JOC The Journal of Organic Chemistry

Article

Visible-light-driven Difluoromethylation of Isocyanides with S-(Difluoromethyl)diarylsulfonium Salt: Access to a Wide Variety of Difluoromethylated Phenanthridines and Isoquinolines

Wen-Bing Qin, Wei Xiong, Xin Li, Jia-Yi Chen, Li-Ting Lin, Henry Nai Ching Wong, and Guo-Kai Liu

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.0c00816 • Publication Date (Web): 15 Jul 2020

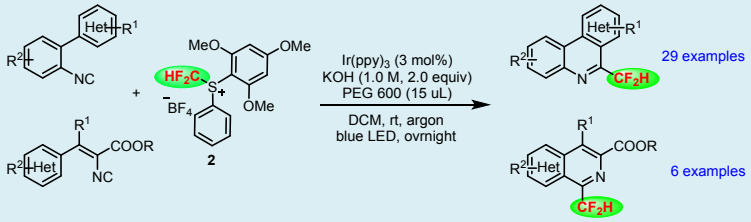
Visible-light-driven Difluoromethylation of Isocyanides with *S*-(Difluoromethyl)diarylsulfonium Salt: Access to a Wide Variety of Difluoromethylated Phenanthridines and Isoquinolines

Wen-Bing Qin,[a] Wei-Xiong,[a] Xin Li,[a] Jia-Yi Chen,[a] Li-Ting Lin,[a] Henry N. C. Wong,[b] and Guo-Kai Liu*[a]

[a] School of Pharmaceutical Sciences, Shenzhen University Health Science Centre, Shenzhen University, 3688 Nanhai Ave., Shenzhen 518060, China

[b] Department of Chemistry, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong SAR, China

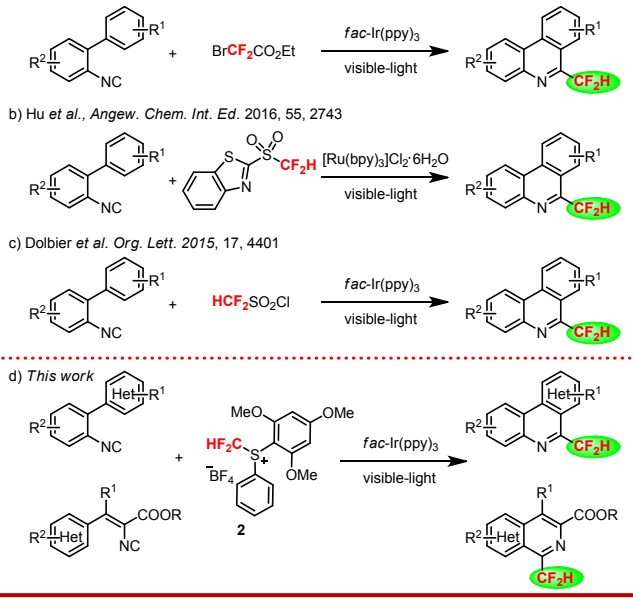
Supporting Information



ABSTRACT: A highly efficient approach of visible-light-driven radical difluoromethylation of isocyanides to access a wide variety of difluoromethylated phenanthridines and isoquinolines was herein described. Electrophilic *S*-(difluoromethyl)diarylsulfonium salt proved to be a good difluoromethyl radical precursor under photoredox catalysis. Broad range of isocyanides were tolerated to furnish the corresponding difluoromethylated phenanthridines, isoquinolines, furo[3,2-c]pyridine and pyrido[3,4-b]indole in moderate to excellent yields under mild conditions. A plausible mechanism was also proposed.

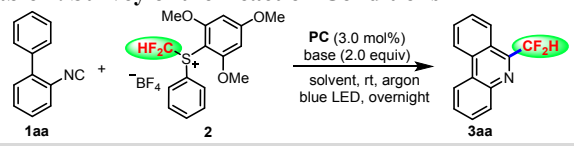
INTRODUCTION

Scheme 1. Visible-light Photoredox Radical Difluoromethylation of Isocyanides



Difluoromethyl group (CF_2H) is a useful structural moiety in pharmaceuticals,[1] agrochemicals,[2] and materials,[3] because of its contribution to a profound and beneficial alternation in chemical, physical and biological properties of the parent compounds.[4] In particular, CF_2H unit plays an important role in drug discovery and development, since it can act as a bioisostere to CH_3OH and SH units[1h, 5] and serve in hydrogen-bond donor with more lipophilicity and metabolic-stability,[6] thereby benefitting the ADME (Absorption, Distribution, Metabolism and Excretion) of drugs.[1h,4f] Therefore, the introduction of a CF_2H group into common organic molecules represents a significant synthetic goal. Among the existing strategies for the synthesis of difluoromethylated compounds, the visible-light photoredox radical approach has been emerged recently as one of the most powerful synthetic tools, due to its numerous advantages such green, highly efficient, mild conditions, environment-friendly and economic, etc. In the past few years, several research groups have contributed this research area,[7] including Dolbier,[8] Qing,[9] and Akita[10] etc. However, most of these previous reports chose to focus on radical difluoromethylation of alkenes. A direct radical difluoromethylation of isocyanides to install difluoromethylated phenanthridines and isoquinolines is still underdeveloped. More importantly, both phenanthridines and isoquinolines are very useful skeletons which frequently occur in natural products and biologically active molecules.[11] Consequently, the facile synthesis of difluoromethylated phenanthridines and isoquinolines from the corresponding isocyanides via a radical pathway has attracted considerable attention in the past few years. The current methods to access difluoromethylated phenanthridines and isoquinolines mainly involve transition-metal catalysis[12] or metal-free conditions.[13] However, very few visible-light-driven protocols have been recorded. Yu and co-worker disclosed the first visible-light-driven approach for radical difluoromethylation of isocyanides using $BrCF_2CO_2Et$ as the difluoromethyl radical regent (Scheme 1a).[14] Subsequently, Hu[15] and Dolbier[16] employed difluoromethylsulfone (Scheme 1b) and HCF_2SO_2Cl (Scheme 1c) to realize the same goal under visible-light photoredox catalysis, respectively. Although the aforementioned progress has been rather useful, a facile and practical direct difluoromethylation of isocyanides is still lacking. Very recently, we developed the bench-stable *S*-(difluoromethyl)diarylsulfonium salts **2** as a highly efficient electrophilic difluoromethylating reagent and difluorocarbene precursor.[17] As a part of our continuous effort for the synthesis of biologically active fluorinated compounds, herein we disclose a facile visible-light-driven photoredox process for radical difluoromethylation of isocyanides to assemble 6-difluoromethyl phenanthridine derivatives with **2** as a difluoromethyl radical reagent.

Table 1. Survey of the Reaction Conditions[a]

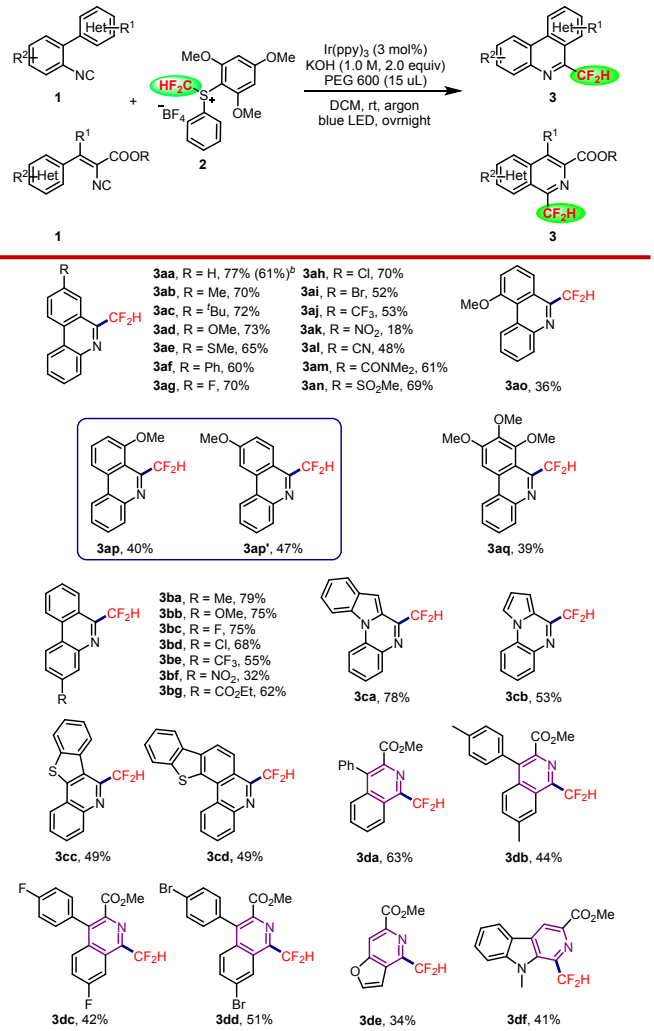


1aa 2 3aa

entry	[PC]	base/(equiv)	solvent	yield (%)
1	$Ir(ppy)_3$	--	DCM	37
2	$Ru(bpy)_2Cl_2$	--	DCM	ND
3	Eosin Y	--	DCM	ND
4	4CzPN	--	DCM	26
5[b]	$Ir(ppy)_3$	--	DCM	ND
6	$Ir(ppy)_3$	--	1,4-doxane	30
7	$Ir(ppy)_3$	--	THF	31
8	$Ir(ppy)_3$	--	MeCN	19
9	$Ir(ppy)_3$	Et_3N (2.0 equiv)	DCM	4
10	$Ir(ppy)_3$	$(iPr)_2NEt$ (2.0 equiv)	DCM	8
11	$Ir(ppy)_3$	DBU (2.0 equiv)	DCM	26
12	$Ir(ppy)_3$	KOH (1M, 2.0 equiv)	DCM	71
13	$Ir(ppy)_3$	NaOH (1M, 2.0 equiv)	DCM	58
14	$Ir(ppy)_3$	K_2HPO_4 (1M, 2.0 equiv)	DCM	34
15	$Ir(ppy)_3$	KOAc (1M, 2.0 equiv)	DCM	46
16	$Ir(ppy)_3$	KOH (2.0 equiv)	DCM	18
17[c]	$Ir(ppy)_3$	KOH (1M, 2.0 equiv)	DCM	79

[a] **Reaction conditions (unless otherwise specified): 1a (0.1 mmol), photocatalyst (3.0 mol%), solvent and 2 (0.2 mmol) was added in a tube, the reaction were irradiated with a 12 W blue LED at room temperature under argon atmosphere overnight, isolated yield.** [b] **Without blue LED.** [c] **PEG 600 (15 μL) was added. Eosin Y = 2,4,5,7-Tetrabromofluorescein disodium salt, 4CzPN = 3,4,5,6-tetrakis(carbazol-9-yl)-1,2-dicyanobenzene**

Scheme 2. Substrates Scope of Difluoromethylation of Isocyanides[a]



[a] Reaction conditions (unless otherwise specified): **1** (0.1 mmol), **2** (0.2 mmol), $Ir(ppy)_3$ (3 mol%), PEG 600 (15 μL) and KOH (1M, 2.0 equiv) in DCM (2 mL) were irradiated with a 12 W blue LED at room temperature under argon atmosphere overnight, isolated yields. [b] This reaction was performed in 3.0 mmol scale of **1aa** to give 61% isolated yield of **3aa**.

