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Graphical Abstract

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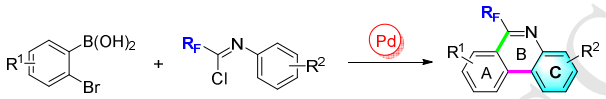

√ Pd-catalyzed √ readily functionalization on C ring √ 20 examples
√ yield up to 97% √ dual C-C bond fromation √ oxidant-free

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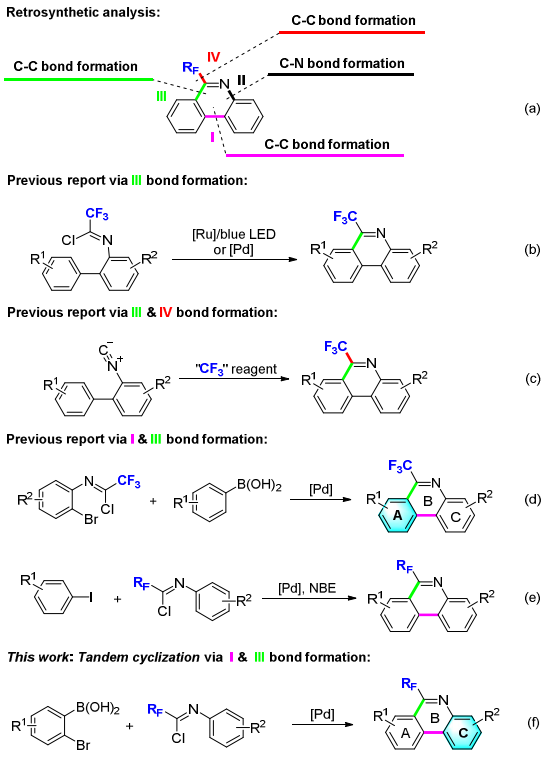
ABSTRACT

An efficient method has been developed to synthesize 6-fluoroalkyl-phenanthridines via the palladium-catalyzed tandem cyclization of fluorinated imidoyl chlorides with 2-bromophenylboronic acid. This methodology facilitates the rapid synthesis of 6-fluoroalkyl-phenanthridines through dual C–C bond formation in an oxidant-free *one-pot* manner.

1. Introduction

Phenanthridines are ubiquitous fused-heterocyclic motifs found in many biologically active molecules,[1] pharmaceuticals and natural products.[2] In particular, fluoroalkyl-containing phenanthridines often increase metabolic stability and lipophilicity, which have the potential to improve their biological functions.[3] Hence, it is essential to explore efficient methodologies for the synthesis of 6-fluoroalkyl-phenanthridines and consequently many powerful synthetic strategies have been developed in this area.[4-9] The retrosynthetic analysis of 6-fluoroalkyl-phenanthridines can be oriented to C–C bond (I, III, and IV, Scheme 1a) and C–N bond formations (II, Scheme 1a). Utilizing an one bond formation strategy, Fu and co-workers[4] developed intramolecular cyclization of N-biaryltrifluoroacetimidoyl chloride to realize **III** bond formation for the construction of 6-trifluoromethyl-phenanthridines (Scheme 1b), but the low bonding efficiency limits its application. Presently, a strategy to synthesize 6-trifluoromethyl-phenanthridines via two or more chemical bond formations in a single step is desired. For instance, Studer[5] and others[6] achieved trifluoromethylation of 2-arylisocyanides by using radical trifluoromethylating reagents, where **III** and **IV** bonds were formed (Scheme 1c). For the formation of **I** and **III** bonds, Zhang and co-workers[7] developed a tandem Suzuki/C–H arylation reaction of N-(2-bromophenyl)-trifluoroacetimidoyl chlorides with arylboronic acids to prepare 6-trifluoromethyl-phenanthridines (Scheme 1d). However, the requirement of a stoichiometric oxidant limits its application and



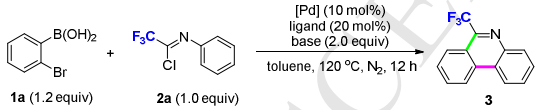
Scheme 1. Retrosynthetic analysis for the construction of 6-fluoroalkyl-phenanthridines

compared to the functionalization on the A ring. The functionalization on the C ring is difficult due to the starting materials not being readily available. Very recently, our group[8] developed a palladium-catalyzed norbornene-mediated dehydrogenative annulation approach to synthesize 6-fluoroalkyl-phenanthridines from aryl iodides and fluorinated imidoyl chlorides (Scheme 1e). As a continuation of our interest in the synthesis of halogen-containing heterocycles,[8, 10] we hope to develop new approaches for the synthesis of 6-fluoroalkyl-phenanthridines via **I** and **III** bond formation in a *one-pot* system. We envision that biologically relevant 6-fluoroalkyl-phenanthridines can be obtained from the combination of fluorinated imidoyl chlorides and 2-bromophenylboronic acid through a palladium-catalyzed tandem cyclization reaction and believe that functionalization on the C ring is easier compared to Zhang's work.[7] (Scheme 1f).

