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

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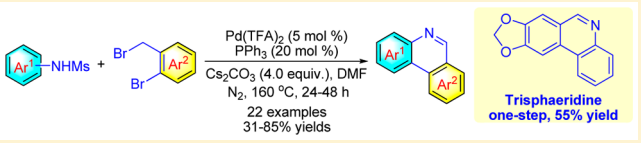
Supporting Information

**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 frequently found in natural products (Figure 1) and compounds incorporating such a motif

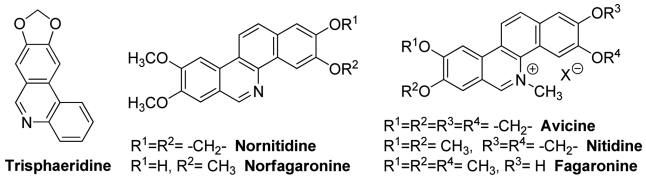
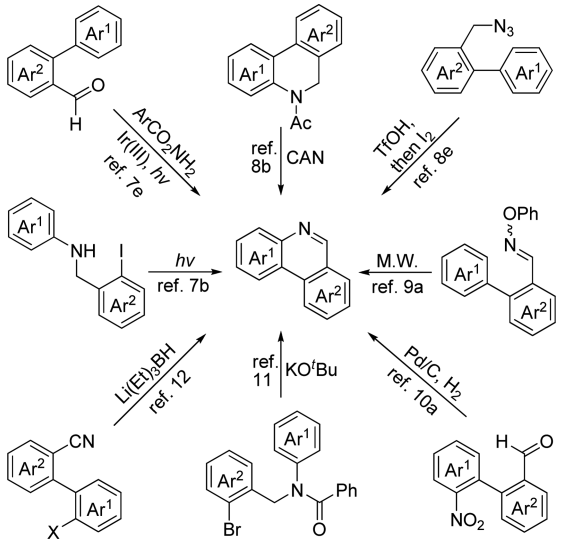



**Figure 1.** Biologically active phenanthridines.

possess several types of bioactivities such as antimalarial, cytotoxicity, antimycobacterial, anticancer, etc.[3,4] Thus, numerous methodologies for the construction of the 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.

**Scheme 1. Synthesis of 6-Unsubstituted 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 a palladium-catalyzed cascade reaction is rare,[8c,16] especially starting from readily accessible substrates.

*N*-Ms arylamines[17] and 2-bromobenzyl bromide derivatives,[18] two kinds of readily accessible precursors, have been

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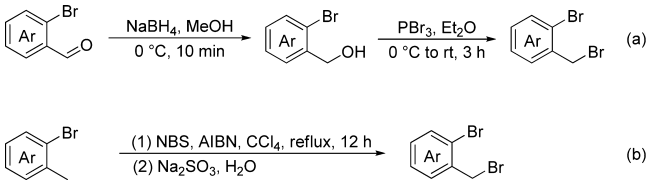
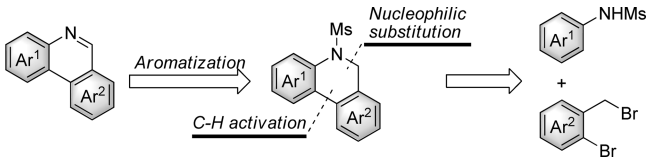
broadly applied in organic synthesis, respectively. Generally, there were two common methods for the synthesis of 2-bromobenzyl bromide derivatives: (i) reduction of *ortho*-bromoarylaldehydes followed by substitution using tribromophosphine gave 2-bromobenzyl bromide derivatives [Scheme 2, eq (a)], and (ii) substitution of *ortho*-bromomethylarenes with *N*-bromosuccinimide using azobis(isobutyronitrile) as radical initiator gave 2-bromobenzyl bromide derivatives [Scheme 2, eq (b)].[19] Therefore, promoted by the importance of this phenanthridine motif, and in continuation of our ongoing interest in the development of 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 nucleophilic substitution/C−H activation/aromatization (Scheme 3).

