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One-pot synthesis of novel poly-substituted phenanthrenes

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ABSTRACT

A one-pot synthesis of novel poly-substituted phenanthrenes is described in this article through a Suzuki–Miyaura cross-coupling followed by a Dieckmann–Thorpe ring closure under microwave irradiation. The selection of the appropriate starting materials allowed us to introduce diversity on various positions of the phenanthrene ring system.

1. Introduction

Phenanthrene rings have gained the interest of the scientific community because of their occurrence in material science[1] and in numerous natural products.[2] A great number of these alkaloids exhibit interesting biological activities[3] among which antitumour activities are the most notable. These pharmacological properties are described, for example, for tylophorine[4] and antofine[5] (Fig. 1), and a number of their simplified analogues have been synthesized.[6] Most of these structures are constituted by poly- methoxy-phenanthrene ring systems substituted on the 9 and 10 positions.

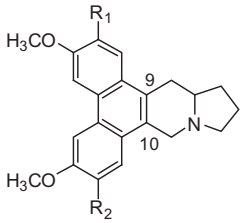
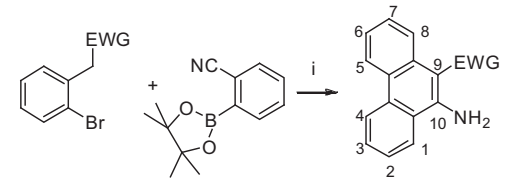


Figure 1. Structure of tylophorine and antofine.

The last few years have seen significant advances in the access towards phenanthrene rings mostly due to the development of transition-metal-catalysed chemistry.[7] However, novel and efficient synthesis methods are still needed in order to obtain these polysubstituted systems.

This is the reason why we have recently described, in a preliminary report, an efficient one-pot synthesis of 10-substituted 9-aminophenanthrenes under microwave irradiation (Scheme 1).[8] For example, to achieve the synthesis of phenanthrene **6**, cyanoboronic ester **5** was engaged in a Suzuki–Miyaura cross-coupling with methyl 2-(2-bromophenyl) acetate **1** followed by an intramolecular Dieckmann–Thorpe ring closure (entry 1 in Table 1).



Scheme 1. General synthesis of novel 10-substituted 9-aminophenanthrenes. Reagents and conditions: (i) $Pd(PPh_3)_4$ cat 5%, Cs_2CO_3 3 equiv, DMF, 150 °C, MW.

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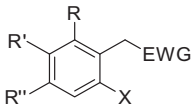
Table 1
General synthesis of aminophenanthrenes according to Scheme 1



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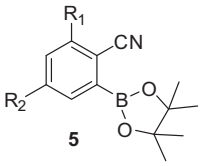

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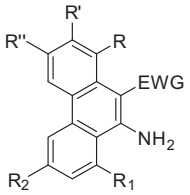


6-9

Entry	*n*°	R	R′	R″	X	EWG	*n*°	R_1	R_2	*n*°	R	R′	R″	R_1	R_2	EWG	Time (min)	Yield[a] (%)
1	**1a**	H	H	H	Br	CO_2CH_3	**5a**	H	H	**6aa**	H	H	H	H	H	CO_2CH_3	20	80
2	**2**	H	H	H	Br	CN	**5a**	H	H	**7a**	H	H	H	H	H	CN	20	85
3	**3**	H	H	H	Br	$COCH_3$	**5a**	H	H	**8a**	H	H	H	H	H	$COCH_3$	55	73
4	**4**	H	H	H	Br	CHO	**5a**	H	H	**9a**	H	H	H	H	H	CHO	45	65
5	**1b**	H	H	OCH_3	Br	CO_2CH_3	**5a**	H	H	**6ba**	H	H	OCH_3	H	H	CO_2CH_3	45	75
6	**1c**	H	OCH_3	OCH_3	Br	CO_2CH_3	**5a**	H	H	**6ca**	H	OCH_3	OCH_3	H	H	CO_2CH_3	50	76
7	**1d**	H	OCH_3	H	Br	CO_2CH_3	**5a**	H	H	**6da**	H	OCH_3	H	H	H	CO_2CH_3	20	72
8	**1e**	Cl	H	H	Cl	CO_2CH_3	**5a**	H	H	**6ea**	Cl	H	H	H	H	CO_2CH_3	45	65
9	**1a**	H	H	H	Br	CO_2CH_3	**5b**	OCH_3	H	**6ab**	H	H	H	OCH_3	H	CO_2CH_3	40	75
10	**1a**	H	H	H	Br	CO_2CH_3	**5c**	H	CF_3	**6ac**	H	H	H	H	CF_3	CO_2CH_3	60	60
11	**2**	H	H	H	Br	CN	**5b**	OCH_3	H	**7b**	H	H	H	OCH_3	H	CN	40	87
12	**2**	H	H	H	Br	CN	**5c**	H	CF_3	**7c**	H	H	H	H	CF_3	CN	55	80
13	**1b**	H	H	OCH_3	Br	CO_2CH_3	**5b**	OCH_3	H	**6bb**	H	H	OCH_3	OCH_3	H	CO_2CH_3	60	65
14	**1c**	H	OCH_3	OCH_3	Br	CO_2CH_3	**5b**	OCH_3	H	**6cb**	H	OCH_3	OCH_3	OCH_3	H	CO_2CH_3	50	63

[a] Isolated yield.

