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One-pot synthesis of new aza- and diaza-aminophenanthrenes

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ABSTRACT

The synthesis of a series of benzo(iso)quinoline and phenanthroline derivatives has been achieved using an efficient one-pot procedure. It proceeds through a Suzuki–Miyaura cross-coupling followed by a Dieckmann–Thorpe ring closure under microwave irradiation and provides easy access to building blocks not readily available through other methods.

1. Introduction

Benzo(iso)quinolines are important scaffolds in chemistry either for their use as metal ligands,[1] or due to their occurrence in numerous biological and pharmacological species.[2] More recently benzo[*h*]quinolines have been used widely as rigid substrates to develop C–H functionalization methodology.[3] Because of this importance, many syntheses have been explored to access these scaffolds. Most of the synthesis proceeds through the formation of the pyridine ring from an already substituted naphthalene precursor (Fig. 1, route A).[4] Contrary to the phenanthrene series, the construction of the benzo(iso)quinolines central ring has received less attention. Some approaches have produced such compounds from aza-stilbene starting materials (Fig. 1, route B), using a radical[5] or a photocyclisation–oxidation processes.[6] More recently, a new approach has been described starting from phenylpyridine precursors (Fig. 1, route C).[7]

However, few examples of benzo(iso)quinolines bearing a substituent on their central ring has been described, and hence efforts are still needed in order to obtain these new derivatives.

We have recently described an efficient one-pot synthesis of 10-substituted 9-aminophenanthrenes under microwave irradiation.[8]

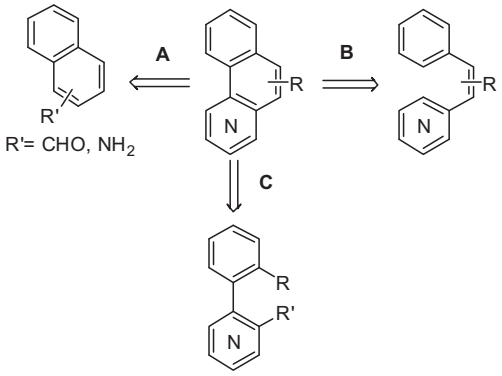

Fig. 1. General access to benzo(iso)quinolines.

These novel polycyclic systems were generally obtained starting from *o*-cyanophenylboronic ester and methyl 2-(2-bromophenyl) acetate **1** and its analogs (Fig. 2) which were successively involved in a Suzuki–Miyaura cross-coupling followed by an intramolecular Dieckmann–Thorpe ring closure.

In order to extend the scope of this methodology, we imagined applying these conditions to adequate aza-substrate in order to obtain some novel aza and diaza-aminophenanthrenes. Indeed our laboratory has already described the synthesis of some *ortho*-cyanopyridylboronic acids and esters **3a**–**c** (Scheme 1), and investigated their

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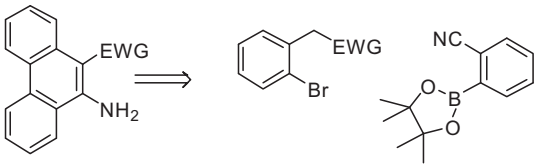
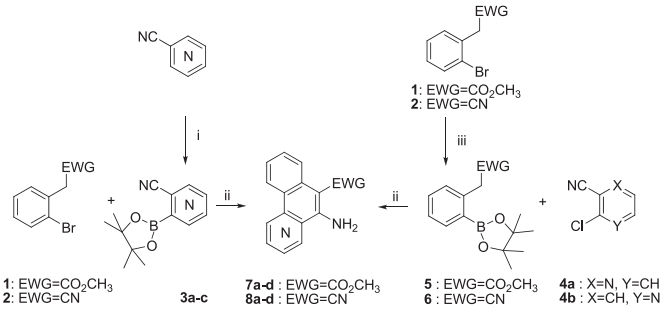


Fig. 2. Retrosynthetic access to 10-substituted 9-aminophenanthrenes.



