Synthesis of 6-(arylthio)phenanthridines by cyclization reaction of 2-isocyanobiphenyls with thiols

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Abstract
An efficient method for the synthesis of 6-(arylthio)phenanthridines by *tert*-butyl peroxybenzoate (TBPB)-promoted cyclization reaction of 2-isocyanobiphenyls with thiols is developed. A radical pathway is proposed and evidenced for the reaction mechanism. It tolerates a wide range of substrates and represents a practical approach to 6-arylthiophenanthridines.

Keywords: Phenanthridines, thiols, isocyanides, cyclization, radical reactions

Introduction

Phenanthridines are common constituents of some alkaloids and potential pharmaceuticals (Figure 1), and these heterocycles show biological activities,[1-5] such as antitumor, antileukemic, antiviral, and antifungal properties.[6-11] In addition, they have excellent optical and electronic properties in the fields of functional materials.[12,13]

In recent years, the synthesis of phenanthridine derivatives via the radical addition and cyclization of 2-isocyanobiphenyls has received much attention. Several radical precursors have been used, such as boronic acids,[14] CF_3 reagents,[15-17] aldehydes,[18] acyl peroxides,[19] simple alkanes,[20] halides,[21,22] diphenylphosphine oxide,[23] arenesulfonyl chlorides,[24] α-oxocarboxylic acids and hydrazines,[25,26] and as a result the corresponding 6-functionalized phenanthridine derivatives were prepared. However, only a few examples of the construction of 6-arylthio-substituted phenanthridines have been reported. The formation of 6-arylthiophenanthridines from 2-isocyanobiaryls and disulfides was first described by Han and Pan.[27] However, this method requires a large excess (6 equiv) of peroxide and non-atom economic disulfides. And 6-arylthiophenanthridines can be obtained by the reaction of 2-biaryl isothiocyanates and diaryliodonium salts, which are costly.[28] In addition, they can also be obtained from the nucleophilic substitution of 6-chlorophenanthridines with thiophenols.[29,30] Methods for the construction of 6-arylthiophenanthridines are still desired. To this end, we report the radical addition and cyclization of 2-isocyanobiphenyls with thiophenols to prepare 6-arylthiophenanthridines.

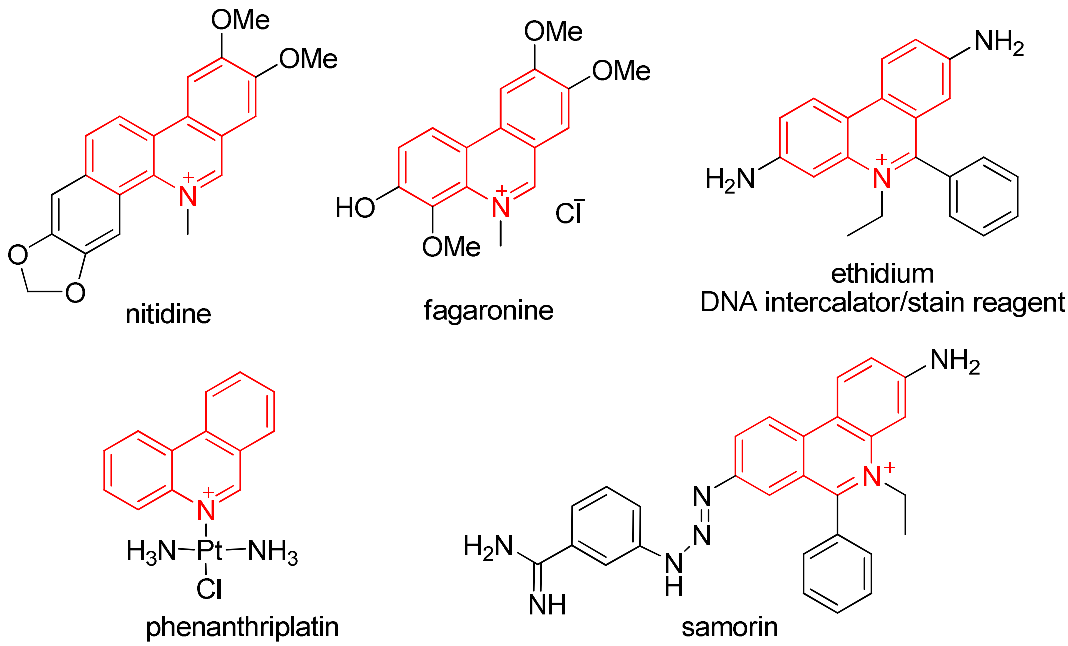


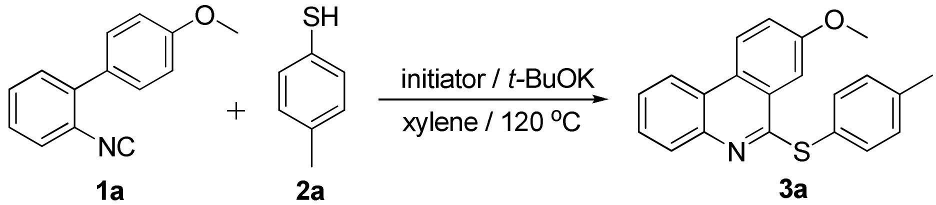
Figure 1. Biologically active phenanthridines.

Results and Discussion

Initially, 2-isocyano-4′-methoxybiphenyl (**1a**) and *p*-toluenethiol (**2a**) were selected as model substrates for optimization of the reaction conditions (Table 1). When a mixture of **1a** and **2a** with *t*-BuOK was heated at 120 °C in xylene for 5 h under argon, no product was obtained (Table 1, entry 1). The addition of azobisisobutyronitrile (AIBN) provided the product **3a**, although in only 19% yield (entry 2). Several other radical initiators were then examined. Phthaloyl peroxide, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and $Na_2S_2O_8$ did not give the required product (Table 1, entries 6, 8 and 9). Interestingly, benzoyl peroxide (BPO), *t*-butyl peroxide (DTBP) and dicumyl peroxide (DCP) all promoted the reaction, in 29%, 30% and 33% yields respectively, while *tert*-butyl peroxybenzoate (TBPB) afforded a 53% yield (entries 3-7). Therefore, TBPB was chosen for further study. We found that an increase in the amount of TBPB slightly decreased the yield (Table 1, entry 10).

A base is also essential for this reaction. Without a base, **3a** was obtained in only 34% yield (Table 2, entry 1). Improved yields were observed when inorganic bases such as K_2CO_3, Cs_2CO_3 and NaOH were used (Table 2, entries 2-4). When organic bases were examined, DBU and NEt_3 were found to be unfavorable (Table 2, entries 5 and 6), while *t*-BuOK and MeONa gave moderate yields (Table 2, entries 8 and 9). Further increase of the amount of base resulted in a decrease in the yield (Table 2, entry 10).

