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Synthesis of 6-trifluoromethylphenanthridines via radical trifluoromethylation of isocyanides with sodium triflinate under visible light

Jianbin Li,[a],[c] Clarice A. D. Caiuby,[a],[b],[c] Márcio W. Paixão*[b] and Chao-Jun Li*[a]

Abstract: Trifluoromethylation enabled by photochemistry enriched the toolbox of synthetic chemists, allowing the simple and efficient installation of CF_3 group in organic molecules. Herein, we report a cascade addition/annulation reaction of 2-isocyanobiphenyls towards synthesizing 6-trifluoromethylphenanthridines. This reaction was proposed to be triggered by the CF_3 radical generated from photoexcited 2,3-butanedione (diacetyl) and sodium triflinate. In contrast to classical aromatic trifluoromethylations, this work does not require any additives and features a C-CF_3 bond formation with the concomitant construction of an aromatic scaffold.

Introduction

The installation of CF_3 moiety in organic molecules – the so called trifluoromethylation - has attracted the interest of the synthetic community over the past decades.[1] Upon introducing the CF_3 group, the altered chemical and physical properties could lead to biological and pharmacological benefits include greater lipophilicity, enhanced metabolic stability and bioavailability.[1c, 2] Intensive research over the years featured diverse synthetically appealing C-CF_3 bond formation strategies. Among them, transition-metal catalyzed or mediated cross coupling reactions showed successful achievements.[3] Recently, radical trifluoromethylation induced by light emerged as a unique and robust method to shuttle CF_3 radical toward unsaturated bonds.[4] Typically, the combination of visible light photochemistry and trifluoromethylating reagents, i.e. Togni's reagents,[5] Umemoto's reagents,[6] CF_3SO_2X (X = Cl[7] or Na[8], Langlois's reagent), CF_3X (X = I[9] or TMS[10], Ruppert-Prakash reagent) and others displayed particular advantages, offering a mild route to construct C-CF_3 bond.[11]

Arylisocyanides are of synthetically versatile heterocyclic scaffolds and well established as a radical acceptor in tandem reactions.[12] Radical-triggered addition and sequential annulation of readily prepared biarylisocyanides enabled rapid construction of the phenanthridine frameworks, which represented one of the most ubiquitous structures in natural products and biological compounds.[13] Well-known members comprised ethidium (a common DNA stain),[14] trisphaeridine (DNA intercalator)[15] and fagaronine (protein kinase C and DNA topoisomerase 1 inhibitor).[13a]

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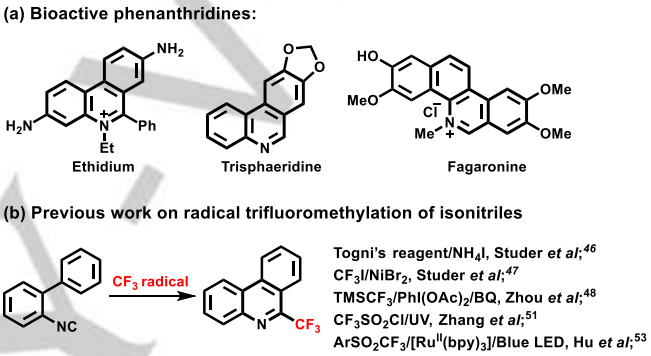
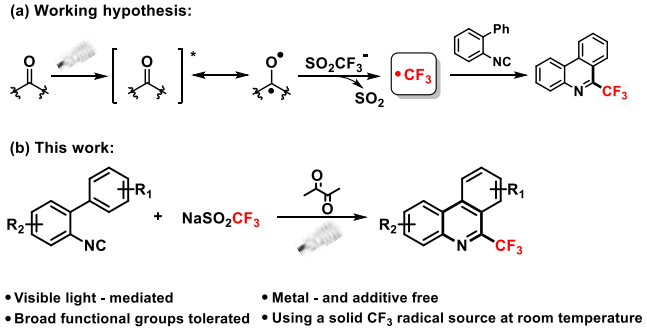


Scheme 1. (a) Biologically active phenanthridines. (b) Selected work on trifluoromethylation of biarylisocyanides enabled by different CF_3 radical sources.