Scheme 1. General synthesis of novel aza-aminophenanthrenes. Reagents and conditions: (i) (a) LTMP −78 °C; (b) B(*O*-*i*Pr)$_3$ −78 °C; (c) pinacol rt, 18–95% (ii) Pd(PPh$_3$)$_4$, K$_3$PO$_4$, DMF, 150 °C, MW, 25–85%. (iii) KOAc, PdCl$_2$(dppf), *bis*(pinacolato)diboron, CH$_2$Cl$_2$, 75–95%.

reactivity.[9] Herein we wish to describe the optimization of the reaction conditions and the synthesis of unknown aminobenzo(iso) quinolines from these reactive substrates.

2. Results and discussion

ortho-Cyanopyridylboronic esters are obtained using an *ortho*-metalation procedure from the corresponding cyanopyridines, using triisopropylborate as an electrophile, followed by addition of pinacol to afford **3a**–**c** in a one-pot procedure (Scheme 1).[9b] Starting from 3-cyanopyridine, the lower yield observed for the synthesis of **3b**, could be explained by the lithiation in both the 2- and the 4-positions.[9a] Unfortunately only the 3-cyano-4-pyridyl boronic ester **3b** could be isolated, due to the well described tendency of 2-pyridylboronic acids to undergo protodeboronation.[10] Because of its good reactivity in Suzuki–Miyaura cross-coupling,[9a] **3b** was chosen to optimize the synthesis of benzoisoquinolines.

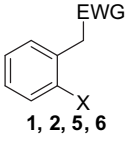
Our first attempt was run according to the optimized conditions developed in the phenanthrene series: using 1 equiv of the bromide **1**, 1.1 equiv of the boronic ester **3b**, 3 equiv of Cs_2CO_3 as a base, 5% of $Pd_3(PPh_3)_4$ as a catalyst in dimethylformamide (Scheme 1).[8a] Unfortunately, after 20 min heating at 150 °C under microwave irradiation, no traces of the expected benzoisoquinoline were detected. No improvement was found with prolonged reaction time. We therefore decided to reinvestigate the reaction conditions and more precisely the influence of the base. The best results were found when 3 equiv of K_3PO_4 were used and when the reaction mixture was heated for 90 min at 150 °C under microwave irradiation, affording the ester **7b** in 85% yield (Table 1, entry 3). This procedure was then applied to the nitrile **2** to afford the requested benzoisoquinoline **8b** with 65% yield (Table 1, entry 4). The three dimensional structure of compound **8b** was corroborated by X-ray crystallography (Fig. 3).[11]

Using the boronic ester **3c**, the reaction led to two novel benzoisoquinolines **7c** and **8c** (Table 1, entry 5 and 6). Unfortunately when the boronic ester **3a** was used, no traces of the expected tricycles were found. Under these conditions 3-cyanopyridine was isolated, resulting from the protodeboronation of **3a**.

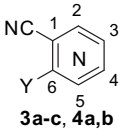
Because of the instability of the *ortho*-cyanopyridylboronic esters and in order to obtain the two benzoquinoline isomers, bearing a nitrogen atom in position 1 and 4 (Table 1), we decided to explore the feasibility of a reverse process. Hence we applied our one-pot methodology to the coupling of *ortho*-halogenocyanopyridine **4** and the boronic esters **5** and **6** (Scheme 1). The latter were obtained from the corresponding bromides **1** and **2** through the palladium-catalyzed cross-coupling reaction with bis(pinacolato)diboron developed by Miyaura.[12] The reactions proceeded with moderate to good yields to give four novel benzoquinoline derivatives **7a**,**d** and **8a**,**d** (Table 1, entry 7 to 10), whose structures were confirmed by X-ray crystallography.[11]

Table 1
General synthesis of aza-aminophenanthrenes according to Scheme 1

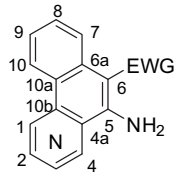
Entry



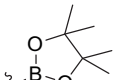
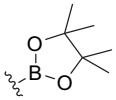
1, 2, 5, 6



3a-c, **4a,b**



7a-d, **8a-d**

	No	X	EWG	No	N position	Y	No	N position	EWG	Time (min)	Yield (%)[a]
1	**1**		CO_2CH_3	**3a**	2		**7a**	4	CO_2CH_3	90	/
2	**2**		CN	**3a**	2		**8a**	4	CN	90	/
3	**1**	Br	CO_2CH_3	**3b**	3		**7b**	3	CO_2CH_3	90	85
4	**2**		CN	**3b**	3		**8b**	3	CN	90	65
5	**1**		CO_2CH_3	**3c**	4		**7c**	2	CO_2CH_3	90	25
6	**2**		CN	**3c**	4		**8c**	2	CN	90	77
7	**5**		CO_2CH_3	**4b**	5		**7d**	1	CO_2CH_3	90	60
8	**6**		CN	**4b**	5		**8d**	1	CN	90	67
9	**5**		CO_2CH_3	**4a**	2	Cl	**7a**	4	CO_2CH_3	90	72
10	**6**		CN	**4a**	2		**8a**	4	CN	90	67

[a] Isolated yield.

