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Concise synthesis of 2,4-bis(fluoroalkyl)quinoline derivatives from arylamines

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ABSTRACT

Quinolines and their derivatives bearing fluorine-containing substituents are essential structural motifs found in numerous bioactive compounds and advanced functional materials. Therefore, there is an urgent need to develop new synthetic methods for fluoroalkylated quinoline derivatives. In this study, we present a facile and efficient approach to access fluoroalkylated quinoline derivatives by using Eaton's reagent as a cost-effective, and commercially available reagent. This Combes cyclization reaction demonstrated compatibility with various arylamines bearing diverse functional groups, resulting in the synthesis of 2,4-bis(trifluoromethyl)quinolines and 2,4-bis(difluoromethyl)quinolines in moderate to high yields. Furthermore, this reaction can be conveniently carried out in a solvent-free one-pot protocol.

1. Introduction

The selective introduction of fluoroalkyl groups into small molecules has attracted much attention from chemists due to the unique electronic properties of fluorine and the importance of fluoroalkyl groups in materials, pharmaceuticals, agrochemicals and fine chemicals [1]. In particular, quinolines and their derivatives bearing fluorine-containing substituents represent crucial structural motifs of numerous bioactive compounds and advanced functional materials, and this introduction of fluorine can significantly improve metabolic stability, lipophilicity and binding properties of those compounds [2]. In recent years, bis(fluoroalkylated) *N*-heterocyclic compounds (**I**, **II**, **III**, Fig. 1) have been effectively utilized as pharmaceutical and agrochemicals [3–5], while a novel fluorescent dye was synthesized by preparing a 2,4-trifluoromethyl quinoline derivative (**IV**, Fig. 1) with electron-donor and -acceptor substituents [6].

Numerous classical methods have been employed for the synthesis of quinoline derivatives, including Skraup, Doebner-von Miller, Pfitzinger, Conrad-Limpach, Friedländer and Combes [7]. Additionally, several novel approaches have been developed to facilitate quinoline synthesis [8]. However, there is currently a scarcity of methodologies available for the synthesis of fluoroalkylated quinoline derivatives from simple arylamines.

Aniline based routes to fluoroalkylated quinolines are shown in Scheme 1. The most common method is the acid-catalyzed intramolecular cyclization of enaminoketones from fluoroalkylated building blocks (**1a**, **1b**, **1c** or **1d**, Scheme 1) via a two-step reaction. Linderman reported the synthesis of trifluoromethyl substituted quinolines from trifluoroacetyl acetylenes (**1a**) in the presence of polyphosphoric acid (PPA), and the mixtures of regioisomeric 2- and 4-CF_3-quinolines are formed in some cases [9]. The enaminoketones can also be obtained from anilines and 4-methoxy-1,1,1-trifluorobut-3-en-2-ones (**1b**) [10], 4-*tert*-butyl amino-l,l,l-trifluorobut-3-en-2-one (**1c**) [11] or 3-(R-phenoxy)-3-perfluoroalkyl-prop-2-enals (**1d**) [12]. Treatment of 4-dimethylamino-1,1,1-trifluoro-3-buten-2-one with triflic anhydride resulted in the formation of 3-trifloxy-3-trifluoromethyl propeniminium triflate which was found to react with aromatic amines to give the 2-trifluoromethyl quinolines in good yields [13]. When anilines and α-fluoroalkyl aldehydes (**1e**) were heated in the presence of acetic acid, 2-fluoroalkyl quinolines were prepared [14]. By reacting arylamines with 1-iodo-3,3,4,4,4-pentafluorobutyl acetate (**1f**), the corresponding 2-trifluoromethyl quinolines are synthesized in high yields [15]. Mass reported a convenient synthesis of 4-trifluoromethyl quinolines from 1-trifluoromethyl-prop-2-yne 1-iminium triflates (**1g**) and anilines in a

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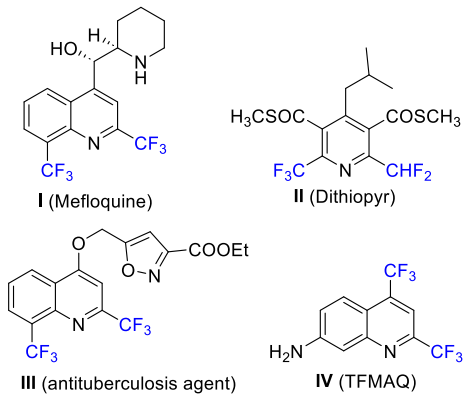
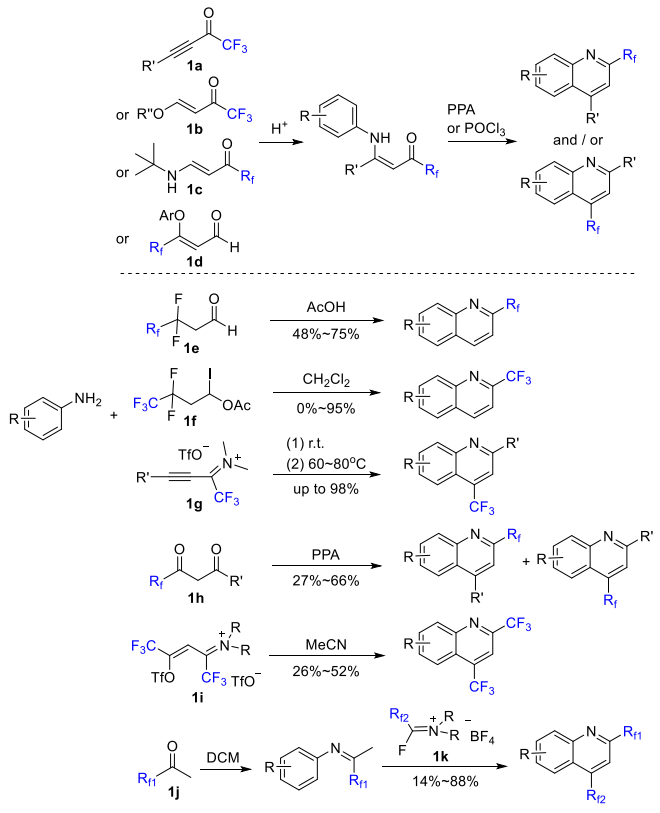


Fig. 1. Representative fluoroalkylated quinoline derivatives in biochemistry and materials chemistry.



Scheme 1. Aniline based routes to fluoroalkylated quinolines.

one-pot two-step Michael addition/intramolecular cyclization reaction [16]. Sloop employed the 1,3-diketones (**1h**) having a CF_3 substituent with anilines to provide regio-mixtures of fluoroalkyl quinolines in the presence of PPA [17a], and this type of Combes reaction was applied to the cyclization of substrates with specific structures by using acetic acid, trifluoroacetic acid or phosphoric acid in medium yield [17]. Recently, 1,3-bis(trifluoromethyl)prop-2-ene 1-iminium triflate salts (**1i**) were prepared to react with anilines, forming the 2,4-bis(trifluoromethyl) quinolines [18]. An unprecedented use of fluoroalkyl amino reagents (**1k**) to afford 2,4-bis(fluoroalkyl)-substituted quinoline derivatives in two steps was reported [20], and this approach enables for the synthesis of quinoline derivatives bearing two identical or different fluoroalkyl substituents in the C2 and C4 positions [19]. Ethyl 4,4,4-trifluoroacetoacetate can be condensed with anilines and subsequently cyclized to give 4-trifluoromethyl-2-quinolinones in the presence of a large excess of polyphosphoric acid [20]. In addition, when the *ortho* position of anilines are substituted by formyl or vinyl groups, the corresponding 2-fluoroalkylated quinolines are synthesized from 1,3-diketones (**1h**) or polyfluoroalkanoic acids in good yields [21].