Herein we wish to report the application of this strategy to various substrates in order to extend the scope of this reaction and to describe the synthesis of novel and highly valuable poly-substituted phenanthrenes.

2. Results and discussion

Our first goal was to extend the reactivity to diverse aryl bromides (entries 1–4 in Table 1). The optimization work we have previously carried out[8] led to the discovery of an efficient reaction procedure. The boronic ester **5a** and the methylene activated substrate **1a** were solved in DMF and irradiated with a microwave at 150 °C using $Pd(PPh_3)_4$ as a catalyst and Cs_2CO_3 as a base. The reaction was highly efficient with both the nitrile **2** and the ketone **3** (Scheme 1) and two novel phenanthrenes **7a** and **8a** were obtained with 85% and 73% yields, respectively (entries 2 and 3 in Table 1).[8] In order to complete the scope of this reaction, 2-(2-bromophenyl) acetaldehyde **4** was employed and after 45 min the reaction afforded a 65% yield of the expected aldehyde **9a** (entry 4 in Table 1).

To study the scope and limitations of the cascade reaction, we examined a variety of substituted benzonitrile or aryl halides.

In the first attempt, a series of substituted phenyl acetates **1b**–**e** were engaged in the general procedure (entries 5–8 in Table 1) and led to the formation of four aminoesters **6ba**–**ea** with good yields.[8] The three dimensional structure of compound **6ba** was assessed by realizing its X-ray crystallography (Fig. 2).[9]

In order to introduce, for the first time, some substitutions on the second ring we decided to synthesize novel cyanoboronic esters. In our approach **5a** was obtained through ortho-lithiation of benzonitrile (Scheme 2) according to Begtrup's procedure.[10] We tried to adapt this strategy to substituted benzonitriles, as described by the same group.[11] The lithiation was carried out on two benzonitriles **10b**,**c** using 1.2 equiv of LTMP as a base followed by the addition of 1.4 equiv of triisopropylborate. In order to stabilize the boronic species the intermediates were treated, after acidic quench, with 1.5 equiv of pinacol. This methodology led to the synthesis of two novel esters **5b**,**c** with good yields (Scheme 2).

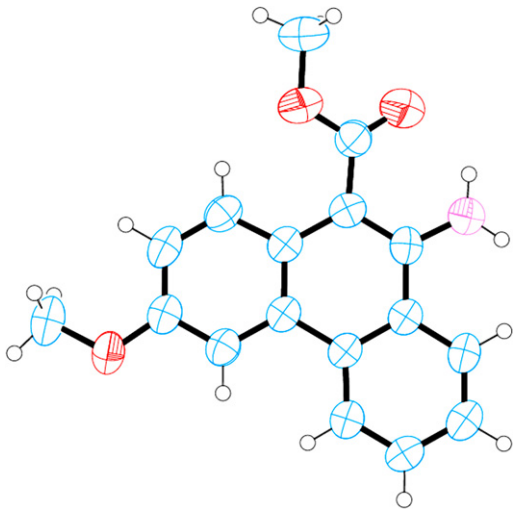
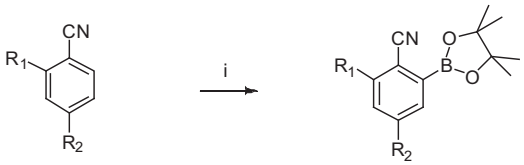


Figure 2. X-ray structure of compound **6ba:** CCDC 759470.[9]



10a R_1=H R_2=H
10b R_1=OCH_3 R_2=H
10c R_1=H R_2=CF_3

5a R_1=H R_2=H
5b R_1=OCH_3 R_2=H
5c R_1=H R_2=CF_3

Scheme 2. Ortho-lithiation of benzonitriles **10b**,**c**. Reagents and conditions: (i) (a) LTMP 0 °C; (b) BuLi 0 °C; (c) $B(O\text{-}i\text{-}Pr)_3$ −78 °C; (c) pinacol rt.

The influence of this novel substitution on the Suzuki–Miyaura cross-coupling was then tested by involving these two novel esters **5b**,**c** in the previously described one-pot reaction. Treated with methyl 2-(2-bromophenyl) acetate **1a** or the nitrile **4** the procedure

afforded good to excellent yields of four novel phenanthrenes **6ab**,**ac** and **7b**,**c**, respectively (entries 9–12 in Table 1).

The coupling of substituted methyl ester **1b** or **1c** with the boronic ester **5b** afforded, for the first time, 9-aminophenanthrenes substituted on both side rings **6bb**,**cb** with moderate yields (entries 13 and 14 in Table 1).

