 90.1-91.3 °C (lit.[7a] mp 90.1-91.1 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.22 (s, 1H), 8.58 (d, *J* = 8.4 Hz, 1H), 8.34 (s, 1H), 8.08 (d, *J* = 8.4 Hz, 1H), 8.02 (d, *J* = 8.0 Hz, 1H), 7.84 (td, *J* = 1.2, 7.6 Hz, 1H), 7.69 (td, *J* = 1.2, 7.6 Hz, 1H), 7.57 (dd, *J* = 1.2, 8.4 Hz, 1H), 2.63 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 152.7, 142.8, 137.1, 132.4, 130.9, 130.5, 129.9, 128.8, 127.4, 126.6, 124.0, 121.9, 22.1. HRMS (ESI-TOF) Calcd. for $C_{14}H_{12}N$ $[M+H]^+$: 194.0964; found: 194.0962.

2-Methoxyphenanthridine (4h). White solid, 39.5 mg, 63% yield, mp 103.7-105.1 °C (lit.[22b] mp 89-90 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.09 (s, 1H), 8.42 (d, *J* = 8.4 Hz, 1H), 8.07 (d, *J* = 9.2 Hz, 1H), 7.94 (d, *J* = 8.0 Hz, 1H), 7.79 (d, *J* = 2.8 Hz, 1H), 7.75 (d, *J* = 7,6 Hz, 1H), 7.62 (d, *J* =

7,6 Hz, 1H), 7.32 (dd, J = 2.4, 8.8 Hz, 1H), 3.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4, 151.0, 139.7, 132.0, 131.4, 130.5, 128.6, 127.5, 126.5, 125.1, 121.8, 118.5, 103.0, 55.6; HRMS (ESI-TOF) Calcd. for $C_{14}H_{12}NO$ $[M+H]^+$: 210.0913; found: 210.0912.

2-Fluorophenanthridine (4i). Light yellow solid, 35.5 mg, 60% yield, mp 130.8-132.5 °C; IR (KBr) ν (cm^{-1}) 3446, 3059, 2925, 1618, 1495, 1445, 1187, 864, 751; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.23 (s, 1H), 8.48 (d, J = 8.4 Hz, 1H), 8.19-8.15 (m, 2H), 8.05 (d, J = 8.4 Hz, 1H), 7.89-7.85 (m, 1H), 7.76-7.73 (m, 1H), 7.51-7.45 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5 (d, J = 245.8 Hz, 1C), 152.9 (d, J = 2.7 Hz, 1C), 141.4, 132.4 (d, J = 9.2 Hz, 1C), 132.1 (d, J = 4.3 Hz, 1C), 131.2, 128.6 (d, J = 66.1 Hz, 1C), 126.5, 125.7, 125.6, 122.2, 117.7 (d, J = 24.1 Hz, 1C), 107.3 (d, J = 23.0 Hz, 1C). HRMS (ESI-TOF) Calcd. for $C_{13}H_9FN$ $[M+H]^+$: 198.0714; found: 198.0713.

2-Chlorophenanthridine (4j). White solid, 32.7 mg, 51% yield, mp 155.8-157.2 °C (lit.[7b] mp 154-157 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 (s, 1H), 8.43-8.42 (m, 2H), 8.07 (d, J = 8.4 Hz, 1H), 8.00 (d, J = 8.4 Hz, 1H), 7.82 (t, J = 7.6 Hz, 1H), 7.70 (t, J = 7.6 Hz, 1H), 7.63 (dd, J = 0.4, 8.4 Hz, 1H).^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8, 142.8, 133.1, 131.6, 131.5, 131.3, 129.2, 128.9, 128.2, 126.5, 125.2, 122.0, 121.9; HRMS (ESI-TOF) Calcd. for $C_{13}H_9ClN$ $[M+H]^+$: 214.0418; found: 214.0417.

