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SYNTHESIS OF HIGHLY SUBSTITUTED 5,6-DIHYDROBENZO[*j*]PHENANTHRIDINE DERIVATIVES VIA DOMINO REACTION

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Abstract – An atom-economical method for diynes with aryl halides under palladium-catalyzed conditions has been developed. Using unactivated simple diynes with aryl halides in the presence of palladium catalytic system afforded various 7,12-diphenyl-5-tosyl-5,6-dihydrobenzo[*j*]phenanthridine derivatives through C–C coupling and C–H bond activation in one step. This cascade reaction was initiated by an intermolecular [2 + 2 + 2] cycloaddition.

INTRODUCTION

Phenanthridine is an important class of compounds in the fields of pharmaceutical and organic chemistry. Phenanthridine skeletons occur in nature[1] and are used as potential pharmaceuticals with remarkable medicinal and biological activities,[2] such as antifungal, antibacterial, antileukemic, antiviral, and antitumor properties.[3] Also, many substituted phenanthridines have excellent optical and electronic properties in the field of functional materials.[4] Therefore, the development of new and efficient methods for the preparation of phenanthridine skeletons and their derivatives is very important and necessary.

Till now numerous methods have been developed to access these compounds, in which the transition-metal catalyzed annulation reaction represents a powerful methodology for the assembly of complex polycyclic skeletons in organic chemistry.[5] It is important to point out that the palladium-catalyzed carbon–carbon bond formation has been the subject of intense research for the past decades. For example, Sakakibara and Heck groups have reported palladium-catalyzed coupling reaction of iodobenzene with dimethyl acetylenedicarboxylate and diphenylacetylene.[6] All kinds of routes have also been developed for the synthesis of phenanthridines through palladium-catalyzed annulation reactions. Lautens's group has reported the synthesis of phenanthridine derivatives by palladium-catalyzed domino direct arylation.[7] In

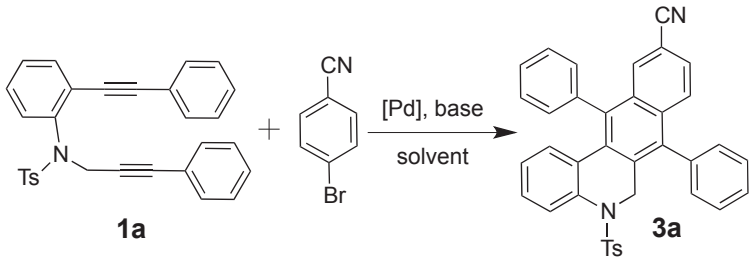
2014, Sha reported a palladium-catalyzed C–H activation of aryl ketone *O*-acetyloximes and arynes to synthesize phenanthridines.[8] Several groups have also successively reported their efforts for the construction of phenanthridines through palladium-catalyzed annulation reaction.[9] The fully intermolecular [2 + 2 + 2] cycloaddition is generally an excellent and efficient process to form fused heterocycles.[10] However, as for the palladium-catalyzed domino cyclization reaction of aryl haides and diynes was rarely reported. Hu's group has developed an extraordinary domino method for the construction of polycyclic aromatic hydrocarbons (various 4,9-diphenyl-2,3-dihydro-1*H*-cyclopenta[*b*]naphthalene derivative) by the palladium(0)-catalyzed reaction of diynes with aryl halides through C–C coupling and C–H bond activation of the incorporated aryl group.[11] Deiters's group has reported the synthesis of phenanthridine skeleton through a microwave mediated [2 + 2 + 2] cyclotrimerization reaction towards dihydrophenanthridines followed by oxidation.[12] In 2013, Wu and co-workers reported rhodium-catalyzed [2 + 2 + 2] cycloaddition reaction between diynes and alkynes leading to CF_3-containing phenanthridines.[13]

In this study, we introduce a diversity-oriented synthesis of highly substituted dihydrophenanthridine four-ring condensed ring system from diynes and aryl halides. The cascade consists of inter-intramolecular Heck reactions and subsequent regioselectively directed arylation by C–H activation of the benzyl ring. Herein, we report on the palladium-catalyzed novel domino reactions of **1a**-**1i** with aryl halides to provide a direct, efficient, and economic methodology for the construction of dihydrophenanthridine through both C–C bond coupling and C–H bond activation.

RESULTS AND DISCUSSION

In our previous research on palladium-catalyzed cyclization,[14] we designed a substance, 4-methyl-*N*-(2-(phenylethynyl)phenyl)-*N*-(3-phenylprop-2-yn-1-yl)benzenesulfonamide. Using 4-methyl-*N*-(2-(phenylethynyl)phenyl)-*N*-(3-phenylprop-2-yn-1-yl)benzenesulfonamide (**1a**) and 4-bromobenzonitrile as the substrates, the [2 + 2 + 2] cycloaddition reaction conditions were optimized (Scheme 1). It can be seen that the reaction efficiency was enhanced considerable when the reaction temperature was increased (Entries 3, 6–8). However, when it was higher than 140 °C, **3a** would decompose (Entry 6). So the optimal temperature was chosen to be 130 °C. Next, the influence of the base utilized on the reaction efficiency was studied. As shown in Table 1 (Entries 5, 11, 12), 86% yield of **3a** was obtained when tributylamine was employed. And it was much higher than that got by using cesium carbonate or sodium hydrogen carbonate. Afterwards, the catalyst was investigated (Entries 5, 13–16). It was clear that the palladium(II) acetate/triphenylphosphine was the most efficient. Additionally, DMF was selected to be the optimal solvent (Entries 3, 9, 10). In conclusion, the optimum reaction conditions were as follows: 2 mol% of palladium(II) catalyst, 4 mol% of Ph_3P, the alkali of $(n\text{-}Bu)_3N$ (2 equiv), the solvent of DMF,

and the temperature of 130 °C.