RESULTS AND DISCUSSION

We initially used isocyanide **1a** as a model substrate to optimize the reaction conditions (Table 1). Reagent **2** was employed to generate the difluoromethyl radical by blue light irritation under $Ir(ppy)_3$ (3 mol%) in DCM. To our delight, the desired difluoromethylphenanthridine (**3a**) was formed in an isolated yield of 37% (entry 1). Although the reagent's byproduct trimethoxyphenyl sulfide is also a very electron-rich arene, which might be a good radical acceptor, no corresponding difluoromethylation side product was found. Probably isocyanide is more active acceptor toward difluoromethyl radical than trimethoxyphenyl sulfide in this reaction. Other photoredox catalysts such as $Ru(bpy)_2Cl_2$, Eosin Y and 4CzPN were next tested, but no desired products were found (entries 2-3) except 4CzPN in 26% yield (entry 4). It should be noted that the reaction does not proceed in the absence of blue LED (entry 5). Using other solvents did not give better results (entries 6-8). In order to improve the reaction efficiency, bases were added to neutralize the acid generated during the reaction course (entries 9-17). It was found that organic bases were ineffective (entries 9-11), and difluoromethylating reagent **2** might be decomposed under Et_3N or $(^iPr)_2NEt$, thus resulting in decreasing yields (entries 9-10). Gratifyingly, we found that aqueous basic solution would promote the reaction (entries 12-15). Thus, aqueous KOH (1M) dramatically increased the yield to 71% (entry 12), while only 18% yield of product was afforded when insoluble KOH powder was used (entry 16). The yields were further slightly improved to 79% when 15 μL of PEG 600 was employed as an additive (entry 17), probably benefiting from its acting as a co-solvent to enhance miscibility of KOH aqueous solution and organic solvent dichloromethane.

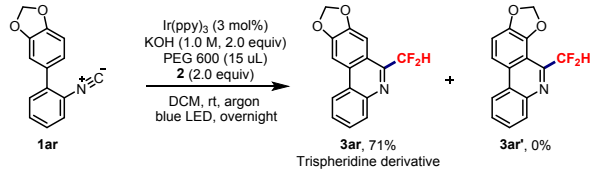
With the optimized reaction conditions in hand (entry 17, Table 1), we then examined the substrate scope of this process under optimized reaction conditions (Scheme 2). These substrates with both electron-donating (**1ab-1af**, **1ap**, **1ba-1bb**) and electron-withdrawing (**1ag-1aj**, **1al-1an**, **1bc-1bg**) substituents, regardless of *para*- or *meta*-positions on the biphenyl moieties of the isocyanides, were compatible to this reaction, leading to the formation of the corresponding products in moderate to good yields, although substrates bearing strongly electron-withdrawing groups (**1ak**, **1bf**) gave poor yields. A 3.0 mmol scale conversion was performed and 419.3 mg **3aa** was isolated (61% yield), revealing the potential application of this method.

However, the *ortho*-OMe substituent and multiple OMe substituents in the benzene ring decreased reactivity to afford lower yields (**3ao**, **3aq**), probably due to their steric hindrance. The 3-methoxy-substituted isocyanide **1ap** gave two corresponding products **3ap** and **3ap'** in yields of 40% and 47%, respectively. Importantly, Substrates containing heteroaryl moieties including indole, pyrrole and thianaphthene were also suitable substrates for this transformation, providing their corresponding products **3ca-3cd** in moderate to good yields.

Remarkably, 2-isocyanoacrylates could also react smoothly with the difluoromethyl radical reagent, offering the desired difluoromethylated isoquinolines (**3da-3dd**), furo[3,2-c]pyridine (**3de**) and pyrido[3,4-b]indole (**3df**) in moderate yields. It is worth noting that direct radical difluoromethylation in a regioselective manner of the parent heterocycles remain still a highly challenge task so far, thus suggesting that this protocol indeed provides a practical and efficient method for the synthesis of a variety of important difluoromethylated heterocyclic compounds which possess high potentials in pharmaceuticals and drug discovery.

To demonstrate the practicability of this radical difluoromethylation method, the synthesis for the drug 6-difluoromethyltrispheridine, which is a DNA intercalator[18], was exploited. As shown in scheme 3, the dioxole derivative **1ar** could smoothly undergo reaction in a regioselectively manner to afford 6-difluoromethylated trispheridine **3ar** as a single isomer in 71% yield under the standard conditions , while no **3ar'** was found, thus clearly suggesting its practicability and potential in medical chemistry and drug discovery.

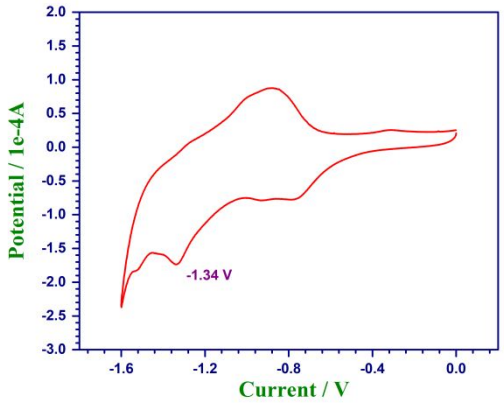
Scheme 3. Synthesis of Difluoromethylated Trispheridine



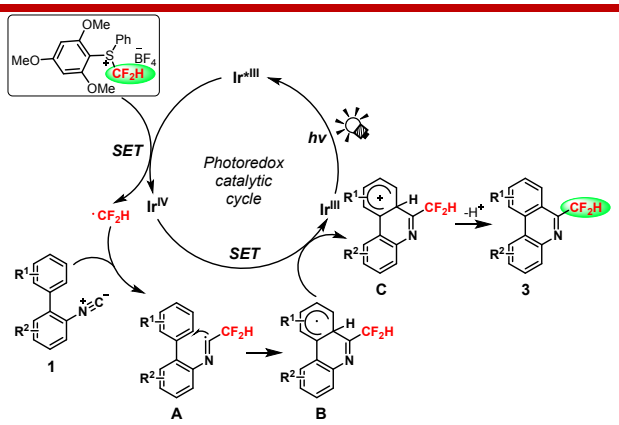
To gain detailed insight into the mechanism, the cyclic voltammogram experiment was carried out. As shown in Scheme 4, the measured reduction potential of *S*-(difluoromethyl)diarylsulfonium salt **2** is E_p^{red} = -1.34 V *vs*. SCE in CH_3CN, thus inferring that reagent **2** could be readily reduced by the selected photoexcited complex [$Ir(ppy)_3$*] ($E_{1/2}^{red}[Ir^{IV}/Ir^{*III}]$ = -1.73 V vs. SCE)[19].

Based on our experimental results and previous mechanistic studies[16], a plausible mechanism is proposed (Scheme 5). Initially, the excited [$Ir(ppy)_3$*] catalyst reduces the

Scheme 4. Cyclic Voltammetry Study of Reagent 2



Scheme 5. Proposed Mechanism



S-(difluoromethyl)diarylsulfonium salt **2** to generate the CF_2H radical, followed by an intermolecular addition to the isocyanide functionality of **1** to form imidoyl radical **A**. Radical **A** subsequently undergoes an intramolecular attack onto the pendant aromatic ring to give cyclohexadienyl-type radical **B**. Then radical **B** is oxidized by the high-valent catalyst Ir^{IV} ($E_{1/2}^{ox}[Ir^{IV}/Ir^{III}]$ = +0.77 V vs. SCE)[19] through a single electron transfer (SET) process to afford the cyclohexadienyl cation **C** along with the regeneration of catalyst. Finally, aromatization of **C** *via* deprotonation leads to the desired product **3**. Another possible pathway is deprotonation of radical **B**, followed by oxidation with Ir^{IV} to give final desired product **3.**

CONCLUSIONS

In conclusion, we have developed an effective and practical approach for the assembling of a wide variety of difluoromethylated phenanthridines, isoquinolines, furo[3,2-*c*]-pyridine and pyrido[3,4-*b*]indole from isocyanides with *S*-(difluoromethyl)diarylsulfonium salt **2** *via* visible-light-driven radical difluoromethylation process under mild reaction conditions. This transformation tolerated a variety of functional groups to furnish desired products in moderate to excellent yields. We believe that this protocol would provide a facile method to access many pharmaceutically important difluoromethylated heterocyclic compounds, and is of interest to organic chemists and medicinal chemists.

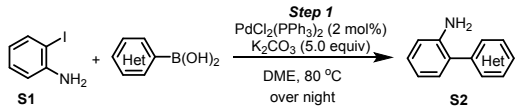
EXPERIMENT SECTION

General Experimental Information: ^1H NMR spectra were recorded on a Bruker Ascend™ 400MHz (400 MHz) or Bruker Ascend™ 500MHz (500 MHz) spectrometer at ambient temperature unless otherwise indicated. Data were reported as follows: chemical shifts in ppm from tetramethylsilane as an internal standard in $CDCl_3$, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet-doublet, m = multiplet, br = broad), coupling constants (Hz), and assignment. ^{13}C NMR spectra were recorded on a Bruker Ascend™ 400MHz (101 MHz), Bruker Ascend™ 500MHz (126 MHz) or Bruker Ascend™ 600MHz (151 MHz) spectrometer at ambient temperature and were proton decoupled. Chemical shifts are reported in ppm from tetramethylsilane on the scale with the solvent resonance employed as the internal standard. ^{19}F NMR spectra were recorded on a Bruker Ascend™ 400MHz (376 MHz)，Bruker Ascend™ 500MHz (471 MHz) spectrometer at ambient temperature. Chemical shifts are reported in ppm from $CFCl_3$ as the internal standard. ESI-MS analyses were performed in positive ionization mode on an Agilent 1260-Infinity LC/MSD. All high resolution mass spectra were obtained on a Thermo Scientific Q-Exactive (HR/AM) Orbitrap™ mass spectrometer. Commercially available reagents were used as received. Reactions were monitored by TLC. Flash chromatography: silica gel (300-400 mesh).

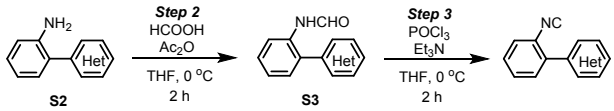
General Procedure for the Preparation of Isocyanides.

All known isocyanides were prepared according to a reported method, and analytical data are in agreement with those reported in the literature. [14, 15, 20]

General Procedure for synthesis of 2-(isocyano)-1,1’-biaryl derivatives A:



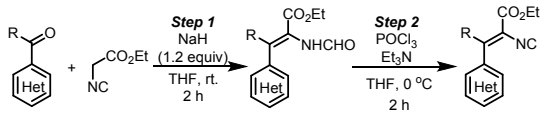
Step 1: 2-Iodoarylamine **S1** (1 mmol, 1.0 equiv), Arylboronic acid (1.2 mmol, 1.2 equiv) and an aqueous solution of K_2CO_3 (2 M, 2.5 mL) were placed in a dry three necked flask under Ar. Then, DME (10 mL) was added and the mixture was stirred for 30 min at room temperature under Ar. To the stirred mixture, $PdCl_2(PPh_3)_2$ (0.02 mmol, 0.02 equiv) was added at room temperature and the mixture was stirred at 80 ℃ (oil bath) over night. The mixture was then cooled to room temperature and diluted with EtOAc. The organic layer was washed with water and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel by using a 30:1 mixture of hexane/EtOAc as an eluent to provide **S2**.



