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Note

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Regioselective Synthesis of Unsymmetric Tetra- and Pentasubstituted Pyrenes with a Strategy for Primary *C*-Alkylation at the 2-Position.

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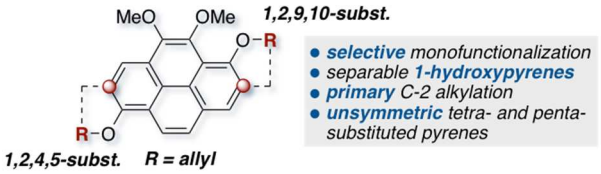
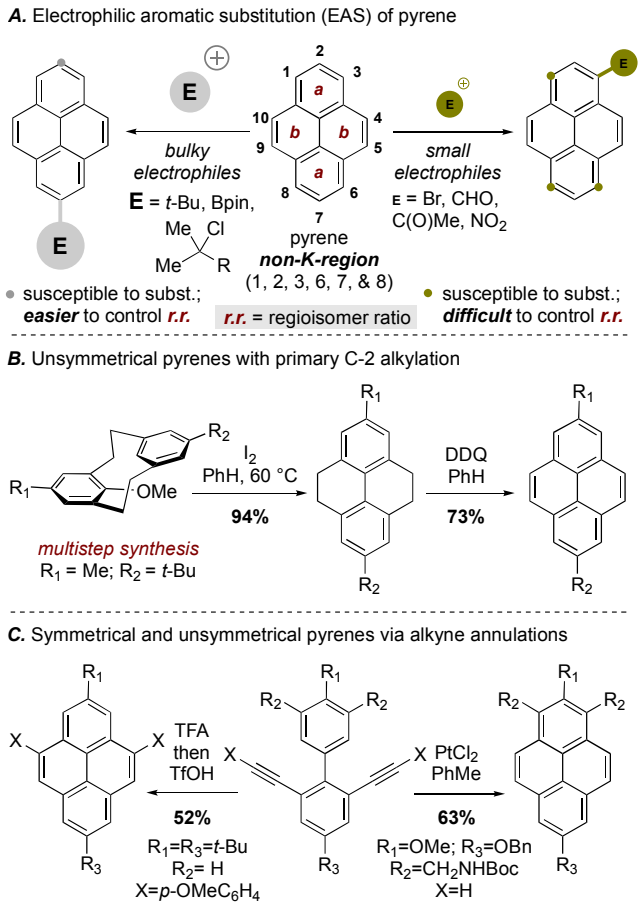


ABSTRACT: The synthesis of 1,2,4,5, 1,2,9,10-tetrasubstituted, and 1,2,4,5,8-pentasubsutituted pyrenes has been achieved by initially functionalizing the K-region of pyrene. Bromination, acylation, and formylation reactions afford high to modest levels of regioselectivity, which facilitate the controlled introduction of other functional groups about 4,5-dimethoxypyrene. Access to 4,5-dimethoxypyren-1-ol and 9,10-dimethoxypyren-1-ol enabled, a rare, C-2 primary alkyl substitution of pyrene.

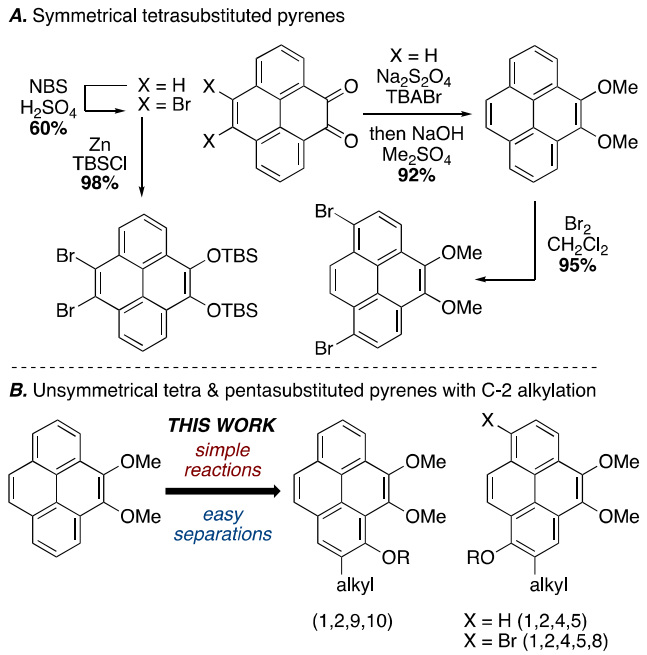
The substitution chemistry of pyrene can be highly predictable based on the nature of electrophilic reagents employed in an (electrophilic) aromatic substitution (EAS) reaction; however, controlling selectivity can be an issue.[1] It is well known that the (most) nucleophilic positions of pyrene are the 1, 3 ,6, and 8-positions and in the presence of small or non-bulky electrophiles, substitution at these positions is generally afforded (Scheme 1A).[2] While selective mono- and tetrasubstitution can be achieved, selective di and trisubstitution at these positions is virtually impossible. In fact, if a selectively di or trisubstituted pyrene is desired it must be prepared using a multistep synthetic sequence.[3] Such indirect methods for forming selectively functionalized pyrenes requires the conversion of [2.2]metacyclophane derivatives into pyrene (Scheme 1B),[4] partial reduction of pyrene (*b* ring hydrogenation) followed by EAS of the resulting 4,5,9,10-tetrahydropyrene,[5] or cyclization reactions of appropriately substituted biphenyl derivatives (Scheme 1C).[6] Substitution of the 2 or 2 and 7 positions directly can be accomplished by using large or bulky electrophilic reagents.[1-3] Particularly, *tert*-butyl substitution at one of the *a* rings of pyrene will block or attenuate further substitution at the neighboring 1 and 3 positions, allowing for selective functionalization of nucleophilic carbons at the unsubstituted apical ring (6, 7, and 8-positions).[7] Direct borylation of the 2 or 2 and 7 positions provides a means for subsequent C-C bond formation that does not require quaternization of the alkyl electrophile (Scheme 1A).[8]

The 4, 5, 9, and 10 positions of pyrene, known as the K-region, are not as susceptible to EAS reactions and typically display alkene-like reactivity.[5] This dichotomy in reactivity has enabled the synthesis of 1,4,5,8-,[9] 2,4,5,7-,[10] and 4,5,9,10-tetrasubstituted pyrene derivatives (Scheme 2A).[11] In all of the aforementioned cases, the pyrene nucleus was subjected to difunctionalization reactions after the K-region was first substituted. Herein, a strategy for the regioselective substitution of the pyrene nucleus that involves monofunctionalization reactions after initial substitution of the K-region (Scheme 2B) is reported. This strategy provides access to unsymmetrically