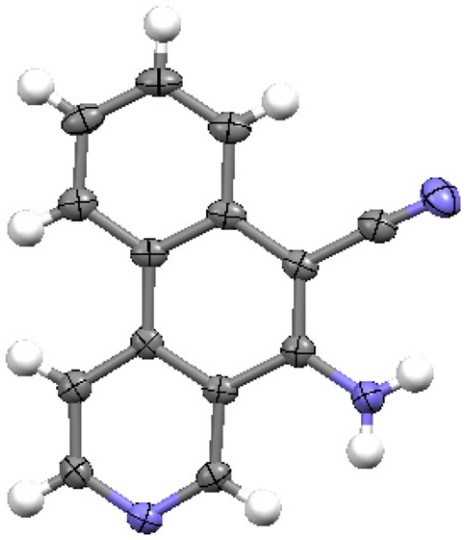
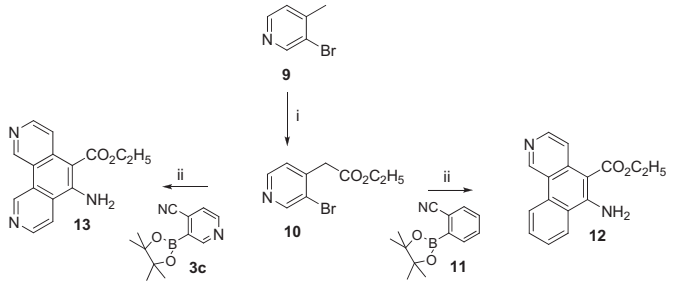


Fig. 3. X-ray structure of compound **8b**: CCDC 822920.[11]

Having assessed the feasibility of the synthesis of 4 novel benzo(iso)quinolines, we decided to explore the introduction of a nitrogen atom in the other ring. Thus, we prepared ethyl (3-bromopyrid-4-yl) acetate **10** by treatment of 3-bromo-4-methylpyridine **9** with LHMDS in THF followed by the addition of diethyl carbonate (Scheme 2).[13] Gratifyingly, when the one-pot protocol, was applied to the coupling of **10** with *ortho*-cyanophenylboronic ester **11** and led to the novel benzisoquinoline **12** in 85% yield.



Scheme 2. General synthesis of novel aza- and diaza-10-substituted 9-aminophenanthrenes Reagents and conditions: (i) EtO_2CO, LHMDS, THF, rt, 63%. (ii) $Pd(PPh_3)_4$, K_3PO_4, DMF, 150 °C, MW, 50–83%.

The reaction was then repeated with pyridylboronic ester **3c** to efficiently afford the novel phenanthroline aminoester **13** in 50% yield (Scheme 2).

3. Conclusion

In summary we have demonstrated that our one-pot sequence incorporating a Suzuki–Miyaura coupling followed by a Dieckmann–Thorpe ring closure, is an efficient and fast method for the synthesis of a large variety of novel benzoquinolines, benzoisoquinolines, and phenanthrolines.

