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Silver-Catalyzed Tandem Trifluoromethylation and Cyclization of Aryl Isonitriles with the Langlois Reagent

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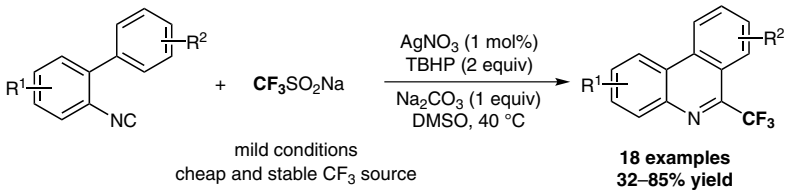

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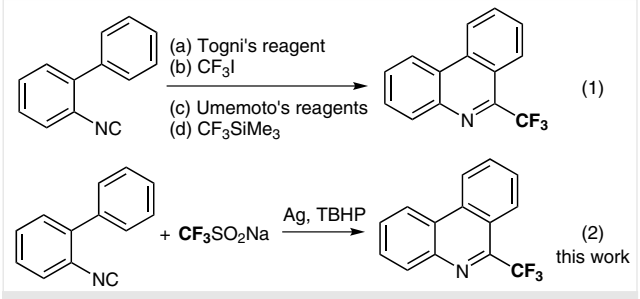
Abstract A mild and efficient procedure for the silver-catalyzed tandem trifluoromethylation and cyclization of aryl isonitriles with the Langlois reagent (sodium triflinate) is developed. A series of trifluoromethylated phenanthridines is prepared in moderate to good yields from a cheap and stable trifluoromethyl source.

Key words phenanthridines, trifluoromethylation, Langlois reagent-cyclization

The phenanthridine structural unit can be found in numerous natural products, for example, trisphaeridine and nitidine,[1] and potential pharmaceuticals with diverse biological activities, including antitumor, antiviral and antifungal.[2] Furthermore, substituted phenanthridines have comprehensive applications in materials science due to their optical and electronic properties.[3] Therefore, various methods have been developed for the construction of the phenanthridine scaffold.[4,5] Recently, the radical isonitrile insertion reaction of 2-isocyanobiphenyls with radical precursors emerged as a versatile tool for the synthesis of 6-substituted phenanthridines.[5] Of these products, trifluoromethylated phenanthridines have received substantial attention because the incorporation of a trifluoromethyl (CF_3) group into organic molecules can enhance their biological activity and has become a powerful and widely used strategy in drug design.[6] For example, Studer and co-workers reported the synthesis of 6-(trifluoromethyl)phenanthridines via radical insertion reactions of isonitriles using Togni's reagent or iodotrifluoromethane (CF_3I) as trifluoromethylation reagents (Scheme 1, eq 1, conditions a and b).[7] Yu and co-workers also developed the trifluoromethylation of isonitriles with Umemoto's reagents (Scheme 1, eq 1, conditions c).[8] In addition, Zhou et al. found that the Ruppert–Prakash reagent could also afford a trifluoromethyl radical, which resulted in oxidative cyclization in the presence of (diacetoxyiodo)benzene [$PhI(OAc)_2$] (2.1 equiv) (Scheme 1, eq 1, conditions d).[9] However, the use of these expensive or unstable trifluoromethylation reagents has limited the utility and applicability of these reactions. As part of our ongoing studies toward the preparation of trifluoromethylated heterocycles,[10] we herein report an efficient synthesis of 6-(trifluoromethyl)phenanthridines through the silver-catalyzed trifluoromethylation and cyclization of aryl isonitriles with the Langlois reagent (sodium triflinate, CF_3SO_2Na), a cheap and stable solid trifluoromethyl source (Scheme 1, eq 2).[11,12]

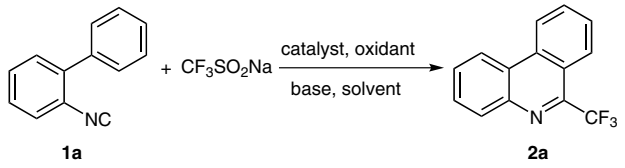


Scheme 1 Synthesis of 6-(trifluoromethyl)phenanthridines

Our preliminary studies were focused on the model reaction of 2-isocyano-1,1′-biphenyl (**1a**) with sodium triflinate in order to develop optimized conditions, and the results are summarized in Table 1. Initially, treatment of substrate **1a** with the Langlois reagent and *tert*-butyl hydroperoxide (TBHP) at 40 °C in acetonitrile afforded the desired product **2a** in 48% yield (Table 1, entry 1). This result encouraged us to examine the use of metal catalysts with the aim of increasing the reaction yield (Table 1, entries 2–4). It was found that silver nitrate ($AgNO_3$) was more

