Article

Additive-Free Radical Cascade Reaction of Oxime Esters# Synthesis of Pyrroline-Functionalized Phenanthridines

Yijie Xue, Dengqi Xue, Qian He, Qianwei Ge, Wei Li, and Liming Shao

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.0c01532 • Publication Date (Web): 11 Sep 2020

Additive-Free Radical Cascade Reaction of Oxime Esters : Synthesis of Pyrroline-Functionalized Phenanthridines

Yijie Xue,[+†] Dengqi Xue,[+†,‡] Qian He,[†] Qianwei Ge,[†] Wei Li,[†] Liming Shao[*,†,‡]

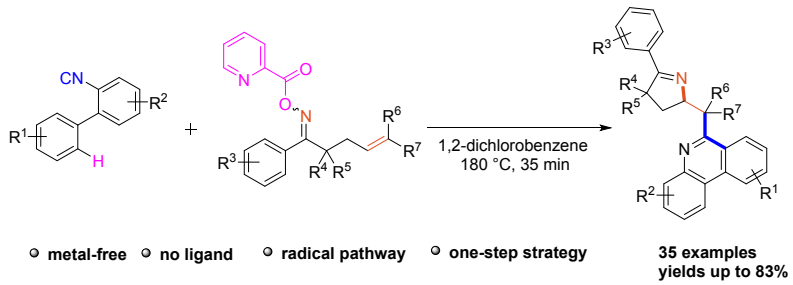
[†]School of Pharmacy, Fudan University, 826 Zhangheng Road, Zhangjiang Hi-tech Park, Pudong, Shanghai 201203, China

[‡]State Key Laboratory of Medical Neurobiology, Fudan University, 138 Yixueyuan Road, Shanghai 200032, China

[*]E-mail: limingshao@fudan.edu.cn

[+]These authors contributed equally to this work

Table of Contents/Abstract Graphic:



ABSTRACT: A variety of dihydropyrrole-functionalized phenanthridines were efficiently synthesized by the metal-free, radical cascade cyclization reaction of 2-isocyanobiphenyls with γ, δ-unsaturated oxime esters. The C−N/C−C/C−C bonds were formed via the oil bath method in a one-pot procedure with broad substrate applicability. The radical process was supported by kinetic isotope effect studies and radical inhibition studies.

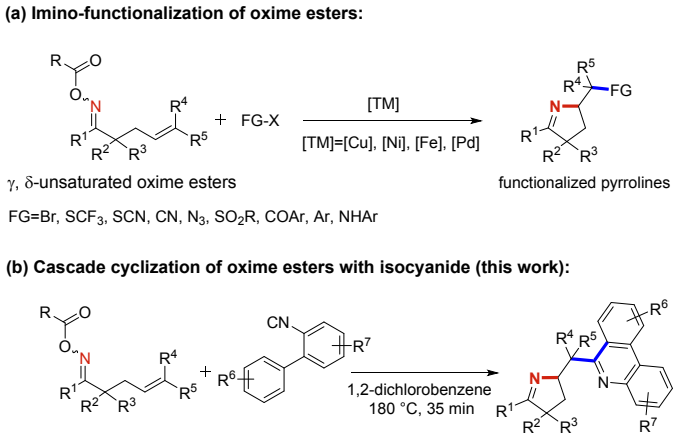
INTRODUCTION

Phenanthridine as a versatile bioactive molecule has attracted extensive attention.[1] Meanwhile, pyrrolines are one of the most important moieties in pharmaceutical and natural products.[2] Consequently, various methodologies for preparing phenanthridine[3] and pyrroline[4] compounds have been developed in recent years. Compounds with these two fragments may possess potential biological and pharmacological activities; however, there has been little

investigation into developing an efficient method for the synthesis of pyrroline-functionalized phenanthridines.

The use of iminyl radicals appears highly promising because of their wide application in the synthesis of heterocycles.[5] Reductive cleavage of the N−O bond in oxime esters or ethers enables the efficient and facile generation of iminyl radicals under transition metal-catalyzed,[6] light irradiation,[7] microwave irradiation[8] or thermal conditions.[9] Although a number of functional groups have been introduced into pyrrolines by iminyl radicals in cascade reactions with unactivated alkenes, these transformations require transition-metal catalysts.[10] To the best of our knowledge, the use of an additive-free system for such a synthesis remains unexplored (Scheme 1a). Designing a reaction protocol without the aid of catalysts toward developing a simple, waste-free, and cost-effective method still remains a challenge.[11] The use of isocyanides as radical acceptors to directly and efficiently construct heterocycles has been widely recognized.[12] Thus, we believe that a free-radical cascade cyclization reaction of γ, δ-unsaturated oxime esters with 2-isocyanobiphenyls should enable the concise synthesis of various pyrroline-functionalized phenanthridines. This strategy involves the one-pot formation of C−N/C−C/C−C bonds (Scheme 1b).

Scheme 1. Previous work of the use of oxime esters-tethered alkenes in cyclization reactions and strategies for this work.



RESULTS AND DISCUSSION

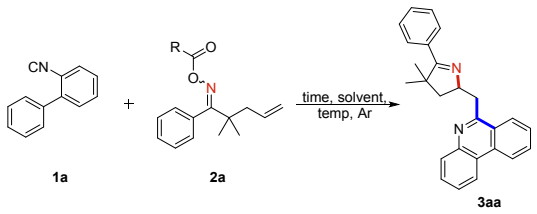
The 2-pyridyl group was a good leaving group to N-O bond cleavage of oxime ester,[10e] so the reaction of 2-isocyanobiphenyl (**1a**) with the oxime ester **2a**-2-Py

was investigated initially (Table 1). To our delight, the desired product pyrroline-functionalized phenanthridine (**3aa**) was obtained in 62% yield at 190 °C in oil-bath heating (entry 1). Then, the effect of the temperature on the reaction rate was investigated (entries 1–4). The reaction at 160 °C gave only traces of the product and extending the reaction time to 24 h improved the yield to 50% (entry 5). The yield was increased to 67% at 180 °C for 60 min. An extensive screening of reaction times (entries 6–8) revealed that a reaction time of 35 min gave the best results of all the reaction times investigated. It should be noted that changing the amount of oxime ester resulted in a decreased yield of the target product (**3aa**) (entries 9 and 10). Altering the solvent (entries 11–13) or the N-based leaving groups (entries 14–17) did not improve the yield of the target product (**3aa**). Performing the reaction under an air atmosphere or in the presence of water led to a lower yield of the product (**3aa**) (entries 18–19). It should be noted that the reaction could also be easily conducted on a gram scale without appreciable loss of yield (entry 20). The reaction generated the equivalent yield with new glassware and stir bar, which could exclude the existence of trace amounts of metals (entry 21).

Under the optimized reaction conditions, the scope of the oxime ester in this cascade sequence was investigated (Table 2). The desired pyrroline-functionalized phenanthridine derivatives (**3aa**–**3ar**) were produced smoothly. The electronic properties and the position of the substituents on the benzene rings of the oxime ester had little or no impact on the transformation, with moderate to good yields observed (**3aa**–**3ah**). Pyridine and naphthalene substituents on the oxime ester afforded the products with acceptable yields (**3ai**–**3ak**). Removal of the *di*-methyl group from the oxime ester led to a low yield of the product **3al**. This was presumably because of the lack of the Thorpe-Ingold effect.[13] Introduction of a *di*-methyl group to the alkene of the oxime ester also worked well (**3am**). A series of spirocyclic products could be obtained conveniently (**3an**–**3ap**). When γ, δ-unsaturated oxime esters bearing a cyclohexene moiety were reacted, the corresponding products were obtained

as single diastereoisomers (**3aq** and **3ar**). These two examples (**3aq** and **3ar**) indicate that the trapping of the cyclization-derived carbon radical from the less sterically hindered *exo* direction was preferred.

Table 1. Modification of the typical reaction conditions[a]

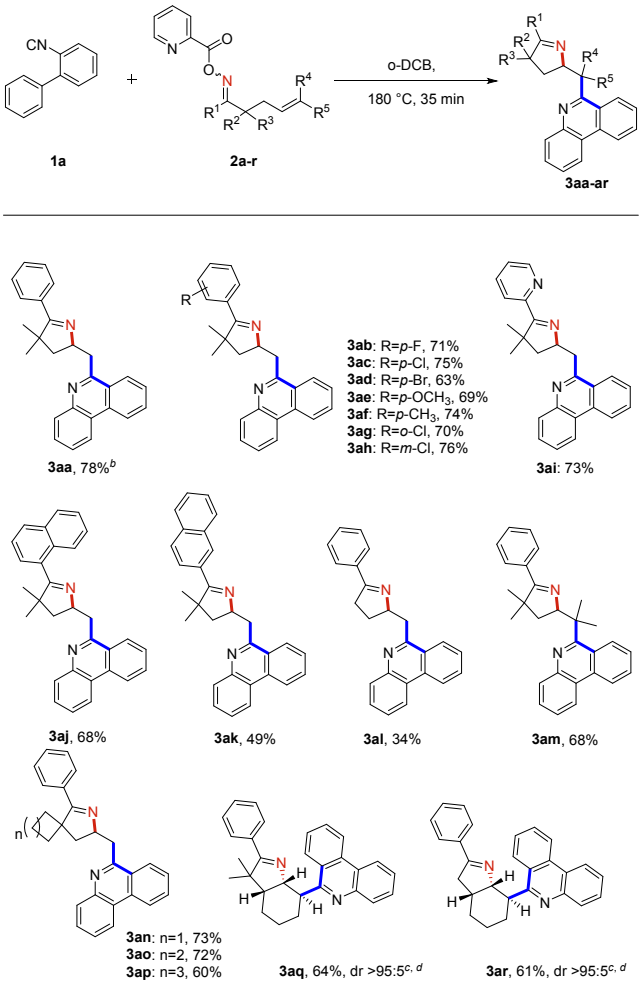


Entry	R	t (min)	Solvent (ml)	T (°C)	yield (%)[b]
1	2-Py	60	o-DCB	190	62
2	2-Py	60	o-DCB	180	67
3	2-Py	60	o-DCB	170	61
4	2-Py	60	o-DCB	160	Trace
5	2-Py	1440	o-DCB	160	50
6	2-Py	30	o-DCB	180	70
7	**2-Py**	**35**	**o-DCB**	**180**	**78**
8	2-Py	40	o-DCB	180	74
9[c]	2-Py	35	o-DCB	180	11
10[d]	2-Py	35	o-DCB	180	51
11	2-Py	35	Xylene	180	54
12	2-Py	35	DMF	180	46
13	2-Py	35	NMP	180	44
14	Me	35	o-DCB	180	18
15	t-Bu	35	o-DCB	180	36
16	Ph	35	o-DCB	180	23
17	C_6F_5	35	o-DCB	180	50
18[e]	2-Py	35	o-DCB	180	14

19[f]	2-Py	35	o-DCB	180	68
20[g]	2-Py	35	o-DCB	180	72
21[h]	2-Py	35	o-DCB	180	76

[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.6 mmol), solvent (1 mL), 180 °C (oil bath), 35 min, Ar, unless otherwise noted. [b]Isolated yields. [c]**2a** (0.3 mmol). [d]**2a** (0.9 mmol). [e]Under air conditions. [f]Water (15 μL) was added. [g]3 mmol scale of substrate was used. [h]New stir bar and tube were used.