Scheme 1

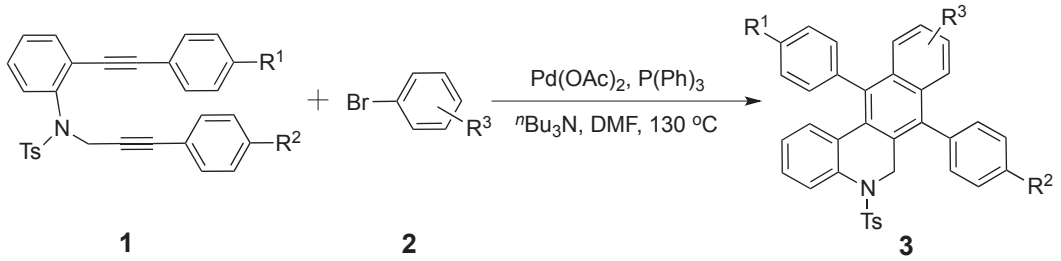
Table 1. Optimization of the Conditions for the One-Step Cascade Reaction

Entry	Catalyst (mol%)	Solvent	Base	Time (h)	Temp[a] (°C)	Yield[b] (%)
1	$Pd(OAc)_2/PPh_3$ (1 : 2)	DMF	$^nBu_3N$	24	130	36
2	$Pd(OAc)_2/PPh_3$ (2 : 4)	DMF	$^nBu_3N$	24	100	7
3	$Pd(OAc)_2/PPh_3$ (2 : 4)	DMF	$^nBu_3N$	24	110	24
4	$Pd(OAc)_2/PPh_3$ (2 : 4)	DMF	$^nBu_3N$	24	120	73
5	$Pd(OAc)_2/PPh_3$ (2 : 4)	DMF	$^nBu_3N$	24	130	86
6	$Pd(OAc)_2/PPh_3$ (2 : 4)	DMF	$^nBu_3N$	24	140	78
7	$Pd(OAc)_2/PPh_3$ (2 : 4)	DMF	$^nBu_3N$	26	130	86
8	$Pd(OAc)_2/PPh_3$ (2 : 4)	DMF	$^nBu_3N$	20	130	75
9	$Pd(OAc)_2/PPh_3$ (2 : 4)	toluene	$^nBu_3N$	24	130	37
10	$Pd(OAc)_2/PPh_3$ (2 : 4)	DMSO	$^nBu_3N$	24	130	22
11	$Pd(OAc)_2/PPh_3$ (2 : 4)	DMF	$NaHCO_3$	24	130	trace
12	$Pd(OAc)_2/PPh_3$ (2 : 4)	DMF	Cs_2CO_3	24	130	9
13	$PdCl_2$ (2)	DMF	$^nBu_3N$	24	130	0
14	$Pd(OAc)_2$ (2)	DMF	$^nBu_3N$	24	130	trace
15	$Pd(PPh_3)_4$ (2)	DMF	$^nBu_3N$	24	130	23
16	$Pd(dba)_2$[c] (2)	DMF	$^nBu_3N$	24	130	17

[a] General conditions: all reactions were carried out under argon. [b] Isolated yield after flash column chromatography. [c] dba = dibenzylideneacetone.

Under the above optimum conditions, the substrate of this domino reaction was studied (Scheme 2). Obviously, one-step domino reaction can be achieved through palladium catalysis with various intramolecular diynes and substituted aryl halides. Dihydrophenanthridine compounds were synthesized with excellent yields when the aryl halides with electron-withdrawing groups (such as acetyl, ethoxycarbonyl, cyano, and formyl groups). In addition, 4-methyl-*N*-(2-(phenylethynyl)phenyl)-*N*-(3-

phenylprop-2-yn-1-yl)benzenesulfonamide was used with all kinds of substituted groups including para-substituted (i.e., methyl and fluoro). With the use of diynes and aryl halides, 7,12-diphenyl-5-tosyl-5,6-dihydrobenzo[*j*]phenanthridines **3a-3c**, **3e**, **3g-3h**, **3j**, **3p**, **3r**, and **3t** were yielded efficiently (above 80%). And it should be pointed out that the yield of compound **3a** was the highest (86%). But, the desired 7,12-diphenyl-5-tosyl-5,6-dihydrobenzo[*j*]phenanthridines were obtained in lower yields ranging from 46% to 67% when aryl bromides being meta-substituted were used in the reaction. Since the R^3 group and the halogen atom were meta-substituted in the substrate **2**, the cyclization reaction became difficult due to the steric hindrance; this resistance led to a decrease in the reaction yield. In the other hand, no dihydrophenanthridine was obtained when the aryl halides with electron-rich substituent (such as methyl) was employed. It revealed that the electron-withdrawing properties of the aryl halide substrates have an important role in the synthesis of the dihydrophenanthridine compound.



1 **2** **3**

Scheme 2

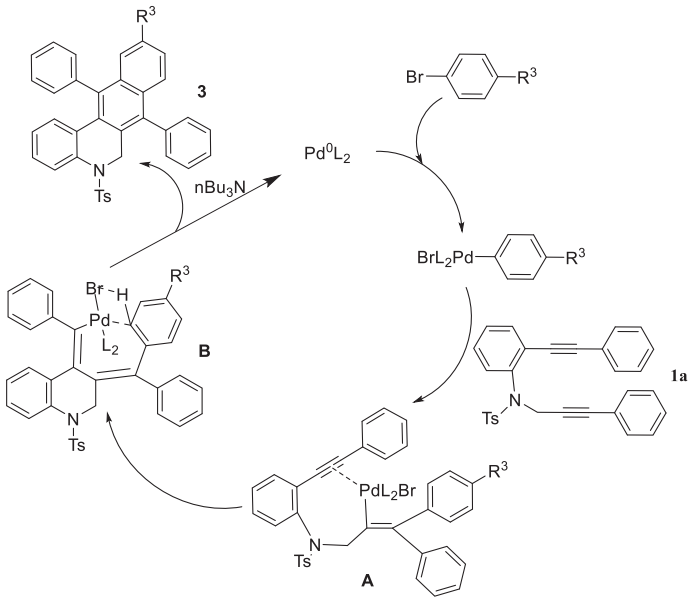
Table 2. Palladium-Catalyzed One-Pot Reaction for the Formation of Various Dihydrophenanthridines

Entry[a]	Product	R^1	R^2	R^3	Yield[b] (%)
1	**3a**	H	H	4-CN	86
2	**3b**	H	H	4-CO_2Et	84
3	**3c**	H	Me	4-CN	81
4	**3d**	H	Me	3-CN	61
5	**3e**	H	Me	4-CO_2Et	80
6	**3f**	H	F	3-CN	67
7	**3g**	H	F	4-COMe	85
8	**3h**	H	F	4-CO_2Et	82
9	**3i**	H	Cl	3-CN	57
10	**3j**	H	Cl	4-COMe	81
11	**3k**	F	H	4-COMe	78
12	**3l**	F	H	4-CO_2Et	79
13	**3m**	F	Me	4-CN	79

14	**3n**	F	Me	3-CN	51
15	**3o**	F	Me	4-CO_2Et	77
16	**3p**	Me	H	4-CN	84
17	**3q**	Me	H	3-CN	62
18	**3r**	Me	F	4-COMe	83
19	**3s**	Me	F	3-COMe	46
20	**3t**	Me	F	4-CO_2Et	81
21	**3u**	EtO	Me	4-COMe	75
22	**3v**	EtO	Me	4-CHO	71

[a] All reactions were carried out under argon using **1a–1i** (1.0 mmol), aryl bromides (1.1 mmol), [$Pd(OAc)_2$] (2 mmol%), Ph_3P (4 mmol%), base (2.0 mmol) and solvent (7 mL) at 130 °C. [b] Isolated yield after flash column chromatography.