effective than iron(III) chloride ($FeCl_3$) and copper(I) bromide (CuBr), and product **2a** was isolated in 58% yield. In view of the role of a base in deprotonation, we next investigated the addition of some common bases (Table 1, entries 5–7). It was found that cesium acetate (CsOAc), potassium carbonate (K_2CO_3) and sodium carbonate (Na_2CO_3) facilitated the reaction, with sodium carbonate providing product **2a** in 84% yield. Further investigations disclosed that both di-*tert*-butyl peroxide (DTBP) and potassium persulfate ($K_2S_2O_8$) were less effective than *tert*-butyl hydroperoxide (Table 1, entries 8 and 9), whilst benzoyl peroxide (BPO) was a completely ineffective oxidant for this reaction (Table 1, entry 10). During the examination of different solvents, lower yields were observed when the reaction was carried out in 1,2-dichloroethane (DCE), *N*,*N*-dimethylformamide and toluene (Table 1, entries 11–13), however, the use of dimethyl sulfoxide provided an 86% yield of **2a** (Table 1, entry 14). It is noteworthy that almost the same yield (85%) was obtained when the loading of silver nitrate was reduced to 1 mol% (Table 1, entry 15).

Table 1 Optimization of the Reaction Conditions[a]



1a **2a**

Entry	Cat.	Oxidant	Solvent	Base	Yield (%)
1	–	TBHP	MeCN	–	48
2	$FeCl_3$	TBHP	MeCN	–	50
3	CuBr	TBHP	MeCN	–	49
4	$AgNO_3$	TBHP	MeCN	–	58
5	$AgNO_3$	TBHP	MeCN	CsOAc	72
6	$AgNO_3$	TBHP	MeCN	K_2CO_3	73
7	$AgNO_3$	TBHP	MeCN	Na_2CO_3	84
8	$AgNO_3$	DTBP	MeCN	Na_2CO_3	63
9	$AgNO_3$	$K_2S_2O_8$	MeCN	Na_2CO_3	71
10	$AgNO_3$	BPO	MeCN	Na_2CO_3	0
11	$AgNO_3$	TBHP	DCE	Na_2CO_3	69
12	$AgNO_3$	TBHP	DMF	Na_2CO_3	72
13	$AgNO_3$	TBHP	toluene	Na_2CO_3	60
14	$AgNO_3$	TBHP	DMSO	Na_2CO_3	86
15	$AgNO_3$[b]	TBHP	DMSO	Na_2CO_3	85

[a] Reaction conditions: **1a** (0.2 mmol), CF_3SO_2Na (0.6 mmol), catalyst (5 mol%), oxidant (0.4 mmol), base (0.2 mmol), solvent (2 mL), 40 °C, N_2 atm, 6 h.
[b] $AgNO_3$ (1 mol%) was used.

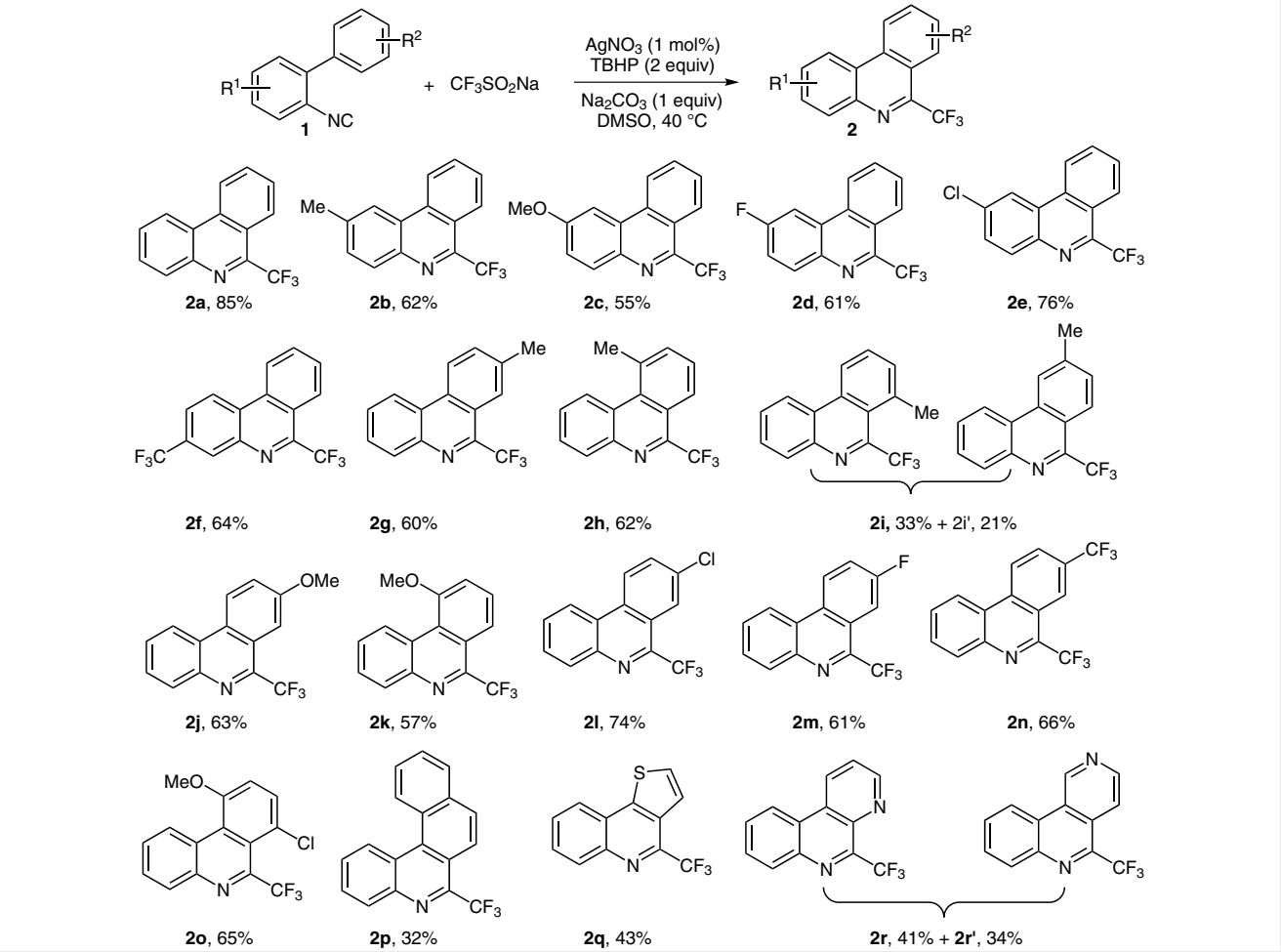
With the optimized reaction conditions established, we subsequently investigated the substrate scope of the aryl isonitriles (Scheme 2). In general, 2-isocyanobiphenyls bearing either electron-donating or electron-withdrawing substituents were suitable substrates, and were transformed into the corresponding 6-(trifluoromethyl)phenanthridines in good yields. For example, 4-methyl- and 4-methoxy-substituted isocyanobenzenes afforded phenanthridines **2b** and **2c** in 62% and 55% yields, respectively, whilst isocyanides containing fluoro, chloro, or trifluoromethyl groups gave products **2d**–**f** in 61–76% yield.