Table 2. Scope of γ, δ-unsaturated oxime esters.[a]



[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.6 mmol), solvent (1 mL), 180 °C (oil bath), 35 min, Ar. [b]Isolated yields. [c]The determination of the ratio of diastereoisomer

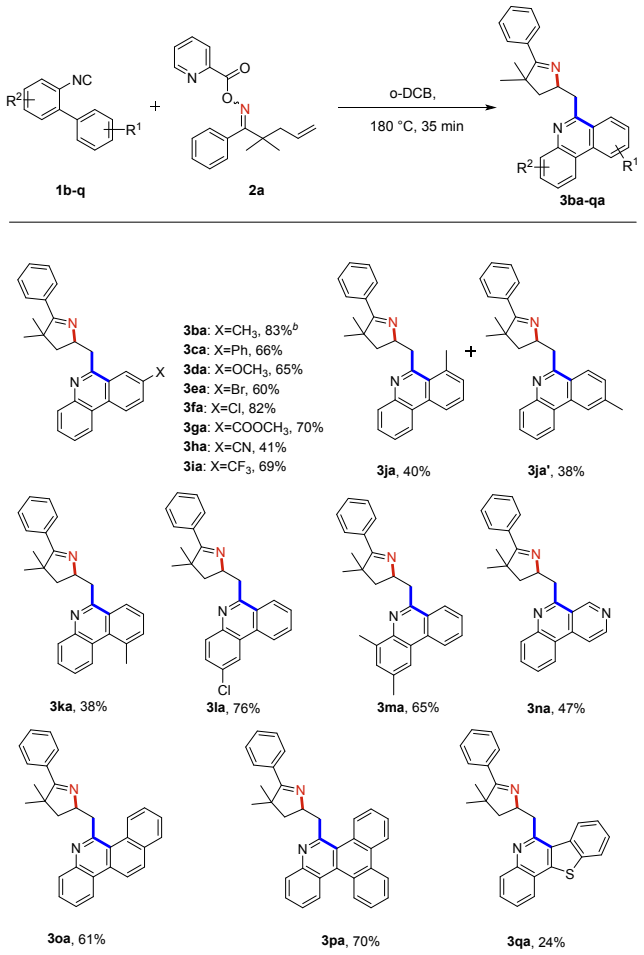
is based on ^{1}H NMR. [d]The configuration of diastereomer was confirmed by coupling constants of ^{1}H NMR and NOE.

2-Isocyanobiphenyl compounds bearing various substituents were also subjected to the optimized conditions with **2a**, delivered the corresponding products (**3ba**–**3qa**) in acceptable yields (Table 3). Substrates bearing electron-donating or electron-withdrawing groups on 2-isocyanobiphenyl reacted with **2a** to afford the corresponding products **3ba**–**3ma** in yields of 38%–82%. When two nonequivalent *ortho* hydrogen atoms were present on the isonitrile phenyl moiety, two isomers **3ja** and **3ja'** were isolated in good yields but with poor regioselectivity. The *ortho*-methylbiphenylisonitrile afforded a lower yield (**3ka**, 38%). Slightly lower yields were obtained in the reaction of **2a** with naphthyl derivative and phenanthryl derivative (**3oa**, **3pa**). In addition, we found that heteroaryl isocyanides were also suitable substrates in this annulation reaction (**3na**, **3qa**).

To gain insight into the mechanism of the reaction, intermolecular competition experiments were performed (Scheme 2). No kinetic isotope effects (KIE, k_H/k_D = 1.0) were found upon using a 1:1 mixture of **1a** and [D_5]-**1a** under the standard reaction conditions. Therefore, the reaction may proceed via a free-radical process which was similar to mechanisms proposed in previous reports.[10e,12d,14] In addition, a radical trapping experiment was conducted (Scheme 3). The addition of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) shut down the reaction, giving TEMPO-trapped pyrroline **4** in 27% yield, which indicated that the reaction was inhibited by TEMPO and an iminyl radical might be involved in the process.

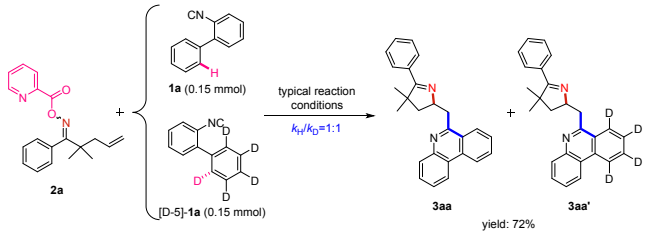
To account for the process of the cascade sequence, we proposed a possible reaction mechanism (Scheme 4).[10] The reaction is initiated by oxime ester **2** to generate an iminyl radical by heating, the iminyl radical then undergoes 5-*exo*-trig cyclization to produce the C-centered radical **B**. The reactive center of **B** forms an intermolecular C−C bond with 2-isocyanobiaryl **1**, which gives the imidoyl radical **C**.

Table 3. Scope of isocyanides[a]

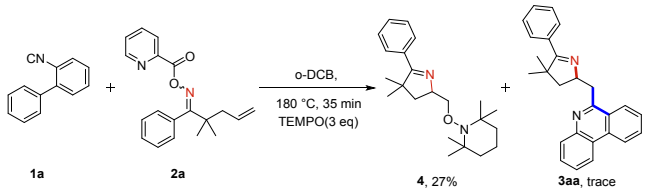


[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.6 mmol), solvent (1 mL), 180 °C (oil bath), 35 min, Ar. [b]Isolated yields.

Scheme 2. KIE studies

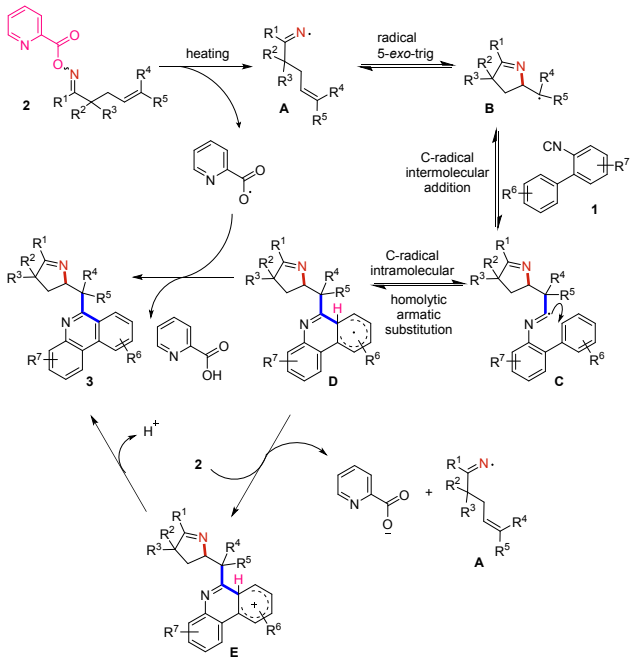


Scheme 3. Radical trapping experiment



Subsequent cyclization results in the cyclohexadienyl radical **D**. The picolinoyl radical abstracts one H from the intermediate **D** to form compound **3** and picolinic acid.[15] Meanwhile, the intermediate **D** is oxidized by oxime ester **2** through a single electron transfer (SET) mechanism to give the cation intermediate **E,** followed by deprotonation to generate compound **3**.

Scheme 4. Possible mechanism



CONCLUSION

In conclusion, we have developed an efficient approach for the rapid construction of a pyrroline-functionalized phenanthridine structure. This approach does not require any catalysts or additives, which makes this method

economical and at the same time simplifies the operation. Further applications of this transformation are in progress in our group.

EXPERIMENTAL SECTION

General Information. Purchased reagents were used without further purification. All the reactions that require heating were heated in oil bath. ^{1}H and ^{13}C spectra were recorded on Varian 400 MHz and Bruker 600 MHz. Chemical shifts are reported in ppm using tetramethylsilane as internal standard. ESI-HRMS (high resolution mass spectrometry) spectra were obtained on AB SCIEX TRIPLE TOF 5600+ mass spectrometer.

General Procedure for Synthesize of Isocyanides 1a-1q.[12g,12h,16] Step 1: $Pd(PPh_3)_4$ (0.05 equiv.), aryl boronic acid (1.5 equiv.), 2-bromoaniline (1.0 equiv.), $K_3PO_4 \cdot 7H_2O$ (3 equiv) and THF (2 mL per mmol) were added subsequently in two-neck flask under argon atmosphere. The reaction mixture was stirred at 100 ^{o}C for 12 h. Upon completion of the reaction, the resulting mixture was cooled to room temperature and filtered through a short path of silica gel, eluting with CH_2Cl_2. The volatile compounds were removed in vacuo and the residue was purified by column chromatography on silica gel, using petroleum ether and ethyl acetate (80 : 1- 50 : 1) as the eluent. Step 2: New aniline (1.0 equiv.) and THF (2 mL per mmol) were added into a flask and cooled to 0 °C. Acetic formic anhydride (2.0 equiv.), which was prepared from the reaction of acetic anhydride with formic acid (1.1 equiv.) at 55 °C for 2 h, was added dropwise into the reaction mixture at 0 °C. After the addition was completed, the mixture was warmed to room temperature and stirred for 1 h. Then, the mixture was treated with saturated solution of $NaHCO_3$ and extracted with EtOAc three times. The extract was dried and concentrated under vacuum to give formamide. These materials were used for the subsequent dehydration without further purification. Step 3: NEt_3 (5.0 equiv.), formamide (1.0 equiv.), THF (1.5 mL per mmol) were added to an oven-dried two-neck flask under argon atmosphere. After cooling the reaction mixture to 0 °C, $POCl_3$ (2.0 equiv.) was added via syring pump for a period of 2 h. After the addition was complete, the resulted mixture was stirred at 0 °C for an additional 1 h. Then, the mixture was quenched with saturated solution of $NaHCO_3$

and extracted with CH_2Cl_2 (25 mL x 3). The combined organic layer was dried with Na_2SO_4, filtered and evaporated followed by a silica gel column chromatography, using petroleum ether and ethyl acetate (100 : 1- 80 : 1) as the eluent.

General Procedure for Synthesize of γ , δ-Unsaturated Oxime Esters.

General procedure for the preparation of **2a**-C_6F_5, **2a**-*t*-Bu, **2a-2l** and **2n-q**.[10e,17] Step 1: A solution of corresponding ketone (1.0 equiv.), *t*-BuOK (1.5 equiv.) and 3-bromoprop-1-ene (3-bromocyclohex-1-ene for **2q**) (1.5 equiv.) in *t*-BuOH (1 mL per mmol) was heated at reflux under argon atmosphere. The mixture was monitored by TLC. The reaction mixture was concentrated in vacuo. The crude mixture was solubilized in EtOAc, washed three times with water (10 mL/mmol), dried with Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, using petroleum ether and ethyl acetate (100 : 1- 70 : 1) as the eluent. Step 2: A solution of $H_2NOH{\cdot}HCl$ (2.0 equiv.) and NaOAc (2.0 equiv.) in EtOH (2 mL/mmol) was stirred at room temperature. Then, appropriate ketone (1.0 equiv.) was added via a syringe. The mixture was heated at 80 ^{o}C for 1 h. After cooling to room temperature, the reaction mixture was concentrated in vacuo. The crude mixture was solubilized in EtOAc, washed with water (10 mL/mmol) and brine (10 mL/mmol), dried with Na_2SO_4. Purification by column chromatography on silica gel to give the corresponding oxime, using petroleum ether and ethyl acetate (70 : 1- 50 : 1) as the eluent. Step 3: A solution of appropriate oxime (1.0 equiv.), picolinic acid (1.1 equiv.), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC·HCl) (1.1 equiv.), N,N-dimethyl-4-aminopyridine (DMAP) (0.05 equiv.) and CH_2Cl_2 (2 mL/mmol). The reaction mixture was stirred at room temperature for 24 h. Then, 1 N NaOHaq (10 mL/mmol) was added. The mixture was extracted with EtOAc (40 mL x 2). The combined organic layer was washed with brine, then dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford the corresponding oxime ester, using petroleum ether and ethyl acetate (10 : 1- 8 : 1) as the eluent.

General procedure for the preparation of **2a**-**Me**, **2a**-Ph.[18] Steps 1) and 2) are same as above-mentioned. Step 3: A mixture of ketoxime (1.0 equiv.) and NEt_3 (2.0 equiv.) in DCM (3mL/mmol) at room temperature was added dropwise benzoyl chloride or acetyl chloride (1.2 equiv.). After stirring overnight, the mixture was concentrated in vacuo until the ketoximes were consumed monitored by TLC. The residual was extracted from water (30mL) with ethyl acetate (30mL ×3) and the combined extracts were washed with saturated brine, and dried with Na_2SO_4, filtered, and removed under reduced pressure. The crude product was purified through silica gel column chromatography to give the corresponding oxime ester, using petroleum ether and ethyl acetate (10 : 1) as the eluent.

