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Regioselective functionalization of 2-(2′-fluorophenyl)-3-cyanopyridine and its cyclization to benzo[*h*]-1,6-naphthyridines

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ABSTRACT

Benzo[*h*]-1,6-naphthyridines and 5-ones, selectively functionalized at C-2, C-3, C-5 and C-10, were obtained by alkyllithium-, lithium amide- or potassium hydroxide-induced anionic cyclization of 3-cyano-2-(2-fluorophenyl)pyridine, which was functionalized regioselectively at positions 4, 5, 6, and 6′.

1. Introduction

The azaphenanthrene ring is found in a number of important biologically active, naturally occuring[1] and synthetic compounds.[2] However, only a few regioselective methods leading to substituted azaphenanthrenes have been described. This limits further exploration of azaphenanthrenes and restricts structure–activity relationship analysis. Recently, two procedures for preparation of azaphenanthrenes based on anionic cyclization of 2-cyano-2′-fluorobiaryl were reported. The 2-cyano-2′-fluorobiaryls were treated with alkyllithium, aryllithium, or lithium amides to give 5-alkyl, phenyl or amino substituted phenantridines.[3] Alternatively, ring closure was effected by treatment of 2-cyano-2′-fluorobiaryls with potassium hydroxide to give phenanthridin-5-ones.[4] These protocols seem suitable for preparation of other azaphenanthrenes, such as benzonaphthyridines and pyridonaphthyridines substituted at the position adjacent to the nitrogen in ring B. Regioselective functionalization of the 2-cyano-2′-fluorobiaryl prior to cyclization would lead to the desired regioselectively-substituted azaphenanthrenes (Fig. 1).

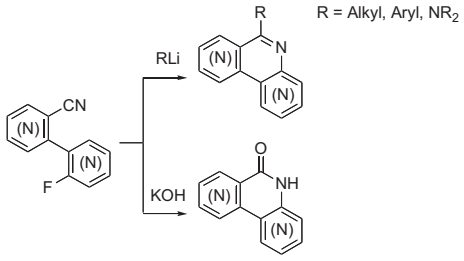

Figure 1. Anionic ring closure of azaphenanthrenes.

The present paper deals with the synthesis of regioselectively-substituted 2-(2-fluorophenyl)nicotinonitriles **1** followed by cyclization to regioselectively-substituted benzo[*h*]-1,6-naphthyridines. Examples on further transformation of substituents after cyclization are given in Figure 2.

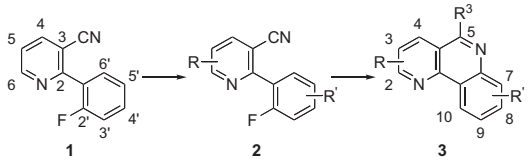

Figure 2. Strategy for the synthesis of substituted benzo[*h*]-1,6-naphthyridines.

2. Results and discussion

The reaction of nicotinonitrile **1**[4a,5] with base depended on the nature of the base. The hard nucleophiles lithium morpholide or potassium hydroxide attacked the nitrile **1** at the cyano group whereupon cyclization took place.[4,5] In contrast, the softer nucleophile phenyllithium reacted with selective addition at the 6-position of **1** affording a mixture of dihydropyridine **4d** and pyridine **2d**.[6] Oxidation of the crude mixture using DDQ afforded pure 2-(2-fluorophenyl)-6-phenylnicotinonitrile **2d** in 66% yield (Table 1).

Similarly, *n*-BuLi and *t*-BuLi reacted with addition at the 6-position of **1**. When adding iodine as an oxidant the aromatic products **2b**–**d** could be obtained in one pot (Table 1). Under identical conditions, the relatively harder nucleophile MeLi reacted both with addition at the 6-position and at the cyano group of **1** producing 2-(2-fluorophenyl)-6-methylnicotinonitrile **2a** and 5-methylbenzo[*h*]-1,6-naphthyridine **3a** in almost equal amounts.

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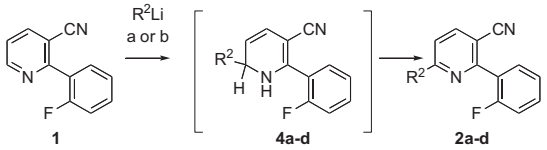
Table 1
Addition of alkyl and phenyllithium to nitrile **1**

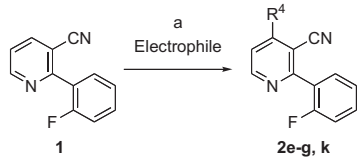


R^2	Conditions	Product	Yield[a] (%)
Me	a	**2a**	19 (42)
n-Bu	a	**2b**	62
t-Bu	a	**2c**	71
Ph	a	**2d**	70
	b	**2d**	66

Conditions a: R^2Li 1.05 equiv, THF, −78 °C, 30 min, rt, 30 min, I_2 2.2 equiv, rt, 1 h. b: R^2Li 1.05 equiv, THF, −78 °C, 30 min, rt, 30 min, DDQ 1.0 equiv, DCM, rt, 1 h.
[a] Isolated yields; yields in parentheses are ^{1}H NMR yields.

Treatment of nitrile **1** with the non-nucleophilic base LiTMP for 30 min at −78 °C caused regioselective abstraction of H-4 since only this proton was exchanged with deuterium when the anion was quenched with CD_3OD. The regioselectivity is in accord with that observed upon deprotonation of 2-chloronicotinonitrile.[7] The anion formed could be trapped with electrophiles, such as iodine, dimethyl disulfide, chlorotrimethylsilane or benzoyl chloride to give 4-substituted nicotinonitriles **2e**–**g** (Table 2). Tetrabromomethane failed to react under similar conditions.

Table 2
ortho-Lithiation of nitrile **1** followed by addition of an electrophile

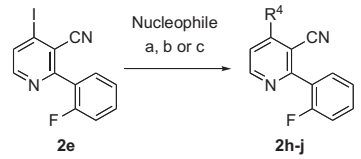


Electrophile	R^4	Product	Yield[a] (%)
I_2	I	**2e**	72
PhCOCl	PhCO	**2f**	26
Me_3SiCl	Me_3Si	**2g**	28
MeSSMe	MeS	**2k**	70

Conditions a: LiTMP 1.05 equiv, THF, −78 °C, 30 min; electrophile 1.1 equiv, THF, −78 °C, 1 h, rt, 16 h.
[a] Isolated yields.

The 4-iodo compound **2e** reacted with nucleophilic displacement of iodide when treated with lithium phenoxide or lithium amide under mild conditions (Table 3).[8] This reaction gives access to a range of 4-subtituted cyanopyridines like **2h**–**j**.

Table 3
Nucleophilic displacement of iodide in the 4-iodo compound **2e**

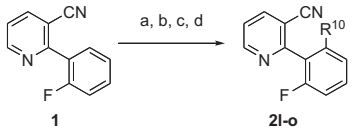


Start. mat.	Nucleophile	Conditions	Product	R^4	Yield[a] (%)
2e	MePhNK	a	**2h**	MePhN	96
2e	MeONa	b	**2i**	MeO	82
2e	C_6H_5OK	c	**2j**	C_6H_5O	60

Conditions a: *N*-methylaniline 1.35 equiv, KHMDS 1.3 equiv, THF, rt, overnight. b: MeONa 3.0 equiv, MeOH, rt, 24 h. c: Phenol 1.35 equiv, KHMDS 1.3 equiv, THF, rt, 16 h.
[a] Isolated yields.

Position 6′ of nicotinonitrile **1** could be functionalized via oxidative palladation using palladium(II) acetate followed by reaction with *N*-chlorosuccinimide.[9] At 100 °C the desired 6′-chloro compound **2l** was obtained in 27% yield. The yield increased to 58% when running the reaction at 150 °C (microwave) in the presence of copper(II) acetate as a co-catalyst (Table 4). When using *N*-bromosuccinimide the corresponding 6′-bromo compound **2m** was obtained in 66% yield. When using (diacetoxyiodo)benzene as the reagent 2-(3-cyanopyridin-2-yl)-3-fluorophenyl acetate **2o** was obtained in 62% yield. If the solvent was changed from acetic acid to acetic acid-methanol 1:1 2-(2-fluoro-6-methoxyphenyl)nicotinonitrile **2n** was obtained in 57% yield, the formation of **2n** failing in the absence of acetic acid. For the reactions using (diacetoxyiodo)benzene higher yields were obtained when copper(II) acetate was omitted.

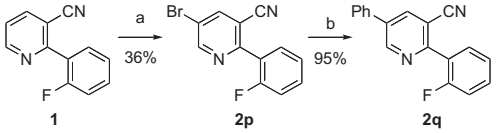
Table 4
Oxidative palladation of **1**



Start. mat.	Conditions	Product	R^{10}	Yield[a] (%)
1	a	**2l**	Cl	58
1	b	**2m**	Br	66
1	c	**2n**	MeO	57
1	d	**2o**	AcO	62

Conditions a: NCS 2 equiv, $Pd(OAc)_2$ 10 mol %, $Cu(OAc)_2$ 10 mol %, MeCN, sealed tube, microwave 150 °C, 2h. b: NBS 2 equiv, $Pd(OAc)_2$ 10 mol %, $Cu(OAc)_2$ 10 mol %, MeCN, sealed tube, microwave, 150 °C, 2 h. c: $PhI(OAc)_2$ 2 equiv, $Pd(OAc)_2$ 10 mol %, MeOH–AcOH 1:1, sealed tube, oil bath 100 °C, 24 h. d: $PhI(OAc)_2$ 2 equiv, $Pd(OAc)_2$ 10 mol %, AcOH, sealed tube, oil bath 80 °C, 24 h.
[a] Isolated yields.