Tolyl-substituted isocyanobenzenes **1g**–**i** underwent the reaction smoothly to afford the corresponding products, although poor regioselectivity was observed in the case of **1i**: two isomers, **2i** and **2i′**, were isolated in 33% and 21% yields, respectively. Methoxy-, fluoro-, chloro- and trifluoromethylphenyl-substituted isocyanobenzenes were well tolerated under the standard conditions to furnish products **2j**–**n** in 57–74% yields. A 2-isocyanobiphenyl bearing two substituents (**1o**) was also converted successfully into product **2o** in 65% yield. Bulky 6-(trifluoromethyl)benzo[*k*]phenanthridine (**2p**) was obtained in 32% yield from the oxidative cyclization of 1-(2-isocyanophenyl)naphthalene (**1p**). As expected, aryl isonitriles bearing a heterocyclic ring were also compatible in this transformation. For example, thieno[3,2-*c*]quinoline **2q** was prepared in 43% yield. Benzonaphthyridines **2r** and **2r′** were isolated in 41% and 34% yields from the trifluoromethylation and cyclization of 3-(2-isocyanophenyl)pyridine (**1r**).

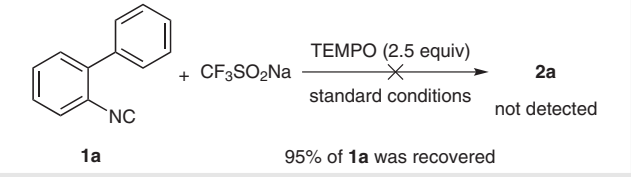
To probe the reaction mechanism, we examined the reaction of substrate **1a** with the Langlois reagent under standard conditions in the presence of 2.5 equivalents of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), a common radical scavenger. The desired product **2a** could not be detected by TLC and GC–MS analysis, and almost 95% of reactant **1a** was recovered (Scheme 3). These results revealed that the tandem reaction might involve a trifluoromethyl radical pathway.

Based on the above experimental results and previous reports,[7] a plausible mechanism is proposed in Scheme 4. Firstly, a *tert*-butoxy radical is generated in situ from the decomposition of *tert*-butyl hydroperoxide in the presence of a trace amount of silver nitrate.[12] Subsequently, the *tert*-butoxy radical reacts with the Langlois reagent to provide a trifluoromethyl radical along with the release of sulfur dioxide (SO_2). Addition of the trifluoromethyl radical to 2-isocyanobiphenyl **1a** affords imidoyl radical intermediate **A**, which is transformed into cyclohexadienyl radical **B** by intramolecular electrophilic cyclization. Subsequent oxidation of radical **B** produces cyclohexadienyl cation **C** through a single electron transfer (SET) involving *tert*-butyl hydroperoxide. [9] Finally, deprotonation of intermediate **C** by the base (Na_2CO_3) affords 6-(trifluoromethyl)phenanthridine **2a**.

