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General method for the synthesis of substituted phenanthridin-6(5*H*)-ones using a KOH-mediated anionic ring closure as the key step

Emmanuelle Dubost, Rosa Magnelli, Thomas Cailly, Rémi Legay, Frédéric Fabis *, Sylvain Rault

Centre d'Etudes et de Recherche sur le Médicament de Normandie, UPRES EA 4258, INC3M FR-CNRS 3038, UFR des Sciences Pharmaceutiques, Université de Caen Basse-Normandie, boulevard Becquerel, 14032 Caen cedex, France

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ABSTRACT

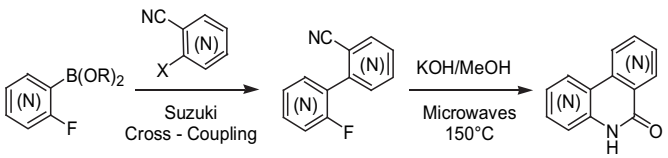
Substituted phenanthridin-6(5*H*)-ones were obtained in a two-step procedure involving a Suzuki cross-coupling reaction followed by a KOH-mediated anionic ring closure. The influence of the nature and the position of the substituents on the cyclization step were studied. This methodology offers a general and practical route to diversely substituted phenanthridin-6(5*H*)-ones.

1. Introduction

The phenanthridin-6(5*H*)-one framework has been extensively used for the design of many compounds exhibiting a wide range of biological activities.[1] Even if the synthesis of phenanthridin-6(5*H*)-one has been known since the beginning of the 20th century,[2] it is only since the development of palladium-catalyzed chemistry that more general routes to diversely substituted phenanthridin-6(5*H*)-ones have been described. The synthesis of the unsubstituted phenanthridin-6(5*H*)-one was reported from *N*-(2-halophenyl) benzamide by the palladium-catalyzed formation of the biaryl bond in a modest yield.[3] The scope of this reaction was later extended to substituted *N*-(2-iodophenyl)benzamides affording substituted phenanthridin-6-ones with low diversity regarding the nature and position of the substituents.[4] More recently, starting from *N*-benzyl-*N*-benzoyl-*o*-iodoanilides, Bernini and co-workers reported the synthesis of diversely substituted phenanthridin-6(5*H*)-ones in good yields.[5] This methodology needs the multistep-formation of the starting materials, including a protection/deprotection sequence to afford the NH free phenanthridin-6(5*H*)-ones. Other strategies using aryl–aryl bond formation and subsequent cyclization were described. Snieckus and Siddiqui described two examples using a Suzuki cross-coupling reaction between *o*-bromobenzamides and *o*-*N*-Boc-arylboronic acids followed by a TFA-mediated cyclization.[6] Palladium[0]-mediated Ullmann cross-coupling reaction starting from 1-bromo-2-nitrobenzene and 2-halobenzoates followed by a reductive cyclization was described more recently by Banwell and co-workers. [7] Only phenanthridin-6(5*H*)-ones substituted on the benzoyl ring were obtained in modest overall yields.

Improvements have been recently described by Ferraccioli, who reported a Pd-catalyzed synthesis of substituted phenanthridin-6(5*H*)-ones and heterocyclic analogues from *o*-substituted iodoarenes and *o*-bromo(hetero)arylcarboxamides.[8] This method allows the creation of both the aryl–aryl and the N–CO bonds in a one-pot process, but *ortho*-electron-donating groups on the iodoarenes were required for the reaction to work well, limiting thus the scope of this methodology. More recently, a domino process using two substituted 2-bromo-*N*-phenylbenzamides was described.[9] Although, some symmetrical substituted phenanthridin-6(5*H*)-ones were obtained in good yields in this one-pot procedure, the formation of unsymmetrical products remained tricky.

We have recently reported a two-step synthesis of unsubstituted phenanthridin-6(5*H*)-one, benzo-, and pyridonaphtyridinones involving a Suzuki cross-coupling followed by a new and high-yielding KOH-mediated anionic ring closure (Scheme 1).[10] This procedure has been recently used by Begtrup and Cailly for the synthesis of some substituted benzo[*h*]-1,6-naphthyridin-5(6*H*)-ones.[11] We thought that this methodology could offer a general route to diversely substituted phenanthridin-6(5*H*)-ones and we wish to report here our efforts to study the influence of the nature and position of substituents in the KOH-mediated anionic ring closure from biphenyl derivatives (Scheme 2).



Scheme 1. Synthesis of naphtyridinones by Cailly et al.[10]

* Corresponding author. Tel.: +33 231 56 6808; fax: +33 231 56 6803; e-mail address: frederic.fabis@unicaen.fr (F. Fabis).

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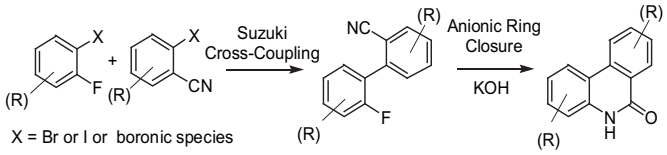
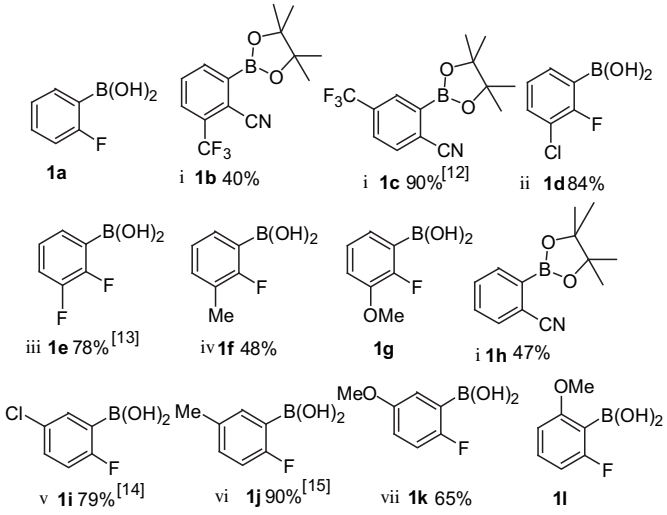


Scheme 2. General scheme of the work described herein.

2. Results and discussion

We started our study by the synthesis of the key substituted 2′-fluorobiphenyl-2-carbonitriles via a Suzuki cross-coupling reaction. Commercially available substituted 2-bromo(iodo)fluoroarenes, 2-bromobenzonitriles and boronic acids **1a**, **1g**, and **1l** were used. Boronic acids **1c**,[12] **1e**,[13] **1i**,[14] and **1j**[15] were obtained from diversely substituted fluorobenzenes using previously described conditions. The synthesis of boronic acids or esters **1b**, **1d**, **1f**, **1h**, and **1k** was achieved using *ortho*-metalation strategy (Scheme 3).

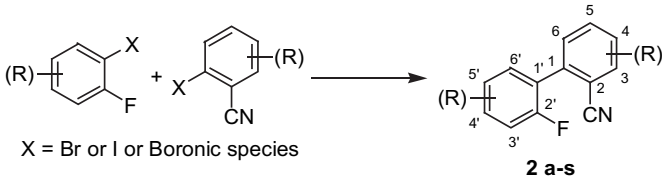


Scheme 3. Boronic species. Isolated yields starting from the corresponding substituted fluoroarenes or benzonitriles: (i) LTMP 1.2 equiv, B(O*i*-Pr)$_3$ 1.4 equiv, THF, −78 °C, overnight and then pinacol 1.5 equiv, AcOH 1.4 equiv; (ii) *s*-BuLi 1.05 equiv 1 h, B(O*i*-Pr)$_3$ 1.05 equiv 1 h, THF, −78 °C; (iii) *n*-BuLi 1.05 equiv 1 h, B(O*i*-Pr)$_3$ 1.05 equiv 1 h 30 min, THF, −78 °C; (iv) LiCKOR 1.05 equiv 2 h, B(O*i*-Pr)$_3$ 1.05 equiv 1 h, THF, −78 °C; (v) LTMP 1.05 equiv, B(O*i*-Pr)$_3$ 1.1 equiv, THF, −78 °C, 1 h; (vi) *s*-BuLi 1.05 equiv 1 h, B(OMe)$_3$ 1.05 equiv 2 h, THF, −78 °C; (vii) LTMP 1.05 equiv, B(O*i*-Pr)$_3$ 1.2 equiv, THF, −78 °C, 1 h.

The Suzuki cross-coupling conditions were adjusted depending on the starting materials. Compounds **2a**–**b** and **2h**–**s** were synthesized using microwave heating conditions, Pd(PPh$_3$)$_4$ with either K_3PO_4 in DMF or Cs_2CO_3 in a toluene/ethanol mixture. The microwave heating allowed a dramatic decrease in the reaction times[16] and afforded the expected biaryls in 50–84% yields (Table 1, conditions A and D). For compound **2e**, conditions A were used with conventional heating, microwaves heating leading to a lower yield. Compounds **2c**, **2d**, and **2f** were obtained in 81–93% yields using Na_2CO_3 as base and DME/H_2O as solvent (Table 1, conditions B). Finally, the sterically hindered 2′-fluoro-6-methylbiphenyl-2-carbonitrile **2g** was synthesized in 64% yield using *S*-Phos as the ligand (Table 1, conditions C).[17]

We then explored the anionic ring closure reaction starting from 2′,4′-difluorobiphenyl-2-carbonitrile **2m**. When we applied the previously described conditions (KOH, MeOH, 150 °C),[10b] the complete conversion of the starting material was observed but led to an 1:1 mixture (^{1}H NMR) of the expected 3-fluorophenanthridin-6(5*H*)-one **3m** and 2′-fluoro-4′-methoxybiphenyl-2-carbonitrile **2o**

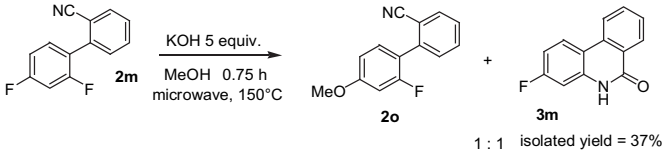
Table 1
Synthesis of substituted 2′-fluorobiphenyl-2-carbonitrile **2a**–**s** via Suzuki cross-coupling



Coupling partners		Conditions[a]	Product	Yield[b] (%)
Boronic	ArBr(I)			
1a	2-Br-1-CN	A 0.5 h 150 °C μW	**2a**	81
1b	1-Br-2-F	A 1.25 h 150 °C μW	**2b** 3-CF_3	78
1a	2-Br-5-MeO-1-CN	B 48 h Reflux	**2c** 4-MeO	81
1a	2-Br-5-NO2-1-CN	B 48 h Reflux	**2d** 4-NO_2	85
1c	1-Br-2-F	A 16 h 105 °C	**2e** 5-CF_3	63
1a	2-Br-4-Me-1-CN	B 48 h Reflux	**2f** 5-Me	93
1a	2-Br-3-Me-1-CN	C 48 h Reflux	**2g** 6-Me	64
1d	2-Br-1-CN	A 1.5 h 150 °C μW	**2h** 3′-Cl	50
1e	2-Br-1-CN	A 1.25 h 150 °C μW	**2i** 3′-F	73
1f	2-Br-1-CN	A 2 h 150 °C μW	**2j** 3′-Me	84
1g	2-Br-1-CN	A 1 h 150 °C μW	**2k** 3′-MeO	73
1h	1-I-4-Cl-2-F	D 1 h 110 °C μW	**2l** 4′-Cl	57
1h	1-Br-2,4-F	D 1.25 h 125 °C μW	**2m** 4′-F	81
1h	1-Br-2-F-4-Me	D 1.25 h 150 °C μW	**2n** 4′-Me	67
1h	1-Br-2-F-4-MeO	D 2 h 125 °C μW	**2o** 4′-MeO	65
1i	2-Br-1-CN	A 1 h 150 °C μW	**2p** 5′-Cl	53
1h	1-Br-2,5-F	D 1.75 h 130 °C μW	**2q** 5′-F	78
1j	2-Br-1-CN	A 2 h 150 °C μW	**2r** 5′-Me	72
1k	2-Br-1-CN	A 0.5 h 150 °C μW	**2s** 5′-MeO	51

[a] Conditions: (A) Pd(PPh$_3$)$_4$ 5 mol %, arylbromide 1 equiv, boronic species 1.2 equiv, K_3PO_4 2 equiv, DMF; (B) Pd(OAc)$_2$ 5 mol %, PPh$_3$ 10 mol %, aryl halide 1 equiv, boronic species 1.5 equiv, Na_2CO_3 4 equiv, DME/H_2O 2:1; (C) Pd(OAc)$_2$ 5 mol %, *S*-Phos 10 mol %, arylbromide 1 equiv, boronic species 1.5 equiv, Na_2CO_3 4 equiv, DME/H_2O 2/1; (D) Pd(PPh$_3$)$_4$ 5 mol %, arylbromide 1 equiv, boronic species 1.2 equiv, Cs_2CO_3 2 equiv, toluene/ethanol 9:1.
[b] Isolated yields.