By bromination of the nicotinonitrile **1** only the 5-substituted derivative **2p** was observed. The highest yields (36%) were obtained by heating a solution of **1** in AcOH to 100 °C with a large excess of bromine and sodium acetate. As the solvent acetic acid was superior to DMF, dioxane, acetonitrile or CCl_4. Addition of catalytic amounts of $AlCl_3$ or iron powder did not improve the yield. The bromo compound **2p** could be arylated by palladium catalyzed cross-coupling with phenylboronic acid to give **2q**[10] (Scheme 1).

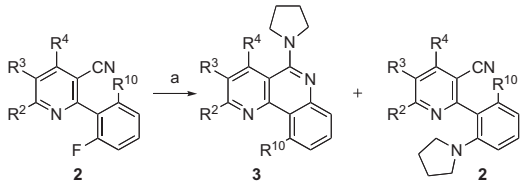


Scheme 1. Bromination of nitrile **1** followed by arylation. Conditions a: Br_2 10 equiv, AcONa 10 equiv, 100 °C, 24 h, AcOH. b: $PhB(OH)_2$, 1.5 equiv, $NaHCO_3$ 4.0 equiv, PPh_3 10 mol %, $Pd(OAc)_2$ 5 mol %, DME–H_2O 2:1, 80 °C 24 h.

A selection of the functionalized phenylpyridines thus obtained was treated with lithium pyrrolidide, which attacks the cyano group producing an iminum anion then replacing fluoride with the formation of a ring (Table 5). It has been demonstrated that dry lithium chloride promotes the cyclization reaction in favor of undesired competing replacement of fluoride with pyrrolidide.[5] Promoted by lithium chloride, **1** and lithium pyrrolidide provided the cyclized product **3** and the substitution product **2** in the ratio 84:16. Similarly **2b**, **d**, **p**, **q**, **l**, and **m** produced a mixture of corresponding **3** and **2** (Table 5). Compound **2m** reacted more sluggishly than **2l**. Presumably, the bulky bromine atom of **2m** impedes the geometrical requirements for successful cyclization. In contrast **2b**, reacted selectively to give the cyclization product **3b** exclusively,

while **2e**, **2i**, **2j**, and **2k** reacted with substitution at the 4-position all to give 2-(2-fluorophenyl)-4-pyrrolidin-1-ylnicotinonitrile **2y**. Under similar conditions neither **2h** nor **2y** did react with lithium pyrrolidide (Table 6).

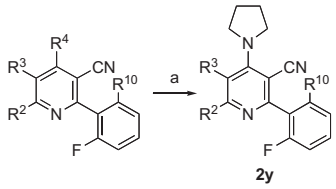
Table 5
Anionic cyclization of cyanopyridines **2** by treatment with lithium pyrrolidide



Start. mat.	R^2	R^3	R^4	R^{10}	Product	Yield[a] (%)	Product	Yield[a] (%)
2b	*n*-Bu	H	H	H	**3b**	23 (32)	**2r**	0
2d	Ph	H	H	H	**3c**	50 (52)	**2s**	32 (48)
2P	H	Br	H	H	**3d**	(0)	**2t**	0
2q	H	Ph	H	H	**3e**	53 (83)	**2u**	(17)
2l	H	H	H	Cl	**3f**	38 (45)	**2v**	43 (55)
2m	H	H	H	Br	**3g**	43 (45)	**2x**	29 (39)

Conditions a: Li-pyrrolidide 1.2 equiv, LiCl 5 equiv, THF, −78 °C, 16 h.
[a] Isolated yields; yields in parentheses are ^{1}H NMR yields.

Table 6
Nucleophilic substitution at C-4 of cyanopyridines **2** by treatment with lithium pyrrolidide



Start. mat.	R^2	R^3	R^4	R^{10}	Product	Yield (%)[a]
2e	H	H	I	H	**2y**	83 (100)
2h	H	H	PhMeN	H	No reaction	
2y	H	H	1-Pyrrolidinyl	H	No reaction	
2i	H	H	MeO	H	**2y**	(65)
2j	H	H	PhO	H	**2y**	(61)
2k	H	H	MeS	H	**2y**	(100)

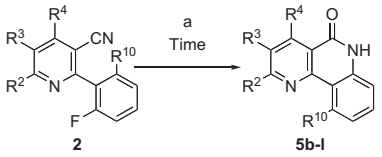
Conditions a: Li-pyrrolidide 1.2 equiv, LiCl 5 equiv, THF, −78 °C, 16 h.
[a] Isolated yields; yields in parentheses are ^{1}H NMR yields.

The failure of 4-substituted-2-(2-fluorophenyl)nicotinonitriles **2h** and **2y** to cyclize when treated with lithium pyrrolidide may be due steric impediment or to competing nucleophilic addition of pyrrolidide to C-4 with the formation of a 4-pyrrolidinyl-dihydropyridine, which during work-up eliminates pyrrolidine reversibly with regeneration of the starting material.

Selected substituted phenylpyridines were then subjected to potassium hydroxide-mediated cyclization. Reactions were run in methanol at 150 °C using microwave irradiation (Table 7). Compounds **2b** and **2d** furnished the expected products **5b** and **5c** within 10 min in 65 and 91% yield. Again the 6-*n*-butyl compound **2b** reacted more sluggishly than the 6-phenyl analog **2d**. In the case of **2l**, the reaction time had to be extended to 1 h to give **5k** in 62% yield. Attempts to cyclize **2p**, **2e** gave low conversion while **2i** gave a complex mixture.

As an example, the phenanthridinone **5a**[4a] was treated with phosphorus oxychloride to provide 5-chlorobenzo[*h*]-1,6-naphthyridine **3h**. The 5-chloronaphthyridines served as versatile intermediates for further transformations like dehalogenation to give **3i** in 78% yield, palladium catalyzed cross-coupling with aryl boronic acids to give **3j** in 92% yield or aromatic nucleophilic substitution to give **3k** in 75% yield (Table 8).

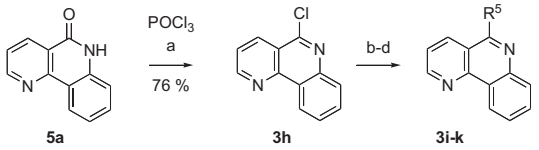
Table 7
Anionic cyclization of cyanopyridines **2** by treatment with potassium hydroxide



Start. mat.	R^2	R^3	R^4	R^{10}	Time (min)	Product	Yield[a] (%)
2b	*n*-Bu	H	H	H	10	**5b**	65
2d	Ph	H	H	H	10	**5c**	91
2p	H	Br	H	H	60	**5d**	Trace
2q	H	Ph	H	H	10	**5e**	76
2e	H	H	I	H	10	**5f**	Trace
2h	H	H	PhMeN	H	10	**5g**	0
2y	H	H	1-Pyrrolidinyl	H	10	**5h**	0
2i	H	H	MeO	H	10	**5i**	Trace
2j	H	H	PhO	H	10	**5j**	0
21	H	H	H	Cl	60	**5k**	62
2n	H	H	H	MeO	120	**5l**	60

Conditions a: KOH 5.0 equiv, MeOH sealed tube, 150 °C, mw.
[a] Isolated yields.

Table 8
Synthesis of 5-substituted benzo[*h*]-1,6-naphthyridines **3** from benzonaphthyridin-5-ones **5a**



Start. mat.	R^5	Conditions	Product	Yield[a] (%)
5a	H	a, b	**3i**	78
5a	2-Benzothiophen-2-yl	a, c	**3j**	92
5a	2-Me-(C_6H_4)-NH	a, b	**3k**	75

Conditions a: $POCl_3$ 100 °C, 24 h. b: $HCOONH_4$ 4.0 equiv, Pd/C 10 mol %, MeOH reflux, 24 h. c: Benzothiophene-2-yl boronic acid 1.5 equiv, $NaHCO_3$ 4 equiv, PPh_3 10 mol %, $Pd(OAc)_2$ 5 mol %, DME-H_2O 2:1, 80 °C, 24 h. d: *o*-Toluidine 3.0 equiv, NaHMDS 1.5 equiv, THF, rt overnight.
[a] Isolated yields in the last reaction step.