4. Experimental part

4.1. General

All commercial solvents and reagents were used as-received except THF, which was distilled over Na/benzophenone under argon. Flash chromatography was realized on silica gel (SDS AAC 60, 70–200 μm) or on neutral alumina gel (Merck 90, 63–200 μm). IR spectra were recorded on KBr disks with a Perkin–Elmer BX FTIR apparatus. ^1H and ^{13}C NMR spectra were recorded, respectively, at 400 and 100 MHz with a Jeol Lambda 400 NMR spectrometer. Chemical shifts δ are reported in parts per million with the solvent resonance as the internal standard; coupling constants J are given in hertz. Multiplicity is given as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). The microwave reactions were performed using a Biotage Initiator Microwave oven using 2–5 mL sealed vials. Temperature was measured with an IR-sensor and reaction times are given as hold times. LC/MS (ESI) analyses were realized with a Waters alliance 2695 as separating module using the following gradient: A (95%)/B (5%) to A (5%)/B(95%) in 10 min. This ratio was hold during 3 min before return to initial conditions in 1 min. Initial conditions were then maintained for 5 min (A: H_2O, B: CH_3CN; each containing HCOOH: 0.1%; Column: C18 Xterra MSC118/2.1_50 mm). MS detection was performed with a Micromass ZMD 2000 by positive ESI. High Resolution Mass Spectra were performed at 70 eV by electronic impact (HREIMS) or positive or negative electrospray (HRESIMS). Melting points were determined on Kofler melting point apparatus.

4.2. General one-pot procedure

*4.2.1. Methyl 5-aminobenzo[h]quinoline-6-carboxylate (**7a**).* To a solution of aryl halide **4a** (48 mg, 0.35 mmol) in 2 mL dimethylformamide were added boronic ester **5** (106 mg, 0.385 mmol), $Pd(PPh_3)_4$ (20 mg, 5 mol %), and K_3PO_4 (242 mg, 1.11 mmol). The mixture was irradiated at 150 °C for 90 min using a microwave reactor. The reaction mixture was then diluted with EtOAc, filtrated on a small pad of Celite, and concentrated under vacuum. The crude mixture was then purified by column chromatography (DCM/CyHex 7/3) to afford 63 mg of the corresponding phenanthrene **7a** (72% yield). Off-white solid; mp 90 °C; IR (KBr) ν 3479, 3355 (NH_2), 2941, 2851 (CH), 1672 (CO), 1538, 1515, 1419, 1304, 1226, 776, 736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.84 (m, 2H, H_1, H_3), 8.48 (d, J=8.8 Hz, 1H, H_{10}), 8.39 (d, J=7.8 Hz, 1H, H_7), 7.61 (dd, J=8.8, 4.9 Hz, 1H, H_2), 7.53 (dd, J=8.0, 7.8 Hz, 1H, H_8), 7.43 (br s, 2H, NH_2), 7.38 (dd, J=8.8, 8.0 Hz, 1H, H_9), 4.04 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9 (CO), 148.0, 147.4, 140.0, 131.1(2C), 128.1, 127.4, 125.6, 123.9, 123.2, 123.0, 122.5, 101.4, 51.6; LCMS: ES^+ 253.13 (M^+); HRESIMS $[M+H]^+$ m/z 253.0975 (calcd for $C_{15}H_{13}N_2O_2$ 253.0977).

*4.2.2. 5-Aminobenzo[f]quinoline-6-carbonitrile (**8a**).* Starting from the halide **4a** (48 mg, 0.35 mmol) and the boronic ester **6** (94 mg, 0.385 mmol), following the general procedure described for **7a**, **8a** was obtained as an off-white solid (51 mg, 67%); mp 210 °C; IR (KBr) ν 3462, 3350 (NH_2), 2208 (CN), 1641 (CO), 1493, 1393, 1289, 1169, 791, 744, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.84 (m, 2H, H_1, H_3), 8.41 (d, J=8.8 Hz, 1H, H_{10}), 8.00 (d, J=8.8 Hz, 1H, H_7), 7.67 (dd, J=8.8, 4.9 Hz, 1H, H_2), 7.64 (dd, J=8.8, 7.8 Hz, 1H, H_8), 7.48 (dd, J=8.8, 7.8 Hz, 1H, H_9), 6.17 (br s, 2H, NH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.1(C_5), 148.6(C_3), 138.6(C_{4a}), 131.4(C_1), 130.2(C_{6a}), 129.1(C_8), 127.6(C_{10b}), 124.3(C_2), 124.3(C_9), 123.9(C_7), 123.1(C_{10a}), 122.7(C_{10}), 117.5(CN), 85.4(C_6); LCMS: ES^+ 220.39; HRESIMS $[M+H]^+$ m/z 220.0865 (calcd for $C_{14}H_{10}N_3$ 220.0875). X-ray structure available in Supplementary data.[11]