2. Results/Discussion

Initially, the reaction of 2-bromophenylboronic acid **1a** with fluorinated imidoyl chloride **2a**, was conducted under a nitrogen atmosphere with 10 mol% $Pd(OAc)_2$ as the catalyst and 20 mol% PPh_3 as the ligand in the presence of Cs_2CO_3 (base) in toluene at 120 °C. After 12 h, the desired product **3** was obtained in 51% isolated yield (Table 1, entry 1). Screening of bases revealed Cs_2CO_3 to be the optimal base (Table 1, entries 2-5). Subsequently, a series of ligands including diphosphines and monophosphines were evaluated for this transformation, and to our delight, the yield of **3** was significantly increased to 81% with the use of P(4-F-C_6H_4)$_3$ as the ligand (Table 1, entries 6-12). To further improve the yield, a range of solvents were tested, including MeCN, DMF, *o*-xylene, and DCE, but toluene was found to be most efficient (compare entry 8 with entries 13-16). Among the Pd(0) and Pd(II) catalysts investigated, Pd(II) catalysts were found to be the most efficient (Table 1, entries 17-20). It is worth noting that 97% yield could be obtained via the catalysis with $PdCl_2(PPh_3)_2$ (Table 1, entry 20). Further investigation regarding the ratio of **1a** and **2a** did not give a better result (Table 1, entry 21). In addition, lowering the reaction temperature to 100 °C gave an inferior result (Table 1, entry 22). Finally, the reaction of **1a** (1.2 equiv) with **2a** (1.0 equiv) in the presence of $PdCl_2(PPh_3)_2$ (10 mol%) and Cs_2CO_3 (2.0 equiv) in toluene under nitrogen atmosphere at 120 ℃ for 12 h was the optimal condi tion.

Table 1. Optimization of reaction conditions[a].

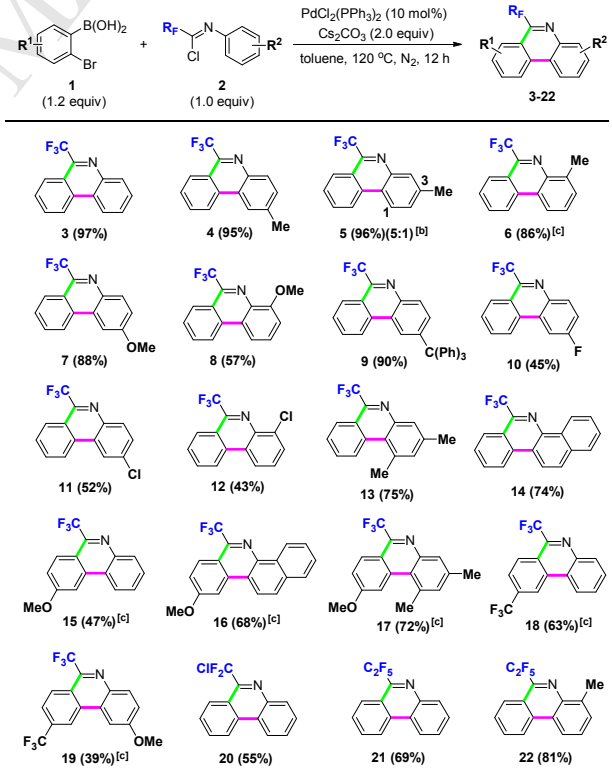


1a (1.2 equiv) **2a** (1.0 equiv) **3**

entry	[Pd]	ligand	base	yield(%) [b]
1	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	51%
2	$Pd(OAc)_2$	PPh_3	Na_2CO_3	ND[c]
3	$Pd(OAc)_2$	PPh_3	K_3PO_4	ND[c]
4	$Pd(OAc)_2$	PPh_3	NaOH	ND[c]
5	$Pd(OAc)_2$	PPh_3	KOAc	25%
6	$Pd(OAc)_2$	P(2-Me-C_6H_4)$_3$	Cs_2CO_3	ND[c]
7	$Pd(OAc)_2$	P(4-Me-C_6H_4)$_3$	Cs_2CO_3	ND[c]
8	$Pd(OAc)_2$	P(4-F-C_6H_4)$_3$	Cs_2CO_3	81%
9	$Pd(OAc)_2$	P(4-CF_3-C_6H_4)$_3$	Cs_2CO_3	62%
10[d]	$Pd(OAc)_2$	DPPF	Cs_2CO_3	50%
11[d]	$Pd(OAc)_2$	DPPE	Cs_2CO_3	25%
12[d]	$Pd(OAc)_2$	DPPB	Cs_2CO_3	36%
13[e]	$Pd(OAc)_2$	P(4-F-C_6H_4)$_3$	Cs_2CO_3	53%
14[f]	$Pd(OAc)_2$	P(4-F-C_6H_4)$_3$	Cs_2CO_3	ND[c]
15[g]	$Pd(OAc)_2$	P(4-F-C_6H_4)$_3$	Cs_2CO_3	33%
16[h]	$Pd(OAc)_2$	P(4-F-C_6H_4)$_3$	Cs_2CO_3	15%
17	$Pd(PPh_3)_4$	------	Cs_2CO_3	61%
18	$Pd_2(dba)_3$	------	Cs_2CO_3	ND[c]
19	$Pd(dppf)Cl_2$	------	Cs_2CO_3	45%
20	**$PdCl_2(PPh_3)_2$**	**------**	**Cs_2CO_3**	**97%**
21[i]	$PdCl_2(PPh_3)_2$	------	Cs_2CO_3	82%
22[j]	$PdCl_2(PPh_3)_2$	------	Cs_2CO_3	79%

[a] Reaction Conditions: the reactions were carried out with **1a** (0.48 mmol), **2a** (0.4 mmol), [Pd] (0.04 mmol), ligand (0.08 mmol), base (0.8 mmol), toluene (3.0 mL) under a nitrogen atmosphere for 12 h. [b] isolated yield. [c] ND = not detected. [d] ligand (10 mol %). [e] MeCN 3.0 mL. [f] DMF 3.0 mL. [g] *o*-xylene 3.0 mL. [h] DCE 3.0 mL. [i] **1a** (0.4 mmol), **2a** (0.6 mmol). [j] the reaction was run at 100 °C.