Step 2: Acetic formic anhydride, which was prepared from the reaction of acetic anhydride (0.34 mL) with formic acid (0.76 mL) at 55 ℃ (oil bath) for 2 h, was added dropwise to a stirred solution of **S2** at 0 ℃ in THF (6 mL) and the mixture was stirred for 2 h at room temperature. Volatiles were removed in vacuum to afford **S3** as white solid. This material was used for the subsequent dehydration without further purification.

Step 3: A THF solution (6 mL) of the whole amount of **S3** and Et_3N (1 mL, 7 mmol) was cooled to 0 ℃. Then, $POCl_3$ (0.3 mL, 3 mmol) was added drop wise and the mixture was stirred at 0 ℃ for 2 h. After the reaction was completed, the mixture was quenched by aqueous saturated Na_2CO_3 solution and stirred for 1 h. The mixture was extracted with $CHCl_3$ three times. The combined organic layer was dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography on silica gel by using a 20:1 mixture of hexane/EtOAc as an eluent to provide analytical pure product Isocyanides.

General Procedure for synthesis of 2-(isocyano)acrylates B:



Step 1: A mixture of Arylaldehyde or Arylketone (**S4**, 5.0 mmol) and methyl isocyanoacetate (5.0 mmol) in THF (10 ml) was added dropwise to a suspension of NaH (60% in oil) (0.24 g, 6.0 mmol) in THF (10.0 ml) at room temperature. After stirring for 2 h at room temperature, 10% AcOH was added to the mixture at 0 °C until there is no hydrogen release. The solvent was removed under reduced pressure and the residue was extracted with CH_2Cl_2 three times and the extract was washed with H_2O, dried over Na_2SO_4 and concentrated under reduced pressure. Further recrystallization in MeOH afforded the product **S5** as a white solid.

Step 2: THF (10.0 mL), NEt_3 (2.8 mL, 20 mmol) and S5 (5.0 mmol) were added to an oven-dried three necked flask under N_2 atmosphere and cooled to 0 °C. $POCl_3$ (0.47 mL, 5.0 mmol) was added dropwise and the mixture was stirred for 2 h at 0 °C after the addition was completed. Then the mixture was quenched by sat. Na_2CO_3 and stirred for another 1 h. The mixture was extracted with CH_2Cl_2 three times, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/EtOAc = 20/1) to give analytical pure product **1da-df**.

*2-isocyano-3',4',5'-trimethoxy-1,1'-biphenyl (**1aq**).* Following general procedure A, **1aq** was purified by silica gel chromatography (PE/EtOAc =20/1) as a white solid (142.7 mg, 53%). Mp: 88.5-90.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.43 (m, 3H), 7.42 – 7.34 (m, 1H), 6.75 (s, 2H), 3.93 (s, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 166.8, 153.2, 138.8, 138.3, 132.4, 130.4, 129.5, 128.1, 128.0, 124.5, 106.4, 61.0, 56.3. HRMS (ESI) m/z $[M+H]^+$ calculated for $C_{16}H_{16}NO_3$ 270.1125; found 270.1123.

*Methyl 2-isocyano-[1,1'-biphenyl]-4-carboxylate (**1bg**).* Following general procedure A, **1bg** was purified by silica gel chromatography (PE/EtOAc =5/1) as a white solid (165.8 mg, 66%). Mp: 57.1-58.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, J = 1.5 Hz, 1H), 8.14 (dd, J = 8.1, 1.7 Hz, 1H), 7.57 – 7.47 (m, 6H), 4.45 (q, J = 7.1 Hz, 2H), 1.45 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 167.79, 164.7, 142.8, 136.1, 130.8, 130.6, 130.4, 129.0, 128.9, 128.8, 128.7, 124.7, 61.7, 14.3. HRMS (ESI) m/z $[M+H]^+$ calculated for $C_{16}H_{14}NO_2$ 252.1020; found 252.1019.

*Methyl (Z)-3-(furan-2-yl)-2-isocyanoacrylate (**1de**).* Following general procedure B, **1de** was purified by silica gel chromatography (PE/EtOAc =20/1) as a white solid (310.4 mg, 35%). Mp: 70.8-72.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 1.8 Hz, 1H), 7.61 (s, 1H), 7.35 (d, J = 3.7 Hz, 1H), 6.67 (dd, J = 3.7, 1.8 Hz, 1H), 3.93 (s, 3H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 173.9, 161.7, 147.9, 146.7, 126.1, 119.6, 113.5, 110.8, 53.4. HRMS (ESI) m/z $[M+H]^+$ calculated for $C_9H_8NO_3$ 178.0499; found 178.0495.

*Methyl (Z)-2-isocyano-3-(1-methyl-1H-indol-3-yl)acrylate (**1df**).* Following general procedure B, **1df** was purified by silica gel chromatography (PE/EtOAc =5/1) as a white solid (564.6 mg, 47%). Mp: 154.1-155.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (s, 1H), 7.75 (d, J = 7.8 Hz, 1H), 7.70 (s, 1H), 7.41 – 7.31 (m, 3H), 3.93 (s, 3H), 3.90 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 163.8, 162.8, 137.8, 136.7, 135.7, 129.1, 123.4, 122.0, 117.9, 110.2, 108.5, 107.7, 52.5, 33.8. HRMS (ESI) m/z $[M+H]^+$ calculated for $C_{14}H_{13}N_2O_2$ 241.0972; found 241.0970.

General Procedure for Radical Difluoromethylation of Isocyanides

In a 15 mL flame-dried Schlenk tube (Synthware Glass, Beijing F580810) was charged with isocyanide **1** (0.1 mmol, 1.0 equiv), diarylsulfonium salt **2** (0.2 mmol, 2.0 equiv), *fac*-$Ir(ppy)_3$ (0.003 mmol, 0.03 equiv), PEG 600 (15 μL). The flask was evacuated and backfilled with argon for 3 times. KOH (1.0 M, 200 μL, 2.0 equiv) and CH_2Cl_2 (2.0 mL) was added with syringe under argon. The mixture was then irradiated by a 12W blue LED (450 nm) strip overnight (laid 0.5 CM away from the Schlenk tube). The mixture was poured into a separatory funnel containing 10 mL H_2O and 10 mL CH_2Cl_2. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2×10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure after filtration. The residue was purified by flash chromatography on silica gel to afford the desired product difluoromethylated phenanthridines and isoquinolines **3**.

3.0 mmol scale Procedure for Radical Difluoromethylation of Isocyanides

In a 100 mL flame-dried Schlenk tube (Synthware Glass, Beijing F588100N) was charged with isocyanide **1aa** (3.0 mmol, 1.0 equiv), diarylsulfonium salt **2** (6.0 mmol, 2.0 equiv), *fac*-$Ir(ppy)_3$ (0.09 mmol, 0.03 equiv), PEG 600 (450 μL). The flask was evacuated and backfilled with argon for 3 times. KOH (1.0 M, 6.0 mL, 2.0 equiv) and CH_2Cl_2 (60 mL) was added with syringe under argon. The mixture was then irradiated by a 12W blue LED (450 nm) strip overnight (laid 0.5 CM away from the Schlenk tube). The mixture was poured into a separatory funnel containing 60 mL H_2O and 30 mL CH_2Cl_2. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2×30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure after filtration. The residue was purified by flash chromatography on silica gel to afford the desired product 6-(difluoromethyl)phenanthridine (**3aa**) as a white solid (419.3 mg, 61%).

*6-(difluoromethyl)phenanthridine (**3aa**).*[15] Following general procedure, **3aa** was purified by silica gel chromatography (PE/EA = 30/1) as a white solid (17.7 mg, 77%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.67 (d, J = 8.3 Hz, 1H), 8.59 (d, J = 7.8 Hz, 2H), 8.22 (d, J = 7.7 Hz, 1H), 7.90 (t, J = 7.6 Hz, 1H), 7.83 – 7.72 (m, 3H), 7.05 (t, J = 54.4 Hz, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 151. 34 (t, J = 26.4 Hz), 142.4, 133.8, 131.2, 130.6, 129.1, 128.7, 127.8, 126.5 (t, J = 4.1 Hz), 125.0, 122.4, 122.2, 118.5 (t, J = 243.4 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ -111.1 (d, J = 54.2 Hz).

*6-(difluoromethyl)-8-methylphenanthridine (**3ab**).*[15] Following general procedure, **3ab** was purified by silica gel chromatography (PE/EA = 30/1) as a white solid (17.0 mg, 70%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49 – 8.44 (m, 2H), 8.25 (s, 1H), 8.16 – 8.05 (m, 1H), 7.69 – 7.61 (m, 3H), 6.95 (t, J = 54.4 Hz, 1H), 2.53 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 151.0 (t, J = 26.4 Hz), 142.0, 137.9, 133.1, 131.7, 130.4, 128.6, 128.6, 125.7 (t, J = 4.1 Hz), 125.1, 122.6, 122.3, 122.0, 118.3 (t, J = 243.4 Hz), 21.9. ^{19}F NMR (471 MHz, $CDCl_3$) δ -111.3 (d, J = 54.5 Hz).

*8-(tert-butyl)-6-(difluoromethyl)phenanthridine (**3ac**).*[15] Following general procedure, **3ac** was purified by silica gel chromatography (PE/EA = 30/1) as a white solid (20.6 mg, 72%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.62 (d, J = 8.8 Hz, 1H), 8.60 – 8.55 (m, 2H), 8.21 (dd, J = 6.9, 2.5 Hz, 1H), 8.00 (dd, J = 8.8, 1.9 Hz, 1H), 7.75 (tt, J = 7.1, 5.2 Hz, 2H), 7.07 (t, J = 54.4 Hz, 1H), 1.50 (s, 9H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$)

δ 151.4 (t, *J* = 26.3 Hz), 150.9, 142.2, 131.7, 130.4, 129.7, 128.7, 128.5, 125.0, 122.5 (t, *J* = 1.8 Hz), 122.2, 122.0, 121.9 (t, *J* = 4.4 Hz), 118.5 (t, *J* = 243.5 Hz), 35.2, 31.2. ^{19}F NMR (471 MHz, $CDCl_3$) δ -111.3 (d, *J* = 54.3 Hz).