**Scheme 2. Synthesis of 2-Bromobenzyl Bromide Derivatives**

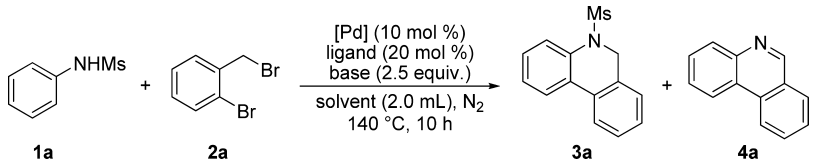



**Scheme 3. Strategy of Our Proposed Methodology**




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 a 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 at 160 °C, suggesting that the aromatization process would readily proceed at high

**Table 1. Optimization of Reaction Conditions**[a]




| entry | [Pd]/ligand | base | solvent | yield (%)[b] 3a | yield (%)[b] 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[d,e] | $Pd(TFA)_2/PPh_3$ | $Cs_2CO_3$ | DMF | 69 | 16 |
| 18[d,e,f] | $Pd(TFA)_2/PPh_3$ | $Cs_2CO_3$ | DMF | 44 | 40 |
| 19[d,e,f,g] | $Pd(TFA)_2/PPh_3$ | $Cs_2CO_3$ | 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 a $N_2$ 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 of $Cs_2CO_3$ were used.



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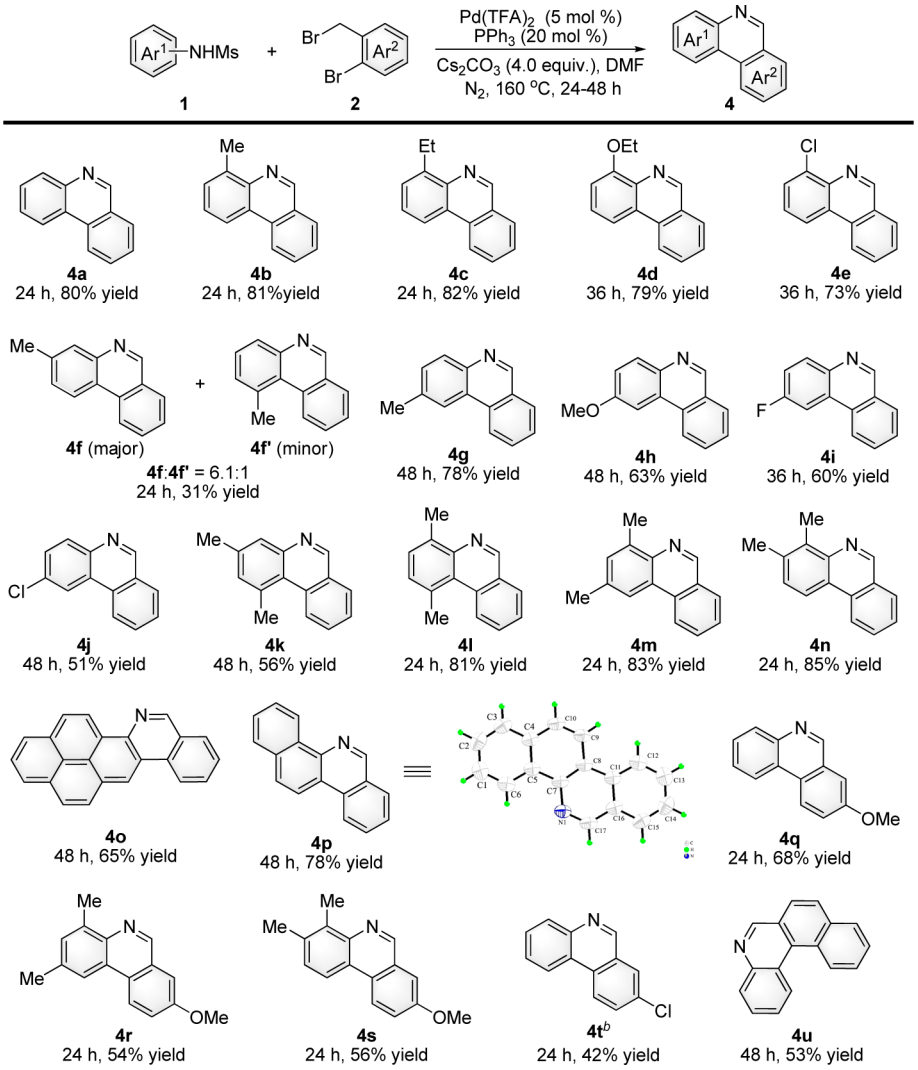
**Scheme 4. Substrate Scope**[a]