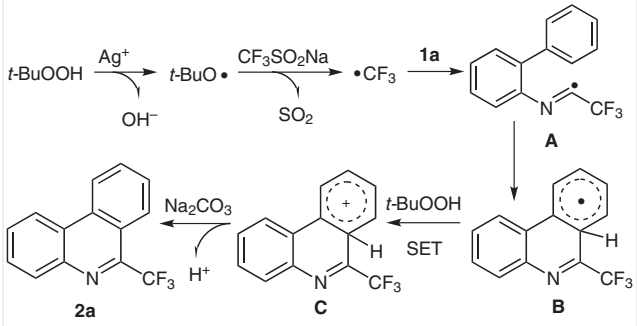
In conclusion, we have developed a mild oxidative cyclization for the efficient synthesis of 6-(trifluoromethyl)phenanthridines that employs the cheap and stable



Scheme 2 Reactions of CF_3SO_2Na with different isocyanides. *Reaction conditions*: isocyanide **1a** (0.2 mmol), CF_3SO_2Na (0.6 mmol), TBHP (0.4 mmol), Na_2CO_3 (0.2 mmol), $AgNO_3$ (1 mol%), DMSO (2 mL), 40 °C, 6 h, N_2 atm. Yields are those of isolated products.



Scheme 3 A control experiment



Scheme 4 A possible mechanism

Langlois reagent. In the presence of silver nitrate (1 mol%), *tert*-butyl hydroperoxide, and sodium carbonate, a wide variety of aryl isonitriles were transformed into the corresponding phenanthridines, in moderate to good yields, via a tandem trifluoromethylation–cyclization process. The present procedure might prove useful for the convenient synthesis of other trifluoromethylated heterocycles.

Chemicals were either purchased or were purified by standard techniques. All reactions under a nitrogen atmosphere were conducted using standard Schlenk techniques. Column chromatography was performed using EM Silica gel 60 (300–400 mesh). Petroleum ether (PE)

refers to the fraction boiling in the 60–90 °C range. Melting points were obtained using a TAIRON 4-X digital display microscopic melting point detector. IR spectra were recorded using a Nicolet iS10 spectrophotometer. ^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded at room temperature on a Bruker Avance-III 500 MHz spectrometer, using $CDCl_3$ as the solvent and tetramethylsilane (TMS) as an internal standard. Chemical shifts (δ) are quoted relative to TMS, and the coupling constants (*J*) are given in Hz. ^{19}F NMR (470 MHz) spectra were recorded on the same instrument and are reported relative to $CFCl_3$ as the internal standard. Low-resolution mass spectra were recorded using a Shimadzu GC-MS-QP2010 Plus mass spectrometer. High-resolution mass spectra were obtained using a Bruker micrOTOF-QII mass spectrometer.

6-(Trifluoromethyl)phenanthridines; General Procedure

A mixture of 2-isocyano-1,1′-biphenyl **1** (0.2 mmol), CF_3SO_2Na (93.6 mg, 0.6 mmol), $AgNO_3$ (0.33 mg, 1 mol%), TBHP (0.4 mmol, 36.0 mg) and Na_2CO_3 (21.2 mg, 0.2 mmol) in DMSO (2 mL) was stirred at 40 °C under an N_2 atm for 6 h, or until complete consumption of the starting material as monitored by TLC or GC–MS analysis. After the reaction was complete, the mixture was poured into EtOAc (10 mL) and evaporated under vacuum. The residue was purified by flash column chromatography (PE–EtOAc) to afford the desired product **2a**–**r**.

6-(Trifluoromethyl)phenanthridine (2a)[10]

Yield: 42.0 mg (85%); yellow solid; mp 72–74 °C.

IR (neat): 1613, 1179, 1115, 759, 719 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.67 (d, *J* = 8.5 Hz, 1 H), 8.57 (d, *J* = 7.5 Hz, 1 H), 8.37 (d, *J* = 8.5 Hz, 1 H), 8.27 (d, *J* = 7.5 Hz, 1 H), 7.91–7.88 (m, 1 H), 7.80–7.73 (m, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 146.5 (q, *J* = 32.8 Hz), 141.8, 134.0, 131.3, 131.1, 129.3, 129.2, 128.0, 125.9, 125.1, 122.5, 122.04, 121.96 (q, *J* = 275.4 Hz), 121.8.

^{19}F NMR (470 MHz, $CDCl_3$): δ = –63.4 (3 F).

MS (EI, 70 eV): *m*/*z* (%) = 247 (100) [M]$^+$, 178 (69), 151 (31), 123 (6), 75 (6).

2-Methyl-6-(trifluoromethyl)phenanthridine (2b)[10]

Yield: 32.4 mg (62%); brown solid; mp 103–105 °C.