On the other hand, a myriad of radical precursors generated by boronic acid,[16] halides,[17] aldehydes,[18] peroxides,[19] amides,[20] ethers,[21] alkanes,[22] hydrazines[23] and others were proven effective in tailoring the phenanthridine scaffolds. In 2013, Studer and co-workers have disclosed a pioneering work by the application of Bu_4NI as an initiator for the synthesis of 6-trifluoromethylphenanthridines. In this approach, Togni's reagent was used as CF_3 radical precursor.[24] Later, the same group unveiled another methodology based on Ni-catalyzed or thermally promoted homolysis of CF_3I.[25] Meanwhile, Zhou and co-workers reported an important work on oxidative cyclization of 2-isocyanobiphenyls mediated by $PhI(OAc)_2$ with $TMSCF_3$ as CF_3 radical source and benzoquinone as additive.[26] Shortly thereafter, several effective strategies were also developed.[27] Notably, photoredox chemistry, which has witnessed its renaissance in organic synthesis, offered routes to access CF_3 radical *via* single-electron transfer (SET) process in a controlled manner. Transforming CF_3SO_2Cl to CF_3 radical *via* UV-promoted homolysis, Zhang's group reported a photocatalyst-free tandem addition/cyclization reaction of 2-isocyanobiphenyls initiated by CF_3 radical generation.[27c] Almost concurrently, Hu and co-worker displayed an elegant and innovative example to afford CF_3 radical species from



Scheme 2. (a) Working hypothesis inspired by prior art. (b) Visible-light-mediated radical trifluoromethylation of biarylisocyanides to synthesize 6-trifluorophenanthridines.

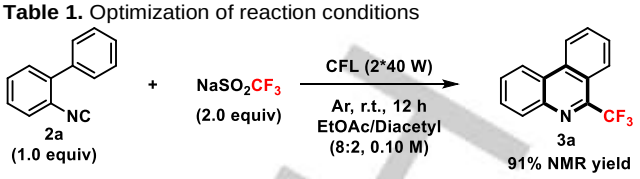
fluorinated sulfones by polypyridyl metal complexes-based visible light photoredox catalysis.[27e] Subsequent radical addition and intramolecular homolytic aromatic substitution (HAS) proceeded smoothly under mild conditions.

Despite the enormous success accomplished above, producing CF_3 radical generally necessitated elevated temperature, environmentally unfriendly additives, precious transition metal/ligands or special equipment (quartz tubes for UV radiation). Recently, our group described a simple and clean trifluoromethylation method on arenes *via* a photoinduced radical process by employing diacetyl as photosensitizer, which showcased diradical properties under visible light.[8a] This prompted us to envision our contribution to aforementioned isocyanide chemistry. Herein, we wish to report a radical trifluoromethylation reaction of 2-isocyanobiphenyls towards synthesizing the 6-trifluoromethylphenanthridines by using the visible-light-excited diacetyl and sodium triflinate.

Results and Discussion

To test the feasibility of our hypothesis, we began our investigation by choosing 2-isocyano-1,1'-biphenyl (**2a**) as our model substrates. To our delight, when our model substrate was subject to EtOAc/diacetyl (9:1, 0.1 M) mixed solvent, the reaction proceeded in accordance to our expectation and resulted in 13% desired product after 12-hour compact-fluorescence-light (CFL) lumination at room temperature (Table 1, entry 1). Strikingly, slight increase of the ratio of photosensitizer productively led to quantitative product formation, marking the optimal conditions. The reaction in THF and ^{i}PrOH also proceeded well albeit in inferior yields (entries 2-3). Concentrating the reaction mixture dramatically curtailed the product formation (entry 4). Doubling the dosage of $NaSO_2CF_3$ exhibited deleterious effect as product yield dropped to 63% (entry 5). UV radiation was beneficial to this transformation since both diacetyl and acetone displayed similarly high reactivity (entries 6 and 7). Reaction efficiency decreased to some extent if blue LED (centered at 455 nm) was employed, which was explained by the broad absorption range of diacetyl in visible region (entry