Table 1. Optimization of oxidant for the reaction [a]

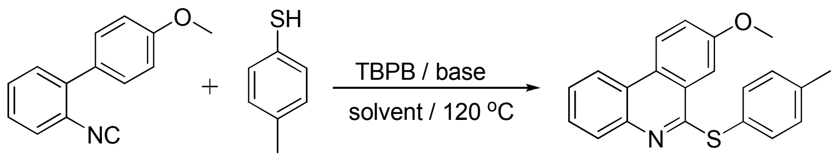


Entry	Initiator	Yield (%) [b]	Entry	Initiator	Yield (%) [b]
1	none	ND	6	Phthaloyl peroxide	ND [c]
2	AIBN	19	7	TBPB	53
3	BPO	29	8	DDQ	ND
4	DTBP	30	9	$Na_2S_2O_8$	ND
5	DCP	33	10 [d]	TBPB	48

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.36 mmol), initiator (0.9 mmol), *t*-BuOK (0.3 mmol), xylene (3 mL), 120 °C for 5 h under nitrogen. [b] Yields were determined by ^{1}H NMR with 1,2-dichloroethane as an internal standard. [c] ND: not detected. [d] TBPB 1.8 mmol.

Furthermore, the effect of solvents was explored. Solvents also play an important role in the reaction. When the reaction was carried out in polar solvents, such as DMF, DMSO and NMP, the yield of the desired product decreased dramatically (Table 2, entries 11-13). Toluene and chlorobenzene gave similar yields compared with xylene (Table 2, entries 15 and 16).

Table 2. Optimization of base and solvent for the reaction [a]



Entry	Base	Solvent	Yield [b] (%)	Entry	Base	Solvent	Yield [b] (%)
1	none	xylene	34	9	MeONa	xylene	54
2	K_2CO_3	xylene	43	10	MeONa [c]	xylene	28
3	NaOH	xylene	44	11	MeONa	DMF	25
4	Cs_2CO_3	xylene	35	12	MeONa	DMSO	ND
5	DBU	xylene	10	13	MeONa	NMP	34
6	NEt_3	xylene	33	14	MeONa	trifluorotoluene	39

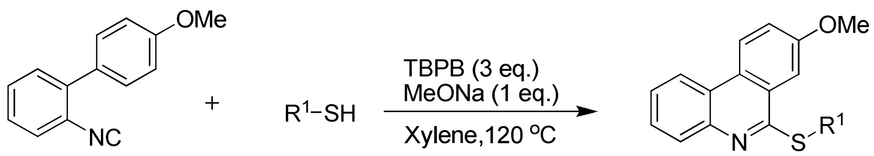
Table 2 (continued)

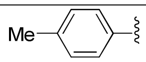
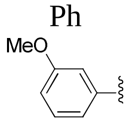
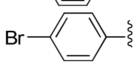
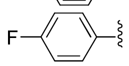
Entry	Base	Solvent	Yield [b] (%)	Entry	Base	Solvent	Yield [b] (%)
7	NaOAc	xylene	46	15	MeONa	chlorobenzene	53
8	*t*-BuOK	xylene	53	16	MeONa	toluene [d]	52

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.36 mmol), TBPB (0.9 mmol), base (0.3 mmol), solvent (3 mL), 120 °C for 5 h under nitrogen. [b] Yields were determined by ^{1}H NMR with 1,2-dichloroethane as an internal standard. [c] MeONa (0.6 mmol). [d] The reaction was carried out in a sealed tube.

After the establishment of the optimal reaction conditions, various thiophenols and also ethylthiol were tested for this oxidative thiolation / cyclization reaction with 2-isocyano-4′-methoxybiphenyl. As is evident from Table 3, *ortho* and *para* substituents on thiophenol ring did not have any significant influence on the yield of the reaction (45%-68% for **3a**-**3d**, Table 3, entries 1-4). However, fluorine substitution decreased the yield to 30% (Table 3, entry 5). Not only could thiophenols give moderate yields, but also ethylthiol gave a yield of 45% (Table 3, entry 6).

Table 3. Reaction of 2-isocyano-4′-methoxybiphenyl with various thiols [a]

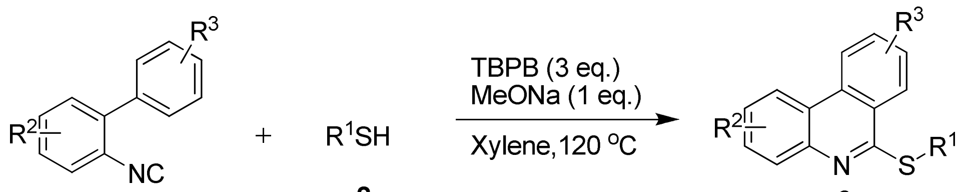


Entry	R^1	Product	Yield/% [b]
1		**3a**	53
2	Ph	**3b**	58
3		**3c**	45
4		**3d**	68
5		**3e**	30
6	Et	**3f**	45

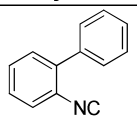
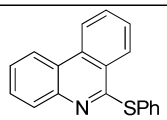
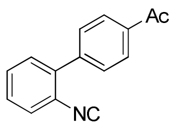
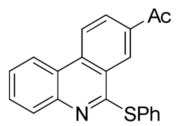
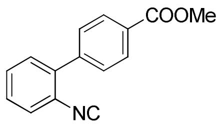
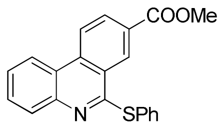
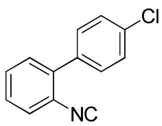
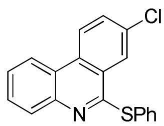
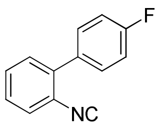
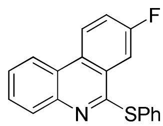
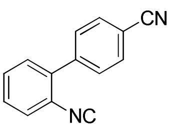
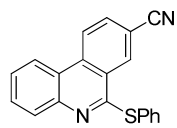
[a] Reaction conditions: 2-isocyano-4′-methoxy-biphenyl (0.3 mmol), R^1-SH (0.36 mmol), TBPB (0.9 mmol), MeONa (0.3 mmol), solvent (3 mL), 120 °C for 5 h under nitrogen. [b] Isolated yield.