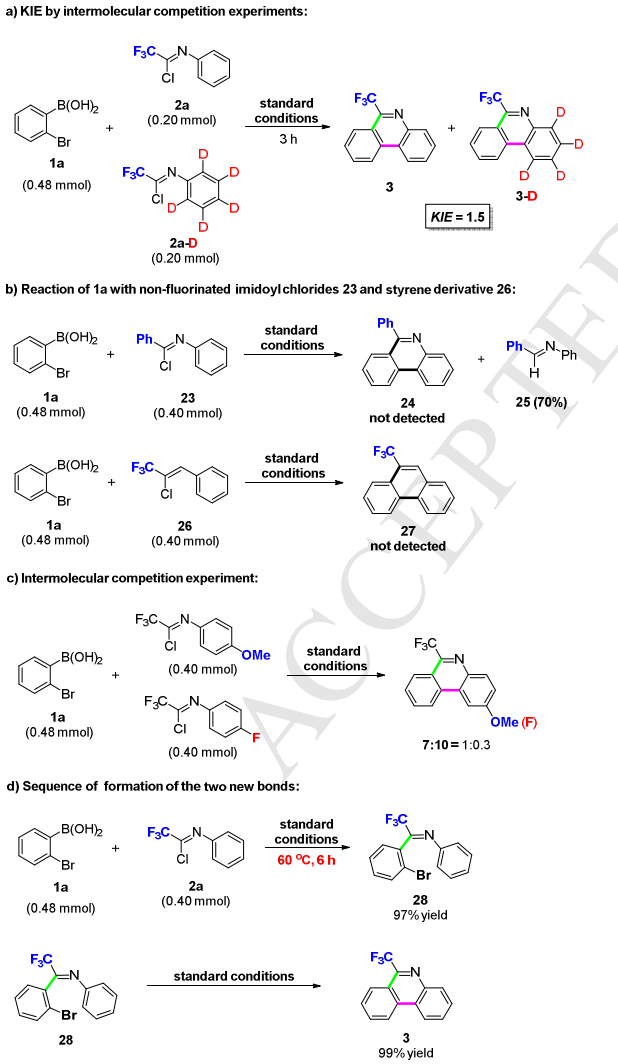
Table 2. Substrate scope of the reaction[a].



[a] Reaction conditions: the reactions were carried out with **1** (0.48 mmol), **2** (0.4 mmol), $PdCl_2(PPh_3)_2$ (0.04 mmol), Cs_2CO_3 (0.8 mmol) in toluene (3.0 mL) under a nitrogen atmosphere for 12 h. [b] Regioselectivity ratio (the major isomer is substituted at the 3-position as indicated，major isomer: 80% yield, minor isomer: 16% yield). [c] Cs_2CO_3 (6.0 equiv)

With the optimized reaction conditions known, we next surveyed the substrate scope of this reaction (Table 2).

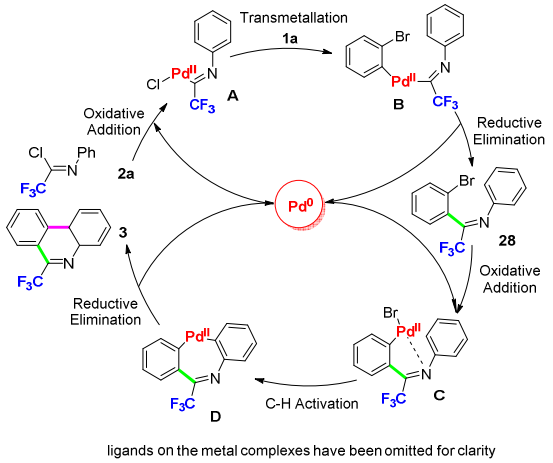
First, a variety of fluorinated imidoyl chlorides were investigated, which could be easily prepared from fluorinated carboxylic acids and the corresponding aniline. *p*-, *m*-, *o*-methyl substituents on the phenyl ring of **2** were well tolerated, and the desired 6-fluoroalkyl-phenanthridines **4**-**6** were isolated in 86%-96% yields. Among them, **5** was obtained with good regioselectivity (5:1) when *m*-methyl-substituted substrate was used. Moreover, various fluorinated imidoyl chlorides containing electron-donating (-OMe, -C(Ph)$_3$) and electron-withdrawing (-F, -Cl) substituents attached at the *o*- and *p*-position participated in this reaction, producing the desired products in moderate to good yields (**7**-**12**). Fluorinated imidoyl chloride with multiple substituents was also employed, providing **13** in 75% yield. Likewise, 6-(trifluoromethyl)benzo[c]phenanthridine, **14**, was also obtained (74% yield) in our reaction system. Subsequently, various substituents on the 2-bromophenylboronic acid were tested, along with multi-substituted fluorinated imidoyl chlorides, and all of them reacted efficiently, providing the corresponding products **15**-**19** in 39%-72% yield. Notably, in addition to CF_3, different fluorine-containing groups, such as CF_2Cl, CF_2CF_3 could also be introduced on phenanthridines through this transformation (**20**-**22**). It should be noted that, in some cases, 6.0 equiv of Cs_2CO_3 were required to achieve satisfactory results.