Table 1. Optimization of reaction conditions

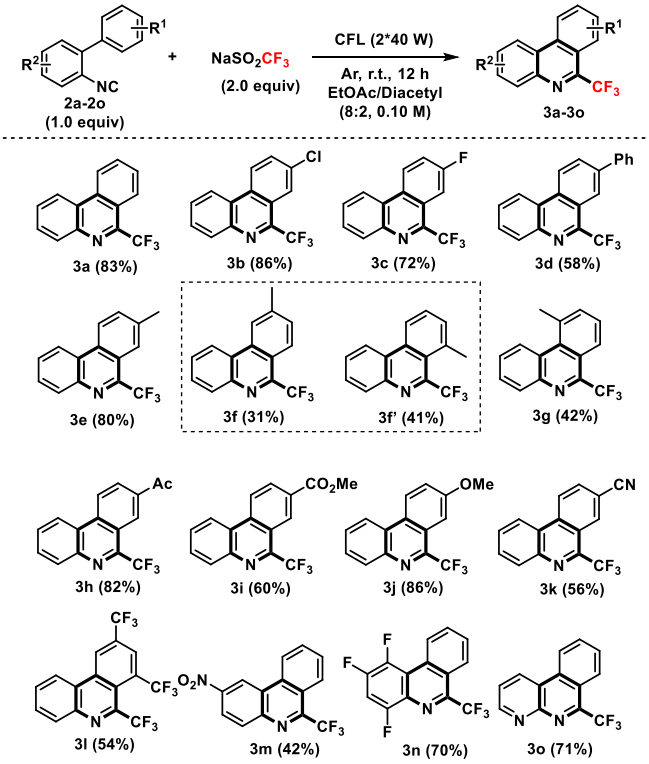


Entry	Variation from 'optimal conditions'	Yield[a]
1	EtOAc/diacetyl (9:1, 0.10 M)	13
2	THF/diacetyl (8:2, 0.10 M)	72
3	^{i}PrOH/diacetyl (8:2, 0.10 M)	83
4	EtOAc/diacetyl (8:2, 0.20 M)	26
5	4.0 equiv $NaSO_2CF_3$	63
6	UV (254 nm), EtOAc/diacetyl (8:2, 0.10 M)	72
7	UV (254 nm), acetone (0.10 M)	71
8	blue LED (455 nm)	70
9	50 ℃, in the dark	NR
10	6 hrs instead of 12 hrs	91

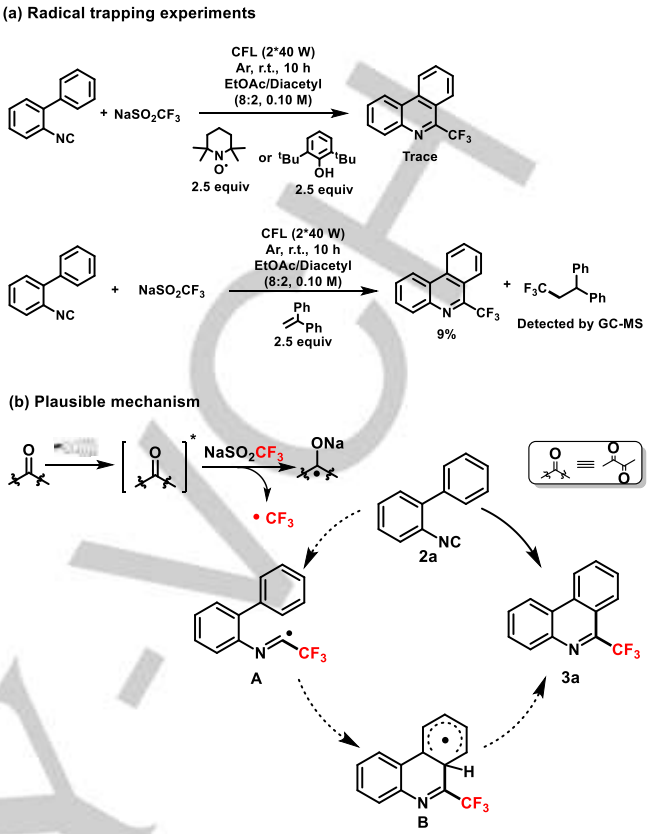
[a]Determined through ^{1}H NMR analysis by using 1,3,5-trimethoxybenzene as internal standard; NR = no reaction.

8). Light was found essential in this reaction as substrates remained intact under thermal conditions (entry 9). GC-MS monitoring indicated that the reaction was completed after 6-hour CFL irradiation (entry 10).

With the optimized conditions in hand, we prepared various biarylisocyanides **2a**-**2o** from commercially available and cheap 2-bromoanilines and examined the generality of this methodology. Initially, the tolerance of different functionalities installed at the *para*-position on biphenyl core was examined. Electronic bias was not observed in this transformation, since both substrates with electron-withdrawing and electron-donating functional groups were proven effective, resulting in moderate to good yields. Chloro (**3b**), fluoro (**3c**) and methoxy (**3j**) groups were well tolerated despite phenyl (**3d**) and methoxycarbonyl (**3i**) led to slight decrease of on-target reactivity. Gratifyingly, potentially sensitive acetyl (**3h**) and cyano (**3k**) remained intact during the reaction, furnishing 82% and 56% of the desired products, respectively. Difunctionalized biarylisocyanides underwent the reaction smoothly and 6,7,9-tri(trifluoromethyl)phenanthridine (**3l**) was obtained in 54% yield. Substituents at *meta*- and *ortho*-positions were also compatible with our protocol. As expected, the method suffered from regiocontrol with **2f**, giving two isomers (**3f** and **3f'**) in similar quantity. Presumably due to only one *ortho* hydrogen being available, the reaction incurred significant yield drop with **3g**. Besides, substrates bearing functionalities on the aromatic rings of the isocyano group were also investigated. Nitro group (**3m**), known to be vulnerable toward photochemical conditions, worked well in this chemistry albeit with a lower yield. Multiple fluorine atoms present did not affect the efficacy, successfully affording a semi-perfluorophenanthridine building block (**3n**). Notably, the reaction was still high-yielding in the case of 6-(trifluoromethyl)benzo[c][1,8]naphthyridine (**3o**), which incorporated a heteroatom in the biaryl framework.