IR (neat): 1616, 1174, 1118, 827, 770 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.64 (d, *J* = 8.5 Hz, 1 H), 8.35–8.33 (m, 2 H), 8.15 (d, *J* = 8.5 Hz, 1 H), 7.88–7.85 (m, 1 H), 7.74–7.71 (m, 1 H), 7.60 (d, *J* = 8.5 Hz, 1 H), 2.64 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 145.5 (q, *J* = 32.6 Hz), 140.1, 139.5, 133.7, 131.1, 131.0, 130.8, 127.8, 125.8, 125.2, 122.5, 122.1 (q, *J* = 275.3 Hz), 121.9, 121.6, 22.1.

^{19}F NMR (470 MHz, $CDCl_3$): δ = –63.3 (3 F).

MS (EI, 70 eV): *m*/*z* (%) = 261 (100) [M]$^+$, 241 (32), 192 (19), 165 (15), 95 (10).

2-Methoxy-6-(trifluoromethyl)phenanthridine (2c)

Yield: 30.5 mg (55%); brown solid; mp 93–95 °C.

IR (neat): 1620, 1166, 1100, 824, 761 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.44 (d, *J* = 8.0 Hz, 1 H), 8.23 (d, *J* = 8.0 Hz, 1 H), 8.07 (d, *J* = 9.0 Hz, 1 H), 7.76–7.73 (m, 2 H), 7.64–7.61 (m, 1 H), 7.29 (d, *J* = 9.0 Hz, 1 H), 3.92 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.0, 143.7 (q, *J* = 32.7 Hz), 136.8, 133.1, 132.4, 130.7, 128.0, 126.4, 125.6, 122.4, 122.1 (q, *J* = 275.0 Hz), 121.8, 119.3, 102.6, 55.6.

^{19}F NMR (470 MHz, $CDCl_3$): δ = –63.1 (3 F).

MS (EI, 70 eV): *m*/*z* (%) = 277 (100) [M]$^+$, 262 (15), 234 (51), 184 (32), 164 (9).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{11}F_3NO$: 278.0787; found: 278.0793.

2-Fluoro-6-(trifluoromethyl)phenanthridine (2d)[10]

Yield: 32.4 mg (61%); gray solid; mp 115–117 °C.

IR (neat): 1620, 1172, 1130, 973, 864, 770 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.29–8.27 (m, 1 H), 8.19 (d, *J* = 8.0 Hz, 1 H), 8.09–8.06 (m, 1 H), 7.92–7.89 (m, 1 H), 7.73–7.70 (m, 1 H), 7.63–7.60 (m, 1 H), 7.36–7.32 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.6 (d, *J* = 249.3 Hz), 145.8 (q, *J* = 33.0 Hz), 138.5, 133.5, 133.3, 131.3, 128.7, 126.7, 125.9, 123.0, 122.6, 121.9 (q, *J* = 275.3 Hz), 118.4 (d, *J* = 24.4 Hz), 107.1 (d, *J* = 23.5 Hz).

^{19}F NMR (470 MHz, $CDCl_3$): δ = –63.5 (s, 3 F), –108.8 (s, 1 F).

MS (EI, 70 eV): *m*/*z* (%) = 265 (100) [M]$^+$, 196 (67), 176 (8), 169 (18), 138 (19).

2-Chloro-6-(trifluoromethyl)phenanthridine (2e)[10]

Yield: 42.7 mg (76%); yellow solid; mp 118–120 °C.

IR (neat): 1610, 1179, 1124, 830, 768 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.47 (d, *J* = 8.0 Hz, 1 H), 8.41 (s, 1 H), 8.27 (d, *J* = 8.0 Hz, 1 H), 8.10 (d, *J* = 8.5 Hz, 1 H), 7.84–7.81 (m, 1 H), 7.71–7.68 (m, 1 H), 7.63 (d, *J* = 8.5 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 146.7 (q, *J* = 33.0 Hz), 140.1, 135.4, 132.8, 132.5, 131.6, 129.9, 128.7, 126.1, 125.9, 122.5, 121.9, 121.75 (q, *J* = 275.5 Hz), 121.71.

^{19}F NMR (470 MHz, $CDCl_3$): δ = –63.6 (3 F).

MS (EI, 70 eV): *m*/*z* (%) = 281 (100) [M]$^+$, 213 (38), 177 (54), 150 (10), 123 (6).

3,6-Bis(trifluoromethyl)phenanthridine (2f)[8]

Yield: 40.3 mg (64%); white solid; mp 105–108 °C.

IR (neat): 1630, 1338, 1158, 1119, 775, 727 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.63–8.59 (m, 2 H), 8.49 (s, 1 H), 8.33 (d, *J* = 8.5 Hz, 1 H), 7.92–7.87 (m, 2 H), 7.79–7.75 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 148.0 (q, *J* = 33.3 Hz), 141.1, 133.3, 132.0, 131.3 (q, *J* = 33.1 Hz), 129.3, 128.7, 127.3, 126.2, 125.0, 123.8 (q, *J* = 270.8 Hz), 123.2, 122.9, 122.4, 121.7 (q, *J* = 275.6 Hz).

^{19}F NMR (500 MHz, $CDCl_3$): δ = –62.5 (3 F), –63.7 (3 F).