6-(difluoromethyl)-8-methoxyphenanthridine ***(3ad)***.[14,15] Following general procedure, **3ad** was purified by silica gel chromatography (PE/EA = 30/1) as a white solid (19.0 mg, 73%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.47 (d, *J* = 9.1 Hz, 1H), 8.44 – 8.37 (m, 1H), 8.13 – 8.04 (m, 1H), 7.81 (d, *J* = 2.1 Hz, 1H), 7.66 – 7.59 (m, 2H), 7.43 (dd, *J* = 9.1, 2.6 Hz, 1H), 6.95 (t, *J* = 54.4 Hz, 1H), 3.92 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 158.8, 150. 3 (t, *J* = 26.6 Hz), 141.6, 130.4, 128.7, 128.3, 128.1, 125.1, 124.0, 123.7 (d, *J* = 2.1 Hz), 122.5, 121.7, 118.6 (t, *J* = 243.3 Hz), 105. 9 (t, *J* = 4.6 Hz), 55.6. ^{19}F NMR (471 MHz, $CDCl_3$) δ -111.9 (d, *J* = 54.3 Hz).

6-(difluoromethyl)-8-(methylthio)phenanthridine ***(3ae)***.[15] Following general procedure, **3ae** was purified by silica gel chromatography (PE/EA = 30/1) as a white solid (17.9 mg, 65%). ^{1}H NMR (500 MHz, $CDCl_3$) δ8.56 (d, *J* = 8.7 Hz, 1H), 8.55 – 8.52 (m, 1H), 8.34 – 8.31 (m, 1H), 8.22 – 8.18 (m, 1H), 7.80 – 7.74 (m, 3H), 7.04 (t, *J* = 54.4 Hz, 1H), 2.67 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 150.1 (t, *J* = 26.7 Hz), 141.5, 139.6, 131.1, 130.3, 130.2, 128.9, 128.9, 124.9, 122.8, 122.6, 121.9, 121.4 (t, *J* = 4.6 Hz), 118.0 (t, *J* = 243.6 Hz), 15.4. ^{19}F NMR (471 MHz, $CDCl_3$) δ -110.8 (d, *J* = 54.4 Hz).

6-(difluoromethyl)-8-phenylphenanthridine ***(3af)***.[14,15] Following general procedure, **3af** was purified by silica gel chromatography (PE/EA = 30/1) as a white solid (18.4 mg, 60%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.75 (d, *J* = 1.8 Hz, 1H), 8.67 (d, *J* = 8.6 Hz, 1H), 8.55 (dd, *J* = 7.6, 1.7 Hz, 1H), 8.19 (dd, *J* = 7.9, 1.4 Hz, 1H), 8.10 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.78 – 7.70 (m, 4H), 7.52 (t, *J* = 7.6 Hz, 2H), 7.43 (t, *J* = 7.4 Hz, 1H), 7.05 (t, *J* = 54.4 Hz, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 151.4 (t, *J* = 26.5 Hz), 142.4, 140.6, 140.0, 132.8, 130.6, 130.5, 129.1, 129.0, 128.7, 128.1, 127.5, 124.8, 124.3 (t, *J* = 4.3 Hz), 123.0, 122.8, 122.2, 118.5 (t, *J* = 243.4 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ -111.0 (d, *J* = 54.5 Hz).

6-(difluoromethyl)-8-fluorophenanthridine ***(3ag)***.[15] Following general procedure, **3ag** was purified by silica gel chromatography (PE/EA = 30/1) as a white solid (17.3 mg, 70%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.64 (dd, *J* = 9.1, 5.2 Hz, 1H), 8.50 (dd, *J* = 6.8, 2.7 Hz, 1H), 8.23 – 8.17 (m, 2H), 7.80 – 7.73 (m, 2H), 7.64 (ddd, *J* = 9.1, 8.1, 2.6 Hz, 1H), 7.00 (t, *J* = 54.3 Hz, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 161.4 (d, *J* = 249.3 Hz), 150.5 (dt, *J* = 27.1, 4.2 Hz), 142.1 (d, *J* = 1.3 Hz), 130.7, 130.5, 129.1, 129.0, 124.9 (d, *J* = 8.6 Hz), 124.53, 123.4 (dt, *J* = 8.8, 1.7 Hz), 121.9, 120.6 (d, *J* = 24.1 Hz), 118.2 (t, *J* = 243.4 Hz), 111.2 (dt, *J* = 22.7, 4.5 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ -111.1 (m, 1F), -111.5 (d, *J* = 53.4 Hz, 2F).

8-chloro-6-(difluoromethyl)phenanthridine ***(3ah)***.[15] Following general procedure, **3ah** was purified by silica gel chromatography (PE/EA = 30/1) as a white solid (18.5 mg, 70%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.46 (d, *J* = 8.9 Hz, 1H), 8.43 (d, *J* = 1.8 Hz, 1H), 8.40 (dd, *J* = 8.2, 1.3 Hz, 1H), 8.09 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.72 (dd, *J* = 8.9, 2.1 Hz, 1H), 7.69 (td, *J* = 7.2, 1.4 Hz, 1H), 7.66 (td, *J* = 7.2, 1.3 Hz, 1H), 6.90 (t, *J* = 54.3 Hz, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 150.3 (t, *J* = 26.9 Hz), 142.3, 133.9, 132.1, 131.8, 130.7, 129.4, 129.1, 125.7 (t, *J* = 4.7 Hz), 124.3, 124.0, 123.1 (t, *J* = 1.8 Hz), 122.0, 118.1 (t, *J* = 243.6 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ -111.1 (d, *J* = 54.0 Hz).

8-bromo-6-(difluoromethyl)phenanthridine ***(3ai)***.[15] Following general procedure, **3ai** was purified by silica gel chromatography (PE/EA = 30/1) as a white solid (16.1 mg, 52%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.69 (d, *J* = 1.8 Hz, 1H), 8.53 – 8.50 (m, 1H), 8.49 (d, *J* = 8.8 Hz, 1H), 8.18 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.96 (dd, *J* = 8.9, 2.0 Hz, 1H), 7.80 (td, *J* = 8.2, 7.6, 1.5 Hz, 1H), 7.76 (td, *J* = 7.8, 7.3, 1.4 Hz, 1H), 6.99 (t, *J* = 54.3 Hz, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 150.2 (t, *J* = 26.8 Hz), 142.3, 134.4, 132.4, 130.7, 129.4, 129.1, 128.8 (t, *J* = 4.7 Hz), 124.3, 124.1, 123.4 (t, *J* = 1.8 Hz), 122.0, 121.9, 118.1 (t, *J* = 243.6 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ -111.0 (d, *J* = 54.6 Hz).

6-(difluoromethyl)-8-(trifluoromethyl)phenanthridine ***(3aj)***.[15] Following general procedure, **3aj** was purified by silica gel chromatography (PE/EA = 10/1) as a white solid (15.8 mg, 53%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.87 (s, 1H), 8.79 (d, *J* = 8.7 Hz, 1H), 8.62 (d, *J* = 8.1 Hz, 1H), 8.26 (d, *J* = 8.0 Hz, 1H), 8.11 (d, *J* = 8.7 Hz, 1H), 7.88 (t, *J* = 7.5 Hz, 1H), 7.83 (t, *J* = 7.6 Hz, 1H), 7.06 (t, *J* = 54.2 Hz, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 151.2 (t, *J* = 26.9 Hz), 143.0, 135.9, 130.8, 130.3, 129.7 (q, *J* = 33.0 Hz), 129.3, 127.1 (q, *J* = 3.1 Hz), 124.0 (q, *J* = 4.0 Hz), 124.0, 123.8 (q, *J* = 272.6 Hz), 123.5, 122.5, 121.6 (t, *J* = 1.7 Hz), 118.1 (t, *J* = 243.6 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.9, -110.4 (d, *J* = 54.1 Hz).

6-(difluoromethyl)-8-nitrophenanthridine ***(3ak)***.[15] Following general procedure, **3ak** was purified by silica gel chromatography (PE/EA = 10/1) as a white solid (5.0 mg, 18%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.54 – 9.44 (m, 1H), 8.85 (d, *J* = 9.1 Hz, 1H), 8.70 (dd, *J* = 9.1, 2.3 Hz, 1H), 8.67 (d, *J* = 8.1 Hz, 1H), 8.29 (d, *J* = 8.1 Hz, 1H), 7.94 (td, *J* = 8.1, 1.3 Hz, 1H), 7.88 (td, *J* = 8.2, 1.2 Hz, 1H), 7.05 (t, *J* = 54.1 Hz, 1H). ^{19}F NMR (471 MHz, $CDCl_3$) δ -110.2 (d, *J* = 54.4 Hz).

6-(difluoromethyl)phenanthridine-8-carbonitrile ***(3al)***. Following general procedure, **3al** was purified by silica gel chromatography (PE/EA = 10/1) as a white solid (12.2 mg, 48%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.95 (s, 1H), 8.79 (d, *J* = 8.6 Hz, 1H), 8.63 (d, *J* = 8.1 Hz, 1H), 8.27 (d, *J* = 8.1 Hz, 1H), 8.10 (d, *J* = 8.6 Hz, 1H), 7.93 (t, *J* = 7.5 Hz, 1H), 7.87 (t, *J* = 7.6 Hz, 1H), 7.03 (t, *J* = 54.1 Hz, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 150.7 (t, *J* = 27.4 Hz), 143.3, 136.2, 132.4, 132.0 (t, *J* = 4.8 Hz), 131.0, 130.9, 129.6, 123.8, 123.7, 122.7, 121.7, 118.0 (t, *J* = 243.6 Hz), 111.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ -109.6 (d, *J* = 54.3 Hz). HRMS (ESI) m/z $[M+H]^+$ calculated for $C_{15}H_9F_2N_2$ 255.0729; found 255.0722.

6-(difluoromethyl)-N,N-dimethylphenanthridine-8-carboxamide ***(3am)***.[15] Following general procedure, **3am** was purified by silica gel chromatography (PE/EA = 4/1) as a white solid (18.4 mg, 61%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.72 (d, *J* = 8.6 Hz, 1H), 8.63 – 8.61 (m, 1H), 8.59 (dd, *J* = 8.0, 1.4 Hz, 1H), 8.21 (dd, *J* = 8.0, 1.3 Hz, 1H), 8.01 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.82 (td, *J* = 8.1, 7.6, 1.6 Hz, 1H), 7.78 (td, *J* = 7.7, 7.2, 1.5 Hz, 1H), 7.02 (t, *J* = 54.3 Hz, 1H), 3.21 (s, 3H), 3.09 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 170.4, 151.2 (t, *J* = 26.7 Hz), 142.8, 135.3, 134.4, 130.7, 130.2, 129.7, 129.0, 125.2 (t, *J* = 4.4 Hz), 124.4, 123.0, 122.4, 121.6 (t, *J* = 1.7 Hz), 118.3 (t, *J* = 243.5 Hz), 39.7, 35.6. ^{19}F NMR (471 MHz, $CDCl_3$) δ -110.6 (d, *J* = 54.0 Hz).