Scheme 3 depicted the plausible mechanism of the cross-coupling reaction. Firstly, the intermediate **A** was formed by the coordination and insertion of arylpalladium(II) halide to the diyne moiety **1a**. In this step, the alkylacetylene reacted firstly in the insertion step due to its larger electron cloud density than that of the bisarylacetylene, which was helpful for the next step of the arylpalladium(II) halide's electrophilic attack. Additionally, the bisaryl carbon generated by the insertion reaction of arylpalladium species because of the priority of the alkyl carbon due to its larger electron cloud density than the aryl carbon's in the diyne and the requirement for the formation of more stable ring in the next step. Then, it reacted with the triple bond of the second C≡C by a carbopalladation reaction to give **B**. A σ-bond metathesis[11,15] with the aryl group in **B**, followed by a proton abstraction by the base generates **3**.



Scheme 3. The mechanism of the domino reaction

In conclusion, the diversely substituted 5,6-dihydrobenzo[*j*]phenanthridines was synthesized from diynes and various aryl halides based on the palladium-catalyzed domino reaction through multistep C–C bond formation and C–H activation of the incorporated aryl group. It developed a new synthesis method of 5,6-dihydrobenzo[*j*]phenanthridine derivatives with a higher yield and an excellent regioselectivity. This methodology will aid in generating more interesting structures for use in biological studies. Further investigations to understand this catalytic transformation, an evaluation of the process with a broader scope of substrates, and synthesis of more complex π-system heterocycles are in progress.

EXPERIMENTAL

All the catalytic reactions were performed under argon in oven dried Schlenk flask. The chemicals were purchased from Alfa Aesar and Acros Organics. All solvents and materials were dried, redistilled, or recrystallized before use. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Bruker Avance 300 spectrometer with $CDCl_3$ as the solvent. Chemical shifts are reported in ppm relative to TMS for the ^{1}H NMR spectra (0.00 ppm) and to $CDCl_3$ for the ^{13}C spectra (77.0 ppm). Column chromatography was performed on 300–400 mesh silica gels. Melting points were determined using a Gallenkamp melting point apparatus and are uncorrected. The Fourier-transform IR spectra were recorded with KBr pellets or thin film from $CHCl_3$ on the NaCl window in the range 4000–400 cm^{-1} on a Nicolet 5DX spectrometer. All HRMS spectra were recorded in the EI or APCI at 70 eV.

X-Ray crystallography diffraction data of **2b** and **2j** were collected at rt with a Bruker SMART Apex CCD diffractometer with graphite monochromatic Mo-Kα radiation (λ = 0.71073 Å) in the ω-scan mode. Data reductions and absorption corrections were performed with SAINT and SADABS software, respectively. The structure was solved by direct methods and refined on F^2 by full-matrix least squares using SHELXTL. All non-hydrogen atoms were treated anisotropically. The positions of hydrogen atoms were generated geometrically.

The structures of all the resulting fused dihydrophenanthridine compounds were confirmed by various spectroscopic techniques (^{1}H and ^{13}C NMR, IR spectroscopy, and HRMS). The molecular structure and relative configuration of **3b** and **3j** were confirmed by X-ray diffraction (Figures 1 and 2).[16] More details are provided in the Supporting Information.

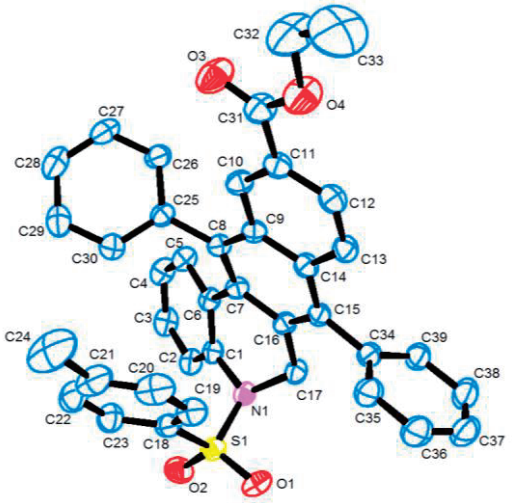


Figure 1. Molecular structure of compound **3b**

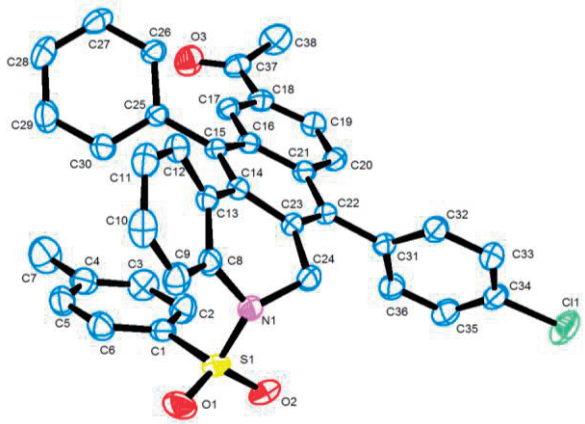


Figure 2. Molecular structure of compound **3j**

Starting Materials. General procedure for the preparation of starting materials (**1a-1i**).[17]

Typical procedure for the preparation of 7,12-diphenyl-5-tosyl-5,6-dihydrobenzo[*j*]phenanthridines (3).

7,12-Diphenyl-5-tosyl-5,6-dihydrobenzo[*j*]phenanthridine-10-carbonitrile (3a): Diyne **1a** (1.0 mmol), 4-bromobezonitrile (1.1 mmol), [$Pd(OAc)_2$] (2 mol%), Ph_3P (4 mol%), and $(n\text{-}Bu)_3N$ (2 mmol) were added to a degassed DMF (7 mL). The mixture was stirred at rt for 30 min then heated to 130 °C for 24 h. The mixture was then cooled and the reaction was quenched with H_2O (5 mL). The mixture was extracted with EtOAc (30 mL) and the organic layers were combined and washed successively with 10% aq HCl (6 mL), 10% aq $NaHCO_3$ (6 mL), and sat. aq NaCl (6 mL) then dried ($MgSO_4$) and concentrated. The residue was purified by flash column chromatography on silica gel (30:1 PE–EtOAc) to give **3a** (86%); a white solid; mp 262–263 °C; IR (KBr) 3022.5, 1593.2, 1456.3, 1352.1, 1159.2, 1084.0, 1010.7, 854.5, 810.1, 773.5, 665.4 cm^{-1}; ^1H NMR δ 7.88 (s, 1 H), 7.59–7.72 (m, 5 H), 7.38–7.51 (m, 6 H), 7.16–7.25 (m,

3 H), 6.65–6.81 (m, 6 H), 4.74 (s, 2 H), 2.04 (s, 3 H); ^{13}C NMR δ 143.5, 138.0, 136.5, 136.3, 135.9, 134.6, 133.0, 131.8, 130.6, 130.2, 130.1, 129.4, 129.3, 129.2, 129.1, 128.9, 128.8, 128.7, 128.5, 128.2, 127.6, 127.3, 126.5, 125.7, 119.4, 109.2, 49.6, 21.2; HRMS (APCI) *m/z* [M + H]$^+$ calcd for $C_{37}H_{26}N_2O_2S$: 563.1788; found: 563.1778.