3. Conclusion

Representative series of regioselectively-substituted benzo[*h*]-1,6-naphthyridines **3** functionalized at C-2, C-3, C-5, and C-10 have been obtained by cyclization of anions generated from correspondingly substituted 2-(2-fluorophenyl)nicotinonitriles **1**. The nature of the substituent at C-5 is determined by the base used for effecting the cyclization. Thus, hard carbon nucleophiles or lithium amides at low temperatures afforded naphthyridines **3** with carbon or nitrogen substituents at C-5, while potassium hydroxide at elevated temperatures yielded naphthyridin-5-ones **5**. Treatment of these with $POCl_3$ led to 5-chloronaphthyridines that underwent facile arylation at C-5 or replacement of the chlorine with nucleophiles. The substituents at C-2, C-3, and C-10 of benzonaphthyridines **3** were introduced in the parent cyanopyridine **1** prior to the base promoted cyclization. Thus, the 6-positon of cyanopyridine **1** could be functionalized with alkyl or aryl groups by nucleophilc addition of soft carbon bases followed by oxidation. The 5-position of cyanopyridine **1** could be brominated and the bromine replaced with an aryl group using a Suzuki cross-coupling protocol. The 6′-position of cyanopyridine **1** could be functionalized with Cl, Br, OMe or OAc via oxidative palladation before cyclization to the corresponding C-10 substituted naphthyridines **5**. The 4-position of cyanopyridine **1** could be functionalized regioselectively via deprotonation using KHMDS followed by addition of an

electrophile. Halogen thus introduced was replaced with oxygen and nitrogen nucleophiles. However, the 4-substituted 3-cyanopyridines did not cyclize to the corresponding C-4 substituted benzonaphthyridines when treated with alkyllithium, lithium amide or potassium hydroxide. The developed protocols may be useful for the synthesis of other substituted cyanoarylpyridines and azaphenanthrenes.

4. Experimental section

4.1. General methods

All reactions involving air- and moisture sensitive reagents were performed under N_2 using syringe-septum cap techniques. THF was distilled from Na/benzophenone and MeCN from P_2O_5. LiCl was dried under vacuum for 2 h at 130 °C prior to use. *n*-Butyllithium, *tert*-butyllithium, phenyllithium, and methyllithium commercial solutions were titrated prior to use.[11] Benzoyl chloride was distilled prior to use. All other chemicals were used as received from commercial suppliers. All ^{1}H NMR spectra were recorded at 300 MHz on a Varian Mercury spectrometer except for compound **3j** for which the spectrum was recorded on a Bruker Avance DRX-600 at 600 MHz. All ^{13}C NMR spectra were recorded at 75 MHz on a Varian Gemini spectrometer except for compound **3j** for which the spectrum was recorded on a Bruker Avance DRX-600 at the frequency of 150 MHz. Melting points were recorded on an automated OptiMelt, from Stanford research systems. The microwave reactions were performed using a Biotage Initiator microwave oven. Temperatures were measured with an IR-sensor and the reactions are given as hold times. Silica gel 60 (0.063–0.200 nm) was used for silica gel chromatography.

4.2. General procedure for the synthesis of 6-substituted-2-(2-fluorophenyl)nicotinonitrile 2a–d

A flamed dried Schlenk flask under nitrogen was charged with 2-(2-fluorophenyl)nicotinonitrile **1** (0.200 g, 1.01 mmol) and THF (6 mL). The flask was cooled to −80 °C and the chosen aryl or alkyllithium reagent (1.06 mmol) was added. After stirring for 0.5 h, the reaction vessel was allowed to reach room temperature. After 0.5 h at room temperature a solution of water (0.036 mL, 2.02 mmol) in THF (3 mL) was added. The obtained solution was stirred for 5 min and a solution of iodine (0.564 g, 2.22 mmol) in THF (6 mL) was added. The resulting mixture was stirred for 1 h, a saturated solution of sodium thiosulfate (35 mL) was poured into the flask and extraction was performed using EtOAc (3×35 mL). The organic phases were dried over $MgSO_4$, filtered and solvents were removed under reduced pressure. The crude mixture was then purified by silica gel chromatography.

*4.2.1. 2-(2-Fluorophenyl)-6-methylnicotinonitrile **2a**.* Following the general procedure, using methyllithium (1.060 mL, 1 M THF/cumene) and EtOAc/*n*-heptane (1/4) as the eluent for the chromatography giving **2a** as a yellow powder (0.041 g, 19%). Mp 49–50 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.71 (s, 3H), 7.19–7.31 (m, 3H), 7.44–7.50 (m, 1H), 7.55 (td, *J*=7.5 and 1.7 Hz, 1H), 7.95 (d, ^3J=7.8 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=25.6, 107.8 (d, *J*=1 Hz), 116.6 (d, ^2J=22 Hz), 117.3 (d, *J*=1 Hz), 122.4, 124.9 (d, *J*=3 Hz), 126.2 (d, ^2J=14 Hz), 131.6 (d, *J*=2 Hz), 132.2 (d, ^3J=8 Hz), 141.0, 151.2 (d, *J*=1 Hz), 160.1 (d, ^1J=249 Hz), 163.2 ppm. $C_{13}H_9FN_2$ (212.23): calcd C, 73.57; H, 4.27; N, 13.20, found C, 73.27; H, 4.15; N, 13.01. *5-Methylbenzo[h]-1,6-naphthyridine **3a***: yellow powder (0.060 g, 31%). Mp 96–98 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.05 (s, 3H), 7.62 (dd, ^3J=8.2 and 4.4 Hz, 1H), 7.67–7.72 (m, 1H), 7.78–7.83 (m, 1H), 8.09 (dd, *J*=8.2 and 1.2 Hz, 1H), 8.48 (dd, ^3J=8.2 Hz, ^4J=1.7 Hz, 1H), 9.08 (dd, *J*=8.2 and 1.5 Hz, 1H), 9.14 (dd, ^3J=4.4 Hz, ^4J=1.7 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=23.0, 120.8, 122.7, 124.0, 125.1, 127.2, 128.9, 130.7, 134.3, 145.9, 148.8, 153.0, 158.8 ppm. HRMS (ESI) calcd for $C_{13}H_{11}N_2$ 195.0922, found 195.0929.

*4.2.2. 6-Butyl-2-(2-fluorophenyl)nicotinonitrile **2b**.* Following the general procedure, using *n*-butyllithium (0.628 mL, 1.6 M in *n*-hexane) and EtOAc/*n*-heptane (1/9) as the eluent for the chromatography giving **2b** as a colorless oil (0.159 g, 62%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.97 (t, *J*=7.3 Hz, 3H), 1.42 (st, *J*=7.6 Hz, 2H), 1.76 (m, 2H), 2.92 (t, *J*=7.9 Hz, 2H), 7.18–7.30 (m, 3H), 7.43–7.50 (m, 1H), 7.56 (td, *J*=7.5 and 1.7 Hz, 1H), 7.95 (d, ^3J=8.3 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.3, 22.9, 32.1, 38.9, 107.8, 116.7 (d, ^2J=21 Hz), 117.4, 121.7, 124.9 (d, *J*=4 Hz), 126.3 (d, ^2J=14 Hz), 131.7, 132.2 (d, ^3J=8 Hz), 141.1, 157.1, 160.1 (d, ^1J=250 Hz), 167.3 ppm. $C_{16}H_{15}FN_2$ (254.31): calcd C, 75.57; H, 5.95; N, 11.02, found C, 75.52; H, 5.79; N, 10.94.

*4.2.3. 6-tert-Butyl-2-(2-fluorophenyl)nicotinonitrile **2c**.* Following the general procedure, using *tert*-butyllithium (0.624 mL, 1.7 M in pentane) and EtOAc/*n*-heptane (1/9) as the eluent for the chromatography giving **2c** as an orange oil (0.180 g, 71%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.41 (s, 9H), 7.17–7.25 (m, 1H), 7.29 (td, *J*=7.5 and 1.7 Hz, 1H), 7.44 (d, ^3J=8.2 Hz, 1H), 7.44–7.52 (m, 1H), 7.61 (td, *J*=7.5 and 1.7 Hz, 1H), 7.97 (d, ^3J=8.2 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=30.2, 38.8, 107.3 (d, *J*=1 Hz), 116.6 (d, ^2J=22 Hz), 117.6 (d, *J*=1 Hz), 118.1, 124.7 (d, *J*=3 Hz), 126.7 (d, ^2J=14 Hz), 132.0 (d, ^3J=5 Hz), 132.0 (br s), 141.2, 156.2 (d, *J*=1 Hz), 160.2 (d, ^1J=249 Hz), 173.8 ppm. HRMS (ESI) calcd for $C_{16}H_{15}FN_2Na$ 277.1115, found 277.1120.

*4.2.4. 2-(2-Fluorophenyl)-6-phenylnicotinonitrile **2d**.* Following the general procedure, using phenyllithium (1.060 mL, 2 M in Bu_2O) and EtOAc/*n*-heptane (1/9) as the eluent for the chromatography giving **2d** as a white powder (0.196 g, 70%). Mp 101–103 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.26 (t, *J*=9.0 Hz, 1H), 7.33 (t, *J*=7.5 Hz, 1H), 7.47–7.54 (m, 4H), 7.69 (td, *J*=7.5 and 1.7 Hz, 1H), 7.85 (d, ^3J=8.3 Hz, 1H), 8.08–8.12 (m, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=108.3, 116.4 (d, ^2J=21 Hz), 117.6, 118.6, 124.6 (d, *J*=3 Hz), 126.2 (d, ^2J=14 Hz), 127.6, 129.2, 130.8, 131.7 (d, *J*=2 Hz), 132.1 (d, ^2J=8 Hz), 137.5, 141.5, 157.2, 160.1, 160.1 (d, ^1J=250 Hz) ppm. $C_{18}H_{11}FN_2$ (274.30): calcd C, 78.82; H, 4.04; N, 10.21, found C, 78.34; H, 3.82; N, 10.10.