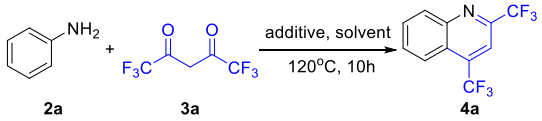
Despite these achievements, there remains a substantial demand for the development of efficient and convenient synthetic approaches for fluoroalkylated quinoline derivatives [22]. In this study, we present a facile and efficient protocol for synthesis of fluoroalkylated quinoline derivatives using Eaton's reagent (7.5/92.5 % by weight of P_2O_5/$MeSO_3H$, phosphorus pentoxide–methanesulfonic acid) [23] as a cost-effective, and commercially available reagent under solvent-free conditions.

2. Results and discussion

2.1. Optimization of reaction conditions

In our initial investigation we estimated the reactivity of the one-pot model reaction between aniline **2a** (1 mmol) and hexafluoroacetylacetone (1,1,1,5,5,5-hexafluoropentane-2,4-dione) **3a** with several additives and solvents (Table 1). Substrate **2a** (1.0 mmol) was introduced into a dry sealed tube, followed by the addition of **3a** (2.0 mmol, 2.0 equiv.), additives and solvents (2 mL), which were added dropwise using a syringe. The resulting reaction mixture was stirred at a temperature of 120 °C for 10 h while being monitored via ^{19}F NMR spectroscopy. A range of acids including H_2SO_4, PPA, *p*-toluenesulfonic acid (*p*-TsOH), CF_3COOH and CH_3COOH were screened (Table 1, entries 1–6). The presence of H_2SO_4 or *p*-TsOH in different solvents (CH_3COOH or toluene) resulted in the detection of only trace amounts of 2,4-bis(trifluoromethyl)quinoline **4a** (entries 1,4). Under the solvent-free conditions, low yields (15 % or 37 %) of **4a** were observed in H_2SO_4 (1.0 mL) or PPA (1.6 mL) (entries 2–3), while CF_3COOH (1.0 mL) and CH_3COOH (2.0 mL) gave trace products (entries 5–6). The utilization of Lewis acids, such as $AlCl_3$, did not yield any observable product (entry 7), and very few products were given in the presence of trimethylchlorosilane (TMSCl) and DMF (entry 8). With $POCl_3$ as an additive the cyclization could be performed, however, only 6 % of the product was detected (entry 9). As an alternative to polyphosphoric acid (PPA), Eaton's reagent (7.5/92.5 % by weight of P_2O_5/$MeSO_3H$) has been utilized in chemical synthesis, particularly for cycloacylation reactions [23,24]. This reagent offers the advantages of inexpensive, readily available, low viscosity, and safe to handle with convenient and clean work-ups of the

Table 1
Screen of reaction conditions for the synthesis of 2,4-bis(trifluoromethyl) quinoline (**4a**).[a]



Entry	Additive	Solvent	Yield (%)[b]
1	H_2SO_4 (1.0 equiv.)	CH_3COOH	trace
2	H_2SO_4 (1.0 mL)	–	15
3	PPA (1.6 mL)	–	37
4	*p*-TsOH (1.0 equiv.)	Toluene	trace
5	CF_3COOH (1.0 mL)	–	trace
6	CH_3COOH (2.0 mL)	–	trace
7	$AlCl_3$ (1.0 equiv.)	Toluene	-[c]
8	TMSCl (1.0 equiv.)	DMF	trace
9	$POCl_3$ (1.0 equiv.)	Toluene	6
10	Eaton's reagent (1.0 mL)	–	42

[a] Reaction scale: **2a** (1.0 mmol), **3a** (2.0 mmol), solvent (2 mL).
[b] The yields were determined by ^{19}F NMR analysis of the crude mixture using trifluoromethoxybenzene as an internal standard.
[c] Not detected.

reaction mixture. Furthermore, almost all organic compounds can be dissolved in this medium. Notably, we were pleased to find that the cyclization reaction of aniline **2a** with hexafluoroacetylacetone **3a** can be processed facilely in Eaton's reagent (1.0 mL) to obtain he 2,4-bis(trifluoromethyl) quinoline **4a** in 42 % yield (entry 10).

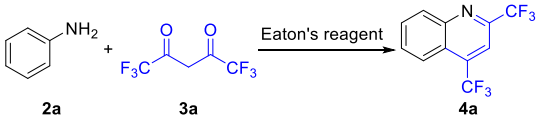
Subsequently, the influence of the amount of Eaton's reagent and various reaction conditions were investigated (Table 2). In the presence of 2.0 mL of Eaton's reagent used as catalyst and reaction medium, the desired product 2,4-bis(trifluoromethyl) quinoline **4a** was obtained in a relatively low yield (27 % or 31 %) when using 1.2 or 1.5 equivalents of hexafluoroacetylacetone **3a** (Table 2, entries 1–2). By employing 2.0 equivalents of **3a**, a moderately efficient synthesis of **4a** was achieved with a yield of approximately 57 % (entry 3), which further improved to 80 % when extending the reaction time to 10 h (entry 4). However, conducting the reaction at 80 °C for 5 h resulted in significantly lower yield (5 %) (entry 5), and even increasing the reaction temperature to 100 °C did not provide satisfying results with only 46 % yield for product **4a** (entry 6). The highest yield (82 %) was obtained by performing the reaction in 3 mL of Eaton's reagent at 150 °C for 5 h while using 3.0 equivalents of compound **3a** (entry10).