Despite the successful utilization of the cascade reaction, this strategy is still dependent on the availability of the corresponding *o*-cyanophenyl-boronic species. Obtained according to a directed ortho metalation (DOM) strategy, this methodology is however less regioselective when the starting benzonitrile is substituted on *para* and *meta* positions by directed metalation groups (DMG).[11] We therefore decided to assess the feasibility of the reverse process, starting from a boronic species **11** and an *o*-halogenated benzonitrile **12** (Fig. 3).

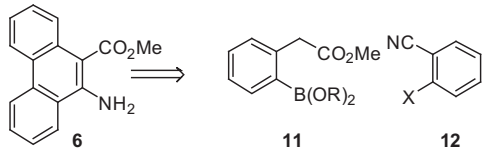
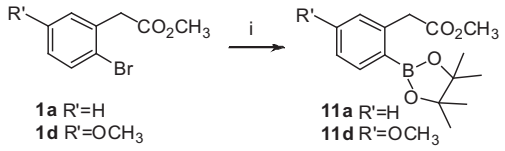


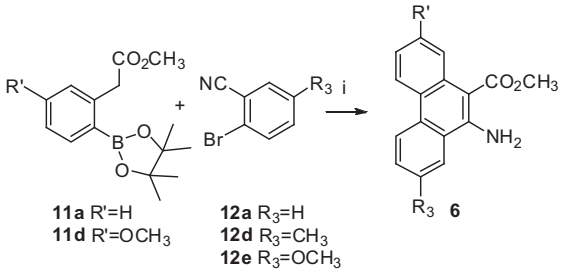
Figure 3. Retrosynthetic analysis of the reverse process.

Firstly, methyl [*o*-(boronic ester)phenyl] acetates **11** were synthesized. Our first approach was to test a bromine-lithium exchange strategy[12] on bromine ester **1a** followed by in situ trapping with triisopropylborate at −78 °C. Unfortunately, this strategy only led to dehalogenated structures. An alternative strategy was then applied to the bromine esters **1** (Scheme 3), where **1a**,**d** were engaged in a palladium-catalysed cross-coupling reaction with bis(pinacolato)diboron, developed by Miyaura,[13] which led to the boronic esters **11a**,**d** with quantitative yields.



Scheme 3. Synthesis of boronic esters **11a**,**d**. Reagents and conditions: KOAc, $PdCl_2(dppf)$, bis(pinacolato)diboron, CH_2Cl_2.

In order to test the validity of the reverse process, **11a**,**d** were first engaged in the one-pot reaction with *o*-bromobenzonitrile **12a** (Scheme 4). The corresponding phenanthrenes **6aa**,**da** were obtained with good yields comparable to those obtained in the original process (entries 1 and 2 in Table 2).



Scheme 4. Reverse general synthesis of 9-aminophenanthrenes. Reagents and conditions: (i) $Pd(PPh_3)_4$ cat 5%, Cs_2CO_3 3 equiv, DMF, 150 °C, MW.

It was impossible to synthesize 2-substituted methyl 10-aminophenanthrene-9-carboxylates according to the original cascade reaction.[11] Therefore, substituted *o*-bromobenzonitriles **12d**,**e** were employed in our reverse process with **11a**,**d**, which produced the expected phenanthrenes **6ad**,**ae** and **6de**, for the first time, and with good yields (entries 3–5 in Table 2).

3. Conclusion

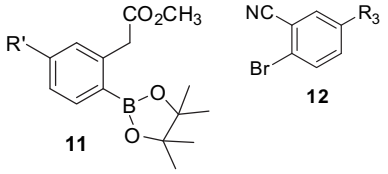
In summary, we have demonstrated that a cascade of Suzuki–Miyaura coupling Dieckmann–Thorpe ring closures is an efficient and fast method for the synthesis of functionalized phenanthrenes. This one-pot procedure appears to be robust and applicable to the synthesis of multiple substituted phenanthrenes according to the original or reverse process. The reactivity of the highly functionalized compounds obtained through this route will be reported in due course.

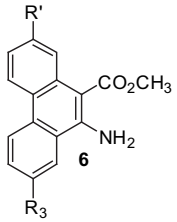
4. Experimental

4.1. General

All commercial solvents and reagents were used as received except tetrahydrofurane, which was distilled over Na/benzophenone under argon. Flash chromatography was undertaken on silica gel (SDS AAC 60, 70–200) or on neutral alumina gel (Merck 90, 63–200). IR spectra were recorded on KBr disks with a Perkin–

Table 2
General synthesis of aminophenanthrenes according to Scheme 4





Entry	Starting materials		*n*°	R′	R_3	Time (min)	Yield[a] (%)
1	**11a**	**12a**	**6aa**	H	H	25	85
2	**11d**	**12a**	**6da**	OCH_3	H	40	80
3	**11a**	**12d**	**6ad**	H	CH_3	40	70
4	**11a**	**12e**	**6ae**	H	OCH_3	50	77
5	**11d**	**12e**	**6de**	OCH_3	OCH_3	40	83

[a] Isolated yield.