A broad range of 2-isocyanobiphenyls were then investigated under standard reaction conditions; the results are summarized in Table 4. The electronic effect of the substituents on the aromatic ring with the isocyano group was unnoticeable. The functional groups, such as acetyl, ester, cyano, *t*-butyl, fluorine and chlorine were all tolerated well, and the desired products were obtained in moderate yields (Table 4，entries 1-7). Next, a variety of substituted thiophenols were subjected to the reaction. Once again, 4-bromothiophenol, thiophenol, 3-methoxybenzene-thiol, 4-toluenethiol, 2-naphthalenethiol and 4-fluorothiophenol worked well, providing the desired products in moderate yields. In addition, reactions with different isocyanides also proceeded smoothly, which furnished the desired product **3n, 3o, 3q, 3r, 3s** and **3t** in 41%, 55%, 29%, 40%, 41% and 60% yields, respectively. To investigate the regioselectivity of the cyclization, 2-isocyanobiphenyl bearing a *m*-methoxy (Table 4，entry 15) was investigated, which resulted in a mixture of two regioisomers in a ratio of 3:2. Gratifyingly, 3-(2-isocyano-phenyl)pyridine gave the corresponding products in 79% yield and 3:2 regioselectivity (Table 4, Entry 16).

Table 4. Preparation of phenanthridine derivatives [a]

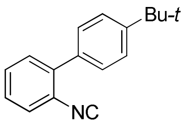
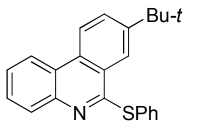
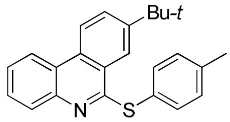
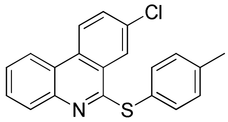
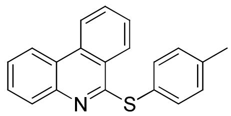
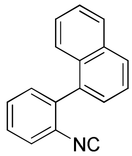
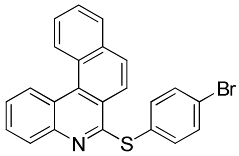
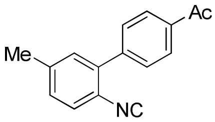
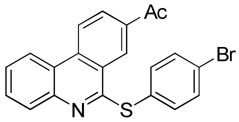
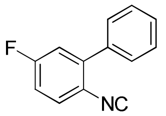
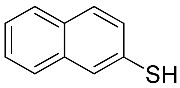
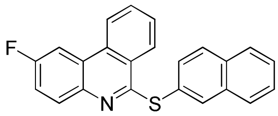
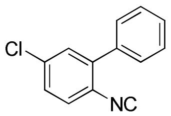
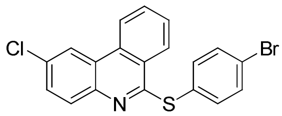
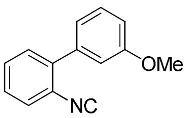
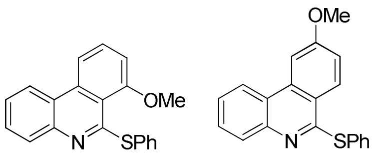
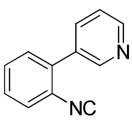
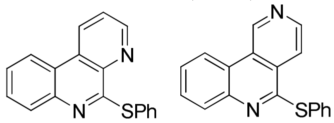


1 **2** **3**

Entry	Isocyanides (**1**)	R^1SH (**2**)	Product (**3**)	Yield (%) [b]
1	 **1b**	PhSH	 **3g**	53
2	 **1c**	PhSH	 **3h**	41
3	 **1d**	PhSH	 **3i**	50
4	 **1e**	PhSH	 **3j**	47
5	 **1f**	PhSH	 **3k**	52
6	 **1g**	PhSH	 **3l**	45

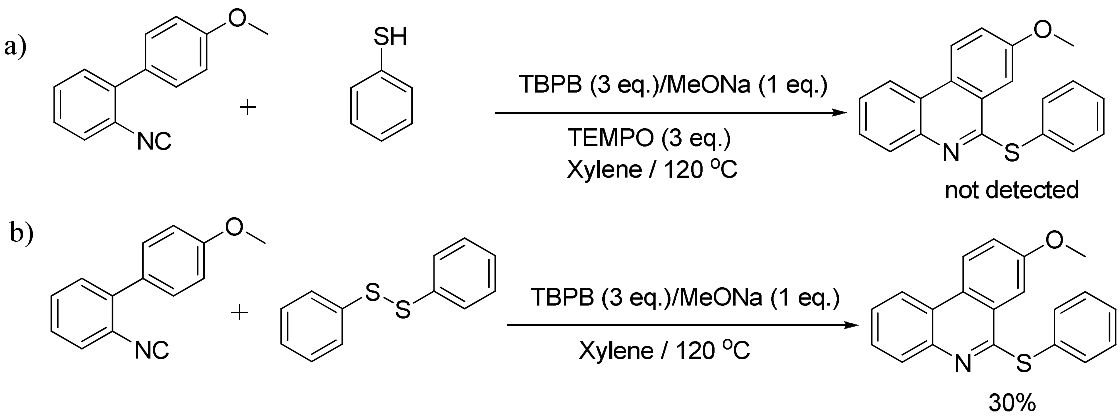
Footnotes: see foot of Table continuation

Table 4 (continued)

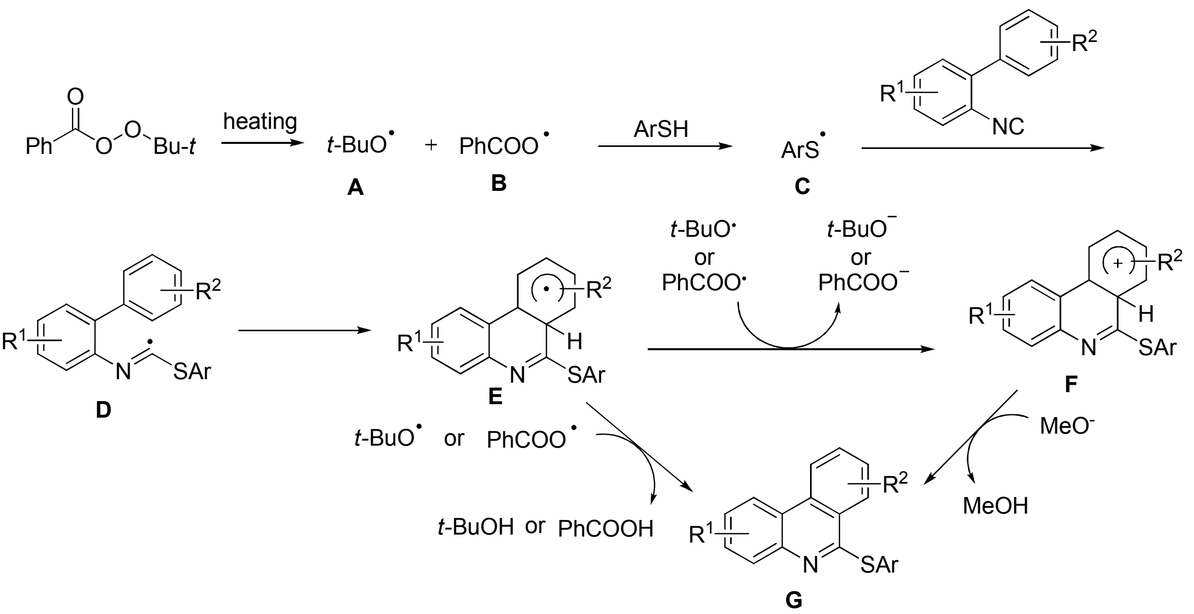
Entry	Isocyanides (**1**)	R^1SH (**2**)	Product (**3**)	Yield (%) [b]
7	 **1h**	PhSH	 **3m**	60
8	**1h**	4-MeC_6H_4SH	 **3n**	41
9	**1e**	4-MeC_6H_4SH	 **3o**	55
10	**1b**	4-MeC_6H_4SH	 **3p**	55
11	 **1i**	4-BrC_6H_4SH	 **3q**	29
12	 **1j**	4-BrC_6H_4SH	 **3r**	40
13	 **1k**		 **3s**	41
14	 **1l**	4-BrC_6H_4SH	 **3t**	60
15	 **1m**	PhSH	 **3u** + **3u′** (3 : 2)[c]	50
16	 **1n**	PhSH	 **3v** + **3v′** (3 : 2)[c]	79