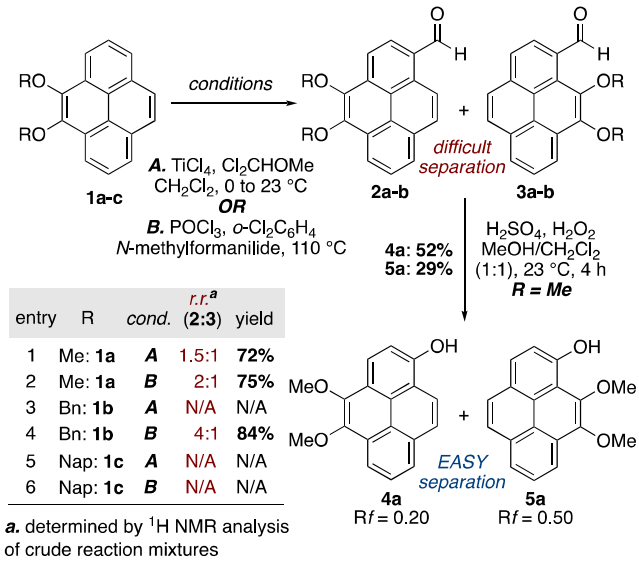
Scheme 1. EAS chemistry of pyrene and indirect synthesis of symmetrical and unsymmetrical pyrenes.

substituted pyrene derivatives and sterically hindered or unhindered hydroxypyrene derivatives, which can be used for direct, primary *C*-allylation of the 2-position. The latter has been a longstanding challenge for pyrene-based chemical synthesis. The *C*-allyl unit provides a functional group handle from which two identical pyrene systems can be brought together by a metathesis reaction. Furthermore, a regioselectively functionalized 1,2,4,5,8-pentasubstituted pyrene derivative has been synthetized using sequential monofunctionalization reactions.



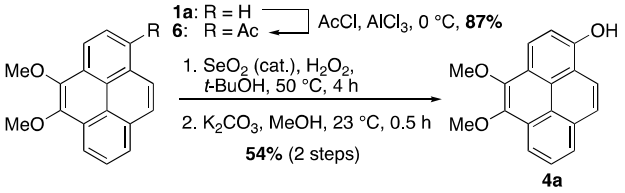
Scheme 2. Synthesis of tetrasubstituted pyrenes via K-region substitution.

Selective substitution of the pyrene K-region can be achieved using a known method to afford 4,5-dimethoxypyrene.[12] While several groups have used **1a** or related alkoxy pyrenes in the preparation of regioselectively functionalized pyrene derivatives,[10-12] to the best of our knowledge, the successful incorporation of a single substituent or functional group (directly) at the 1-position of **1a** has not been reported. Access to such a strategy would allow for preparation of unsymmetrically substituted pyrene derivatives, which have been limited using direct substitution methods. One of the most useful monofunctionalization reactions of pyrene is the Rieche formylation, and this reaction has been employed in the synthesis of several pyrene-1-carbaldehyde derivatives.[7a,b,d] Based on the precedent for 4,5-dimethoxypyrene to undergo 1,8-dibromination, leaving the 3 and 6 positions untouched (Scheme 2A), we anticipated that only 4,5-dimethoxypyrene-1-carbaldehyde (**2a**) would be afforded upon treatment of **1a** with dichloromethyl methyl ether in the presence of $TiCl_4$. To our surprise, a 1.5:1 ratio of **2a** and 9,10-dimethoxypyrene-1-carbaldehyde (**3a**) (effective substitution at the 3-position, see pyrene numbering in Scheme 1A) was produced. A Vilsmeier-Haack-type formylation of **1a** produced a slight increase in regioselectivity (2:1 *r.r.*, **2a**:**3a**) and comparable yield of 75%. To attenuate formylation at the effective 3-postiton of **1a**, larger substituents were placed at the 4 and 5 positions. The introduction of both benzyl (Bn) and 2-naphthyl (Nap) groups could be achieved,[13] however, attempts to install bulky silyl groups proved to be limiting. Alkylation with both TBDPSCl and TIPSCl was sluggish and did not result in formation of the desired silyl ethers. Furthermore, isolation 4,5-dihydroxypyrene can be problematic and thus using the more reactive silyl triflate derivatives was not an option. Indeed, formylation of benzylated pyrene derivative **1b** gave a 4:1 ratio of constitutional isomers, in favor of **2b** (entry 4, Scheme 3). Unfortunately, **1b** and **1c** succumbed to dealkylation under Rieche, or Rieche and Vilsmeier-Haak formylation conditions, respectively (entries 3, 5, and 6, Scheme 3).



entry	R	*cond.*	*r.r.*[a] (2:3)	yield
1	Me: **1a**	***A***	1.5:1	**72%**
2	Me: **1a**	***B***	2:1	**75%**
3	Bn: **1b**	***A***	N/A	N/A
4	Bn: **1b**	***B***	4:1	**84%**
5	Nap: **1c**	***A***	N/A	N/A
6	Nap: **1c**	***B***	N/A	N/A

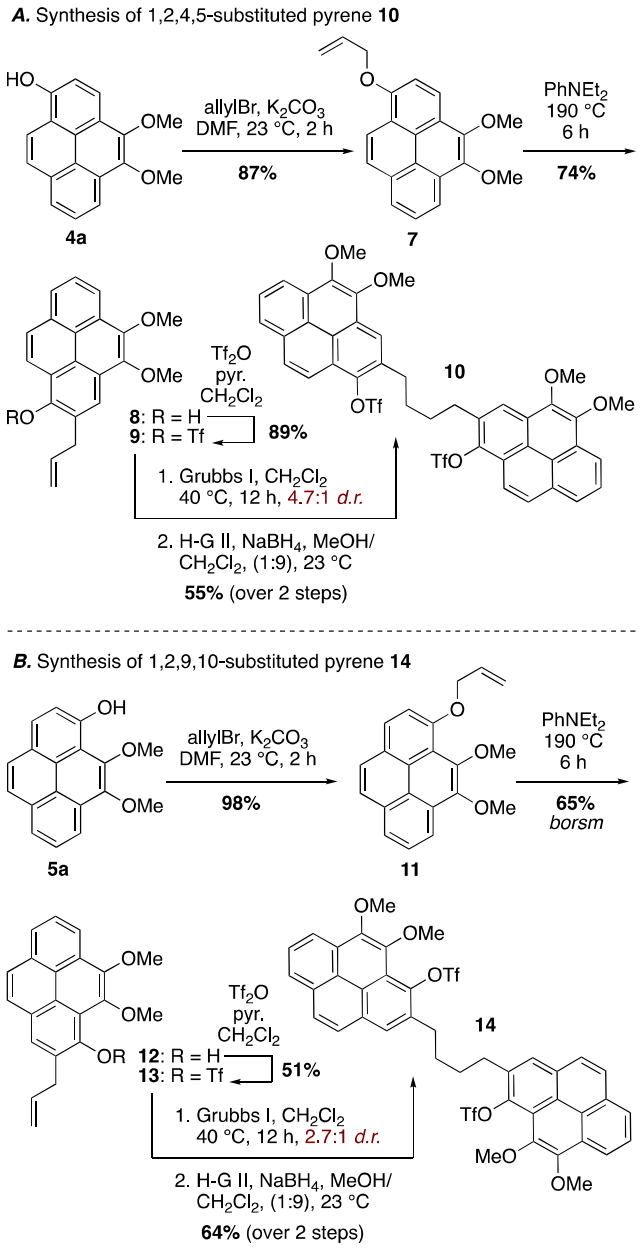
a. determined by ^{1}H NMR analysis of crude reaction mixtures