6-(difluoromethyl)-8-(methylsulfonyl)phenanthridine ***(3an)***.[15] Following general procedure, **3an** was purified by silica gel chromatography (PE/EA = 4/1) as a white solid (21.2 mg, 69%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.19 (s, 1H), 8.89 (d, *J* = 8.6 Hz, 1H), 8.67 (d, *J* = 8.2 Hz, 1H), 8.41 (d, *J* = 8.6 Hz,

1H), 8.29 (d, *J* = 8.0 Hz, 1H), 7.93 (t, *J* = 7.5 Hz, 1H), 7.88 (t, *J* = 7.5 Hz, 1H), 7.06 (t, *J* = 54.2 Hz, 1H), 3.22 (s, 3H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 151.3 (t, *J* = 26.8 Hz), 143.3, 139.6, 137.0, 131.0, 130.9, 129.6, 128.3, 126.9 (t, *J* = 4.2 Hz), 124.3, 123.7, 122.8, 121.8, 117.9 (t, *J* = 243.8 Hz), 44.8. ^{19}F NMR (471 MHz, $CDCl_3$) δ -110.3 (d, *J* = 54.1 Hz).

6-(difluoromethyl)-10-methoxyphenanthridine ***(3ao)***.[15] Following general procedure, **3ao** was purified by silica gel chromatography (PE/EA = 30/1) as a white solid (9.4 mg, 36%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.47 (dd, *J* = 8.4, 1.4 Hz, 1H), 8.19 – 8.11 (m, 2H), 7.74 – 7.65 (m, 2H), 7.64 (t, *J* = 8.1 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 6.98 (t, *J* = 54.4 Hz, 1H), 4.10 (s, 3H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 158.3, 151.0 (t, *J* = 25.8 Hz), 143.0, 130.4, 128.5, 128.4, 128.0, 128.0, 124.8, 124.5, 124.3, 118.5, 118.5 (t, *J* = 4.7 Hz), 118.5 (t, *J* = 244.1 Hz), 112.1, 55.9. ^{19}F NMR (471 MHz, $CDCl_3$) δ -111.6 (d, *J* = 54.5 Hz).

6-(difluoromethyl)-7-methoxyphenanthridine ***(3ap)***.[15] Following general procedure, **3ap** was purified by silica gel chromatography (PE/EA = 30/1) as a white solid (10.2 mg, 40%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (d, *J* = 7.8 Hz, 1H), 8.30 (d, *J* = 8.7 Hz, 1H), 8.25 (d, *J* = 8.3 Hz, 1H), 7.81 – 7.75 (m, 2H), 7.74 – 7.70 (m, 1H), 7.70 (t, *J* = 54.8 Hz, 1H), 7.13 (d, *J* = 8.0 Hz, 1H), 4.08 (s, 3H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 157.2, 149.9 (t, *J* = 20.2 Hz), 142.5, 135.8, 131.7, 130.8, 129.3, 128.4, 124.2, 122.5, 115.1, 114.9, 112.1 (t, *J* = 240.7 Hz), 108.6, 56.1. ^{19}F NMR (471 MHz, $CDCl_3$) δ -118.8 (d, *J* = 54.8 Hz).

6-(difluoromethyl)-9-methoxyphenanthridine ***(3ap')***.[15] Following general procedure, **3ap'** was purified by silica gel chromatography (PE/EA = 30/1) as a white solid (12.0 mg, 47%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56 – 8.47 (m, 2H), 8.19 (d, *J* = 7.8 Hz, 1H), 7.97 (d, *J* = 2.5 Hz, 1H), 7.78 (t, *J* = 8.2, 1.3 Hz, 1H), 7.73 (t, *J* = 8.2, 1.3 Hz, 1H), 7.35 (dd, *J* = 9.1, 2.5 Hz, 1H), 7.01 (t, *J* = 54.4 Hz, 1H), 4.07 (s, 3H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 161.7, 150.9 (d, *J* = 26.4 Hz), 136.2, 130.5, 129.2, 128.4 (t, *J* = 4.3 Hz), 128.1, 124.7, 122.2, 118.3 (d, *J* = 243.1 Hz), 118.1, 117.3, 103.1, 55.6. ^{19}F NMR (471 MHz, $CDCl_3$) δ -110.8 (d, *J* = 54.5 Hz).

6-(difluoromethyl)-7,8,9-trimethoxyphenanthridine ***(3aq)***. Following general procedure, **3aq** was purified by silica gel chromatography (PE/EA = 20/1) as a white solid (12.5 mg, 39%). Mp: 124.7-126.1 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41 (d, *J* = 7.8 Hz, 1H), 8.26 – 8.20 (dd, *J* = 8.1, 0.8 Hz, 1H), 7.76 (s, 1H), 7.74 – 7.69 (m, 1H), 7.68 – 7.63 (m, 1H), 7.65 (t, *J* = 54.9 Hz, 1H), 4.13 (s, 3H), 4.12 (s, 3H), 3.99 (s, 3H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 156.8, 150.7, 149.0 (t, *J* = 20.6 Hz), 142.5, 142.4, 131.8, 130.9, 128.9, 128.0, 123.8, 121.8, 113.9, 112.3 (t, *J* = 240.5 Hz), 98.7, 61.7, 61.1, 56.2. ^{19}F NMR (471 MHz, $CDCl_3$) δ -118.1 (d, *J* = 55.0 Hz). HRMS (ESI) m/z $[M+H]^+$ calculated for $C_{17}H_{16}F_2NO_3$ 320.1093; found 320.1092.

6-(difluoromethyl)-[1,3]dioxolo[4,5-j]phenanthridine ***(3ar)***.[12a] Following general procedure, **3ar** was purified by silica gel chromatography (PE/EA = 30/1) as a white solid (19.4 mg, 71%). Mp: 179.8-181.6 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (d, *J* = 8.1 Hz, 1H), 8.15 (d, *J* = 7.8 Hz, 1H), 7.94 (s, 1H), 7.88 (s, 1H), 7.76 – 7.66 (m, 2H), 6.98 (t, *J* = 54.4 Hz, 1H), 6.19 (s, 2H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 151.5, 149.9 (t, *J* = 26.3 Hz), 148.5, 142.2, 132.0, 130.4, 128.4, 128.2, 125.1, 122.0, 118.9, 118.6 (t, *J* = 243.5 Hz), 103.6 (t, *J* = 4.9 Hz), 102.2, 100.2. ^{19}F NMR (471 MHz, $CDCl_3$) δ -111.3 (d, *J* = 54.6 Hz). HRMS (ESI) m/z $[M+H]^+$ calculated for $C_{15}H_9F_2NO_2$ 274.0674; found 274.0671.

6-(difluoromethyl)-3-methylphenanthridine ***(3ba)***.[15] Following general procedure, **3ba** was purified by silica gel chromatography (PE/EA = 30/1) as a white solid (19.2 mg, 79%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (d, *J* = 8.3 Hz, 1H), 8.47 (d, *J* = 8.2 Hz, 1H), 8.36 (d, *J* = 8.4 Hz, 1H), 7.90 (s, 1H), 7.78 (ddd, *J* = 8.2, 7.1, 1.1 Hz, 1H), 7.62 (ddd, *J* = 8.2, 7.1, 1.0 Hz, 1H), 7.48 (dd, *J* = 8.3, 1.4 Hz, 1H), 6.94 (t, *J* = 54.4 Hz, 1H), 2.51 (s, 3H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 151.3 (t, *J* = 26.5 Hz), 142.5, 139.4, 133.9, 131.2, 130.4, 130.0, 127.3, 126.4 (t, *J* = 4.1 Hz), 122.6, 122.2, 122.1 (t, *J* = 1.7 Hz), 121.9, 118.3 (t, *J* = 243.4 Hz), 21.5. ^{19}F NMR (471 MHz, $CDCl_3$) δ -111.0 (d, *J* = 54.4 Hz).

6-(difluoromethyl)-3-methoxyphenanthridine ***(3bb)***.[15] Following general procedure, **3bb** was purified by silica gel chromatography (PE/EA = 30/1) as a white solid (19.5 mg, 75%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (t, *J* = 9.8 Hz, 2H), 8.45 (d, *J* = 9.1 Hz, 1H), 7.84 (ddd, *J* = 8.3, 7.1, 1.1 Hz, 1H), 7.66 (ddd, *J* = 8.2, 7.1, 1.1 Hz, 1H), 7.58 (d, *J* = 2.7 Hz, 1H), 7.37 (dd, *J* = 9.0, 2.7 Hz, 1H), 7.01 (t, *J* = 54.4 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 160.3, 151.7 (t, *J* = 26.2 Hz), 144.1, 134.0, 131.2, 126.7, 126.3 (t, *J* = 4.1 Hz), 123.3, 121.9, 121.5, 119.9, 119.1, 118.2 (t, *J* = 243.5 Hz), 110.0, 55.7. ^{19}F NMR (471 MHz, $CDCl_3$) δ -111.2 (d, *J* = 54.2 Hz).

6-(difluoromethyl)-3-fluorophenanthridine ***(3bc)***.[15] Following general procedure, **3bc** was purified by silica gel chromatography (PE/EA = 30/1) as a white solid (18.6 mg, 75%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60 – 8.54 (m, 2H), 8.54 – 8.48 (m, 1H), 7.89 (t, *J* = 7.7 Hz, 1H), 7.83 (d, *J* = 9.3 Hz, 1H), 7.73 (t, *J* = 7.6 Hz, 1H), 7.49 (t, *J* = 8.4 Hz, 1H), 7.01 (t, *J* = 54.4 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 162.7 (d, *J* = 249.4 Hz), 152.6 (t, *J* = 26.6 Hz), 143.6 (d, *J* = 12.0 Hz), 133.6, 131.6, 127.6, 126.5 (t, *J* = 4.3 Hz), 124.1 (d, *J* = 9.4 Hz), 122.1, 121.9 (d, *J* = 1.3 Hz), 121.6 (d, *J* = 1.8 Hz), 118.1 (t, *J* = 243.5 Hz), 117.8 (d, *J* = 23.8 Hz), 115.0 (d, *J* = 20.6 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ -111.3 (d, *J* = 54.6 Hz, 2F), -111.6 (m, 1F).

3-chloro-6-(difluoromethyl)phenanthridine ***(3bd)***.[14,15] Following general procedure, **3bd** was purified by silica gel chromatography (PE/EA = 30/1) as a white solid (17.9 mg, 68%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.55 (t, *J* = 7.7 Hz, 2H), 8.43 (d, *J* = 8.8 Hz, 1H), 8.15 (d, *J* = 2.0 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.74 (t, *J* = 7.7 Hz, 1H), 7.65 (dd, *J* = 8.8, 2.0 Hz, 1H), 6.99 (t, *J* = 54.3 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 152.5 (t, *J* = 26.6 Hz), 143.0, 134.7, 133.3, 131.6, 129.7, 129.1, 128.7, 128.0, 126.5 (t, *J* = 4.3 Hz), 123.4, 123.3, 122.2, 118.1 (t, *J* = 243.8 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ -111.3 (d, *J* = 54.4 Hz).