1,3-Dimethylphenanthridine (4k). Light yellow solid, 34.8 mg, 56% yield, mp 141.9-143.3 °C (lit.[22a] mp 142-143 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.22 (s, 1H), 8.85 (d, J = 8.4 Hz, 1H), 8.07 (d, J = 8.4 Hz, 1H), 7.90 (s, 1H), 7.84 (td, J = 1.6, 8.0 Hz, 1H), 7.69 (d, J = 8.0 Hz, 1H), 7.37 (s, 1H), 3.10 (s, 3H), 2.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8, 141.6, 138.0, 135.3, 134.0,

133.1, 130.5, 129.3, 128.8, 127.4, 126.4, 126.3, 26.7, 21.3; HRMS (ESI-TOF) Calcd. for $C_{15}H_{14}N$ $[M+H]^+$: 208.1121; found: 208.1119.

1,4-Dimethylphenanthridine (4l). Light yellow solid, 50.4 mg, 81% yield, mp 86.7-88.2 °C; IR (KBr) ν (cm^{-1}) 3451, 2964, 1585, 1448, 1246, 811, 750; ^1H NMR (400 MHz, $CDCl_3$) δ 9.29 (s, 1H), 8.88 (d, J = 8.4 Hz, 1H), 8.09 (d, J = 8.0 Hz, 1H), 7.86-7.82 (m, 1H), 7.71 (td, J = 0.8, 7.6 Hz, 1H), 7.52 (d, J = 7.4 Hz, 1H), 7.42 (d, J = 7.4 Hz, 1H), 3.09 (s, 3H), 2.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.3, 144.7, 136.0, 134.2, 133.1, 130.8, 130.2, 129.1, 128.9, 127.5, 126.7, 126.6, 123.8, 26.9, 19.4. HRMS (ESI-TOF) Calcd. for $C_{15}H_{14}N$ $[M+H]^+$: 208.1121; found: 208.1121.

2,4-Dimethylphenanthridine (4m). Light yellow solid, 51.6 mg, 83% yield, mp 117.0-118.5 °C (lit.[8c] mp 117-118 °C); ^1H NMR (400 MHz, $CDCl_3$) δ 9.22 (s, 1H), 8.53 (d, J = 8.4 Hz, 1H), 8.16 (s, 1H), 7.99 (d, J = 8.0 Hz, 1H), 7.78 (d, J = 7.6 Hz, 1H), 7.64 (d, J = 7.6 Hz, 1H), 7.41 (s, 1H), 2.85 (s, 3H), 2.56 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 151.3, 141.6, 137.3, 136.4, 132.6, 131.3, 130.6, 128.6, 127.1, 126.3, 123.9, 122.1, 119.7, 22.0, 18.7. HRMS (ESI-TOF) Calcd. for $C_{15}H_{14}N$ $[M+H]^+$: 208.1121; found: 208.1121.

3,4-Dimethylphenanthridine (4n). Light yellow solid, 52.9 mg, 85% yield, mp 145.1-146.4 °C (lit.[8c] mp 90-91 °C); ^1H NMR (400 MHz, $CDCl_3$) δ 9.27 (s, 1H), 8.53 (d, J = 8.4 Hz, 1H), 8.29 (d, J = 8.4 Hz, 1H), 7.99 (d, J = 8.0 Hz,1H), 7.78 (t, J = 7.6 Hz, 1H), 7.63 (t, J = 7.6 Hz, 1H), 7.46 (d, J = 8.4 Hz, 1H), 2.83 (s, 3H), 2.53 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 143.2, 136.9, 135.5, 133.0, 130.7, 129.3, 128.6, 126.9, 125.7, 122.0, 121.9, 119.2, 20.8, 14.0; HRMS (ESI-TOF) Calcd. for $C_{15}H_{14}N$ $[M+H]^+$: 208.1121; found: 208.1119.

Phenaleno[1,9-*bc*]phenanthridine (4o). Yellow solid, 59.2 mg, 65% yield, mp 273.8-275.6 °C; IR (KBr) ν (cm^{-1}) 3444, 3038, 1620, 1238, 867, 747; ^1H NMR (400 MHz, DMSO-d_6 + $CDCl_3$) δ 9.61-9.58 (m, 2H), 9.51 (s, 1H), 9.12 (d, J = 8.0 Hz, 1H), 8.40 (d, J = 9.2 Hz, 1H), 8.36-8.31 (m, 2H), 8.29-8.24 (m, 2H), 8.19-8.13 (m, 1H), 8.09-8.02 (m, 2H), 7.86 (t, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6 + $CDCl_3$) δ 153.0, 138.2, 132.5, 131.7, 131.5, 131.1, 130.1, 129.3, 128.9, 128.6, 128.3, 128.2, 128.1, 127.0, 126.5, 126.1, 125.7, 124.3, 123.9, 123.1, 121.6, 119.1; HRMS (ESI-TOF) Calcd. for $C_{23}H_{14}N$ $[M+H]^+$: 304.1121; found: 304.1119.