Scheme 3. Substrate scope. All reactions were performed on 0.10 mmol scale in 1.0 mL of EtOAc/diacetyl (8:2) mixed solvent at r.t. under argon atmosphere irradiated by CFL (2*40 W) for 12 hrs and all yields reported are referred to isolated ones and in parentheses



Scheme 4. (a) Radical trapping experiments by different types of radical scavengers. (b) Proposed mechanism.

To confirm the radical nature of this tandem addition/annulation reaction, several control experiments were performed (Scheme 4a). It was found that the reaction was almost quenched in the presence of different types of radical scavengers. Among them, (3,3,3-trifluoropropane-1,1-diyl)dibenzene was formed in the case of 1,1-diphenylethylene, indicating the involvement of CF_3 radical.

Additionally, photophysical properties of this reaction were explored in order to gain more mechanistic insight (see electronic supplementary information for details). UV-Vis spectrometry revealed that both diacetyl and **2a** showed absorption in the visible region; however, considering the stoichiometry, the excessive diacetyl was probably the major active photosensitizer. Furthermore, the Stern-Volmer relationship demonstrated the excited state-quencher interaction between the diacetyl and $NaSO_2CF_3$.

Based on the mechanistic study above and previous literature,[24-27] a plausible mechanism was proposed (Scheme 4b). Upon visible light excitation, the carbonyl group of diacetyl was promoted from ground state to (n, π*) excited state, which exhibited as a diradical species. Reductive quenching of the excited diacetyl by $NaSO_2CF_3$ will generate the CF_3 radical with concomitant release of one equivalent of SO_2. Subsequently, terminal carbon in **2a** was attacked by the CF_3 radical, which induced an intramolecular HAS process to afford intermediate **B** with cyclohexadienyl radical moiety. DFT calculation by Studer has shown that the re-aromatization of **B** to give the final product **3a** is feasible.[24]

Conclusions

In summary, we have developed a simple and efficient route to synthesize the 6-trifluoromethylphenanthridines *via* a radical-triggered pathway involving the CF_3 radical generated from visible-light-excited diacetyl and $NaSO_2CF_3$. 2-arylisocynides bearing a broad range of functionalities were viable for this transformation at room temperature, which did not involve transition metal catalyst and additional additives.

Experimental Section

General Procedure: To a reaction tube (5.0 mL) equipped with a Teflon-coated magnetic stirring bar was added the isocyanide (0.10 mmol, 1.0 equiv), sodium triflinate (0.20 mmol, 2.0 equiv), diacetyl (0.20 mL) and EtOAc (0.80 mL). The resulting mixture was evacuated by three freeze-pump-thaw cycles and back-filled with ultra-purified argon (>99.999%). The reaction was stirred at room temperature under photo irradiation by using Compact Fluorescent Lamp (2*40W) until the starting material was completely consumed as monitored by TLC. The reaction mixture was then diluted with EtOAc, filtered through a pad of silica gel and the organic

solvent was evaporated. The desired product was isolated by flash column chromatography on silica gel.

6-(Trifluoromethyl)phenanthridine (3a): According to the general procedure, the 2-isocyano-1,1'-biphenyl (**2a**) (18 mg, 0.1 mmol) afforded **3a** (83%, 20.5 mg) as a light solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.70 (d, *J* = 8.4 Hz, 1H), 8.61 (dd, *J* = 7.1, 2.4 Hz, 1H), 8.41 – 8.36 (m, 1H), 8.31 – 8.28 (m, 1H), 7.95 – 7.90 (m, 1H), 7.84 – 7.75 (m, 3H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 146.5 (q, *J* = 32.9 Hz), 141.8, 134.0, 131.4, 131.2, 129.4, 129.2, 128.1, 126.0 (q, *J* = 3.3 Hz), 125.1, 122.6, 122.1, 122.0 (q, *J* = 277.1 Hz),121.8. **^{19}F NMR (471 MHz, $CDCl_3$)** δ -63.45 (s, 3F). **M.P.:** 74.1-75.1 ºC. **HRMS:** calculated for $C_{14}H_8F_3NNa$ $(M+Na)^+$ 270.0507; found 270.0501.

8-Chloro-6-(trifluoromethyl)phenanthridine (3b): According to the general procedure, the 4'-chloro-2-isocyano-1,1'-biphenyl (**2b**) (21.3 mg, 0.1 mmol) afforded **3b** (86%, 24.2 mg) as a light solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.63 (d, *J* = 8.9 Hz, 1H), 8.58 – 8.53 (m, 1H), 8.35 (dd, *J* = 3.7, 1.8 Hz, 1H), 8.32 – 8.28 (m, 1H), 7.88 (dd, *J* = 8.9, 2.1 Hz, 1H), 7.85 – 7.81 (m, 2H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 145.4 (q, *J* = 33.4 Hz), 141.7, 134.3, 132.3, 132.1, 131.3, 129.7 (d, *J* = 1.1 Hz), 125.2 (q, *J* = 3.5 Hz), 124.9, 124.5, 124.2, 122.5, 121.9, 121.6 (q, *J* = 277.0 Hz). **^{19}F NMR (471 MHz, $CDCl_3$)** δ -63.62 (s, 3F). **M.P.:** 122.1-122.3 ºC. **HRMS:** calculated for $C_{14}H_8ClF_3N$ $(M+H)^+$ 282.0292; found 282.0291.