2.2. Scope and limitation

Having optimized reaction conditions in hand, we first investigated the generality of this process by employing a variety of arylamines substrates. Representative examples of the formation of 2,4-bis(trifluoromethyl) quinoline derivatives **4** are summarized in Table 3. In the case of *ortho*- and *para*-substituted anilines, the reaction proceeded smoothly, and the corresponding 2,4-bis(trifluoromethyl) quinoline products **4b-4l** were obtained in 42%–69 % yield. The reaction was compatible with many functional groups, such as fluorine, chlorine, bromine, alkyl, trifluoromethyl, trifluoromethoxy and amino substituents, and these functional groups are possible for further elaboration through cross-coupling reactions or other condensation reactions. *Meta*-methyl or amino substituted aniline could be easily converted into 7-methyl-2,4-bis(trifluoromethyl)quinoline **4m** or 7-amino-2,4-bis(trifluoromethyl) quinoline **4n** in good yields (**4m**: 89 %, **4n**: 86 %). It was found that under the acidic reaction condition, *m*-bromoaniline and *m*-chloroaniline also showed good reactivity towards cyclization with hexafluoroacetylacetone, and the corresponding products 7-bromo-2,4-bis(trifluoromethyl)quinoline **4o** and 7-chloro-2,4-bis(trifluoromethyl) quinoline **4p** were obtained respectively (**4o**: 70 %, **4p**: 69 %). It is noteworthy that, as the regioisomers of **4o** and **4p**, 5-bromo-2,4-bis(trifluoromethyl)quinoline **4o′** and 5-chloro-2,4-bis(trifluoromethyl)quinoline **4p′** were isolated from the reaction mixture with low yields (**4o'**: 13 %, **4p'**: 4 %). The reaction also proceeded using other 2,4-disubstituted anilines, such as 4-fluoro-2-iodoaniline and 2,4-dichloroaniline, to give products **4q** and **4r**. Benzoheterocycles were converted into 2,4-bis(trifluoromethyl)-substituted quinoline derivatives **4s**, **4t** and **4u** with moderate yields. Our synthetic strategy also allows a convenient approach to synthesize bis(fluoroalkylated) *N*-heterocyclic compounds **4v** and **4w**, deriving from isoquinolin-4-amine and pyridine-2,6-diamine, and high yields were obtained in case of **4w**.

We further examined the cyclization reaction by using 1,1,5,5-tetrafluoro-2,4-pentanedione (**3b**) to prepare 2,4-bis(difluoromethyl)quinolines. The results were summarized in Table 4. It was found that under similar reaction condition (Eaton'reagent/150 °C/5h), aniline and methyl substituent anilines showed good reactivity towards cyclization with 1,1,5,5-tetrafluoro-2,4-pentanedione, and the corresponding 2,4-

Table 2
The optimization of reaction conditions to for the synthesis of 2,4-bis(trifluoromethyl) quinoline (**4a**).[a]

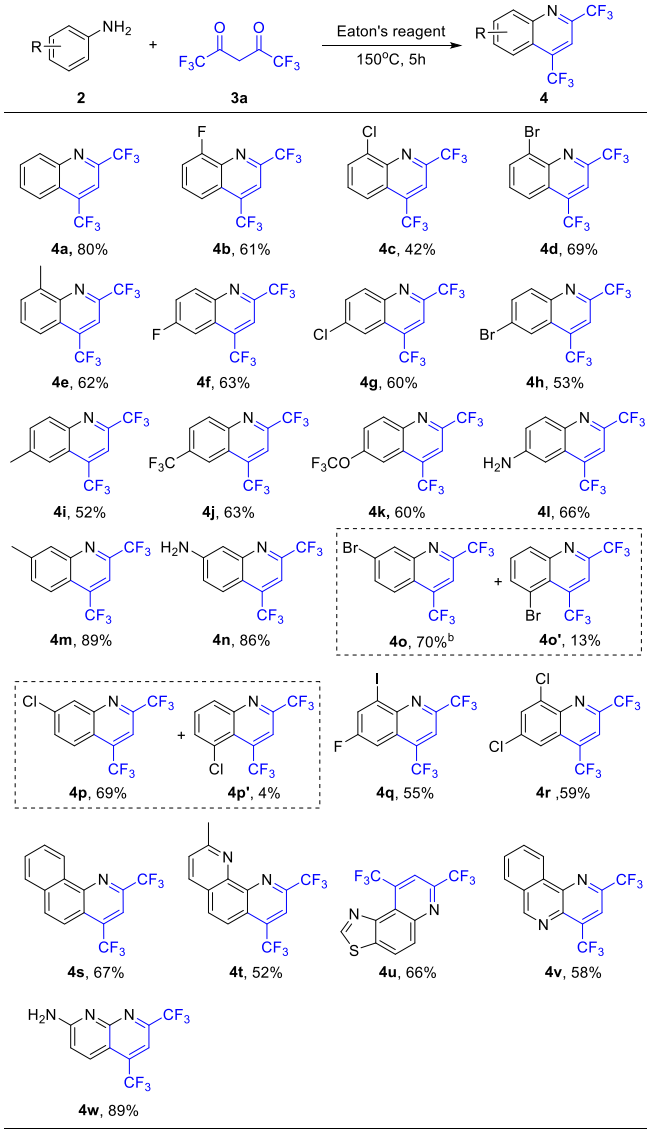


2a **3a** **4a**

Entry	3a (equiv.)	Eaton's Reagent (mL)	Temp. (°C)	Time (h)	Yield (%)[b]
1	1.2	2	120	5	27
2	1.5	2	120	5	31
3	2.0	2	120	5	57
4	2.0	2	120	10	80
5	2.0	2	80	5	5
6	2.0	2	100	5	46
7	2.0	2	150	5	61
8	2.0	1	150	5	62
9	2.0	3	150	5	66
10	3.0	3	150	5	82 (80)[c]

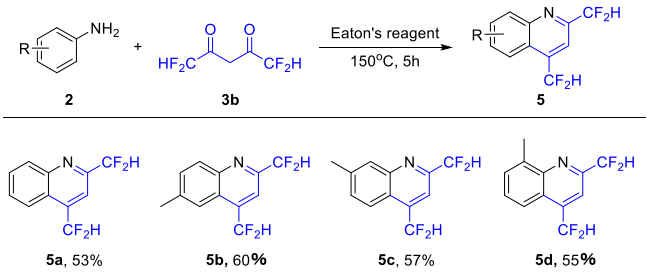
[a] Reaction scale: **2a** (1.0 mmol).
[b] The yields were determined by ^{19}F NMR analysis of the crude mixture using trifluoromethoxybenzene as an internal standard.
[c] Isolated yield was given in parenthese.

Table 3
Syntheses of 2,4-bis(trifluoromethyl) quinoline derivatives.[a]



[a] Reaction conditions: **2** (1.0 mmol, 1 equiv.), **3a** (3.0 mmol, 3 equiv.), Eaton's reagent (3 mL), performed at 150 °C for 5 h. The yields are isolated yields.

Table 4
Syntheses of 2,4-bis(difluoromethyl) quinoline derivatives.[a]



[a] Reaction conditions: **2** (0.5 mmol, 1 equiv.), **3b** (1.5 mmol, 3 equiv.), Eaton's reagent (3 mL), performed at 150 °C for 5 h. The yields are isolated yields.

bis(difluoromethyl)quinoline products (**5a**-**5d**) were obtained in moderate yields (53–60 %, Table 4).