Ethyl 7,12-diphenyl-5-tosyl-5,6-dihydrobenzo[*j*]phenanthridine-10-carboxylate (3b): a white solid; mp 220–221 °C; IR (KBr) 3034.0, 1707.0, 1512.2, 1348.2, 1251.8, 1161.2, 1087.9, 1020.3, 756.1, 686.7, 655.8 cm^{-1}; ^{1}H NMR δ 8.30 (s, 1H), 7.92–7.95 (m, 1H), 7.72 (d, 1H, *J* = 8.1 Hz), 7.57–7.66 (m, 4H), 7.41 (d, 5H, *J* = 5.4 Hz), 7.20 (d, 3H, *J* = 7.8 Hz), 6.66–6.80 (m, 6H), 4.74 (s, 2H), 4.32 (q, 2H, *J* = 6.9 Hz), 2.00 (s, 3H), 1.33 (t, 3H, *J* = 6.9 Hz); ^{13}C NMR δ 166.7, 143.4, 138.6, 137.9, 137.5, 137.0, 136.0, 133.8, 133.5, 131.9, 130.9, 130.7, 130.2, 129.8, 129.1, 128.7, 128.4, 128.2, 128.1, 127.8, 127.6, 127.5, 127.3, 126.5, 125.6, 125.4, 61.1, 49.6, 21.2, 14.3; HRMS (APCI) *m/z* [M + H]$^+$ calcd for $C_{39}H_{31}NO_4S$: 610.2047; found: 610.2039.

12-Phenyl-7-(*p*-tolyl)-5-tosyl-5,6-dihydrobenzo[*j*]phenanthridine-10-carbonitrile (3c): a white solid; mp 234–235 °C; IR (KBr) 3057.2, 1637.6, 1352.1, 1224.8, 1159.2, 1087.9, 842.9, 769.6, 706.0 cm^{-1}; ^{1}H NMR δ 7.87 (s, 1 H), 7.66–7.73 (m, 2 H), 7.50 (s, 1 H), 7.43 (s, 5 H), 7.16–7.27 (m, 5 H), 6.65–6.81 (m, 6 H), 4.74 (s, 2 H), 2.53 (s, 3 H), 2.03 (s, 3 H); ^{13}C NMR δ 143.5, 138.6, 138.1, 138.0, 136.4, 136.3, 136.0, 134.6, 133.2, 133.1, 133.0, 131.8, 130.7, 130.2, 130.1, 130.0, 129.2, 129.1, 128.7, 128.5, 128.2, 128.0, 127.7, 127.6, 127.3, 126.4, 125.7, 119.4, 109.2, 49.6, 21.5, 21.2; HRMS (APCI) *m/z* [M + H]$^+$ calcd for $C_{38}H_{28}N_2O_2S$: 577.1944; found: 577.1935.

12-Phenyl-7-(*p*-tolyl)-5-tosyl-5,6-dihydrobenzo[*j*]phenanthridine-9-carbonitrile (3d): a white solid; mp 265–266 °C; IR (KBr) 3022.5, 2881.7, 1600.9, 1496.8, 1454.3, 1344.4, 1159.2, 1085.9, 810.1, 754.2, 661.6 cm^{-1}; ^{1}H NMR δ 7.96 (s, 1 H), 7.73 (d, 1 H, *J* = 7.8 Hz), 7.58 (d, 1 H, *J* = 8.7 Hz), 7.47 (s, 1 H), 7.42 (t, 5 H, *J* = 7.8 Hz), 7.17–7.27 (m, 5 H), 6.66–6.81 (m, 6 H), 4.74 (s, 2 H), 2.55 (s, 3 H), 2.00 (s, 3 H); ^{13}C NMR δ 143.4, 138.8, 138.4, 138.2, 136.7, 136.0, 135.9, 133.9, 133.1, 132.9, 132.6, 131.0, 130.7, 130.4, 130.2, 130.2, 130.1, 130.0, 129.1, 128.9, 128.7, 128.6, 128.0, 127.7, 127.3, 126.0, 125.7, 119.3, 109.4, 49.5, 21.5, 21.1; HRMS (APCI) *m/z* [M + H]$^+$ calcd for $C_{38}H_{28}N_2O_2S$: 577.1944; found: 577.1937.

Ethyl 12-phenyl-7-(*p*-tolyl)-5-tosyl-5,6-dihydrobenzo[*j*]phenanthridine-10-carboxylate (3e): a white solid; mp 243–244 °C; IR (KBr) 3057.2, 2922.2, 1707.1, 1610.6, 1350.2, 1255.7, 1163.1, 1089.8, 893.0, 817.8, 771.5, 657.7 cm^{-1}; ^{1}H NMR δ 8.29 (s, 1 H), 7.94 (d, 1 H, *J* = 8.7 Hz), 7.72 (d, 1 H, *J* = 7.8 Hz), 7.64 (d, 1 H, *J* = 8.7 Hz), 7.41–7.45 (m, 6 H), 7.29 (s, 1 H), 7.19 (t, 3 H, *J* = 8.1 Hz), 6.65–6.80 (m, 6 H), 4.75 (s, 2 H), 4.31 (q, 2 H, *J* = 7.2 Hz), 2.53 (s, 3 H), 1.98 (s, 3 H), 1.33 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR δ 166.7, 143.4, 138.7, 138.2, 137.9, 137.3, 136.1, 136.0, 133.9, 133.6, 131.9, 130.9, 130.7, 130.4, 130.2, 130.1, 129.8, 128.7, 128.2, 128.0, 127.8, 127.6, 127.5, 127.4, 127.3, 126.6, 125.8, 125.5, 125.3, 61.1, 49.7, 21.5, 21.1, 14.3; HRMS (APCI) *m/z* [M + H]$^+$ calcd for $C_{40}H_{33}NO_4S$: 624.2203; found: 624.2199.