Elmer BX FTIR apparatus. ^{1}H 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 undertaken with a Waters alliance 2695 as separating module using the following gradient: A (95%)/B (5%) to A (5%)/B (95%) in 10 min. The final conditions were held for 3 min before returning to initial conditions for 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. EIMS and HRMS (EI) were performed at 70 eV with a JEOL JMS GCMate. Melting points were determined on Kofler melting point apparatus.

4.2. General one-pot procedure

*4.2.1. Methyl 10-amino-9-phenanthrene-carboxylate (**6aa**).* Method (a) To a solution of aryl bromide **1a** (0.37 mmol) in 2 mL dioxane were added cyanoboronic ester **5a** (0.41 mmol), $Pd(PPh_3)_4$ (5 mol %) and Cs_2CO_3 (1.11 mmol). The mixture was irradiated at 150 °C for 20 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 the corresponding phenanthrene **6aa** with 80% yield.

Method (b) The same procedure was applied to the aryl bromide **12a** and the boronic ester **13a** to afford the expected phenanthrene **6aa** with 85% yield after 25 min.

Orange solid; mp 68–70 °C; IR (KBr) ν 3459, 3352 (NH_2), 1672 (CO), 1597, 1431, 1302, 1225, 1149, 1092, 742, 730, 717 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (d, J=8.0 Hz, 1H, H4), 8.51 (d, J=8.0 Hz, 1H, H5), 8.26 (d, J=8.0 Hz, 1H, H8), 7.94 (d, J=8.0 Hz, 1H, H1), 7.71 (t, J=8.0 Hz, 1H, H3), 7.61 (t, J=8.0 Hz, 1H, H2), 7,53 (t, J=8.0 Hz, 1H, H6), 7.40 (t, J=8.0 Hz, 1H, H7), 6.30 (s, 2H, NH_2), 4.04 (s, 3H, CO_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.38 (CO), 144.56, 131.57, 129.58, 127.90, 126.26, 125.75, 124.52, 124.25, 123.13, 122.43, 122.27, 121.51, 120.88, 101.75, 50.69; HRMS (EI) calcd for $C_{16}H_{13}NO_2$ 251.09461, found 251.09501.

Using method (a) and/or method (b) the following compounds were prepared according to the time described in Table 1 and Table 2, respectively.

*4.2.2. 10-Amino-9-cyanophenanthrene (**7a**).* White solid; method (a) 85%; mp 177–179 °C; IR (KBr) ν 3451, 3369 (NH_2), 2200 (CN), 1641, 1579, 1499, 1457, 1415, 1249, 746, 719 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, J=7.8 Hz, 1H, H4), 8.53 (d, J=7.8 Hz, 1H, H5), 8.01 (d, J=7.8 Hz, 1H, H8), 7.91 (d, J=7.8 Hz, 1H, H1), 7.80 (t, J=7.8 Hz, 1H, H3), 7.68 (dd, J=7.8, 6.8 Hz, 1H, H2), 7.63 (dd, J=7.8, 6.8 Hz, 1H, H6), 7.50 (t, J=6.8 Hz, 1H, H7), 5.27 (s, 2H, NH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.17, 132.47, 129.83, 129.73, 128.38, 127.16, 124.83, 124.50, 123.99, 123.72, 122.72, 122.46, 121.74, 117.86, 87.00; HRMS (EI) calcd for $C_{15}H_{10}N_2$ 218.08439, found 218.08534.

*4.2.3. 1-(10-Aminophenanthren-9-yl)ethanone (**8a**).* White solid; method (a) 73%; mp 142–144 °C; IR (KBr) ν 3427, 3289 (NH_2), 1605 (CO), 1551, 1508, 1492, 1421, 1227, 748, 726 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, J=7.8 Hz, 1H, H4), 8.50 (d, J=7.8 Hz, 1H, H5), 7.95 (d, J=7.8 Hz, 1H, H1), 7.75 (d, J=7.8 Hz, 1H, H8), 7.72 (dd, J=7.8, 6.8 Hz, 1H, H3), 7.62 (t, J=7.8 Hz, 1H, H2), 7.50 (t, J=6.8 Hz, 1H, H6), 7.42 (dd, J=7.8, 6.8 Hz, 1H, H7), 6.62 (s, 2H, NH_2)2.66 (s, 3H, $COCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.85 (CO), 143.45, 132.75, 131.02, 129.13, 127.00, 126.97, 125.64, 125.43, 124.60, 123.55, 123.49, 122.92, 122.12, 112.93, 32.02; HRMS (EI) calcd for $C_{16}H_{13}NO$ 235.0997, found 235.10073.

*4.2.4. 10-Aminophenanthrene-9-carbaldehyde (**9a**).* Yellow oil; method (a) 65%; IR (KBr) ν 3375, 3192(NH_2), 2958, 2925, 2855, 1730(CO), 1630, 1609, 1410, 1262, 1123, 1100, 1075, 743, 703 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.78 (s, CHO), 8.56 (d, J=7.8 Hz, 1H, H4), 8.43 (d, J=7.8 Hz, 1H, H5), 8.24 (d, J=7.8 Hz, 1H, H8), 7.93 (d, J=7.8 Hz, 1H, H1), 7.70 (t, J=7.8 Hz, 1H, H3), 7.56 (t, J=7.8 Hz, 1H, H2), 7.48 (m, 3H, NH_2, H6), 7.36 (t, J=7.8 Hz, 2H, H7); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.36 (CO), 149.54, 134.14, 132.23, 130.86, 130.40, 128.83, 128.13, 127.00, 123.72, 123.63, 123.52, 123.27, 122.21, 119.19; HRMS (EI) calcd for $C_{15}H_{11}NO$ 221.08405, found 221.08464.