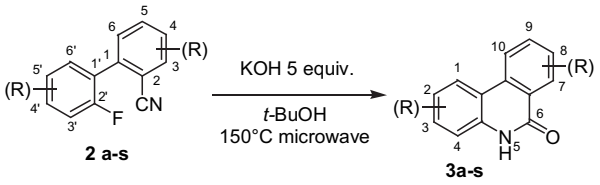
(Scheme 4). The 3-fluorophenanthridin-6(5*H*)-one **3m** was isolated in 37% yield. It has to be noticed that the competitive nucleophilic substitution of the fluorine atom *para* to the aryl group has not been observed after the cyclization. The electron-donating effect of the nitrogen atom on the **3m** prevents the SN_{Ar} to occur. Under these conditions the nucleophilic displacement of the fluorine atom *ortho* to the aryl group did not occurred before the cyclization. As previously described, using lower temperature led only to hydrolysis of the nitrile without cyclization.[10b]



Scheme 4. Cyclization of compound **2m** in MeOH.

In order to avoid the formation of **2o**, we decided to use non-nucleophilic solvents. Using non-protic solvents, such as NMP or DMF led to mixtures of products. Finally we were pleased to find that the use of *t*-BuOH instead of methanol allowed the isolation of **3m** in a good 87% yield without formation of by-products (Table 2). We then applied these conditions to biphenyls **2a**–**s**. Substituted phenanthridin-6(5*H*)-ones **3a**–**s** were isolated pure after a simple dilution of the reaction mixture with water and filtration. In all cases, total conversion of the starting material to the expected substituted phenanthridin-6(5*H*)-one was observed (TLC monitoring). All the compounds were obtained in 78–99% yields except compounds **3b**, **3c**, **3e**, and **3g** for which the lower yields are due to

Table 2
KOH-mediated anionic ring closure

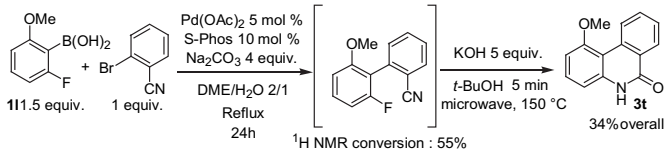


Starting material	Time (min)[a]	Product	Yield[b] (%)
2a	10	**3a**	99
2b 3-CF_3	25	**3b** 7-CF_3	33
2c 4-MeO	5	**3c** 8-MeO	67
2d 4-NO_2	11	**3d** 8-NO_2	99
2e 5-CF_3	8	**3e** 9-CF_3	70
2f 5-Me	13	**3f** 9-Me	99
2g 6-Me	5	**3g** 10-Me	61
2h 3′-Cl	30	**3h** 4-Cl	85
2i 3′-F	30	**3i** 4-F	90
2j 3′-Me	60	**3j** 4-Me	96
2k 3′-MeO	5	**3k** 4-MeO	85
2l 4′-Cl	20	**3l** 3-Cl	99
2m 4′-F	30	**3m** 3-F	87
2n 4′-Me	60	**3n** 3-Me	94
2o 4′-MeO	40	**3o** 3-MeO	88
2p 5′-Cl	20	**3p** 2-Cl	86
2q 5′-F	60	**3q** 2-F	99
2r 5′-Me	40	**3r** 2-Me	97
2s 5′-MeO	75	**3s** 2-MeO	78

[a] The poor solubility in *t*-BuOH of some phenanthridin-6(5*H*)-ones may cause vials breakage due to the formation of hotspots under elongated microwave heating times (especially for **3c**, **3e**, **3g**, and **3k**).
[b] Isolated yields.

their partial solubility in water and poor solubility in organic solvents. Even for compound **3b**, no formation of by-products was observed (TLC monitoring). Interestingly, this anionic ring closure occurred even with electron-donating groups (**3j**,**k**, **3n**,**o**, and **3r**,**s**). The quantitative formation of **3a** in a shorter time clearly demonstrates the superiority of *t*-BuOH over MeOH in this KOH-mediated anionic ring closure.[10b] The very short reaction times observed for some compounds (**3c**, **3e**, **3g**, and **3k**) could be correlated to the very poor solubility of these phenanthridin-6(5*H*)-ones in *t*-BuOH, favoring thus the ring closure. Moreover, the reaction proceeds via an addition/elimination mechanism as the formation of an aryne intermediate is excluded from biaryls **2h**–**k**.

As substituted phenanthridin-6(5*H*)-ones were isolated after a very simple work-up, we thought that these two steps could be achieved in a sequential procedure without purification of the biphenyl compound. As an example, the Suzuki cross-coupling of 2-fluoro-6-methoxyphenylboronic acid **1l** and 2-bromobenzonitrile followed by the KOH-mediated anionic ring closure of the crude intermediate led to isolation of the pure 1-methoxyphenanthridin-6(5*H*)-one **3t** in 34% overall yield (Scheme 5). This modest yield was mainly due to the poor conversion (^{1}H NMR, 55%) observed in the cross-coupling step, which has not been further investigated.



Scheme 5. Sequential synthesis of 1-methoxyphenanthridin-6(5*H*)-one **3t**.

3. Conclusions

In summary, we have shown that the KOH-mediated anionic ring closure of substituted 2′-fluorobiphenyl-2-carbonitriles offers a general methodology for the synthesis of substituted phenanthridin-6(5*H*)-ones. This reaction has been shown to work with both electron-withdrawing and electron-donating groups and allows a practical synthesis of phenanthridin-6(5*H*)-ones substituted in all positions.

4. Experimental section

4.1. General methods

Melting points were determined on a Kofler melting point apparatus. IR spectra were recorded on KBr discs. ^{1}H and ^{13}C NMR spectra were recorded, respectively, at 400 and 100 MHz or at 500 and 125 MHz, using $CDCl_3$ or DMSO-d_6 as solvents. High Resolution Mass Spectra (HRMS-EI) were performed at 70 eV. Elemental Analyses were performed at 'Institut de Recherche en Chimie Organique Fine' (Rouen, France). For microwave reactions temperature were measured with an IR-sensor and reaction times given as hold times. THF was distilled from Na/benzophenone under N_2. All commercially available compounds were used as received except *n*-butyllithium and *sec*-butyllithium commercial solutions, which were titrated prior to use.[18]

4.2. Synthesis of boronic species 1b–d, 1f, 1h and 1k

2-Fluorobenzeneboronic acid **1a**, 2-fluoro-3-methoxybenzeneboronic acid **1g**, and 2-fluoro-6-methoxybenzeneboronic acid **1l** were bought from chemical suppliers. 2,3-Difluorobenzeneboronic acid **1e**,[13] 5-chloro-2-fluorobenzeneboronic acid **1i**[14] and 2-fluoro-5-methylbenzeneboronic acid **1j**[15] were prepared according to literature methods.

4.2.1. 6-Trifluoromethyl-2-(4,4,5,5-tetramethyl-[1,2]-dioxoborolan-2-yl)benzonitrile ***1b***. *n*-BuLi 2.5 M in *n*-hexane (2.80 mL, 7.01 mmol) was added to a solution of 2,2,6,6-tetramethylpiperidine (1.18 mL, 7.01 mmol) in 10 mL of THF under N_2 at −10 °C. The solution was stirred for 15 min, cooled to −78 °C and B(O*i*-Pr)$_3$ (1.89 mL, 8.18 mmol) was added. After 10 min, a solution of 4-trifluoromethylbenzonitrile (1.00 g, 5.84 mmol) in 5 mL of THF was added via syringe. The mixture was stirred at −78 °C for 2 h and subsequently warm to room temperature over 2 h. The reaction was quenched with AcOH (0.47 mL, 8.18 mmol) and pinacol (1.04 g, 8.76 mmol) was added. The reaction mixture was stirred at room temperature for 1 h, diluted with water (100 mL), and extracted with dichloromethane (3×100 mL). The combined organic layers were washed with a 15% KH_2PO_4 solution (3×50 mL), dried over $MgSO_4$, filtrated, and concentrated in vacuo. The crude product was recrystallized from *n*-heptane to give 6-trifluoromethyl-2-(4,4,5,5-tetramethyl-[1,2]-dioxoborolan-2-yl)benzonitrile **1b** as white crystals (600 mg, 40%); mp 78–79 °C; IR (KBr) ν (cm^{-1}) 2989, 2230 (CN), 1372, 1126; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (s, 12H), 7.69 (t, J=7.8 Hz, 1H), 7.85 (d, J=7.8 Hz, 1H), 8.06 (t, J=7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.8, 85.3, 114.7, 115.0, 122.6 (q, ^1J=273 Hz), 128.4 (q, J=5 Hz), 131.5, 133.6 (q, ^2J=32 Hz), 138.7; HRMS-EI m/z [M$^+$] calcd for $C_{14}H_{15}BNO_2F_3$ 297.11478, found 297.11591.