6-(difluoromethyl)-3-(trifluoromethyl)phenanthridine ***(3be)***.[14,15] Following general procedure, **3be** was purified by silica gel chromatography (PE/EA = 30/1) as a white solid (16.4mg, 55%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.86 (s, 1H), 8.79 (d, *J* = 8.7 Hz, 1H), 8.62 (d, *J* = 8.1 Hz, 1H), 8.25 (d, *J* = 8.0 Hz, 1H), 8.10 (d, *J* = 8.7 Hz, 1H), 7.87 (t, *J* = 7.5 Hz, 1H), 7.83 (t, *J* = 7.5 Hz, 1H), 7.05 (t, *J* = 54.2 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 151.2 (t, *J* = 26.8 Hz), 143.0, 135.9, 130.8, 130.3, 129.7 (d, *J* = 32.9 Hz), 129.3, 127.1 (q, *J* = 3.2 Hz), 124.0 (q, *J* = 4.0 Hz), 124.0, 123.5, 123.8 (q, *J* = 272.4 Hz), 122.5, 121.7 (t, *J* = 1.8 Hz), 118.1 (t, *J* = 243.6 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ -63.0 (s, 3F), -110.4 (d, *J* = 54.2 Hz, 2F).

*6-(difluoromethyl)-3-nitrophenanthridine (**3bf**).*[15] Following general procedure, **3bf** was purified by silica gel chromatography (PE/EA = 10/1) as a white solid (8.8 mg, 32%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.96 (d, *J* = 2.3 Hz, 1H), 8.63 (d, *J* = 8.9 Hz, 2H), 8.57 (d, *J* = 8.3 Hz, 1H), 8.44 (dd, *J* = 9.0, 2.4 Hz, 1H), 7.96 – 7.92 (m, 1H), 7.84 – 7.80 (m, 1H), 6.94 (t, *J* = 54.2 Hz, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 153.8 (t, *J* = 26.9 Hz), 147.6, 141.8, 132.7, 132.2, 129.9, 129.4, 126.9 (t, *J* = 4.4 Hz), 126.3, 123.7, 123.3, 123.3, 122.2, 117.8 (t, *J* = 244.1 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ -111.6 (d, *J* = 54.3 Hz).

*Methyl 6-(difluoromethyl)phenanthridine-3-carboxylate (**3bg**).* Following general procedure, **3bg** was purified by silica gel chromatography (PE/EA = 10/1) as a white solid (18.7 mg, 62%). Mp: 117.2-119.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (d, *J* = 1.7 Hz, 1H), 8.70 (d, *J* = 8.3 Hz, 1H), 8.62 (t, *J* = 7.3 Hz, 2H), 8.37 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.96 (t, *J* = 7.7 Hz, 1H), 7.83 (t, *J* = 7.7 Hz, 1H), 7.04 (t, *J* = 54.3 Hz, 1H), 4.50 (q, *J* = 7.1 Hz, 2H), 1.50 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.0, 152.3 (t, *J* = 26.6 Hz), 141.9, 133.2, 132.5, 131.6, 130.9, 128.8, 128.5, 128.1, 126.6 (t, *J* = 4.3 Hz), 123.0, 122.4, 118.1 (t, *J* = 243.8 Hz), 61.5, 14.4. ^{19}F NMR (376 MHz, $CDCl_3$) δ -110.8 (d, *J* = 54.3 Hz). HRMS (ESI) m/z $[M+H]^+$ calculated for $C_{17}H_{14}F_2NO_2$ 302.0988; found 302.0980.

*6-(difluoromethyl)indolo[1,2-a]quinoxaline (**3ca**).* Following general procedure, **3ca** was purified by silica gel chromatography (PE/EA = 20/1) as a white solid (20.9 mg, 78%). Mp: 112.0-114.1 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.47 (d, *J* = 8.4 Hz, 1H), 8.43 (d, *J* = 8.7 Hz, 1H), 8.01 (t, *J* = 9.3 Hz, 2H), 7.68 (t, *J* = 7.8 Hz, 1H), 7.59 (t, *J* = 7.8 Hz, 1H), 7.52 – 7.42 (m, 3H), 6.79 (t, *J* = 54.1 Hz, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 148.8 (t, *J* = 27.4 Hz), 134.4, 132.6, 131.1, 131.0, 130.2, 129.2, 125.1, 124.9, 124.3, 123.2, 123.1, 115.5 (t, *J* = 240.5 Hz), 114.8, 114.4, 101.2 (t, *J* = 2.7 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -117.9 (d, *J* = 54.3 Hz). HRMS (ESI) m/z $[M+H]^+$ calculated for $C_{16}H_{11}F_2N_2$ 269.0885; found 269.08790.

*4-(difluoromethyl)pyrrolo[1,2-a]quinoxaline (**3cb**).* Following general procedure, **3cb** was purified by silica gel chromatography (PE/EA = 30/1) as a white solid (11.6 mg, 53%). Mp: 92.8-94.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (dd, *J* = 2.6, 1.1 Hz, 1H), 7.97 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.85 (dd, *J* = 8.3, 1.0 Hz, 1H), 7.57 (td, *J* = 7.7, 1.3 Hz, 1H), 7.46 (td, *J* = 7.7, 1.3 Hz, 1H), 7.21 – 7.16 (m, 1H), 6.94 (dd, *J* = 4.0, 2.7 Hz, 1H), 6.71 (t, *J* = 54.3 Hz, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 147.3 (t, *J* = 27.3 Hz), 134.5, 130.6, 129.3, 128.0, 125.5, 122.0, 115.4 (t, *J* = 242.3 Hz), 115.0, 114.6, 113.8, 107.7 (t, *J* = 2.4 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ -117.7 (d, *J* = 54.5 Hz). HRMS (ESI) m/z $[M+H]^+$ calculated for $C_{12}H_9F_2N_2$ 219.0729; found 219.0724.

*6-(difluoromethyl)benzo[4,5]thieno[3,2-c]quinolone (**3cc**).*[15] Following general procedure, **3cc** was purified by silica gel chromatography (PE/EA = 20/1) as a white solid (14.1 mg, 49%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.66 (d, *J* = 8.5 Hz, 1H), 8.16 (d, *J* = 8.3 Hz, 1H), 8.05 (d, *J* = 4.0, 0.8 Hz, 1H), 7.93 – 7.88 (m, 1H), 7.71 (ddd, *J* = 8.4, 7.0, 1.3 Hz, 1H), 7.64 – 7.60 (m, 1H), 7.51 (td, *J* = 8.3, 7.7, 1.4 Hz, 1H), 7.47 (td, *J* = 7.6, 1.3 Hz, 1H), 7.08 (t, *J* = 54.8 Hz, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 147.9, 145.9 (t, *J* = 28.6 Hz), 142.0, 137.7, 132.4, 129.4, 128.9, 127.6, 126.0, 124.9 (t, *J* = 8.0 Hz), 124.8, 124.6, 123.7, 122.9, 121.7, 117.1 (t, *J* = 243.0 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ -114.6 (d, *J* = 54.9 Hz).

*6-(difluoromethyl)benzo[4,5]thieno[3,2-k]phenanthridine (**3cd**).*[15] Following general procedure, **3cd** was purified by silica gel chromatography (PE/EA = 20/1) as a white solid (16.5 mg, 49%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.14 (d, *J* = 8.3 Hz, 1H), 8.70 (d, *J* = 8.7 Hz, 1H), 8.50 (d, *J* = 8.7 Hz, 1H), 8.32 (t, *J* = 8.5 Hz, 2H), 8.02 (dd, *J* = 6.2, 2.2 Hz, 1H), 7.92 (t, *J* = 7.6 Hz, 1H), 7.87 (t, *J* = 7.5 Hz, 1H), 7.62 – 7.56 (m, 2H), 7.12 (t, *J* = 54.4 Hz, 1H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 151.4 (t, *J* = 26.2 Hz), 143.4, 140.2, 137.9, 134.2, 134.0, 131.1, 130.4, 128.9, 128.8, 127.8, 125.5, 125.2, 124.5, 122.8 (t, *J* = 4.9 Hz), 122.3, 122.3, 122.2, 121.3, 118.6 (t, *J* = 244.2 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ -110.1 (d, *J* = 54.6 Hz).

*Methyl 1-(difluoromethyl)-4-phenylisoquinoline-3-carboxylate (**3da**).* Following general procedure, **3da** was purified by silica gel chromatography (PE/EA = 10/1) as a white solid (19.8 mg, 63%). Mp: 119.1-120.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (d, *J* = 8.3 Hz, 1H), 7.83 – 7.77 (m, 1H), 7.77 – 7.71 (m, 2H), 7.58 – 7.51 (m, 3H), 7.40 – 7.33 (m, 2H), 7.09 (t, *J* = 54.1 Hz, 1H), 3.73 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.8, 150.6 (t, *J* = 27.2 Hz), 140.1, 137.0, 136.9, 135.4, 131.3, 129.5, 129.5, 128.4, 128.3, 127.3, 125.5, 125.4 (t, *J* = 4.0 Hz), 117.8 (t, *J* = 242.8 Hz), 52.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ -109.6 (d, *J* = 54.4 Hz). HRMS (ESI) m/z $[M+H]^+$ calculated for $C_{18}H_{14}F_2NO_2$ 314.0988; found 314.0986.

*Methyl 1-(difluoromethyl)-7-methyl-4-(p-tolyl)isoquinoline-3-carboxylate (**3db**).* Following general procedure, **3db** was purified by silica gel chromatography (PE/EA = 10/1) as a white solid (15.0 mg, 44%). Mp: 130.5-131.7 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.65 (d, *J* = 8.7 Hz, 1H), 7.56 (dd, *J* = 8.7, 1.5 Hz, 1H), 7.34 (d, *J* = 7.8 Hz, 2H), 7.25 – 7.20 (m, 2H), 7.06 (t, *J* = 54.2 Hz, 1H), 3.75 (s, 3H), 2.63 (s, 3H), 2.49 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 167.0, 149.5 (t, *J* = 27.1 Hz), 134.0, 139.3, 138.0, 137.1, 135.4, 133.5, 132.5, 129.3, 129.0, 127.1, 125.8, 124.1 (t, *J* = 3.8 Hz), 118.0 (t, *J* = 242.5 Hz), 52.6, 22.1, 21.4. ^{19}F NMR (376 MHz, $CDCl_3$) δ -109.9 (d, *J* = 54.0 Hz). HRMS (ESI) m/z $[M+H]^+$ calculated for $C_{20}H_{18}F_2NO_2$ 342.1301; found 342.1300.

*Methyl 1-(difluoromethyl)-7-fluoro-4-(4-fluorophenyl)isoquinoline-3-carboxylate (**3dc**).*Following general procedure, **3dc** was purified by silica gel chromatography (PE/EA = 10/1) as a white solid (14.7 mg, 42%). Mp: 131.8-134.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 – 8.20 (m, 1H), 7.71 (dd, *J* = 9.4, 5.4 Hz, 1H), 7.52 (ddd, *J* = 9.5, 7.9, 2.5 Hz, 1H), 7.33 – 7.28 (m, 2H), 7.25 – 7.21 (m, 2H), 7.03 (t, *J* = 54.0 Hz, 1H), 3.74 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 166.4, 162.9 (d, *J* = 248.8 Hz), 162.1 (d, *J* = 254.3 Hz), 150.2 (td, *J* = 27.3, 5.7 Hz), 139.8, 135.9, 134.2, 131.2 (d, *J* = 8.1 Hz), 130.9 (d, *J* = 3.5 Hz), 130.1 (d, *J* = 9.0 Hz), 126.6 (d, *J* = 9.7 Hz), 122.1 (d, *J* = 25.3 Hz), 118.4 (d, *J* = 242.7 Hz), 115.7 (d, *J* = 21.7 Hz), 109.6 (dt, *J* = 23.1, 4.2 Hz), 52.7. ^{19}F NMR (471 MHz, $CDCl_3$) δ -106.6 (m, 1F), -110.83 (d, *J* = 54.9 Hz, 2F), -113.1 (m, 1F). HRMS (ESI) m/z $[M+H]^+$ calculated for $C_{18}H_{12}F_4NO_2$ 350.0799; found 350.0795.