8-Fluoro-6-(trifluoromethyl)phenanthridine (3c): According to the general procedure, the 4'-fluoro-2-isocyano-1,1'-biphenyl (**2c**) (17.7 mg, 0.1 mmol) afforded **3c** (72%, 17.1 mg) as a light solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.74 (dd, *J* = 9.2, 5.3 Hz, 1H), 8.61 – 8.56 (m, 1H), 8.34 – 8.29 (m, 1H), 8.06 – 8.01 (m, 1H), 7.86 – 7.81 (m, 2H), 7.71 (ddd, *J* = 9.2, 7.9, 2.6 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 161.5 (q, *J* = 250.1 Hz), 145.6, 141.5, 131.3, 130.7, 129.7, 129.3, δ 125.2 (d, *J* = 8.7 Hz), 124.8, 122.9 (d, *J* = 8.7 Hz), 121.9, 121.7 (q, *J* = 276.9 Hz) 120.9 (d, *J* = 24.0 Hz), 110.8 (dq, *J* = 23.2 Hz, 3.5 Hz). **^{19}F NMR (471 MHz, $CDCl_3$)** δ -63.03 (s, 3F), -109.91 a -109.96 (m, 1F). **M.P.:** 91.3 - 93.8 ºC. **HRMS:** calculated for $C_{14}H_8F_4N$ $(M+H)^+$ 266.0587; found 266.0585.

8-Phenyl-6-(trifluoromethyl)phenanthridine (3d): According to the general procedure, the 2-isocyano-1,1':4',1''-terphenyl (**2d**) (25.5 mg, 0.1 mmol) afforded **3d** (58%, 18.8 mg) as a light solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.75 (d, *J* = 8.7 Hz, 1H), 8.62 (dd, *J* = 6.0, 3.4 Hz, 1H), 8.56 (s, 1H), 8.31 (dd, *J* = 6.0, 3.3 Hz, 1H), 8.16 (dd, *J* = 8.6, 1.5 Hz, 1H), 7.84 – 7.78 (m, 2H), 7.75 (d, *J* = 7.4 Hz, 2H), 7.55 (t, *J* = 7.6 Hz, 2H), 7.46 (t, *J* = 7.4 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 146.6 (q, *J* = 33.0 Hz), 141.7, 141.0, 139.8, 133.0, 131.2, 130.8, 129.4, 129.3, 129.2, 128.3, 127.5, 125.0, 123.8 (q, *J* = 3.3 Hz), 123.2, 122.2, 122.1, 122.0 (q, *J* = 277.1 Hz). **^{19}F NMR (471 MHz, $CDCl_3$)** δ -63.33 (s, 3F). **M.P.:** 138.5 - 139.5 ºC. **HRMS:** calculated for $C_{20}H_{13}F_3N$ $(M+H)^+$ 324.0995; found 324.0990.

8-Methyl-6-(trifluoromethyl)phenanthridine (3e): According to the general procedure, the 2-isocyano-4'-methyl-1,1'-biphenyl (**2e**) (19.3 mg, 0.1 mmol) afforded **3e** (80%, 20.9 mg) as a light solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.64 – 8.53 (m, 1H), 8.33 – 8.24 (m, 1H), 8.16 (s, 1H), 7.82 – 7.77 (m, 1H), 7.77 – 7.74 (m, 1H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 146.2 (q, *J* = 32.8 Hz), 141.4, 138.2, 133.2, 131.9, 131.1, 129.1, 128.9, δ 125.2 (q, *J* = 3.2 Hz), 125.2, 122.4, 122.0 (q, *J* = 277.2 Hz),122.0, 121.9, 21.9. **^{19}F NMR (471 MHz, $CDCl_3$)** δ -64.76 (s, 3F). **M.P.:** 122.1 - 122.3 ºC. **HRMS:** calculated for $C_{15}H_{11}F_3N$ $(M+H)^+$ 262.0838; found 262.0836.