4.2.2. 4-Trifluoromethyl-2-(4,4,5,5-tetramethyl-[1,2]-dioxoborolan-2-yl)benzonitrile ***1c***[12]. *n*-BuLi 2.5 M in *n*-hexane (2.80 mL, 7.01 mmol) was added to a solution of 2,2,6,6-tetramethylpiperidine (1.18 mL, 7.01 mmol) in 10 mL of THF under N_2 at −10 °C. The solution was stirred for 15 min, cooled to −78 °C and B(O*i*-Pr)$_3$ (1.89 mL, 8.18 mmol) was added. After 10 min, a solution of 4-trifluoromethylbenzonitrile (1.00 g, 5.84 mmol) in 5 mL of THF was added via syringe. The mixture was stirred at −78 °C for 2 h and subsequently warm to room temperature over 2 h. The reaction was quenched with AcOH (0.47 mL, 8.18 mmol) and pinacol (1.04 g,

8.76 mmol) was added. The reaction mixture was stirred at room temperature for one hour, diluted with water (100 mL), and extracted with dichloromethane (3×100 mL). The combined organic layers were washed with a 15% KH_2PO_4 solution (3×50 mL), dried over $MgSO_4$, filtrated, and concentrated in vacuo. The crude product was recrystallized from petroleum ether to give 4-trifluoromethyl-2-(4,4,5,5-tetramethyl-[1,2]-dioxoborolan-2-yl)benzonitrile **1c** as a yellow powder (1.69 g, 90%); mp 208–209 °C; IR (KBr) ν (cm^{-1}) 2973, 2235 (CN), 1682, 1330, 1130; ^1H NMR (400 MHz, $CDCl_3$) δ 1.40 (s, 12H), 7.78–7.84 (m, 2H), 8.15 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.8, 85.3, 117.7, 120.7, 123.2 (q, ^1J=272 Hz), 127.8 (q, J=4 Hz), 132.6 (q, J=4 Hz), 133.3 (q, ^2J=33 Hz), 133.7; HRMS-EI m/z [M^+] calcd for $C_{14}H_{15}BNO_2F_3$ 297.11478, found 297.11462.

4.2.3. 3-Chloro-2-fluorobenzeneboronic acid ***1d****.* A solution of *s*-BuLi 1.3 M in cyclohexane/hexane 92:8 (6.18 mL, 8.04 mmol) was added to a stirred solution of 1-chloro-2-fluorobenzene (0.80 mL, 7.66 mmol) in 10 mL of THF at −78 °C. The reaction mixture was stirred at −78 °C for 1 h, and B(O*i*-Pr)$_3$ (1.86 mL, 8.04 mmol) was added. The solution was stirred for 1 h and warmed to room temperature. HCl 3 M was added until pH=1, the resulting mixture was extracted with ethyl acetate (3×100 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated. 3-Chloro-2-fluorobenzeneboronic acid **1d** was obtained as a white powder (1.13 g, 84%); mp 246–247 °C; IR (KBr) ν (cm^{-1}) 3295, 1603, 1446, 1332, 729; ^1H NMR (400 MHz, $CDCl_3$) δ 5.20 (s, 1H), 5.21 (s, 1H), 7.16 (t, J=7.8 Hz, 1H), 7.52 (t, J=7.8 Hz, 1H), 7.72–7.75 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 120.7 (d, ^2J=21 Hz), 125.2 (d, J=4 Hz), 134.0, 134.4, 135.0 (d, J=6 Hz), 162.7 (d, ^1J=244 Hz); HRMS-EI m/z [M^+] calcd for $C_6H_5BO_2FCl$ 174.0055, found 174.0059.

4.2.4. 2-Fluoro-3-methylbenzeneboronic acid ***1f****.* *n*-BuLi 2.5 M in *n*-hexane (3.81 mL, 9.53 mmol) was added to a solution of *t*-BuOK (1.07 g, 9.53 mmol) in 10 mL of THF under N_2 at −78 °C. The solution was stirred for 15 min and 1-fluoro-2-methylbenzene (1.00 mL, 9.08 mmol) was added in 10 mL of THF at −78 °C. Stirring was continued for 2 h before B(O*i*-Pr)$_3$ (2.20 mL, 9.53 mmol) was added neat via syringe. The mixture was stirred at −78 °C for 1 h and subsequently warm to room temperature over 3–4 h. The reaction mixture was quenched with water and a solution of HCl 1 M until pH=1. Extraction with ethyl acetate (3×50 mL), drying of the combined organic layers other $MgSO_4$, and evaporation of solvents led to 2-fluoro-3-methylbenzeneboronic acid **1f** as a white powder. Recrystallization from petroleum ether gave white crystals (670 mg, 48%); mp 160–161 °C; IR (KBr) ν (cm^{-1}) 3301, 1615, 1429, 1322, 742; ^1H NMR (400 MHz, $CDCl_3$) δ 2.28 (s, 3H), 5.46 (s, 1H), 5.48 (s, 1H), 7.10 (t, J=6.8 Hz, 1H), 7.31 (t, J=7.8 Hz, 1H), 7.66 (t, J=6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4 (d, J=4 Hz), 123.4 (d, ^2J=29 Hz), 123.4 (d, J=4 Hz), 132.7 (d, J=9 Hz), 132.8 (d, J=5 Hz), 163.8 (d, ^1J=242 Hz); HRMS-EI m/z [M^+] calcd for $C_7H_8BO_2F$ 154.06013, found 154.06067.

4.2.5. 2-(4,4,5,5-Tetramethyl-[1,2]-dioxoborolan-2-yl)benzonitrile ***1h****.* *n*-BuLi 2.5 M in *n*-hexane (2.33 mL, 5.82 mmol) was added to a solution of 2,2,6,6-tetramethylpiperidine (0.98 mL, 5.82 mmol) in 10 mL of THF under N_2 at −10 °C. The solution was stirred for 15 min, cooled to −78 °C and B(O*i*-Pr)$_3$ (1.57 mL, 6.79 mmol) was added. After 10 min, a solution of benzonitrile (0.50 mL, 4.85 mmol) in 2.5 mL of THF was added via syringe. The mixture was stirred at −78 °C and warmed to room temperature overnight. The reaction was quenched with AcOH (0.39 mL, 6.79 mmol) and pinacol (859 mg, 7.27 mmol) was added. The reaction mixture was stirred at room temperature for 1 h, diluted with water (100 mL), and extracted ethyl acetate (3×50 mL). The combined organic layers were dried over $MgSO_4$, filtrated, and evaporated to afford an orange solid. Recrystallization from *n*-heptane gave 2-(4,4,5,5-tetramethyl-[1,2]-dioxoborolan-2-yl)benzonitrile **1h** as white crystals (520 mg, 47%); mp 85–86 °C; IR (KBr) ν (cm^{-1}) 2984, 2226 (CN), 1332, 1352; ^1H NMR (400 MHz, $CDCl_3$) δ 1.39 (s, 12H), 7.51–7.60 (m, 2H), 7.70 (d, ^3J=8.8 Hz, 1H), 7.89 (dd, J=6.8, 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.8, 84.8, 117.3, 119.0, 131.1, 131.6, 133.4, 135.8; HRMS-EI m/z [M^+] calcd for $C_{13}H_{16}BNO_2$ 229.1274, found 229.12684. Anal. Calcd for $C_{13}H_{16}BNO_2$: C, 68.16; H, 7.04; N, 6.11. Found: C, 68.03; H, 7.24; N, 6.43.

4.2.6. 2-Fluoro-5-methoxybenzeneboronic acid ***1k****.* *n*-BuLi 2.5 M in *n*-hexane (68 mL, 0.17 mol) was added to a solution of 2,2,6,6-tetramethylpiperidine (29 mL, 0.17 mol) in 200 mL of THF under N_2 at −10 °C. The solution was stirred for 15 min, cooled to −78 °C and B(O*i*-Pr)$_3$ (43.8 mL, 0.19 mol) was added. After 5 min, a solution of 4-methoxyfluorobenzene (18 mL, 0.16 mol) in 10 mL of THF was added via syringe. The mixture was stirred at −78 °C for 1 h and subsequently warmed to room temperature over 1 h. Water (200 mL) was added and the resulting mixture was washed with diethyl ether (3×100 mL), the aqueous layer was acidified with a HCl 3 M solution until pH=1. The product was extracted with diethyl ether (3×300 mL), the organic layers were dried over $MgSO_4$, filtrated, and concentrated in vacuo. 2-Fluoro-5-methoxybenzeneboronic acid **1k** was obtained as a white powder after recrystallization from petroleum ether (17.4 g, 65%); mp 195–196 °C; IR (KBr) ν (cm^{-1}) 3286, 2964, 1492, 1029; ^1H NMR (400 MHz, DMSO-d_6) δ 3.71 (s, 3H), 6.90–6.95 (m, 1H), 7.00 (t, ^4J=8.8 Hz, 1H), 7.04–7.06 (m, 1H), 8.22 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 55.5, 115.6 (d, ^2J=26 Hz), 116.7 (d, ^3J=9 Hz), 119.4 (d, ^3J=9 Hz), 122.8, 155.0 (d, ^4J=2 Hz), 159.8 (d, ^1J=236 Hz). Anal. Calcd for $C_7H_8BFO_3$: C, 49.47; H, 4.74. Found: C, 49.36; H, 4.77.

4.3. General procedures for the synthesis of substituted 2′-fluorobiphenyl-2-carbonitriles 2a–s

Conditions A: To a degassed solution of aryl halide (1 equiv) in DMF (5 mL/mmol of aryl halide) were added $K_3PO_4 \cdot H_2O$ (2 equiv), boronic species (1.2 equiv), and $Pd(PPh_3)_4$ (5 mol %). The suspension was heated under N_2 (conditions described in Table 1). The resulting mixture was partitioned in water and ethyl acetate and filtrated through a short pad of Celite. The organic layer was washed with water, dried over $MgSO_4$, filtrated, and evaporated. The crude product was then purified by silica gel chromatography.

Conditions B: To a degassed solution of triphenylphosphine (10 mol %) in a mixture of DME/water 2:1 (12 mL/mmol of aryl halide) was added $Pd(OAc)_2$ (5 mol %) at room temperature. The resulting mixture was heated at 80 °C for 10 min. Aryl halide (1 equiv), boronic species (1.5 equiv), and Na_2CO_3 (4 equiv) were added. The suspension was then heated under N_2 (conditions described in Table 1). The mixture was poured in water and extracted with ethyl acetate. The combined layers were filtrated through a short pad of Celite. The organic layer was washed with water, dried over $MgSO_4$, filtrated, and evaporated. The crude product was then purified by silica gel chromatography.

Conditions C: To a degassed solution of 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl (*S*-PHOS) (10 mol %) in a mixture of DME/water 2:1 (12 mL/mmol of aryl halide) was added $Pd(OAc)_2$ (5 mol %) at room temperature. The resulting mixture was heated at 80 °C for 10 min. Aryl halide (1 equiv), boronic species (1.5 equiv), and Na_2CO_3 (4 equiv) were added. The suspension was heated under N_2 (conditions described in Table 1). The mixture was poured in water and extracted with ethyl acetate. The combined layers were filtrated through a short pad of Celite. The organic layer was washed with water, dried over $MgSO_4$, filtrated, and evaporated. The crude product was then purified by silica gel chromatography.

Conditions D: To a degassed solution of aryl halide (1 equiv) in a mixture of toluene/ethanol (9:1, 5 mL/mmol of aryl halide) were

added Cs_2CO_3 (2 equiv), boronic species (1.2 equiv), and $Pd(PPh_3)_4$ (5 mol %). The suspension was heated under N_2 (conditions described in Table 1). The resulting mixture was partitioned in water and ethyl acetate and filtrated through a short pad of Celite. The organic layer was washed with water, dried over $MgSO_4$, filtrated, and evaporated. The crude product was then purified by silica gel chromatography.