*4.2.3. Methyl 5-aminobenzo[f]isoquinoline-6-carboxylate (**7b**).* Starting from the halide **1** (80 mg, 0.35 mmol) and the boronic ester **3b** (89 mg, 0.385 mmol), following the general procedure described for **7a**,**b** was obtained as an orange solid (75 mg, 85%); mp 212 °C; IR (KBr) ν 3427, 3396 (NH_2), 3002, 2947, 1680 (CO), 1631, 1610, 1446, 1318, 1269, 1221, 1006, 780 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.38 (s,1H, H_4), 8.82 (d, J=5.8 Hz, 1H, H_1), 8.49 (d, J=7.8 Hz, 1H, H_{10}), 8.37 (d, J=5.8 Hz, 1H, H_2), 8.31 (d, J=8.8 Hz, 1H, H_7), 7.61 (dd, J=8.8, 6.8 Hz, 1H, H_8), 7.44 (dd, J=7.8, 6.8 Hz, 1H, H_9), 6.45 (s, 2H, NH_2), 4.03 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$)

δ 169.7 (CO), 147.5, 145.9, 145.1, 137.8, 132.5, 129.6, 125.9, 123.8, 123.3, 123.1, 119.5, 116.3, 105.9, 51.9; HRESIMS $[M+H]^+$ *m/z* 253.0979 (calcd for $C_{15}H_{13}N_2O_2$ 253.0977).

*4.2.4. 5-Aminobenzo[f]isoquinoline-6-carbonitrile (**8b**).* Starting from the halide **2** (69 mg, 0.35 mmol) and the boronic ester **3b** (89 mg, 0.385 mmol), following the general procedure described for **7a**, **8b** was obtained as a yellow solid (50 mg, 65%); mp 220 °C; IR (KBr) ν 3421, 3327 (NH_2), 3157, 2923, 2205 (CN), 1658, 1615, 1569, 1445, 1188, 832, 757, 727, 621 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6): 9.74 (s, 1H, H_4), 8.87 (d, *J*=5.8 Hz, 1H, H_1), 8.71 (d, *J*=7.8 Hz, 1H, H_{10}), 8.62 (d, *J*=5.8 Hz, 1H, H_2), 7.91 (d, *J*=7.8 Hz, 1H, H_7), 7.75 (dd, *J*=7.8, 6.8 Hz, 1H, H_8), 7.52 (dd, *J*=7.8, 6.8 Hz, 1H, H_9), 6.84 (br s, 2H, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ 149.4, 148.5, 147.1, 137.2, 132.9, 130.4, 129.9, 124.8, 123.1, 122.0, 121.7, 117.6, 116.5, 82.3; HRESIMS $[M+H]^+$ *m/z* 220.0879 (calcd for $C_{14}H_{10}N_3$ 220.0875). X-ray structure available in Supplementary data.[11]

*4.2.5. Methyl 5-aminobenzo[h]isoquinoline-6-carboxylate (**7c**).* Starting from the halide **1** (80 mg, 0.35 mmol) and the boronic ester **3c** (89 mg, 0.385 mmol), following the general procedure described for **7a**,**c** was obtained as a yellow solid (22 mg, 25%); mp 152 °C; IR (KBr) ν 3431, 3336 (NH_2), 3204, 3075, 2951 (CH), 1706 (CO), 1659, 1606, 1588, 1436, 1408, 1237, 1193 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.00 (s, 1H, H_1), 8.76 (d, *J*=5.8 Hz, 1H, H_3), 8.63 (d, *J*=8.8 Hz, 1H, H_{10}), 8.24 (d, *J*=7.8 Hz, 1H, H_7), 7.71 (d, *J*=5.8 Hz, 1H, H_4), 7.57 (dd, *J*=7.8, 6.8 Hz, 1H, H_8), 7.48 (d, *J*=8.8, 6.8 Hz, 1H, H_9), 6.16 (br s, 2H, NH_2), 4.06 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 147.4, 145.5, 143.1, 132.1, 132.0, 130.7, 128.1, 125.7, 124.3, 124.0, 121.9, 114.8, 106.1, 52.0; LCMS: ES^+ 253.15 (M^+); HRESIMS $[M+H]^+$ *m/z* 253.0968 (calcd for $C_{15}H_{13}N_2O_2$ 253.0977).