General procedure for the preparation of **2m**.[19] Step 1: A solution of diisopropylamine (1.1 equiv.) and *n*-BuLi (1.05 equiv.) in THF was stirred at 0 ºC for 30 min under argon atmosphere. Then isobutyronitrile (1.0 equiv.) was slowly added. After stirring for 1 h, 1-bromo-3-methylbut-2-ene (1.2 equiv.) was added dropwise and the reaction mixture was allowed to warm up to room temperature while stirring overnight. The reaction was quenched with saturated aqueous NH_4Cl solution, then extracted three times with EtOAc. The organic phase was washed with water and brine, and dried over Na_2SO_4. After filtration, the solvent was evaporated to give a crude mixture, which was purified by flash column chromatography, using petroleum ether and ethyl acetate (5 : 1) as the eluent. Step 2: A solution of 2,2,5-trimethylhex-4-enenitrile (1.0 equiv.) in anhydrous diethyl ether (Et_2O) (1 mL/mmol) was cooled to 0 °C under argon atmosphere and PhMgBr (1.5 equiv.) was slowly added to the reaction flask. Then, the mixture was stirred overnight in a sealed tube at 60 °C. After cooling down to 0 °C, reaction was quenched with 3 N HCl (aq.) and warmed up for 4 h to finish the hydrolysis. The crude mixture was then extracted with EtOAc, washed with brine, dried over Na_2SO_4 and concentrated. The crude product was purified by flash column chromatography to give the ketone, using petroleum ether and ethyl acetate (100 : 1) as the eluent. Steps 3) and 4) are same as above-mentioned.

General procedure for the preparation of **2r**.[10g] Step 1: To a solution of the ethyl 3-oxo-3-phenylpropanoate (1.0 equiv.) in anhydrous THF (5 mL/mmol) was added NaH (1.0 equiv., 60% dispersion in mineral oil). The mixture was stirred at room temperature until gas evolution ceased (10 minutes). The 3-bromocyclohex-1-ene (1.1 equiv.) was then added via syringe and the mixture was heated at 50 ºC for 16 hours. The mixture was cooled to room temperature and THF (2 mL/mmol), MeOH (1 mL/mmol), water (1 mL/mmol) and KOH (5.0 equiv.) were added. The mixture was then heated at reflux for 16 hours. After cooling to room temperature, the mixture was acidified with aq. 1 M HCl (8 mL/mmol) and extracted with Et_2O (20 mL/mmol). The organic extracts were washed with brine (100 mL), dried (Na_2SO_4) and concentrated in vacuo. Purification by column chromatography on silica gel to give the ketone, using petroleum ether and ethyl acetate (100 : 1) as the eluent. Steps 2), and 3) are same as above-mentioned.

General Procedure for Synthesize of Compounds 3. 2-Isocyanobiaryls **1** (1 equiv., 0.3 mmol), γ, δ-unsaturated oxime esters **2** (2 equiv., 0.6 mmol) and o-dichlorobenzene (1 mL) were added to a 5 mL reaction tube, equipped with a stirrer bar. Then the tube was charged with argon and sealed. The mixture was heated in oil bath to stirred at 180 °C for 35 min. After cooled to room temperature, the reaction mixture was purified with chromatography column on silica gel directly (PE/EtOAc: 10/1) to afford the desired products **3**.

6-((4,4-dimethyl-5-phenyl-3,4-dihydro-2H-pyrrol-2-yl)methyl)phenanthridine (3aa). 3aa (85.4 mg, 78%) was obtained as a yellow oil after purification by column chromatography (petroleum ether/ethyl acetate = 10/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 – 8.63 (m, 1H), 8.57 (d, J = 7.4 Hz, 1H), 8.50 – 8.43 (m, 1H), 8.20 – 8.13 (m, 1H), 7.90 – 7.81 (m, 2H), 7.73 (s, 3H), 7.40 (d, J = 4.3 Hz, 3H), 4.80 (s, 1H), 4.30 (d, J = 14.0 Hz, 1H), 3.44 – 3.32 (m, 1H), 2.19 – 2.10 (m, 2H), 1.97 – 1.85 (m, 1H), 1.35 (dd, J = 7.6, 5.1 Hz, 6H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 179.8, 159.7, 143.7, 134.8, 132.9, 130.3, 129.7, 129.4, 128.5, 128.1, 127.9, 127.2, 126.7, 126.4, 125.7, 123.7, 122.3, 121.9, 67.8, 50.5, 48.2, 42.9, 27.3, 26.1. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{26}H_{25}N_2$ 365.2012; Found 365.2014.

6-((5-(4-fluorophenyl)-4,4-dimethyl-3,4-dihydro-2H-pyrrol-2-yl)methyl)phenanthridine (3ab). 3ab (81.5 mg, 71%) was obtained as a yellow oil after purification by column chromatography (petroleum ether/ethyl acetate = 10/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, J = 8.2 Hz, 1H), 8.56 (d, J = 8.1 Hz, 1H), 8.45 (d, J = 8.2 Hz, 1H), 8.15 (d, J = 7.9 Hz, 1H), 7.85 (t, J = 7.5 Hz, 1H), 7.72 (t, J = 7.1 Hz, 4H), 7.63 (t, J = 7.4 Hz, 1H), 7.06 (t, J = 8.2 Hz, 2H), 4.76 (d, J = 6.7 Hz, 1H), 4.24 (dd, J = 14.0, 4.8 Hz, 1H), 3.36 (dd, J = 13.6, 9.6 Hz, 1H), 2.12 (dd, J = 12.5, 6.5 Hz, 1H), 1.97 – 1.81 (m, 1H), 1.34 (d, J = 10.9 Hz, 6H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 178.6, 163.6 (d, J = 241.6 Hz), 159.7, 143.7, 132.9, 130.9 (d, J = 3.0 Hz), 130.4, 130.0 (d, J = 7.6 Hz), 129.7, 128.5, 127.3, 126.7, 126.4, 125.7, 123.8, 122.4, 122.0, 115.2 (d, J = 21.1 Hz), 67.7, 50.4, 48.4, 42.9, 27.3, 26.1. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{26}H_{24}FN_2$ 383.1918; Found 383.1921.

6-((5-(4-chlorophenyl)-4,4-dimethyl-3,4-dihydro-2H-pyrrol-2-yl)methyl)phenanthridine (3ac). 3ac (89.8 mg, 75%) was obtained as a yellow solid after purification by column chromatography (petroleum ether/ethyl acetate = 10/1); m.p.: 80.2-80.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (t, J = 8.4 Hz, 1H), 8.58 (d, J = 8.0 Hz, 1H), 8.46 (d, J = 8.5 Hz, 1H), 8.17 (s, 1H), 7.87 (d, J = 7.5 Hz, 1H), 7.76 – 7.62 (m, 4H), 7.36 (d, J = 8.6 Hz, 2H), 7.25 (d, J = 9.1 Hz, 1H), 4.78 (s, 1H), 4.24 (d, J = 4.9 Hz, 1H), 3.40 (s, 1H), 2.14 (s, 1H), 2.01 – 1.81 (m, 1H), 1.34 (t, J = 7.9 Hz, 6H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 178.9, 159.6, 135.8, 133.0, 130.6, 129.4, 128.6, 128.5, 127.3, 126.9, 126.6, 125.7, 123.8, 122.4, 122.0, 67.7, 50.5, 48.3, 42.6, 27.3, 26.1. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{26}H_{24}ClN_2$ 399.1623; Found 399.1619.

6-((5-(4-bromophenyl)-4,4-dimethyl-3,4-dihydro-2H-pyrrol-2-yl)methyl)phenanthridine (3ad). **3ad** (83.8 mg, 63%) was obtained as a yellow solid after purification by column chromatography (petroleum ether/ethyl acetate = 10/1); m.p.: 108.9-111.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (d, J = 7.9 Hz, 1H), 8.58 (d, J = 7.8 Hz, 1H), 8.45 (d, J = 7.9 Hz, 1H), 8.17 (d, J = 7.8 Hz, 1H), 7.91 – 7.84 (m, 1H), 7.74 (t, J = 7.6 Hz, 2H), 7.64 (dd, J = 20.8, 7.6 Hz, 3H), 7.52 (d, J = 7.9 Hz, 2H), 4.79 (s, 1H), 4.31 – 4.17 (m, 1H), 3.39 (s, 1H), 2.15 (dd, J = 12.2, 6.5 Hz, 1H), 1.94 – 1.86 (m, 1H), 1.34 (d, J = 6.5 Hz, 6H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 178.8, 159.6,

133.5, 133.0, 131.4, 130.5, 129.6, 128.6, 127.3, 126.8, 126.6, 125.7, 124.1, 123.8, 122.4, 122.0, 67.8, 50.5, 48.3, 42.6, 27.3, 26.1. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{26}H_{24}BrN_2$ 443.1117; Found 443.1114.

6-((5-(4-methoxyphenyl)-4,4-dimethyl-3,4-dihydro-2H-pyrrol-2-yl)methyl)phenanthridine (3ae). 3ae (81.7 mg, 69%) was obtained as a yellow solid after purification by column chromatography (petroleum ether/ethyl acetate = 10/1); m.p.: 133.5-135.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, J = 7.3 Hz, 1H), 8.57 (d, J = 7.2 Hz, 1H), 8.48 (d, J = 7.8 Hz, 1H), 8.15 (d, J = 7.2 Hz, 1H), 7.85 (d, J = 7.1 Hz, 1H), 7.74 (s, 4H), 7.65 (d, J = 6.4 Hz, 1H), 6.90 (d, J = 7.0 Hz, 2H), 4.75 (s, 1H), 4.28 (d, J = 13.5 Hz, 1H), 3.85 (d, J = 9.4 Hz, 3H), 3.35 (s, 1H), 2.18 – 2.04 (m, 1H), 1.94 – 1.86 (m, 1H), 1.37 (d, J = 18.0 Hz, 6H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 179.0, 160.9, 159.8, 143.8, 132.9, 130.4, 129.8, 129.7, 128.5, 127.3, 126.9, 126.4, 125.8, 123.8, 122.4, 122.0, 113.6, 67.3, 55.3, 50.3, 48.5, 43.0, 27.5, 26.3. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{28}H_{27}N_2O_2$ 423.2067; Found 423.2071.

6-((4,4-dimethyl-5-(p-tolyl)-3,4-dihydro-2H-pyrrol-2-yl)methyl)phenanthridine (3af). 3af (84.0 mg, 74%) was obtained as a yellow oil after purification by column chromatography (petroleum ether/ethyl acetate = 10/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ8.66 (d, J = 7.9 Hz, 1H), 8.57 (d, J = 7.6 Hz, 1H), 8.48 (d, J = 8.3 Hz, 1H), 8.15 (d, J = 8.0 Hz, 1H), 7.86 (s, 1H), 7.77 – 7.58 (m, 5H), 7.20 (d, J = 6.2 Hz, 2H), 4.79 (s, 1H), 4.33 (d, J = 12.1 Hz, 1H), 3.42 – 3.29 (m, 1H), 2.38 (s, 3H), 2.12 (dd, J = 11.4, 6.3 Hz, 1H), 1.96 – 1.85 (m, 1H), 1.36 (d, J = 12.3 Hz, 6H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 179.0, 158.6, 142.7, 131.9, 129.4, 128.7, 128.0, 127.9, 127.5, 127.1, 126.3, 125.8, 125.4, 124.7, 122.8, 121.3, 120.9, 66.3, 49.4, 47.2, 41.8, 26.4, 25.2, 20.4. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{27}H_{27}N_2$ 379.2169; Found 379.2171.

6-((5-(2-chlorophenyl)-4,4-dimethyl-3,4-dihydro-2H-pyrrol-2-yl)methyl)phenanthridine (3ag). 3ag (83.8 mg, 70%) was obtained as a yellow oil after purification by column chromatography (petroleum ether/ethyl acetate = 10/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, J = 8.1 Hz, 1H), 8.57 (d, J = 7.9 Hz, 1H), 8.47 (d, J = 8.0 Hz, 1H), 8.16 (d, J = 8.0 Hz, 1H), 7.86 (t, J = 7.4 Hz, 1H), 7.74 (s, 4H), 7.64 (t, J = 7.4 Hz, 1H), 7.40 (s, 2H), 4.80 (s, 1H), 4.30 (dd, J = 13.7, 4.9 Hz, 1H), 3.37 (dd, J = 13.9,

9.5 Hz, 1H), 2.13 (dd, *J* = 12.7, 6.5 Hz, 1H), 1.91 (dd, *J* = 12.6, 8.7 Hz, 1H), 1.36 (d, *J* = 9.6 Hz, 6H). $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) δ 179.8, 159.7, 134.9, 133.1, 132.7, 130.9, 129.9, 129.5, 129.2, 128.8, 127.6, 127.0, 126.7, 126.1, 125.6, 123.8, 122.4, 122.0, 69.5, 53.4, 53.0, 45.8, 26.6, 25.8. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{26}H_{24}ClN_2$ 399.1623; Found 399.1624.