Scheme 3. Synthesis of 1-hydroxypyrenes **4a** and **5a**

Separation of the mixture of aldehydes afforded from both formylation protocols was possible, however, tedious chromatography was required (see Supporting Information). As such, this mixture (R = Me) was directly subjected to a Dakin oxidation reaction to afford an easily separable pair of 1-hydroxypyrenes **4a** and **5a** (Scheme 4). It should be noted that both **4a** and **5a** are soluble in $CDCl_3$, however, the ^{1}H NMR spectrum of **4a** is poorly resolved in this solvent. The faster moving (R_f = 0.50, 1:4 EtOAc/hexanes) 1-hydroxypyrene **5a** gave a well-resolved ^{1}H NMR spectrum in $CDCl_3$ (see Supporting Information). Direct access of **4a** could be achieved by following a slightly modified synthetic protocol. Treatment of **1a** with AcCl and $AlCl_3$ in dichloromethane at 0 °C afforded monoacylation product **6** in 87% yield. The conversion ketone **6** to **4a** was not trivial and required several weeks of optimization. Standard Bayer-Villiger oxidation conditions using *m*-CBPA or related peroxy acids led to either poor yields of the desired acetate ester, or the formation of numerous unidentified by-products. Employing a boric acid-mediated protocol that had been reported by Harvey and co-workers for the synthesis of 1-hydroxypyrene,[14] gave

the desired acetate ester, however, complete consumption of the ketone was not achieved, resulting in a low overall yield of **4a**. Finally, it was discovered that clean conversion of **1a** to **4a** could be achieved by first oxidizing the methyl ketone to the corresponding acetate ester, in the presence of a catalytic amount of SeO_2 and H_2O_2,[15] followed by direct hydrolysis of the crude material to afford **4a** in 5% overall yield.

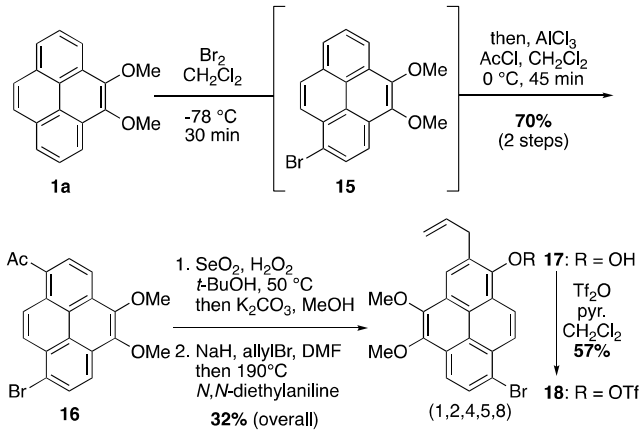


Scheme 4. Synthesis of primary alkylated, tetrasubstituted pyrenes **10** and **14**.

At this juncture, hydroxypyrenes **4a** and **5a** were subjected to an identical five-step sequence, which centered on the installation of a primary *C*-allyl group at the 2-position. Upon *O*-allylation of **4a** under standard conditions, 1-allyloxy-4,5-dimethoxypyrene (**7**) was afforded in 87% yield (Scheme 4A). Heating **7** to 190 °C in *N*,*N*-diethylaniline for 6 hours brought about a Claisen rearrangement that produced **8** in 74% yield. Subjecting hydroxypyrene **5a** to the same two-step sequence produced **12** in comparable yield, however, **11** proved to be (moderately) susceptible to deallylation. Approximately 10% of **5a** was produced in this reaction, along with 18% of unreacted starting material. The free alcohols of **8** and **12** were sulfonylated to give **9** and **13** in 89% and 51% yields, respectively. Olefin metathesis in the presence of Grubbs first-generation catalyst gave a 4.7:1 mixture of alkene diastereomers, in the case of **9**, which were directly subjected to transfer hydrogenation using the Hoveyda-Grubbs second-generation catalyst to afford **10** in 55% overall yield. It should be noted that a one-pot metathesis, transfer hydrogenation sequence using only the Hoveyda-Grubbs second-generation catalyst,[16] was attempted, however, a much lower yield of **10** was obtained. In the case of triflate **13**, a 2.7:1 mixture of alkene diastereomers was produced when subjected to identical olefin metathesis conditions. Transfer hydrogenation of this mixture afforded **14** in 64% yield over two steps.

Determination of the regiochemical outcome of the formylation reaction that produced both **2a** and **3a** (Scheme 3), was initially made on the basis of ^{1}H NMR analysis. In particular, the major constitutional isomer displayed a doublet at 9.38 ppm, which is indicative of a K-region proton flanked by an aldehyde group at the 1-position of pyrene. The absence of this signal from the minor regioisomer produced in this reaction suggested 9,10-dimethoxypyren-1-carbaldehyde as its structure. Secondly, the assumption that only 1-acetyl-4,5-dimethoxypyrene was afforded upon acylation of **1a** with AcCl, and matching the NMR data of the hydrolysis product **4a** with that obtained from the Dakin oxidation of **2a** further supported the assignment of **2a** and **4a**. Nonetheless, a single crystal suitable for X-ray crystallographic analysis of **10** was obtained, allowing for the unambiguous assignment of the substitution pattern of the tetrasubstituted pyrenes synthesized (see Supporting Information, Figure SI-2).

Access to triflated pyrenes such as **10** and **14**, should enable the synthesis of arylated derivatives via cross-coupling reactions. Arylated pyrenes are of importance in the development of liquid crystalline and optoelectonic, pyrene-based materials.[17] Furthermore, the bridging butyl and butenyl units can be subjected to benzylic and alyllic oxidation reactions to afford 1,4-diketones, which have been used in the synthesis of macrocyclic benzenoid systems.[16a,18] With this in mind, the synthesis of a pentasubstituted pyrene **18**, with both bromide



Scheme 5. Synthesis of 1,2,4,5,8-pentasubstituted pyrene **18**.

and triflate cross-coupling handles was pursued. Low temperature bromination of **1a**, followed by acylation of the intermediate monobromide **15**, furnished bromoketone **16** in 70% overall yield

(Scheme 5). Subjecting **16** to the same reaction sequence as described above, gave 1,2,4,5,8-pentasubstituted pyrene **17** in 32% overall yield. Sulfonylation of the free alcohol in **17** afforded triflate **18** in 57% yield. The substitution pattern of **18**, and the orthogonal nature of aryl bromides and triflates in cross-coupling and functional group interconversion reactions, will be of great use in the development of synthetic approaches to pi-extended macrocyclic systems, such as carbon nanobelts.

In conclusion, the regioselective synthesis of 1,2,4,5 and 1,2,9,10-tetrasubstituted pyrenes has been achieved using sequential monofunctionalization reactions of 4,5-dimethoxypyrene. Formylation, followed by Dakin oxidation, of 4,5-dimethoxypyrene provides access to separable 1-hydroxypyrene derivatives (1,4,5 and 1,9,10 substituted), while acetylation, followed by Baeyer-Villiger oxidation to a single 1-hydroxy-4,5-dimethoxyprene. The 2 position of pyrene can be subsequently *C*-allylated a via Claisen rearrangement, which represents a rare example of direct, primary alkylation at the 2-position of pyrene. A 1,2,4,5,8-pentasubstituted pyrene derivative **18**, containing both bromide and triflate cross-coupling handles has been synthesized using sequential monofunctionalization reactions. Finally, olefin metathesis has enabled the synthesis of a 1,4-bis(1-pyrenyl)butane (and but-2-ene) derivatives **10** and **14**. The conversion such compounds into 1,4-diketones and their application pi-extended macrocycle synthesis is underway in our laboratory. The synthesis of these macrocycles will be reported in due course.