*Methyl 7-bromo-4-(4-bromophenyl)-1-(difluoromethyl)isoquinoline-3-carboxylate (**3dd**).* Following general procedure, **3dd** was purified by silica gel chromatography (PE/EA = 10/1) as a white solid (23.9 mg, 51%). Mp: 188.8-189.9 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ

8.79 – 8.71 (m, 1H), 7.81 (dd, J = 9.1, 1.9 Hz, 1H), 7.70 – 7.64 (m, 2H), 7.53 (d, J = 9.1 Hz, 1H), 7.23 – 7.17 (m, 2H), 7.02 (t, J = 53.9 Hz, 1H), 3.76 (s, 3H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 166.2, 149.9 (t, J = 27.6 Hz), 140.1, 135.8, 135.4, 135.2, 133.7, 131.8, 131.0, 128.6, 127.8 (t, J = 4.4 Hz), 126.3, 124.7, 123.1, 117.5 (t, J = 243.0 Hz), 52.8. ^{19}F NMR (471 MHz, $CDCl_3$) δ -110.2 (d, J = 53.9 Hz). HRMS (ESI) m/z $[M+H]^+$ calculated for $C_{18}H_{12}Br_2F_2NO_2$ 469.9198, 471.9177, 473.9157; found 469.9193, 471.9176, 473.9155.

*Methyl 4-(difluoromethyl)furo[3,2-c]pyridine-6-carboxylate (**3de**).* Following general procedure, **3de** was purified by silica gel chromatography (PE/EA = 10/1) as a white solid (7.7 mg, 34%). Mp: 87.3-89.0 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.46 – 8.41 (m, 1H), 7.93 (d, J = 2.3 Hz, 1H), 7.21 (dd, J = 2.0, 1.1 Hz, 1H), 6.95 (t, J = 54.5 Hz, 1H), 4.06 (s, 3H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 165.2, 160.8, 149.4, 146.7 (t, J = 29.2 Hz), 142.6, 124.7, 115.0 (t, J = 239.8 Hz), 111.2, 105.4 (t, J = 2.2 Hz), 53.2. ^{19}F NMR (471 MHz, $CDCl_3$) δ -114.0 (d, J = 54.5 Hz). HRMS (ESI) m/z $[M+H]^+$ calculated for $C_{10}H_8F_2NO_3$ 228.0467; found 228.0462.

*Methyl 1-(difluoromethyl)-9-methyl-9H-pyrido[3,4-b]indole-3-carboxylate (**3df**).* Following general procedure, **3df** was purified by silica gel chromatography (PE/EA = 10/1) as a white solid (12.0 mg, 41%). Mp: 161.0-163.0 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.98 (s, 1H), 8.21 (d, J = 7.8 Hz, 1H), 7.70 (ddd, J = 8.3, 7.2, 1.1 Hz, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.41 (t, J = 7.5 Hz, 1H), 7.17 (d, J = 54.7 Hz, 1H), 4.15 (t, J = 2.2 Hz, 3H), 4.08 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 165.9, 143.0, 135.7, 135.6, 134.8 (t, J = 29.8 Hz), 131.9, 129.7, 121.5, 121.3, 121.1, 119.7, 118.2 (d, J = 240.4 Hz), 110.3, 52.9, 32.8 (t, J = 8.2 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ -104.5 (d, J = 54.7 Hz). HRMS (ESI) m/z $[M+H]^+$ calculated for $C_{15}H_{13}F_2N_2O_2$ 291.0940; found 291.0937.

Cyclic Voltammetry Studies of reagent 2

The cyclic voltammetry measurements were performed on a CHI660E electrochemical workstation, using a standard three-electrode setup with a platinum wire counter electrode, and a glassy carbon electrode as the working electrode) and a SCE (the saturated calomel electrode) as the reference electrode. The solution were prepared with reagent **2** (0.05 mmol) in the supporting electrolyte n-Bu_4NPF_6 in dry acetonitrile (50 mL, 0.1 M). Solutions thoroughly bubbled with dry nitrogen for 15 min to remove oxygen before any experiment and kept under positive pressure of nitrogen. Cyclic voltammetry (CV) with the following settings: Scan Rates= 0.1 V/s, Sweep Segments = 4, Sample Interval = 0.001 V, Quiet Time = 2 sec.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Detailed experimental procedures, characterization data, ^1H, ^{13}C, ^{19}F NMR spectra, and HRMS (PDF)

AUTHOR INFORMATION

Corresponding Author

* E-mail: gkliu@szu.edu.cn.

ORCID

Guo-Kai Liu: 0000-0001-7617-4267

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

This work was financially supported by the Natural Science Foundation of Shenzhen (No. KQJSCX20180328095508144) and the Natural Science Foundation of Guangdong Province (No. 2020A1515010874). We thank the Instrumental Analysis Center of Shenzhen University for analytical work.

REFERENCES

(1) (a) Ojima, I. *Fluorine in Medicinal Chemistry and Chemical Biology*, Blackwell, Oxford, **2009**, and references therein.(b) Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. Fluorine in pharmaceutical industry: fluorine-containing drugs introduced to the market in the last decade (2001–2011), *Chem. Rev.* **2014**, *114*, 2432-2506, and references therein. (c) Bassetto, M.; Ferla, S.; Pertusati, F. Polyfluorinated groups in medicinal chemistry. *Future Med. Chem.* **2015**, *7*, 527-549, and references therein.

(2) (a) Goure, W. F.; Leschinsky, K. L.; Wratten, S. J.; Chupp, J. P. Synthesis and herbicidal activity of N-substituted 2,6-bis(polyfluoromethyl)dihydropyridine-3,5-dicarboxylates. *J. Agric. Food Chem.* **1991**, *39*, 981-986. (b) Pérez, R. A.; Sánchez-Brunete, C.; Miguel, E.; Tadeo, J. L. Analytical methods for the determination in soil of herbicides used in forestry by GC–NPD and GC/MS. *J. Agric. Food Chem.* **1998**, *46*, 1864-1869.

(3) (a) Kirsch, P.; Bremer, M. Nematic liquid crystals for active matrix displays: molecular design and synthesis. *Angew. Chem., Int. Ed.* **2000**, *39*, 4216-4239. (b) Tasaka, T.; Takenaka, S.; Kabu, K.; Morita, Y.; Okamoto, H. Smectic phase exhibited by dissymmetric liquid crystals: effect of a terminal fluoromethyl group on mesomorphic properties. *Ferroelectronics* **2002**, *276*, 83-92. (c) Boltalina, O. V.; Nakajima, T. *New Fluorinated Carbons: Fundamentals and Applications*, Elsevier, Amsterdam, **2016**.

(4) (a) Shimizu, M.; Hiyama, T. Modern synthetic methods for fluorine - substituted target molecules. *Angew. Chem. Int. Ed.* **2005**, *44*, 214-231. (b) Müller, K.; Faeh; C.; Diederich, F. Fluorine in pharmaceuticals: looking beyond intuition. *Science* **2007**, *317*, 1881-1886. (*c*) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. Fluorine in medicinal chemistry. *Chem. Soc. Rev.* **2008**, *37*, 320-330. (d) Bégué, J.-P.; Bonnet-Delpon, D. *Bioorganic and Medicinal Chemistry of Fluorine*, Wiley-VCH, Weinheim, **2008**. (e) Hu, J.; Zhang, W.; Wang, F. Selective difluoromethylation and monofluoromethylation reactions. *Chem. Commun.* **2009**, 7465-7578. (f) Kirsch, P. *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*, 2nd Ed., Wiley-VCH, Weinheim, **2013**.

(5) (a) Prakash, G. K. S.; Mandal, M.; Schweizer, S.; Petasis, N. A.; Olah, G. A. Stereoselective synthesis of anti-α-(Difluoromethyl)-β-amino alcohols by boronic acid based three-component condensation. stereoselective preparation of (2S,3R)-difluorothreonine. *J. Org. Chem.* **2002**, *67*, 3718-3723. (b) Chowdhury, M. A.; Abdellatif, K. R. A.; Dong, Y.; Das, D.; Suresh, M. R.; Knaus, E. E. Synthesis of celecoxib analogues possessing a N-difluoromethyl-1,2-dihydropyrid-2-one 5-lipoxygenase pharmacophore: biological evaluation as dual inhibitors of cyclooxygenases and 5-lipoxygenase with anti-inflammatory activity. *J. Med. Chem.* **2009**, *52*, 1525-1529. (c) Meanwell, N. A. Synopsis of some recent tactical application of bioisosteres in drug design. *J. Med. Chem.* **2011**, *54*, 2529-2591, and references therein.

(6) (a) Erickson, J. A.; McLoughlin, J. I. Hydrogen bond donor properties of the difluoromethyl group. *J. Org. Chem.***1995**, *60*, 1626-1631. (b) Zafrani, Y.; Yeffet, D.; Sod-Moriah, G.; Berliner, A.; Amir, D.; Marciano, D.; Gershonov, E.; Saphier. S. Difluoromethyl Bioisostere: Examining the "Lipophilic Hydrogen Bond Donor" Concept. *J. Med. Chem.* **2017**, *60*, 797-804. (c) Zafrani, Y.; Sod-Moriah, G.; Yeffet, D.; Berliner, A.; Amir, D.; Marciano, D.; Elias, S.; Katalan, S.; Ashkenazi, N.; Madmon, M.; Gershonov, E.; Saphier, S. CF_2H, a functional group-dependent hydrogen-bond donor: Is it a more or less lipophilic bioisostere of OH, SH, and CH_3?. *J. Med. Chem.* **2019**, *62*, 5628-5637.

(7) For the progress in photochemical radical difluoromethylation,

see the recent review: (a) Barata-Vallejo, S.; Bonesi, S. M.; Postigo, A. Photocatalytic fluoroalkylation reactions of organic compounds, *Org. Biomol. Chem.* **2015**, *13*, 11153. (b) Rong, J.; Ni, C.; Wang, Y.; Kuang, C.; Gu, Y.; Hu, J. Radical fluoroalkylation of aryl alkenes with fluorinated sulfones by visible-light photoredox catalysis, *Acta Chim. Sinica* **2017**, *75*, 105. (c) Koike, T.; Akita, M. Recent progress in photochemical radical di- and mono-fluoromethylation. *Org. Biomol. Chem.* **2019**, *17*, 5413-5419, and references therein.