[a] Reaction conditions: Isocyanides (1) (0.3 mmol), Thiophenols(2) (0.36 mmol), TBPB (0.9 mmol), MeONa (0.3 mmol), solvent (3 mL), 120 °C for 5 h under nitrogen. [b] Isolated yield.
[c] The ratio of isolated products

To probe the mechanism, the control experiment with the radical scavenger was carried out (Scheme 1). When the radical scavenger (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) was added to the reaction mixture, none of the desired product was detected (**Scheme 1 a**). This result provides evidence for a free radical mechanism. The reaction did not proceed in the absence of TBPB (Table 1, entry 1), which indicated that TBPB plays the role of reaction promoter. In addition, we performed the reaction of 2-isocyano-4′-methoxybiphenyl **(1a)** with 1,2-diphenyldisulfane under the standard conditions**,** only giving a 30% yield (**Scheme 1 b**). So we excluded the possibility that thiophenol was oxidized to 1,2-diphenyldisulfane on the major pathway in the reaction. Accordingly, a possible mechanism is illustrated in Scheme 2. Firstly, the homolytic cleavage of TBPB produces a *t*-butoxy radical (**A**) and a benzoate radical (**B**) which abstracts the *S*-H-atom from the thiophenol to give thiophenyl radical (**C**). Then, addition of the radical species (**C**) to the isonitrile produces another radical intermediate (**D**). Subsequently, intermediate (**D**) cyclizes to generate the cyclohexadienyl radical (**E**). Further reaction of the radical **E** has two plausible directions. One is further oxidation by the benzoate radical or *t*-butoxyl radical to give the intermediate (**F**), and then the phenanthridine (**G**) is delivered after deprotonation. The other is that the benzoate radical or the *t*-butoxyl radical will abstract the H-atom from the intermediate (**E**), resulting in the product (**G**).



Scheme 1. The control experiments for the mechanism.



Scheme 2. Proposed mechanism for the phenanthridine formation.

In conclusion, we have developed a TBPB-promoted phenanthridinylation of simple thiol sources with 2-isocyanobiphenyls. A radical pathway was proposed and evidenced for the reaction mechanism. The functional group, such as acetyl, ester, cyano, *t*-butyl, fluorine and chlorine were all tolerated well, and the desired products were obtained in moderate yields. This represents a practical approach to access 6-arylthiophenanthridines.

Experimental Section

General. Melting points were measured on a Novel X-5 melting point instrument. All ^{1}H NMR (400 MHz) and ^{13}C NMR (125 Hz) spectra were measured in $CDCl_3$ and recorded on Bruker Avance II 400 (^{1}H NMR) or Bruker Avance III 500 (^{13}C NMR) spectrometer with chemical shifts reported as ppm (with TMS as an internal standard). For chromatography, neutral aluminum oxide or silica gel was employed. HRMS were conducted on GCT mass spectrometer (EI) or a LTQ Orbitrap XLTM spectrometer in positive electrospray ionization (ESI+) mode. 2-isocyanobiphenyls (**1**) were synthesized via a three step route according to the paper previously.[17] The newly synthesized 6-arylthiophenanthridines compounds are described below.

2-Isocyano-4′-methoxybiphenyl (1a).[16] Pale white solid; yield 78%, 1438 mg; mp: 66 – 67 °C (lit.[16] mp: 56 – 57 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.46 – 7.40 (5H, m, ArH), 7.34 – 7.32 (1H, m, ArH), 7.01 (2H, d, $^3J_{HH}$ 8.8 Hz, ArH), 3.86 (3H, s, OCH_3).

2-Isocyanobiphenyl (1b).[16] Green liquid; yield 83%, 1188 mg; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.52 – 7.40 (8H, m, ArH), 7.36 (1H, d, $^3J_{HH}$ 7.8 Hz, ArH).

1-(2′-Isocyano-[1,1′-biphenyl]-4-yl)ethanone (1c).[20] White solid; yield 82%, 1449 mg; mp: 93 – 94°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.07 (2H, d, $^3J_{HH}$ 8.3 Hz, ArH), 7.62 (2H, d, $^3J_{HH}$ 8.4 Hz, ArH), 7.50 – 7.43 (4H, m, ArH), 2.65 (3H, s, $COCH_3$).

Methyl 2′-isocyano-[1,1′-biphenyl]-4-carboxylate (1d).[16] White solid; yield 84%, 1592 mg; mp: 146 – 147 °C (lit.[16] mp: 136 – 138 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.15 (2H, d, $^3J_{HH}$ 8.1Hz, ArH), 7.59 (2H, d, $^3J_{HH}$ 8.1Hz, ArH), 7.52 – 7.40 (4H, m, ArH), 3.95 (3H, s, $COOCH_3$).

4′-Chloro-2-isocyanobiphenyl (1e).[16] Pale yellow solid; yield 72%, 1226 mg; mp: 85 – 89 °C (lit.[16] mp: 85 – 89 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.50 – 7.39 (8H, m, ArH).

4′-Fluoro-2-isocyanobiphenyl (1f).[18] Green liquid; yield 83%, 1308 mg; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.50 – 7.44 (4H, m, ArH), 7.41 – 7.37 (2H, m, ArH), 7.17 (2H, d, $^3J_{HH}$ 8.7 Hz, ArH).

2′-Isocyano-[1,1′-biphenyl]-4-carbonitrile (1g).[16] White solid; yield 62%, 1001 mg; mp: 121 – 122 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.78 (2H, d, $^3J_{HH}$ 8.4 Hz, ArH), 7.64 (2H, d, $^3J_{HH}$ 8.5 Hz, ArH), 7.56 – 7.38 (4H, m, ArH).