6-((5-(3-chlorophenyl)-4,4-dimethyl-3,4-dihydro-2H-pyrrol-2-yl)methyl)phenanthridine (3ah). 3ah (90.9 mg, 76%) was obtained as a yellow solid after purification by column chromatography (petroleum ether/ethyl acetate = 10/1); m.p.: 98.0-100.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (d, *J* = 7.6 Hz, 1H), 8.56 (d, *J* = 7.0 Hz, 1H), 8.45 (d, *J* = 7.1 Hz, 1H), 8.16 (d, *J* = 7.0 Hz, 1H), 7.86 (s, 1H), 7.80 – 7.68 (m, 3H), 7.65 (d, *J* = 6.1 Hz, 1H), 7.57 (d, *J* = 6.1 Hz, 1H), 7.36 (s, 1H), 7.31 (d, *J* = 7.3 Hz, 1H), 4.79 (s, 1H), 4.23 (d, *J* = 13.8 Hz, 1H), 3.48 – 3.30 (m, 1H), 2.15 (d, *J* = 5.9 Hz, 1H), 1.90 (t, *J* = 10.6 Hz, 1H), 1.34 (s, 6H). $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) δ 178.6, 159.6, 143.6, 136.6, 134.3, 133.0, 130.5, 129.7, 129.5, 129.4, 128.6, 128.2, 127.3, 126.8, 126.5, 125.9, 125.7, 123.8, 122.4, 122.0, 68.0, 50.6, 48.2, 42.7, 27.2, 26.1. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{26}H_{24}ClN_2$ 399.1623; Found 399.1622.

6-((4,4-dimethyl-5-(pyridin-2-yl)-3,4-dihydro-2H-pyrrol-2-yl)methyl)phenanthridine (3ai). 3ai (80.0 mg, 73%) was obtained as a yellow oil after purification by column chromatography (petroleum ether/ethyl acetate = 10/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, *J* = 8.2 Hz, 1H), 8.59 (dd, *J* = 11.5, 6.5 Hz, 2H), 8.46 (d, *J* = 8.2 Hz, 1H), 8.18 (d, *J* = 8.1 Hz, 1H), 7.99 (d, *J* = 7.9 Hz, 1H), 7.87 (t, *J* = 7.6 Hz, 1H), 7.78 – 7.61 (m, 4H), 7.27 (d, *J* = 4.6 Hz, 1H), 4.84 (q, *J* = 8.2, 7.5 Hz, 1H), 4.23 (dd, *J* = 14.0, 5.5 Hz, 1H), 3.43 (dd, *J* = 14.0, 9.1 Hz, 1H), 2.16 (dd, *J* = 12.8, 7.1 Hz, 1H), 1.90 (dd, *J* = 12.8, 8.4 Hz, 1H), 1.48 (d, *J* = 13.4 Hz, 6H). $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) δ 179.2, 159.7, 153.8, 148.4, 143.6, 136.1, 133.0, 130.4, 129.7, 128.6, 127.2, 126.9, 126.5, 125.8, 124.1, 123.8, 123.4, 122.4, 122.0, 68.4, 50.8, 47.9, 42.9, 27.3, 26.0. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{25}H_{24}N_3$ 366.1965; Found 366.1968.

6-((4,4-dimethyl-5-(naphthalen-1-yl)-3,4-dihydro-2H-pyrrol-2-yl)methyl)phenanthridine (3aj). 3aj (84.6 mg, 68%) was obtained a yellow oil after purification by

column chromatography (petroleum ether/ethyl acetate = 10/1); m.p.: 79.1-81.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (dd, J = 8.3, 3.4 Hz, 1H), 8.57 (dd, J = 8.3, 3.3 Hz, 1H), 8.50 (dd, J = 8.4, 3.3 Hz, 1H), 8.18 (dd, J = 11.3, 3.5 Hz, 2H), 7.92 – 7.82 (m, 5H), 7.74 (dq, J = 8.6, 5.4, 5.0 Hz, 2H), 7.65 (dd, J = 8.0, 3.1 Hz, 1H), 7.51 (dd, J = 6.2, 3.5 Hz, 2H), 4.97 – 4.71 (m, 1H), 4.32 (dt, J = 14.2, 4.2 Hz, 1H), 3.46 (d, J = 3.3 Hz, 1H), 2.17 (ddd, J = 12.9, 6.7, 3.3 Hz, 1H), 1.96 (td, J = 8.9, 4.2 Hz, 1H), 1.44 (dd, J = 5.3, 3.2 Hz, 6H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 179.7, 159.8, 143.7, 133.8, 132.9, 132.8, 132.0, 130.4, 129.7, 128.7, 128.6, 127.9, 127.7, 127.6, 127.3, 126.9, 126.8, 126.5, 126.3, 125.8, 125.6, 123.8, 122.4, 122.0, 67.8, 53.4, 48.4, 42.9, 27.5, 26.3.

HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{30}H_{26}N_2Na$ 437.1988; Found 437.1987.

6-((4,4-dimethyl-5-(naphthalen-2-yl)-3,4-dihydro-2H-pyrrol-2-yl)methyl)phenanthridine (3ak). 3ak (60.9 mg, 49%) was obtained as a yellow solid after purification by column chromatography (petroleum ether/ethyl acetate = 10/1); m.p.: 90.2-92.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (d, J = 8.2 Hz, 1H), 8.59 (d, J = 8.1 Hz, 1H), 8.52 (d, J = 8.2 Hz, 1H), 8.28 – 8.12 (m, 2H), 7.88 (dt, J = 17.6, 8.7 Hz, 5H), 7.75 (q, J = 8.2 Hz, 2H), 7.65 (t, J = 7.5 Hz, 1H), 7.57 – 7.46 (m, 2H), 5.03 – 4.74 (m, 1H), 4.34 (dd, J = 14.0, 4.8 Hz, 1H), 3.44 (dd, J = 13.8, 9.5 Hz, 1H), 2.20 (dd, J = 12.6, 6.7 Hz, 1H), 1.97 (dd, J = 12.5, 8.9 Hz, 1H), 1.45 (d, J = 4.0 Hz, 6H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 179.8, 159.7, 149.5, 143.7, 133.9, 133.0, 132.9, 130.4, 129.7, 128.7, 128.6, 127.9, 127.7, 127.3, 126.9, 126.5, 126.3, 125.8, 125.6, 123.8, 122.4, 122.0, 67.7, 50.6, 48.4, 42.8, 27.6, 26.4. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{30}H_{27}N_2$ 415.2169; Found 415.2169.

6-((5-phenyl-3,4-dihydro-2H-pyrrol-2-yl)methyl)phenanthridine (3al). 3al (34.3 mg, 34%) was obtained as a yellow solid after purification by column chromatography (petroleum ether/ethyl acetate = 10/1); m.p.: 101.1-103.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, J = 8.2 Hz, 1H), 8.58 (d, J = 8.0 Hz, 1H), 8.47 (d, J = 8.2 Hz, 1H), 8.16 (d, J = 8.0 Hz, 1H), 7.93 – 7.83 (m, 3H), 7.73 (d, J = 6.0 Hz, 2H), 7.65 (t, J = 7.4 Hz, 1H), 7.44 (d, J = 6.8 Hz, 3H), 5.01 (s, 1H), 4.23 (d, J = 12.3 Hz, 1H), 3.33 (d, J = 10.1 Hz, 1H), 3.11 (s, 1H), 2.99 (d, J = 7.3 Hz, 1H), 2.24 (s,

1H), 2.04 (s, 1H). $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) δ 159.6, 132.9, 130.5, 129.7, 128.6, 128.5, 128.0, 127.3, 126.9, 126.5, 125.7, 123.8, 122.4, 122.0, 42.3, 35.0, 29.7, 28.3. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{24}H_{21}N_2$ 337.1699; Found 337.1698.

6-(2-(4,4-dimethyl-5-phenyl-3,4-dihydro-2H-pyrrol-2-yl)propan-2-yl)phenanthridine (3am). 3am (80.1 mg, 68%) was obtained as a yellow solid after purification by column chromatography (petroleum ether/ethyl acetate = 10/1); m.p.: 122.2-124.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (d, J = 8.3 Hz, 1H), 8.71 (d, J = 8.1 Hz, 1H), 8.55 (d, J = 8.0 Hz, 1H), 8.13 (d, J = 7.8 Hz, 1H), 7.81 (s, 1H), 7.76 (s, 2H), 7.73 – 7.59 (m, 3H), 7.41 (s, 3H), 5.21 (s, 1H), 2.08 (s, 3H), 1.65 (s, 5H), 1.35 (s, 3H), 1.19 (s, 3H). $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) δ 164.7, 142.8, 134.0, 130.4, 129.4, 128.4, 128.2, 128.1, 127.9, 126.6, 126.2, 124.8, 123.4, 123.0, 121.6, 50.2, 47.4, 44.0, 28.2, 26.7, 23.6. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{28}H_{29}N_2$ 393.2325; Found 393.2323.

6-((5-phenyl-6-azaspiro[3.4]oct-5-en-7-yl)methyl)phenanthridine (3an). 3an (82.5 mg, 73%) was obtained as a yellow solid after purification by column chromatography (petroleum ether/ethyl acetate = 10/1); m.p.: 109.1-110.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (d, J = 8.2 Hz, 1H), 8.55 (d, J = 8.0 Hz, 1H), 8.43 (d, J = 8.2 Hz, 1H), 8.18 (d, J = 8.1 Hz, 1H), 7.82 (dd, J = 17.2, 8.6 Hz, 3H), 7.71 (q, J = 8.9, 8.3 Hz, 2H), 7.63 (t, J = 7.4 Hz, 1H), 7.43 (s, 3H), 4.79 – 4.62 (m, 1H), 4.22 (dd, J = 14.0, 4.6 Hz, 1H), 3.30 (dd, J = 13.8, 9.9 Hz, 1H), 2.75 – 2.66 (m, 1H), 2.58 – 2.51 (m, 1H), 2.47 (dd, J = 12.8, 6.7 Hz, 1H), 2.19 (dd, J = 12.8, 7.2 Hz, 1H), 2.13 – 1.97 (m, 3H), 1.96 – 1.84 (m, 1H). $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) δ 178.1, 159.7, 143.7, 135.1, 132.9, 130.3, 129.8, 129.4, 128.5, 128.3, 127.8, 127.3, 126.8, 126.4, 125.7, 123.8, 122.4, 121.9, 68.2, 55.1, 47.0, 42.5, 32.2, 32.0, 16.4. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{27}H_{25}N_2$ 377.2012; Found 377.2013.

6-((1-phenyl-2-azaspiro[4.4]non-1-en-3-yl)methyl)phenanthridine(3ao). 3ao (84.3 mg, 72%) was obtained as a yellow oil after purification by column chromatography (petroleum ether/ethyl acetate = 10/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, J = 8.0 Hz, 1H), 8.56 (d, J = 7.9 Hz, 1H), 8.47 (d, J = 8.0 Hz, 1H), 8.16 (d, J = 8.0 Hz, 1H), 7.85 (t, J = 7.3 Hz, 1H), 7.68 (ddd, J = 25.9, 18.1, 7.4 Hz, 5H), 7.39 (s,

3H), 4.75 (s, 1H), 4.30 (dd, *J* = 13.8, 4.7 Hz, 1H), 3.35 (dd, *J* = 13.5, 9.8 Hz, 1H), 2.16 (dd, *J* = 12.4, 6.4 Hz, 1H), 1.91 – 1.53 (m, 9H). $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) δ 179.2, 159.8, 143.8, 134.8, 132.9, 130.3, 129.8, 129.4, 128.5, 128.2, 128.1, 128.0, 127.3, 126.8, 126.4, 125.8, 123.8, 122.4, 121.9, 68.5, 60.9, 48.1, 42.9, 37.7, 36.4, 25.7, 25.3. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{28}H_{27}N_2$ 391.2169; Found 391.2170.