7-(4-Fluorophenyl)-12-phenyl-5-tosyl-5,6-dihydrobenzo[*j*]phenanthridine-9-carbonitrile (3f): a white solid; mp 232–234 °C; IR (KBr) 2978.1, 1629.9, 1508.3, 1246.0, 1168.9, 1087.9, 817.8, 707.9, 657.7 cm^{-1}; ^1H NMR δ 7.89 (s, 1 H), 7.79 (d, 1 H, J = 7.8 Hz), 7.72 (d, 1 H, J = 6.9 Hz), 7.61 (d, 1 H, J = 9.0 Hz), 7.53 (d, 1 H, J = 9.3 Hz), 7.36–7.44 (m, 7 H), 7.14–7.22 (m, 2 H), 6.66–6.82 (m, 6 H), 4.72 (s, 2 H), 2.06 (s, 3 H); ^{13}C NMR δ 164.6 (d, J_{C-F} = 257.1 Hz), 143.5, 138.3, 138.2, 136.4, 136.0, 135.4, 134.0, 133.4, 132.1, 132.0, 131.9, 131.8, 130.9, 130.7, 130.2, 130.1, 128.9, 128.8, 128.2, 128.1, 127.5, 127.3, 126.3, 125.7, 119.1, 116.7, 116.4, 109.7, 49.4, 21.1; HRMS (APCI) *m/z* $[M + H]^+$ calcd for $C_{37}H_{25}FN_2O2S$: 581.1694; found: 581.1680.

1-(7-(4-Fluorophenyl)-12-phenyl-5-tosyl-5,6-dihydrobenzo[*j*]phenanthridin-10-yl)ethanone (3g): a white solid; mp 229–230 °C; IR (KBr) 3045.6, 2918.3, 1685.8, 1602.9, 1514.1, 1342.5, 1240.2, 1161.2, 1078.2, 844.8, 773.5, 706.0 cm^{-1}; ^1H NMR δ 8.15 (s, 1 H), 7.93 (d, 1 H, J = 7.2 Hz), 7.72 (d, 1 H, J = 7.5 Hz), 7.58 (d, 1 H, J = 9.0 Hz), 7.34–7.44 (m, 7 H), 7.16–7.22 (m, 3 H), 6.67–6.81 (m, 6 H), 4.73 (s, 2 H), 2.47 (s, 3 H), 2.02 (s, 3 H); ^{13}C NMR δ 198.0, 164.4 (d, J_{C-F} = 248.2 Hz), 143.4, 138.6, 137.9, 136.0, 135.0, 134.3, 134.1, 133.9, 132.8, 132.0, 131.9, 131.8, 130.8, 130.4, 130.1, 129.0, 128.8, 128.7, 128.2, 128.0, 127.4, 127.3, 126.5, 125.7, 124.3, 116.4, 116.1, 49.6, 26.5, 21.2; HRMS (APCI) *m/z* $[M + H]^+$ calcd for $C_{38}H_{28}FNO_3S$: 598.1847; found: 598.1836.

Ethyl 7-(4-fluorophenyl)-12-phenyl-5-tosyl-5,6-dihydrobenzo[*j*]phenanthridine-10-carboxylate (3h): a white solid; mp 213–214 °C; IR (KBr) 3057.2, 2956.5, 1708.9, 1602.9, 1512.2, 1352.1, 1251.8, 1163.1, 1089.8, 1022.3, 893.0, 844.8, 761.9, 704.0, 655.8 cm^{-1}; ^1H NMR δ 8.31 (s, H), 7.9–7.97 (m, 1 H), 7.72 (d, 1 H, J = 7.8 Hz), 7.56 (d, 1 H, J = 8.7 Hz), 7.33–7.41 (m, 7 H), 7.21 (s, 1 H), 7.18 (d, 2 H, J = 8.4 Hz), 6.66–6.80 (m, 6 H), 4.73 (s, 2 H), 4.32 (q, 2 H, J = 6.9 Hz), 2.02 (s, 3 H), 1.34 (t, 3 H, J = 6.9 Hz); ^{13}C NMR δ 166.6, 164.4 (d, J_{C-F} = 255.3 Hz), 143.5, 138.5, 137.9, 137.8, 136.0, 134.9, 133.8, 132.9, 132.8, 132.0, 131.9, 131.8, 130.9, 130.5, 130.2, 129.9, 128.7, 128.2, 128.1, 127.9, 127.7, 127.4, 127.3, 126.2, 125.6, 116.4, 116.1, 61.1, 49.6, 21.2, 14.2; HRMS (APCI) *m/z* $[M + H]^+$ calcd for $C_{39}H_{30}FNO_4S$: 628.195; found: 628.1947.

7-(4-Chlorophenyl)-12-phenyl-5-tosyl-5,6-dihydrobenzo[*j*]phenanthridine-9-carbonitrile (3i): a white solid; mp 254–255 °C; IR (KBr) 3055.2, 2881.7, 1595.1, 1491.0, 1342.5, 1159.2, 1087.9, 1014.6, 839.0, 756.1, 659.7 cm^{-1}; ^1H NMR δ 7.87 (s, 1 H), 7.58–7.72 (m, 4 H), 7.33–7.47 (m, 6 H), 7.22 (s, 1 H), 7.18 (d, 2 H, J = 7.8 Hz), 6.67–6.81 (m, 6 H), 4.71 (s, 2 H), 2.03 (s, 3 H); ^{13}C NMR δ 143.5, 138.2, 138.1, 136.5, 135.9, 135.2, 134.4, 134.0, 133.2, 132.0, 131.8, 131.4, 130.8, 130.7, 130.4, 130.2, 130.1, 130.0, 129.7, 129.0, 128.8, 128.2, 128.1, 127.5, 127.3, 126.3, 125.7, 119.1, 109.8, 49.3, 21.1; HRMS (APCI) *m/z* $[M + H]^+$ calcd for $C_{37}H_{25}ClN_2O_2S$: 597.1398; found: 597.1390.

1-(7-(4-Chlorophenyl)-12-phenyl-5-tosyl-5,6-dihydrobenzo[*j*]phenanthridin-10-yl)ethanone (3j): a white solid; mp 249–250 °C; IR (KBr) 3032.1, 2955.0, 2918.3, 1683.9, 1595.1, 1508.3, 1477.5, 1413.8,

1340.5, 1288.5, 1236.4, 1155.4, 1078.2, 887.3, 842.9, 810.1, 761.9, 706.0, 655.8 cm^{-1}; ^1H NMR δ 8.15 (s, 1 H), 7.93 (d, 1 H, *J* = 9.0 Hz), 7.72 (d, 1 H, *J* = 7.8 Hz), 7.55–7.64 (m, 3 H), 7.34–7.44 (m, 5 H), 7.20 (s, 1 H), 7.18 (d, 2 H, *J* = 9.0 Hz), 6.67–6.81 (m, 6 H), 4.72 (s, 2 H), 2.47 (s, 3 H), 2.02 (s, 3 H); ^{13}C NMR δ 198.0, 143.3, 138.5, 138.0, 137.8, 136.0, 135.3, 134.8, 134.7, 134.3, 133.9, 133.6, 131.9, 131.5, 130.8, 130.4, 130.1, 129.5, 129.0, 128.8, 128.7, 128.4, 128.3, 128.0, 127.4, 127.3, 126.5, 125.7, 124.3, 49.5, 26.5, 21.2; HRMS (APCI) *m/z* $[M + H]^+$ calcd for $C_{38}H_{28}ClNO_3$: 614.1551; found: 614.1543.