4′-(*t*-Butyl)-2-isocyano-biphenyl (1h).[19] Green oil; yield 84%, 1579 mg; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.50 – 7.34 (8H, m, ArH), 1.37 (9H, s, *t*-Bu).

1-(2-Isocyanophenyl)naphthalene (1i). Green solid; yield 78%, 1428 mg; mp: 86 – 87 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.93 (2H, dd, $^3J_{HH}$ 8.1 Hz, $^4J_{HH}$ 3.1 Hz, ArH), 7.58 – 7.42 (9H, m, ArH). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 166.3, 138.1, 134.9, 133.7, 131.8, 131.4, 129.0, 128.5, 127.4, 127.3, 126.5, 126.0, 125.2. HRMS (EI): [M] calcd for $C_{17}H_{11}N$ 229.0891; found, 229.0899.

1-(2′-Isocyano-5′-methyl-[1,1′-biphenyl]-4-yl)ethanone (1j).[17] White solid; yield 79%, 1485 mg; mp: 93 – 94°C (lit.[17] mp: 97 – 99 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.06 (2H, d, $^3J_{HH}$ 8.6 Hz, ArH), 7.61 (2H, d, $^3J_{HH}$ 8.3 Hz, ArH), 7.40 (1H, d, $^3J_{HH}$ 7.9 Hz, ArH), 7.22 (2H, d, $^3J_{HH}$ 9.1 Hz, ArH), 2.66 (3H, s, $COCH_3$), 2.43 (3H, s, CH_3).

5-Fluoro-2-isocyanobiphenyl (1k).[20] Green liquid; yield 81%, 1276 mg; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.50 – 7.44 (6H, m, ArH), 7.2 – 7.1 (1H, m, ArH), 7.1 – 7.0 (1H, m, ArH).

5-Chloro-2-isocyanobiphenyl (1l).[14] Pale green solid; yield 87%, 1482 mg; mp: 71 – 72 °C (lit.[14] mp: 71 – 73 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.49 – 7.42 (7H, m, ArH), 7.34 (1H, dd, $^3J_{HH}$ 8.5, $^4J_{HH}$ 2.3 Hz, ArH).

2-Isocyano-3′-methoxybiphenyl (1m).[16] Green solid; yield 78%, 1304 mg; mp: 53 – 55 °C (lit.[16] mp: 52 – 53 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.48 – 7.36 (5H, m, ArH), 7.08 (1H, d, $^3J_{HH}$ 7.6 Hz, ArH), 7.04 (1H, s, ArH), 6.97 (1H, d, $^3J_{HH}$ 9.1 Hz, ArH), 3.85 (3H, s, OCH_3).

3-(2-Isocyanophenyl)pyridine (1n). Orange solid; yield 75%, 1086 mg; mp: 52 – 53 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.73 (1H, d, $^3J_{HH}$ 2.9 Hz, ArH), 8.68 (1H, dd, $^3J_{HH}$ 4.9, $^4J_{HH}$ 1.6 Hz, ArH), 7.91 – 7.87 (1H, m, ArH), 7.56 – 7.48 (2H, m, ArH), 7.48 – 7.40 (3H, m, ArH). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 167.5, 149.53, 149.50, 136.3, 135.2, 132.9, 130.4, 129.9, 129.1, 128.0, 123.2. HRMS (ESI): $[M + H]^+$ calcd for $[C_{12}H_9N_2]^+$ 181.0760; found, 181.0760.

General procedure for thiolation of isocyanide and intramolecular radical aromatic cyclization reaction

To a Schlenk tube were added 2-isocyanobiphenyls **1** (0.30 mmol), thiols **2** (0.36 mmol), xylene (3 mL), TBPB (0.9 mmol), then the tube was charged with nitrogen, and was stirred at 120 °C for 5 h. After the reaction was finished, the reaction mixture was diluted in 20 mL ethyl acetate, washed with a saturated solution of brine (15 mL×3), dried with anhydrous sodium sulfate and concentrated in vacuum, and the resulting residue was purified by neutral aluminum oxide (200 – 300 mesh) or silica gel (200 – 300 mesh), chromatography to afford the product 6-arylthiophenanthridines **3**.

8-Methoxy-6-(*p*-tolylthio)phenanthridine (3a). White solid; yield 53%, 52 mg; mp: 155 – 156 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.42 (1H, d, $^3J_{HH}$ 9.0 Hz, ArH), 8.34 – 8.31(1H, m, ArH), 7.82 – 7.74 (2H, m, ArH), 7.57 – 7.45 (4H, m, ArH), 7.40 (1H, dd, $^3J_{HH}$ 9.0 Hz, $^4J_{HH}$ 2.6 Hz, ArH), 7.23 (2H, d, $^3J_{HH}$ 8.0 Hz, ArH), 3.94 (3H, s, OCH_3), 2.40 (3H, s, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 158.8, 158.2, 143.3, 138.6, 134.9, 129.8, 129.3, 127.6, 126.9, 126.9, 126.7, 126.2, 124.1, 123.3, 121.5, 121.5, 105.8, 55.6, 21.4. HRMS (ESI): $[M + H]^+$ calcd for $[C_{21}H_{18}NOS]^+$ 332.1104; found, 332.1105.

8-Methoxy-6-(phenylthio)phenanthridine (3b).[27] White solid; yield 58%, 55 mg; mp: 81 – 82 °C (lit.[27] mp: 81 – 82 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.49 (1H, d, $^3J_{HH}$ 9.1 Hz, ArH), 7.40 – 7.38 (1H, m, ArH) 7.81 – 7.77 (2H, m, ArH), 7.66 – 7.64 (2H, m, ArH), 7.54 – 7.53 (2H, m, ArH), 7.45 – 7.41 (4H, m, ArH), 3.98 (3H, s, OCH_3).

8-Methoxy-6-[(3-methoxyphenyl)thio]phenanthridine (3c). White solid; yield 45%, 47 mg; mp: 114 – 115 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.50 (1H, d, $^3J_{HH}$ 9.0 Hz, ArH), 8.40 (1H, d, $^3J_{HH}$ 9.5 Hz, ArH), 7.86 (1H, d, $^3J_{HH}$ 9.5 Hz, ArH), 7.78 (1H, d, $^3J_{HH}$ 2.6 Hz, ArH), 7.58 – 7.53 (2H, m, ArH), 7.47 (1H, dd, $^3J_{HH}$ 9.0Hz, $^4J_{HH}$ 2.7 Hz, ArH), 7.32 (1H, t, $^3J_{HH}$ 7.9 Hz, ArH), 7.24 – 7.22 (2H, m, ArH), 6.94 (1H, d, $^3J_{HH}$ 9.2 Hz, ArH), 3.98 (3H, s, OCH_3), 3.81 (3H, s, OCH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 159.8, 158.8, 157.6, 143.3, 132.1, 129.6, 129.4, 127.7, 127.1, 126.4, 124.1, 123.5, 121.7, 121.5, 119.3, 114.6, 106.0, 55.6, 55.4. HRMS (ESI): $[M + H]^+$ calcd for $[C_{21}H_{17}NO_2S]^+$ 348.1053; found, 348.1054.