*4.2.6. 5-Aminobenzo[h]isoquinoline-6-carbonitrile (**8c**).* Starting from the halide **2** (69 mg, 0.35 mmol) and the boronic ester **3c** (89 mg, 0.385 mmol), following the general procedure described for **7a**, **8c** was obtained as a yellow solid (59 mg, 77%); mp >260 °C; IR (KBr) ν 3418, 3355 (NH_2), 3225, 2924 (CH), 2205 (CN), 1665, 1580, 1466, 1117, 754 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 10.13 (s, 1H, H_1), 8.85 (d, *J*=8.8 Hz, 1H, H_{10}); 8.82 (d, *J*=5.8 Hz, 1H, H_3), 8.25 (d, *J*=5.8 Hz, 1H, H_4), 7.93 (d, *J*=7.8 Hz, 1H, H_8), 7.71 (dd, *J*=7.8, 6.8 Hz, 1H, H_8), 7.55 (d, *J*=8.8, 5.8 Hz, 1H, H_9), 6.74 (br s, 2H, NH_2); ^{13}C NMR (100 MHz, acetone-d_6) δ 148.5, 147.0, 132.7, 132.6, 130.0, 129.5, 129.3, 127.1, 125.6, 124.2, 123.5, 117.4, 116.4, 99.1; LCMS: ES^+ 220.12 (M^+); ES^- 218.09 (M^-); HRESIMS $[M+H]^+$ *m/z* 220.0862 (calcd for $C_{14}H_{10}N_3$ 220.0875). X-ray structure available in Supplementary data.[11]

*4.2.7. Methyl 5-aminobenzo[h]quinoline-6-carboxylate (**7d**).* Starting from the halide **4b** (48 mg, 0.35 mmol) and the boronic ester **5** (106 mg, 0.385 mmol), following the general procedure described for **7a**, **7d** was obtained as a yellow solid (53 mg, 60%); mp 144 °C; IR (KBr) ν 3477, 3403 (NH_2), 2947, 2924, 2850 (CH), 1679 (CO), 1610, 1434, 1305, 1241, 1233, 787, 727 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.17 (d, *J*=6.8 Hz, 1H, H_{10}), 9.02 (dd, *J*=1.96, 5.8 Hz, 1H, H_2); 8.30 (d, *J*=8.8 Hz, 1H, H_7), 8.24 (dd, *J*=1.96, 6.8 Hz, 1H, H_4), 7.59 (dd, *J*=8.8, 6.8 Hz, 1H, H_8), 7.51 (dd, *J*=5.8, 8.8 Hz, 1H, H_3), 7.46 (dd, *J*=6.8 Hz, 1H, H_9), 6.32 (br s, 2H, NH_2), 4.04 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 150.7, 148.4, 145.1, 132.1, 130.0, 129.0, 126.6, 125.0, 124.5, 123.7, 121.5, 119.0, 103.0, 51.8; LCMS: ES^+ 253.12 (M^+); ES^- 251.15 (M^-); HRESIMS $[M+H]^+$ *m/z* 253.0965 (calcd for $C_{15}H_{13}N_2O_2$ 253.0977).

*4.2.8. 5-Aminobenzo[h]quinoline-6-carbonitrile (**8d**).* Starting from the halide **4b** (48 mg, 0.35 mmol) and the boronic ester **6** (94 mg, 0.385 mmol), following the general procedure described for **7a**, **8d** was obtained as an off-white solid (51 mg, 67%); mp 190 °C; IR (KBr) ν 3443, 3321 (NH_2), 3214, 2198 (CN), 1650, 1597, 1491, 1406, 756, 725 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.13 (d, *J*=7.8 Hz, 1H, H_{10}), 9.09 (dd, *J*=1.96, 3.8 Hz, 1H, H_2); 8.21 (d, *J*=8.8 Hz, 1H, H_7), 7.99 (d, *J*=7.8 Hz, 1H, H_4), 7.72 (dd, *J*=8.8, 6.8 Hz, 1H, H_8), 7.61 (dd, *J*=3.8, 7.8 Hz, 1H, H_3), 7.56 (d, *J*=7.8, 6.8 Hz, 1H, H_9), 5.23 (br s, 2H, NH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.4, 148.3, 147.5, 131.4, 130.1, 129.8, 126.2, 124.9, 124.9, 123.3, 121.8, 117.6, 117.3, 75.0; LCMS: ES^+ 220.10 (M^+); ES^- 218.11 (M^-); HRESIMS $[M+H]^+$ *m/z* 220.0866 (calcd for $C_{14}H_{10}N_3$ 220.0875). X-ray structure available in Supplementary data.[11]