6-((1-phenyl-2-azaspiro[4.5]dec-1-en-3-yl)methyl)phenanthridine (3ap). 3ap (72.8 mg, 60%) was obtained as a yellow oil after purification by column chromatography (petroleum ether/ethyl acetate = 10/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (d, *J* = 8.1 Hz, 1H), 8.59 (d, *J* = 7.9 Hz, 1H), 8.49 (d, *J* = 7.9 Hz, 1H), 8.20 (d, *J* = 7.5 Hz, 1H), 7.89 (t, *J* = 7.3 Hz, 1H), 7.71 (dt, *J* = 32.4, 7.3 Hz, 5H), 7.43 (s, 3H), 4.88 (s, 1H), 4.40 (s, 1H), 3.43 (s, 1H), 2.43 (s, 1H), 1.84 (s, 2H), 1.70 – 1.51 (m, 6H), 1.42 – 1.27 (m, 2H), 1.16 (d, *J* = 11.7 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) δ 180.9, 159.7, 143.7, 135.8, 132.9, 130.4, 129.8, 129.0, 128.5, 128.1, 128.0, 127.3, 126.8, 126.4, 125.7, 123.8, 122.4, 122.0, 68.5, 56.6, 43.3, 40.9, 35.7, 32.3, 25.6, 23.3, 23.0. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{29}H_{29}N_2$ 405.2325; Found 405.2327.

6-((3aR*,7S*,7aS*)-3,3,3a,7,7a-pentamethyl-2-phenyl-3a,4,5,6,7,7a-hexahydro-3H-indol-7-yl)phenanthridine (3aq). 3aq (77.6 mg, 64%) was obtained as a yellow oil after purification by column chromatography (petroleum ether/ethyl acetate = 10/1). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.65 (dd, *J* = 8.3, 1.1 Hz, 1H), 8.54 (dd, *J* = 8.2, 1.4 Hz, 1H), 8.37 – 8.32 (m, 1H), 8.16 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.80 (ddd, *J* = 8.2, 6.9, 1.3 Hz, 1H), 7.68 (dddd, *J* = 22.3, 7.8, 5.8, 2.1 Hz, 4H), 7.60 (ddd, *J* = 8.3, 6.9, 1.4 Hz, 1H), 7.36 (dd, *J* = 5.2, 2.1 Hz, 3H), 4.95 (t, *J* = 5.6 Hz, 1H), 4.45 (d, *J* = 5.2 Hz, 1H), 2.71 (dt, *J* = 9.9, 6.2 Hz, 1H), 2.07 – 1.95 (m, 2H), 1.78 (ddd, *J* = 11.0, 8.2, 4.8 Hz, 1H), 1.54 (tddd, *J* = 17.9, 10.4, 8.1, 4.8 Hz, 2H), 1.47 (s, 4H), 1.32 (s, 3H). $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) δ 180.1, 163.9, 143.6, 135.8, 133.1, 130.1, 129.9, 129.2, 128.2, 128.1, 127.7, 127.1, 126.2, 126.1, 125.0, 123.4, 122.5, 121.8, 70.3, 53.3, 49.0, 41.6, 28.5, 25.3, 23.7, 21.7, 20.3. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{29}H_{29}N_2$ 405.2325; Found 405.2324.

6-((3aR*,7S*,7aS*)-3a,7,7a-trimethyl-2-phenyl-3a,4,5,6,7,7a-hexahydro-3H-indol-7-yl)phenanthridine (3ar). 3ar (68.9 mg, 61%) was obtained as a yellow oil after purification by column chromatography (petroleum ether/ethyl acetate = 10/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (d, J = 9.0 Hz, 1H), 8.60 – 8.52 (m, 1H), 8.30 – 8.21 (m, 1H), 8.22 – 8.13 (m, 1H), 7.86 – 7.57 (m, 6H), 7.40 (d, J = 9.6 Hz, 3H), 4.90 (s, 1H), 4.12 (s, 1H), 3.14 (d, J = 15.2 Hz, 2H), 2.90 (d, J = 13.1 Hz, 1H), 2.07 – 1.83 (m, 3H), 1.62 (s, 2H), 1.50 (s, 1H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 163.8, 143.7, 133.1, 130.0, 128.4, 128.3, 127.8, 127.0, 126.3, 126.2, 125.2, 123.5, 122.4, 121.9, 73.8, 53.4, 40.9, 36.8, 29.0, 27.1, 20.2. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{27}H_{25}N_2$ 377.2012; Found 377.2015.

6-((4,4-dimethyl-5-phenyl-3,4-dihydro-2H-pyrrol-2-yl)methyl)-8-methylphenanthridine (3ba). 3ba (94.2 mg, 83%) was obtained as a yellow oil after purification by column chromatography (petroleum ether/ethyl acetate = 10/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (t, J = 7.6 Hz, 2H), 8.21 (s, 1H), 8.12 (d, J = 7.3 Hz, 1H), 7.74 (d, J = 5.9 Hz, 3H), 7.64 (d, J = 6.9 Hz, 2H), 7.35 (d, J = 6.4 Hz, 2H), 7.19 (s, 1H), 4.77 (s, 1H), 4.30 (d, J = 10.5 Hz, 1H), 3.44 – 3.22 (m, 1H), 2.57 (s, 3H), 2.11 (s, 1H), 1.94 – 1.82 (m, 1H), 1.32 (d, J = 7.0 Hz, 6H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 180.3, 158.1, 142.1, 136.5, 131.6, 129.9, 129.3, 128.1, 127.4, 127.3, 127.3, 125.6, 125.5, 124.7, 122.9, 121.3, 120.8, 66.2, 49.5, 46.9, 41.2, 26.3, 25.3, 20.8. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{27}H_{27}N_2$ 379.2169; Found 379.2172.

6-((4,4-dimethyl-5-phenyl-3,4-dihydro-2H-pyrrol-2-yl)methyl)-8-phenylphenanthridine (3ca). 3ca (87.2 mg, 66%) was obtained as a yellow oil after purification by column chromatography (petroleum ether/ethyl acetate = 10/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 – 8.66 (m, 2H), 8.58 (t, J = 8.2 Hz, 1H), 8.21 – 8.05 (m, 2H), 7.75 (q, J = 9.9, 8.6 Hz, 3H), 7.67 (s, 3H), 7.53 – 7.47 (m, 2H), 7.46 – 7.29 (m, 4H), 4.79 (s, 1H), 4.31 (d, J = 7.3 Hz, 1H), 3.57 – 3.33 (m, 1H), 2.20 – 2.12 (m, 1H), 1.95 – 1.86 (m, 1H), 1.34 (s, 6H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 180.1, 160.0, 143.6, 142.0, 140.1, 132.0, 129.7, 129.7, 129.1, 128.5, 128.2, 128.0, 127.8, 127.6, 126.6, 126.2, 125.1, 123.7, 123.0, 122.0, 67.8, 50.5, 48.3, 43.0, 27.3, 26.1. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{32}H_{29}N_2$ 441.2325; Found 441.2327.

6-((4,4-dimethyl-5-phenyl-3,4-dihydro-2H-pyrrol-2-yl)methyl)-8-methoxyphenanthridine (3da). 3da (76.9 mg, 65%) was obtained as a yellow solid after purification by column chromatography (petroleum ether/ethyl acetate = 10/1); m.p.: 123.0-125.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, J = 8.8 Hz, 1H), 8.48 (d, J = 8.0 Hz, 1H), 8.14 (d, J = 7.8 Hz, 1H), 7.80 – 7.71 (m, 3H), 7.64 (dt, J = 21.3, 7.1 Hz, 2H), 7.49 (d, J = 9.1 Hz, 1H), 7.41 (s, 3H), 4.83 (s, 1H), 4.29 (d, J = 13.8 Hz, 1H), 3.99 (s, 3H), 3.34 (dd, J = 13.9, 9.9 Hz, 1H), 2.18 (dd, J = 12.3, 6.4 Hz, 1H), 1.95 – 1.87 (m, 1H), 1.36 (d, J = 5.9 Hz, 6H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 180.8, 158.9, 158.5, 142.5, 130.1, 129.5, 128.4, 128.2, 127.6, 127.3, 127.0, 126.6, 124.1, 123.9, 121.5, 121.3, 106.9, 67.1, 55.8, 50.6, 48.1, 42.6, 27.4, 26.2. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{27}H_{27}N_2O$ 395.2118; Found 395.2120.

8-bromo-6-((4,4-dimethyl-5-phenyl-3,4-dihydro-2H-pyrrol-2-yl)methyl)phenanthridine (3ea). 3ea (79.8 mg, 60%) was obtained as a yellow solid after purification by column chromatography (petroleum ether/ethyl acetate = 10/1); m.p.: 145.3-146.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (s, 1H), 8.52 (d, J = 8.4 Hz, 2H), 8.14 (d, J = 8.1 Hz, 1H), 7.94 (d, J = 8.7 Hz, 1H), 7.83 – 7.70 (m, 3H), 7.65 (t, J = 7.6 Hz, 1H), 7.42 (s, 3H), 4.77 (s, 1H), 4.11 (s, 1H), 3.39 (dd, J = 14.1, 8.4 Hz, 1H), 2.22 (s, 1H), 1.92 – 1.86 (m, 1H), 1.40 (d, J = 5.2 Hz, 6H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 158.8, 143.6, 133.6, 131.7, 129.9, 129.7, 128.9, 128.3, 128.1, 127.2, 126.9, 124.2, 123.2, 121.8, 121.3, 67.5, 50.5, 48.4, 42.8, 27.3, 26.2. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{26}H_{24}BrN_2$ 443.1117; Found 443.1114.

8-chloro-6-((4,4-dimethyl-5-phenyl-3,4-dihydro-2H-pyrrol-2-yl)methyl)phenanthridine (3fa). 3fa (98.1 mg, 82%) was obtained as a yellow oil after purification by column chromatography (petroleum ether/ethyl acetate = 10/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, J = 8.6 Hz, 1H), 8.49 (d, J = 9.3 Hz, 2H), 8.14 (d, J = 8.1 Hz, 1H), 7.84 – 7.70 (m, 4H), 7.64 (t, J = 7.4 Hz, 1H), 7.40 (s, 3H), 4.82 – 4.67 (m, 1H), 4.09 (dd, J = 13.9, 5.7 Hz, 1H), 3.37 (dd, J = 13.8, 8.3 Hz, 1H), 2.19 (dd, J = 12.5, 6.5 Hz, 1H), 1.98 – 1.81 (m, 1H), 1.43 – 1.31 (m, 6H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 178.9, 157.9, 142.7, 133.6, 132.1, 130.3, 129.9, 128.8, 128.6, 127.8, 127.2, 127.0,

125.8, 125.5, 123.0, 122.2, 120.8, 66.7, 49.5, 47.4, 41.8, 26.2, 25.1. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{26}H_{24}ClN_2$ 399.1623; Found 399.1620.

Methyl-6-((4,4-dimethyl-5-phenyl-3,4-dihydro-2H-pyrrol-2-yl)methyl)phenanthridine-8-carboxylate (3ga). 3ga (88.7 mg, 70%) was obtained as a yellow solid after purification by column chromatography (petroleum ether/ethyl acetate = 10/1); m.p.: 161.9-164.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.18 (s, 1H), 8.69 (d, J = 8.5 Hz, 1H), 8.58 (d, J = 8.1 Hz, 1H), 8.46 (d, J = 8.5 Hz, 1H), 8.17 (d, J = 8.1 Hz, 1H), 7.77 (dd, J = 17.8, 7.1 Hz, 3H), 7.67 (t, J = 7.4 Hz, 1H), 7.38 (d, J = 6.8 Hz, 3H), 4.89 – 4.75 (m, 1H), 4.25 (dd, J = 14.2, 5.8 Hz, 1H), 4.02 (s, 3H), 3.44 (dd, J = 13.9, 8.7 Hz, 1H), 2.21 (dd, J = 12.5, 6.4 Hz, 1H), 1.95 – 1.84 (m, 1H), 1.38 (s, 6H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 179.0, 165.6, 159.3, 143.5, 135.0, 133.6, 129.2, 128.9, 128.6, 128.6, 128.3, 127.6, 127.2, 127.0, 125.8, 124.4, 122.1, 121.6, 121.5, 66.7, 51.4, 49.5, 47.5, 41.7, 26.3, 25.1. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{28}H_{27}N_2O_2$ 423.2067; Found 423.2071.