6-[(4-Bromophenyl)thio]-8-methoxyphenanthridine (3d). Orange solid; yield 68%, 80 mg; mp: 178 – 179 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.46 (1H, d, $^3J_{HH}$ 9.0 Hz, ArH), 8.36 (1H, d, $^3J_{HH}$ 9.0 Hz, ArH), 7.79 (1H, d, $^3J_{HH}$ 7.2 Hz,), 7.70 (1H, s, ArH), 7.56 – 7.50 (6H, m, ArH), 7.44 (1H, dd, $^3J_{HH}$ 9.0 Hz, $^4J_{HH}$ 2.5 Hz, ArH), 3.97 (3H, s, OCH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 158.9, 157.1, 143.2, 136.3, 132.1, 129.7, 129.3, 127.8, 127.0, 126.5, 124.2, 123.4, 121.7, 121.5, 105.6, 55.6. HRMS (ESI): $[M + H]^+$ calcd for $[C_{20}H_{15}BrNOS]^+$ 396.0052; found, 396.0053.

6-[(4-Fluorophenyl)thio]-8-methoxyphenanthridine (3e). Yellow solid; yield 30%, 30 mg; mp: 141 – 142 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.44 (1H, d, $^3J_{HH}$ 9.0 Hz, ArH), 8.34 (1H, d, $^3J_{HH}$ 7.4 Hz, ArH), 7.75 – 7.69 (2H, m, ArH), 7.65 – 7.62 (2H, m, ArH), 7.54 – 7.47 (2H, m, ArH), 7.43 (1H, dd, $^3J_{HH}$ 9.0 Hz, 2.6 Hz, ArH), 7.14 (2H, t, $^3J_{HH}$ 8.7 Hz, ArH), 3.97 (3H, s, OCH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 164.5, 162.0, 158.9, 157.8, 143.2, 137.4, 137.3, 129.2, 127.7, 126.3, 124.2, 121.6, 121.5, 116.2, 116.0, 105.5, 55.6. HRMS (ESI): $[M + H]^+$ calcd for $[C_{20}H_{15}FNOS]^+$ 336.0853; found, 336.0855.

6-(Ethylthio)-8-methoxyphenanthridine (3f). Yellow liquid; yield 45%, 36 mg. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.44 (1H, d, $^3J_{HH}$ 9.1 Hz,), 8.38 – 8.36 (1H, m, ArH), 7.99 (1H, d, $^3J_{HH}$ 8.1 Hz, ArH), 7.62 – 7.58 (2H, m, ArH), 7.53 – 7.51 (1H, m, ArH), 7.41 (1H, d, $^3J_{HH}$ 9.0Hz, ArH), 3.97 (3H, s, OCH_3), 3.49 (2H, q, $^3J_{HH}$ 7.4Hz, CH_2CH_3), 1.50 (3H, t, $^3J_{HH}$ 7.4Hz, CH_2CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 157.7, 157.3, 142.4, 127.6, 126.6, 125.9, 125.3, 124.6, 123.0, 121.8, 120.6, 120.2, 104.4, 54.5, 23.2, 13.6. HRMS (ESI): $[M + H]^+$ calcd for $[C_{16}H_{16}NOS]^+$ 270.0947; found, 270.0955.

6-(Phenylthio)phenanthridine (3g).[27] Pale yellow solid; yield 53%, 45 mg; mp: 73 – 75 ^{o}C (lit.[27] mp: 71 – 72 ^{o}C). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.53 (1H, d, $^3J_{HH}$ 8.2 Hz, ArH), 8.44 (1H, d, $^3J_{HH}$ 8.6 Hz, ArH), 8.41 (1H, s, ArH), 7.81 – 7.77 (2H, m, ArH), 7.67 – 7.63 (3H, m, ArH), 7.58 – 7.48 (2H, m, ArH), 7.45 – 7.37 (3H, m, ArH).

1-(6-(Phenylthio)phenanthridin-8-yl)ethanone (3h).[27] White solid; yield 41%, 41 mg; mp: 107 – 108 ^{o}C (lit.[27] mp: 107 – 108 ^{o}C). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.99 (1H, s, ArH), 8.59 (1H, d, $^3J_{HH}$ 8.6 Hz, ArH), 8.44 (1H, d, $^3J_{HH}$ 8.1 Hz, ArH), 8.36 (1H, d, $^3J_{HH}$ 8.8 Hz, ArH), 7.79 (1H, d, $^3J_{HH}$ 8.0 Hz, ArH), 7.69 – 7.64 (3H, m, ArH), 7.57 – 7.55 (1H, t, ArH), 7.46 – 7.44 (3H, m, ArH), 2.76 (3H, s, CH_3).

Methyl 6-(phenylthio)phenanthridine-8-carboxylate (3i). Yellow solid; yield 50%, 52 mg; mp: 129 – 130 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.13 (1H, s, ArH), 8.56 (1H, d, $^3J_{HH}$ 8.6 Hz, ArH), 8.40 (2H, dd, $^3J_{HH}$ 11.5 Hz, $^4J_{HH}$ 4.1 Hz, ArH), 7.75 (1H, dd, $^3J_{HH}$ 8.1, $^4J_{HH}$ 1.1 Hz, ArH), 7.70 – 7.59 (2H, m, ArH), 7.63 – 7.59 (1H, t, ArH), 7.55 – 7.51 (1H, t, ArH), 7.48 – 7.43 (3H, m, ArH), 4.02 (3H, s, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 166.3, 159.7, 144.8, 135.7, 135.4, 130.7, 129.8, 129.7, 129.4, 129.0, 128.9, 128.8, 127.8, 126.4, 124.8, 122.8, 122.6, 122.4, 52.5. HRMS (ESI): $[M + H]^+$ calcd for $[C_{21}H_{16}NO_2S]^+$ 346.0896; found, 346.0888.

8-Chloro-6-(phenylthio)phenanthridine (3j).[28] White solid; yield 47%, 45 mg; mp: 112 – 114 °C (lit.[28] mp: 115 – 116 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.43 (1H, s, ArH), 8.40 (1H, s, ArH), 8.32 (1H, dd, $^3J_{HH}$ 8.0 Hz, $^4J_{HH}$ 1.4 Hz, ArH), 7.76 – 7.70 (2H, m, ArH), 7.66 – 7.64 (2H, m, ArH), 7.58 – 7.54 (1H, m, ArH), 7.52 – 7.48 (1H, m, ArH), 7.45 – 7.41 (3H, m, ArH).