[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 a $N_2$ atmosphere at 160 °C for a specified reaction time. Isolated yields were given. [b]Using $PdCl_2$ instead of $Pd(TFA)_2$ at 120 °C.

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, by increasing the equivalents 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).

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 the 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 substituents provided good yields (**4g** and **4h**), whereas the electron-deficient groups led to 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 arylamines, 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**, with the substrates bearing an 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 proven to be a good candidate for this transformation; the expected product **4u** could be obtained in 53% yield.

To evaluate the practicability of the established methodology, the palladium-catalyzed cascade process was conducted on a larger scale 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



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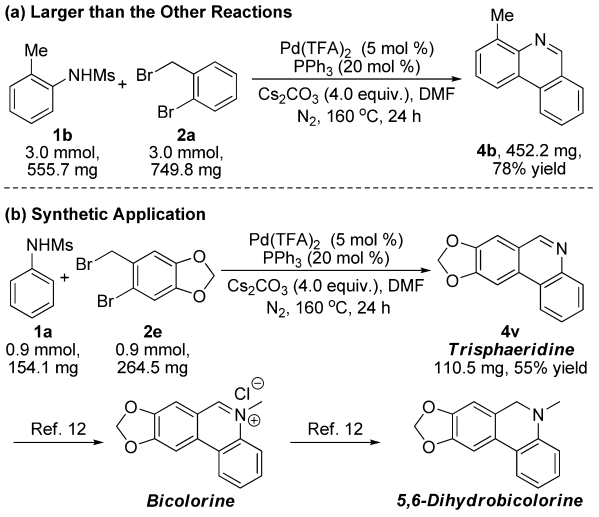
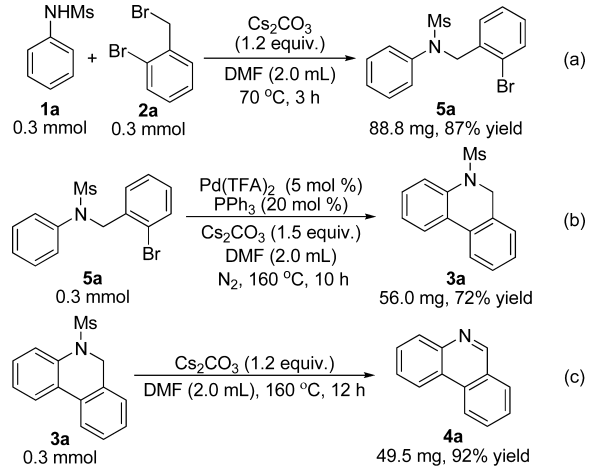
**Scheme 5. Larger than the Other Reactions and the Synthetic Application**




represented the shortest route for trisphaeridine starting from commercially available materials to date.[7a,c,e,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]