1-(12-(4-Fluorophenyl)-7-phenyl-5-tosyl-5,6-dihydrobenzo[*j*]phenanthridin-10-yl)ethanone (3k): a white solid; mp 245–247 °C; IR (KBr) 3026.3, 2955.0, 2916.4, 1680.0, 1602.9, 1510.3, 1431.2, 1365.6, 1344.4, 1292.3, 1222.9, 1161.2, 1087.9, 891.1, 858.3, 814.0, 761.9, 692.4 cm^{-1}; ^1H NMR δ 8.13 (s, 1 H), 7.92 (d, 1 H, *J* = 7.5 Hz), 7.73 (d, 1 H, *J* = 7.5 Hz), 7.58–7.67 (m, 4 H), 7.41 (d, 2 H, *J* = 6.9 Hz), 7.10–7.22 (m, 5 H), 6.65–6.86 (m, 6 H), 4.74 (s, 2 H2), 2.51 (s, 3 H), 2.00 (s, 3 H); ^{13}C NMR δ 197.9, 164.1 (d, $J_{C\text{-}F}$ = 248.3 Hz), 143.3, 138.0, 136.8, 136.4, 136.1, 134.6, 134.3, 134.0, 133.8, 132.6, 132.5, 131.9, 130.4, 130.1, 130.0, 129.2, 128.7, 128.6, 128.4, 128.3, 127.6, 127.3, 127.0, 125.7, 124.3, 116.1, 115.8, 49.6, 26.6, 21.1; HRMS (APCI) *m/z* $[M + H]^+$ calcd for $C_{38}H_{28}FNO_3S$: 598.1847; found: 598.1840.

Ethyl 12-(4-fluorophenyl)-7-phenyl-5-tosyl-5,6-dihydrobenzo[*j*]phenanthridine-10-carboxylate (3l): a white solid; mp 245–246 °C; IR (KBr) 3074.5, 2978.1, 1707.0, 1508.3, 1357.9, 1253.7, 1159.2, 1089.8, 754.2, 686.7 cm^{-1}; ^1H NMR δ 8.27 (s, 1 H), 7.96 (d, 1 H, *J* = 9.0 Hz), 7.73 (d, 1 H, *J* = 7.8 Hz), 7.58–7.66 (m, 4 H), 7.41 (d, 2 H, *J* = 6.6 Hz), 7.08–7.24 (m, 5 H), 6.64–6.85 (m, 6 H), 4.74 (s, 2 H), 4.34 (q, 2 H, *J* = 7.2 Hz), 2.00 (s, 3 H), 1.35 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR δ 166.6, 164.1 (d, $J_{C\text{-}F}$ = 255.3Hz), 143.4, 138.0, 136.9, 136.3, 136.1, 134.5, 133.8, 133.6, 132.6, 131.8, 130.5, 130.2, 130.1, 129.4, 129.1, 128.7, 128.5, 128.2, 128.0, 127.7, 127.6, 127.3, 126.6, 125.7, 125.6, 116.0, 115.7, 61.2, 49.7, 21.2, 14.3; HRMS (APCI) *m/z* $[M + H]^+$ calcd for $C_{39}H_{30}FNO_4S$: 628.1952; found: 628.1938.

12-(4-Fluorophenyl)-7-(*p*-tolyl)-5-tosyl-5,6-dihydrobenzo[*j*]phenanthridine-10-carbonitrile (3m): a white solid; mp 295–296 °C; IR (KBr) 3030.2, 2916.4, 1599.0, 1508.3, 1357.9, 1222.9, 1166.9, 1084.0, 860.3, 771.5, 707.9 cm^{-1}; ^1H NMR δ 7.84 (s, 1 H), 7.70 (t, 2 H, *J* = 8.4 Hz), 7.43–7.51 (m, 4 H), 7.14–7.24 (m, 6 H), 6.64–6.87 (m, 6 H), 4.74 (s, 2 H), 2.53 (s, 3 H), 2.03 (s, 3 H); ^{13}C NMR δ 164.2 (d, $J_{C\text{-}F}$ = 253.0 Hz), 143.5, 138.7, 138.1, 136.7, 136.0, 135.1, 134.7, 133.9, 133.2, 133.1, 132.5, 132.4, 131.8, 130.1, 129.97, 129.92, 129.9, 129.5, 128.7, 127.8, 127.7, 127.3, 126.5, 125.8, 119.2, 116.4, 116.1, 109.4, 49.6, 21.4, 21.2; HRMS (APCI) *m/z* $[M + H]^+$ calcd for $C_{38}H_{27}FN_2O_2S$: 595.1850; found: 595.1839.

12-(4-Fluorophenyl)-7-(*p*-tolyl)-5-tosyl-5,6-dihydrobenzo[*j*]phenanthridine-9-carbonitrile (3n): a white solid; mp 248–249 °C; IR (KBr) 3066.8, 1602.9, 1510.3, 1342.5, 1232.5, 1159.2, 1085.9, 883.4, 808.2, 758.0, 707.9, 665.4 cm^{-1}; ^1H NMR δ 7.97 (s, 1 H), 7.73 (d, 1 H, *J* = 8.1 Hz), 7.56 (d, 1 H, *J* = 9.0 Hz), 7.47 (d, 3 H, *J* = 6.6 Hz), 7.09–7.27 (m, 8 H), 6.84 (t, 1 H, *J* = 7.5 Hz), 6.65–6.74 (m, 4 H), 4.74 (s, 2 H), 2.55 (s, 3 H), 2.00 (s, 3 H); ^{13}C NMR δ 164.1 (d, $J_{C\text{-}F}$ = 246.6 Hz), 143.4, 138.9, 138.3, 137.0, 136.0,

134.7, 134.3, 133.9, 133.2, 132.8, 132.7, 132.4, 131.8, 131.0, 130.7, 130.1, 129.9, 128.8, 128.7, 127.8, 127.6, 127.3, 126.3, 125.8, 119.2, 116.2, 115.9, 109.5, 49.5, 21.5, 21.1; HRMS (APCI) *m/z* $[M + H]^+$ calcd for $C_{38}H_{27}FN_2O_2S$: 595.1850; found: 595.1849.