6-((4,4-dimethyl-5-phenyl-3,4-dihydro-2H-pyrrol-2-yl)methyl)phenanthridine-8-carbonitrile (3ha). 3ha (47.9 mg, 41%) was obtained as a yellow solid after purification by column chromatography (petroleum ether/ethyl acetate = 10/1); m.p.: 104.1-106.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (s, 1H), 8.71 (d, J = 8.6 Hz, 1H), 8.54 (d, J = 8.0 Hz, 1H), 8.18 (d, J = 8.1 Hz, 1H), 8.01 (d, J = 8.6 Hz, 1H), 7.82 (t, J = 7.4 Hz, 1H), 7.71 (d, J = 12.6 Hz, 3H), 7.45 – 7.34 (m, 3H), 4.83 – 4.56 (m, 1H), 4.02 (dd, J = 13.9, 6.8 Hz, 1H), 3.49 – 3.41 (m, 1H), 2.31 – 2.24 (m, 1H), 1.92 – 1.84 (m, 1H), 1.39 (d, J = 7.5 Hz, 6H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 179.2, 158.4, 143.7, 134.6, 133.3, 132.0, 130.5, 129.4, 129.3, 129.0, 128.8, 127.3, 126.9, 126.3, 124.4, 122.5, 121.5, 121.5, 117.7, 109.6, 66.7, 49.5, 47.6, 41.7, 26.2, 25.1. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{27}H_{24}N_3$ 390.1965; Found 390.1966.

6-((4,4-dimethyl-5-phenyl-3,4-dihydro-2H-pyrrol-2-yl)methyl)-8-(trifluoromethyl)phenanthridine (3ia). 3ia (89.5 mg, 69%) was obtained as a yellow solid after purification by column chromatography (petroleum ether/ethyl acetate = 10/1); m.p.: 107.0-109.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 – 8.71 (m, 2H), 8.57 (d, J = 8.0 Hz, 1H), 8.18 (d, J = 8.1 Hz, 1H), 8.04 (d, J = 8.5 Hz, 1H), 7.79 (t, J = 7.5 Hz, 1H),

7.75 – 7.63 (m, 3H), 7.37 (d, J = 6.7 Hz, 3H), 4.81 – 4.70 (m, 1H), 4.12 (dd, J = 14.2, 6.5 Hz, 1H), 3.46 (dd, J = 14.2, 7.7 Hz, 1H), 2.26 (dd, J = 12.7, 6.6 Hz, 1H), 1.89 (dd, J = 12.6, 9.1 Hz, 1H), 1.39 (d, J = 7.3 Hz, 6H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 207.0, 180.1, 160.0, 144.4, 135.2, 134.5, 129.9, 129.7, 128.9 (q, J = 32.6 Hz), 128.2, 127.9, 127.0, 126.2, 125.3, 125.1, 124.7 (d, J = 4.4 Hz), 123.4, 123.3, 122.8, 122.3, 67.8, 50.5, 48.6, 42.6, 27.2, 26.1. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{27}H_{24}F_3N_2$ 433.1886; Found 433.1889.

6-((4,4-dimethyl-5-phenyl-3,4-dihydro-2H-pyrrol-2-yl)methyl)-7-methylphenanthridine (3ja). 3ja (45.4 mg, 40%) was obtained as a yellow oil after purification by column chromatography (petroleum ether/ethyl acetate = 10/1). ^1H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 2H), 8.12 (s, 1H), 7.82 (s, 2H), 7.70 (s, 2H), 7.63 (s, 1H), 7.53 (s, 1H), 7.44 (s, 3H), 4.95 (s, 1H), 4.71 (s, 1H), 3.51 (s, 1H), 3.11 (s, 3H), 2.39 (s, 1H), 1.80 (s, 1H), 1.40 (s, 6H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 159.2, 142.3, 137.1, 134.6, 132.0, 129.9, 129.0, 128.5, 126.5, 126.2, 123.8, 122.3, 120.9, 67.4, 50.3, 48.6, 29.7, 27.5, 26.7, 26.3. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{27}H_{27}N_2$ 379.2169; Found 379.2166.

6-((4,4-dimethyl-5-phenyl-3,4-dihydro-2H-pyrrol-2-yl)methyl)-9-methylphenanthridine (3ja'). 3ja' (43.1 mg, 38%) was obtained as a yellow oil after purification by column chromatography (petroleum ether/ethyl acetate = 10/1). ^1H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, J = 7.6 Hz, 1H), 8.44 (s, 1H), 8.37 (d, J = 7.9 Hz, 1H), 8.16 (d, J = 7.5 Hz, 1H), 7.73 (s, 3H), 7.62 (t, J = 7.4 Hz, 1H), 7.56 (d, J = 7.4 Hz, 1H), 7.40 (s, 3H), 4.77 (s, 1H), 4.28 (d, J = 14.4 Hz, 1H), 3.42 – 3.25 (m, 1H), 2.65 (d, J = 7.2 Hz, 3H), 2.09 (d, J = 6.7 Hz, 1H), 1.97 – 1.83 (m, 1H), 1.35 (d, J = 11.7 Hz, 6H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 180.2, 159.5, 143.5, 141.0, 134.5, 133.2, 129.7, 129.4, 129.1, 128.5, 128.2, 128.1, 126.8, 126.3, 123.8, 123.7, 122.1, 122.0, 67.7, 50.6, 48.1, 42.7, 27.3, 26.1, 22.3. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{27}H_{27}N_2$ 379.2169; Found 379.2168.

6-((4,4-dimethyl-5-phenyl-3,4-dihydro-2H-pyrrol-2-yl)methyl)-10-methylphenanthridine (3ka). 3ka (43.1 mg, 38%) was obtained as a yellow oil after purification by column chromatography (petroleum ether/ethyl acetate = 10/1). ^1H NMR (400

MHz, $CDCl_3$) δ 8.73 (d, J = 7.6 Hz, 1H), 8.33 (d, J = 7.3 Hz, 1H), 8.13 (d, J = 6.8 Hz, 1H), 7.66 (d, J = 4.9 Hz, 4H), 7.59 – 7.48 (m, 2H), 7.33 (s, 3H), 4.73 (s, 1H), 4.27 (d, J = 13.1 Hz, 1H), 3.39 – 3.21 (m, 1H), 3.09 (d, J = 14.4 Hz, 3H), 2.05 (dd, J = 11.2, 6.4 Hz, 1H), 1.93 – 1.72 (m, 1H), 1.28 (d, J = 12.2 Hz, 6H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 179.1, 158.9, 143.7, 134.5, 133.7, 133.5, 131.4, 128.9, 128.6, 127.2, 127.1, 127.0, 126.8, 126.1, 125.7, 125.6, 124.6, 124.2, 124.2, 66.6, 49.5, 47.2, 42.4, 26.3, 25.9, 25.1. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{27}H_{27}N_2$ 379.2169; Found 379.2172.

2-chloro-6-((4,4-dimethyl-5-phenyl-3,4-dihydro-2H-pyrrol-2-yl)methyl)phenanthridine (3la). 3la (90.9 mg, 76%) was obtained as a yellow solid after purification by column chromatography (petroleum ether/ethyl acetate = 10/1); m.p.: 115.3-117.4 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, J = 8.2 Hz, 1H), 8.52 (s, 1H), 8.47 (d, J = 8.2 Hz, 1H), 8.08 (d, J = 8.7 Hz, 1H), 7.88 (t, J = 7.6 Hz, 1H), 7.77 (t, J = 7.6 Hz, 1H), 7.72 (d, J = 5.5 Hz, 2H), 7.66 (d, J = 8.7 Hz, 1H), 7.39 (d, J = 6.5 Hz, 3H), 4.78 (d, J = 6.0 Hz, 1H), 4.24 (dd, J = 14.2, 5.0 Hz, 1H), 3.35 (dd, J = 14.0, 9.4 Hz, 1H), 2.15 (dd, J = 12.7, 6.8 Hz, 1H), 1.88 (dd, J = 12.6, 8.7 Hz, 1H), 1.36 (d, J = 5.7 Hz, 6H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 180.1, 160.1, 142.2, 134.7, 132.2, 131.9, 131.3, 130.7, 129.6, 129.0, 128.2, 128.0, 128.0, 126.9, 125.9, 124.9, 122.4, 121.6, 67.6, 50.6, 48.3, 42.9, 27.4, 26.2. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{26}H_{24}ClN_2$ 399.1623; Found 399.1626.

6-((4,4-dimethyl-5-phenyl-3,4-dihydro-2H-pyrrol-2-yl)methyl)-2,4-dimethylphenanthridine (3ma). 3ma (76.5 mg, 65%) was obtained as a yellow oil after purification by column chromatography (petroleum ether/ethyl acetate = 10/1). ^1H NMR (400 MHz, $CDCl_3$) δ 8.64 (d, J = 8.2 Hz, 1H), 8.37 (d, J = 8.1 Hz, 1H), 8.20 (s, 1H), 7.80 (d, J = 6.5 Hz, 3H), 7.69 (t, J = 7.1 Hz, 1H), 7.43 (s, 4H), 4.98 (s, 1H), 4.37 (d, J = 15.0 Hz, 1H), 3.46 – 3.28 (m, 1H), 2.85 (s, 3H), 2.58 (s, 3H), 2.35 (dd, J = 12.5, 6.2 Hz, 1H), 1.89 (dd, J = 12.4, 8.3 Hz, 1H), 1.40 (s, 6H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 156.5, 140.6, 137.3, 135.6, 132.8, 130.9, 129.8, 128.3, 128.1, 127.0, 126.1, 125.5, 123.3, 122.6, 119.4, 67.2, 50.5, 48.6, 42.5, 27.6, 26.3, 21.9, 18.3. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{28}H_{29}N_2$ 393.2325; Found 393.2328.

5-((4,4-dimethyl-5-phenyl-3,4-dihydro-2H-pyrrol-2-yl)methyl)benzo[c][2,7]naphthyridine (3na). 3na (51.5 mg, 47%) was obtained as a yellow solid after purification by column chromatography (petroleum ether/ethyl acetate = 10/1); m.p.: 109.7-110.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.83 (s, 1H), 8.95 (s, 1H), 8.54 (s, 1H), 8.40 (s, 1H), 8.18 (s, 1H), 7.85 (s, 1H), 7.72 (d, J = 15.1 Hz, 3H), 7.39 (s, 3H), 4.83 (s, 1H), 4.22 (s, 1H), 3.51 (s, 1H), 2.24 (s, 1H), 1.91 (s, 1H), 1.40 (s, 6H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 206.9, 159.6, 150.9, 148.4, 145.1, 137.9, 130.8, 130.0, 128.3, 128.1, 127.1, 122.5, 121.8, 120.9, 115.5, 67.5, 53.4, 50.5, 48.4, 27.3, 26.1. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{25}H_{24}N_3$ 366.1965; Found 366.1968.

5-((4,4-dimethyl-5-phenyl-3,4-dihydro-2H-pyrrol-2-yl)methyl)benzo[i]phenanthridine (3oa). 3oa (75.9 mg, 61%) was obtained as a yellow solid after purification by column chromatography (petroleum ether/ethyl acetate = 10/1); m.p.: 162.4-164.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.10 (d, J = 8.5 Hz, 1H), 8.64 (dd, J = 8.2, 4.1 Hz, 2H), 8.19 (dd, J = 17.2, 8.6 Hz, 2H), 8.04 (d, J = 7.8 Hz, 1H), 7.75 (dq, J = 24.9, 8.7, 7.9 Hz, 6H), 7.39 (d, J = 5.0 Hz, 3H), 5.19 (s, 1H), 4.82 (dd, J = 15.0, 4.1 Hz, 1H), 3.67 (dd, J = 15.0, 10.0 Hz, 1H), 2.17 (dd, J = 12.6, 6.7 Hz, 1H), 1.59 – 1.44 (m, 1H), 1.35 (s, 3H), 1.27 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 179.9, 158.2, 143.8, 135.1, 133.7, 133.4, 131.8, 130.3, 129.4, 129.3, 128.9, 128.9, 128.7, 128.2, 128.1, 128.0, 127.9, 127.8, 127.1, 126.5, 126.3, 123.2, 123.2, 122.5, 120.3, 68.1, 50.4, 48.7, 48.6, 27.4, 26.1. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{30}H_{27}N_2$ 415.2169; Found 415.2172.