*4.2.5. Methyl 10-amino-6-methoxyphenanthrene-9-carboxylate (**6ba**).* Orange solid; method (a) 75%; mp 155–157 °C; IR (KBr) ν 3421, 3306 (NH_2), 3207, 1634 (CO), 1617, 1598, 1507, 1435, 1366, 1248, 1217, 1177, 1032, 862, 855, 763 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, J=7.8 Hz, 1H, H4), 8.22 (d, J=8.8 Hz, 1H, H8), 7.96 (d, J=6,8 Hz, 1H, H1), 7.91 (d, J=2,9 Hz, 1H, H5), 7,71 (dd, J=8.8, 7.8 Hz, 1H, H3), 7.63 (t, J=6.8 Hz, 1H, H2), 7.17 (dd, J=8.8, 2.9 Hz, 1H, H7), 6.14 (s, 2H, NH_2), 4.03 (s, 3H, CO_2CH_3), 3.97 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.37 (CO), 155.89, 144.06, 132.10, 128.70, 127.16, 126.94, 126.65, 124.82, 124.75, 123.52, 122.14, 116.49, 104.77, 103.14, 55.46, 51.73; HRMS (EI) calcd for $C_{17}H_{15}NO_3$, 281.10518, found 281.10598.

*4.2.6. Methyl 10-amino-6,7-dimethoxyphenanthrene-9-carboxylate (**6ca**).* Orange solid; method (a) 76%; mp 139–141 °C; IR (KBr) ν 3450 (NH_2), 2917, 2849, 1732 (CO), 1610, 1462, 1376, 1261, 1234, 1079, 967, 799, 759, 720, 699 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, J=8.8 Hz, 1H, H4), 7.92 (d, J=7.8 Hz, 1H, H1), 7.86 (s, 1H, H5), 7.83 (s, 1H, H8), 7.69 (t, J=6.8 Hz, 1H, H3), 7.56 (dd, J=7.8, 6.8 Hz, 1H, H2), 6.20 (s, 2H, NH_2), 4.06 (s, 3H, CO_2CH_3), 4.05 (s, 3H, OCH_3), 4.01 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.24 (CO), 149.43, 146.55, 144.89, 132.18, 128.74, 125.78, 125.61, 123.43, 123.02, 122.19, 119.59, 106.97, 103.73, 102.70, 55.92, 55.63, 51.65; HRMS (EI) calcd for $C_{18}H_{17}NO_4$ 311.11573, found 311.11661.

*4.2.7. Methyl 10-amino-7-methoxyphenanthrene-9-carboxylate (**6da**).* Orange solid, method (a) 72%; method (b) 80%; mp 85–87 °C; IR (KBr) ν 3444, 3329 (NH_2), 2947, 1668 (CO), 1599, 1581, 1433, 1307, 1225, 1184, 1174, 1095, 1041, 849, 774, 714 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, J=7.8 Hz, 1H, H4), 8.41 (d, J=8,8 Hz, 1H, H5), 7.90 (d, J=8.8 Hz, 1H, H1), 7.80 (d, J=2.9 Hz, 1H, H8), 7.68 (dd, J=7.8, 6.8 Hz, 1H, H3), 7.54 (t, J=7.8 Hz, 1H, H2), 7.03 (dd, J=8.8, 2.9 Hz, 1H, H6), 6.31 (s, 2H, NH_2), 4.03 (s, 3H, CO_2CH_3), 3.97 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.40 (CO), 158.82, 146.56, 132.84, 132.18, 129.10, 125.79, 124.11, 123.07, 123.01, 121.94, 119.62, 112.37, 107.79, 102.20, 55.20, 51.66; HRMS (EI) calcd for $C_{17}H_{15}NO_3$ 281.10518, found 281.10568.

*4.2.8. Methyl 10-amino-8-chlorophenanthrene-9-carboxylate (**6ea**).* Yellowsolid; method (a) 80%; mp 107–109 °C; IR (KBr) ν 3462, 3369 (NH_2), 2947, 1673 (CO), 1616, 1433, 1248, 1205, 757 (CCl), 748, 732 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, J=7.8 Hz, 1H, H4), 8.43 (d, J=7.8 Hz, 1H, H5), 7.94 (d, J=7.8 Hz, 1H, H1), 7.72 (t, J=7.8 Hz, 1H, H3), 7.66 (t, J=7.8 Hz, 1H, H2), 7.44 (d, J=7.8 Hz, 1H, H7), 7.34 (t, J=7.8 Hz, 1H, H6), 5.73 (s, 2H, NH_2), 3.92 (s, 3H, CO_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.48 (CO), 143.87, 133.60, 132.86, 132.00, 130.60, 129.40, 129.13, 127.95, 127.54, 124.38, 123.90, 123.80, 122.01, 121.26, 51.16; HRMS (EI) calcd for $C_{16}H_{12}NO_2Cl$ 285.05564, found 285.05486.