Ethyl 12-(4-fluorophenyl)-7-(*p*-tolyl)-5-tosyl-5,6-dihydrobenzo[*j*]phenanthridine-10-carboxylate (3o): a white solid; mp 244–245 °C; IR (KBr) 3012.5, 2993.5, 1705.1, 1602.9, 1510.3, 1357.9, 1257.6, 1089.8, 1020.3, 846.8, 765.7, 686.7, 655.8 cm^{-1}; ^1H NMR δ 8.26 (s, 1 H), 7.95 (d, 1 H, *J* = 8.7 Hz), 7.73 (d, 1 H, *J* = 8.1 Hz), 7.65 (d, 1 H, *J* = 8.7 Hz), 7.45 (d, 2 H, *J* = 7.8 Hz), 7.10–7.29 (m, 8 H), 6.83 (t, 1 H, *J* = 7.5 Hz), 6.63–6.71 (m, 4 H), 4.75 (s, 2 H), 4.33 (q, 2 H, *J* = 6.9 Hz), 2.53 (s, 3 H), 1.99 (s, 3 H), 1.35 (t, 3 H, *J* = 6.9 Hz); ^{13}C NMR δ 166.6, 164.0 (d, J_{C-F} = 242.6Hz), 143.3, 138.3, 138.0, 136.4, 136.0, 134.6, 133.9, 133.8, 133.7, 132.6, 132.4, 131.8, 130.6, 130.3, 130.0, 129.8, 129.4, 128.6, 128.4, 128.2, 127.7, 127.3, 126.7, 125.6, 125.4, 116.0, 115.7, 61.1, 49.7, 21.5, 21.1, 14.3; HRMS (APCI) *m/z* $[M + H]^+$ calcd for $C_{40}H_{32}FNO_4S$: 642.2109; found: 642.2105.

7-Phenyl-12-(*p*-tolyl)-5-tosyl-5,6-dihydrobenzo[*j*]phenanthridine-10-carbonitrile (3p): a white solid; mp 222–223 °C; IR (KBr) 3026.3, 2955.0, 2920.2, 1595.1, 1508.3, 1456.3, 1348.2, 1288.5, 1163.1, 1085.9, 889.2, 856.4, 812.0, 760.0, 706.0, 663.5 cm^{-1}; ^1H NMR δ 7.90 (s, 1 H), 7.72 (d, 1 H, *J* = 7.8 Hz), 7.58–7.63 (m, 4 H), 7.49 (d, 1 H, *J* = 8.7 Hz), 7.39 (d, 2 H, *J* = 5.7 Hz), 7.15–7.24 (m, 5 H), 6.71–6.84 (m, 6 H), 4.73 (s, 2 H), 2.47 (s, 3 H), 2.03 (s, 3 H); ^{13}C NMR δ 143.5, 138.0, 137.9, 136.7, 136.4, 136.1, 135.9, 134.9, 134.5, 133.2, 133.0, 132.0, 130.5, 130.3, 130.1, 129.8, 129.6, 129.4, 129.2, 129.1, 128.7, 128.6, 128.4, 127.6, 127.3, 126.4, 125.7, 119.4, 109.1, 49.6, 21.4, 21.2; HRMS (APCI) *m/z* $[M + H]^+$ calcd for $C_{38}H_{28}N_2O_2S$: 577.1944; found: 577.1946.

7-Phenyl-12-(*p*-tolyl)-5-tosyl-5,6-dihydrobenzo[*j*]phenanthridine-9-carbonitrile (3q): a white solid; mp 236–237 °C; IR (KBr) 3066.8, 2918.3, 1647.2, 1597.1, 1491.0, 1454.3, 1354.0, 1163.1, 1078.2, 1014.6, 889.2, 841.0, 771.5, 709.8, 651.9 cm^{-1}; ^1H NMR δ 7.91 (s, 1 H), 7.59–7.72 (m, 5 H), 7.37–7.44 (m, 3 H), 7.16–7.25 (m, 5 H), 6.72–6.82 (m, 6 H), 4.72 (s, 2 H), 2.46 (s, 3 H), 2.01 (s, 3 H); ^{13}C NMR δ 143.4, 138.1, 137.8, 136.4, 136.2, 136.0, 135.9, 135.3, 134.1, 133.0, 132.4, 130.9, 130.5, 130.3, 130.2, 130.1, 129.6, 129.4, 129.2, 128.9, 128.7, 128.6, 128.1, 127.6, 127.3, 126.0, 125.7, 119.3, 109.4, 49.4, 21.4, 21.1; HRMS (APCI) *m/z* $[M + H]^+$ calcd for $C_{38}H_{28}N_2O_2S$: 577.1944; found: 577.1942.

1-(7-(4-Fluorophenyl)-12-(*p*-tolyl)-5-tosyl-5,6-dihydrobenzo[*j*]phenanthridin-10-yl)ethanone (3r): a white solid; mp 232–233 °C; IR (KBr) 3066.8, 2955.0, 2918.3, 1676.1, 1602.9, 1512.2, 1492.9, 1417.7, 1346.3, 1288.5, 1224.8, 1161.2, 1085.9, 891.1, 844.8, 812.0, 761.9, 707.9, 655.8 cm^{-1}; ^1H NMR δ 8.18 (s, 1 H), 7.92 (d, 1 H, *J* = 9.0 Hz), 7.72 (d, 1 H, *J* = 8.1 Hz), 7.57 (d, 1 H, *J* = 8.7 Hz), 7.36 (d, 4 H, *J* = 8.1 Hz), 7.15–7.22 (m, 5 H), 6.71–6.83 (m, 6 H), 4.72 (s, 2 H), 2.49 (s, 3 H), 2.47 (s, 3 H), 2.01 (s, 3 H); ^{13}C NMR δ 198.1, 164.4 (d, J_{C-F} = 248.8 Hz), 143.4, 138.0, 137.8, 137.7, 136.0, 135.4, 134.8, 134.2, 134.1, 133.9, 132.9, 132.1, 132.0, 131.9, 130.6, 130.2, 129.5, 129.1, 128.7, 128.1, 127.4, 127.3, 126.5, 125.7,

124.2, 116.4, 116.1, 49.6, 26.6, 21.4, 21.2; HRMS (APCI) *m/z* $[M + H]^+$ calcd for $C_{39}H_{30}FNO_3S$: 612.2003; found: 612.1995.