Benzo[*c*]phenanthridine (4p). Light yellow solid, 53.7 mg, 78% yield, mp 133.5-135.1 °C (lit.[8c] mp 126-129 °C); ^1H NMR (400 MHz, $CDCl_3$) δ 9.48 (s, 1H), 9.42 (d, J = 8.0 Hz, 1H), 8.65 (d, J = 8.0 Hz, 1H), 8.52 (d, J = 8.0 Hz, 1H), 8.13 (d, J = 7.2 Hz, 1H), 8.03-7.98 (m, 2H), 7.87 (t, J = 6.8 Hz, 1H), 7.79 (t, J = 7.2 Hz, 1H), 7.74-7.67 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 141.6, 133.4, 132.9, 132.1, 130.9, 128.8, 128.0, 127.8, 127.5, 127.2, 127.1, 127.0, 124.8, 122.3, 121.2, 120.0; HRMS (ESI-TOF) Calcd. for $C_{17}H_{12}N$ $[M+H]^+$: 230.0964; found: 230.0965.

8-Methoxyphenanthridine (4q). Yellow solid, 42.7 mg, 68% yield, mp 109.1-110.5 °C; IR (KBr) ν (cm^{-1}) 3444, 2952, 1614, 1460, 1366, 1241, 1031, 837, 756; ^1H NMR (400 MHz, $CDCl_3$) δ 9.23 (s, 1H), 8.52-8.48 (m, 2H), 8.17 (d, J = 8.0 Hz, 1H), 7.71-7.64 (m, 2H), 7.50-7.47 (m, 1H), 7.38 (s, 1H), 3.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 152.9, 143.7, 130.2, 127.8, 127.3, 127.1, 124.4, 123.7, 122.2, 121.9, 108.1, 55.7; HRMS (ESI-TOF) Calcd. for $C_{14}H_{12}NO$ $[M+H]^+$: 210.0913; found: 210.0917.

8-Methoxy-2,4-dimethylphenanthridine (4r). Light yellow solid, 38.4 mg, 54% yield, mp 140.8-142.1 °C; IR (KBr) ν (cm^{-1}) 3437, 2923, 1616, 1458, 1369, 1209, 1028, 827; ^1H NMR (400

MHz, $CDCl_3$) δ 9.19 (s, 1H), 8.48 (d, J = 9.2 Hz, 1H), 8.12 (s, 1H), 7.44 (dd, J = 2.0, 9.2 Hz, 1H), 7.38 (s, 1H), 7.34 (d, J = 2.0 Hz, 1H), 3.98 (s, 3H), 2.84 (s, 3H), 2.57 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7, 150.6, 140.9, 137.3, 136.6, 130.5, 127.7, 127.2, 124.2, 123.9, 121.9, 119.3, 107.7, 55.7, 22.1, 18.7; HRMS (ESI-TOF) Calcd. for $C_{16}H_{16}NO$ $[M+H]^+$: 238.1226; found: 238.1225.

8-Methoxy-3,4-dimethylphenanthridine (4s). Light yellow solid, 39.9 mg, 56% yield, mp 146.3-147.3 °C; IR (KBr) ν (cm^{-1}) 3450, 2924, 1614, 1471, 1258, 1203, 1023, 840, 756; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.22 (s, 1H), 8.46 (d, J = 8.8 Hz, 1H), 8.24 (d, J = 8.8 Hz, 1H), 7.47-7.42 (m, 2H), 7.34-7.33 (m, 1H), 3.98 (s, 3H), 2.82 (s, 3H), 2.53 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.5, 151.4, 142.5, 135.9, 135.4, 129.5, 127.6, 127.0, 123.7, 122.2, 122.0, 118.8, 107.7, 55.7, 20.8, 14.0; HRMS (ESI-TOF) Calcd. for $C_{16}H_{16}NO$ $[M+H]^+$: 238.1226; found: 238.1226.