*4.2.9. Ethyl 6-aminobenzo[h]isoquinoline-5-carboxylate (**12**).* Starting from the halide **10** (85 mg, 0.35 mmol) and the boronic ester **11** (88 mg, 0.385 mmol), following the general procedure described for **7a**, **12** was obtained as a colorless solid (77 mg, 83%); mp 172 °C; IR (KBr) ν 3361, 3203 (NH_2), 2982, 2933, 1668 (CO), 1626, 1597, 1544, 1260, 1211, 1190, 1096, 763, 540 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.74 (s, 1H, H_1), 8.72 (d, *J*=7.8 Hz, 1H, H_{10}), 8.53 (d, *J*=5.8 Hz, 1H, H_3), 8.30 (d, *J*=5.8 Hz, 1H, H_4), 7.99 (d, *J*=7.8 Hz, 1H, H_7), 7.79 (t, *J*=7.8 Hz, 1H, H_9), 7.67 (t, *J*=7.8 Hz, 1H, H_8), 7.14 (br s, 2H, NH_2), 4.53 (q, *J*=6.8 Hz, 2H, OCH_2), 1.51 (t, *J*=6.8 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 150.3, 145.9, 136.2, 131.9, 130.1, 128.4, 127.5, 124.0, 122.7, 122.0, 120.1, 118,6, 99.1, 61.0, 14.4; LCMS: ES^+ 267.19 (M^+); ES^- 265.20 (M^-); HRESIMS $[M+H]^+$ *m/z* 267.1130 (calcd for $C_{16}H_{15}N_2O_2$ 267.1134).

*4.2.10. Ethyl 6-amino-2,9-phenanthroline-5-carboxylate (**13**).* Starting from the halide **10** (85 mg, 0.35 mmol) and the boronic ester **3c** (89 mg, 0.385 mmol), following the general procedure described for **7a**, **13** was obtained as a yellow solid (47 mg, 50%); mp 214 °C; IR (KBr) ν 3462, 3420 (NH_2), 2923, 2849, 1636 (CO), 1261, 1201, 1112, 1022, 801, 623 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.12 (s, 1H, H_{10}), 9.90 (s, 1H, H_1), 8.86 (d, *J*=4.8 Hz, 1H, H_8), 8.62 (d, *J*=5.8 Hz, 1H, H_3), 8.32 (d, *J*=5.8 Hz, 1H, H_4), 7.75 (d, *J*=4.8 Hz, 1H, H_7), 7.00 (br s, 2H, NH_2), 4.56 (q, *J*=6.8 Hz, 2H, OCH_2), 1.52 (t, *J*=6.8 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8 (CO), 148.0, 146.9, 146.8, 146.6, 145.3, 136.1, 128.8, 125.9, 118.8, 114.7, 103.7, 101.7, 61.5, 14.4; LCMS: ES^+ 268.42 (M^+); HRESIMS $[M+H]^+$ *m/z* 268.1082 (calcd for $C_{15}H_{14}N_3O_2$ 268.1086).