(8) (a) Tang, X. J.; Thomoson, C. S.; Dolbier Jr., W. R. Photoredox-catalyzed tandem radical cyclization of N-arylacrylamides: general methods To construct fluorinated 3,3-disubstituted 2-oxindoles using fluoroalkylsulfonyl chlorides. *Org. Lett.* **2014**, *16*, 4594-4597. (b) Tang, X. J.; Dolbier Jr., W. R. Efficient Cu-catalyzed atom transfer radical addition reactions of fluoroalkylsulfonyl chlorides with electron-deficient alkenes induced by visible light. *Angew. Chem. Int. Ed.* **2015**, *54*, 4246-4249. (c) Tang, X. J.; Zhang, Z.; Dolbier Jr., W. R. Direct photoredox-catalyzed reductive difluoromethylation of electron-deficient alkenes. *Chem. – Eur. J.* **2015**, *21*, 18961-18965. (d) Zhang, Z.; Tang, X. J.; Thomoson, C. S.; Dolbier Jr., W. R. Photoredox-catalyzed intramolecular aminodifluoromethylation of unactivated alkenes. *Org. Lett.* **2015**, *17*, 3528-3531. (e) Zhang, Z.; Tang, X. J.; Dolbier Jr., W. R. Photoredox-catalyzed intramolecular difluoromethylation of N-benzylacrylamides coupled with a dearomatizing spirocyclization: Access to CF_2H-containing 2-azaspiro[4.5]deca-6,9-diene-3,8-diones. *Org. Lett.* **2016**, *18*, 1048-1051. (f) Zhang, Z.; Martinez, H.; Dolbier Jr., W. R. Photoredox catalyzed intramolecular fluoroalkylarylation of unactivated alkenes. *J. Org. Chem.* **2017**, *82*, 2589-2598.

(9) (a) Lin, Q.-Y.; Xu, X.-H.; Zhang, K.; Qing, F.-L. Visible-light-induced hydrodifluoromethylation of alkenes with a bromodifluoromethylphosphonium bromide. *Angew. Chem. Int. Ed.* **2016**, *55*, 1479-1483. (b) Lin, Q.-Y.; Ran, Y.; Xu, X.-H.; Qing, F.-L. Photoredox-catalyzed bromodifluoromethylation of alkenes with (difluoromethyl)triphenylphosphonium bromide. *Org. Lett.* **2016**, *18*, 2419-2422. (c) Ran, Y.; Lin, Q.-Y.; Xu, X.-H.; Qing, F.-L.Visible light Induced oxydifluoromethylation of styrenes with difluoromethyltriphenylphosphonium bromide. *J. Org. Chem.* **2016**, *81,* 7001-7007. (d) Hu, W.-Q.; Xu, X.-H.; Qing, F.-L. Visible light induced hydrodifluoromethylation of alkenes derived from oxindoles with (difluoromethyl)triphenylphosphonium bromide. *J. Fluorine Chem.* **2018**, *208*, 73-79.

(10) (a) Arai, Y.; Tomita, R.; Ando, G.; Koike, T.; Akita, M. Oxydifluoromethylation of alkenes by photoredox catalysis: simple synthesis of CF2H-containing alcohols. *Chem. Eur. J.* **2016**, *22*, 1262-1265. (b) Noto, N.; Koike, T.; Akita, M. Metal-free di- and trifluoromethylation of alkenes realized by visible-light-induced perylene photoredox catalysis. *Chem. Sci.* **2017**, *8*, 6375-6379. (c) Noto, N.; Tanaka, Y.; Koike, T.; Akita, M. Strongly reducing (diarylamino)anthracene catalyst for metal-free visible-light photocatalytic fluoroalkylation. *ACS Catal.* **2018**, *8*, 9408-9419. (d) Nakayama, Y.; Ando, G.; Abe, M.; Koike, T.; Akita, M. Keto-difluoromethylation of aromatic alkenes by photoredox catalysis: step-economical synthesis of α-CF_2H-substituted ketones in flow. *ACS Catal.* **2019**, *9*, 6555-6563.

(11) (a) Suffness, M.; Cordell, G. A. The Alkaloids; Academic Press: New York, **1985**, *25*, 178. (b) Nakanishi, T.; Suzuki, M. J. Revision of the structure of fagaridine based on the comparison of UV and NMR data of synthetic compounds. *J. Nat. Prod.* **1998**, *61*, 1263-1267. (c) Nakanishi, T.; Suzuki, M.; Saimoto, A.; Kabasawa, T. J. Structural considerations of NK109, an antitumor benzo[c]phenanthridine alkaloid. *J. Nat. Prod.* **1999**, *62*, 864-867. (d) Nakanishi, T.; Suzuki, M. Synthesis and cytotoxic activities of a new benzo[c]phenanthridine alkaloid, 7-hydroxynitidine, and some 9-oxygenated benzo[c]phenanthridine derivatives. *Org. Lett.* **1999**, *1*, 985-988. (e) Nakanishi, T.; Masuda, A.; Suwa, M.; Akiyama, Y.; Hoshino-Abe, N.; Suzuki, M. Synthesis of derivatives of NK109, 7-OH Benzo[*c*]phenanthridine alkaloid, and evaluation of their cytotoxicities and reduction-resistant properties. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2321-2323.

(12) (a) Gu, J.-W.; Zhang, X. Palladium-catalyzed difluoroalkylation of isocyanides: Access to difluoroalkylated phenanthridine derivatives. *Org. Lett.* **2015**, *17*, 5384-5387. (b) Wan, W.; Ma, G.; Li, J.; Chen, Y.; Hu, Q.; Li, M.; Jiang, H.; Deng, H.; Hao, J. Silver-catalyzed oxidative decarboxylation of difluoroacetates: efficient access to C–CF_2 bond formation. *Chem. Commun.* **2016**, *52*, 1598-1601. (c) Wan, W.; Xu, X.; Chen, Y.; Jiang, H.; Wang, Y.; Deng, H.; Hao, J. Ag^I-prmoted difluoromethylation of isocyanides to give difluoromethylate d phenanthridines. *Eur. J. Org. Chem.* **2017**, 3145-3151. (d) Liu, Y.; Zhang, K.; Jiang, W.; Yang, Y.; Jiang, Y.; Liu, X.; Xie, Y.; Wu, J.; Cai, J.; Xu, X.-H. Synthesis of 1-difluoroalkylated isoquinolines via palladium-catalyzed radical cascade difluoroalkylation-cyclization of vinyl isocyanides with bromodifluoroacetic derivatives. *Chem. Asian J.* **2017**, *12*, 568-576. (e) Liu, X.; Wu, C.; Zhang, J.; Shi, Y.; Zhang, S.; Geng, Y.; Tung, C.-H.; Wang, W. Cobalt-catalyzed radical cyclization of isocyanides forming phenanthridine derivatives. *Org. Chem. Front.* **2018**, *5*, 2997-3002. (f) Ma, X.; Mai, S.; Zhou, Y.; Cheng, G.-J.; Song, Q. Dual role of ethyl bromodifluoroacetate in the formation of fluorine-containing heteroaromatic compounds. *Chem. Commun.* **2018**, *54*, 8960-8963.

(13) Xiao, P.; Rong, J.; Ni, C.; Guo, J.; Li, X.; Chen, D.; Hu, J. Radical (phenylsulfonyl)difluoromethylation of isocyanides with $PhSO_2CF_2H$ under transition-metal-free conditions. *Org. Lett.* **2016**, *18*, 5912-5915.

(14) Sun, X., Yu, S. Visible-light-mediated fluoroalkylation of isocyanides with ethyl bromofluoroacetates: unified synthesis of mono- and difluoromethylated phenanthridine derivatives. *Org. Lett.* **2014**, *16*, 2938-2941.

(15) Rong, J.; Deng, L.; Tan, P.; Ni, C.; Gu, Y.; Hu, J. Radical fluoroalkylation of isocyanides with fluorinated sulfones by visible-light photoredox catalysis. *Angew. Chem. Int. Ed.* **2016**, *55*, 2743-2747.

(16) Zhang, Z.; Tang, X.; Dolbier Jr., W. R. Photoredox-catalyzed tandem insertion/cyclization reactions of difluoromethyl and 1,1-difluoroalkyl radicals with biphenyl isocyanides. *Org. Lett.* **2015**, *17*, 4401-4403.

(17) (a) Lu, S.-L.; Li, X.; Qin, W.-B.; Liu, J.-J.; Huang, Y.-Y.; Wong, H. N. C.; Liu, G.-K. Air- and light-stable S-(difluoromethyl)sulfonium salts: C-selective electrophilic difluoromethylation of β-ketoesters and malonates. *Org. Lett*. **2018**, *20*, 6925-6929. (b) Liu, G.-K.; Li, X.; Qin, W.-B.; Peng, X.-S.; Wong, H. N. C.; Zhang, L.; Zhang, X. Facile difluoromethylation of aliphatic alcohols with an *S*-(difluoro-methyl)sulfonium salt: reaction, scope and mechanistic study. *Chem. Commun.* **2019**, *55*, 7446-7449. (c) Liu, G.-K.; Qin, W.-B.; Li, X.; Lin, L.-T.; Wong, H. N. C. Difluoromethylation of phenols and thiophenols with the S -(difluoromethyl)sulfonium salt: reaction, scope, and mechanistic study. *J. Org. Chem.* **2019**, *84(24)*, 15948-15957.

(18) (a) Ali, A. A.; El Sayed, H. M.; Abdallah, O. M.; Steglich, W. Oxocrinine and other alkaloids from Crinum americanum. *Phytochemistry* **1986**, *25*, 2399-2401. (b) Viladomat, F.; Selles, M.; Codina, C.; Bastida, J. Alkaloids from Narcissus asturiensis. *Planta Med.* **1997**, *63*, 583-583. (c) Abdel-Halim, O. B.; Morikawa, T.; Ando, S.; Matsuda, H.; Yoshikawa, M. New crinine-type alkaloids with inhibitory effect on induction of inducible nitric oxide synthase from crinum yemense. *J. Nat. Prod.* **2004**, *67*, 1119-1124. (d) Sripada, L.; Teske, J. A.; Deiters, A. Phenanthridine synthesis *via* [2+2+2] cyclotrimerization reactions. *Org. Biomol. Chem*. **2008**, *6*, 263-265.

(19) C. K. Prier, D. A. Rankic, D. W. C. MacMillan, Visible light photoredox catalysis with transition metal complexes: applications in organic synthesis. *Chem. Rev.* **2013**, *113*, 5322-5363.

(20) (a) Q. Wang, X. Dong, T. Xiao and L. Zhou, $PhI(OAc)_2$-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. (b) H. Jiang, Y. Cheng, R. Wang, Y. Zhang and S. Yu, Synthesis of isoquinolines *via* visible light-promoted insertion of vinyl isocyanides with diaryliodonium salts. *Chem. Commun.*, **2014**, *50*, 6164-6167. (c) F. Ding, Y. Jiang, K. Lin and L. Shi, Tandem radical cyclization for the construction of 1-difluoroalkylated isoquinolines *via* Cu catalyzed and visible light-promoted pathways.*Org. Biomol. Chem.,* **2018**, *16*, 1812-1815.