8-Chlorophenanthridine (4t). White solid, 26.9 mg, 42% yield, mp 97.5-99.9 °C (lit.[16d] mp 96.5-97.2 °C); ^{1}H NMR (400 MHz, CDCl3) δ 9.21 (s, 1H), 8.56-8.53 (m, 2H), 8.20 (d, J = 8.0 Hz, 1H), 8.03 (s, 1H), 7.83-7.76 (m, 2H), 7.73-7.69 (m, 1H); ^{13}C NMR (100 MHz, CDCl3) δ 152.4, 144.5, 133.5, 131.8, 131.1, 130.4, 129.2, 127.9, 127.7, 127.3, 123.9, 123.7, 122.3; HRMS (ESI-TOF) Calcd. for $C_{13}H_9ClN$ $[M+H]^+$: 214.0418; found: 214.0410.

Benzo[*k*]phenanthridine (4u). Light yellow solid, 36.5 mg, 53% yield, mp 108.7-110.1 °C (lit.[9a] mp 108-110 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.31 (s, 1H), 9.18-9.12 (m, 1H), 9.08-9.03 (m, 1H), 8.32 (dd, J = 1.2, 8.0 Hz, 1H), 8.05-8.02 (m, 1H), 7.98-7.95 (m, 1H), 7.91-7.87 (m, 1H), 7.81-7.77 (m, 1H), 7.73-7.70 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.7, 146.6, 135.2, 131.2, 130.3, 129.0, 128.8, 128.3, 128.2, 127.9, 127.1, 127.0, 126.9, 125.3, 125.1, 124.7; HRMS (ESI-TOF) Calcd. for $C_{17}H_{12}N$ $[M+H]^+$: 230.0964; found: 230.0962.

Large preparation of compound 4b [Scheme 5, Eq. (a)]. A 50 mL flame-dried flask with a stir bar was charged with *N*-*o*-tolylmethanesulfonamide (**1b**) (555.0 mg, 3.0 mmol), 1-bromo-2-(bromomethyl)benzene (**2a**) (750.0 mg, 3.0 mmol), Cs_2CO_3 (3909.8 mg, 12.0 mmol), $Pd(TFA)_2$ (49.9 mg, 0.15 mmol), and PPh_3 (157.4 mg, 0.6 mmol) in 20.0 mL of dry DMF under nitrogen atmosphere at 160 °C for 24 h. After the completion of the reaction detected by thin layer chromatography (TLC), brine (100.0 mL) was added, and the mixture was extracted with EtOAc (5 x 100 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated by rotary evaporation. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 5:1) to afford the desired product **4b** as a light yellow solid (452.2 mg, 78%).

Synthesis of trisphaeridine (4v) [Scheme 5, Eq. (b)]. A 10 mL flame-dried vial with a stir bar was charged with *N*-phenylmethanesulfonamide (**1a**) (154.1 mg, 0.9 mmol), 5-bromo-6-(bromomethyl)benzo[*d*][1,3]dioxole (**2e**) (264.5 mg, 0.9 mmol), Cs_2CO_3 (1173.0 mg, 3.6 mmol), $Pd(TFA)_2$ (15.0 mg, 0.045 mmol), and PPh_3 (47.2 mg, 0.18 mmol) in 6.0 mL of dry DMF under nitrogen atmosphere at 160 °C for 24 h. After the completion of the reaction detected by thin layer chromatography (TLC), brine (30.0 mL) was added, and the mixture was extracted with EtOAc (5 x 30 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated by rotary evaporation. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 5:1) to afford trisphaeridine (**4t**) as a white solid (110.5 mg, 55%). White solid, mp 145.1-146.7 °C (lit.[7a] mp 140-141 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.09 (s, 1H), 8.37 (d, J = 8.0 Hz, 1H), 8.14 (d, J = 8.0 Hz, 1H), 7.91 (s, 1H), 7.71-7.67 (m, 1H), 7.65-7.61 (m, 1H), 7.34 (s, 1H), 6.17 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ

151.9, 151.7, 148.3, 144.2, 130.4, 130.2, 128.2, 126.8, 124.4, 123.2, 122.1, 105.7, 102.1, 100.1; HRMS (ESI-TOF) Calcd. for $C_{14}H_{10}NO_2$ $[M+H]^+$: 224.0706; found: 224.0706.