EXPERIMENTAL SECTION

General experimental conditions: All reactions were run in flame or oven-dried (120 °C) glassware and cooled under a positive pressure of ultra high pure nitrogen or argon gas. All chemicals were used as received from commercial sources, unless otherwise stated. Anhydrous reaction solvents were purified and dried by passing HPLC grade solvents through activated columns of alumina (Glass Contour SDS). All solvents used for chromatographic separations were HPLC grade (hexanes, ethyl acetate and dichloromethane). Chromatographic separations were preformed using flash chromatography, as originally reported by Still and co-workers, on silica gel 60 (particle size 43-60 μm), and all chromatography conditions have been reported as diameter × height in centimeters. Reaction progress was monitored by thin layer chromatography (TLC), on glass-backed silica gel plates (pH = 7.0). TLC plates were visualized using a handheld UV lamp (254 nm or 365 nm) and stained using an aqueous ceric ammonium molybdate (CAM) solution. Plates were dipped, wiped clean, and heated from the back. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded at 400 or 600 MHz, calibrated using residual undeuterated solvent as an internal reference ($CHCl_3$, δ 7.27 and 77.2 ppm), reported in parts per million relative to trimethylsilane (TMS, δ 0.00 ppm), and presented as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, dd = doublet of doublets, ddt = doublet of doublet of triplets, bs = broad singlet, m = multiplet), coupling constants (*J*, Hz), and integration. High-resolution mass spectrometric (HRMS) data were obtained using a quadrupole time-of-flight (Q-TOF) spectrometer and electrospray ionization (ESI).

4,5-Dibenzyloxypyrene (**1b**)**:** Sodium dithionite (0.56 g, 3.2 mmol) and tetrabutylammonium bromide (0.11 g, 0.32 mmol) were added to a stirred solution of pyrene-4,5-dione (0.25 g, 1.1 mmol) in THF (10 mL) and H_2O (10 mL) at room temperature. After 15 min., a solution of NaOH (0.52 g, 13 mmol) in water (10 mL) was added to the reaction mixture followed by benzyl bromide (0.94 g, 5.4 mmol). The resulting mixture was stirred at room temperature for 12 h. The reaction was diluted with EtOAc (20 mL), the layers were separated, and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with H_2O (30 mL) and brine (30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (2.5 × 18 cm, 50% dichloromethane/hexanes) to afford **1b** as a light brown solid (0.064 g, 33%) and compound **21** (0.19 g, 54%): R_f = 0.21 (60% dichloromethane/hexanes). Compound **21** (0.19 g, 0.60 mmol) was re-subjected to the alkylation conditions described above to afford **1b** (0.098 g, 39%): R_f = 0.82 (60% dichloromethane/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.54 (d, *J* = 7.8 Hz, 2H), 8.18 (d, *J* = 7.7, Hz, 2H), 8.09 (s, 2H), 8.07 – 8.01 (m, 2H), 7.64 (d, *J* = 7.4 Hz, 4H), 7.47 – 7.44 (m, 4H), 7.42 – 7.38 (m, 2H), 5.43 (s, 4H); ^{13}C{^{1}H}NMR (151 MHz, $CDCl_3$) δ 144.3, 137.6, 131.1, 128.7, 128.52, 128.50, 128.3, 127.4, 126.1, 124.7, 123.0, 119.7, 75.6; HRMS (ESI) calculated for $C_{30}H_{23}O_2$ ($[M+H]^+$) *m/z* = 415.1698, found 415.1701.

4,5-Bis(2-naphthyloxy)pyrene (**1c**)**:** Sodium dithionite (0.34 g, 1.9 mmol) and tetrabutylammonium bromide (0.065 g, 0.19 mmol) were added to a stirred solution of pyrene-4,5-dione (0.14 g, 0.59 mmol) in THF (7 mL) and H_2O (7 mL) at room temperature. After 15 min., a solution of KOH (0.27 g, 4.8 mmol) in water (10 mL) was added to the reaction mixture, followed by 2-(bromomethyl)naphthalene (0.69 g, 3.1 mmol). The resulting mixture was stirred at room temperature for 12 h. The reaction was diluted with EtOAc (20 mL), the layers were separated, and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with H_2O (30 mL) and brine (30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (2.5 × 18 cm, 70% dichloromethane/hexanes) to afford **1c** as a white solid (0.050 g, 17%) and compound **22** (0.020 g, 9%): R_f = 0.28 (60% dichloromethane/hexanes). Compound **22** (0.020 g, 0.053 mmol) was re-subjected to the alkylation conditions described above to afford **1c** (0.010 g, 36%): R_f = 0.80 (60% dichloromethane/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.65 (d, *J* = 7.8 Hz, 2H), 8.20 (d, *J* = 7.6 Hz, 2H), 8.11 (s, 2H), 8.10 – 8.05 (m, 4H), 7.94 – 7.90 (m, 4H), 7.81 (d, *J* = 7.8 Hz, 2H), 7.78 (d, *J* = 8.3 Hz, 2H), 7.57 – 7.51 (m, 4H), 5.61 (s, 4H); ^{13}C{^{1}H}NMR (151 MHz, $CDCl_3$) δ 144.5, 135.1, 133.4, 133.2, 131.2, 128.6, 128.4, 128.2, 127.8, 127.5, 127.3, 126.30, 126.25, 126.20, 124.7, 123.1, 119.7, 75.9 (only 18 of 19 carbons observed); HRMS (ESI) calculated for $C_{38}H_{27}O_2$ ($[M+H]^+$) *m/z* = 515.2011, found 515.2015.

4,5-Dimethoxypyrene-1-carbaldehyde (**2a**) and *9,10-dimethoxypyrene-1-carbaldehyde* (**3a**): $POCl_3$ (9.8 g, 64 mmol) was added dropwise to a stirred 0 °C solution of *N*-methylformanilide (4.3 g, 32 mmol) in 1,2-dichlorobenzene (15 mL). After 10 min., the cooling bath was removed and a solution of 4,5-dimethoxypyrene (2.66 g, 10.1 mmol) in 1,2-dichlorobenzene (10 mL) was added. The reaction was then

heated at 90 °C. After 48 h, the reaction mixture was poured into ice, neutralized with 1 M NaOH, and diluted with EtOAc (60 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (2 × 60 mL). The combined organic extracts were washed with brine (80 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (5 cm × 15 cm; 80% dichloromethane/hexanes) to afford a mixture of **2a** and **3a** (2:1 *r.r*) as a yellow solid (2.2 g, 75%): R_f = 0.31 (80% dichloromethane/hexanes); a small portion of **2a** was isolated from a single chromatography fraction and characterized: ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.74 (s, 1H), 9.41 (d, *J* = 9.2 Hz, 1H), 8.60 (dd, *J* = 7.8, 1.1 Hz, 1H), 8.56 (d, *J* = 8.1 Hz, 1H), 8.45 (d, *J* = 8.2 Hz, 1H), 8.28 (d, *J* = 9.2 Hz, 1H), 8.25 (dd, *J* = 7.6, 1.1 Hz, 1H), 8.11 – 8.07 (m, 1H), 4.26 (s, 3H), 4.18 (s, 3H); ^{13}C{^{1}H}NMR (151 MHz, $CDCl_3$) δ 193.4, 147.8, 144.3, 133.4, 132.1, 131.2, 131.0, 130.6, 128.3, 127.1, 126.9, 126.6, 123.2, 122.9, 122.5, 121.7, 118.9, 61.6, 61.4; HRMS (ESI) calculated for the mixture of constitutional isomers $C_{19}H_{15}O_3$ ($[M+H]^+$) *m/z* = 291.1021, found 291.1057.