9-Methyl-6-(trifluoromethyl)phenanthridine (3f): According to the general procedure, the 2-isociano-3'-metil-1,1'-bifenil (**2f**) (19.3 mg, 0.1 mmol) afforded **3f** (31%, 8.13 mg) as a light solid. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.63 – 8.60 (m, 1H), 8.49 (s, 1H), 8.31 – 8.27 (m, 2H), 7.84 – 7.76 (m, 2H), 7.61 (d, J = 8.5 Hz, 1H), 2.69 (s, 3H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 146.4 (q, *J* = 32.9 Hz), 142.1, 142.0, 134.2, 131.1, 129.9, 129.2, 128.9, 125.8 (q, *J* = 3.3 Hz), 125.0, 122.1, 122.0 (d, *J* = 277.1 Hz), 122.1, 119.9, 22.4. **^{19}F NMR (377 MHz, $CDCl_3$)** δ -63.52 (s, 3F). **M.P.:** 85.0 – 86.0 ºC. **HRMS:** calculated for $C_{15}H_{11}F_3N$ $(M+H)^+$ 262.0838; found 262.0849.

7-Methyl-6-(trifluoromethyl)phenanthridine (3f'): According to the general procedure, the 2-isociano-3'-metil-1,1'-bifenil (**2f**) (19.3 mg, 0.1 mmol) afforded **3f'** (41%, 10.75 mg) as a colorless liquid. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.69 – 8.60 (m, 2H), 8.30 – 8.24 (m, 1H), 7.85 – 7.76 (m, 3H), 7.65 (d, *J* = 7.2 Hz, 1H), 2.96 (d, *J* = 2.1 Hz, 3H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 145.1 (q, *J* = 35.3 Hz), 140.7, 136.0, 135.6, 132.7, 130.7, 130.6, 129.2, 129.1, 125.4, 122.4, 122.3, 122.1 (q, *J* = 275.9 Hz), 120.8, 23.5 (q, *J* = 8.8 Hz). **^{19}F NMR (377 MHz, $CDCl_3$)** δ -59.80 (s, 3F). **HRMS:** calculated for $C_{15}H_{11}F_3N$ $(M+H)^+$ 262.0838; found 262.0839.

10-Methyl-6-(trifluoromethyl)phenanthridine (3g): According to the general procedure, the 2-isocyano-2'-methyl-1,1'-biphenyl (**2g**) (19.3 mg, 0.1 mmol) afforded **3g** (42%, 11.0 mg) as a light solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.67 – 8.59 (m, 1H), 8.51 (s, 1H), 8.35 – 8.25 (m, 2H), 7.81 (m, 2H), 7.62 (d, *J* = 8.5 Hz, 1H), 2.70 (s, 3H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 146.5 (q, *J* = 30.24 Hz), 142.1, 142.0, 134.2, 131.1, 129.9, 129.2, 128.9, 125.8 (q, *J* = 3.3 Hz), 125.0, 122.1, 122.1, 121.5 (q, *J* = 277.2 Hz), 119.9, 22.4. **^{19}F NMR (471 MHz, $CDCl_3$)** δ -62.99 (s, 3F). **M.P.:** 122.1 – 122.3 ºC. **HRMS:** calculated 262.0838 for $C_{15}H_{11}NF_3$ $(M+H)^+$; found 262.0839.

1-(6-(Trifluoromethyl)phenanthridin-8-yl)ethan-1-one (3h): According to the general procedure, the 1-(2'-isocyano-[1,1'-biphenyl]-4-yl)ethan-1-one (**2h**) (22.1 mg, 0.1 mmol) afforded **3h** (82%, 23.7 mg) as a light solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.11 – 8.09 (m, 1H), 7.66 – 7.63 (m, 2H), 7.56 – 7.50 (m, 2H), 7.48 – 7.43 (m, 2H), 2.69 (s, 3H). **^{13}C NMR (125 MHz, Acetone-d_6)** δ 196.1, 146.3 (q, *J* = 32.6 Hz), 142.3, 136.6, 136.4, 130.9, 130.7, 130.3, 130.1, 125.7 (q, *J* = 3.3 Hz), 124.5, 124.1 (q, J = 276.2 Hz),123.8, 123.4, 120.9, 26.0. **^{19}F NMR (471 MHz, Acetone-d_6)** δ -63.82 (s, 3F). **M.P.:** 116.3-119.0 ºC. **HRMS:** calculated for $C_{16}H_{11}F_3NO$ $(M+H)^+$ 290.0787; found 290.0785.

Methyl 6-(trifluoromethyl)phenanthridine-8-carboxylate (3i): According to the general procedure, the methyl 2'-isocyano-[1,1'-biphenyl]-4-carboxylate (**2i**) (23.7 mg, 0.1 mmol) afforded **3i** (60%, 18.3 mg) as a light solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 9.12 – 9.07 (m, 1H), 8.78 (d, *J* = 8.7 Hz, 1H), 8.66 (d, *J* = 8.0 Hz, 1H), 8.55 (dd, *J* = 8.7, 1.6 Hz, 1H), 8.34 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.93 – 7.84 (m, 2H), 4.07 (s, 3H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 166.0, 147.0 (q, *J* = 35.3 Hz), 142.5, 136.8, 131.3, 131.2, 130.5, 129.7,128.1 (q, *J* = 3.5 Hz)., 124.5, 123.0, 122.7, 121.6 (q, *J* = 275.5 Hz), 121.3, 52.7. **^{19}F NMR (471 MHz, $CDCl_3$)** δ -63.21 (s, 3F). **M.P.:** 161.6 - 162.7 ºC. **HRMS:** calculated for $C_{16}H_{10}F_3NO_2Na$ $(M+Na)^+$ 328.0556; found 328.0565.