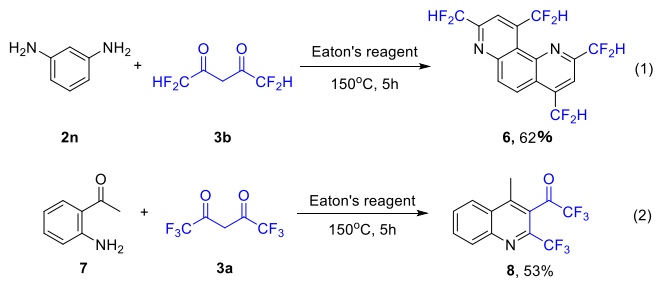
Furthermore, when we reacted one equivalent of *meta*-aminoaniline (**2n**) with three equivalents of **3b** in this one-pot cyclization reaction, 2,4,8,10-tetrakis(difluoromethyl)-1,7-phenanthroline (**6**) was obtained in 62 % yield (Scheme 2, eq 1), while the reagent **3a** gave the different 7-amino-2,4-bis(trifluoromethyl)quinoline **4n** in 86 % yield (Table 3). In addition, we found that this methodology can also be applied to Friedländer quinoline synthesis [7c]. When a carbonyl group is at the β-position of aniline (compound **7**), the corresponding product **8** was obtained in moderate yield (53 %) under the promotion by Eaton's reagent (Scheme 2, eq 2).

It is noteworthy that the molecular structures of **4f**, **5a** and **6** were confirmed by single-crystal X-ray diffraction (Fig. 2) [25].

This Combes cyclization reaction provides a convenient synthetic strategy for the synthesis of fluoroalkylated quinolines, and the reaction mechanism mainly contains three steps. Firstly, under acidic conditions (using Eaton's reagent), nucleophilic addition of a fluoroalkylated diketone to aniline leads to the formation of the corresponding imine or enamine through tautomerism. Subsequently, acid-catalyzed ring closure of the intermediate takes place as the second step. Finally, protonation of the hydroxyl group is followed by dehydration to yield fluoroalkylated quinolines.

3. Conclusions

In summary, we developed a facile and efficient approach to access fluoroalkylated quinoline derivatives by using Eaton's reagent as a cost-effective, and commercially available reagent. This Combes cyclization reaction demonstrated compatibility with various arylamines bearing diverse functional groups, resulting in the synthesis of 2,4-bis(trifluoromethyl)quinolines and 2,4-bis(difluoromethyl)quinolines in moderate to high yields. Furthermore, this reaction can be conveniently carried out in a solvent-free one-pot preparation. Future studies will focus on expanding the conditions employed in this study to enable the formation of other fluoroalkylated quinolines.



Scheme 2. Syntheses of fluoroalkylated quinolines **6** and **8**.

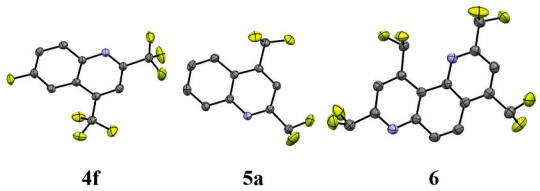


Fig. 2. Crystal structure of **4f**, **5a** and **6**.

4. Experimental section

4.1. General process of synthesis of fluoroalkylated quinolines and its derivatives

Aromatic amine (1.0 mmol) was added to a dry sealed tube, then hexafluoroacetylacetone (3.0 mmol) and Eaton's reagent (3 mL) were added dropwise with a syringe and the reaction mixture was stirred at 150 °C for 5 h without solvent. The reaction was monitored with ^{19}F NMR, and after the reaction was completed, the reaction mixture was diluted with water (5 mL) and the pH of the reaction solution was adjusted to neutral with 1 mol/L NaOH solution. It was subsequently extracted with ethyl acetate, and the organic phase was dried with anhydrous sodium sulfate, and the solvent was removed under reduced pressure. After TLC detection, the reaction mixture was purified by short-column chromatography (silica gel, petroleum ether: ethyl acetate, 20: 1) to obtain the corresponding fluoroalkylated quinoline derivatives.

4.1.1. 2,4-Bis(trifluoromethyl)quinoline (**4a**)

White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, J = 8.6 Hz, 1H), 8.25–8.18 (m, 1H), 8.01 (s, 1H), 7.93 (ddt, J = 8.4, 6.9, 1.4 Hz, 1H), 7.83 (ddt, J = 8.4, 6.9, 1.4 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −61.51 (s, 3F), −67.68 (s, 3F). MS (EI, *m/z*): 265.0 (M^+); HRMS (EI, *m/z*): calcd. For $C_{11}H_5F_6N$ (M^+) 265.0320, found 265.0326. The characterization data are consistent with previous report [18].

4.1.2. 8-Fluoro-2,4-bis(trifluoromethyl)quinoline (**4b**)

White solid. M.p. 65–67 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 8.01 (d, J = 8.7 Hz, 1H), 7.79 (td, J = 8.3, 5.1 Hz, 1H), 7.63 (t, J = 8.7 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.17 (s, 3F), −68.10 (s, 3F), −120.06 (dd, J = 9.5, 5.0 Hz, 1F). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.56 (d, J = 262.2 Hz), 147.83 (q, J = 36.8 Hz), 138.83 (d, J = 12.9 Hz), 137.53–136.04 (m), 130.96 (d, J = 8.3 Hz), 125.30, 122.74 (q, J = 274.8 Hz), 120.14–119.86 (m), 120.91(q, J = 275.9 Hz), 115.46-115.16 (m). IR (film): 1624, 1577, 1557, 1431, 1326, 1276, 1161, 1057, 915, 863, 846, 763, 715, 656, 545 cm^{-1}. MS (ESI, *m/z*): 283.0 (M + H)$^+$; HRMS (ESI, *m/z*): calcd. For $C_{11}H_5F_7N$ (M + H)$^+$ 284.0305, found 284.0307.

4.1.3. 8-Chloro-2,4-bis(trifluoromethyl)quinoline (**4c**)

Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16–8.07 (m, 2H), 8.03 (d, J = 7.6 Hz, 1H), 7.75 (t, J = 8.1 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −61.74 (s, 3F), −68.05 (s, 3F). ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.94 (q, J = 37.1, 36.7 Hz), 144.66, 137.28 (q, J = 32.9 Hz), 135.96, 131.84, 130.47, 125.34, 122.72 (q, J = 275.9 Hz), 122.95 (d, J = 2.1 Hz), 120.89 (q, J = 274.7 Hz), 115.38-115.05 (m). IR (film): 1606, 1510, 1460, 1278, 1263, 1198, 1130, 1110, 880, 850, 820, 742, 714, 694, 651 cm^{-1}. MS (EI, *m/z*): 298.9 (M^+); HRMS (EI, *m/z*): calcd. For $C_{11}H_4ClF_6N$ (M^+) 298.9931, found 298.9930.

4.1.4. 8-Bromo-2,4-bis(trifluoromethyl)quinoline (**4d**)

Yellow solid. M.p. 44–46 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, J = 7.5 Hz, 1H), 8.18 (d, J = 8.7 Hz, 1H), 8.07 (s, 1H), 7.67 (t, J = 7.9 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −61.64 (s, 3F), −68.08 (s,3F). ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.63 (q, J = 37.8 Hz), 145.93, 137.86 (q,

J = 32.8 Hz), 136.03, 131.36, 127.54, 125.84, 124.24, 123.16 (q, J = 272.2 Hz), 121.32 (q, J = 275.9 Hz), 116.22–115.19 (m). IR (film): 1603, 1563, 1507, 1455, 1425, 1282, 1266, 1200, 1142, 902, 879, 849, 788, 741, 686 cm^{-1}. MS (ESI, *m/z*): 343.9 $[M+H]^+$; HRMS (ESI, *m/z*): calcd. For $C_{11}H_5BrF_6N^+$ $[M+H]^+$ 343.9504, found 343.9507.