*4.2.9. Methyl 10-amino-1-methoxyphenanthrene-9-carboxylate (**6ab**).* Yellow solid; method (a) 75%; mp 89–91 °C; IR (KBr) ν 3461,

3363(NH_2), 2942, 1670 (CO), 1588, 1433, 1289, 1254, 1224, 1201, 1086, 1014, 759, 657 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, J=8.8 Hz, 1H, H5), 8.23 (d, J=8.8 Hz, 1H, H4), 8.12 (d, J=7.8 Hz, 1H, H8), 7.96 (s, 2H, NH_2), 7.57 (dd, J=8.8, 7.8 Hz, 1H, H3), 7.44 (dd, J=8.8, 6.8 Hz, 1H, H6), 7.28 (t, J=6.8 Hz, 1H, H7), 7.03 (d, J=7.8 Hz, 1H, H2), 4.00 (s, 3H, OCH_3), 3.99 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.68 (CO), 158.91, 149.02, 135.66, 131.64, 129.12, 127.47, 124.88, 124.24, 123.35, 122.41, 116.57, 115.11, 108.34, 100.11, 56.38, 51.42; HRMS (EI) calcd for $C_{17}H_{15}NO_3$ 281.10518, found 281.10505.

*4.2.10. Methyl 10-amino-3-(trifluoromethyl)phenanthrene-9-carboxylate (**6ac**).* Yellow solid; method (a) 60%; mp 143–145 °C; IR (KBr) ν 3445, 3372 (NH_2), 2957, 2921, 1714 (CO), 1687, 1621, 1292, 1159, 1119, 1079, 1000, 774, 752 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.88 (s, 1H, H4), 8.50 (d, J=8.8 Hz, 1H, H5), 8.23 (d, J=8.8 Hz, 1H, H8), 8.03 (d, J=8.8 Hz, 1H, H1), 7.79 (d, J=8.8 Hz, 1H, H2), 7.55 (dd, J=8.8, 6.8 Hz, 1H, H6), 7.44 (t, J=6.8 Hz, 1H, H7), 6.17 (s, 2H, NH_2), 4.05 (s, 3H, CO_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.03 (CO), 144.20, 132.84, 132.31, 131.47, 130.9, 128.92, 128.15, 125.70, 124.86, 123.94, 123.00, 122.60, 120.90, 120.85, 104.97, 51.96; HRMS (EI) calcd for $C_{17}H_{12}NO_2F_3$ 319.08199, found 319.08265.

*4.2.11. 10-Amino-1-methoxyphenanthrene-9-carbonitrile (**7b**).* Yellow solid; method (a) 87%; mp 220–222 °C; IR (KBr) ν 3466, 3350 (NH_2), 2944, 2196 (CN), 1621, 1603, 1584, 1575, 1246, 1170, 1087, 1013, 740 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.54 (d, J=8.8 Hz, 1H, H5), 8.35 (d, J=7.8 Hz, 1H, H4), 7.73 (d, J=8.8 Hz, 1H, H4), 7.70 (m, 2H, H8, H3), 7.57 (dd, J=7.8, 6.8 Hz, 1H, H6), 7.36 (t, J=7.8 Hz, 1H, H7), 7.32 (s, 2H, NH_2), 7.27 (d, J=8.8 Hz, 1H, H2), 4.03 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.23, 151.21, 134.60, 130.84, 130.66, 128.82, 124.00, 123.31, 123.06, 121.95, 118.29, 116.27, 112.82, 109.30, 81.34, 56.55; HRMS (EI) calcd for $C_{16}H_{12}N_2O$ 248.09495, found 248.09389.

*4.2.12. 10-Amino-3-(trifluoromethyl)phenanthrene-9-carbonitrile (**7c**).* Beige solid; method (a) 80%; mp 209–211 °C; IR (KBr) ν 3460, 3365 (NH_2), 2948, 2209 (CN), 1652, 1592, 1433, 1311, 1231, 1176, 1166, 1120, 747 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.91 (s, 1H, H4), 8.52 (d, J=8.8 Hz, 1H, H5), 8.02 (d, J=7.8 Hz, 2H, H1, H8), 7.87 (d, J=8.8 Hz, 1H, H2), 7.68 (t, J=6.8 Hz, 1H, H6), 7.52 (dd, J=8.8, 6.8 Hz, 1H, H7), 6.17 (s, 2H, NH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.27, 132.27, 131.46, 131.13, 130.10, 129.32, 125.25, 124.47, 124.35, 123.12, 123.08, 122.73, 121.20, 121.10, 117.15, 92.40; HRMS (EI) calcd for $C_{16}H_9F_3N_2$ 286.07177, found 286.07152.