4.3. Boronic ester synthesis

*4.3.1. 4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinonitrile (**3b**).* In a dry 500 mL flask under N_2 2,2,6,6-tetramethylpiperidine (57.6 mmol) was dissolved in dry THF (200 mL) and the mixture was cooled to −10 °C before *n*-BuLi (57.6 mmol, 2.5 M in *n*-hexane) was added over 2 min. The mixture was stirred for 10 min before cooling to −78 °C. At −78 °C, B(*O*-*i*-Pr)$_3$ (65.3 mmol) was added over 2 min and stirred for 5 min at −78 °C before 3-cyanopyridine (48 mmol) dissolved in dry THF (50 mL) was added dropwise over 5 min. The reaction was left in the dry ice bath, allowed to reach room temperature overnight and quenched with glacial acetic acid (67.2 mmol) followed by addition of pinacol (72 mmol). The mixture was stirred for 2 h at room temperature and then transferred to a separating funnel with CH_2Cl_2 (75 mL) and washed with aqueous KH_2PO_4 (10 w/v %) (4×60 mL). The combined aqueous layers was back-extracted once with CH_2Cl_2 (15 mL), the combined organic phase was dried over $MgSO_4$, and the solvents were evaporated to give cyanopyridineboronic ester **3b** as a yellow solid with 18% yield; mp 88 °C; IR (KBr) ν 3097, 2968, 2930, 2238 (CN), 1618, 1522, 1476, 1464, 1421, 1385, 1373, 1337, 1201, 1113, 1046, 963, 882, 849, 778, 765, 714, 655, 578 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.86 (s, 1H, H_2), 8.74 (d, *J*=4.6 Hz, 1H, H_6), 7.70 (d, *J*=4.6 Hz, 1H, H_5), 1.34 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.3, 152.1, 129.3, 117.1, 114.2, 85.8, 83.1, 25.0.

*4.3.2. 2-(4,4,5,5-Tetramethyl-[1,2]-dioxoborolan-2-yl)benzonitrile (**11**).* Compound **11** was obtained according to the same procedure

starting from benzonitrile, as a colorless solid with 50% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89(dd, J=6.8, 2.0 Hz, 1H, H_6), 7.70(d, J=8.8 Hz, 1H, H_3), 7.51–7.60(m, 2H, H_4, H_5), 1.39(s, 12H). Other analyses are consistent with the previously described product.[14]

*4.3.3. Methyl [2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl] acetate (**5**).* To a solution of methyl 2-(2-bromophenyl)acetate (300 mg, 1.31 mmol) in 4.3 mL of dioxane were successively added at room temperature bis(pinacoloto)diboron (382 mg, 1.5 mmol) and potassium acetate (553 mg, 5.63 mmol) The reaction mixture was the then flushed twice with argon and $PdCl_2$(dppf) (76 mg, 0.1 mmol) was then added. The reaction mixture was heated for 3 h under reflux before cooling and diluting with Et_2O. The organic phase was washed with H_2O and brine and dried ($MgSO_4$). The crude product was purified by silica gel chromatography (CH_2Cl_2/CyHex 6/4) to afford **5** as colorless oil (345 mg, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, J=5.8 Hz, 1H, H_3), 7.38 (dd, J=7.8, 5.8 Hz, 1H, H_4), 7.26 (dd, J=7.8, 6.9 Hz, 1H, H_5), 7.18 (d, J=6.9 Hz, 1H, H_6), 3.98 (s, 2H, CH_2), 3.66 (s, 3H, OCH_3), 1.31 (s, 12H). Other analyses are consistent with the previously described product.[15]

*4.3.4. 2-[2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]acetonitrile (**6**).* Compound **6** was obtained according to the same procedure and starting from **2** (300 mg, 1.53 mmol) as colorless oil (279 mg, 75%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J=6.8 Hz, 1H), 7.46 (m, 2H), 7.33 (m, 1H), 4.11 (s, 2H), 1.37 (s, 12H). Other analyses are consistent with the previously described product.[16]

4.4. Ethyl 2-(3-bromopyridin-4-yl)acetate (10)

LiHMDS (1 M in THF, 10 mL, 10.1 mmol) was added at 0 °C to a solution of pyridine derivative (1.16 g, 6.8 mmol) and Et_2CO_3 (1.03 mL, 8.51 mmol) in THF (20 mL). After 5 h LiHMDS (5 mL, 5 mmol) was added at 20 °C. The solution was then stirred for 2 h and a saturated solution of NH_4Cl was added. The aqueous layer was washed with Et_2O and the combined organic layers were washed with brine and dried over $MgSO_4$. Evaporation of the solvent and flash chromatography (cyclohexane/EtOAc: 3/1) afforded the title compound as a yellow oil (1.03 g, 62% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (s, 1H, H_2), 8.47 (d, J=4.9 Hz, 1H, H_6), 7.26 (d, J=4.9 Hz, 1H, H_5), 4.19 (q, J=7.1 Hz, 2H), 3.78 (s, 2H), 1.27 (t, J=7.1 Hz, 3H). Other analyses are consistent with the previously described product.[13c]

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2011.05.116. These data include MOL files and InChiKeys of the most important compounds described in this article.

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