8-Methoxy-6-(trifluoromethyl)phenanthridine (3j): According to the general procedure, the 2-isocyano-4'-methoxy-1,1'-biphenyl (**2j**) (21.0 mg, 0.1 mmol) afforded **3j** (86%, 23.8 mg) as a light solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.61 (d, *J* = 9.1 Hz, 1H), 8.53 (dd, *J* = 6.1, 3.5 Hz, 1H), 8.29 – 8.26 (m, 1H), 7.80 – 7.74 (m, 2H), 7.70 (s, 1H), 7.56 (dd, *J* = 9.1, 2.5 Hz, 1H). **^{13}C NMR (125 MHz, Acetone-d_6)** δ 159.4, 144.9 (q, *J* = 32.6 Hz), 140.9, 130.7, 129.7, 128.6, 128.4, 125.3, 124.9, 122.9, 122.4, δ 122.2 (q, *J* = 276.2 Hz), 122.2, 105.3 (q, *J* = 3.5 Hz), 55.2. **^{19}F NMR (471 MHz, Acetone-d_6)** δ -64.76 (s, 3F). **M.P.:** 97.0-101.0 ºC. **HRMS:** calculated for $C_{15}H_{11}F_3NO$ $(M+H)^+$ 278.0787; found 278.0785.

6-(Trifluoromethyl)phenanthridine-8-carbonitrile (3k): According to the general procedure, the 2'-isocyano-[1,1'-biphenyl]-4-carbonitrile (**2k**) (20.5 mg, 0.1 mmol) afforded **3k** (80%, 21.8 mg) as a light solid. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.81 (d, *J* = 8.7 Hz, 1H), 8.71 (s, 1H), 8.63 (d, *J* = 7.8 Hz, 1H), 8.35 (d, *J* = 7.9 Hz, 1H), 8.11 (dd, *J* = 8.7, 1.5 Hz, 1H), 7.98 – 7.87 (m, 2H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 145.7 (q, *J* = 33.8 Hz), 142.6, 136.3, 132.5, 131.5, 131.3 – 131.1 (m), 130.2, 123.6 (d, *J* = 277.1 Hz), 124.0, 123.8, 122.6, 121.1, 120.3, 118.0, 111.9. **^{19}F NMR (377 MHz, $CDCl_3$)** δ -63.24 (s, 3F). **M.P.:** 177.3 - 179.9 ºC. **HRMS:** calculated for $C_{15}H_8F_3N_2$ $(M+H)^+$ 273.0634; found 273.0633.

6,7,9-Tris(trifluoromethyl)phenanthridine (3l): According to the general procedure, the 2-isocyano-3',5'-bis(trifluoromethyl)-1,1'-biphenyl (**2l**) (31.5 mg, 0.1 mmol) afforded **3l** (52%, 20.0 mg) as a light solid. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 9.18 (s, 1H), 8.70 – 8.61 (m, 1H), 8.37 (dd, J = 8.1, 1.3 Hz, 1H), 8.33 (s, 1H), 7.96 (dtd, J = 15.0, 7.1, 1.4 Hz, 2H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 144.9 (q, *J* = 35.3 Hz), 141.8, 135.2, 131.9 (q, *J* = 34.3 Hz), 131.2, 130.7, 130.6, 129.9 (q, *J* = 33.8 Hz), 125.2(m), 123.0 (q, *J* = 300.6 Hz), 123.6 (d, J = 3.8 Hz), 123.0, 122.9 (q, J = 273.1 Hz), 122.1, 120.5 (q, *J* = 276.7 Hz), 118.0. **^{19}F NMR (377 MHz, $CDCl_3$)** δ -55.15 (q), -61.86 (q), -63.04 (s). **M.P.:** 200.5 - 204.2 ºC. **HRMS:** calculated for $C_{16}H_7F_9N$ $(M+H)^+$ 383.0362; found 383.0354.