5-((4,4-dimethyl-5-phenyl-3,4-dihydro-2H-pyrrol-2-yl)methyl)dibenzo[i,k]phenanthridine (3pa). 3pa (97.6 mg, 70%) was obtained as a yellow solid after purification by column chromatography (petroleum ether/ethyl acetate = 10/1); m.p.: 191.8-193.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (d, J = 7.7 Hz, 1H), 8.71 (dt, J = 17.0, 8.0 Hz, 4H), 8.21 (d, J = 8.3 Hz, 1H), 7.86 – 7.64 (m, 7H), 7.61 (d, J = 7.1 Hz, 1H), 7.35 (s, 3H), 5.17 (s, 1H), 4.55 (s, 1H), 3.58 (s, 1H), 2.05 (s, 1H), 1.48 – 1.38 (m, 1H), 1.34 (s, 3H), 1.22 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ179.7, 157.1, 145.5, 134.7, 134.4, 132.3, 130.7, 129.8, 129.4, 129.0, 128.5, 128.4, 128.3, 128.2, 128.1, 127.9, 127.2, 127.0, 126.9, 125.7, 123.7, 123.6, 123.4, 122.5, 68.5, 50.2, 48.4,

46.6, 27.2, 26.0. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{34}H_{29}N_2$ 465.2325; Found 465.2328.

6-((4,4-dimethyl-5-phenyl-3,4-dihydro-2H-pyrrol-2-yl)methyl)benzo[4,5]thieno [3,2-c]quinoline (3qa). 3qa (30.2 mg, 24%) was obtained as a yellow oil after purification by column chromatography (petroleum ether/ethyl acetate = 10/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (d, J = 8.0 Hz, 1H), 8.23 (d, J = 8.0 Hz, 1H), 8.15 (d, J = 7.5 Hz, 1H), 8.05 (d, J = 7.9 Hz, 1H), 7.75 (d, J = 6.6 Hz, 3H), 7.62 (d, J = 8.2 Hz, 2H), 7.56 (t, J = 7.2 Hz, 1H), 7.42 (s, 3H), 4.94 (s, 1H), 4.64 (d, J = 13.4 Hz, 1H), 3.63 – 3.45 (m, 1H), 2.18 (s, 1H), 2.02 – 1.96 (m, 1H), 1.38 (d, J = 19.9 Hz, 6H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 180.5, 155.9, 147.1, 144.2, 139.0, 135.5, 134.9, 129.6, 129.5, 129.3, 128.2, 128.0, 127.8, 126.4, 126.2, 125.6, 125.3, 123.8, 123.2, 123.0, 66.7, 50.7, 48.2, 45.5, 27.4, 26.2. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{28}H_{25}N_2S$ 421.1733; Found 421.1734.

Gram-Scale Synthesis of 3aa. 2-Isocyanobiaryls **1a** (1 equiv., 3 mmol), γ, δ-unsaturated oxime esters **2a** (2 equiv., 6 mmol) and o-dichlorobenzene (10 mL) were added to a 50 mL reaction tube, equipped with a stirrer bar. Then the tube was charged with argon and sealed. The mixture was heated in oil bath to stirred at 180 °C for 35 min. After cooled to room temperature, the reaction mixture was purified with chromatography column on silica gel directly (PE/EtOAc: 10/1) to afford the desired products **3aa** as a yellow oil. 788.4 mg, 72% yield.

The kinetic isotope effect study between 1a and [D5]-1a. [D5]-**1a** (0.5 equiv., 0.15 mmol), **1a** (0.5 equiv., 0.15 mmol), γ, δ-unsaturated oxime esters **2a** (2 equiv., 0.6 mmol) and o-dichlorobenzene (1 mL) were added to a 5 mL reaction tube, equipped with a stirrer bar. Then the tube was charged with argon and sealed. The mixture was heated in oil bath to stirred at 180 °C for 35 min. After cooled to room temperature, the reaction mixture was purified with chromatography column on silica gel directly (PE/EtOAc: 10/1) to afford the mixture of products **3aa** and **3aa'** (79.3 mg, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (d, J = 8.3 Hz, 1H), 8.56 (d, J = 8.1 Hz, 2H), 8.47 (d, J = 8.2 Hz, 1H), 8.16 (d, J = 8.1 Hz, 2H), 7.85 (t, J = 7.6 Hz, 1H), 7.72 (t, J = 6.8 Hz, 7H), 7.63 (t, J = 7.5 Hz, 2H), 7.39 (d, J = 5.3 Hz, 6H), 4.79 (p, J =

8.7 Hz, 2H), 4.28 (dd, *J* = 14.1, 5.1 Hz, 2H), 3.36 (dd, *J* = 14.0, 9.5 Hz, 2H), 2.11 (dd, *J* = 12.7, 6.7 Hz, 2H), 1.90 (dd, *J* = 12.5, 8.8 Hz, 2H), 1.35 (d, *J* = 10.3 Hz, 12H).

Radical Inhibition Studies. 1a (1 equiv., 0.3 mmol), γ, δ-unsaturated oxime esters **2a** (2 equiv., 0.6 mmol), TEMPO (3 equiv., 0.9 mmol) and o-dichlorobenzene (1 mL) were added to a 5 mL reaction tube, equipped with a stirrer bar. Then the tube was charged with argon and sealed. The mixture was heated in oil bath to stirred at 180 °C for 35 min. After cooled to room temperature, the reaction mixture was purified with chromatography column on silica gel directly (PE/EtOAc: 10/1) to afford the mixture of products **4** as a yellow oil. And almost no **3aa** was observed. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (s, 2H), 7.38 (s, 3H), 4.17 (d, *J* = 35.0 Hz, 2H), 3.96 (s, 1H), 2.06 (s, 1H), 1.90 (s, 1H), 1.52 – 1.33 (m, 12H), 1.18 – 1.03 (m, 8H). MS (ESI) *m/z*: 315.2 $[M + H]^+$.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

^{1}H and ^{13}C NMR spectra for new compounds, and 2D NMR spectra (PDF)

ACKNOWLEDGMENTS

Financial support was provided by the National Natural Science Foundation of China (No. 81673292 and 81973162) for financial support.

REFERENCES

(1) (a) Almerico, A. M.; Mingoia, F.; Diana, P.; Barraja, P.; Montalbano, A.; Lauria, A.; Loddo, R.; Sanna, L.; Delpiano, D.; Setzu, M. G.; Musiu, C. Pyrrolo[1,2-f]phenanthridines and related non-rigid analogues as antiviral agents. *Eur. J. Med. Chem.* **2002**, *37*, 3-10. (b) Lamoral-Theys, D.; Andolfi, A.; Van Goietsenoven, G.; Cimmino, A.; Le Calve, B.; Wauthoz, N.; Megalizzi, V.; Gras, T.; Bruyere, C.; Dubois, J.; Mathieu, V.; Kornienko, A.; Kiss, R.; Evidente, A. Lycorine, the Main Phenanthridine Amaryllidaceae Alkaloid, Exhibits Significant

Antitumor Activity in Cancer Cells That Display Resistance to Proapoptotic Stimuli: An Investigation of Structure-Activity Relationship and Mechanistic Insight. *J. Med. Chem.* **2009**, *52*, 6244-6256. (c) Nakanishi, T.; Suzuki, M.; Mashiba, A.; Ishikawa, K.; Yokotsuka, T. Synthesis of NK109, an anticancer benzo[c]phenanthridine alkaloid. *J. Org. Chem.* **1998**, *63*, 4235-4239. (d) Ishikawa, T. Benzo[c]phenanthridine bases and their antituberculosis activity. *Med. Res. Rev.* **2001**, *21*, 61-72. (e) Maiti, M.; Kumar, G. S. Molecular aspects on the interaction of protoberberine, benzophenanthridine, and aristolochia group of alkaloids with nucleic acid structures and biological perspectives. *Med. Res. Rev.* **2007**, *27*, 649-695. (f) Sripada, L.; Teske, J. A.; Deiters, A. Phenanthridine synthesis via [2+2+2] cyclotrimerization reactions. *Org. Biomol. Chem.* **2008**, *6*, 263-265.

(2) (a) Magedov, I. V.; Luchetti, G.; Evdokimov, N. M.; Manpadi, M.; Steelant, W. F. A.; Van Slambrouck, S.; Tongwa, P.; Antipin, M. Y.; Kornienko, A. Novel three-component synthesis and antiproliferative properties of diversely functionalized pyrrolines. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1392-1396. (b) Moya, P.; Cantin, A.; Castillo, M. A.; Primo, J.; Miranda, M. A.; Primo-Yufera, E. Isolation, structural assignment, and synthesis of N-(2-methyl-3-oxodecanoyl)-2-pyrroline, a new natural product from Penicillium brevicompactum with in vivo anti-juvenile hormone activity. *J. Org. Chem.* **1998**, *63*, 8530-8535. (c) Mandal, R.; Kutala, V. K.; Khan, M.; Mohan, I. K.; Varadharaj, S.; Sridhar, A.; Carnes, C. A.; Kalai, T.; Hideg, K.; Kuppusamy, P. N-hydroxy-pyrroline modification of verapamil exhibits antioxidant protection of the heart against ischemia/reperfusion-induced cardiac dysfunction without compromising its calcium antagonistic activity. *J. Pharmacol. Exp. Ther.* **2007**, *323*, 119-127. (d) Gein, V. L.; Bobrovskaya, O. V.; Valiev, R. T.; Odegova, T. F.; Gartman, G. A. Synthesis and Antibacterial Activity of 1-[2-(4-Aminosulfonylphenyl)Ethyl]-5-Aryl-4-Aroyl-3-Hydroxy-3-Pyrrolin-2-Ones. *Pharm. Chem. J.* **2015**, *49*, 602-604.

(3) (a) Maiti, D.; Halder, A.; De Sarkar, S. Base-Promoted Aerobic Oxidation/Homolytic Aromatic Substitution Cascade toward the Synthesis of Phenanthridines. *Adv. Synth. Catal.* **2019**, *361*, 4941-4948. (b) Chowdhury, D.; Dana, S.; Mandal, A.; Baidya, M. A ruthenium-catalyzed free amine directed (5+1) annulation of anilines with olefins: diverse synthesis of phenanthridine derivatives. *Chem. Commun.* **2019**, *55*, 11908-11911. (c) Lv, P.; Huang, K. L.; Xie, L. G.; Xu, X. H. Palladium-catalyzed tandem reaction to construct benzo[c]phenanthridine: application to the total synthesis of benzo[c]phenanthridine alkaloids. *Org. Biomol. Chem.* **2011**, *9*, 3133-3135.

(4) (a) Cai, S.-H.; Wang, D.-X.; Ye, L.; Liu, Z.-Y.; Feng, C.; Loh, T.-P. Pyrroline Synthesis via Visible-Light-Promoted Hydroimination of Unactivated Alkenes with N, N'-Dimethylpropylene Urea as H-Donor. *Adv. Synth. Catal.* **2018**, *360*, 1262-1266. (b) Usami, K.; Yamaguchi, E.; Tada, N.; Itoh, A. Visible-Light-Mediated Iminyl Radical Generation from Benzyl Oxime Ether: Synthesis of Pyrroline via Hydroimination Cyclization. *Org. Lett.* **2018**, *20*, 5714-5717. (c) Úr, G.; Kálai, T.; Hideg, K. Facile syntheses of 3,4-disubstituted pyrroline nitroxides and their further synthetic applications. *Tetrahedron Lett.* **2016**, *57*, 778-780.

(5) (a) Zard, S. Z. Iminyl radicals: A fresh look at a forgotten species (and some of its relatives). *Synlett* **1996**, 1148. (b) Jackman, M. M.; Cai, Y.; Castle, S. L. Recent Advances in Iminyl Radical Cyclizations. *Synthesis* **2017**, *49*, 1785-1795. (c) Yin, W. Q.; Wang, X. L. Recent advances in iminyl radical-mediated catalytic cyclizations and ring-opening reactions. *New. J. Chem.* **2019**, *43*, 3254-3264. (d) Chen, C.; Zhao, J.; Shi, X.; Liu, L.; Zhu, Y.-P.; Sun, W.; Zhu, B. Recent advances in cyclization reactions of unsaturated oxime esters (ethers): synthesis of versatile functionalized nitrogen-containing scaffolds. *Org. Chem. Front.* **2020**, *7*, 1948-1969.