4,5-Dibenzyloxypyrene-1-carbaldehyde (**2b**) and *9,10-dibenzyloxypyrene-1-carbaldehyde* (**3b**): $POCl_3$ (0.022 g, 0.14 mmol) was added dropwise to a stirred 0 °C solution of *N*-methylformanilide (0.009 g, 0.07 mmol) in 1,2-dichlorobenzene (0.6 mL). After 10 min., the cooling bath was removed and the temperature was increased to 80 °C. After 15 min., a solution of **1b** (0.010 g, 0.024 mmol) in 1,2-dichlorobenzene (0.3 mL) was added and the reaction was heated at 80 °C for 24 h. The reaction mixture was cooled to room temperature, diluted with dichloromethane (10 mL), then poured into ice water (10 mL), and the layers were separated. The aqueous phase was extracted with dichloromethane (3 × 5 mL). The combined organic extracts were washed with brine (25 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (1.3 × 18 cm; 60% dichloromethane/hexanes) to afford an inseparable mixture of constitutional isomers **2b** and **3b** (3.8:1 *r.r*) as a yellow solid (0.0084 g, 84%): R_f = 0.36 (60% dichloromethane/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ 11.51 (s, 1H), 10.77 (s, 3H), 9.47 (d, *J* = 9.2 Hz, 4H), 8.66 (d, *J* = 7.8 Hz, 4H), 8.63 – 8.61 (m, 5H), 8.52 (d, *J* = 8.1 Hz, 1H), 8.46 (d, *J* = 8.1 Hz, 4H), 8.34 (d, *J* = 9.2 Hz, 4H), 8.30 (d, *J* = 7.6 Hz, 4H), 8.27 (d, *J* = 7.6 Hz, 1H), 8.23 – 8.18 (m, 3H), 8.13 – 8.08 (m, 7H), 7.63 – 7.60 (m, 18H), 7.50 – 7.48 (m, 3H), 7.47 – 7.43 (m, 19H), 7.42 – 7.38 (m, 10H), 5.53 (s, 2H), 5.49 (s, 7H), 5.41 (s, 7H), 5.29 (s, 2H); HRMS (ESI) calculated for the mixture of constitutional isomers $C_{31}H_{23}O_3$ ($[M+H]^+$) *m/z* = 443.1647, found 443.1642.

4,5-Dimethoxypyren-1-ol (**4a**): Concentrated $H_2S_2O_4$ (5 drops) and a 35% solution (w/w) of hydrogen peroxide in water (5 drops) were added to a stirred solution of **2a** and **3a** (2:1 *r.r*, 0.212 g, 0.731 mmol) in 1:1 methanol/dichloromethane (8 mL) at room temperature. After 4 h, the reaction mixture was poured into water (50 mL), the layers were separated, and the aqueous phase was extracted with dichloromethane (3 × 35 mL). The combined organic extracts were sequentially washed with water (2 × 30 mL), a saturated solution of $NaHCO_3$ (60 mL) and brine (60 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (2.5 × 18 cm; 10% EtOAc/hexanes) to afford **4a** as a brown solid (0.11 g, 52%): R_f = 0.20 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, CD_3OD) δ 8.35 (d, *J* = 9.1 Hz, 1H), 8.29 – 8.23 (m, 2H), 7.98 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.94 – 7.87 (m, 2H), 7.51 (d, *J* = 8.5 Hz, 1H), 4.14 (s, 3H), 4.09 (s, 3H); ^{13}C{^{1}H}NMR (101 MHz, CD_3OD) δ 151.7, 145.0, 142.0, 131.8, 128.8, 125.7, 125.1, 124.2, 123.01, 122.91, 121.04, 120.70, 119.92, 118.80, 117.78, 112.4, 60.1, 59.9; HRMS (ESI) calculated for $C_{18}H_{15}O_3$ ($[M+H]^+$) *m/z* = 279.1021, found 279.1009.

9,10-Dimethoxypyren-1-ol (**5a**): isolated as a yellow solid (0.058 g, 29%): R_f = 0.50 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.01 (s, 1H), 8.30 (dd, *J* = 7.7, 1.2 Hz, 1H), 8.07 – 8.00 (m, 2H), 7.99 – 7.93 (m, 1H), 7.91 (d, *J* = 8.9 Hz, 1H), 7.83 (d, *J* = 8.9 Hz, 1H), 7.52 (d, *J* = 8.4 Hz, 1H), 4.29 (s, 3H), 4.14 (s, 3H); ^{13}C{^{1}H}NMR (101 MHz, $CDCl_3$) δ 153.2, 145.6, 143.9, 132.2, 128.7, 127.7, 126.9, 126.5, 124.7, 124.6, 124.5, 124.3, 124.0, 117.7, 115.3, 112.7, 62.1, 61.1; HRMS (ESI) calculated for $C_{18}H_{15}O_3$ ($[M+H]^+$) *m/z* = 279.1021, found 279.1021.

1-(4,5-Dimethoxypyren-1-yl)ethanone (**6**): Acetyl chloride (0.065 g, 0.84 mmol) was added to a stirred 0 °C solution of $AlCl_3$ (0.25 g, 1.7 mmol) and 4,5-dimethoxypyrene (0.20 g, 0.76 mmol) in dichloromethane (8 mL). After 15 min., the reaction mixture was poured into ice water (10 mL), the layers were separated, and the aqueous phase was extracted with dichloromethane (3 × 10 mL). The combined organic extracts were washed with a saturated solution of $NaHCO_3$ (20 mL) and brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (2.5 × 15 cm, dichloromethane) to afford **6** as a bright yellow solid (0.20 g, 87%): R_f = 0.12 (80% dichloromethane/hexane); ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.09 (d, *J* = 9.3 Hz, 1H), 8.58 (d, *J* = 7.8 Hz, 1H), 8.49 (d, *J* = 8.3 Hz, 1H), 8.43 (d, *J* = 8.3 Hz, 1H), 8.25 – 8.18 (m, 2H), 8.11 – 8.06 (m, 1H), 4.26 (s, 3H), 4.21 (s, 3H), 2.92 (s, 3H); ^{13}C{^{1}H}NMR (151 MHz, $CDCl_3$) δ 202.3, 146.7, 144.2, 131.8, 131.5, 130.6, 129.9, 129.7, 128.4, 127.7, 126.7, 125.8, 125.1, 123.3, 122.7, 120.9, 118.3, 61.5, 61.4, 30.7; HRMS (ESI) calculated for **6** $C_{20}H_{17}O_3$ ($[M+H]^+$) *m/z* = 305.1178, found 305.1190.