1-(7-(4-Fluorophenyl)-12-(*p*-tolyl)-5-tosyl-5,6-dihydrobenzo[*j*]phenanthridin-9-yl)ethanone (3s): a white solid; mp 221–222 °C; IR (KBr) 3028.2, 2918.3, 1672.3, 1600.9, 1510.3, 1356.0, 1257.6, 1163.1, 1087.9, 891.1, 763.8, 709.8, 663.5 cm^{-1}; ^1H NMR δ 8.11 (s, 1 H), 7.86 (d, 1 H, *J* = 7.2 Hz), 7.72 (d, 1 H, *J* = 8.1 Hz), 7.59 (d, 1 H, *J* = 9.0 Hz), 7.39 (t, 4 H, *J* = 8.4 Hz), 7.13–7.23 (m, 6 H), 6.69–6.83 (m, 5 H), 4.73 (s, 2 H), 2.53 (s, 3 H), 2.46 (s, 3 H), 2.00 (s, 3 H); ^{13}C NMR δ 197.9, 164.5 (d, J_{C-F} = 248.2 Hz), 143.4, 138.0, 137.5, 136.5, 136.2, 135.9, 135.7, 135.0, 134.5, 132.7, 132.3, 132.0, 131.9, 131.1, 130.6, 130.3, 129.5, 128.7, 128.3, 127.9, 127.6, 127.5, 127.2, 125.7, 123.6, 116.5, 116.2, 49.5, 26.6, 21.4, 21.1; HRMS (APCI) *m/z* $[M + H]^+$ calcd for $C_{39}H_{30}FNO_3S$: 612.2003; found: 612.2000.

Ethyl 7-(4-fluorophenyl)-12-(*p*-tolyl)-5-tosyl-5,6-dihydrobenzo[*j*]phenanthridine-10-carboxylate (3t): a white solid; mp 226–227 °C; IR (KBr) 3033.6, 2932.5, 1629.9, 1498.7, 1352.1, 1234.4, 1163.1, 1082.1, 889.2, 835.2, 760.0, 707.9, 661.6 cm^{-1}; ^1H NMR δ 8.34 (s, 1 H), 7.92 (t, 1 H, *J* = 6.9 Hz), 7.71 (d, 1 H, *J* = 7.8 Hz), 7.54 (d, 1 H, *J* = 8.7 Hz), 7.36 (d, 4 H, *J* = 7.5 Hz), 7.14–7.25 (m, 6 H), 6.70–6.82 (m, 5 H), 4.75 (s, 2 H), 4.33 (q, 2 H, *J* = 6.9 Hz), 2.45 (s, 3 H), 2.01 (s, 3 H), 1.35 (t, 3 H, *J* = 6.9 Hz); ^{13}C NMR δ 166.7, 164.4 (d, J_{C-F} = 247.5Hz), 143.5, 137.9, 137.8, 137.6, 136.0, 135.4, 134.7, 133.8, 132.9, 132.1, 132.0, 131.9, 130.7, 130.2, 130.1, 129.5, 128.7, 128.2, 128.1, 127.6, 127.4, 127.3, 126.2, 125.6, 125.5, 116.4, 116.1, 61.1, 49.6, 21.4, 21.2, 14.3; HRMS (APCI) *m/z* $[M + H]^+$ calcd for $C_{40}H_{32}FNO_4S$: 642.2109; found: 642.2108.

1-(12-(4-Ethoxyphenyl)-7-(*p*-tolyl)-5-tosyl-5,6-dihydrobenzo[*j*]phenanthridin-10-yl)ethanone (3u): a white solid; mp 237–238 °C; IR (KBr) 3036.0, 2978.1, 2875.9, 1681.9, 1606.7, 1512.2, 1348.2, 1240.2, 1159.2, 1087.9, 1045.4, 891.1, 814.0, 765.7, 690.5 cm^{-1}; ^1H NMR δ 8.20 (s, 1 H), 7.90 (d, 1 H, *J* = 7.5 Hz), 7.72 (d, 1 H, *J* = 7.8 Hz), 7.65 (d, 1 H, *J* = 9.0 Hz), 7.44 (d, 2 H, *J* = 7.8 Hz), 7.17–7.28 (m, 6 H), 6.95 (d, 2 H, *J* = 7.5 Hz), 6.86 (d, 1 H, *J* = 7.8 Hz), 6.68–6.61 (m, 4 H), 4.73 (s, 2 H), 4.12 (q, 2 H, *J* = 6.9 Hz), 2.53 (s, 3 H), 2.49 (s, 3 H), 1.96 (s, 3 H), 1.50 (t, 3 H, *J* = 6.9 Hz); ^{13}C NMR δ 198.1, 158.6, 143.3, 138.2, 137.9, 137.2, 136.0, 134.1, 134.0, 133.9, 133.8, 132.6, 132.2, 131.9, 130.9, 130.5, 130.1, 129.8, 129.0, 128.6, 128.4, 128.2, 128.0, 127.6, 127.3, 126.8, 125.7, 123.9, 114.8, 63.6, 49.7, 26.6, 21.5, 21.1, 14.9; HRMS (APCI) *m/z* $[M + H]^+$ calcd for $C_{41}H_{35}NO_4S$: 638.2361; found: 638.2354.

12-(4-Ethoxyphenyl)-7-(*p*-tolyl)-5-tosyl-5,6-dihydrobenzo[*j*]phenanthridine-10-carbaldehyde (3v): a white solid; mp 241–242 °C; IR (KBr) 3055.2, 2980.0, 1685.8, 1608.6, 1512.2, 1350.2, 1247.9, 1161.9, 1085.9, 841.0, 756.1, 709.8, 655.8 cm^{-1}; ^1H NMR δ 9.94 (s, 1 H), 8.04 (s, 1H), 7.83 (d, 1 H, *J* = 8.7 Hz), 7.69 (t, 2 H, *J* = 9.0 Hz), 7.45 (d, 2 H, *J* = 7.5 Hz), 7.16–7.28 (m, 6 H), 6.95 (d, 2 H, *J* = 7.8 Hz), 6.84 (t, 1 H, *J* = 7.5 Hz), 6.71 (t, 4 H, *J* = 8.1 Hz), 4.74 (s, 2 H), 4.13 (q, 2 H, *J* = 6.9 Hz), 2.53 (s, 3 H), 1.96 (s, 3 H), 1.50 (d, 3 H, *J* = 6.9 Hz); ^{13}C NMR δ 192.4, 158.7, 143.3, 138.4, 137.9, 137.2, 136.3, 136.1, 134.9,

134.6, 133.7, 132.4, 131.9, 130.7, 130.4, 130.2, 130.1, 130.0, 129.9, 128.9, 128.6, 128.3, 128.1, 127.6, 127.5, 127.3, 125.7, 122.6, 114.9, 63.6, 49.7, 21.4, 21.1, 14.9; HRMS (APCI) *m/z* $[M + H]^+$ calcd for $C_{40}H_{33}NO_4S$: 624.2204; found: 624.2204.

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16. Crystallographic data for compound **2b** and **2j** have been deposited with the accession CCDC 1538949 and 1538948, and can be obtained free of charge from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44(1233)336033; E-mail: deposit@ccdc.cam.ac.uk; Web site: www.ccdc.cam.ac.uk/conts/retrieving.html.
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