4.1.5. 8-Methyl-2,4-bis(trifluoromethyl)quinoline (4e)

White solid. M.p. 48–50 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 8.5 Hz, 1H), 8.00 (s, 1H), 7.75 (d, J = 7.0 Hz, 1H), 7.71–7.66 (m, 1H), 2.86 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −61.36 (s, 3F), −67.59 (s, 3F). ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.24, 146.03 (q, J = 35.7, 35.2 Hz), 139.65, 137.20–135.58 (m), 131.50, 130.20, 123.95, 123.03 (q, J = 275.9 Hz), 121.75, 121.14 (q, J = 274.7 Hz), 114.59–113.20 (m), 18.13. IR (film): 1516, 1471, 1386, 1263, 1208, 1134, 1114, 1087, 1067,890, 840,763, 710, 653, 620 cm^{-1}. MS (EI, *m/z*): 279.0 (M^+); HRMS (EI, *m/z*): calcd. For $C_{12}H_7F_6N$ (M^+) 279.0477, found 279.0476.

4.1.6. 6-Fluoro-2,4-bis(trifluoromethyl)quinoline (4f)

White solid. M.p. 57–59 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.34 (dd, J = 9.3, 5.5 Hz, 1H), 8.03 (s, 1H), 7.81 (d, J = 9.4 Hz, 1H), 7.74–7.66 (m, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.28 (s, 3F), −67.74 (s, 3F), −104.77 (td, J = 8.6, 5.4 Hz, 1F). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.71 (d, J = 255.3 Hz), 146.99 (dd, J = 36.5, 3.8 Hz), 145.37, 136.27, (dd, J = 34, 6.3Hz), 134.01 (d, J = 10.1 Hz), 125.02 (d, J = 11.1 Hz), 122.72 (q, J = 275.1 Hz), 122.42 (d, J = 26.0 Hz), 120.99 (q, J = 275.1 Hz), 115.19-114.93 (m), 108.38 (d, J = 24.9 Hz). IR (film): 1626, 1517, 1480, 1220, 1192, 1147, 1123, 1091, 1000, 901, 859, 846, 824, 623, 502 cm^{-1}. MS (EI, *m/z*): 283.0 (M^+); HRMS (EI, *m/z*): calcd. For $C_{11}H_4F_7N$ (M^+) 283.0226, found 283.0222.

4.1.7. 6-Chloro-2,4-bis(trifluoromethyl)quinoline (4g)

White solid. M.p. 77–79 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, J = 9.0 Hz, 1H), 8.14 (s, 1H), 8.01 (s, 1H), 7.83 (dd, J = 9.1, 2.2 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −61.88 (s, 3F), −67.90 (s, 3F), ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.79 (q, J = 36.1 Hz), 146.56, 137.23, 135.89 (q, J = 32.9 Hz), 132.74 (d, J = 27.1 Hz), 123.18 (d, J = 2.4 Hz), 124.41, 122.66 (q, J = 275.9 Hz), 120.94 (q, J = 275.9 Hz), 115.86–113.87 (m). IR (film): 1608, 1493, 1459, 1272, 1192, 1137, 1100, 1075, 897, 874, 844, 792, 663, 511, 425 cm^{-1}. MS (EI, *m/z*): 298.9 (M^+); HRMS (EI, *m/z*): calcd. For $C_{11}H_4ClF_6N$ (M^+) 298.9931, found 298.9935.

4.1.8. 6-Bromo-2,4-bis(trifluoromethyl)quinoline (4h)

Yellow solid. M.p. 94–96 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 1H), 8.18 (d, J = 9.0 Hz, 1H), 8.01–7.96 (m, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −61.67 (s, 3F), −67.84 (s, 3F). ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.88 (q, J = 36.2 Hz), 146.76, 135.78 (q, J = 33.0 Hz), 135.48, 132.61, 126.51 (d, J = 2.2 Hz), 125.70, 124.79, 122.64 (q, J = 275.6, 275.1 Hz), 122.64 (q, J = 275.9 Hz), 115.15-115.04 (m). IR (film): 1602, 1521, 1491, 1458, 1273, 1193, 1140, 1098, 1067, 890, 842, 729, 668, 644, 528 cm^{-1}. MS (EI, *m/z*): 342.9 (M^+); HRMS (EI, *m/z*): calcd. For $C_{11}H_4BrF_6N$ (M^+) 342.9426, found 342.9424.

4.1.9. 6-Methyl-2,4-bis(trifluoromethyl)quinoline (4i)

White solid. M.p. 67–69 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, J = 8.7 Hz, 1H), 7.95 (d, J = 10.2 Hz, 2H), 7.74 (dd, J = 8.7, 1.9 Hz, 1H), 2.63 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −61.64 (s, 3F), −67.57 (s, 3F). ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.89, 146.54 (d, J = 36.5 Hz), 141.37, 135.64 (q, J = 32.3 Hz), 133.97, 130.78, 124.00, 123.04 (q, J = 275.1 Hz), 122.89, 121.22 (q, J = 275.9 Hz), 114.35-114.02 (m), 22.38. IR (film): 1507, 1479, 1386, 1271, 1218, 1184, 1135, 1091, 1017, 991, 913,894, 855, 717, 510 cm^{-1}. MS (EI, *m/z*): 279.0 (M^+); HRMS (EI, *m/z*): calcd. For $C_{12}H_7F_6N$ (M^+) 279.0477, found 279.0483.

4.1.10. 2,4,6-Tris(trifluoromethyl)quinoline (4j)

Yellow solid. M.p. 55–57 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, J = 9.6 Hz, 2H), 8.27–8.00 (m, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −61.72 (s, 3F), −63.47 (s, 3F), −68.41 (s, 3F). MS (EI, *m/z*): 333.0 (M^+); HRMS (EI, *m/z*): calcd. For $C_{12}H_4F_9N$ (M^+) 333.0195, found 333.0193. The characterization data are consistent with previous report [18].

4.1.11. 6-(Trifluoromethoxy)-2,4-bis(trifluoromethyl)quinoline (4k)

White solid. M.p. 52–54 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, J = 9.3 Hz, 1H), 8.06 (s, 1H), 8.00 (s, 1H), 7.79 (dd, J = 9.3, 2.6 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −57.87 (s, 3F), −62.00 (s, 3F), −67.87 (s, 3F). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.93, 148.12 (q, J = 36.2 Hz), 146.29, 136.80 (q, J = 33.0 Hz), 133.67, 125.60, 124.45, 122.64 (q, J = 275.9 Hz), 120.90 (q, J = 275.5 Hz), 120.72 (q, J = 318.8 Hz), 115.43-115,16 (m), 114.39. IR (film): 1626, 1517, 1480, 1369, 1259, 1224, 1165, 1151, 1130, 1093, 897, 857, 846, 703, 667 cm^{-1}. MS (EI, *m/z*): 349.0 (M^+); HRMS (EI, *m/z*): calcd. For $C_{12}H_4F_9NO$ (M^+) 349.0144, found 349.0139.