Alternative synthesis of 4,5-dimethoxypyren-1-ol (**4a**): SeO_2 (0.001 g, 0.001 mmol) and a 30% solution (w/w) of hydrogen peroxide in water (0.13 mL, 1.1 mmol) were added to a stirred 50 °C solution of **6** (0.086 g, 0.28 mmol) in *t*-BuOH (3 mL). After 4 h, the reaction mixture was cooled to room temperature, poured into water (30 mL) and further diluted with dichloromethane (15 mL). The layers were separated, and the aqueous phase was extracted with dichloromethane (3 × 15 mL). The combined organic extracts were washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford **23** as a light brown solid: R_f = 0.45 (dichloromethane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 – 8.39 (m, 2H), 8.16 (d, *J* = 7.7, 1H), 8.13 – 8.07 (m, 2H), 8.05 (d, *J* = 7.8 Hz, 1H), 7.83 (d, *J* = 8.5 Hz, 1H), 4.23 (s, 3H), 4.22 (s, 3H) 2.58 (s, 3H); ^{13}C{^{1}H}NMR (101 MHz, $CDCl_3$) δ 170.0, 144.7, 144.6, 144.1, 130.9, 128.6, 128.1, 126.7, 126.5, 124.8, 123.8, 123.1, 122.7, 120.1, 119.91, 119.86, 119.6, 61.2, 21.2; HRMS (ESI) calculated for $C_{20}H_{17}O_4$ ($[M+H]^+$) *m/z* = 321.1127, found 321.1111. Potassium carbonate (0.64 g, 4.6 mmol) was added to a stirred solution of **23** in MeOH (20 mL) at room temperature. After 30 min., the reaction mixture was poured into ice water (10 mL)

and neutralized with 1 M HCl (10 mL), the layers were separated and the aqueous phase was extracted with dichloromethane (3 × 10 mL). The combined organic extracts were washed with a saturated solution of $NaHCO_3$ (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (1.3 cm × 15 cm, dichloromethane) to afford **4a** as a light yellow solid (0.042 g, 54% overall).

1-Allyloxy-4,5-dimethoxypyrene (**7**): K_2CO_3 (0.126 g, 0.912 mmol) and allyl bromide (0.11 g, 0.91 mmol) were added to a stirred solution of **4a** (0.168 g, 0.603 mmol) in DMF (13 mL) at room temperature. After 2 h, the reaction mixture was poured into water (100 mL) and further diluted with 1 M HCl (50 mL). The resulting mixture was extracted with EtOAc (5 × 20 mL), the combined organic extracts were washed with 1 M HCl (3 × 30 mL) and a saturated solution of $NaHCO_3$ (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (2.5 cm × 15 cm; 50% dichloromethane/hexanes) to afford **7** as a yellow solid (0.15 g, 87%): R_f = 0.39 (50% dichloromethane/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.53 (d, *J* = 9.1 Hz, 1H), 8.46 – 8.39 (m, 2H), 8.11 (d, *J* = 7.6 Hz, 1H), 8.08 – 8.00 (m, 2H), 7.55 (d, *J* = 8.6 Hz, 1H), 6.27 (ddt, *J* = 17.3, 10.4, 5.1 Hz, 1H), 5.62 (dd, *J* = 17.3, 1.6 Hz, 1H), 5.42 (dd, *J* = 10.6, 1.5 Hz, 1H), 4.94 – 4.85 (m, 2H), 4.26 (s, 3H), 4.22 (s, 3H); ^{13}C{^{1}H}NMR (151 MHz, $CDCl_3$) δ 152.6, 145.1, 143.0, 133.5, 131.8, 129.2, 126.5, 126.4, 124.3, 123.9, 123.2, 122.3, 121.4, 120.8, 120.1, 118.9, 117.8, 109.7, 69.9, 61.3, 61.2; HRMS (ESI) calculated for $C_{21}H_{19}O_3$ ($[M+H]^+$) *m/z* = 319.1334, found 319.1348.

4,5-Dimethoxy-2-(2-propen-1-yl)pyren-1-ol (**8**): Compound **7** (0.105 g, 0.331 mmol) was dissolved in *N,N*-diethylaniline (0.2 mL) and heated to 190 °C. After 12 h, the solvent was evaporated under a gentle stream of nitrogen and the residue was purified by flash chromatography (1.3 × 15 cm; 10% EtOAc/hexanes) to afford **8** as an off-white solid (0.078 g, 74%): R_f = 0.27 (10% EtOAc/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.47 – 8.21 (m, 3H), 8.16 – 7.89 (m, 3H), 6.22 (ddt, *J* = 16.6, 10.1, 6.2 Hz, 1H), 5.94 – 5.89 (m, 1H), 5.39 – 5.29 (m, 2H), 4.24 (s, 3H), 4.19 (s, 3H), 3.89 (bs, 2H); ^{13}C{^{1}H}NMR (151 MHz, $CDCl_3$) δ 148.8, 145.0, 143.1, 136.4, 131.42, 128.9, 126.7, 126.3, 123.9, 123.5, 123.1, 122.7, 122.2, 121.4, 120.8, 119.6, 118.9, 117.7, 61.4, 61.2, 37.0; HRMS (ESI) calculated for $C_{21}H_{19}O_3$ ($[M+H]^+$) *m/z* = 319.1334, found 319.1336.

1-(Trifluorometanesulfonyl)oxy-4,5-dimethoxy-2-(2-propen-1-yl)pyrene (**9**): Triflic anhydride (0.14 g, 0.35 mmol) and pyridine (0.03 g, 0.3 mmol) were added to a stirred 0 °C solution of **8** (0.056 g, 0.18 mmol) in dichloromethane (3.5 mL). The cooling bath was removed and 10 min. later the reaction mixture was poured into 1 M HCl (30 mL). The resulting mixture was extracted with dichloromethane (3 × 15 mL), the combined organic extracts were washed with and brine (35 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (1.3 × 12 cm; 20% dichloromethane/hexanes) to afford **9** as a yellow solid (0.071 g, 89%): R_f = 0.32 (20% dichloromethane/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.54 (d, *J* = 7.8, 1.1 Hz, 1H), 8.41 (s, 1H), 8.28 (d, *J* = 9.2 Hz, 1H), 8.22 – 8.15 (m, 2H), 8.10 – 8.02 (m, 1H), 6.17 (ddt, *J* = 16.1, 10.6, 6.6 Hz, 1H), 5.33 – 5.26 (m, 2H), 4.23 – 4.21 (m, 6H), 4.00 (d, 2H); ^{13}C{^{1}H}NMR (151 MHz, $CDCl_3$) δ 145.8, 144.1, 140.1, 135.5, 131.4, 130.5, 129.7, 128.55, 128.52, 126.9, 125.7, 124.7, 122.9, 122.2, 121.3, 120.9, 120.1, 119.0 ($J_{C\text{-}F}$ = 318 Hz), 117.8, 61.41, 61.39, 35.4; HRMS (ESI) calculated for $C_{22}H_{16}O_5F_3S$ ($[M\text{-}H]^-$) *m/z* = 449.0676, found 449.0667.