Scheme 2. Control experiments

To gain more insight into the details of this transformation, a series of control experiments were carried out. First, to understand the C–H activation process, the kinetic isotope effect (KIE) was measured by intermolecular competition experiments under the standard conditions, and the KIE value was found to be 1.5, which suggested the C–H bond cleavage was not involved in the rate-determining step of the catalytic cycle (Scheme 2a). When non-fluorinated imidoyl chloride **23** was used instead of **2**, the corresponding annulation product **24** was not detected in the reaction, and ca. 70% yield of **25** was isolated. It is likely that the strong electron-withdrawing ability of the CF_3 group is essential to activate the C–Cl bond.[11] Furthermore, the cyclization product **27** was not detected with styrene derivative **26** as the substrate, which signified that the imine group may played a key role in promoting oxidative addition and the C–H activation processes via the coordination with Pd species (Scheme 2b). Intermolecular competition experiments between electronically distinct substituted fluorinated imidoyl chlorides were attempted and substrates with electron-donating groups were preferentially converted (Scheme 2c). To further validate the sequence of the formation of the two new chemical bonds, two control experiments were conducted. First, with the reaction between **1a** and **2a** under standard conditions at 60 °C for 6 h, **3** was not detected, while **28** was isolated in 97% yield. Subsequently, **28** could be converted into the corresponding 6-fluoroalkyl-phenanthridine in 99% yield under standard conditions at 120 °C, which demonstrated the preferential formation of **III** bond.

On the basis of these results and previous reports,[7] a possible mechanism is proposed in Scheme 3. The reaction may proceed through a Pd(0)/Pd(II) pathway although a Pd(II)/Pd(IV) pathway could not be dismissed.[12, 13] First, Pd(0) reacts with fluorinated imidoyl chloride **2a** to produce the Pd(II) intermediate **A** via oxidative addition. This is followed by transmetallation with **1a** to form the Pd(II) intermediate **B**, and the following C–Pd(II)–C reductive elimination affords **28** and regenerates the Pd(0) catalyst. Subsequently, the oxidative addition of the C–Br bond, followed by C–H activation can provide a seven-membered metallacyclic Pd(II) intermediate **D**, which undergoes reductive elimination to give the desired product **3** and regenerates the Pd(0) catalyst species to complete the catalytic cycle. Further study on the details of the mechanism is in process.



Scheme 3. Possible mechanism

3. Conclusion

In conclusion, we have developed a Pd-catalyzed tandem cyclization of fluorinated imidoyl chlorides using 2-bromophenylboronic acid for the synthesis 6-fluoroalkyl-phenanthridines without the use of an oxidant. Fluorinated imidoyl chlorides served as fluorine-containing synthons for the construction of fluorinated heterocycles, which could be easily prepared from simple starting materials. Therefore, this strategy can be considered as a route for the synthesis of 6-fluoroalkyl-phenanthridines.

4. Experimental Section

4.1. General information:

The ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR were recorded with Bruker 400 MHz spectrometer instruments in $CDCl_3$. The chemical shifts (δ) of ^{1}H NMR and ^{13}C NMR were measured in ppm, referenced to residual ^{1}H and ^{13}C signals of nondeuterated $CDCl_3$ (δ = 7.26 and 77.00), as internal standards. All solvents were obtained from commercial sources and were purified according to standard procedures. Purification of products was accomplished by flash chromatography using silica gel (200~300 mesh). Thin layer chromatography (TLC) was performed on Merck silica gel GF254 plates and visualized by UV-light (254 nm). Melting points were obtained on a Yanaco-241 apparatus and are uncorrected. HRMS were recorded on VG ZAB-HS mass spectrometer with ESI resource. Substituted imidoyl chlorides were synthesized according to the literature procedures.[8] Other substituted 2-bromophenylboronic acids were commercially available.

*4.2 General procedure for the synthesis of **3-22***

A sealed tube contained $PdCl_2(PPh_3)_2$ (10 mol %, 0.04 mmol) and Cs_2CO_3 (0.8 ~ 2.4 mmol) was evacuated and purged with nitrogen gas three times. Then, **1** (0.48 mmol) and **2** (0.4 mmol) in toluene (3.0 mL) were added to the system via syringe under a nitrogen atmosphere and the reaction was allowed to stir at 120 °C for 12 h. The reaction solution was concentrated in vacuo and the residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 100:1) to afford the desired pure products **3-22**.

*4.2.1 6-(trifluoromethyl)phenanthridine **(3)***

White solid (96 mg, 97%). M.p.: 63-65 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (d, *J* = 8.4 Hz, 1H), 8.63 – 8.59 (m, 1H), 8.42 – 8.36 (m, 1H), 8.32 – 8.27 (m, 1H), 7.96 – 7.90 (m, 1H), 7.85 – 7.75 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.55 (q, *J* = 32.8 Hz), 141.81, 134.00, 131.35, 131.18, 129.32, 129.20, 128.05, 125.95 (q, *J* = 3.0 Hz), 125.14, 122.54, 122.06, 121.95 (q, *J* = 277.1 Hz), 121.81. ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.45 (s). ESI-MS: Calcd for $C_{14}H_8F_3N$: $[M+H^+]$ 248.0682, found 248.0680.

*4.2.2 2-methyl-6-(trifluoromethyl)phenanthridine **(4)***

White solid (99 mg, 95%). M.p.: 65-67 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, *J* = 8.4 Hz, 1H), 8.39 – 8.28 (m, 2H), 8.14 (d, *J* = 8.4 Hz, 1H), 7.90 – 7.80 (m, 1H), 7.72 (m, 1H), 7.60 (dd, *J* = 8.4, 1.6 Hz, 1H), 2.63 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.46 (q, *J* = 32.8 Hz), 140.00, 139.45, 133.54, 131.02, 131.00, 130.71, 127.80, 125.73 (q, *J* = 3.3 Hz), 124.88, 122.40, 122.02 (q, *J* = 276.8 Hz), 121.76, 121.57, 22.07. ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.30 (s). ESI-MS: Calcd for $C_{15}H_{10}F_3N$: $[M+H^+]$ 262.0838, found 262.0840.