4.3.1. 2′-Fluorobiphenyl-2-carbonitrile ***2a***[19]. Starting from 2-bromobenzonitrile (867 mg, 4.76 mmol) and 2-fluorobenzeneboronic acid **1a** (1.00 g, 7.15 mmol) following general procedure A and using cyclohexane/EtOAc (9:1) as eluent, 2′-fluorobiphenyl-2-carbonitrile **2a** was obtained as a white powder (763 mg, 81%); mp=83–84 °C; IR (KBr) ν (cm^{-1}) 3064, 2235 (CN), 1579, 1439; ^1H NMR (400 MHz, $CDCl_3$) δ 7.20–7.29 (m, 2H), 7.41–7.52 (m, 4H), 7.67 (m, 1H), 7.79 (d, J=7.8 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 112.8, 116.1 (d, ^2J=21 Hz), 118.0, 124.3 (d, J=3 Hz), 125.8 (d, ^2J=15 Hz), 128.2, 130.8, (d, J=7 Hz), 130.9 (d, J=2 Hz), 131.2 (d, J=3 Hz), 132.5, 133.2, 139.5, 159.4 (d, ^2J=248 Hz); HRMS-EI m/z [M^+] calcd for $C_{13}H_8NF$ 197.06407, found 197.06394.

4.3.2. 2′-Fluoro-3-trifluoromethylbiphenyl-2-carbonitrile ***2b***. Starting from 6-trifluoromethyl-2-(4,4,5,5-tetramethyl-[1,2]-dioxoborolan-2-yl)benzonitrile **1b** (418 mg, 1.41 mmol) and 2-bromofluorobenzene (0.13 mL, 1.17 mmol), following general procedure A and using cyclohexane/EtOAc (9:1) as eluent, 2′-fluoro-3-trifluoromethylbiphenyl-2-carbonitrile **2b** was obtained as a yellow oil (242 mg, 78%); IR (KBr) ν (cm^{-1}) 3087, 2234 (CN), 1464, 759; ^1H NMR (400 MHz, DMSO-d_6) δ 7.39–7.47 (m, 2H), 7.56–7.65 (m, 2H), 7.95–7.97 (m, 1H), 8.02–8.07 (m, 1H), 8.09–8.12 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 109.0 (q, J=2 Hz), 114.3, 116.0 (d, J=22 Hz), 122.6 (q, ^1J=274 Hz), 124.4 (d, J=15 Hz), 125.0 (d, J=4 Hz), 126.6 (q, J=5 Hz), 131.5 (q, ^2J=32 Hz), 131.6 (d, J=2 Hz), 132.0 (d, J=8 Hz), 134.1, 135.2, 141.6, 158.7 (d, ^1J=246 Hz); HRMS-EI m/z [M^+] calcd for $C_{14}H_7NF_4$ 265.05145, found 265.05219.

4.3.3. 2′-Fluoro-4-methoxybiphenyl-2-carbonitrile ***2c***. Starting from 2-bromo-5-methoxybenzonitrile (500 mg, 2.36 mmol) and 2-fluorobenzeneboronic acid **1a** (493 mg, 3.54 mmol), following general procedure B and using cyclohexane/EtOAc (95:5) as eluent, 2′-fluoro-4-methoxybiphenyl-2-carbonitrile **2c** was obtained as a white powder (433 mg, 81%); mp 80–81 °C; IR (KBr) ν (cm^{-1}) 2964, 2227 (CN), 1482, 1260; ^1H NMR (400 MHz, $CDCl_3$) δ 3.88 (s, 3H), 7.17–7.25 (m, 4H), 7.38–7.42 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.7, 113.4, 116.0 (d, ^2J=22 Hz), 117.6, 118.0, 119.2, 124.3 (d, J=4 Hz), 125.5 (d, ^2J=16 Hz), 130.4 (d, J=8 Hz), 131.4 (d, J=2 Hz), 131.8, 132.2 (d, J=2 Hz), 159.0, 159.6 (d, ^1J=246 Hz); HRMS-EI m/z [M^+] calcd for $C_{14}H_{10}NFO$ 227.07463, found 227.07352.

4.3.4. 2′-Fluoro-4-nitrobiphenyl-2-carbonitrile ***2d***. Starting from 2-bromo-5-nitrobenzonitrile (500 mg, 2.20 mmol) and 2-fluorobenzeneboronic acid **1a** (460 mg, 3.30 mmol), following general procedure B and using cyclohexane/EtOAc (9:1) as eluent, 2′-fluoro-4-nitrobiphenyl-2-carbonitrile **2d** was obtained as a yellow powder (453 mg, 85%); mp 136–137 °C; IR (KBr) ν (cm^{-1}) 3064, 2233 (CN), 1524, 1352; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26–7.36 (m, 2H), 7.46 (dt, J=7.8, 2.0 Hz, 1H), 7.51–7.57 (m, 1H), 7.75 (d, J=8.8 Hz, 1H), 8.51 (dd, J=8.8, 2.0 Hz, 1H), 8.65 (d, J=3.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 114.3, 116.0, 116.6 (d, ^2J=21 Hz), 123.8 (d, ^2J=15 Hz), 124.8 (d, J=4 Hz), 127.1, 128.3, 130.8 (d, J=2 Hz), 132.3 (d, J=8 Hz), 132.4 (d, J=2 Hz), 145.6, 147.1, 159.2 (d, ^1J=250 Hz); HRMS-EI m/z [M^+] calcd for $C_{13}H_7N_2O_2F$ 242.04914, found 242.04929.

4.3.5. 2′-Fluoro-5-trifluoromethylbiphenyl-2-carbonitrile ***2e***. Starting from 4-trifluoromethyl-2-(4,4,5,5-tetramethyl-[1,2]-dioxoborolan-2-yl)benzonitrile **1c** (406 mg, 1.37 mmol) and 2-bromofluorobenzene (0.13 mL, 1.14 mmol), following general procedure A and using cyclohexane/EtOAc (95:5) as eluent, 2′-fluoro-5-trifluoromethylbiphenyl-2-carbonitrile **2e** was obtained as a yellow oil (190 mg, 63%); IR (KBr) ν (cm^{-1}) 2235 (CN), 1488, 1333, 1123, 764; ^1H NMR (500 MHz, $CDCl_3$) δ 7.23–7.33 (m, 2H), 7.44 (dt, J=7.5, 2.0 Hz, 1H), 7.48–7.52 (m, 1H), 7.75–7.78 (m, 2H), 7.91–7.93 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 116.6 (d, ^2J=21 Hz), 116.9, 123.1 (q, ^1J=273 Hz), 124.6 (d, J=15 Hz), 124.8 (d, J=4 Hz), 125.2 (q, J=4 Hz), 128.1 (m), 131.2, 131.8 (d, J=7 Hz), 132.8, 134.0, 134.6 (q, ^2J=33 Hz), 140.7, 159.4 (d, ^1J=250 Hz); HRMS-EI m/z [M^+] calcd for $C_{14}H_7NF_4$ 265.05145, found 265.05063.

4.3.6. 2′-Fluoro-5-methylbiphenyl-2-carbonitrile ***2f***. Starting from 2-bromo-4-methylbenzonitrile (2.00 g, 10.20 mmol) and 2-fluorobenzeneboronic acid **1a** (2.13 g, 15.30 mmol), following general procedure B and using cyclohexane/EtOAc (9:1) as eluent, 2′-fluoro-5-methylbiphenyl-2-carbonitrile **2f** was obtained as a white powder (2.0 g, 93%); mp 70–71 °C; IR (KBr) ν (cm^{-1}) 2917, 2221 (CN), 1608, 1216; ^1H NMR (400 MHz, DMSO-d_6) δ 2.44 (s, 3H), 7.34–7.41 (m, 2H), 7.44–7.51 (m, 3H), 7.53–7.58 (m, 1H), 7.86 (d, J=8.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.2, 108.9, 115.8 (d, ^2J=22 Hz), 118.1, 124.7 (d, J=3 Hz), 125.6 (d, ^2J=15 Hz), 129.5, 131.1 (d, J=8 Hz), 131.4 (d, J=6 Hz), 131.5, 133.0, 138.6, 144.0, 158.9 (d, ^1J=246 Hz); HRMS-EI m/z [M^+] calcd for $C_{14}H_{10}NF$ 211.07972, found 211.08007.

4.3.7. 2′-Fluoro-6-methylbiphenyl-2-carbonitrile ***2g***. Starting from 2-bromo-3-methylbenzonitrile (200 mg, 1.02 mmol) and 2-fluorobenzeneboronic acid **1a** (210 mg, 1.53 mmol), following general procedure B and using cyclohexane/EtOAc (9:1) as eluent, 2′-fluoro-6-methylbiphenyl-2-carbonitrile **2g** was obtained as a yellow oil (209 mg, 64%); IR (KBr) ν (cm^{-1}) 2927, 2228 (CN), 1459, 754; ^1H NMR (400 MHz, DMSO-d_6) δ 2.18 (s, 3H), 7.21 (t, J=8.8 Hz, 1H), 7.26–7.29 (m, 1H), 7.39 (t, J=7.8 Hz, 1H), 7.42–7.48 (m, 2H), 7.52 (d, J=7.8 Hz, 1H), 7.61 (d, J=7.7 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 20.0 (d, ^5J=2 Hz), 113.5, 115.9 (d, ^2J=21 Hz), 118.0, 124.3 (d, J=4 Hz), 124.9 (d, J=16 Hz), 128.3, 130.3, 130.6 (d, J=8 Hz), 131.0 (d, J=3 Hz), 134.2, 138.5, 138.9, 159.2 (d, ^1J=246 Hz); HRMS-EI m/z [M^+] calcd for $C_{14}H_{10}NF$ 211.07972, found 211.07944.

4.3.8. 3′-Chloro-2′-fluorobiphenyl-2-carbonitrile ***2h***. Starting from 3-chloro-2-fluorobenzeneboronic acid **1d** (575 mg, 3.30 mmol) and 2-bromobenzonitrile (500 mg, 2.75 mmol), following general procedure A and using cyclohexane/EtOAc (9:1) as eluent, 3′-chloro-2′-fluorobiphenyl-2-carbonitrile **2h** was obtained as white crystals (320 mg, 50%); mp 114–115 °C; IR (KBr) ν (cm^{-1}) 2222 (CN), 1447, 1431, 1230, 759; ^1H NMR (400 MHz, $CDCl_3$) δ 7.21 (dt, J=7.9, 1.2 Hz, 1H), 7.33 (ddd, J=7.8, 6.5, 1.7 Hz, 1H), 7.48–7.54 (m, 3H), 7.68 (dt, J=7.8, 1.4 Hz, 1H), 7.80 (ddd, J=7.6, 1.4, 0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 112.8, 117.8, 122.0 (d, ^2J=18 Hz), 124.7 (d, J=5 Hz), 127.3 (d, ^2J=15 Hz), 128.7, 129.6 (d, J=2 Hz), 130.8 (d, J=2 Hz), 131.4, 132.5, 133.4, 138.5, 155.0 (d, ^1J=250 Hz); HRMS-EI m/z [M^+] calcd for $C_{13}H_7FNCl$ 231.0251, found 231.02534.

4.3.9. 2′,3′-Difluorobiphenyl-2-carbonitrile ***2i***. Starting from 2,3-difluorobenzeneboronic acid **1e** (521 mg, 3.30 mmol) and 2-bromobenzonitrile (500 mg, 2.75 mmol), following general procedure A and using cyclohexane/EtOAc (9:1) as eluent, 2′,3′-difluorobiphenyl-2-carbonitrile **2i** was obtained as white crystals (432 mg, 73%); mp 94–95 °C; IR (KBr) ν (cm^{-1}) 2226 (CN), 1465, 758; ^1H NMR (500 MHz, $CDCl_3$) δ 7.18–7.30 (m, 3H), 7.51–7.55 (m, 2H), 7.69 (dt, J=7.8, 1.4 Hz, 1H), 7.80–7.81 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 112.8, 117.8, 118.0 (d, ^2J=17 Hz), 124.4 (dd, J=7, 5 Hz), 126.0 (d, J=4, 1.2 Hz), 127.9 (d, J=9 Hz), 128.7, 130.9 (d, J=1 Hz), 132.7, 133.4, 138.2 (d, J=3 Hz), 147.8 (dd, J=251 Hz,

^{2}J=14 Hz), 150.9 (d, ^{1}J=248 Hz, ^{2}J=13 Hz); HRMS-EI *m*/*z* [M^{+}] calcd for $C_{13}H_7NF_2$ 215.05464, found 215.05441.