1,4-Bis(1-(trifluorometanesulfonyl)oxy-4,5-dimethoxypyren-2-yl)butane (**10**): Hoveyda-Grubbs second-generation catalyst (0.010 g, 0.016 mmol) and $NaBH_4$ (0.025 g, 0.66 mmol) were added to stirred solution of **19** (0.110 g, 0.126 mmol) in 1:9 methanol/dichloromethane (14 mL). After 2 h, the reaction mixture was poured into water (30 mL) and further diluted with 1 M HCl (15 mL). The resulting mixture was extracted with dichloromethane (3 × 10 mL), and the combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (1.3 × 15 cm; 40% dichloromethane/hexanes) to afford **10** as an off-white solid (0.070 g, 70% BORSM, 0.010 g of **19**): R_f = 0.21 (40% dichloromethane/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.55 (d, *J* = 7.9, 1.1 Hz, 2H), 8.40 (s, 2H), 8.26 (d, *J* = 9.2 Hz, 2H), 8.23 – 8.17 (m, 4H), 8.13 – 8.07 (m, 2H), 4.22 (s, 6H), 4.19 (s, 6H), 3.32 (t, 4H), 2.12 – 2.02 (m, 4H); ^{13}C{^{1}H}NMR (151 MHz, $CDCl_3$) δ 148.1, 142.9, 140.1, 133.6, 130.7, 130.6, 128.6, 127.8, 126.6, 126.4, 126.0, 125.7, 123.0, 122.2, 121.2, 120.3, 117.9 ($J_{C\text{-}F}$ = 318 Hz), 61.7, 60.8, 30.5, 30.2; HRMS (ESI) calculated for $C_{42}H_{33}O_{10}F_6S_2$ ($[M+H]^+$) *m/z* = 875.1419, found 875.1459.

1-Allyloxy-9,10-dimethoxypyrene (**11**): K_2CO_3 (0.091 g, 0.66 mmol) and allyl bromide (0.08 g, 0.7 mmol) were added to a stirred solution of **5a** (0.061 g, 0.22 mmol) in DMF (7 mL) at room temperature. After 20 h, the reaction mixture was poured into water (20 mL) and further diluted with 1 M HCl (25 mL). The resulting mixture was extracted with diethyl ether (3 × 15 mL), the combined organic extracts were washed with brine (40 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (1.3 × 15 cm; 40% dichloromethane/hexanes) to afford **11** as a light brown solid (0.045 g, 98%): R_f = 0.22 (40% dichloromethane/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, *J* = 7.5 Hz, 1H), 8.11 – 7.85 (m, 5H), 7.60 (d, *J* = 8.5 Hz, 1H), 6.40 – 6.23 (m, 1H), 5.62 (d, *J* = 17.2 Hz, 1H), 5.41 (d, *J* = 10.1 Hz, 1H), 4.89 (d, *J* = 5.6 Hz, 2H), 4.23 (s, 3H), 4.10 (s, 3H); ^{13}C{^{1}H}NMR (101 MHz, $CDCl_3$) δ 153.6, 146.9, 146.3, 133.7, 132.0, 128.8, 127.6, 126.5, 126.0, 125.8, 125.39, 125.35, 124.2, 123.6, 118.4, 118.1, 118.0, 112.7, 71.4, 70.0, 61.5; HRMS (ESI) calculated for $C_{21}H_{19}O_3$ ($[M+H]^+$) *m/z* = 319.1334, found 319.1324.

9,10-Dimethoxy-2-(2-Propen-1-yl)pyren-1-ol (**12**): Compound **11** (0.229 g, 0.719 mmol) was dissolved in *N,N*-diethylaniline (0.3 mL) and heated to 190 °C. After 9 h, the solvent was evaporated under a gentle stream of nitrogen and the residue was purified by flash chromatography (1.3 × 15 cm; 40% dichloromethane/hexanes) to afford **12** as a dark yellow solid (0.13 g, 62% BORSM, 0.022 g recovered of **11** and 0.041 g of **5a**): R_f = 0.35 (40% dichloromethane/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.31 (s, 1H), 8.28 (d, *J* = 7.2 Hz, 1H), 8.04 (d, *J* = 7.5 Hz, 1H), 7.98 – 7.88 (m, 3H), 7.84 (d, *J* = 8.8 Hz, 1H), 6.24 (ddt, *J* = 16.7, 10.1, 6.5 Hz, 1H), 5.24 – 5.13 (m, 2H), 4.30 (s, 3H), 4.14 (s, 3H), 3.81 (d, *J* = 6.4 Hz,

2H); $^{13}C\{^{1}H\}$NMR (101 MHz, $CDCl_3$) δ 151.1, 145.7, 144.1, 137.1, 131.9, 128.5, 127.5, 127.4, 126.17, 126.14, 124.5, 124.4, 124.2, 123.9, 123.5, 117.7, 116.0, 112.4, 62.2, 61.2, 34.8; HRMS (ESI) calculated for $C_{21}H_{19}O_3$ ($[M+H]^+$) *m/z* = 319.1334, found 319.1319.

1-(Trifluorometanesulfonyl)oxy-2-(2-Propen-1-yl)-9,10-dimethoxypyrene (**13**): Triflic anhydride (0.22 g, 0.60 mmol) was added to a stirred 0 °C solution of **12** (0.064 g, 0.20 mmol) in pyridine (2 mL). The cooling bath was removed and the temperature increased to 40 °C. After 4 h, the reaction mixture was cooled to room temperature, diluted with dichloromethane (10 mL), and poured into 1 M HCl (50 mL). The layers were separated and the aqueous phase was extracted with dichloromethane (3 × 15 mL), the combined organic extracts were washed with 1 M HCl (20 mL), a saturated solution of $NaHCO_3$ (20 mL) and brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (1.3 × 15 cm; 20% dichloromethane/hexanes) to afford **13** as a light yellow solid (0.046 g, 51%): R_f = 0.23 (20% dichloromethane/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.54 (d, *J* = 7.7 Hz, 1H), 8.18 (d, *J* = 7.5 Hz, 1H), 8.10 – 8.01 (m, 3H), 7.99 (d, *J* = 9.0 Hz, 1H), 7.81 (d, *J* = 8.8 Hz, 1H), 6.12 – 6.08 (m, 1H), 5.37 – 5.25 (m, 2H), 4.32 (s, 3H), 3.99 (s, 3H), 3.95 (d, *J* = 7.0 Hz, 2H); $^{13}C\{^{1}H\}$NMR (151 MHz, $CDCl_3$) δ 148.4, 143.2, 140.1, 135.7, 131.6, 131.0, 130.8, 128.8, 128.1, 126.8, 126.7, 126.3, 126.1, 123.4, 122.3, 121.4, 120.5, 119.1 ($J_{C\text{-}F}$ = 317 Hz), 118.0, 61.9, 61.1, 34.6; HRMS (ESI) calculated for $C_{22}H_{18}O_5F_3S$ ($[M+H]^+$) *m/z* = 451.0827, found 451.0825.