MS (EI, 70 eV): *m*/*z* (%) = 315 (100) [M]$^+$, 246 (63), 226 (32), 177 (24), 123 (5).

8-Methyl-6-(trifluoromethyl)phenanthridine (2g)[9]

Yield: 31.3 mg (60%); brown solid; mp 101–103 °C.

IR (neat): 1609, 1175, 1119, 826, 769 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.51–8.49 (m, 2 H), 8.19 (d, *J* = 7.5 Hz, 1 H), 8.06 (s, 1 H), 7.70–7.66 (m, 3 H), 2.55 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 146.2 (q, *J* = 32.5 Hz), 141.5, 138.2, 133.2, 131.9, 131.1, 129.1, 128.9, 125.24, 125.21, 122.4, 121.97 (q, *J* = 273.1 Hz), 121.96, 121.8, 21.9.

^{19}F NMR (470 MHz, $CDCl_3$): δ = –63.5 (3 F).

MS (EI, 70 eV): *m*/*z* (%) = 261 (100) $[M]^+$, 241 (31), 190 (17), 165 (15), 96 (10).

10-Methyl-6-(trifluoromethyl)phenanthridine (2h)[9]

Yield: 32.4 mg (62%); yellow solid; mp 90–92 °C.

IR (neat): 1660, 1166, 1133, 761, 737 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.61–8.57 (m, 2 H), 8.28–8.26 (m, 1 H), 8.14 (s, 1 H), 7.80–7.75 (m, 3 H), 2.64 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 146.2 (q, *J* = 32.0 Hz), 141.4, 138.2, 133.2, 131.9, 131.0, 129.1, 128.9, 125.3, 125.2, 122.4, 121.963, 121.957 (q, *J* = 273.1 Hz), 121.9, 21.9.

^{19}F NMR (470 MHz, $CDCl_3$): δ = –63.5 (3 F).

MS (EI, 70 eV): *m*/*z* (%) = 261 (100) $[M]^+$, 241 (8), 192 (28), 165 (19), 131(5).

7-Methyl-6-(trifluoromethyl)phenanthridine (2i)[10]

Yield: 17.2 mg (33%); brown solid; mp 44–46 °C.

IR (neat): 1607, 1171, 1119, 963, 763 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.62–8.57 (m, 2 H), 8.25–8.23 (m, 1 H), 7.80–7.74 (m, 3 H), 7.61 (d, *J* = 7.5 Hz, 1 H), 2.93 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 145.1 (q, *J* = 33.1 Hz), 140.7, 135.9, 135.6, 132.7, 130.7, 130.5, 129.2, 129.1, 125.4, 122.4, 122.3, 122.0 (q, *J* = 274.0 Hz), 120.8, 23.4.

^{19}F NMR (470 MHz, $CDCl_3$): δ = –59.8 (3 F).

MS (EI, 70 eV): *m*/*z* (%) = 261 (100) $[M]^+$, 241 (7), 192 (35), 177 (10), 165 (22).

9-Methyl-6-(trifluoromethyl)phenanthridine (2i')[10]

Yield: 11.0 mg (21%); yellow solid; mp 67–69 °C.

IR (neat): 1620, 1174, 1119, 971, 759 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.54 (d, *J* = 7.5 Hz, 1 H), 8.42 (s, 1 H), 8.20 (d, *J* = 7.5 Hz, 2 H), 7.74–7.70 (m, 2 H), 7.53 (d, *J* = 8.5 Hz, 1 H), 2.66 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 146.4 (q, *J* = 32.8 Hz), 142.1, 141.9, 134.2, 131.1, 129.8, 129.2, 128.9, 125.8, 125.0, 122.12, 122.05, 122.03 (q, *J* = 275.4 Hz), 119.9, 22.3.

^{19}F NMR (470 MHz, $CDCl_3$): δ = –63.5 (3 F).

MS (EI, 70 eV): *m*/*z* (%) = 261 (100) $[M]^+$, 241 (11), 192 (40), 165 (33), 121 (7).

8-Methoxy-6-(trifluoromethyl)phenanthridine (2j)[9]

Yield: 34.9 mg (63%); white solid; mp 101–103 °C.

IR (neat): 1623, 1169, 1131, 765, 735 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.59 (d, *J* = 9.0 Hz, 1 H), 8.51 (d, *J* = 9.0 Hz, 1 H), 8.26 (d, *J* = 9.0 Hz, 1 H), 7.77–7.73 (m, 2 H), 7.67 (s, 1 H), 7.54 (d, *J* = 9.0 Hz, 1 H), 4.00 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.0, 145.5 (d, *J* = 32.4 Hz), 141.0, 131.1, 129.2, 128.5, 128.3, 125.3, 124.1, 123.2, 122.5, 122.0 (q, *J* = 273.2 Hz), 121.6, 105.6, 55.6.

^{19}F NMR (470 MHz, $CDCl_3$): δ = –64.1 (3 F).