Synthesis of compound 5a [Scheme 6, Eq. (a)]. A 4 mL vial with a stir bar was charged with *N*-phenylmethanesulfonamide (**1a**) (51.4 mg, 0.3 mmol), 1-bromo-2-(bromomethyl)benzene (**2a**) (75.0 mg, 0.3 mmol), and Cs_2CO_3 (117.3 mg, 0.36 mmol) in 2.0 mL of dry DMF at 70 °C for 3 h. After the completion of the reaction detected by thin layer chromatography (TLC), brine (10.0 mL) was added, and the mixture was extracted with EtOAc (5 x 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated by rotary evaporation. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 5:1) to afford the desired product **5a** as a white solid (88.8 mg, 87%). White solid, mp 112.3-113.8 °C; IR (KBr) ν (cm^{-1}) 3470, 2931, 1632, 1403, 1337, 1153, 1027, 959, 757; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 7.6 Hz, 1H), 7.48 (d, J = 7.6 Hz, 1H), 7.40-7.34 (m, 4H), 7.30-7.26 (m, 2H), 7.10 (t, J = 7.6 Hz, 1H), 5.05 (s, 2H), 3.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.1, 135.3, 132.7, 130.3, 129.4, 129.2, 128.3, 128.1, 127.6, 123.3, 54.3, 37.9; HRMS (ESI-TOF) Calcd. for $C_{14}H_{14}BrNNaO_2S$ $[M+Na]^+$: 361.9821; found: 361.9816.

Synthesis of compound 3a starting from compound 5a [Scheme 6, Eq. (b)]. A 4 mL flame-dried vial with a stir bar was charged with *N*-(2-bromobenzyl)-*N*-phenylmethanesulfonamide (**5a**) (102.1 mg, 0.3 mmol), Cs_2CO_3 (146.6 mg, 0.45 mmol), $Pd(TFA)_2$ (5.0 mg, 0.015 mmol), and PPh_3 (15.7 mg, 0.06 mmol) in 2.0 mL of dry DMF under nitrogen atmosphere at 160 °C for 10 h. After the completion of the reaction detected by thin layer chromatography (TLC), brine (10.0 mL) was added, and the mixture was extracted with EtOAc (5

x 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated by rotary evaporation. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 5:1) to afford the desired product **3a** as a white solid (56.0 mg, 72%). White solid, mp 73.2-74.8 °C (lit.[22c] mp 73-74 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85-7.80 (m, 2H), 7.71-7.69 (m, 1H), 7.46-7.31 (m, 5H), 4.83 (s, 2H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.9, 132.2, 131.3, 129.9, 129.0, 128.9, 128.7, 128.0, 127.7, 126.2, 124.2, 123.8, 49.6, 37.8; HRMS (ESI-TOF) Calcd. for $C_{14}H_{13}NNaO_2S$ $[M+Na]^+$: 282.0559; found: 282.0554.

Synthesis of compound 4a starting from compound 3a [Scheme 6, Eq. (c)]. A 4 mL flame-dried vial with a stir bar was charged with 5-(methylsulfonyl)-5,6-dihydrophenanthridine (**3a**) (77.8 mg, 0.3 mmol), and Cs_2CO_3 (117.3 mg, 0.36 mmol) in 2.0 mL of dry DMF at 160 °C for 12 h. After the completion of the reaction detected by thin layer chromatography (TLC), brine (10.0 mL) was added, and the mixture was extracted with EtOAc (5 x 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated by rotary evaporation. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 5:1) to afford the desired product **4a** as a white solid (49.5 mg, 92%).

Supporting Information Available NMR spectra, X-ray crystal structure and the CIF file of **4p**. This material is available free of charge via the Internet at http://pubs.acs.org.

Acknowledgements

We are grateful for financial support from Science and Technology Department of Guizhou

Province (No. 2015GZ18284 and QKHRCTD-2014-4002), Education Department of Guizhou Province (QJHRCTDZ-2012-03), and New Century Excellent Talent of the Ministry of Education (NCET-13-1069). Special thanks are expressed to Prof. Zeli Yuan (Zunyi Medical University) for his help of single crystal analysis.

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