*4.2.13. Methyl 10-amino-1,6-dimethoxyphenanthrene-9-carboxylate (**6bb**).* Orange solid; method (a) 65%; mp 98–100 °C; IR (KBr) ν 3491, 3375 (NH_2), 3002, 2953, 1657 (CO), 1583, 1563, 1492, 1285, 1263, 1228, 1211, 1174, 1085, 1053, 1022, 817, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J=8.8 Hz, 1H, H4), 8.08 (d, J=8.8 Hz, 1H, H8), 7.81 (s, 2H, NH_2), 7.80 (d, J=2.9 Hz, 1H, H5), 7.56 (dd, J=8.8, 7.8 Hz, 1H, H3), 7.12 (dd, J=8.8, 2.9 Hz, 1H, H7), 7.02 (d, J=7.8 Hz, 1H, H2), 4.02 (s, 3H, CO_2CH_3), 3.98 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.58(CO), 158.96, 155.22, 147.60, 135.02, 128.85, 126.47, 125.92, 125.35, 116.82, 116.60, 115.55, 108.43, 105.52, 100.17, 56.36, 55.45, 51.37; HRMS (EI) calcd for $C_{18}H_{17}NO_4$ 311.11573, found 311.11700.

*4.2.14. Methyl 10-amino-1,6,7-trimethoxyphenanthrene-9-carboxylate (**6cb**).* Colourless oil; method (a) 63%; IR (KBr) ν 3445 (NH_2), 2924, 2853, 1668 (CO), 1594, 1517, 1464, 1376, 1261, 1164, 1088, 1024, 789 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J=8.8 Hz, 1H, H4), 7.87 (s, 2H, NH_2), 7.76 (s, 1H, H5), 7.69 (s, 1H, H8), 7.55 (dd, J=8.8, 7.8 Hz, 1H, H3), 6.96 (d, J=7.8 Hz, 1H, H2), 4.04 (s, 3H, CO_2CH_3), 4.03 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.41 (CO), 159.12, 149.68, 148.43, 145.93, 135.13, 128.91, 126.74, 121.38, 118.33, 116.10, 114.37, 107.15, 106.25, 104.68, 56.30, 55.87, 55.55, 51.32; HRMS (EI) calcd for $C_{19}H_{19}NO_5$ 341.12629, found 341.12731.

*4.2.15. Methyl 10-amino-2-methylphenanthrene-9-carboxylate (**6ad**).* Colourless oil; method (b) 70%; IR (KBr) ν 3447, 3373 (NH_2), 2948, 2922, 1711 (CO), 1682, 1615, 1435, 1231, 1090, 769, 749, 726 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8,53 (d, J=7.8 Hz, 1H, H4), 8.47 (d, J=7.8 Hz, 1H, H5), 8.24 (d, J=7.8 Hz, 1H, H8), 7.72 (s, 1H, H1), 7.54 (d, J=7.8 Hz, 1H, H3), 7.46 (t, J=7.8 Hz, 1H, H6), 7.39 (t, J=7.8 Hz, 1H, H7), 6.27 (s, 2H, NH_2), 4.03 (s, 3H, CO_2CH_3), 2.58 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.64 (CO), 154.52, 136.62, 133.85, 133.71, 130.62, 130.26, 126.87, 125.50, 125.40, 124.26, 123.47, 123.27, 122.33, 121.74, 51.69, 21.74; HRMS (EI) calcd for $C_{17}H_{15}NO_2$ 265.11027, found 265.10938.

*4.2.16. Methyl 10-amino-2-methoxyphenanthrene-9-carboxylate (**6ae**).* Orange solid; method (b) 77%; mp 117–119 °C; IR (KBr) ν 3444, 3362 (NH_2), 2951, 2927, 1684 (CO), 1617, 1433, 1261, 1224, 1040, 826 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, J=8.8 Hz, 1H, H4), 8.40 (d, J=7.8 Hz, 1H, H5), 8.21 (d, J=7.8 Hz, 1H, H8), 7.45 (t, J=6.8 Hz, 1H, H6), 7.37 (dd, J=8.8, 7.8 Hz, 1H, H7), 7.31 (dd, J=2.9, 8.8 Hz, 1H, H3), 7.25 (d, J=2.9 Hz, 1H, H1), 6.10 (s, 2H, NH_2), 4.03 (s, 3H, CO_2CH_3), 3.95 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.46 (CO), 158.57, 144.75, 131.96, 130.87, 129.40, 126.68, 126.30, 125.49, 125.16, 123.43, 121.98, 119.16, 118.17, 103.82, 55.48, 51.30; HRMS (EI) calcd for $C_{17}H_{15}NO_3$ 281.10518, found 281.10618.