*4.2.3 3-methyl-6-(trifluoromethyl)phenanthridine **(5)***

White solid (100 mg, 96%). M.p.: 64-66 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.96 (d, *J* = 8.6 Hz, 0.2 H), 8.66 (d, *J* = 8.4 Hz, 1H), 8.48 (d, *J* = 8.4 Hz, 1H), 8.43 (d, *J* = 8.4 Hz, 0.22H), 8.36 (d, *J* = 8.4 Hz, 1H), 8.19 (d, *J* = 7.9 Hz, 0.2H), 8.09 (s, 1H), 7.91 (m, 1.18H), 7.81 – 7.67 (m, 1.41H), 7.66 – 7.57 (m, 1.16H), 3.13 (s, 0.6H), 2.61 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.50 (q, *J* = 32.8 Hz), 143.31, 141.96, 139.69, 135.23, 135.06, 134.06, 133.45, 131.24, 130.98, 130.61, 130.44, 130.10, 128.40, 127.56, 127.20, 126.94, 125.90 (q, *J* = 3.2 Hz), 125.81 (q, *J* = 3.6 Hz), 122.82, 122.68, 122.35, 121.99 (q, *J* = 277.1 Hz), 121.81, 121.52, 26.66, 21.40. ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.33 (s), -63.44 (s). ESI-MS: Calcd for $C_{15}H_{10}F_3N$: $[M+H^+]$ 262.0838, found 262.0840.

*4.2.4 4-methyl-6-(trifluoromethyl)phenanthridine **(6)***

White solid (90 mg, 86%). M.p.: 53-55 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, *J* = 8.4 Hz, 1H), 8.43 – 8.34 (m, 2H), 7.91 – 7.84 (m, 1H), 7.77 – 7.71 (m, 1H), 7.66 – 7.61 (m, 2H), 2.90 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.82 (q, *J* = 32.9 Hz), 140.53, 139.44, 134.24, 130.91, 129.89, 128.74, 127.73, 125.71 (q, *J* = 3.3 Hz), 124.98, 122.72, 122.10 (q, *J* = 277.0 Hz), 121.51, 119.70, 17.93. ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.43 (s). ESI-MS: Calcd for $C_{15}H_{10}F_3N$: $[M+H^+]$ 262.0838, found 262.0840.

*4.2.5 2-methoxy-6-(trifluoromethyl)phenanthridine **(7)***

White solid (98 mg, 88%). M.p.: 103-105 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, *J* = 8.4 Hz, 1H), 8.36 (d, *J* = 8.4 Hz, 1H), 8.20 (d, *J* = 9.0 Hz, 1H), 7.93 – 7.85 (m, 2H), 7.81 – 7.69 (m, 1H), 7.43 (dd, *J* = 9.0, 2.7 Hz, 1H), 4.05 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.19, 143.96 (q, *J* = 32.8 Hz), 137.07, 133.33, 132.65, 130.80, 128.10, 126.57, 125.86 (q, *J* = 3.3 Hz), 122.54, 122.17 (q, *J* = 276.7 Hz), 122.02, 119.38, 102.87, 55.74. ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.18 (s). ESI-MS: Calcd for $C_{15}H_{10}F_3NO$: $[M+H^+]$ 278.0787, found 278.0786.

*4.2.6 4-methoxy-6-(trifluoromethyl)phenanthridine **(8)***

White solid (63 mg, 57%). M.p.: 105-107 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (d, *J* = 8.4 Hz, 1H), 8.44 – 8.36 (m, 1H), 8.18 (d, *J* = 8.1 Hz, 1H), 7.95 – 7.88 (m, 1H), 7.81 – 7.69 (m, 2H), 7.21 (d, *J* = 7.9 Hz, 1H), 4.14 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.71, 145.06 (q, *J* = 33.3 Hz), 133.94, 132.92, 131.28, 129.75, 128.22, 126.59, 125.87 (q, *J* = 3.2 Hz), 123.09, 122.02 (q, *J* = 276.8 Hz), 121.97, 113.80, 109.02, 56.49. ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.02 (s). ESI-MS: Calcd for $C_{15}H_{10}F_3NO$: $[M+H^+]$ 278.0787, found 278.0786.

*4.2.7 6-(trifluoromethyl)-2-tritylphenanthridine **(9)***

Yellow solid (176 mg, 90%). M.p.: 160-162 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.18 (td, *J* = 7.4, 1.2 Hz, 1H), 7.14 (dd, *J* = 7.8, 1.9 Hz, 1H), 7.12 – 7.05 (m, 10H), 6.99 – 6.97 (m, 5H), 6.95 – 6.90 (m, 2H), 6.65 (d, *J* = 8.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.86 (q, *J* = 35.3 Hz), 146.44, 145.01, 144.26, 133.01, 132.76, 131.33, 131.29, 131.07, 130.29, 127.41, 127.19, 126.00, 121.41, 120.08, 119.34 (q, *J* = 279.2 Hz), 64.58. ^{19}F NMR (376 MHz, $CDCl_3$) δ -70.11 (s). ESI-MS: Calcd for $C_{33}H_{22}F_3N$: $[M+H^+]$ 490.1777, found 490.1776.