4.1.12. 2,4-Bis(trifluoromethyl)quinolin-6-amine (4l)

Yellow solid. M.p. 100–102 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 9.1 Hz, 1H), 7.86 (s, 1H), 7.32–7.26 (m, 1H), 7.14 (s, 1H), 4.36 (s, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −63.21 (s, 3F), −67.60 (s, 3F). ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.04, 143.35, 142.82 (q, J = 36.0 Hz), 132.82 (q, J = 32.2, 31.6 Hz), 132.53, 126.22, 123.34, 123.31 (q, J = 274.6 Hz), 121.45 (q, J = 274.7 Hz), 114.85-114.58 (m), 102.71. IR (film): 1639, 1561, 1488, 1369, 1275, 1258, 1185, 1155, 1098, 991, 860, 792, 773, 670,511, 486 cm^{-1}. MS (EI, *m/z*): 280.0 (M^+); HRMS (EI, *m/z*): calcd. For $C_{11}H_6F_6N_2$ (M^+) 280.0426, found 280.0430.

4.1.13. 7-Methyl-2,4-bis(trifluoromethyl)quinoline (4m)

Gray solid. M.p. 84–86 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 10.7 Hz, 2H), 7.93 (s, 1H), 7.64 (dd, J = 8.8, 1.8 Hz, 1H), 2.62 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −61.55 (s, 3F), −67.69 (s, 3F). ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.50, 147.50 (q, J = 35.2 Hz), 142.52, 136.32 (q, J = 32.4 Hz), 132.88, 130.04, 123.69, 123.02 (q, J = 275.1 Hz), 121.96, 121.15 (q, J = 275.4 Hz), 113.46-113.17 (m), 21.85. IR (film): 1627, 1516, 1448, 1274, 1252, 1199, 1182, 1129, 1091, 1049, 864, 823, 780, 665, 594 cm^{-1}. MS (EI, *m/z*): 279.0 (M^+); HRMS (EI, *m/z*): calcd. For $C_{12}H_7F_6N$ (M^+) 279.0477, found 279.0474.

4.1.14. 2,4-Bis(trifluoromethyl)quinolin-7-amine (4n)

Yellow solid. M.p. 120–122 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (dd, J = 9.1, 2.2 Hz, 1H), 7.69 (s, 1H), 7.35 (d, J = 2.5 Hz, 1H), 7.19 (dd, J = 9.1, 2.5 Hz, 1H), 4.32 (s, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −61.88 (s, 3F), −68.37 (s, 3F). MS (EI, *m/z*): 280.0 (M^+); HRMS (EI, *m/z*): calcd. For $C_{11}H_6F_6N_2$ (M^+) 280.0430, found 280.0435. The characterization data are consistent with previous report [6b].

4.1.15. 7-Bromo-2,4-bis(trifluoromethyl)quinoline (4o)

White solid. M.p. 68–70 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, J = 2.0 Hz, 1H), 8.10 (d, J = 9.3 Hz, 1H), 8.03 (s, 1H), 7.92 (dd, J = 9.1, 1.9 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −61.95 (s, 3F), −68.33 (s, 3F). ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.70, 148.64 (q, J = 36.2 Hz), 136.98 (q, J = 32.6 Hz), 134.16 (d, J = 2.8 Hz), 133.43 (d, J = 2.1 Hz), 126.34, 125.28, 122.66 (q, J = 274.9 Hz), 122.53, 120.81 (q, J = 275.6 Hz), 114.60-114.35 (m). IR (film): 1603, 1501, 1439, 1420, 1324, 1272, 1197, 1135, 1094, 981, 904, 861, 664, 597, 446 cm^{-1}. MS (EI, *m/z*): 342.9 (M^+); HRMS (EI, *m/z*): calcd. For $C_{11}H_4BrF_6N$ (M^+) 342.9426, found 342.9422.

4.1.16. 5-Bromo-2,4-bis(trifluoromethyl)quinoline (4o')

White solid. M.p. 72–74 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, J = 8.4 Hz, 1H), 8.25 (d, J = 7.7 Hz, 1H), 8.21 (s, 1H), 7.73 (t, J = 8.0 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −53.07 (s, 3F), −68.44 (s, 3F). MS (EI, *m/z*): 342.9 (M^+); HRMS (EI, *m/z*): calcd. For $C_{11}H_4BrF_6N$ (M^+) 342.9426, found 342.9424.

4.1.17. 7-Chloro-2,4-bis(trifluoromethyl)quinoline (**4p**)

White solid. M.p. 52–54 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, J = 2.2 Hz, 1H), 8.17 (dd, J = 9.2, 2.0 Hz, 1H), 8.02 (s, 1H), 7.79 (dd, J = 9.2, 2.1 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −61.49 (s, 3F), −67.86 (s, 3F). ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.74 (q, J = 36.5 Hz), 148.61, 138.12, 136.89 (q, J = 32.8 Hz), 131.68, 130.07, 125.38, 122.69 (q, J = 275.1 Hz), 122.27, 120.84 (q, J = 275.3 Hz), 114.49-114.24 (m). IR (film): 2957, 1609, 1503, 1443, 1274, 1245, 1130, 1096, 902, 889, 862, 735, 661, 606, 490 cm^{-1}. MS (EI, m/z): 298.9 (M^+); HRMS (EI, m/z): calcd. For $C_{11}H_4ClF_6N$ (M^+) 298.9931, found 298.9927.

4.1.18. 5- Chloro-2,4-bis(trifluoromethyl)quinoline (**4p'**)

White solid. M.p. 56–58 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, J = 8.4 Hz, 1H), 8.21 (s, 1H), 7.97 (d, J = 7.6 Hz, 1H), 7.83 (t, J = 8.0 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −54.93 (s, 3F), −68.46 (s, 3F). MS (EI, m/z): 298.9 (M^+); HRMS (EI, m/z): calcd. For $C_{11}H_4ClF_6N$ (M^+) 298.9931, found 298.9928.

4.1.19. 6-Fluoro-8-iodo-2,4-bis(trifluoromethyl)quinoline (**4q**)

White solid. M.p. 99–101 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47–8.21 (m, 1H), 8.08 (s, 1H), 7.96–7.77 (m, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −61.74 (s, 3F), −67.52 (s, 3F), −104.56 (t, J = 8.3 Hz,1F). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.87 (d, J = 258.9 Hz), 147.71 (qd, J = 37.1, 3.4 Hz), 144.64, 137.25 (qd, J = 33.4, 6.5 Hz), 133.04 (d, J = 27.5 Hz), 124.68 (d, J = 10.9 Hz), 122.44 (q, J = 275.9 Hz), 120.68 (q, J = 275.9 Hz), 116.14–115.73 (m), 108.78 (dd, J = 24.1, 2.1 Hz), 106.59 (d, J = 9.3 Hz). IR (film): 1610, 1566, 1458, 1266, 1224, 1173, 1130, 1101, 884, 861, 825, 780, 728, 678, 508 cm^{-1}. MS (EI, m/z): 408.9 (M^+); HRMS (EI, m/z): calcd. For $C_{11}H_3F_7IN$ (M^+) 408.9193, found 408.9188.