8-Fluoro-6-(phenylthio)phenanthridine (3k).[27] White solid; yield 52%, 47 mg; mp: 101 – 102 ^{o}C (lit.[27] mp: 97 – 98 ^{o}C). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.50 (1H, dd, $^3J_{HH}$ 9.1 Hz, $^4J_{HH}$ 5.3 Hz, ArH), 8.33 (1H, d, $^3J_{HH}$ 8.0 Hz, ArH), 8.07 (1H, dd, $^3J_{HH}$ 9.7, 2.6 Hz, ArH), 7.77 (1H, dd, $^3J_{HH}$ 8.0 Hz, $^4J_{HH}$ 1.3 Hz, ArH), 7.66 – 7.63 (2H, m, ArH), 7.57 – 7.49 (3H, m, ArH), 7.45 – 7.40 (3H, m, ArH).

6-(Phenylthio)phenanthridine-8-carbonitrile (3l). Yellow solid; yield 45%, 42 mg; mp: 182 – 183 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.75 (1H, s, ArH), 8.57 (1H, d, $^3J_{HH}$ 8.6 Hz, ArH), 8.38 (1H, d, $^3J_{HH}$ 8.0 Hz, ArH), 7.95 (1H, d, $^3J_{HH}$ 8.6 Hz, ArH), 7.76 (1H, d, $^3J_{HH}$ 8.0 Hz, ArH) 7.67 – 7.63 (3H, m, ArH), 7.59 – 7.55 (1H, m, ArH), 7.47 – 7.46 (3H, m, ArH). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 158.6, 145.0, 135.4, 135.3, 132.1, 130.9, 130.5, 129.6, 129.1, 126.9, 124.8, 123.7, 122.5, 121.8, 118.4, 110.9. HRMS (ESI): $[M + H]^+$ calcd for $[C_{20}H_{13}N_2S]^+$ 313.0794; found, 313.0788.

8-(*t*-Butyl)-6-(phenylthio)phenanthridine (3m). Orange liquid; yield 60%, 62 mg. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.47 (1H, d, $^3J_{HH}$ 8.7 Hz, ArH), 8.41 – 8.39 (2H, m, ArH), 7.88 (1H, dd, $^3J_{HH}$ 8.7 Hz, $^4J_{HH}$ 1.9 Hz, ArH), 7.79 (1H, dd, $^3J_{HH}$ 8.1 Hz, $^4J_{HH}$ 1.1 Hz, ArH), 7.66 (2H, dd, $^3J_{HH}$ 7.8 Hz, 1.5 Hz, ArH), 7.55 – 7.50 (2H, m, ArH), 7.43 – 7.37 (3H, m, ArH), 1.44 (9H, s, *t*-Bu). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 159.1, 150.8, 143.9, 134.8, 130.9, 130.5, 129.4, 129.3, 129.0, 128.4, 128.3, 126.2, 125.4, 123.3, 122.3, 121.9, 121.6, 35.2, 31.4. HRMS (ESI): $[M+H]^+$ calcd for $[C_{23}H_{22}NS]^+$ 344.1467; found, 344.1468.

8-(*t*-Butyl)-6-(*p*-tolylthio)phenanthridine (3n). Yellow liquid; yield 60%, 64 mg. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.49 (1H, d, $^3J_{HH}$ 8.7 Hz, ArH), 8.43 – 8.40 (2H, m, ArH), 7.90 (1H, dd, $^3J_{HH}$ 8.7 Hz, $^4J_{HH}$ 1.9 Hz, ArH), 7.79 (1H, dd, $^3J_{HH}$ 8.1Hz, $^4J_{HH}$ 1.2 Hz, ArH), 7.56 – 7.49 (4H, m, ArH), 7.24 (2H, d, $^3J_{HH}$ 7.9 Hz, ArH), 2.41 (3H, s, CH_3), 1.46 (9H, s, *t*-Bu). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 159.5, 150.7, 143.9, 138.5, 135.0, 130.4, 129.7, 129.3, 129.2, 128.2, 126.9, 126.0, 125.3, 123.3, 122.2, 121.8, 121.5, 35.2, 31.3, 21.4. HRMS (ESI): $[M + H]^+$ calcd for $[C_{24}H_{24}NS]^+$ 358.1624; found, 358.1627.

8-Chloro-6-(*p*-tolylthio)phenanthridine (3o). Pale green solid; yield 55%, 55 mg; mp: 141 – 142 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.48 (1H, d, $^3J_{HH}$ 8.8 Hz, ArH), 8.44 (1H, s, ArH), 8.38 (1H, d, $^3J_{HH}$ 8.0 Hz, ArH), 7.77 (2H, t, $^3J_{HH}$ 7.0 Hz, ArH), 7.60 – 7.51 (4H, m, ArH), 7.26 (2H, d, $^3J_{HH}$ 8.0 Hz, ArH), 2.43 (3H, s, ArH). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 158.3, 144.0, 138.9, 135.3, 133.4, 131.4, 131.0, 129.8, 129.4, 129.0, 126.4, 126.3, 126.0, 125.1, 124.2, 122.5, 121.8, 21.4. HRMS (ESI): $[M+H]^+$ calcd for $[C_{20}H_{15}NSCl]^+$ 336.0608; found, 336.0609.

6-(*p*-Tolylthio)phenanthridine (3p).[27] White solid; yield 55%, 50 mg; mp: 106 – 107 ºC (lit.[27] mp: 106 – 107 ºC). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.54 (1H, d, $^3J_{HH}$ 8.2 Hz, ArH), 8.43 (2H, dd, $^3J_{HH}$ 12.6 Hz, $^4J_{HH}$ 4.6 Hz, ArH), 7.82 – 7.78 (2H, m, ArH), 7.68 – 7.64 (1H, m, ArH), 7.58 – 7.50 (4H, m, ArH), 7.25 – 7.22 (2H, m, ArH), 2.41 (3H, s, CH_3).

6-[(4-Bromophenyl)thio]benzo[*k*]phenanthridine (3q). Pale yellow solid; yield 55%, 68 mg; mp: 179 – 181 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.12 – 9.10 (1H, m, ArH), 8.92 (1H, d, $^3J_{HH}$ 8.3 Hz, ArH), 8.34 (1H, d, $^3J_{HH}$ 8.8 Hz, ArH), 8.07 – 8.04 (1H, m, ArH), 8.00 (1H, d, $^3J_{HH}$ 8.8 Hz, ArH), 7.93 (1H, d, $^3J_{HH}$ 8.0 Hz, ArH), 7.75 – 7.72 (2H, m, ArH), 7.68 – 7.52 (6H, m, ArH). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 157.7, 145.9, 136.4, 135.0, 132.0, 131.8, 123.0, 129.3, 129.1, 128.7, 128.7, 128.5, 128.4, 128.0, 127.1, 127.0, 126.0, 124.1, 123.6, 122.9, 121.8. HRMS (ESI): $[M + H]^+$ calcd for $[C_{23}H_{15}BrNS]^+$ 416.0103; found, 415.9980.