*4.2.8 2-fluoro-6-(trifluoromethyl)phenanthridine **(10)***

White solid (48 mg, 45%). M.p.: 84-86 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, *J* = 8.4 Hz, 1H), 8.39 (d, *J* = 8.4 Hz, 1H), 8.29 (dd, *J* = 9.0, 5.6 Hz, 1H), 8.20 (dd, *J* = 9.9, 2.7 Hz, 1H), 7.97 – 7.91 (m, 1H), 7.84 – 7.78 (m, 1H), 7.55 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.68 (d, *J* = 250.6 Hz), 145.90 (q, *J* = 33.3 Hz), 138.63, 133.60 (d, *J* = 9.5 Hz), 133.41 (d, *J* = 4.4 Hz), 131.42, 128.73, 126.79 (d, *J* = 9.5 Hz), 126.03 (q, *J* = 3.3 Hz), 122.72, 121.88 (q, *J* = 276.9 Hz), 121.85, 118.47 (d, *J* = 24.5 Hz), 107.18 (d, *J* = 23.7 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.49 (s), -

108.78 (s). ESI-MS: Calcd for $C_{14}H_7F_4N$: $[M+H^+]$ 266.0587, found 266.0586.

4.2.9 2-chloro-6-(trifluoromethyl)phenanthridine ***(11)***

White solid (59 mg, 52%). M.p.: 76-78 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, *J* = 8.4 Hz, 1H), 8.48 (d, *J* = 2.2 Hz, 1H), 8.36 (d, *J* = 8.4 Hz, 1H), 8.18 (d, *J* = 8.8 Hz, 1H), 7.95 – 7.87 (m, 1H), 7.82 – 7.75 (m, 1H), 7.72 (dd, *J* = 8.8, 2.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.65 (q, *J* = 33.2 Hz), 140.05, 135.39, 132.83, 132.48, 131.60, 129.92, 128.69, 126.07, 125.95 (q, *J* = 3.1 Hz), 122.47, 121.74 (q, *J* = 277.2 Hz), 121.85, 121.71. ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.52 (s). ESI-MS: Calcd for $C_{14}H_7ClF_3N$: $[M+H^+]$ 282.0292, found 282.0294.

4.2.10 4-chloro-6-(trifluoromethyl)phenanthridine ***(12)***

White solid (48 mg, 43%). M.p.: 125-127 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, *J* = 8.4 Hz, 1H), 8.42 (d, *J* = 8.4 Hz, 1H), 8.40 – 8.32 (m, 1H), 7.94 – 7.87 (m, 1H), 7.84 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.81 – 7.74 (m, 1H), 7.63 (t, *J* = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.72 (q, *J* = 33.5 Hz), 138.13, 135.63, 133.70, 131.67, 129.65, 128.99, 128.60, 126.68, 125.90 (q, *J* = 3.4 Hz), 122.74, 121.71 (q, *J* = 277.3 Hz), 121.69, 120.77. ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.37 (s). ESI-MS: Calcd for $C_{14}H_7ClF_3N$: $[M+H^+]$ 282.0292, found 282.0294.

4.2.11 1,3-dimethyl-6-(trifluoromethyl)phenanthridine ***(13)***

White solid (83 mg, 75%). M.p.: 133-135 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (d, *J* = 8.7 Hz, 1H), 8.40 (d, *J* = 8.3 Hz, 1H), 7.98 (s, 1H), 7.92 – 7.83 (m, 1H), 7.74 (dd, *J* = 11.4, 4.0 Hz, 1H), 7.45 (s, 1H), 3.07 (s, 3H), 2.55 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.18 (q, *J* = 32.8 Hz), 143.51, 138.52, 135.28, 135.22, 134.69, 130.35, 129.66, 126.69, 126.62, 125.76 (q, *J* = 3.3 Hz), 122.48, 122.39, 122.05 (q, *J* = 277.1 Hz), 26.47, 20.96. ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.32 (s). ESI-MS: Calcd for $C_{16}H_{12}F_3N$: $[M+H^+]$ 276.0995, found 276.0993.

4.2.12 6-(trifluoromethyl)benzo[c]phenanthridine ***(14)***

White solid (88 mg, 74%). M.p.: 150-152 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.44 (d, *J* = 8.3 Hz, 1H), 8.78 (d, *J* = 8.5 Hz, 1H), 8.56 (d, *J* = 9.0 Hz, 1H), 8.48 (d, *J* = 8.5 Hz, 1H), 8.13 (d, *J* = 9.0 Hz, 1H), 7.97 (m, 2H), 7.81 (m, 2H), 7.77 – 7.69 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.87 (q, *J* = 33.4 Hz), 138.98, 134.23, 133.29, 132.07, 131.06, 130.16, 127.98, 127.86, 127.65, 125.77 (q, *J* = 3.1 Hz), 125.00, 122.95, 122.77, 122.46, 122.34 (q, *J* = 276.8 Hz), 119.35. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.89 (s). ESI-MS: Calcd for $C_{18}H_{10}F_3N$: $[M+H^+]$ 298.0838, found 298.0839.

4.2.13 8-methoxy-6-(trifluoromethyl)phenanthridine ***(15)***

White solid (52 mg, 47%). M.p.: 70-72 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, *J* = 9.2 Hz, 1H), 8.55 – 8.49 (m, 1H), 8.29 – 8.22 (m, 1H), 7.80 – 7.71 (m, 2H), 7.68 (d, *J* = 1.8 Hz, 1H), 7.55 (m, 1H), 4.01 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.04, 145.57 (q, *J* = 32.4 Hz), 141.06, 131.11, 129.24, 128.53, 128.32, 125.31, 124.15, 123.21, 122.49, 122.06 (q, *J* = 277.0 Hz), 121.58, 105.61 (q, *J* = 3.6 Hz), 55.59. ^{19}F NMR (376 MHz, $CDCl_3$) δ -64.10 (s). ESI-MS: Calcd for $C_{15}H_{10}F_3NO$: $[M+H^+]$ 278.0787, found 278.0788.