4.1.20. 6,8-Dichloro-2,4-bis(trifluoromethyl)quinoline (**4r**)

White solid. M.p. 58–60 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 2H), 8.02 (d, J = 2.1 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −61.47 (s, 3F), −67.65 (s, 3F). ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.05 (q, J = 37.1 Hz), 143.34, 137.18, 136.57 (q, J = 32.9 Hz), 136.71 (d, J = 3.0 Hz), 132.69, 125.50, 122.42 (d, J = 275.9 Hz), 120.72 (q, J = 275.4 Hz), 122.07 (d, J = 3.3 Hz), 116.27-116.01 (m). IR (film): 1598, 1565, 1454, 1266, 1195, 1174, 1120, 1085, 896, 863, 787, 673, 576, 508, 434 cm^{-1}. MS (EI, m/z): 332.9 (M^+); HRMS (EI, m/z): calcd. For $C_{11}H_3Cl_2F_6N$ (M^+) 332.9541, found 332.9539.

4.1.21. 2,4-Bis(trifluoromethyl)benzo[h]quinoline (**4s**)

White solid. M.p. 118–120 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.38 (d, J = 7.3 Hz, 1H), 8.14 (s, 1H), 8.12–8.02 (m, 2H), 8.02–7.96 (m, 1H), 7.87–7.82 (m, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −60.93 (s, 3F), −67.30 (s, 3F). MS (EI, m/z): 315.0 (M^+); HRMS (EI, m/z): calcd. For $C_{15}H_7F_6N$ (M^+) 315.0477, found 315.0474. The characterization data are consistent with previous report [17c].

4.1.22. 9-Methyl-2,4-bis(trifluoromethyl)-1,10-phenanthroline (**4t**)

Brown solid. M.p. 120–122 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (td, J = 4.3, 2.3 Hz, 2H), 8.18–8.10 (m, 1H), 8.07 (dd, J = 9.4, 2.2 Hz, 1H), 7.69–7.61 (m, 1H), 3.00 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −61.35 (s, 3F), −67.00 (s, 3F). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.54, 147.23 (q, J = 36.2 Hz), 146.54, 144.87, 136.49, 136.61 (q, J = 32.8 Hz), 131.05, 127.11, 125.58, 125.47, 122.96 (q, J = 275.4 Hz), 121.35 (q, J = 274.7 Hz) 120.43, 116.06-115.80 (m), 25.83. IR (film): 1609, 1331, 1162, 1128, 1103, 1077, 970, 901, 807, 776, 744, 663, 635, 580, 455 cm^{-1}. MS (EI, m/z): 330.0 (M^+); HRMS (EI, m/z): calcd. For $C_{15}H_8F_6N_2$ (M^+) 330.0586, found 330.0584.

4.1.23. 7,9-Bis(trifluoromethyl)thiazolo [4,5-f]quinoline (**4u**)

Yellow solid. M.p. 136–138 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.27 (s, 1H), 8.44 (d, J = 9.0 Hz, 1H), 8.34 (d, J = 8.9 Hz, 1H), 8.29 (s, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −61.70 (s, 3F), −67.99 (s, 3F). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.37, 148.76, 147.27 (q, J = 35.8 Hz), 146.20, 136.78, 135.49 (q, J = 34.9, 34.4 Hz), 128.81, 125.08, 122.94 (q, J = 275.9 Hz), 121.14 (q, J = 275.9 Hz) 120.72, 116.31-116.12 (m). IR (film): 3077, 1498, 1422, 1384, 1265, 1204, 1163, 1145, 1119, 833, 794, 773, 731, 694, 585 cm^{-1}. MS (EI, m/z): 321.9 (M^+); HRMS (EI, m/z): calcd. For $C_{12}H_4F_6N_2S$ (M^+) 321.9994, found 321.9990.

4.1.24. 2,4-Bis(trifluoromethyl)benzo[c] [1,5]naphthyridine (**4v**)

White solid. M.p. 134–136 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.55 (s, 1H), 9.25 (d, J = 8.2 Hz, 1H), 8.26 (s, 1H), 8.19 (d, J = 8.0 Hz, 1H), 8.06 (t, J = 7.5 Hz, 1H), 7.96 (t, J = 7.6 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −61.73(s, 3F), −67.67 (s, 3F). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.65, 146.92 (q, J = 36.1 Hz), 142.55, 137.36 (q, J = 31.9 Hz), 136.22, 132.88, 132.61, 131.05, 128.63, 128.43, 124.33, 122.64 (q, J = 275.9Hz), 121.14 (q, J = 275.9Hz), 117.00-116.71(m). IR (film): 1366, 1271, 1206, 1185, 1089, 1062, 846, 824, 767, 715, 612, 590, 518, 499, 484 cm^{-1}. MS (EI, m/z): 316.0 (M^+); HRMS (EI, m/z): calcd. For $C_{14}H_6F_6N_2$ (M^+) 316.0430, found 316.0432.

4.1.25. 5,7-Bis(trifluoromethyl)-1,8-naphthyridin-2-amine (**4w**)

Yellow solid. M.p. 188–190 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (dd, J = 9.3, 1.9 Hz, 1H), 7.75 (s, 1H), 7.01 (d, J = 9.2 Hz, 1H), 5.79 (s, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −60.77 (s, 3F), −68.11 (s, 3F). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.52, 156.75, 150.18 (q, J = 36.1, 35.7 Hz), 137.24 (q, J = 32.3, 31.8 Hz), 134.23, 122.67 (q, J = 274.7 Hz), 120.84 (q, J = 275.9 Hz), 116.35, 114.54, 110.95-110.64 (m). IR (film): 1632, 1593, 1570, 1427, 1384, 1274, 1189,1118, 978, 870, 835, 783, 696, 663, 469 cm^{-1}. MS (EI, m/z): 281.0 (M^+); HRMS (EI, m/z): calcd. For $C_{10}H_5F_6N_3$ (M^+) 281.0382, found 281.0388.

4.1.26. 2,4-Bis(difluoromethyl)quinoline (**5a**)

White solid. M.p. 50–52 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (dd, J = 8.6, 1.3 Hz, 1H), 8.15 (dd, J = 8.5, 1.7 Hz, 1H), 7.92 (s, 1H), 7.87 (ddd, J = 8.4, 6.9, 1.4 Hz, 1H), 7.75 (ddd, J = 8.4, 7.0, 1.3 Hz, 1H), 7.20 (t, J = 54.3 Hz, 1H), 6.81 (t, J = 55.1 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −114.95 (d, J = 54.9 Hz,2F), −115.67 (d, J = 54.5 Hz, 2F). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.64 (t, J = 27.1 Hz), 147.73, 139.87 (t, J = 22.0 Hz), 130.86, 130.76, 129.28, 124.78, 123.50, 114.31, 114.31 (t, J = 241.3 Hz), 113.07 (t, J = 240.9 Hz). IR (film): 1615, 1513, 1470, 1384, 1357, 1324, 1173, 1119, 1088, 963, 904, 797, 727, 698, 596 cm^{-1}. MS (EI, m/z): 229.0 (M^+); HRMS (EI, m/z): calcd. For $C_{11}H_7F_4N$ (M^+) 229.0509, found 229.0508.