4.3.10. 2′-Fluoro-3′-methylbiphenyl-2-carbonitrile ***2j***. Starting from 2-fluoro-3-methylbenzeneboronic acid **1f** (508 mg, 3.30 mmol) and 2-bromobenzonitrile (500 mg, 2.75 mmol), following general procedure A and using cyclohexane/EtOAc (9:1) as eluent for the chromatography, 2′-fluoro-3′-methylbipheny-2-carbonitrile **2j** was obtained as white crystals (489 mg, 84%); mp 70–71 °C; IR (KBr) ν (cm^{-1}) 3063, 2235(CN), 1462, 1203; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (d, *J*=2.0 Hz, 3H), 7.26 (t, *J*=7.6 Hz, 1H), 7.31 (dt, *J*=7.2, 1.6 Hz, 1H), 7.42–7.46 (m, 1H), 7.60 (d, *J*=8.0 Hz, 1H), 7.65 (dt, *J*=7.6, 1.2 Hz, 1H), 7.82 (dt, *J*=8.0, 1.6 Hz, 1H), 7.98 (dd, *J*=7.6, 0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2 (d, *J*=4 Hz), 30.7, 111.8, 117.9, 124.3 (d, *J*=4 Hz), 124.9 (d, ^{2}J=18 Hz), 125.2 (d, ^{2}J=16 Hz), 128.8 (d, *J*=2 Hz), 129, 130.9, 132.5 (d, *J*=5 Hz), 133.3 (d, *J*=15 Hz), 139.0, 157.2 (d, ^{1}J=245 Hz); HRMS-EI *m*/*z* [M^{+}] calcd for $C_{14}H_{10}NF$ 211.07972, found 211.08049.

4.3.11. 2′-Fluoro-3′-methoxybiphenyl-2-carbonitrile ***2k***. Starting from 2-fluoro-3-methoxybenzeneboronic acid **1g** (800 mg, 4.71 mmol) and 2-bromobenzonitrile (715 mg, 3.93 mmol), following general procedure A and using cyclohexane/EtOAc (8:2) as eluent, 2′-fluoro-3′-methoxybiphenyl-2-carbonitrile **2k** was obtained as white crystals (654 mg, 73%); mp 133–134 °C; IR (KBr) ν (cm^{-1}) 3016, 2224 (CN), 1483, 1275; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.93 (s, 3H), 6.97 (dt, *J*=6.3, 1.3 Hz, 1H), 7.06 (dt, *J*=8.2, 1.6 Hz, 1H), 7.18 (dt, *J*=7.8, 1.5 Hz, 1H), 7.46–7.52 (m, 2H), 7.65 (dt, *J*=7.8, 1.4 Hz, 1H), 7.77 (ddd, *J*=7.8, 1.4, 0.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 56.3, 112.7, 113.9 (d, *J*=2 Hz), 118.0, 122.2, 124.0, 126.5 (d, ^{2}J=12 Hz), 128.2, 130.9, 132.4, 133.2 (d, *J*=3 Hz), 139.3, 148.1 (d, *J*=11 Hz), 149.3 (d, ^{1}J=249 Hz); HRMS-EI *m*/*z* [M^{+}] calcd for $C_{14}H_{10}ONF$ 227.07463, found 227.07359.

4.3.12. 4′-Chloro-2′-fluorobiphenyl-2-carbonitrile ***2l***. Starting from 4-chloro-1-iodo-2-fluorobenzene (500 mg, 1.95 mmol) and 2-(4,4,5,5-tetramethyl-[1,2]-dioxoborolan-2-yl)benzonitrile **1h** (536 mg, 2.34 mmol), following general procedure D and using cyclohexane/EtOAc (9:1) as eluent, 4′-chloro-2′-fluorobiphenyl-2-carbonitrile **2l** was obtained as white crystals (256 mg, 57%); mp 107–108 °C; IR (KBr) ν (cm^{-1}) 3435, 2932, 2224 (CN), 1609, 1402, 1215, 767; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–7.29 (m, 2H), 7.37 (t, *J*=7.8 Hz, 1H), 7.48 (d, *J*=7.8 Hz, 1H), 7.51 (dt, *J*=7.8, 1.0 Hz, 1H), 7.67 (dt, *J*=7.8, 1.0 Hz, 1H), 7.79 (dd, *J*=7.8, 1.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 112.8, 117.0 (d, ^{2}J=26 Hz), 117.8, 124.4 (d, *J*=15 Hz), 124.9 (d, *J*=4 Hz), 128.5, 130.9 (d, *J*=2 Hz), 131.9 (d, *J*=3 Hz), 132.6, 133.3, 136.00 (d, *J*=10 Hz), 138.45, 159.2 (d, ^{1}J=252 Hz); HRMS-EI *m*/*z* [M^{+}] calcd for $C_{13}H_7ClFN$ 231.0251, found 231.0251.

4.3.13. 2′,4′-Difluorobiphenyl-2-carbonitrile ***2m***. Starting from 1-bromo-2,4-difluorobenzene (0.14 mL, 1.24 mmol) and 2-(4,4,5,5-tetramethyl-[1,2]-dioxoborolan-2-yl)benzonitrile **1h** (340 mg, 1.49 mmol), following general procedure D and using cyclohexane/EtOAc (9:1) as eluent, 2′,4′-difluorobiphenyl-2-carbonitrile **2m** was obtained as white crystals (217 mg, 81%); mp 102–103 °C; IR (KBr) ν (cm^{-1}) 3067, 2235 (CN), 1593, 960, 856, 768; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95–7.03 (m, 2H), 7.41 (dt, *J*=8.6, 6.3 Hz, 1H), 7.47–7.52 (m, 2H), 7.67 (dt, *J*=7.7, 1.4 Hz, 1H), 7.78 (ddd, *J*=7.7, 1.4, 0.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 104.5 (t, ^{2}J=26 Hz), 112.0, 112.3 (dd, ^{2}J=21 Hz, *J*=4 Hz,), 117.8, 122.1 (dd, *J*=15, 4 Hz), 129.1, 131.1, 132.8 (dd, *J*=10, 4 Hz), 133.3, 133.5, 137.9, 159.1 (dd, ^{1}J=248 Hz, ^{3}J=12 Hz), 162.8 (dd, ^{1}J=248 Hz, ^{3}J=12 Hz); HRMS-EI *m*/*z* [M^{+}] calcd for $C_{13}H_7NF_2$ 215.05464, found 215.05473.

4.3.14. 2′-Fluoro-4′-methylbiphenyl-2-carbonitrile ***2n***. Starting from 1-bromo-2-fluoro-4-methylbenzene (0.20 mL, 1.59 mmol) and 2-(4,4,5,5-tetramethyl-[1,2]-dioxoborolan-2-yl)benzonitrile **1h** (437 mg, 1.91 mmol), following general procedure D and using cyclohexane/EtOAc (9:1) as eluent, 2′-fluoro-4′-methylbiphenyl-2-carbonitrile **2n** was obtained as white crystals (226 mg, 67%); mp 89–90 °C; IR (KBr) ν (cm^{-1}) 2925, 2225 (CN), 1627, 1438, 1266, 1127, 765; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.41 (s, 3H), 7.02–7.05 (m, 2H), 7.07 (ddd, *J*=7.8, 1.6, 0.7 Hz, 1H), 7.30 (t, *J*=7.8 Hz, 1H), 7.46 (dt, *J*=7.6, 1.2 Hz, 1H), 7.49 (ddt, *J*=7.9, 1.2, 0.6 Hz, 1H), 7.64 (dt, *J*=7.6, 1.4 Hz, 1H), 7.76 (ddd, *J*=7.7, 1.4, 0.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2, 112.8, 116.6 (d, ^{2}J=22 Hz), 118.2, 125.1 (d, *J*=3 Hz), 127.9, 130.8 (d, *J*=4 Hz), 131.0 (d, *J*=2 Hz), 132.5, 133.2, 139.8, 141.61 (d, *J*=8 Hz), 141.62, 159.2 (d, ^{1}J=248.0 Hz); HRMS-EI *m*/*z* [M^{+}] calcd for $C_{14}H_{10}FN$ 211.07972, found 211.07967.

4.3.15. 2′-Fluoro-4′-methoxybiphenyl-2-carbonitrile ***2o***. Starting from 1-bromo-2-fluoro-4-methoxybenzene (600 mg, 2.93 mmol) and 2-(4,4,5,5-tetramethyl-[1,2]-dioxoborolan-2-yl)benzonitrile **1h** (805 mg, 3.52 mmol), following general procedure D and using cyclohexane/EtOAc (9:1) as eluent, 2′-fluoro-4′-methoxybiphenyl-2-carbonitrile **2o** was obtained as white crystals (410 mg, 65%); mp 69–70 °C; IR (KBr) ν (cm^{-1}) 3079, 2223 (CN), 1624, 1477, 1125, 757; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.86 (s, 3H), 6.77 (dd, *J*=11.8, 2.0 Hz, 1H), 6.82 (ddd, *J*=8.0, 2.0, 0.7 Hz, 1H), 7.34 (t, *J*=8.7 Hz, 1H), 7.45 (dt, *J*=7.7, 1.3 Hz, 1H), 7.48 (dd, *J*=8.3, 2.0 Hz, 1H), 7.63 (dt, *J*=7.8, 1.4 Hz, 1H), 7.76 (ddd, *J*=8.0, 1.4, 0.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.7, 102.1 (d, ^{2}J=26 Hz), 110.4 (d, *J*=3 Hz), 112.9, 117.9, 118.2 (d, ^{2}J=22 Hz), 127.8, 131.1 (d, *J*=2 Hz), 131.7 (d, *J*=4 Hz), 132.5, 133.2, 139.6, 160.1 (d, ^{1}J=248 Hz), 161.7; HRMS-EI *m*/*z* [M^{+}] calcd for $C_{14}H_{10}NOF$ 227.07463, found 227.07538.

4.3.16. 5′-Chloro-2′-fluorobiphenyl-2-carbonitrile ***2p***. Starting from 5-chloro-2-fluorobenzeneboronic acid **1i** (575 mg, 3.30 mmol) and 2-bromobenzonitrile (500 mg, 2.75 mmol), following general procedure A and using cyclohexane/EtOAc (95:5) as eluent, 5′-chloro-2′-fluorobiphenyl-2-carbonitrile **2p** was obtained as white crystals (300 mg, 53%); mp 108–109 °C; IR (KBr) ν (cm^{-1}) 3074, 2221(CN), 1466, 1215, 808, 760; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (t, *J*=8.9 Hz, 1H), 7.38–7.45 (m, 2H), 7.48 (d, *J*=7.8 Hz, 1H), 7.52 (t, *J*=7.7 Hz, 1H), 7.66–7.70 (m, 1H), 7.79 (d, *J*=7.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 112.9, 117.5 (d, ^{2}J=24 Hz), 117.6, 127.3 (d, ^{2}J=17 Hz), 127.6, 128.8, 129.5 (d, *J*=4 Hz), 130.7 (d, *J*=8 Hz), 130.8 (d, *J*=1 Hz), 130.9 (d, *J*=3 Hz), 134.3, 138.2, 157.9 (d, ^{1}J=247 Hz); HRMS-EI *m*/*z* [M^{+}] calcd for $C_{13}H_7ClFN$ 231.0251, found 231.0244.