2-Nitro-6-(trifluoromethyl)phenanthridine (3m): According to the general procedure, the 2-isocyano-5-nitro-1,1'-biphenyl (**2m**) (22.4 mg, 0.1 mmol) afforded **3m** (42%, 12.3 mg) as a light solid. **^{1}H NMR (500 MHz, Acetone-d_6)** δ 9.70 (d, *J* = 2.4 Hz, 1H), 9.22 (d, *J* = 8.4 Hz, 1H), 8.67 (dd, *J* = 9.0, 2.4 Hz, 1H), 8.50 (t, *J* = 7.0 Hz, 2H), 8.24 (t, *J* = 7.7 Hz, 1H), 8.12 – 8.07 (m, 1H). **^{13}C NMR (125 MHz, Acetone-d_6)** δ 149.1 (q, *J* = 33.2 Hz), 147.8, 144.3, 134.1, 133.1, 132.6, 130.0, 125.8 (d, *J* = 3.4 Hz), 125.4, 123.8, 123.3, 121.7 (d, *J* = 276.8 Hz),121.7, 119.1. **^{19}F NMR (471 MHz, Acetone-d_6)** δ -63.22 (s, 3F). **M.P.:** 205.6 - 205.8 ºC. **HRMS:** calculated for $C_{14}H_8F_3N_2O_2$ $(M+H)^+$ 293.0532; found 293.0526.

1,2,4-Trifluoro-6-(trifluoromethyl)phenanthridine (3n): According to the general procedure, the 2,3,5-trifluoro-6-isocyano-1,1'-biphenyl (**2n**) (23.3 mg, 0.1 mmol) afforded **3n** (70%, 21.1 mg) as a light solid. **^{1}H NMR (500 MHz, Acetone-d_6)** δ 9.16 – 9.08 (m, 1H), 8.56 – 8.46 (m, 1H), 8.20 (td, J = 7.2, 1.2 Hz, 1H), 8.10 (ddd, J = 8.3, 7.2, 1.1 Hz, 1H), 7.91 (ddd, J = 10.5, 9.6, 7.0 Hz, 1H). **^{13}C NMR (125 MHz, Acetone-d_6)** δ 155.9 - 153.8 (m), 146.4 -148.7 (m), 146.4 (m), 144.9 - 142.9 (m), 133.1, 130.2, 127.4, 127.2, 126.2 (q, J = 261.3 Hz), 125.8 (q, J = 3.4 Hz), 122.8, 122.1, 120.6, 105.7 – 105.1 (m). **^{19}F NMR (471 MHz, Acetone-d_6)** δ – 64.25 (s, 3F), -122.50 to -122.57 (m, 2F), -132.71 to -132.79 (m, 1F). **M.P.:** 122.1-122.3 ºC. **HRMS:** calculated for $C_{14}H_6F_6N$ $(M+H)^+$ 302.0399; found 302.0390.

6-(Trifluoromethyl)benzo[c][1,8]naphthyridine (3o): According to the general procedure, the 2-isocyano-3-phenylpyridine (**2o**) (18.0 mg, 0.1 mmol) afforded **3o** (71%, 17.6 mg) as a light solid. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 9.20 (s, 1H), 9.01 (dd, *J* = 8.3, 1.3 Hz, 1H), 8.74 (d, *J* = 8.3 Hz, 1H), 8.49 (d, *J* = 8.4 Hz, 1H), 8.04 (t, *J* = 7.7 Hz, 1H), 7.89 (t, *J* = 7.7 Hz, 1H), 7.78 (dd, *J* = 8.2, 4.2 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 152.4, 151.2, 150.0 (q, *J* = 33.8 Hz), 134.4, 132.1, 131.5, 129.0, 126.3 (q, *J* = 3.3 Hz), 124.1, 123.7 (d, *J* = 277.8 Hz), 122.7, 121.9, 120.3. **^{19}F NMR (377 MHz, $CDCl_3$)** δ -63.63 (s, 3F). **M.P.:** 111.6-116.1 ºC. **HRMS:** calculated for $C_{13}H_7F_3N_2Na$ $(M+Na)^+$ 271.0454; found 271.0456.

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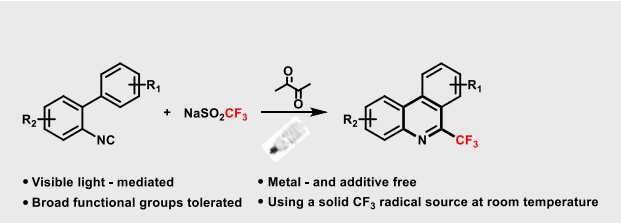

A simple method to rapidly construct the 6-trifluoromethylphenathridine scaffolds was developed by employing diacetyl as a visible light sensitizer. In the absence of transition metals and additives, this CF_3 radical-triggered cyclization reaction proceeded smoothly and tolerated a broad scope of functionalities.

Key Topic*

Trifluoromethylation • Phenanthridines

Jianbin Li, Clarice A. D. Caiuby, Márcio W. Paixão and Chao-Jun Li**

Page No. – Page No.

Synthesis of 6-trifluoromethylphenanthridines via radical trifluoromethylation of isocyanides with sodium triflinate under visible light