1-{6-[(4-Bromophenyl)thio]-2-methylphenanthridin-8-yl}ethanone (3r). Orange oil; yield 40%, 50 mg. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.92 (1H, s, ArH), 8.56 (1H, d, $^3J_{HH}$ 8.5 Hz, ArH), 8.33 (1H, d, $^3J_{HH}$ 8.4 Hz, ArH), 8.21 (1H, s, ArH), 7.70 (1H, d, $^3J_{HH}$ 8.2 Hz, ArH), 7.58 – 7.47 (5H, m, ArH), 2.76 (3H, s, $COCH_3$), 2.57 (3H, s, $ArCH_3$). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 197.0, 157.6, 143.2, 136.8, 136.5, 135.6, 135.4, 132.1, 131.7, 129.2, 129.1, 126.7, 124.8, 123.2, 123.0, 122.31, 122.27, 26.7, 21.9. HRMS (ESI): $[M + H]^+$ calcd for $[C_{22}H_{17}NOS]^+$ 422.0209; found, 422.0210.

2-Fluoro-6-(naphthalen-2-ylthio)phenanthridine (3s). White solid; yield 41%, 44 mg; mp: 169 – 170 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.50 (1H, d, $^3J_{HH}$ 8.0 Hz, ArH), 8.45 (1H, d, $^3J_{HH}$ 8.4 Hz, ArH), 8.18 (1H, s, ArH), 8.05 (1H, dd, $^3J_{HH}$ 10.0 Hz, $^4J_{HH}$ 2.7 Hz, ArH), 7.89 – 7.83 (4H, m, ArH), 7.74 – 7.68 (3H, m, ArH), 7.56 – 7.51 (2H, m, ArH), 7.30 – 7.25 (1H, m, ArH). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 161.8, 159.8, 158.5, 141.0, 140.9, 134.0, 133.8, 133.1, 132.1, 131.5, 131.4, 131.0, 128.2, 128.2, 127.9, 127.8, 127.7, 126.7, 126.3, 125.9, 125.5, 124.5, 124.4, 122.6, 117.4, 117.2, 107.1, 107.0. HRMS (ESI): $[M + H]^+$ calcd for $[C_{23}H_{15}FNS]^+$ 356.0904; found, 356.0906.

6-[(4-Bromophenyl)thio]-2-chlorophenanthridine (3t). Yellow solid; yield 60%, 72 mg; mp: 142 – 143 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.51 (1H, d, $^3J_{HH}$ 8.2 Hz, ArH), 8.42 – 8.41 (2H, m, ArH), 7.88 (1H, t, $^3J_{HH}$ 7.7 Hz, ArH), 7.77 – 7.70 (2H, dd, $^3J_{HH}$ 17.6Hz, $^4J_{HH}$ 7.9 Hz, ArH), 7.60 – 7.52 (5H, m, ArH). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 158.9, 142.3, 136.9, 132.1, 132.0, 131.5, 131.3, 130.7, 129.2, 128.8, 128.2, 125.5, 125.2, 124.2, 123.3, 122.5, 121.7. HRMS (ESI): $[M + H]^+$ calcd for $[C_{19}H_{12}BrClNS]^+$ 399.9557; found, 399.9560.

7-Methoxy-6-(phenylthio)phenanthridine (3u) and 9-methoxy-6-(phenylthio) phenanthridine (3u′) (3u: 3u′ = 3:2)[27]. **3u**: Pale yellow solid; yield 30%, 29 mg; mp: 126 – 127 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.40 (2H, d, $^3J_{HH}$ 9.0 Hz, ArH), 7.90 (1H, d, $^3J_{HH}$ 2.5 Hz, ArH), 7.79 (1H, dd, $^3J_{HH}$ 8.1 Hz, $^4J_{HH}$ 1.2 Hz, ArH), 7.65 – 7.63 (2H, m, ArH), 7.59 – 7.57 (1H, m, ArH), 7.54 – 7.52 (1H, m, ArH), 7.44 – 7.39 (3H, m, ArH),7.28 (1H, dd, $^3J_{HH}$ 9.0 Hz, $^4J_{HH}$ 2.5 Hz, ArH), 4.04 (3H, s, OCH_3). **3u′**: Pale yellow solid; yield 20%, 20 mg; mp: 116 – 117 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.37 (1H, d, $^3J_{HH}$ 8.0 Hz, 1H), 8.17 (1H, d, $^3J_{HH}$ 8.0 Hz, ArH), 7.73 (1H, t, $^3J_{HH}$ 8.1 Hz, ArH), 7.66 – 7.64 (2H, m, ArH), 7.52 – 7.51 (2H, m, ArH), 7.49 – 7.42 (4H, m, ArH), 7.13 (1H, d, $^3J_{HH}$ 7.9 Hz, ArH), 4.14 (3H, s, OCH_3).

5-(Phenylthio)benzo[*f*][1,7]naphthyridine (3v) and 5-(phenylthio)benzo[c][2,6]naphthyridine (3v′) (3v: 3v′ = 3:2). **3v**: Yellow solid; yield 47%, 41 mg; mp: 109 – 110 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.04 (1H, dd, $^3J_{HH}$ 4.4 Hz, $^4J_{HH}$ 1.5 Hz, ArH), 8.83 (1H, dd, $^3J_{HH}$ 8.4 Hz, $^4J_{HH}$ 1.5 Hz, ArH), 8.37 (1H, dd, $^3J_{HH}$ 8.0 Hz, $^4J_{HH}$ 1.2 Hz, ArH), 7.78 – 7.75 (4H, m, ArH), 7.63 – 7.59 (1H, m, ArH), 7.56 – 7.47 (4H, m, ArH). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 162.2, 149.6, 144.3, 140.2, 135.9, 130.7, 129.5, 129.4, 128.8, 128.8, 126.2, 122.1, 122.0. HRMS (ESI): $[M + H]^+$ calcd for $[C_{18}H_{13}N_2S]^+$ 289.0794; found, 289.0796. **3v′**: Yellow solid; yield 32%, 28 mg; mp: 108 – 109 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.99 (1H, s, ArH), 8.87 (1H, d, $^3J_{HH}$ 5.6 Hz, ArH), 8.58 – 8.49 (1H, m, ArH), 8.15 (1H, d, $^3J_{HH}$ 5.6 Hz, ArH), 7.82 – 7.77 (1H, m, ArH), 7.68 – 7.58 (4H, m, ArH), 7.48 – 7.44 (3H, m, ArH). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 158.3, 147.1, 146.5, 144.6, 135.3, 129.6, 129.5, 129.1, 129.0, 128.9, 128.6, 127.2, 126.5, 121.4, 121.1, 117.6. HRMS (ESI): $[M+H]^+$ calcd for $[C_{18}H_{13}N_2S]^+$ 289.0794; found, 289.0796.

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