4.3. General procedure for the synthesis of 4-substituted-2-(2-fluorophenyl)nicotinonitrile 2e–g, 2k by *ortho*-lithiation

A flamed dried Schlenk flask under nitrogen was charged with 2,2,6,6-tetramethylpiperidine (0.094 mL, 0.55 mmol) and THF (4 mL). The reaction was cooled to −10 °C and *n*-butyllithium (0.330 mL, 0.53 mmol, 1.6 M in *n*-hexane) was added. The reaction was stirred between −10 °C and 0 °C for 10 min and then cooled to −80 °C. A solution of 2-(2-fluorophenyl)nicotinonitrile **1** (0.100 g, 0.50 mmol) in THF (5 mL) was added to the reaction mixture and stirred for 0.5 h. The electrophile (0.55 mmol) was added and the solution was slowly warmed to room temperature overnight before water (20 mL) was added and extraction with EtOAc (3×35 mL). The organic phases were dried over $MgSO_4$, filtered and solvents were removed under reduced pressure. The crude mixture was then purified by silica gel chromatography.

*4.3.1. 2-(2-Fluorophenyl)-4-iodonicotinonitrile **2e**.* Following the general procedure, using iodine (0.140 g, 0.55 mmol) in THF (10 mL) as the electrophile and a saturated solution of sodium thiosulfate (20 mL) for the hydrolysis. EtOAc/*n*-heptane (1/9 and 1/4) was used as the eluents for the chromatography giving **2e** as a white powder (0.118 g, 72%). Mp 104–105 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.19–7.28 (m, 2H), 7.46–7.55 (m, 2H), 7.88 (d, ^3J=5.3 Hz, 1H), 8.43 (d, ^3J=5.3 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=111.8, 116.7 (d, ^2J=21 Hz), 117.8 (d,

J=1 Hz), 119.3, 124.9 (d, J=4 Hz), 125.7 (d, ^2J=14 Hz), 131.5 (d, J=2 Hz), 132.8 (d, ^3J=8 Hz), 133.2, 151.9, 158.8, 160.0 (d, ^1J=249 Hz) ppm. $C_{12}H_6FIN_2$ (324.10): calcd C, 44.47; H, 1.87; N, 8.64, found C, 44.78; H, 1.80; N, 8.64.

4.3.2. 4-Benzoyl-2-(2-fluorophenyl)nicotinonitrile ***2f***. Following the general procedure, using benzoyl chloride (0.070 mL, 0.55 mmol) as the electrophile and washing the organic phases with an ammonia solution (3×20 mL, 2 M in water). EtOAc/*n*-heptane (1/4) was used as the eluent for the chromatography giving **2f** as a white powder (0.040 g, 26%). Mp 104–106 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.21–7.28 (m, 1H), 7.28–7.35 (td, J=7.6 and 1.0 Hz, 1H), 7.48–7.57 (m, 4H), 7.62 (td, J=7.5 and 1.7 Hz, 1H), 7.67–7.72 (m, 1H), 7.84–7.87 (m, 2H), 9.00 (d, ^3J=5.0 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=108.3 (d, J=1 Hz), 114.9 (d, J=1 Hz), 116.7 (d, ^2J=21 Hz), 121.3, 125.0 (d, J=4 Hz), 125.6 (d, ^2J=14 Hz), 129.5, 130.8, 131.7 (d, J=2 Hz), 132.8 (d, ^3J=8 Hz), 134.9, 135.4, 150.6, 152.8, 159.1 (d, J=1 Hz), 160.1 (d, ^1J=249 Hz), 192.4 ppm. HRMS (ESI) calcd for $C_{19}H_{12}FN_2O$ 303.0934, found 303.0930.

4.3.3. 2-(2-Fluorophenyl)-4-trimethylsilanylnicotinonitrile ***2g***. Following the general procedure, using chlorotrimethylsilane (0.070 mL, 0.55 mmol) as the electrophile and EtOAc/*n*-heptane (1/9 and 1/4) as the eluents for the chromatography giving **2g** as a white powder (0.075 g, 26%). Mp 61–62 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.50 (s, 9H), 7.19–7.25 (m, 1H), 7.29 (td, J=7.6 and 1.2 Hz, 1H), 7.44–7.51 (m, 1H), 7.50 (d, ^3J=4.9 Hz, 1H), 7.55 (td, J=7.4 and 1.7 Hz, 1H), 8.79 (d, ^3J=4.9 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=−1.4, 115.1 (d, J=1 Hz), 116.6 (d, ^2J=21 Hz), 117.9 (d, J=1 Hz), 124.8 (d, J=4 Hz), 126.5 (d, ^2J=14 Hz), 127.7, 131.8 (d, J=3 Hz), 132.2 (d, ^3J=8 Hz), 151.3, 156.1, 157.7 (d, J=1 Hz), 160.1 (d, ^1J=248 Hz) ppm. HRMS (ESI) calcd for $C_{15}H_{16}FN_2Si$ 271.1067, found 271.1062.

4.3.4. 2-(2-Fluorophenyl)-4-(methylsulfanyl)nicotinonitrile ***2k***. Following the general procedure, using dimethyl disulfide (0.050 mL, 0.55 mmol) as the electrophile and EtOAc/*n*-heptane (1/4) as the eluent for the chromatography giving **2k** as a white powder (0.086 g, 70%). Mp 102–104 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.61 (s, 3H), 7.14 (d, ^3J=5.4 Hz, 1H), 7.18–7.25 (m, 1H), 7.27 (td, J=7.6 and 1.0 Hz, 1H), 7.43–7.49 (m, 1H), 7.53 (td, J=7.5 and 1.7 Hz, 1H), 8.63 (d, ^3J=5.4 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.7, 108.1 (d, J=1 Hz), 115.0 (d, J=1 Hz), 116.6 (d, ^2J=11 Hz), 117.1, 124.8 (d, J=4 Hz), 125.9 (d, ^2J=14 Hz), 131.5 (d, J=3 Hz), 132.4 (d, ^3J=8 Hz), 151.4, 156.9, 157.9 (d, J=1 Hz), 160.0 (d, ^1J=249 Hz) ppm. $C_{13}H_9FN_2S$ (244.29): calcd C, 63.92; H, 3.71; N, 11.47, found C, 63.62; H, 3.47; N, 11.36.

4.4. 2-(2-Fluorophenyl)-4-[methyl(phenyl)-amino]nicotinonitrile 2h

A flamed dried Schlenk flask under nitrogen at room temperature was charged with, respectively, 2-(2-fluorophenyl)-4-iodonicotinonitrile **2e** (0.100 g, 0.31 mmol), *N*-methylaniline (0.045 mL, 0.41 mmol), THF (10 mL) and a KHMDS solution (0.800 mL, 0.41 mmol, 0.5 M in toluene). The solution was stirred overnight. After quenching with water (20 mL), the mixture was extracted with EtOAc (3×35 mL). The organic phases were dried over $MgSO_4$, filtered and solvents were removed under reduced pressure. The crude mixture was then purified by silica gel chromatography using EtOAc/*n*-heptane (1/4 and 1/1) as the eluents giving **2h** as a yellow powder (0.090 g, 96%). Mp 138–140.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.58 (s, 3H), 6.73 (d, ^3J=6.2 Hz, 1H), 7.11–7.33 (m, 5H), 7.37–7.53 (m, 4H), 8.40 (d, ^3J=6.2 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=42.8, 98.4, 111.1, 116.4 (d, ^2J=21 Hz), 116.5, 124.7 (d, J=3 Hz), 126.0, 127.1 (d, ^2J=14 Hz), 127.3, 130.5, 131.5 (d, J=2 Hz), 131.9 (d, ^3J=8 Hz), 146.9, 151.8, 157.3, 160.1 (d, ^1J=248 Hz), 160.8 ppm. HRMS (ESI) calcd for $C_{19}H_{15}FN_3$ 304.1250, found 304.1265.

4.5. 2-(2-Fluorophenyl)-4-methoxynicotinonitrile 2i

In a 50 mL round bottom flask, at 0 °C was added 15 mL of MeOH and sodium (0.032 g, 1.33 mmol). The mixture was stirred until sodium was consumed and 2-(2-fluorophenyl)-4-iodonicotinonitrile **2e** (0.144 g, 0.44 mmol) was added. The resulting solution was stirred at room temperature for 24 h. After quenching with water (15 mL), the mixture was extracted with EtOAc (3×30 mL). The organic phases were dried over $MgSO_4$, filtered and solvents were removed under reduced pressure. The crude mixture was then purified by silica gel chromatography using EtOAc/*n*-heptane (1/4 and 1/1) as the eluents giving **2i** as a white powder (0.083 g, 82%). Mp 113–114 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.99 (s, 3H), 6.90 (d, ^3J=5.8 Hz, 1H), 7.21 (m, 1H), 7.24 (td, J=7.6 and 1.2 Hz, 1H), 7.44 (m, 1H), 7.52 (td, J=7.5 and 1.8 Hz, 1H), 8.65 (d, ^3J=5.8 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=57.1, 100.9, 105.8, 114.4, 116.6 (d, ^2J=21 Hz), 124.8 (d, J=3 Hz), 125.9 (d, ^2J=14 Hz), 131.5 (d, J=1 Hz), 132.3 (d, ^3J=8 Hz), 154.2, 159.4, 160.0 (d, ^1J=249 Hz), 167.9 ppm. HRMS (ESI) calcd for $C_{13}H_{10}FN_2O$ 229.0777, found 229.0781.