4.3.17. 2′,5′-Difluorobiphenyl-2-carbonitrile ***2q***. Starting from 1-bromo-2,5-difluorobenzene (0.58 mL, 5.18 mmol) and 2-(4,4,5,5-tetramethyl-[1,2]-dioxoborolan-2-yl)benzonitrile **1h** (1.42 g, 6.22 mmol), following general procedure D and using cyclohexane/EtOAc (9:1) as eluent, 2′,5′-difluorobiphenyl-2-carbonitrile **2q** was obtained as white crystals (862 mg, 78%); mp 87–88 °C; IR (KBr) ν (cm^{-1}) 2224 (CN), 1471, 1180; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13–7.22 (m, 3H), 7.47–7.54 (m, 2H), 7.68 (dt, *J*=7.7, 1.4 Hz, 1H), 7.79 (dd, *J*=7.7, 1.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 112.8, 117.3 (dd, ^{2}J=24 Hz, *J*=8 Hz), 117.4 (dd, ^{2}J=25 Hz, *J*=9 Hz), 117.8 (dd, ^{2}J=25 Hz, *J*=3 Hz), 117.8, 127.0 (dd, ^{2}J=17 Hz, *J*=8.1 Hz), 128.7, 130.8 (d, *J*=1 Hz), 132.7, 133.3, 138.4, 155.5 (dd, ^{1}J=241 Hz, ^{4}J=2 Hz), 158.5 (dd, ^{1}J=243 Hz, ^{4}J=2 Hz); HRMS-EI *m*/*z* [M^{+}] calcd for $C_{13}H_7F_2N$ 215.05464, found 215.05561.

4.3.18. 2′-Fluoro-5′-methylbiphenyl-2-carbonitrile ***2r***. Starting from 2-fluoro-5-methylbenzeneboronic acid **1j** (305 mg, 1.98 mmol) and 2-bromobenzonitrile (300 mg, 1.65 mmol), following general procedure A and using cyclohexane/EtOAc (9:1) as eluent, 2′-fluoro-5′-methylbiphenyl-2-carbonitrile **2r** was obtained as white crystals (251 mg, 72%); mp 77–78 °C; IR (KBr) ν (cm^{-1}) 3038, 2233 (CN),

1487, 1217, 769; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.38 (s, 3H), 7.09 (dd, J=9.8, 8.3 Hz, 1H), 7.19–7.23 (m, 2H), 7.47 (dt, J=7.7, 1.3 Hz, 1H), 7.49 (m, 1H), 7.65 (dt, J=7.7, 1.3 Hz, 1H), 7.77 (ddd, J=7.7, 1.4, 0.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.7, 112.8, 115.8 (d, ^2J=22 Hz), 118.1, 125.3 (d, ^2J=15 Hz), 128.1, 130.9 (d, J=2 Hz), 131.2 (d, J=2 Hz), 131.5 (d, J=3 Hz), 132.5, 133.2, 133.8 (d, J=4 Hz), 139.8, 157.6 (d, ^1J=245 Hz); HRMS-EI m/z [M^+] calcd for $C_{14}H_{10}FN$ 211.07972, found 211.07973.

4.3.19. 2′-Fluoro-5′-methoxybiphenyl-2-carbonitrile ***2s***. Starting from 2-fluoro-5-methoxybenzeneboronic acid **1k** (224 mg, 1.32 mmol) and 2-bromobenzonitrile (200 mg, 1.10 mmol), following general procedure A and using cyclohexane/EtOAc (9:1) as eluent, 2′-fluoro-5′-methoxybiphenyl-2-carbonitrile **2s** was obtained as white crystals (127 mg, 51%); mp 81–82 °C; IR (KBr) ν (cm^{-1}) 2222 (CN), 1475, 1215, 761; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.83 (s, 3H), 6.92–6.96 (m, 2H), 7.13 (t, J=9.1 Hz, 1H), 7.49–7.52 (m, 2H), 7.66 (dt, J=7.7, 1.2 Hz, 1H), 7.78 (dd, J=7.7, 1.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.9, 112.8, 115.8 (d, J=2 Hz), 116.0 (d, J=8 Hz), 116.8 (d, ^2J=24 Hz), 118.0, 126.1 (d, ^2J=17 Hz), 128.3, 130.9 (d, J=2 Hz), 132.6, 133.3, 139.6, 153.7 (d, ^1J=241 Hz), 155.6 (d, J=2 Hz); HRMS-EI m/z [M^+] calcd for $C_{14}H_{10}NOF$ 227.07463, found 227.07553.

4.4. General procedure for the synthesis of substituted phenanthridin-6(5*H*)-ones 3a–s

In a microwave vial were introduced a substituted 2′-fluorobiphenyl-2-carbonitrile (1 equiv) and KOH (5 equiv) in *t*-BuOH (6 mL/mmol of substituted 2′-fluorobiphenyl-2-carbonitrile). The vial was sealed and the suspension was heated under microwaves at 150 °C for the time reported in Table 2. The mixture was diluted with HCl 1 M until complete precipitation. The product was filtrated and washed with water.

4.4.1. Phenanthridin-6(5H)-one ***3a***[20]. Starting from 2′-fluorobiphenyl-2-carbonitrile **2a** (700 mg, 3.55 mmol), **3a** was obtained as a white powder (693 mg, 99%); mp >260 °C; IR (KBr) ν (cm^{-1}) 3047, 1663 (CO), 1369, 748; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.25 (t, ^3J=7.8 Hz, 1H), 7.36 (d, ^3J=8.7 Hz, 1H), 7.48 (t, ^3J=7.8 Hz, 1H), 7.63 (t, ^3J=7.8 Hz, 1H), 7.84 (t, ^3J=7.8 Hz, 1H), 8.31 (d, ^3J=7.8 Hz, 1H), 8.38 (d, ^3J=8.8 Hz, 1H), 8.50 (d, ^3J=8.8 Hz, 1H), 11.69 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 115.9, 117.4, 122.0, 122.3, 123.0, 125.6, 127.3, 127.6, 129.3, 132.5, 134.1, 136.4, 160.6; HRMS-EI m/z [M^+] calcd for $C_{13}H_9NO$ 195.0684, found 195.06911.

4.4.2. 7-Trifluoromethylphenanthridin-6(5H)-one ***3b***. Starting from 2′-fluoro-3-trifluoromethylbiphenyl-2-carbonitrile **2b** (100 mg, 0.38 mmol) **3b** was obtained as a white powder (33 mg, 33%); mp >260 °C; IR (KBr) ν (cm^{-1}) 2921, 1675 (CO), 1303, 750; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.27 (t, ^3J=7.5 Hz, 1H), 7.39 (d, ^3J=8.5 Hz, 1H), 7.53 (t, ^3J=7.5 Hz, 1H), 7.98 (t, ^3J=8.5 Hz, 1H), 8.05 (d, ^3J=7.5 Hz, 1H), 8.42 (d, ^3J=8.0 Hz, 1H), 8.85 (d, ^3J=8.0 Hz, 1H), 11.66 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 115.4, 116.3, 122.0, 123.1, 123.6, 123.8 (q, ^1J=271 Hz), 127.2 (q, J=7 Hz), 127.4, 128.7 (q, ^2J=32 Hz), 130.2, 131.9, 136.7, 137.0, 158.0; HRMS-EI m/z [M^+] calcd for $C_{14}H_8NOF_3$ 263.05578, found 263.05509.

4.4.3. 8-Methoxyphenanthridin-6(5H)-one ***3c***[5]. Starting from 2′-fluoro-4-methoxybiphenyl-2-carbonitrile **2c** (100 mg, 0.44 mmol) **3c** was obtained as a white powder (67 mg, 67%); mp 248–249 °C; IR (KBr) ν (cm^{-1}) 2902, 1667 (CO), 1368, 750; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.90 (s, 3H), 7.23 (t, J=7.8 Hz, 1H), 7.33 (d, J=8.8 Hz, 1H), 7.40–7.42 (m, 2H), 7.74 (s, 1H), 8.29 (d, J=7.8 Hz, 1H), 8.43 (d, J=8.8 Hz, 1H), 11.71 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 55.4, 108.6, 116.0, 117.7, 121.6, 122.3, 122.7, 124.6, 127.1, 127.7, 128.5, 135.5, 159.0, 160.6; HRMS-EI m/z [M^+] calcd for $C_{14}H_{11}NO_2$ 225.07896, found 225.07809.

4.4.4. 8-Nitrophenanthridin-6(5H)-one ***3d***[21]. Starting from 2′-fluoro-4-nitrobiphenyl-2-carbonitrile **2d** (100 mg, 0.41 mmol) **3d** was obtained as a white powder (100 mg, 99%); mp >260 °C; IR (KBr) ν (cm^{-1}) 2892, 1685(CO), 1340, 746; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.34 (d, ^3J=8.0 Hz, 1H), 7.42 (d, ^3J=8.0 Hz, 1H), 7.63 (t, ^3J=8.0 Hz, 1H), 8.49 (d, ^3J=8.0 Hz, 1H), 8.59 (dd, ^3J=8.8 Hz, ^4J=2.4 Hz, 1H), 8.78 (d, ^3J=8.8 Hz, 1H), 9.00 (d, ^3J=2.4 Hz, 1H), 12.05 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 116.2, 116.5, 122.9 (2C), 124.6, 124.8, 126.1, 126.4, 131.7, 137.7, 139.4, 146.3, 159.6; HRMS-EI m/z [M^+] calcd for $C_{13}H_8N_2O_3$ 240.05347, found 240.05334.

4.4.5. 9-Trifluoromethylphenanthridin-6(5H)-one ***3e***. Starting from 2′-fluoro-5-trifluoromethylbiphenyl-2-carbonitrile **2e** (100 mg, 0.38 mmol) **3e** was obtained as a white powder (70 mg, 70%); mp >260 °C; IR (KBr) ν (cm^{-1}) 1675 (CO), 1347, 1284, 1119; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.27–7.31 (m, 1H), 7.40 (d, J=7.5 Hz, 1H), 7.53–7.56 (m, 1H), 7.92 (d, J=8.3 Hz, 1H), 8.50 (d, J=8.3 Hz, 1H), 8.53 (d, J=7.9 Hz, 1H), 8.82 (s, 1H), 11.84 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 116.2, 116.7, 120.2 (q, J=4 Hz), 122.5, 123.8 (q, J=3 Hz), 123.9, 123.9 (q, ^1J=274 Hz), 128.4, 129.0, 130.5, 132.7 (q, ^2J=31 Hz), 134.9, 136.9, 159.9; HRMS-EI m/z [M^+] calcd for $C_{14}H_8NOF_3$ 263.05578, found 263.05559.