MS (EI, 70 eV): *m*/*z* (%) = 277 (100) $[M]^+$, 234 (74), 207 (12), 184 (16), 164 (9).

10-Methoxy-6-(trifluoromethyl)phenanthridine (2k)[9]

Yield: 31.6 mg (57%); yellow solid; mp 103–105 °C.

IR (neat): 1573, 1276, 1177, 1121, 776, 720 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.54 (d, *J* = 8.0 Hz, 1 H), 8.28 (d, *J* = 7.5 Hz, 1 H), 8.00 (d, *J* = 8.0 Hz, 1 H), 7.78–7.75 (m, 2 H), 7.71–7.68 (m, 1 H), 7.37 (d, *J* = 8.0 Hz, 1 H), 4.15 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.3, 146.2 (q, *J* = 32.4 Hz), 142.2, 130.9, 129.0, 128.5, 128.2, 128.0, 125.0, 124.5, 123.8, 122.1 (d, *J* = 275.5 Hz), 118.0, 112.2, 55.9.

^{19}F NMR (470 MHz, $CDCl_3$): δ = –63.3 (3 F).

MS (EI, 70 eV): *m*/*z* (%) = 277 (100) $[M]^+$, 262 (29), 242 (52), 184 (12), 139 (15).

8-Chloro-6-(trifluoromethyl)phenanthridine (2l)[7]

Yield: 41.6 mg (74%); white solid; mp 107–109 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.54–8.52 (m, 1 H), 8.47–8.46 (m, 1 H), 8.28 (s, 1 H), 8.24 (d, *J* = 7.0 Hz, 1 H), 7.81–7.60 (m, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 145.4 (q, *J* = 32.0 Hz), 141.7, 134.3, 132.3, 132.0, 131.2, 129.65, 129.63, 125.2, 124.7, 124.2, 122.5, 121.9, 121.6 (q, *J* = 275.4 Hz).

^{19}F NMR (470 MHz, $CDCl_3$): δ = –63.6 (3 F).

IR (neat): 1610, 1184, 1174, 1112, 983, 760 cm^{-1}.

MS (EI, 70 eV): *m*/*z* (%) = 281 (100) $[M]^+$, 212 (42), 177 (61), 150 (13), 123 (6).

8-Fluoro-6-(trifluoromethyl)phenanthridine (2m)[5e]

Yield: 32.3 mg (61%); yellow solid; mp 84–86 °C.

IR (neat): 1627, 1166, 1120, 766, 737 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.69–8.66 (m, 1 H), 8.53–8.52 (m, 1 H), 8.28–8.27 (m, 1 H), 7.99 (d, *J* = 9.5 Hz, 1 H), 7.80–7.79 (m, 2 H), 7.68–7.65 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.5 (d, *J* = 248.6 Hz), 145.7 (q, *J* = 33.1 Hz), 141.5, 131.3, 130.7, 129.7, 129.2, 125.2, 124.7, 122.9, 121.8, 120.8 (d, *J* = 24.0 Hz), 121.7 (q, *J* = 275.4 Hz), 110.8 (d, *J* = 23.1 Hz).

^{19}F NMR (470 MHz, $CDCl_3$): δ = –64.0 (3 F), –109.9 (1 F).

MS (EI, 70 eV): *m*/*z* (%) = 265 (100) $[M]^+$, 196 (67), 176 (9), 169 (26), 133 (8).

6,8-Bis(trifluoromethyl)phenanthridine (2n)[9]

Yield: 41.6 mg (66%); yellow solid; mp 104–107 °C.

IR (neat): 1627, 1324, 1168, 1124, 764 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.77 (d, *J* = 8.5 Hz, 1 H), 8.62 (s, 1 H), 8.59–8.57 (m, 1 H), 8.30–8.29 (m, 1 H), 8.08 (d, *J* = 8.5 Hz, 1 H), 7.89–7.81 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 146.4 (q, *J* = 33.4 Hz), 142.4, 136.0, 131.4, 130.5, 130.3 (q, *J* = 33.4 Hz), 129.9, 127.2, 124.1, 123.71, 123.65 (q, *J* = 270.9 Hz), 123.4, 122.6, 121.6 (q, *J* = 275.3 Hz), 121.1.

^{19}F NMR (470 MHz, $CDCl_3$): δ = –62.6 (3 F), –63.3 (3 F).

MS (EI, 70 eV): *m*/*z* (%) = 315 (100) $[M]^+$, 296 (12), 246 (57), 226 (32), 207 (10), 177 (22).

7-Chloro-10-methoxy-6-(trifluoromethyl)phenanthridine (2o)

Yield: 40.5 mg (65%); white solid; mp 123–125 °C.