4.2.14 8-methoxy-6-(trifluoromethyl)benzo[c]phenanthridine ***(16)***

White solid(89 mg, 68%). M.p.: 155-157 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.36 (d, *J* = 8.3 Hz, 1H), 8.56 (d, *J* = 9.2 Hz, 1H), 8.37 (d, *J* = 9.1 Hz, 1H), 8.02 (d, *J* = 9.0 Hz, 1H), 7.93 (d, *J* = 7.9 Hz, 1H), 7.81 – 7.74 (m, 1H), 7.71 – 7.65 (m, 2H), 7.51 (dd, *J* = 9.2, 2.5 Hz, 1H), 4.00 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.80, 143.53 (q, *J* = 32.9 Hz), 137.86, 132.73, 132.07, 130.11, 128.99, 127.59, 127.55, 124.65, 124.46, 123.85, 122.91, 122.84, 122.48 (q, *J* = 275.6 Hz), 119.13, 104.52 (q, *J* = 3.3 Hz), 55.53.^{19}F NMR (376 MHz, $CDCl_3$) δ -63.57 (s). ESI-MS: Calcd for $C_{19}H_{12}F_3NO$: $[M+H^+]$ 328.0944, found 328.0945.

4.2.15 8-methoxy-1,3-dimethyl-6-(trifluoromethyl)phenanthridine ***(17)***

White solid (88 mg, 72%). M.p.: 140-142 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (d, *J* = 9.5 Hz, 1H), 7.97 (s, 1H), 7.73 (s, 1H), 7.51 (dd, *J* = 9.4, 2.7 Hz, 1H), 7.44 (s, 1H), 4.01 (s, 3H), 3.06 (s, 3H), 2.55 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.67, 145.29 (q, *J* = 32.8 Hz), 142.77, 137.48, 135.25, 133.85, 129.83, 129.59, 128.12, 123.92, 122.72, 122.16 (q, *J* = 277.3 Hz), 120.88, 105.99 (q, *J* = 3.6 Hz), 55.49, 26.52, 20.93.^{19}F NMR (376 MHz, $CDCl_3$) δ -63.97 (s). ESI-MS: Calcd for $C_{17}H_{14}F_3NO$: $[M+H^+]$ 306.1100, found 306.1101.

4.2.16 6,8-bis(trifluoromethyl)phenanthridine ***(18)***

White solid (80 mg, 63%). M.p.: 83-85 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (d, *J* = 8.8 Hz, 1H), 8.71 – 8.61 (m, 2H), 8.36 (dd, *J* = 8.0, 1.5 Hz, 1H), 8.14 (dd, *J* = 8.8, 1.6 Hz, 1H), 7.96 – 7.84 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.45 (q, *J* = 33.5 Hz), 142.47, 136.10, 131.46, 130.60, 130.08 (q, *J* = 32.4 Hz), 129.92, 127.29 (q, *J* = 3.0 Hz), 124.23, 123.79, 123.66 (q, *J* = 272.6 Hz), 123.51 (q, *J* = 4.2 Hz), 122.47, 121.62 (q, *J* = 277.1 Hz), 121.15. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.54 (s), -63.29(s). ESI-MS: Calcd for $C_{15}H_7F_6N$: $[M+H^+]$ 316.0555, found 316.0553.

4.2.17 2-methoxy-6,8-bis(trifluoromethyl)phenanthridine ***(19)*****:**

White solid (54 mg, 39%). M.p.: 102-105 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (d, *J* = 8.6 Hz, 1H), 8.63 (s, 1H), 8.26 (d, *J* = 9.0 Hz, 1H), 8.09 (d, *J* = 8.6 Hz, 1H), 7.93 (s, 1H), 7.52 (d, *J* = 8.7 Hz, 1H), 4.07 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.70, 143.79 (q, *J* = 33.6 Hz), 137.72, 135.33, 132.97, 130.07 (q, *J* = 33.1 Hz), 126.68 (q, *J* = 3.0 Hz), 125.74, 123.79, 123.69 (q, *J* = 272.4 Hz), 123.42 (q, *J* = 4.0 Hz), 121.85 (q, *J* = 276.5 Hz), 121.38, 120.57, 103.29, 55.84. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.55 (s), -63.00 (s). ESI-MS: Calcd for $C_{16}H_9F_6NO$: $[M+H^+]$ 346.0661, found 346.0611.

4.2.18 6-(chlorodifluoromethyl)phenanthridine ***(20)***

White solid (58 mg, 55%). M.p.: 64-66 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (d, *J* = 8.4 Hz, 1H), 8.64 – 8.56 (m, 1H), 8.57 – 8.49 (m, 1H), 8.33 – 8.24 (m, 1H), 7.98 – 7.87 (m, 1H), 7.85 – 7.73 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.97 (t, *J* = 26.0 Hz), 141.57, 134.30, 131.19, 129.32, 129.12, 127.77, 126.44 (t, *J* = 4.3 Hz), 125.07, 122.62 (t, *J* = 223.8 Hz), 122.02, 121.20, 116.04. ^{19}F NMR (376 MHz, $CDCl_3$) δ -51.33 (s). ESI-MS: Calcd for $C_{14}H_8ClF_2N$: $[M+H^+]$ 264.0386, found 264.0388.