4.4.6. 9-Methylphenanthridin-6(5H)-one ***3f***[22]. Starting from 2′-fluoro-5-methylbiphenyl-2-carbonitrile **2f** (1.8 g, 8.53 mmol) **3f** was obtained as a white powder (1.77 g, 99%); mp 250–251 °C; IR (KBr) ν (cm^{-1}) 2883, 1670 (CO), 1617, 1366, 753; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.52 (s, 3H), 7.24 (t, J=7.8 Hz, 1H), 7.34 (d, J=7.8 Hz, 1H), 7.44–7.47 (m, 2H), 8.19 (d, J=7.8 Hz, 1H), 8.32 (s, 1H), 8.36 (d, J=7.8 Hz, 1H), 11.58 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.6, 116.1, 117.5, 122.2, 122.5, 123.2, 123.4, 127.5, 129.2, 129.5, 134.3, 136.7, 143.0, 160.8; HRMS-EI (g mol^{-1}) calcd for $C_{14}H_{11}NO$ 209.08405, found 209.08421.

4.4.7. 10-Methylphenanthridin-6(5H)-one ***3g***. Starting from 2′-fluoro-6-methylbiphenyl-2-carbonitrile **2g** (100 mg, 0.47 mmol) and obtained as a white powder (61 mg, 61%); mp >260 °C; IR (KBr) ν (cm^{-1}) 2858, 1654 (CO), 1377, 731; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.92 (s, 3H), 7.25 (t, J=7.8 Hz, 1H), 7.40 (d, J=7.8 Hz, 1H), 7.45–7.54 (m, 2H), 7.70 (d, J=7.8 Hz, 1H), 8.31 (d, J=7.8 Hz, 1H), 8.43 (d, J=8.8 Hz, 1H), 11.61 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 25.3, 116.0, 118.6, 121.4, 125.8, 126.9, 127.2, 127.3, 128.5, 133.1, 134.9, 136.7, 136.9, 160.7; HRMS-EI m/z [M^+] calcd for $C_{14}H_{11}NO$ 209.08405, found 209.08472.

4.4.8. 4-Chlorophenanthridin-6(5H)-one ***3h***. Starting from 3′-chloro-2′-fluorobiphenyl-2-carbonitrile **2h** (100 mg, 0.43 mmol) **3h** was obtained as a white powder (83 mg, 85%); mp 222–223 °C; IR (KBr) ν (cm^{-1}) 3056, 1656 (CO), 1608, 1360, 748; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.28 (t, J=7.8 Hz, 1H), 7.64 (d, J=7.8 Hz, 1H), 7.69 (t, J=7.8 Hz, 1H), 7.89 (t, J=7.8 Hz, 1H), 8.34 (d, J=7.8 Hz, 1H), 8.42 (d, J=8.8 Hz, 1H), 8.54 (d, J=8.8 Hz, 1H), 10.78 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 119.3, 113.6, 122.5, 122.8, 123.1, 125.5, 127.6, 128.8, 129.8, 132.8, 133.4, 133.6, 160.8; HRMS-EI m/z [M^+] calcd for $C_{13}H_8NOCl$ 229.02943, found 229.02918.

4.4.9. 4-Fluorophenanthridin-6(5H)-one ***3i***. Starting from 2′,3′-difluorobiphenyl-2-carbonitrile **2i** (100 mg, 0.46 mmol) **3i** was obtained as a white powder (88 mg, 90%); mp 257–258 °C; IR (KBr) ν (cm^{-1}) 1653 (CO), 1430, 1354, 1261, 750; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.27 (dt, J=8.1 Hz, 5.3 Hz, 1H), 7.42 (ddd, J=10.8, 8.1, 1.1 Hz, 1H), 7.70 (dt, J=7.2, 1.0 Hz, 1H), 7.89 (dt, J=7.2, 1.4 Hz, 1H), 8.24 (d, J=8.2 Hz, 1H), 8.36 (dd, J=6.8, 1.1 Hz, 1H), 8.52 (d, J=8.1 Hz,

1H), 11.62 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 114.9 (d, ^2J=17 Hz), 119.0 (d, J=4 Hz), 119.9 (d, J=3 Hz), 122.0 (d, J=7 Hz), 123.1, 125.2 (d, ^2J=13 Hz), 125.9, 127.7, 128.6, 133.1, 133.6 (d, J=2 Hz), 149.5 (d, ^1J=245.3 Hz), 160.6; HRMS-EI m/z [M$^+$] calcd for $C_{13}H_8NOF$ 213.05898, found 213.05881.

4.4.10. 4-Methylphenanthridin-6(5H)-one ***3j***[8]. Starting from 2′-fluoro-3′-methylbiphenyl-2-carbonitrile **2j** (300 mg, 1.42 mmol) **3j** was obtained as a white powder (286 mg, 96%); mp 241–243 °C; IR (KBr) ν (cm^{-1}) 3054, 1674 (CO), 1368, 741; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.51 (s, 3H), 7.20 (t, J=6.8 Hz, 1H), 7.36 (d, J=7.8 Hz, 1H), 7.65 (t, J=6.8 Hz, 1H), 7.87 (t, J=6.8 Hz, 1H), 8.28 (d, J=7.8 Hz, 1H), 8.35 (d, J=7.8 Hz, 1H), 8.53 (d, J=8.8 Hz, 1H), 10.73 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 17.7, 117.6, 121.2, 122.1, 122.8, 124.2, 125.4, 127.5, 127.9, 131.1, 133.0, 134.6, 134.8, 161.2; HRMS-EI m/z [M$^+$] calcd for $C_{14}H_{11}NO$ 209.08405, found 209.08318.

4.4.11. 4-Methoxyphenanthridin-6(5H)-one ***3k***. Starting from 2′-fluoro-3′-methoxybiphenyl-2-carbonitrile **2k** (100 mg, 0.44 mmol) **3k** was obtained as a white powder (84 mg, 85%); mp 167–168 °C; IR (KBr) ν (cm^{-1}) 3394, 1661 (CO), 1266, 1021, 746; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.93 (s, 3H), 7.15 (d, J=7.7 Hz, 1H), 7.22 (t, J=8.0 Hz, 1H), 7.65 (t, J=7.8 Hz, 1H), 7.83–7.87 (m, 1H), 7.95 (d, J=7.7 Hz, 1H), 8.35 (dd, J=8.0, 0.8 Hz, 1H), 8.46 (d, J=8.4 Hz, 1H), 10.55 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 56.0, 110.4, 114.7, 117.9, 121.9, 122.7, 125.7, 126.0, 127.4, 127.8, 132.6, 134.1, 146.0, 160.1; HRMS-EI m/z [M$^+$] calcd for $C_{14}H_{11}NO_2$ 225.07896, found 225.07855.

4.4.12. 3-Chlorophenanthridin-6(5H)-one ***3l***. Starting from 4′-chloro-2′-fluorobiphenyl-2-carbonitrile **2l** (100 mg, 0.43 mmol) **3l** was obtained as a white powder (99 mg, 99%); mp >260 °C; IR (KBr) ν (cm^{-1}) 2858, 1663 (CO), 1609, 762; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.28 (dd, J=8.8, 2.0 Hz, 1H), 7.37 (d, J=2.0 Hz, 1H), 7.65 (t, J=7.8 Hz, 1H), 7.85 (t, J=7.8 Hz, 1H), 8.29 (d, J=7.8 Hz, 1H), 8.39 (d, J=8.8 Hz, 1H), 8.47 (d, J=8.8 Hz, 1H), 11.76 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 115.3, 116.6, 122.2, 122.8, 125.3, 125.5, 127.5, 128.3, 133.1, 133.5, 133.7, 137.6, 160.8; HRMS-EI m/z [M$^+$] calcd for $C_{13}H_8NOCl$ 229.02943, found 229.0294.

4.4.13. 3-Fluorophenanthridin-6(5H)-one ***3m***. Starting from 2′,4′-difluorobiphenyl-2-carbonitrile **2m** (100 mg, 0.47 mmol) **3m** was obtained as a white powder (88 mg, 87%); mp >260 °C; IR (KBr) ν (cm^{-1}) 2873, 1693 (CO), 1358, 759; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.13–7.15 (m, 2H), 7.62–7.66 (m, 1H), 7.84–7.88 (m, 1H), 8.30 (dd, J=8.0 Hz, 1.2 Hz, 1H), 8.44–8.48 (m, 2H), 11.78 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 102.1 (d, ^2J=25 Hz), 110.0 (d, ^2J=23 Hz), 114.5, 122.7, 125.0, 125.9 (d, J=10 Hz), 127.5, 127.9, 133.1, 133.8, 138.1 (d, J=11 Hz), 161.0, 162.5 (d, ^1J=246 Hz); HRMS-EI m/z [M$^+$] calcd for $C_{13}H_8NOF$ 213.05898, found 213.05899.

4.4.14. 3-Methylphenanthridin-6(5H)-one ***3n***. Starting from 2′-fluoro-4′-methylbiphenyl-2-carbonitrile **2n** (100 mg, 0.47 mmol) **3n** was obtained as a white powder (94 mg, 94%); mp >260 °C; IR (KBr) ν (cm^{-1}) 1653 (CO), 1430, 1354, 1261, 750; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.37 (s, 3H), 7.07 (d, J=7.8 Hz, 1H), 7.14 (s, 1H), 7.59 (t, J=7.8 Hz, 1H), 7.81 (t, J=7.8 Hz, 1H), 8.24 (d, J=7.8 Hz, 1H), 8.28 (d, J=7.8 Hz, 1H), 8.43 (d, J=8.8 Hz, 1H), 11.60 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.1, 115.2, 116.0, 122.3, 123.1, 123.5, 125.3, 127.4 (2C), 132.7, 134.4, 136.6, 139.4, 161.0; HRMS-EI m/z [M$^+$] calcd for $C_{14}H_{11}NO$ 209.08405, found 209.08485.

4.4.15. 3-Methoxyphenanthridin-6(5H)-one ***3o***. Starting from 2′-fluoro-4′-methoxybiphenyl-2-carbonitrile **2o** (410 mg, 1.80 mmol) **3o** was obtained as a white powder (359 mg, 88%); mp 250–251 °C; IR (KBr) ν (cm^{-1}) 2875, 1673 (CO), 1506, 766; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.82 (s, 3H), 6.86 (dd, ^3J=6.3 Hz, ^4J=1.3 Hz, 1H), 6.90 (d, J=2.4 Hz, 1H), 7.52–7.56 (m, 1H), 7.76–7.81 (m, 1H), 8.24–8.28 (m, 2H), 8.34 (d, J=8.1 Hz, 1H), 11.58 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 55.2, 99.5, 110.1, 111.1, 121.9, 124.4, 124.7, 126.7, 127.4, 132.7, 134.5, 138.0, 160.3, 161.1; HRMS-EI m/z [M$^+$] for $C_{14}H_{11}NO_2$ 225.07896, found 225.07864.

4.4.16. 2-Chlorophenanthridin-6(5H)-one ***3p***[1c]. Starting from 5′-chloro-2′-fluorobiphenyl-2-carbonitrile **2p** (100 mg, 0.43 mmol) **3p** was obtained as a white powder (85 mg, 86%); mp >260 °C; IR (KBr) ν (cm^{-1}) 2865, 1682 (CO), 1359, 772; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.36 (d, J=8.8 Hz, 1H), 7.51 (dd, J=8.8 Hz, 2.0 Hz, 1H), 7.66 (t, J=6.8 Hz, 1H), 7.84 (t, J=7.8 Hz, 1H), 8.30 (d, J=7.8 Hz, 1H), 8.45 (d, J=2.0 Hz, 1H), 8.54 (d, J=7.8 Hz, 1H), 11.80 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 117.8, 119.0, 122.7, 122.9, 125.7, 126.4, 127.3, 128.5, 129.3, 132.8, 133.1, 135.3, 160.5; HRMS-EI m/z [M$^+$] calcd for $C_{13}H_8NOCl$ 229.02943, found 229.02916.