IR (neat): 1587, 1164, 1141, 994, 761 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.44 (d, *J* = 8.5 Hz, 1 H), 8.22 (d, *J* = 8.0 Hz, 1 H), 7.79–7.76 (m, 1 H), 7.72 (d, *J* = 8.5 Hz, 2 H), 7.23 (d, *J* = 8.5 Hz, 1 H), 4.12 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.9, 143.7 (q, *J* = 34.4 Hz), 141.3, 131.3, 130.4, 129.4, 129.2, 127.5, 127.3, 123.9, 122.3, 121.6 (q, *J* = 274.3 Hz), 122.0, 112.0, 56.1.

^{19}F NMR (470 MHz, $CDCl_3$): δ = –58.3 (3 F).

MS (EI, 70 eV): *m*/*z* (%) = 311 (100) $[M]^+$, 296 (38), 276 (48), 207 (39), 164 (25).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{10}F_3NOCl$: 312.0398; found: 312.0397.

6-(Trifluoromethyl)benzo[*k*]phenanthridine (2p)

Yield: 19.0 mg (32%); yellow solid; mp 53–55 °C.

IR (neat): 1630, 1173, 1117, 754, 730 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.13–9.12 (m, 1 H), 9.06 (d, *J* = 8.0 Hz, 1 H), 8.42 (d, *J* = 8.0 Hz, 1 H), 8.26 (d, *J* = 9.0 Hz, 1 H), 8.10–8.09 (m, 1 H), 8.05 (d, *J* = 9.0 Hz, 1 H), 7.87–7.83 (m, 2 H), 7.80–7.78 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 145.7 (q, *J* = 32.2 Hz), 143.8, 134.7, 133.7, 130.9, 129.2, 129.0, 128.8, 128.72, 128.68, 128.62, 128.5, 127.3, 127.2, 125.4, 122.3 (q, *J* = 273.2 Hz), 121.3, 121.0.

^{19}F NMR (470 MHz, $CDCl_3$): δ = –62.5 (3 F).

MS (EI, 70 eV): *m*/*z* (%) = 297 (100) $[M]^+$, 276 (23), 228 (23), 201 (15), 100 (16).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{11}F_3N$: 298.0838; found: 298.0846.

4-(Trifluoromethyl)thieno[3,2-*c*]quinoline (2q)[9]

Yield: 21.8 mg (43%); yellow solid; mp 59–61 °C.

IR (neat): 1643, 1184, 1118, 759, 711 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.33 (d, *J* = 8.0 Hz, 1 H), 8.18 (d, *J* = 8.0 Hz, 1 H), 7.81–7.78 (m, 2 H), 7.75–7.72 (m, 1 H), 7.70–7.69 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 147.8, 142.9 (q, *J* = 31.0 Hz), 141.9, 131.1, 129.4, 129.1, 129.0, 127.4, 125.1, 123.2, 123.1, 121.8 (q, *J* = 274.5 Hz).

^{19}F NMR (470 MHz, $CDCl_3$): δ = –65.7 (3 F).

MS (EI, 70 eV): *m*/*z* (%) = 253 (100) $[M]^+$, 184 (44), 140 (37), 127 (6), 113 (8).

5-(Trifluoromethyl)benzo[*f*][1,7]naphthyridine (2r)

Yield: 20.4 mg (41%); white solid; mp 112–114 °C.

IR (neat): 1580, 1180, 1131, 986, 764 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.17–9.16 (m, 1 H), 8.97 (d, *J* = 8.5 Hz, 1 H), 8.56 (d, *J* = 8.0 Hz, 1 H), 8.35 (d, *J* = 8.0 Hz, 1 H), 7.90–7.84 (m, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 150.8, 147.5 (q, *J* = 32.3 Hz), 141.7, 138.7, 131.4, 130.4, 130.1, 129.7, 129.3, 125.7, 124.6, 122.1, 121.6 (q, *J* = 275.8 Hz).

^{19}F NMR (470 MHz, $CDCl_3$): δ = –64.3 (3 F).

MS (EI, 70 eV): *m*/*z* (%) = 248 (100) $[M]^+$, 179 (94), 152 (39), 125 (16), 91 (12).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_8F_3N_2$: 249.0634; found: 249.0637.

5-(Trifluoromethyl)benzo[*c*][2,6]naphthyridine (2r′)

Yield: 16.9 mg (34%); yellow solid; mp 159–161 °C.

IR (neat): 1566, 1180, 1116, 770, 718 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.19 (s, 1 H), 8.97–8.96 (m, 1 H), 8.79–8.77 (m, 1 H), 8.38–8.36 (m, 1 H), 8.15–8.14 (m, 1 H), 7.93–7.91 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 147.3, 146.5, 145.6 (q, *J* = 30.3 Hz), 142.4, 131.6, 130.7, 130.4, 127.5, 125.0, 123.3, 121.5, 121.4 (q, *J* = 276.3 Hz), 117.6.

^{19}F NMR (470 MHz, $CDCl_3$): δ = –64.2 (3 F).

MS (EI, 70 eV): *m*/*z* (%) = 248 (100) $[M]^+$, 179 (64), 152 (30), 125 (15), 99 (7).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_8F_3N_2$: 249.0634; found: 249.0632.

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Supporting Information

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