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**,

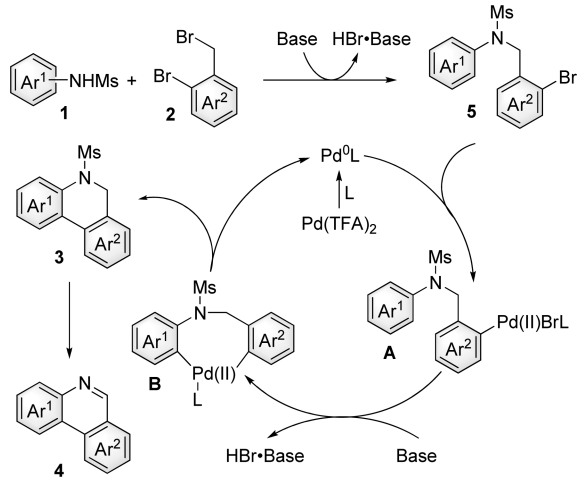
**Scheme 6. Preliminary Mechanism Studies**




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. First, the base promoted the nucleophilic substitution between

**Scheme 7. Proposed Catalytic Cycle**




*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 occurred, 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 a base.

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). $^1H$ NMR (400 MHz) chemical shifts were reported in ppm ($\delta$) 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 ($\delta$) 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



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a nitrogen atmosphere at 160 °C for 24−48 h. After the completion of the reaction was detected by thin layer chromatography (TLC), brine (10.0 mL) was added, and the mixture was extracted with EtOAc (5 × 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, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 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) $\nu$ ($cm^{-1}$) 3414, 2927, 1620, 1528, 1352, 1258, 1092, 750; $^1$H NMR (400 MHz, DMSO-$d_6$ + $CDCl_3$) $\delta$ 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-$d_6$ + $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 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, $CDCl_3$): $\delta$ (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, $CDCl_3$): $\delta$ (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, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 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) $\nu$ ($cm^{-1}$) 3446, 3059, 2925, 1618, 1495, 1445, 1187, 864, 751; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 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) $\nu$ ($cm^{-1}$) 3451, 2964, 1585, 1448, 1246, 811, 750; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 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); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 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); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 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) $\nu$ ($cm^{-1}$) 3444, 3038, 1620, 1238, 867, 747; $^1$H NMR (400 MHz, DMSO-$d_6$ + $CDCl_3$) $\delta$ 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-$d_6$ + $CDCl_3$) $\delta$ 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); $^1$H NMR (400



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MHz, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 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) $\nu$ ($cm^{-1}$) 3444, 2952, 1614, 1460, 1366, 1241, 1031, 837, 756; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 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) $\nu$ ($cm^{-1}$) 3437, 2923, 1616, 1458, 1369, 1209, 1028, 827; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 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) $\nu$ ($cm^{-1}$) 3450, 2924, 1614, 1471, 1258, 1203, 1023, 840, 756; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 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) $\delta$ 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) $\delta$ 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, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 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**) (555.7 mg, 3.0 mmol), 1-bromo-2-(bromomethyl)benzene (**2a**) (749.8 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 a 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 × 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 was detected by thin layer chromatography (TLC), brine (30.0 mL) was added, and the mixture was extracted with EtOAc (5 × 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 (**4v**) 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, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 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 was detected by thin layer chromatography (TLC), brine (10.0 mL) was added, and the mixture was extracted with EtOAc (5 × 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) $\nu$ ($cm^{-1}$) 3470, 2931, 1632, 1403, 1337, 1153, 1027, 959, 757; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 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 a nitrogen atmosphere at 160 °C for 10 h. After the completion of the reaction was detected by thin layer chromatography (TLC), brine (10.0 mL) was added, and the mixture was extracted with EtOAc (5 × 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, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 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 was detected by thin layer chromatography (TLC), brine (10.0 mL) was added, and the mixture was extracted with EtOAc (5 × 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%).

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02145.

NMR spectra, X-ray crystal structure of **4p** (PDF)



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Crystallographic data for **4p** (CIF)

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### Notes

The authors declare no competing financial interest.

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