4.4.17. 2-Fluorophenanthridin-6(5H)-one ***3q***. Starting from 2′,5′-difluorobiphenyl-2-carbonitrile **2q** (650 mg, 3.02 mmol) **3q** was obtained as a white powder (644 mg, 99%); mp >260 °C; IR (KBr) ν (cm^{-1}) 2876, 1690 (CO), 1507, 1151, 769; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.37–7.39 (m, 2H), 7.68 (t, J=7.2 Hz, 1H), 7.84–7.88 (m, 1H), 8.25–8.28 (m, 1H), 8.32 (dd, J=8.0, 1.2 Hz, 1H), 8.51 (d, J=8.4 Hz, 1H), 11.74 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 109.1 (d, ^2J=24 Hz), 117.1 (d, ^2J=24 Hz), 117.8 (d, J=9 Hz), 118.8 (d, J=8 Hz), 123.2, 125.8, 127.4, 128.6, 132.8, 133.1, 133.5 (d, J=3 Hz), 157.8 (d, ^1J=238 Hz), 160.5; HRMS-EI m/z [M$^+$] calcd for $C_{13}H_8NOF$ 213.05898, found 213.05901.

4.4.18. 2-Methylphenanthridin-6(5H)-one ***3r***[23]. Starting from 2′-fluoro-5′-methylbiphenyl-2-carbonitrile **2r** (400 mg, 1.89 mmol) **3r** was obtained as a white powder (386 mg, 97%); mp 256–258 °C; IR (KBr) ν (cm^{-1}) 3012, 1657 (CO), 1608, 770; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.40 (s, 3H), 7.24–7.31 (m, 2H), 7.61 (t, J=7.8 Hz, 1H), 7.83 (t, J=7.8 Hz, 1H), 8.19 (s, 1H), 8.30 (d, J=7.8 Hz, 1H), 8.47 (d, J=7.8 Hz, 1H), 11.60 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 20.7, 116.0, 117.4, 122.6, 123.1, 125.7, 127.5, 127.8, 130.6, 131.2, 132.7, 134.2, 134.4, 160.7; HRMS-EI m/z [M$^+$] calcd for $C_{14}H_{11}NO$ 209.08405, found 209.08402.

4.4.19. 2-Methoxyphenanthridin-6(5H)-one ***3s***. Starting from 2′-fluoro-5′-methoxybiphenyl-2-carbonitrile **2s** (300 mg, 1.32 mmol) **3s** was obtained as a white powder (233 mg, 78%); mp 167–168 °C; IR (KBr) ν (cm^{-1}) 2875, 1674 (CO), 1506, 766; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.86 (s, 3H), 7.14 (dd, J=8.8 Hz, 2.9 Hz, 1H), 7.29 (d, J=8.8 Hz, 1H), 7.63 (t, J=7.8 Hz, 1H), 7.82–7.86 (m, 2H), 8.30 (d, J=7.8 Hz, 1H), 8.54 (d, J=7.8 Hz, 1H), 11.58 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 55.6, 106.1, 106.2, 117.3, 117.8, 118.3, 123.0, 125.9, 127.5, 128.0, 130.7, 132.6, 134.1, 154.8, 160.4; HRMS-EI m/z [M$^+$] calcd for $C_{14}H_{11}NO_2$ 225.07896, found 225.07836.

4.5. Sequential synthesis of 1-methoxyphenanthridin-6(5*H*)-one 3t

To a solution of 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl (*S*-PHOS) (49 mg, 0.12 mmol) in 15 mL of a DME/water mixture (2:1) was added $Pd(OAc)_2$ (13 mg, 0.06 mmol) at room temperature. The solution was heated at 80 °C for 10 min. 2-bromobenzonitrile (200 mg, 1.10 mmol), 2-fluoro-6-methoxybenzeneboronic acid **1l** (374 mg, 2.20 mmol), and Na_2CO_3 (175 mg, 1.65 mmol) were added. The resulting mixture was heated at reflux for 24 h, and partitioned in 30 mL of water and 30 mL of ethyl acetate. The combined layers were filtrated through a short pad of Celite. The organic layer was washed with water (2×30 mL), dried over $MgSO_4$, filtrated, and evaporated. The crude was then

filtrated through a short pad of silica gel using cyclohexane/EtOAc (95:5) as eluent. The crude was introduced in a microwave vial with KOH (309 mg, 5.50 mmol) in 3 mL of *t*-BuOH. The vial was sealed and the suspension was heated under microwaves at 150 °C for 5 min. A solution of HCl 1 M was added to the reaction mixture until precipitation, the resulting product was filtrated and washed with water and diethyl ether. 1-methoxyphenanthridin-6(5*H*)-one **3t** was obtained as a white powder (84 mg, 34%); mp >260 °C; IR (KBr) ν (cm^{-1}) 2964, 1672 (CO), 1606; ^1H NMR (400 MHz, DMSO-d_6) δ 4.02 (s, 3H), 6.92 (d, J=8.8 Hz, 1H), 7.01 (d, J=7.8 Hz, 1H), 7.42 (dt, J=7.8 Hz, 1H), 7.60 (t, J=6.8 Hz, 1H), 7.80 (t, J=7.8 Hz, 1H), 8.36 (d, J=7.8 Hz, 1H), 9.17 (d, J=7.8 Hz, 1H), 11.70 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 55.8, 105.0, 107.0, 108.9, 125.6, 126.8, 127.0, 127.4, 129.5, 132.3, 133.9, 138.2, 158.3, 160.6; HRMS-EI m/z [M^+] calcd for $C_{14}H_{11}NO_2$ 225.07896, found 225.07834.

Supplementary data

Supplementary data that may be helpful in the review process should be prepared and provided as a separate electronic file. That file can then be transformed into PDF format and submitted along with the manuscript and graphic files to the appropriate editorial office. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.05.014.

References and notes

1. (a) Lehtio, L.; Jemth, A. S.; Collins, R.; Loseva, O.; Johansson, A.; Markova, N.; Hammarstro, M.; Flores, A.; Holmberg-Schiavone, L.; Weigelt, J.; Helleday, T.; Schüler, H.; Karlberg, T. *J. Med. Chem.* **2009**, *52*, 3108–3111; (b) Pegoraro, S.; Lang, M.; Dreker, T.; Kraus, J.; Hamm, S.; Meere, C.; Feurle, J.; Tasler, S.; Prütting, S.; Kuras, Z.; Visan, V.; Grissmer, S. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2299–2304; (c) Patil, S.; Kamath, S.; Sanchez, T.; Neamati, N.; Schinazic, R. F.; Buolamwinia, J. K. *Bioorg. Med. Chem.* **2007**, *15*, 1212–1228; (d) Ishida, J.; Yamamoto, H.; Kido, Y.; Kamijo, K.; Murano, K.; Miyake, H.; Ohkubo, M.; Kinoshita, T.; Warizaya, M.; Iwashita, A.; Mihara, K.; Matsuokac, N.; Hattori, K. *Bioorg. Med. Chem.* **2006**, *14*, 1378–1390; (e) Ishida, J.; Hattori, K.; Yamamoto, H.; Iwashita, A.; Miharab, K.; Matsuoka, N. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4221–4225; (f) Li, J. H.; Serdyuk, L.; Ferraris, D. V.; Xiao, G.; Tays, K. L.; Kletzly, P. W.; Li, W.; Lautar, S.; Zhang, J.; Kalish, V. J. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1687–1690; (g) Dow, R. L.; Chou, T. T.; Bechle, B. M.; Goddard, C.; Larson, E. R. *J. Med. Chem.* **1994**, *37*, 2224–2231.
2. (a) Horning, E. C.; Stromberg, V. L.; Lloyd, H. A. *J. Am. Chem. Soc.* **1952**, *74*, 5153–5155; (b) Smith, P. A. S. *J. Am. Chem. Soc.* **1948**, *70*, 320–323.
3. Ames, D. E.; Opalko, A. *Tetrahedron* **1984**, *40*, 1919–1925.
4. Harayama, T.; Kawata, Y.; Nagura, C.; Sato, T.; Miyagoe, T.; Abe, H.; Takeuchi, Y. *Tetrahedron Lett.* **2005**, *46*, 6091–6094.
5. Bernini, R.; Cacchi, S.; Fabrizi, G.; Sferrazza, A. *Synthesis* **2008**, 729–738.
6. Siddiqui, M. A.; Snieckus, V. *Tetrahedron Lett.* **1988**, *29*, 5463–5466.
7. Banwell, M. G.; Lupton, D. W.; Ma, X.; Renner, J.; Sydnes, M. O. *Org. Lett.* **2004**, *6*, 2741–2744.
8. Ferraccioli, R.; Carenzi, D.; Rombola, O.; Catellani, M. *Org. Lett.* **2004**, *6*, 4759–4762.
9. (a) Donati, L.; Michel, S.; Tillequin, F.; Porée, F. H. *Org. Lett.* **2010**, *12*, 156–158; (b) Furuta, T.; Kitamura, Y.; Hashimoto, A.; Fujii, S.; Tanaka, K.; Kan, T. *Org. Lett.* **2007**, *9*, 183–186.
10. (a) Cailly, T.; Fabis, F.; Legay, R.; Oulyadi, H.; Rault, S. *Tetrahedron* **2007**, *63*, 71–76; (b) Cailly, T.; Fabis, F.; Rault, S. *Tetrahedron* **2006**, *62*, 5862–5867.
11. Cailly, T.; Begtrup, M. *Tetrahedron* **2010**, *66*, 1299–1307.
12. Yougnia, R.; Rochais, C.; Sopkovà-de Oliveira Santos, J.; Dallemagne, P.; Rault, S. *Tetrahedron* **2010**, *66*, 2803–2808.
13. Matharu, A. S.; Cowling, S. J.; Wright, G. *Liq. Cryst.* **2007**, *34*, 489–506.
14. Cameron, M.; Foster, B. S.; Lynch, J. E.; Shi, Y. J.; Dolling, U. H. *Org. Process Res. Dev.* **2006**, *10*, 398–402.
15. Vedejs, E.; Chapman, R. W.; Fields, S. C.; Lin, S.; Schrimpf, M. R. *J. Org. Chem.* **1995**, *60*, 3020–3027.
16. (a) Miao, G.; Ye, P.; Yu, L.; Baldino, C. M. *J. Org. Chem.* **2005**, *70*, 2332–2334; (b) Arvela, R. K.; Leadbeater, N. E. *Org. Lett.* **2005**, *7*, 2101–2104; (c) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250–6284.
17. Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685–4696.
18. Suffert, J. *J. Org. Chem.* **1989**, *54*, 509–510.
19. Lysén, M.; Kristensen, J. L.; Vedsø, P.; Begtrup, M. *Org. Lett.* **2002**, *4*, 257–259.
20. Padwa, A.; Brodney, M. A.; Liu, B.; Satake, K.; Wu, T. *J. Org. Chem.* **1999**, *64*, 3595–3607.
21. Nunn, A. J. *J. Chem. Soc.* **1952**, 2797–2803.
22. Zhou, Q. J.; Worm, K.; Dolle, R. E. *J. Org. Chem.* **2004**, *69*, 5147–5149.
23. Grimshaw, J.; Prasanna de Silva, A. *J. Chem. Soc., Chem. Commun.* **1980**, 302–303.