4.1.27. 2,4-Bis(difluoromethyl)-6-methylquinoline (**5b**)

White solid. M.p. 65–67 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 8.7 Hz, 1H), 7.86 (s, 2H), 7.67 (dd, J = 8.6, 1.7 Hz, 1H), 7.15 (t, J = 54.4 Hz, 1H), 6.78 (t, J = 55.1 Hz, 1H), 2.59 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −114.27 (d, J = 55.1 Hz, 2F), −115.36 (d, J = 54.5 Hz, 2F). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.65 (t, J = 27.1 Hz), 146.37, 139.77, 138.98 (t, J = 22.1 Hz), 133.14, 130.35, 124.86, 122.31, 114.18 (t, J = 8.2 Hz), 114.41 (t, J = 241.3 Hz), 113.13 (t, J = 240.8 Hz), 22.22. IR (film): 2923, 1505, 1478, 1381, 1353, 1212, 1146, 1114, 1091, 1028, 1001, 968, 825, 744, 553 cm^{-1}. MS (EI, m/z): 243.0 (M^+); HRMS (EI, m/z): calcd. For $C_{12}H_9F_4N$ (M^+) 243.0666, found 243.0662.

4.1.28. 2,4-Bis(difluoromethyl)-7-methylquinoline (**5c**)

White solid. M.p. 70–72 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 11.1 Hz, 2H), 7.85 (s, 1H), 7.57 (dd, J = 8.7, 1.8 Hz, 1H), 7.16 (t, J = 54.4 Hz, 1H), 6.79 (t, J = 55.2 Hz, 1H), 2.61 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −114.46 (d, J = 55.2 Hz, 2F), −115.13 (d, J = 54.5 Hz, 2F).^{13}C NMR (126 MHz, $CDCl_3$) δ 152.59 (t, J = 27.1 Hz), 148.04, 141.50, 139.60 (t, J = 22.1 Hz), 131.5, 129.66, 123.08, 122.80, 114.38 (t, J = 241.9 Hz), 113.35 (t, J = 7.9 Hz), 113.15 (t, J = 241.0 Hz), 21.87. IR (film): 1626, 1515, 1457, 1384, 1323, 1180, 1121, 1030, 893,

793, 747, 669, 626, 554, 528 cm^{-1}. MS (EI, *m/z*): 243.0 (M^+); HRMS (EI, *m/z*): calcd. For $C_{12}H_9F_4N$ (M^+) 23.0666, found 243.0663.

4.1.29. 2,4-Bis(difluoromethyl)-8-methylquinoline (5d)

White solid. M.p. 34–36 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.01–7.85 (m, 2H), 7.69 (d, J = 7.0 Hz, 1H), 7.61 (t, J = 7.7 Hz, 1H), 7.18 (t, J = 54.4 Hz, 1H), 6.82 (t, J = 55.2 Hz, 1H), 2.83 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −113.76 (d, J = 55.2 Hz, 2F), −115.26 (d, J = 54.4 Hz, 2F). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.30 (t, J = 27.3 Hz), 146.77, 139.84 (t, J = 21.7 Hz), 139.13, 130.87, 128.99, 124.86, 121.10, 114.75 (t, J = 240.9 Hz), 113.75 (t, J = 8.3 Hz), 113.10 (t, J = 241.2 Hz), 18.23. IR (film): 1516, 1474, 1392, 1353, 1308, 1256, 1229, 1096, 1054, 1022, 877, 853, 804, 764, 563 cm^{-1}. MS (EI, *m/z*): 243.0 (M^+); HRMS (EI, *m/z*): calcd. For $C_{12}H_9F_4N$ (M^+) 243.0666, found 243.0672.

4.1.30. 2,4,8,10-Tetrakis(difluoromethyl)-1,7-phenanthroline (6)

Yellow solid. M.p. 135–137 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.62 (t, J = 54.5 Hz, 1H), 8.44 (s, 1H), 8.38 (s, 2H), 8.17 (s, 1H), 7.29 (t, J = 54.1 Hz, 1H), 6.95 (t, J = 55.1 Hz, 1H), 6.90 (t, J = 54.9 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −114.88 (d, J = 54.3 Hz, 2F), −115.86 (d, J = 54.9 Hz, 2F), −116.04 (d, J = 55.1 Hz, 2F), −117.43 (d, J = 54.5 Hz, 2F). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.94 (t, J = 27.0 Hz), 151.85 (t, J = 26.7 Hz), 149.99, 145.59, 143.56 (t, J = 22.8 Hz), 140.45 (t, J = 22.6 Hz), 132.55, 125.41, 125.23, 124.53, 116.78–116.31 (m), 116.10 (d, J = 9.1 Hz), 113.73 (t, J = 241.9 Hz), 113.29 (t, J = 242.4 Hz), 112.73 (t, J = 241.9 Hz), 111.60 (t, J = 240.1 Hz). IR (film): 1448, 1365, 1291, 1254, 1191, 1031, 997, 916, 885, 786, 765, 733, 689, 657, 538 cm^{-1}. MS (EI, *m/z*): 380.0 (M^+); HRMS (EI, *m/z*): calcd. For $C_{16}H_8F_8N_2$ (M^+) 380.0554, found 380.0549.

4.1.31. 2,2,2-Trifluoro-1-(4-methyl-2-(trifluoromethyl)quinolin-3-yl) ethan-1-one (8)

Yellow solid. M.p. 44–46 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, J = 8.4 Hz, 1H), 8.15 (d, J = 8.5 Hz, 1H), 7.97–7.88 (m, 2H), 7.84–7.77 (m, 1H), 2.71 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −63.88 (s 3F), −76.72 (s, 3F). ^{13}C NMR (126 MHz, $CDCl_3$) δ 186.59 (q, J = 39.1, 38.6 Hz), 146.79, 145.74, 143.40 (q, J = 34.0 Hz), 132.38, 131.09, 130.07, 127.48, 124.21, 120.92 (q, J = 277.2 Hz), 115.39 (q, J = 291.6 Hz), 16.29. IR (film): 1755, 1567, 1385, 1219, 1192, 1149, 1131, 1090, 956, 907, 873, 806, 765, 752,590 cm^{-1}. MS (ESI, *m/z*): 308.0 $[M+H]^+$; HRMS (ESI, *m/z*): calcd. For $C_{13}H_8F_6NO^+$ $[M+H]^+$ 308.0505, found 308.0507.

CRediT authorship contribution statement

Yafen He: Writing – original draft, Investigation. **Wei Zhang:** Writing – review & editing, Supervision. **Jinbo Hu:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

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[25]. CCDC 2344112 (**4f**), CCDC 2344114 (**5a**) and CCDC 2344115 (**6**) contain crystallographic data for this paper in the Supplementary data. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.