(6) (a) Faulkner, A.; Race, N. J.; Scott, J. S.; Bower, J. F. Copper catalyzed Heck-like cyclizations of oxime esters. *Chem. Sci.* **2014**, *5*, 2416-2421. (b) Huang, H. W.; Ji, X. C.; Wu, W. Q.; Jiang, H. F. Transition metal-catalyzed C-H

functionalization of N-oxyenamine internal oxidants. *Chem. Soc. Rev.* **2015**, *44*, 1155-1171. (c) Chen, H.; Chiba, S. Copper-catalyzed redox-neutral C-H amination with amidoximes. *Org. Biomol. Chem.* **2014**, *12*, 42-46.

(7) (a) Zard, S. Z. Recent progress in the generation and use of nitrogen-centred radicals. *Chem. Soc. Rev.* **2008**, *37*, 1603-1618. (b) Alonso, R.; Campos, P. J.; Garcia, B.; Rodriguez, M. A. New light-induced iminyl radical cyclization reactions of acyloximes to isoquinolines. *Org. Lett.* **2006**, *8*, 3521-3523. (c) Yu, X. Y.; Chen, J. R.; Xiao, W. J. Visible Light-Driven Radical-Mediated C-C Bond Cleavage/Functionalization in Organic Synthesis. *Chem. Rev.* **2020**, DOI: 10.1021/acs.chemrev.0c00030.

(8) (a) Portela-Cubillo, F.; Scott, J. S.; Walton, J. C. Microwave-assisted preparations of dihydropyrroles from alkenone O-phenyl oximes. *Chem. Commun.* **2007**, 4041-4043. (b) Portela-Cubillo, F.; Scoto, J. S.; Walton, J. C. Microwave-assisted syntheses of n-heterocycles using alkenone-, alkynone- and aryl-carbonyl O-phenyl oximes: Formal synthesis of neocryptolepine. *J. Org. Chem.* **2008**, *73*, 5558-5565. (c) Cai, Y.; Jalan, A.; Kubosumi, A. R.; Castle, S. L. Microwave-Promoted Tin-Free Iminyl Radical Cyclization with TEMPO Trapping: A Practical Synthesis of 2-Acylpyrroles. *Org. Lett.* **2015**, *17*, 488-491. (d) Markey, S. J.; Lewis, W.; Moody, C. J. A New Route to alpha-Carbolines Based on 6 pi-Electrocyclization of Indole-3-alkenyl Oximes. *Org. Lett.* **2013**, *15*, 6306-6308.

(9) Blake, J. A.; Pratt, D. A.; Lin, S. Q.; Walton, J. C.; Mulder, P.; Ingold, K. U. Thermolyses of O-phenyl oxime ethers. A new source of iminyl radicals and a new source of aryloxyl radicals. *J. Org. Chem.* **2004**, *69*, 3112-3120.

(10) (a) Yang, H. B.; Pathipati, S. R.; Selander, N. Nickel-Catalyzed 1,2-Aminoarylation of Oxime Ester-Tethered Alkenes with Boronic Acids. *Acs Catal.* **2017**, *7*, 8441-8445. (b) Su, H. L.; Li, W. F.; Xuan, Z. L.; Yu, W. Copper-Catalyzed Cyclization and Azidation of gamma, delta-Unsaturated Ketone O-Benzoyl Oximes. *Adv. Synth. Catal.* **2015**, *357*, 64-70. (c) Race, N. J.; Faulkner, A.; Shaw, M. H.; Bower, J. F. Dichotomous mechanistic behavior in

Narasaka-Heck cyclizations: electron rich Pd-catalysts generate iminyl radicals. *Chem. Sci.* **2016**, *7*, 1508-1513. (d) Koganemaru, Y.; Kitamura, M.; Narasaka, K. Synthesis of dihydropyrrole derivatives by copper-catalyzed cyclization of gamma,delta-unsaturated ketone O-methoxycarbonyloximes. *Chem. Lett.* **2002**, 784-785. (e) Shimbayashi, T.; Okamoto, K.; Ohe, K. Iron-Catalyzed Aminative Cyclization/Intermolecular Homolytic Aromatic Substitution Using Oxime Esters and Simple Arenes. *Chem. -Asian J.* **2018**, *13*, 395-399. (f) Wang, L.; Wang, C. Copper-Catalyzed Diamination of Oxime Ester-Tethered Unactivated Alkenes with Unprotected Amines. *J. Org. Chem.* **2019**, *84*, 6547-6556. (g) Faulkner, A.; Scott, J. S.; Bower, J. F. An Umpolung Approach to Alkene Carboamination: Palladium Catalyzed 1,2-Amino-Acylation, -Carboxylation, -Arylation, -Vinylation, and -Alkynylation. *J. Am. Chem. Soc.* **2015**, *137*, 7224-7230. (h) Wang, Y. B.; Ding, J.; Zhao, J. H.; Sun, W.; Lian, C.; Chen, C.; Zhu, B. L. Iminyl radical-promoted imino sulfonylation, imino cyanogenation and imino thiocyanation of gamma,delta-unsaturated oxime esters: synthesis of versatile functionalized pyrrolines. *Org. Chem. Front.* **2019**, *6*, 2240-2244. (i) Guo, K.; Zhang, H. L.; Cao, S. J.; Gu, C.; Zhou, H. T.; Li, J.; Zhu, Y. G. Copper-Catalyzed Domino Cyclization/Trifluoromethylthiolation of Unactivated Alkenes: Access to SCF_3-Containing Pyrrolines. *Org. Lett.* **2018**, *20*, 2261-2264.

(11) Brahmachari, G. In *Catalyst-free Organic Synthesis*; Clark J. H., Ed.; Royal Society of Chemistry: India, 2017, p P001-P004.

(12) (a) Tobisu, M.; Koh, K.; Furukawa, T.; Chatani, N. Modular Synthesis of Phenanthridine Derivatives by Oxidative Cyclization of 2-Isocyanobiphenyls with Organoboron Reagents. *Angew. Chem., Int. Edit.* **2012**, *51*, 11363-11366. (b) Xiao, T. B.; Li, L. Y.; Lin, G. L.; Wang, Q. L.; Zhang, P.; Mao, Z. W.; Zhou, L. Synthesis of 6-substituted phenanthridines by metal-free, visible-light induced aerobic oxidative cyclization of 2-isocyanobiphenyls with hydrazines. *Green Chem.* **2014**, *16*, 2418-2421. (c) Xu, Y. L.; Chen, Y. Y.; Li, W.; Xie, Q.; Shao, L. M. Microwave-Assisted Synthesis of Phenanthridines by Radical Insertion/Cyclization of Biphenyl Isocyanides. *J. Org. Chem.* **2016**, *81*,

8426-8435. (d) Xue, D. Q.; Chen, H.; Xu, Y. L.; Yu, H. H.; Yu, L. Q.; Li, W.; Xie, Q.; Shao, L. M. Microwave-assisted synthesis of hydroxyl-containing isoquinolines by metal-free radical cyclization of vinyl isocyanides with alcohols. *Org. Biomol. Chem.* **2017**, *15*, 10044-10052. (e) Leifert, D.; Daniliuc, C. G.; Studer, A. 6-Aroylated Phenanthridines via Base Promoted Homolytic Aromatic Substitution (BHAS). *Org. Lett.* **2013**, *15*, 6286-6289. (f) Li, Z. J.; Fan, F. H.; Yang, J.; Liu, Z. Q. A Free Radical Cascade Cyclization of Isocyanides with Simple Alkanes and Alcohols. *Org. Lett.* **2014**, *16*, 3396-3399. (g) Wang, Q. L.; Dong, X. C.; Xiao, T. B.; Zhou, L. $PhI(OAc)_{(2)}$-Mediated Synthesis of 6-(Trifluoromethyl)phenanthridines by Oxidative Cyclization of 2-Isocyanobiphenyls with CF_3SiMe_3 under Metal-Free Conditions. *Org. Lett.* **2013**, *15*, 4846-4849. (h) Yang, X. L.; Chen, F.; Zhou, N. N.; Yu, W.; Han, B. Synthesis of Isoxazoline-Functionalized Phenanthridines via Iminoxyl Radical-Participated Cascade Sequence. *Org. Lett.* **2014**, *16*, 6476-6479. (i) Xue, D. Q.; Xue, Y. J.; Yu, H. H.; Shao, L. M. Metal-Free Radical Cyclization of Vinyl Isocyanides with Alkanes: Synthesis of 1-Alkylisoquinolines. *Synthesis* **2019**, *51*, 874-884.

(13) (a) Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. The formation and stabillity of spiro-compounds. Part I. Spiro-compounds from cyclo-hexane., *J. Chem. Soc.* **1915**, *107*, 1080-1106. (b) Ingold, C. K. The conditions underlying the formation of unsaturated and of cyclic compounds from halogenated open-chain derivatives Part I Products derived from a-halogenated glutaric acids. *J. Chem. Soc.* **1921**, *119*, 305-329.

(14) (a) Meng, Y.; Guo, L. N.; Wang, H.; Duan, X. H. Metal-free oxidative hydroxyalkylarylation of activated alkenes by direct sp(3) C-H functionalization of alcohols. *Chem. Commun.* **2013**, *49*, 7540-7542. (b) Wei, W. T.; Zhou, M. B.; Fan, J. H.; Liu, W.; Song, R. J.; Liu, Y.; Hu, M.; Xie, P.; Li, J. H. Synthesis of oxindoles by iron-catalyzed oxidative 1,2-alkylarylation of activated alkenes with an aryl C(sp2)-H bond and a C(sp3)-H bond adjacent to a heteroatom. *Angew. Chem., Int. Edit.* **2013**, *52*, 3638-3641. (c) Xu, Y. L.; Chen, H.; Li, W.; Xie, Q.; Yu, L. Q.; Shao, L. M.

Synthetic access to isoxazoline-functionalized isoquinolines via microwave-assisted iminoxyl radical-participated cascade cyclization of vinyl isocyanides. *Org. Biomol. Chem.* **2018**, *16*, 4996-5005. (d) Zhou, M. B.; Song, R. J.; Ouyang, X. H.; Liu, Y.; Wei, W. T.; Deng, G. B.; Li, J. H. Metal-free oxidative tandem coupling of activated alkenes with carbonyl C(sp(2))-H bonds and aryl C(sp(2))-H bonds using TBHP. *Chem. Sci.* **2013**, *4*, 2690-2694.

(15) Sha, W. X.; Yu, J. T.; Jiang, Y.; Yang, H. T.; Cheng, J. The benzoyl peroxide-promoted functionalization of simple alkanes with 2-aryl phenyl isonitrile. *Chem. Commun.* **2014**, *50*, 9179-9181.

(16) (a) Feng, S. B.; Li, T.; Du, C. L.; Chen, P.; Song, D. P.; Li, J. L.; Xie, X. G.; She, X. G. Visible-light-mediated radical insertion/cyclization cascade reaction: synthesis of phenanthridines and isoquinolines from isocyanides. *Chem. Commun.* **2017**, *53*, 4585-4588. (b) Sun, X. Y.; Yu, S. Y. Visible-Light-Mediated Fluoroalkylation of Isocyanides with Ethyl Bromofluoroacetates: Unified Synthesis of Mono- and Difluoromethylated Phenanthridine Derivatives. *Org. Lett.* **2014**, *16*, 2938-2941.

(17) Chen, C.; Bao, Y. W.; Zhao, J. H.; Zhu, B. L. Silver-promoted cascade radical cyclization of gamma, delta-unsaturated oxime esters with P(O)H compounds: synthesis of phosphorylated pyrrolines. *Chem. Commun.* **2019**, *55*, 14697-14700.

(18) (a) Zhang, W. G.; Su, Y. P.; Wang, K. H.; Wu, L. L.; Chang, B. B.; Shi, Y.; Huang, D. F.; Hu, Y. L. Trichloroisocyanuric Acid Promoted Cascade Cyclization/Trifluoromethylation of Allylic Oximes: Synthesis of Trifluoromethylated Isoxazolines. *Org. Lett.* **2017**, *19*, 376-379. (b) Wang, L.; Wang, C. Ni-Catalyzed 1,2-iminoacylation of alkenes via a reductive strategy. *Org. Chem. Front.* **2018**, *5*, 3476-3482.

(19) Cai, S. H.; Xie, J. H.; Song, S. J.; Ye, L.; Feng, C.; Loh, T. P. Visible-Light-Promoted Carboimination of Unactivated Alkenes for the Synthesis of Densely Functionalized Pyrroline Derivatives. *ACS Catal.* **2016**, *6*, 5571-5574.