4.2.19 6-(perfluoroethyl)phenanthridine ***(21)***

White solid (82 mg, 69%). M.p.: 71-73 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, *J* = 8.3 Hz, 1H), 8.46 (dd, *J* = 10.5, 8.6 Hz, 2H), 8.25 – 8.19 (m, 1H), 7.83 (t, *J* = 7.4 Hz, 1H), 7.78 – 7.68 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.49 (t, *J* = 26.4 Hz), 141.55, 133.80, 131.05, 129.21, 129.11, 127.83, 127.13, 125.86 (t, *J* = 6.2 Hz), 124.64, 123.20, 122.48, 121.84, 119.31 (qt, *J* = 286.6, 35.4 Hz), 113.75 (tq, *J* = 256.3, 36.0 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -80.13 (s), -106.76 (s). ESI-MS: Calcd for $C_{15}H_8F_5N$: $[M+H^+]$ 298.0650, found 298.0649.

4.2.20 4-methyl-6-(perfluoroethyl)phenanthridine ***(22)***

White solid (101 mg, 81%). M.p.: 95-97 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, *J* = 8.4 Hz, 1H), 8.45 (d, *J* = 8.4 Hz, 1H), 8.33 (dd, *J* = 6.7, 2.9 Hz, 1H), 7.87 – 7.81 (m, 1H), 7.71 (m, 1H), 7.63 – 7.57 (m, 2H), 2.82 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.01 (t, *J* = 27.5 Hz), 140.17, 139.49, 134.17, 130.85, 129.77, 128.95, 127.66, 125.67 (t, *J* = 5.6 Hz), 124.60, 122.79, 122.05, 119.59, 119.42 (qt, *J* = 286.3, 34.9 Hz), 114.06 (tq, *J* = 255.8, 35.2 Hz), 17.80. ^{19}F NMR (376 MHz, $CDCl_3$) δ -79.66 (s), -105.65 (s). ESI-MS: Calcd for $C_{16}H_{10}F_5N$: [M+H$^+$] 312.0806, found 312.0808.

*4.2.21 (Z)-N-(1-(2-bromophenyl)-2,2,2-trifluoroethylidene)aniline **(28)***

A sealed tube contained $PdCl_2(PPh_3)_2$ (10 mol %, 0.04 mmol) and Cs_2CO_3 (0.8 mmol) was evacuated and purged with nitrogen gas three times. Then, **1a** (0.48 mmol) and **2a** (0.4 mmol) in toluene (3.0 mL) were added to the system via syringe under a nitrogen atmosphere and the reaction was allowed to stir at 60 °C for 6 h. The reaction solution was concentrated in vacuo and the residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 100:1) to afford the desired pure product **28**.

28 Yellow oil (127 mg, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.0 Hz, 1H), 7.24 – 7.17 (m, 1H), 7.16 – 7.06 (m, 4H), 6.96 (t, *J* = 7.4 Hz, 1H), 6.76 (d, J = 7.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.05 (q, *J* = 35.4 Hz), 146.48, 133.04, 132.49, 131.36, 130.34, 128.53, 127.17, 125.99, 121.24, 120.45, 119.31 (q, *J* = 279.0 Hz). ^{19}F NMR (376 MHz, CDCl3) δ -70.44 (s). ESI-MS: Calcd for $C_{14}H_9BrF_3N$: [M+H$^+$] 327.9943, found 327.9941.

4.3 KIE by intermolecular competition experiments:

A sealed tube contained $PdCl_2(PPh_3)_2$ (28.1 mg, 0.04 mmol, 10 mol %), and Cs_2CO_3 (260.7 mg, 0.8 mmol, 2.0 equiv) was evacuated and purged with nitrogen gas three times. Then, **1a** (96.4 mg, 0.48 mmol, 1.2 equiv), **2a** (41.4 mg, 0.2 mmol, 0.5 equiv) and **2a-D** (42.5 mg, 0.2 mmol, 0.5 equiv) in toluene (3.0 mL) were added to the system via syringe under a nitrogen atmosphere and the reaction mixture was stirred at 120 °C for 3 h. The reaction solution was concentrated in vacuo and the residue was purified by a short column chromatography on silica gel (eluent EA) to afford a mixture. The solvent was then removed under reduced pressure and ^{1}H NMR showed K_H/K_D = 1.5.

4.4 Intermolecular competition experiment:

A sealed tube contained $PdCl_2(PPh_3)_2$ (10 mol %, 0.04 mmol) and Cs_2CO_3 (0.8 mmol) was evacuated and purged with nitrogen gas three times. Then, **1a** (0.48 mmol), (Z)-2,2,2-trifluoro-N-(4-methoxyphenyl)acetimidoyl chloride (0.4 mmol) and (Z)-2,2,2-trifluoro-N-(4-fluorophenyl)acetimidoyl chloride (0.4 mmol) in toluene (3.0 mL) were added to the system via syringe under a nitrogen atmosphere and the reaction was allowed to stir at 120 °C for 12 h. The reaction solution was concentrated in vacuo and the residue was purified by a short column chromatography on silica gel (eluent EA) to afford a mixture. The solvent was then removed under reduced pressure and ^{1}H NMR showed **7**:**10** = 1:0.3.

4.5 Sequence of formation of the two new bonds:

A sealed tube contained $PdCl_2(PPh_3)_2$ (10 mol %, 0.04 mmol) and Cs_2CO_3 (0.8 mmol) was evacuated and purged with nitrogen gas three times. Then, **28** (0.4 mmol) in toluene (3.0 mL) was added to the system via syringe under a nitrogen atmosphere and the reaction was allowed to stir at 120 °C for 12 h. The reaction solution was concentrated in vacuo and the residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 100:1) to afford the desired pure product in 99% yield. **3** (white solid, 98.0 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (d, *J* = 8.4 Hz, 1H), 8.60 (dd, *J* = 6.8, 2.7 Hz, 1H), 8.42 – 8.35 (m, 1H), 8.32 – 8.27 (m, 1H), 7.96 – 7.89 (m, 1H), 7.85 – 7.73 (m, 3H).

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