4.6. 2-(2-Fluorophenyl)-4-phenoxynicotinonitrile 2j

A flamed dried Schlenk flask under nitrogen at room temperature was charged with, respectively, 2-(2-fluorophenyl)-4-iodonicotinonitrile **2e** (0.100 g, 0.31 mmol), phenol (0.035 mL, 0.41 mmol), THF (10 mL) and a KHMDS solution (0.800 mL, 0.41 mmol, 0.5 M in toluene). The solution was stirred overnight. After quenching with water (20 mL), the mixture was extracted with EtOAc (3×35 mL). The organic phases were dried over $MgSO_4$, filtered and solvents were removed under reduced pressure. The crude mixture was then purified by silica gel chromatography using EtOAc/*n*-heptane (1/4 and 1/1) as the eluents giving **2j** as a white powder (0.053 g, 60%). Mp 158–159 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.68 (d, ^3J=5.8 Hz, 1H), 7.18–7.38 (m, 5H), 7.48–7.53 (m, 3H), 7.61 (td, J=7.5 and 1.7 Hz, 1H), 8.60 (d, ^3J=5.8 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=101.3, 108.5, 113.9, 116.6 (d, ^2J=22 Hz), 121.2, 124.7 (d, J=3 Hz), 125.7 (d, ^2J=14 Hz), 126.9, 130.7, 131.3 (d, J=1 Hz), 132.3 (d, ^3J=8 Hz), 152.9, 153.6, 159.7, 159.8 (d, ^1J=248 Hz), 167.2 ppm. HRMS (ESI) calcd for $C_{18}H_{12}FN_2O$ 291.0934, found 291.0951.

4.7. 2-(2-Chloro-6-fluorophenyl)nicotinonitrile 2l

A microwave tube was charged with 2-(2-fluorophenyl)nicotinonitrile **1** (0.200 g, 1.01 mmol), *N*-chlorosuccinimide (0.296 g, 2.02 mmol), $Cu(OAc)_2$ (0.018 g, 0.10 mmol), $Pd(OAc)_2$ (0.022 g, 0.10 mmol) and MeCN (5 mL). The tube was sealed and heated for 2 h at 150 °C using microwave. The solvents were evaporated under reduced pressure and the obtained crude mixture purified directly by silica gel chromatography using EtOAc/*n*-heptane (1/9 and 1/4) as the eluents giving **2l** as a white powder (0.160 g, 68%). Mp 95–97 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.12–7.18 (m, 1H), 7.23–7.35 (m, 1H), 7.38–7.45 (m, 1H), 7.49 (dd, ^3J=7.9 and 5.0 Hz, 1H), 8.10 (dd, ^3J=7.9 Hz, ^4J=1.7 Hz, 1H), 8.92 (dd, ^3J=5.0 Hz, ^4J=1.7 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=112.1, 115.1 (d, ^2J=22 Hz), 116.1, 123.5, 125.5 (d, ^2J=19 Hz), 126.2 (d, J=3 Hz), 132.2 (d, ^3J=9 Hz), 134.5 (d, J=4 Hz), 140.8, 153.1, 155.6, 160.6 (d, ^1J=248 Hz) ppm. $C_{12}H_6ClFN_2$ (232.65): calcd C, 61.95; H, 2.60; N, 12.04, found C, 61.68; H, 2.41; N, 11.97.

4.8. 2-(2-Bromo-6-fluorophenyl)nicotinonitrile 2m

A microwave tube was charged with 2-(2-fluorophenyl)nicotinonitrile **1** (0.200 g, 1.01 mmol), *N*-bromosuccinimide (0.358 g, 2.02 mmol), $Cu(OAc)_2$ (0.018 g, 0.10 mmol), $Pd(OAc)_2$ (0.022 g, 0.10 mmol) and MeCN (5 mL). The tube was sealed and heated for 2 h at 150 °C using microwave. The solvents were evaporated under reduced pressure and the obtained crude

mixture purified directly by silica gel chromatography using EtOAc/*n*-heptane (1/9 and 1/4) as the eluents giving **2m** as a white powder (0.185 g, 66%). Mp 79–80 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.20 (td, J=8.5 and 1.0 Hz, 1H), 7.35 (td, J=8.2 and 5.8 Hz, 1H), 7.50 (dd, ^3J=7.9 and 5.0 Hz, 1H), 7.53 (m, 1H), 8.11 (dd, ^3J=7.9 Hz, ^4J=1.7 Hz, 1H), 8.94 (dd, ^3J=5.0 Hz, ^4J=1.7 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=111.8, 115.6 (d, ^2J=22 Hz), 116.1, 123.5, 123.6 (d, J=3 Hz), 127.4 (d, ^2J=19 Hz), 129.3 (d, J=4 Hz), 132.6 (d, ^3J=9 Hz), 140.8, 153.1, 157.0, 160.5 (d, ^1J=250 Hz) ppm. $C_{12}H_6BrFN_2$ (277.10): calcd C, 52.02; H, 2.18; N, 10.11, found C, 51.85; H, 2.01; N, 10.06.

4.9. 2-(2-Fluoro-6-methoxyphenyl)nicotinonitrile 2n

A sealed tube was charged with 2-(2-fluorophenyl)nicotinonitrile **1** (0.200 g, 1.01 mmol), $PhI(OAc)_2$ (0.640 g, 2.02 mmol), $Pd(OAc)_2$ (0.022 g, 0.10 mmol), AcOH (2.5 mL) and MeOH (2.5 mL). The tube was sealed and heated for 24 h at 100 °C. The solvents were evaporated under reduced pressure and the obtained crude mixture purified directly by silica gel chromatography using (1/9 and 1/4) as the eluents giving **2n** as a white powder (0.132 g, 57%). Mp 74–76 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.84 (s, 3H), 6.82–6.88 (m, 2H), 7.40–7.45 (m, 2H), 8.09 (dd, ^3J=7.9 Hz, ^4J=1.7 Hz, 1H), 8.91 (dd, ^3J=5.0 Hz, ^4J=1.7 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=56.5, 107.5 (d, J=3 Hz), 108.8 (d, ^2J=22 Hz), 112.4, 115.5 (d, ^2J=18 Hz), 116.9, 122.7, 132.2 (d, ^3J=11 Hz), 140.7, 152.84, 155.5, 158.4 (d, J=6 Hz), 160.8 (d, ^1J=247 Hz) ppm. $C_{13}H_9FN_2O$ (228.23): calcd C, 68.42; H, 3.97; N, 12.27, found C, 67.93; H, 3.79; N, 11.89.

4.10. 2-(3-Cyanopyridin-2-yl)-3-fluorophenyl acetate 2o

A sealed tube was charged with 2-(2-fluorophenyl)nicotinonitrile **1** (0.200 g, 1.01 mmol), $PhI(OAc)_2$ (0.640 g, 2.02 mmol), $Pd(OAc)_2$ (0.022 g, 0.10 mmol) and MeCN (5 mL). The tube was sealed and heated for 24 h at 80 °C. The solvents were evaporated under reduced pressure and the obtained crude mixture purified directly by silica gel chromatography using EtOAc/*n*-heptane (1/1) as the eluent giving **2o** as a white powder (0.162 g, 62%). Mp 109–111 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.06 (s, 3H), 7.10–7.19 (m, 2H), 7.43–7.54 (m, 2H), 8.09 (dd, ^3J=7.9 Hz, ^4J=1.7 Hz, 1H), 8.89 (dd, ^3J=4.9 Hz, ^4J=1.7 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=21.0, 92.1, 112.2, 114.0 (d, ^2J=22 Hz), 116.4 (d, J=1 Hz), 119.5 (d, J=4 Hz), 123.0, 131.9 (d, ^2J=10 Hz), 140.9, 149.5 (d, J=3 Hz), 152.7, 154.3, 160.5 (d, ^1J=249 Hz), 168.6 ppm. $C_{14}H_9FN_2O_2$ (256.24): calcd C, 65.62; H, 3.54; N, 10.93, found C, 65.44; H, 3.33; N, 10.77.