*4.2.17. Methyl 10-amino-2,7-dimethoxyphenanthrene-9-carboxylate (**6de**).* Orange solid; method (b) 83%; mp 149–151 °C; IR (KBr) ν 3460, 3353 (NH_2), 2921, 1669 (CO), 1609, 1576, 1567, 1428, 1246, 1216, 1050, 1038, 1012, 869, 801 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, J=9.8 Hz, 1H, H4), 8.32 (d, J=8.8 Hz, 1H, H5), 7.75 (d, J=2.0 Hz, 1H, H8), 7.31 (dd, J=8.8, 2.0 Hz, 1H, H6), 7.24 (d, J=2.9 Hz, 1H, H1), 7.01 (dd, J=9.8, 2.9 Hz, 1H, H3), 6.20 (s, 2H, NH_2), 4.04 (s, 3H, CO_2CH_3), 3.96 (s, 3H, OCH_3) 3.92 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.47 (CO), 158.11, 157.89, 145.77, 130.89, 127.03, 124.72, 124.30, 123.51, 119.87, 118.50, 112.57, 107.77, 103.70, 103.25, 55.54, 55.23, 51.70; HRMS (EI) calcd for $C_{18}H_{17}NO_4$ 311.11573, found 311.11653.

4.3. Ortho-lithiation procedure

*4.3.1. 2-Methoxy-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-benzonitrile (**5b**).* In a dry Schlenk flask under N_2 2,2,6,6- tetramethylpiperidine (0.12 mmol) was dissolved in dry THF (25 mL) and the mixture was cooled to −10 °C before *n*-BuLi (0.12 mmol) was added over 2 min. The mixture was stirred for 10 min before cooling to −78 °C. At −78 °C, B(O-*i*-Pr)$_3$ (0,14 mmol) was added over 2 min and stirred for 5 min at −78 °C before the benzonitrile **10b** (0.1 mmol) dissolved in dry THF (10 mL) was added drop-wise over 5 min. The reaction was left in the dry ice bath overnight, slowly reaching room temperature. The reaction was quenched with glacial acetic acid (0.14 mmol) followed by addition of pinacol (0.15 mmol). The mixture was stirred for 1 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 water phase was back-extracted once with CH2Cl2 (15 mL), the combined organic phase was dried over MgSO4, and the solvents were evaporated to give the crude cyanoarylboronic ester as a yellow solid with 98% yield; mp 110–112 °C; IR (KBr) ν 3003, 2985, 2953, 2225 (CN), 1576, 1455, 1351, 1329, 1275, 1042, 849, 802, 750, 678 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (dd, J=7.8, 6.8 Hz, 1H, H4), 7.40 (d, J=6.8 Hz, 1H, H5), 7.05 (d, J=7.8 Hz, 1H, H3), 3.90 (s, 3H, OCH_3), 1.34 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.63, 133.03, 127.31, 115.93, 113.43, 105.95, 84.68, 55.99, 24.70

(the quaternary carbon bonded to the boron was missing); HRMS (EI) calcd for $C_{14}H_{18}BNO_3$ 259.13796, found 259.13719.

*4.3.2. 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl)benzonitrile (**5c**).* Compound **5c** was obtained according to the same procedure and starting from **10c** as a yellow solid with 65% yield; mp 78–80 °C; IR (KBr) ν 2988, 2235 (CN), 1610, 1352, 1305, 1176, 1142, 1080, 1064, 849 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J=2.0 Hz, 1H, H5), 7.83 (d, J=7.8 Hz, 1H, H2), 7.78 (dd, J=7.8, 2.0 Hz, 1H, H3), 1.40 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.73, 132.62, 132.58, 127.82, 127.79, 120.73, 117.69, 85.31, 24.76 (the quaternary carbon bonded to the boron was missing).

4.4. Boronic ester synthesis

*4.4.1. Methyl [2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl] acetate (**11a**).* To a solution of methyl 2-(2-bromophenyl)acetate (1.09 mmol) in 4.3 mL of dioxane were successively added at rt bis(-pinacolato)diboron (1.22 mmol) and potassium acetate (4.1 mmol) The reaction mixture was then flushed twice with argon and $PdCl_2$(dppf) (0.07 mmol) was then added. The reaction mixture was heated for 3 h under reflux before being cooled and diluted 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 **11a** as colourless oil with 98% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, J=5.8 Hz, 1H), 7.38 (dd, J=7.8, 5.8 Hz, 1H), 7.26 (dd, J=7.8, 6.9 Hz, 1H), 7.18 (d, J=6.9 Hz, 1H), 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.[14]

*4.4.2. Methyl 2-(5-methoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate (**11d**).* Compound **11d** was obtained according to the same procedure and starting from **11d** as colourless oil with 85% yield; IR (KBr) ν 3444, 2951, 1739 (CO), 1605, 1569, 1463, 1384, 1352, 1261, 1146, 1113, 1035, 964, 802 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J=7.8 Hz, 1H), 6.79 (dd, J=7.8, 2.9 Hz, 1H), 6.73 (d, J=2.9 Hz, 1H), 3.95 (s, 2H, CH_2), 3.80 (s, 3H, OCH_3), 3.66 (s, 3H, OCH_3), 1.29 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.69 (CO), 161.78, 142.47, 137.90, 129.95, 116.10, 111.52, 83.27, 55.23, 51.80, 41.20, 21.74.

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