4.11. 5-Bromo-2-(2-fluorophenyl)nicotinonitrile 2p

A 250 mL round bottomed flask was charged with 2-(2-fluorophenyl)nicotinonitrile **1** (1.00 g, 5.05 mmol), AcONa (4.14 g, 25 mmol), Br_2 (2.80 mL, 25 mmol) and AcOH (40 mL). The flask was equipped with a reflux condenser and heated at 100 °C for 24 h. After cooling to room temperature, a saturated solution of sodium thiosulfate (60 mL) was added drop wise to the reaction mixture. The resulting solution was extracted with EtOAc (3×75 mL) and organic phases were dried over $MgSO_4$ and filtered. Solvents were removed under reduced pressure. The crude mixture was then purified by silica gel chromatography using EtOAc/*n*-heptane (1/9) as the eluent giving **2p** as a white powder (0.33 g, 36%). Mp 103.5–104 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.20–7.27 (m, 2H), 7.31 (td, J=7.6 and 1.2 Hz, 1H), 7.48–7.60 (m, 2H), 8.20 (d, ^4J=2.4 Hz, 1H), 8.95 (d, ^4J=2.4 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=111.9 (d, J=1 Hz), 115.6 (d, J=1 Hz), 116.8 (d, ^2J=22 Hz), 119.5, 124.8, 125.1 (d, J=4 Hz), 131.5 (d, J=2 Hz), 132.8 (d, ^3J=9 Hz), 143.0, 154.4, 155.8 (d, J=1 Hz), 159.9 (d, ^1J=249 Hz) ppm. $C_{12}H_6BrFN_2$ (277.10): calcd C, 52.02; H 2.18; N, 10.11, found C, 52.08; H 2.07; N, 9.89.

4.12. 2-(2-Fluorophenyl)-5-phenylnicotinonitrile 2q

A 100 mL round bottomed flask was filled with DME (30 mL) and water (15 mL) and degassed with nitrogen for 10 min. $Pd(OAc)_2$ (8 mg, 0.035 mmol) and PPh_3 (12 mg, 0.068 mmol) were then added and the mixture was heated at 50 °C for 10 min. 5-Bromo-2-(2-fluorophenyl)nicotinonitrile **2p** (192 mg, 0.69 mmol), phenylboronic acid (126 mg, 1.04 mmol) and $NaHCO_3$ (233 mg, 2.77 mmol) were added to the solution. The flask was equipped with a reflux condenser and heated at 80 °C for 24 h under nitrogen. After quenching with water (40 mL), the mixture was extracted with EtOAc (3×50 mL). The organic phases were dried over $MgSO_4$, filtered and solvents were removed under reduced pressure. The crude mixture was then purified by silica gel chromatography using EtOAc/*n*-heptane (1/9) as the eluent giving **2q** as a white powder (181 mg, 95%). Mp 150–152 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.23 (m, 1H), 7.30 (td, J=7.6 and 1.2 Hz, 1H), 7.43–7.54 (m, 4H), 7.57–7.65 (m, 3H), 8.21 (d, ^4J=2.4 Hz, 1H), 9.07 (d, ^4J=2.4 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=110.8, 116.8 (d, ^2J=22 Hz), 117.0, 125.0 (d, J=3 Hz), 125.7 (d, ^2J=14 Hz), 127.5, 129.7, 129.9, 131.7, 132.5 (d, ^3J=8 Hz), 135.5, 135.8, 139.1, 151.4, 155.8, 160.2 (d, ^1J=249 Hz) ppm. HRMS (ESI) calcd for $C_{18}H_{12}FN_2$ 275.0985, found 275.0990.

4.13. General procedure for lithium pyrrolidide mediated anionic ring closure 3a–f

A first flame-dried Schlenk flask under nitrogen was charged with the chosen starting material (1 equiv) in THF (10 mL for 0.1 g of starting material) and dry LiCl (5 equiv). In a second flame-dried Schlenk flask under nitrogen was added at room temperature, respectively, pyrrolidine (1.2 equiv), THF (5 mL) and *n*-butyllithium (1.2 equiv). After 5 min of stirring, the content of the second Schlenk flask was transferred to the first one using a syringe. The first Schlenk flask was equipped with a reflux condenser and heated at 75 °C for 16 h. The resulting mixture was quenched with water (20 mL) at room temperature and extracted with EtOAc (3×35 mL). The combined organic phases were dried over $MgSO_4$, filtered and solvents were removed under reduced pressure. The crude mixture was then purified by silica gel chromatography.

4.13.1. 2-Butyl-5-pyrrolidin-1-ylbenzo[h]-1,6-naphthyridine ***3b***. Following the general procedure, using 6-butyl-2-(2-fluorophenyl)nicotinonitrile **2b** (0.100 g, 0.39 mmol), LiCl (0.083 g, 1.96 mmol), pyrrolidine (0.040 mL, 0.47 mmol) and *n*-butyllithium (0.290 mL, 0.47 mmol, 1.6 M in *n*-hexane). DCM/*n*-heptane (1/1), DCM and DCM/EtOAc (9/1) were used as the eluents for the chromatography giving **3b** as an orange oil (0.027 g, 23%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.01 (t, J=7.3 Hz, 3H), 1.49 (st, J=7.4 Hz, 2H), 1.90 (m, 2H), 2.01 (m, 4H), 3.03 (m, 2H), 3.88 (m, 4H), 7.28 (d, ^3J=8.5 Hz, 1H), 7.33–7.38 (m, 1H), 7.57–7.63 (m, 1H), 7.74 (d, J=8.2 Hz, 1H), 8.40 (d, ^3J=8.5 Hz, 1H), 8.93 (dd, J=8.1 and 1.0 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.5, 23.3, 26.4, 31.9, 39.0, 51.7, 114.5, 120.5, 122.9, 124.2, 126.7, 130.5, 134.7, 146.9, 151.2, 156.6, 164.9 ppm (an aromatic carbon signal is missing, due to peak overlap). HRMS (ESI) calcd for $C_{20}H_{24}N_3$ 306.1970, found 306.1957.

4.13.2. 2-Phenyl-5-pyrrolidin-1-ylbenzo[h]-1,6-naphthyridine ***3c***. Following the general procedure, using 2-(2-fluorophenyl)-6-phenylnicotinonitrile **2d** (0.100 g, 0.36 mmol), LiCl (0.077 g, 1.82 mmol), pyrrolidine (0.036 mL, 0.44 mmol) and *n*-butyllithium (0.270 mL, 0.44 mmol, 1.6 M in *n*-hexane). DCM/*n*-heptane (1/1), DCM and DCM/EtOAc (9/1) were used as the eluents for the chromatography giving **3e** as a yellow powder (0.059 g, 50%). Mp 124–126 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.04 (m, 4H), 3.93 (m, 4H), 7.36–7.41 (m, 1H), 7.47–7.58 (m, 3H), 7.58–7.65 (m, 1H), 7.75 (d,

J=8.2 Hz, 1H), 7.90 (d, ^3J=8.8 Hz, 1H), 8.30–8.33 (m, 2H), 8.59 (d, ^3J=8.8 Hz, 1H), 9.06 (dd, J=8.0 and 1.6 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=26.4, 51.7, 115.0, 117.6, 122.9, 124.3, 126.7, 127.9, 129.6, 130.2, 130.8, 135.6, 139.2, 147.2, 148.4, 151.4, 156.3, 158.2 ppm. HRMS (ESI) calcd for $C_{22}H_{20}N_3$ 326.1657, found 326.1653. *6-Phenyl-2-(2-pyrrolidin-1-ylphenyl)nicotinonitrile* ***2s***: white powder (0.059 g, 50%). Mp 110–111 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.81 (m, 4H), 2.98 (m, 4H), 6.87–6.96 (m, 2H), 7.31–7.41 (m, 2H), 7.47–7.52 (m, 3H), 7.73 (d, ^3J=8.2 Hz, 1H), 8.02 (d, ^3J=8.2 Hz, 1H), 8.10–8.13 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=26.2, 51.2, 108.4, 115.1, 117.4, 117.7, 118.1, 125.5, 127.9, 129.3, 130.71, 130.74, 132.4, 138.1, 141.3, 148.0, 159.6, 164.1 ppm. HRMS (ESI) calcd for $C_{22}H_{20}N_3$ 326.1657, found 326.1657.

4.13.3. 3-Phenyl-5-pyrrolidin-1-ylbenzo[h]-1,6-naphthyridine ***3e***. Following the general procedure, using 2-(2-fluorophenyl)-5-phenylnicotinonitrile **2q** (0.44 g, 1.60 mmol), LiCl (0.34 g, 8.02 mmol), pyrrolidine (0.16 mL, 1.92 mmol) and *n*-butyllithium (1.20 mL, 1.92 mmol, 1.6 M in *n*-hexane). EtOAc/*n*-heptane (1/9) was used as the eluent for the chromatography giving **3e** as a yellow powder (0.28 g, 53%). Mp 170–172 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.06 (m, 4H), 3.96 (m, 4H), 7.40 (m, 1H), 7.46 (m, 1H), 7.54 (m, 2H), 7.64 (m, 1H), 7.70 (m, 2H), 7.77 (m, 1H), 8.70 (d, ^4J=2.1 Hz, 1H), 8.87 (dd, J=8.6 and 1.5 Hz, 1H), 9.26 (d, ^4J=2.1 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=26.5, 51.9, 116.3, 122.5, 123.3, 124.0, 126.9, 127.6, 128.6, 129.7, 130.8, 132.6, 1337, 138.1, 146.9, 150.5, 150.7, 156.5 ppm. HRMS (ESI) calcd for $C_{22}H_{20}N_3$ 326.1657, found 326.1669.

4.13.4. 10-Chloro-5-pyrrolidin-1-ylbenzo[h]-1,6-naphthyridine ***3f***. Following the general procedure, using 2-(2-chloro-6-fluorophenyl)nicotinonitrile **2l** (0.100 g, 0.43 mmol), LiCl (0.091 g, 2.15 mmol), pyrrolidine (0.040 mL, 0.52 mmol) and *n*-butyllithium (0.320 mL, 0.52 mmol, 1.6 M in *n*-hexane). EtOAc/*n*-heptane (1/9 and 1/4) was used as the eluents for the chromatography giving **3f** as a yellow powder (0.046 g, 38%). Mp 99–101 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.03 (m, 4H), 3.88 (m, 4H), 7.40–7.79 (m, 2H), 7.50 (dd, ^3J=8.5 and 4.4 Hz, 1H), 7.68 (dd, J=7.6 and 1.7 Hz, 1H), 8.53 (dd, ^3J=8.5 Hz, ^4J=1.7 Hz, 1H), 9.11 (dd, ^3J=4.4 Hz, ^4J=1.7 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=26.4, 51.6, 116.7, 119.6, 120.8, 126.4, 126.8, 129.9, 131.4, 134.2, 149.0, 150.7, 151.3, 156.5 ppm. $C_{16}H_{14}ClN_3$ (283.76): calcd C, 67.72; H, 4.97; N, 14.81, found C, 67.47; H, 4.97; N, 14.53. *2-(2-Chloro-6-pyrrolidin-1-ylphenyl)nicotinonitrile* ***2v***: yellow powder (0.052 g, 43%). Mp 117.5–118 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.76 (m, 4H), 2.82 (m, 4H), 6.77 (d, J=8.5 Hz, 1H), 6.89 (d, J=7.9 Hz, 1H), 7.19–7.25 (m, 1H), 7.39 (dd, ^3J=7.9 and 5.0 Hz, 1H), 8.03 (dd, ^3J=7.9 Hz, ^4J=1.6 Hz, 1H), 8.87 (dd, ^3J=5.0 Hz, ^4J=1.6 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=26.0, 50.9, 113.43, 113.9, 116.8, 118.9, 122.2, 123.2, 131.0, 134.8, 140.4, 149.3, 152.4, 162.1 ppm. HRMS (ESI) calcd for $C_{16}H_{15}ClN_3$ 328.0955, found 328.0947.

4.13.5. 10-Bromo-5-pyrrolidin-1-ylbenzo[h]-1,6-naphthyridine ***3g***. Following the general procedure, using 2-(2-bromo-6-fluorophenyl)nicotinonitrile **2m** (0.100 g, 0.43 mmol), LiCl (0.076 g, 1.80 mmol), pyrrolidine (0.030 mL, 0.36 mmol) and *n*-butyllithium (0.270 mL, 0.36 mmol, 1.6 M in *n*-hexane). EtOAc/*n*-heptane (1/9 and 1/4) were used as the eluents for the chromatography giving **3g** as a white powder (0.052 g, 43%). Mp 94–96 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.01 (m, 4H), 3.86 (m, 4H), 7.34–7.39 (m, 1H), 7.47 (dd, ^3J=8.2 and 4.4 Hz, 1H), 7.66–7.72 (m, 2H), 8.48 (dd, ^3J=8.2 Hz, ^4J=1.7 Hz, 1H), 9.09 (dd, ^3J=4.4 Hz, ^4J=1.7 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=26.3, 51.6, 116.4, 118.7, 120.9, 127.1, 130.3, 130.7, 134.2, 147.8, 149.0, 150.2, 150.9, 156.4 ppm. HRMS (ESI) calcd for $C_{16}H_{15}BrN_3$ 328.0449, found 328.0483. 2-(2-*Bromo*-6-*pyrrolidin*-1-*ylphenyl*)*nicotinonitrile* **2x**: white powder (0.034 g, 29%). Mp 104–105 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.75 (m, 4H), 2.82 (m, 4H), 6.82 (dd, J=8.2 and 1.2 Hz, 1H), 7.06–7.17 (m, 2H), 7.38 (dd, ^3J=8.0 and 4.8 Hz, 1H), 8.02 (dd, ^3J=8.0 Hz, ^4J=1.6 Hz, 1H), 8.87 (dd, ^3J=4.8 Hz, ^4J=1.6 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=26.0, 50.9, 113.3, 114.6, 116.7, 122.31, 122.36, 124.9, 125.0, 131.3, 140.4, 149.3, 152.4, 163.4 ppm. HRMS (ESI) calcd for $C_{16}H_{15}BrN_3$ 328.0449, found 328.0457.

4.13.6. 2-(2-Fluorophenyl)-4-pyrrolidin-1-ylnicotinonitrile ***2y***. Following the general procedure, using 2-(2-fluorophenyl)-4-iodonicotinonitrile **2e** (0.100 g, 0.31 mmol), LiCl (0.065 g, 1.54 mmol), pyrrolidine (0.030 mL, 0.37 mmol) and *n*-butyllithium (0.230 mL, 0.37 mmol, 1.6 M in *n*-hexane). EtOAc/*n*-heptane (1/9 and 1/4) was used as the eluents for the chromatography giving **2y** as a white powder (0.073 g, 89%). Mp 140–140.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.05 (m, 4H), 3.72 (m, 4H), 6.48 (d, ^3J=6.1 Hz, 1H), 7.14–7.26 (m, 2H), 7.40–7.53 (m, 2H), 8.27 (d, ^3J=6.1 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=26.0, 50.3, 93.3, 107.9, 116.3 (d, ^2J=22 Hz), 119.2, 124.6 (d, J=3 Hz), 127.6 (d, ^2J=14 Hz), 131.4 (d, J=2 Hz), 131.6 (d, ^3J=8 Hz), 150.9, 154.1, 160.1 (d, ^1J=247 Hz), 161.0 ppm. HRMS (ESI) calcd for $C_{16}H_{15}FN_3$ 268.1250, found 268.1250.

4.14. General procedure for KOH mediated anionic ring closure 5a–k

A microwave tube was charged with: starting material (1 equiv), KOH (5 equiv) and MeOH (5 mL for 0.1 g of starting material). The tube was sealed and heated at 150 °C using microwave for the indicated time. After cooling to room temperature, water (15 mL) was added and the mixture was filtrated. The solid was then washed several times with Et_2O.

4.14.1. 2-Butylbenzo[h]-1,6-naphthyridin-5(6H)-one ***5b***. Following the general procedure, using 6-butyl-2-(2-fluorophenyl)nicotinonitrile **2b** (0.100 g, 0.39 mmol), KOH (0.110 g, 1.95 mmol) and heating for 10 min, giving **5b** as a white powder (0.059 g, 65%). Mp 196–198 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ=0.96 (t, J=7.3 Hz, 3H), 1.37 (st, J=7.5 Hz, 2H), 1.77 (qt, J=7.5 Hz, 2H), 2.93 (t, J=7.7 Hz, 2H), 7.27 (t, J=7.5 Hz, 1H), 7.34 (d, J=7.9 Hz, 1H), 7.48–7.56 (m; 2H), 8.45 (d, J=8.2 Hz, 1H), 8.58 (d, J=7.0 Hz, 1H) 11.78 (br s, 1H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ=14.7, 22.7, 31.8, 38.6, 116.7, 119.7, 119.9, 123.1, 123.6, 124.8, 131.8, 136.7, 138.8, 150.8, 161.8, 167.6 ppm. HRMS (ESI) calcd for $C_{16}H_{17}N_2O$ 253.1341, found 253.1334.

4.14.2. 2-Phenylbenzo[h]-1,6-naphthyridin-5(6H)-one ***5c***. Following the general procedure, using 2-(2-fluorophenyl)-6-phenylnicotinonitrile **2d** (0.128 g, 0.46 mmol), KOH (0.130 g, 2.31 mmol) and heating for 10 min, giving **5c** as a white powder (0.110 g, 91%). Mp 286–289 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ=7.29–7.36 (m, 1H), 7.39 (d, J=8.3 Hz, 1H), 7.53–7.64 (m, 4H), 8.24 (d, ^3J=8.5 Hz, 1H), 8.37–8.37 (m, 2H), 8.64 (d, ^3J=8.5 Hz, 1H), 8.78 (dd, J=8.0 and 0.9 Hz, 1H), 11.72 (br s, 1H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ=115.9, 118.9, 119.7, 122.4, 124.3, 127.4, 129.0, 130.4, 131.3, 136.9, 137.7, 138.2, 150.4, 159.4, 160.8 ppm. HRMS (ESI) calcd for $C_{18}H_{13}N_2O$ 273.1028, found 273.1027.

4.14.3. 3-Phenylbenzo[h]-1,6-naphthyridin-5(6H)-one ***5e***. Following the general procedure, using 2-(2-fluorophenyl)-5-phenylnicotinonitrile **2q** (0.066 g, 0.24 mmol), KOH (0.067 g, 1.2 mmol) and heating for 10 min giving **5e** as a white powder (0.049 g, 76%). Mp 280–282 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ=7.28–7.59 (m, 6H), 7.87 (d, J=7.3 Hz, 2H), 8.60 (d, J=7.6 Hz, 1H), 8.74 (s, 1H), 9.37 (s, 1H), 11.93 (br s, 1H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ=116.8, 119.6, 122.0, 123.3, 124.8, 127.8, 129.4, 130.1, 131.9, 133.4, 135.7, 137.1,

138.8, 150.4, 153.1, 161.7 ppm. HRMS (ESI) calcd for $C_{18}H_{13}N_2O$ 273.1028, found 273.1025.

4.14.4. 10-Chlorobenzo[h]-1,6-naphthyridin-5(6H)-one ***5k***. Following the general procedure, using 2-(2-chloro-6-fluorophenyl)nicotinonitrile **2l** (0.100 g, 0.43 mmol), KOH (0.120 g, 2.15 mmol) and heating for 1 h, giving **5k** as a white powder (0.061 g, 62%). Mp 266–268 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ=7.34–7.39 (m, 2H), 7.78–7.53 (m, 1H), 7.70 (dd, ^3J=7.9 and 4.4 Hz, 1H), 8.64 (dd, ^3J=7.9 Hz, ^4J=1.7 Hz, 1H), 9.09 (dd, ^3J=4.4 Hz, ^4J=1.7 Hz, 1H), 12.06 (br s, 1H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ=116.2, 116.4, 122.9, 124.1, 127.2, 131.6, 132.3, 136.3, 141.1, 151.1, 153.5, 161.2 ppm. HRMS (ESI) calcd for $C_{12}H_8ClN_2O$ 231.0325, found 231.0322.

4.14.5. 10-Methoxybenzo[h]-1,6-naphthyridin-5(6H)-one ***5l***. Following the general procedure, using 2-(2-Fluoro-6-methoxyphenyl)nicotinonitrile **2n** (0.158 g, 0.69 mmol), KOH (0.194 g, 3.45 mmol) and heating for 2 h, giving **5l** as a white powder (0.093 g, 60%). Mp 169–171 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ=3.92 (s, 3H), 6.91 (d, J=8.2 Hz, 1H), 7.00 (d, J=7.3 Hz, 1H), 7.48 (t, J=8.2 Hz, 1H), 7.59 (dd, ^3J=7.9 and 4.6 Hz, 1H), 8.57 (dd, ^3J=7.9 Hz, ^4J=2.0 Hz, 1H), 9.04 (dd, ^3J=4.6 Hz, ^4J=2.0 Hz, 1H), 11.83 (br s, 1H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ=56.9, 106.9, 109.1, 109.5, 121.9, 122.8, 132.2, 135.9, 140.6, 152.5, 154.1, 159.8, 161.6 ppm. HRMS (ESI) calcd for $C_{13}H_{11}N_2O_2$ 227.0821, found 227.0826.

4.15. 5-Chlorobenzo[*h*]-1,6-naphthyridine 3h

A 100 mL round bottomed flask was charged with benzo[*h*]-1,6-naphthyridin-5(6*H*)-one **5a** (1.00 g, 5.1 mmol) and $POCl_3$ (25 mL). The flask was equipped with a reflux condenser and heated at 100 °C for 24 h. After cooling to room temperature the solution was poured carefully onto a mixture of water and ice. The pH was then carefully adjusted to 10 using a saturated aqueous ammonia solution. Extraction was performed using EtOAc (3×100 mL). The organic phases were dried over $MgSO_4$, filtered and solvents were removed under reduced pressure. The crude mixture was then purified by silica gel chromatography using EtOAc/*n*-heptane (1/4) as the eluent giving **3h** as a white powder (0.83 g, 76%). Mp 114–115 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.69 (dd, ^3J=8.3 and 4.4 Hz, 1H), 7.76 (t, J=7.1 Hz, 1H), 7.84 (td, J=8.3 and 1.4 Hz, 1H), 8.10 (d, J=8.0 Hz, 1H), 8.70 (dd, ^3J=8.3 Hz, ^4J=1.7 Hz, 1H), 9.08 (dd, J=8.1 and 1.2 Hz, 1H), 9.18 (dd, ^3J=4.4 Hz, ^4J=1.7 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=120.4, 123.3, 124.1, 125.2, 127.9, 128.6, 131.1, 135.5, 145.2, 149.9, 150.14, 153.8 ppm. HRMS (ESI) calcd for $C_{12}H_8ClN_2$ 215.0376, found 215.0378.

4.16. Benzo[*h*]-1,6-naphthyridine 3i

A 100 mL round bottomed flask was charged with 5-chlorobenzo[*h*]-1,6-naphthyridine **3h** (0.100 g, 0.46 mmol), MeOH (20 mL), ammonium formate (0.117 g, 1.85 mmol) and palladium on charcoal (10%, 0.050 g, 0.46 mmol). The flask was then equipped with a reflux condenser and heated to reflux for 24 h. After cooling down the resulting mixture was filtrated through a pad of Celite and evaporated to dryness. The crude mixture was then purified by silica gel chromatography using EtOAc/*n*-heptane (1/9 and 1/1) as the eluents giving **3i** as white powder (0.065 g, 78%). Mp 92–94 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.60 (dd, ^3J=8.1 and 4.4 Hz, 1H), 7.74 (td, J=8.2 and 1.2 Hz, 1H), 7.83 (m, 1H), 8.19 (d, J=7.9 Hz, 1H), 8.29 (dd, ^3J=8.1 Hz, ^4J=1.6 Hz, 1H), 9.12 (m, 2H), 9.26 (s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=121.2, 123.1, 124.0, 125.6, 128.0, 129.9, 130.7, 136.4, 147.0, 149.0, 153.1, 153.7 ppm. HRMS (ESI) calcd for $C_{12}H_9N_2$ 181.0766, found 181.0778.

4.17. 5-Benzothiophen-2-ylbenzo[*h*]-1,6-naphthyridine 3j

A 100 mL round bottomed flask was filled with DME (20 mL) and water (10 mL) and degassed with nitrogen for 10 min. $Pd(OAc)_2$ (5 mg, 0.023 mmol) and PPh_3 (12 mg, 0.045 mmol) were then added and the mixture was heated at 50 °C for 10 min. 5-Chlorobenzo[*h*]-1,6-naphthyridine **3h** (100 mg, 0.46 mmol), 2-benzothiophenylboronic acid (124 mg, 0.68 mmol) and $NaHCO_3$ (157 mg, 1.87 mmol) were added to the solution. Flask was equipped with a reflux condenser and heated at 80 °C for 24 h under nitrogen. After quenching with water (30 mL), the mixture was extracted with EtOAc (3×40 mL). The combined organic phases were dried over $MgSO_4$, filtered and solvents were removed under reduced pressure. The crude mixture was then purified by silica gel chromatography using EtOAc/*n*-heptane (1/9) as the eluent giving **3j** as a white powder (113 mg, 78%). Mp 235–238 °C. ^{1}H NMR (600 MHz, DMSO-d_6, 40 °C): δ=7.49 (m, 2H), 7.84 (t, J=7.4 Hz, 1H), 7.91 (dd, ^3J=8.3 and 4.2 Hz, 1H), 7.95 (t, J=7.4 Hz, 1H), 8.03 (m, 1H), 8.09 (m, 1H), 8.17 (d, ^3J=8.3 Hz, 1H), 8.25 (s, 1H), 9.12 (m, 2H), 9.30 (d, J=3.7 Hz, 1H) ppm. ^{13}C NMR (150 MHz, DMSO-d_6, 40 °C): δ=118.6, 122.2, 123.3, 123.5, 124.1, 124.6, 125.7, 127.0, 127.9, 128.9, 130.8, 135.5, 139.8, 139.9, 141.6, 1448, 148.3, 152.7, 153.5 ppm. HRMS (ESI) calcd for $C_{20}H_{13}N_2S$ 313.0799, found 313.0797.

4.18. *N*-2-Methylphenylbenzo[*h*]-1,6-naphthyridin-5-amine 3k

A flame-dried Schlenk flask under nitrogen at room temperature was charged with, respectively, 5-chlorobenzo[*h*]-1,6-naphthyridine **3h** (0.100 g, 0.46 mmol), *o*-toluidine (0.147 mL, 1.38 mmol), NaHMDS solution (0.800 mL, 0.69 mmol, 1 M in toluene) and THF (10 mL). The solution was then stirred overnight. After quenching with water (20 mL), the mixture was extracted with EtOAc (3×35 mL). The organic phases were dried over $MgSO_4$, filtered and solvents were removed under reduced pressure. The crude mixture was then purified by silica gel chromatography using DCM as the eluent giving **3k** as a white powder (0.100 g, 75%). Mp 107–108 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.21 (s, 3H), 7.17 (t, J=8.0 Hz, 1H), 7.26 (t, J=8.0 Hz, 1H), 7.30 (d, J=8.0 Hz, 1H), 7.36 (t, J=8.0 Hz, 1H), 7.45 (d, J=7.8 Hz, 2H), 7.56 (t, J=8.0 Hz, 1H), 7.78 (dd, ^3J=7.8 and 4.4 Hz, 1H), 8.79 (d, J=8.0 Hz, 1H), 8.99 (t, J=8.3 Hz, 1H), 9.14 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=18.3, 114.3, 121.7, 122.6, 122.8, 123.2, 125.2, 126.0, 126.1, 126.7, 130.3, 130.4, 132.4, 134.2, 138.6, 146.1, 149.3, 152.0, 152.7 ppm. HRMS (ESI) calcd for $C_{19}H_{16}N_3$ 286.1266, found 286.1257.

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