1,4-Bis(1-(trifluorometanesulfonyl)oxy-9,10-dimethoxypyren-2-yl)butane (**14**): **14**: Hoveyda-Grubbs second-generation catalyst (0.0005 g, 0.0009 mmol) and $NaBH_4$ (0.006 g, 0.1 mmol) were added to stirred solution of **20** (0.025 g, 0.029 mmol) in 1:9 methanol/dichloromethane (1.5 mL). After 2 h, the reaction mixture was poured into water (25 mL) and diluted with 1 M HCl (15 mL). The resulting mixture was extracted with dichloromethane (3 × 12 mL), the combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (0.5 × 10 cm; 40% dichloromethane/hexanes) to afford **14** as an off-white solid (0.012 g, 95%): R_f = 0.30 (40% dichloromethane/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.52 (d, *J* = 7.8, 1.2 Hz, 2H), 8.17 (d, *J* = 8.0, 7.6 Hz, 2H), 8.08 – 8.02 (m, 4H), 7.99 (s, 2H), 7.91 (d, *J* = 8.9 Hz, 2H), 4.29 (s, 6H), 3.90 (s, 6H), 3.26 (t, *J* = 6.8 Hz, 4H), 2.10 – 1.94 (m, 4H); $^{13}C\{^{1}H\}$NMR (151 MHz, $CDCl_3$) δ 148.1, 142.9, 140.1, 133.6, 130.7, 130.6, 128.6, 127.8, 126.6, 126.4, 126.0, 125.7, 123.0, 122.2, 121.2, 120.3, 118.9 ($J_{C\text{-}F}$ = 317 Hz), 61.7, 60.8, 30.5, 30.2, 29.7; HRMS (ESI) calculated for $C_{42}H_{32}O_{10}F_6S_2Na$ ([M+Na]) *m/z* = 897.1239, found 897.1194.

1-(8-Bromo-4,5-dimethoxypyren-1-yl)ethanone (**16**): Bromine (0.06 g, 0.4 mmol) was added dropwise to a stirred –78 °C solution of 4,5-dimethoxypyrene (0.10 g, 0.38 mmol) in dichloromethane (20 mL). After 10 min., the reaction mixture was directly poured into an aqueous saturated solution of Na_2SO_3 (10 mL), and the resulting mixture was extracted with dichloromethane (3 × 10 mL). The combined organic extracts were washed with water (20 mL) and brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was dissolved in dichloromethane (10 mL) and cooled to 0 °C, followed by addition of acetyl chloride (0.031 g, 0.42 mmol) and $AlCl_3$ (0.14 g, 0.83 mmol). After 30 min., the reaction mixture was directly poured into ice water (20 mL), the layers were separated and the aqueous phase was extracted with dichloromethane (3 × 10 mL). The combined organic extracts were washed water (20 mL) and brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (1.3 × 18 cm; 50% dichloromethane/hexanes) to afford **16** as a bright yellow solid (0.10 g, 70%): R_f = 0.29 (60% dichloromethane/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.09 (d, *J* = 9.6 Hz, 1H), 8.51 – 8.45 (m, 2H), 8.41 (d, *J* = 8.2 Hz, 1H), 8.36 (d, *J* = 8.4 Hz, 1H), 8.24 (d, *J* = 8.4 Hz, 1H), 4.24 (s, 3H), 4.19 (s, 3H), 2.91 (s, 3H); $^{13}C\{^{1}H\}$NMR (151 MHz, $CDCl_3$) δ 201.9, 146.1, 143.9, 131.7, 131.4, 130.6, 129.3, 128.8, 128.08, 128.01, 127.8, 126.4, 123.6, 122.4, 121.2, 120.9, 118.8, 61.4, 61.2, 30.5; HRMS (ESI) calculated for $C_{20}H_{16}BrO_3$ ($[M+H]^+$) *m/z* = 383.0283, found 383.0276.

8-Bromo-4,5-dimethoxy-2-(2-propen-1-yl)pyren-1-ol (**17**): Compound **26** (0.29 g, 0.74 mmol) was dissolved in *N,N*-diethylaniline (2 mL) and heated to 190 °C. After 48 h, the solvent was evaporated under a gentle stream of nitrogen and the residue was purified by flash chromatography (2.5 × 18 cm; 50% dichloromethane/hexanes) to afford **17** as an off-white solid (0.21 g, 74%): R_f = 0.33 (50% dichloromethane/hexanes); HRMS (ESI) calculated for $C_{21}H_{17}BrO_3$ ($[M]^+$) *m/z* = 396.0361, found 396.0365. The ^{1}H and ^{13}C NMR spectra for **17** were poorly resolved. As such, it was subjected to triflation and characterized at a later stage – see below.

Triflate **18**: Trifluoromethanesulfonic anhydride (0.03 g, 0.1 mmol) and pyridine (0.01 g, 0.1 mmol) were added to a stirred 0 °C solution of **17** (0.021 g, 0.053 mmol) in dichloromethane (1.5 mL). After 10 min., the reaction mixture was diluted with dichloromethane (5 mL) and neutralized with 1 M HCl (10 mL). The layers were separated and the aqueous phase was extracted with dichloromethane (3 × 7 mL). The combined organic extracts were washed with 1 M HCl (10 mL), $NaHCO_3$ (10 mL), and brine (10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (0.5 × 10 cm; dichloromethane) to afford **18** as a yellow solid (0.027 g, 57%): R_f = 0.78 (dichloromethane); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.58 (d, *J* = 9.4 Hz, 1H), 8.43 (s, 1H), 8.41 – 8.35 (m, 2H), 8.30 (d, *J* = 8.3 Hz, 1H), 6.13 (ddt, *J* = 16.7, 9.9, 6.7 Hz, 1H), 5.31 – 5.25 (m, 2H), 4.22 – 4.18 (m, 6H), 3.98 (d, *J* = 6.6 Hz, 2H); $^{13}C\{^{1}H\}$NMR (151 MHz, $CDCl_3$) δ 145.3, 144.0, 140.1, 135.0, 132.1, 130.9, 128.9, 128.6, 128.2, 128.0, 124.5, 123.2, 122.1, 121.9, 121.6, 121.5, 120.7, 118.8 ($J_{C\text{-}F}$ = 253 Hz), 117.9, 61.32, 61.27, 35.2; HRMS (ESI) calculated for $C_{22}H_{17}BrF_3O_5S$ ($[M+H]^+$) *m/z* = 528.9932, found 528.9926.

Alkene **19**: Grubbs first-generation catalyst (0.001 g, 0.001 mmol) was added to a stirred 40 °C solution of **9** (0.020 g, 0.043 mmol) in dichloromethane (0.8 mL). After 12 h, the reaction mixture was cooled to room temperature and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (1.3 × 10 cm; 30% dichloromethane/hexanes) to afford **19** (dark yellow solid, 0.014 g, 78%, 4.7:1 *d.r*) as an inseparable mixture of diastereomers: R_f = 0.27 (35% dichloromethane/hexanes); ^{1}H NMR (400

MHz, $CDCl_3$) δ 8.52 – 8.48 (m, 5H), 8.43 – 8.40 (m, 1H), 8.37 (s, 5H), 8.28 – 8.23 (m, 6H), 8.18 (d, *J* = 1.4 Hz, 5H), 8.16 (d, *J* = 1.1 Hz, 5H), 8.07 – 7.94 (m, 9H), 6.19 – 6.15 (m, 1H), 6.02 – 5.96 (m, 5H), 4.15 (s, 14H), 4.13 – 4.10 (m, 2H), 4.07 – 4.04 (m, 18H), 4.02 – 3.98 (m, 13H); $^{13}C\{^1H\}$NMR (151 MHz, $CDCl_3$) δ 145.8, 145.6, 144.1, 144.0, 140.1, 139.9, 131.8, 131.7, 130.5, 130.3, 130.2, 129.7, 129.42, 129.41, 128.62, 128.55, 128.43, 128.38, 127.0, 126.8, 125.7, 125.6, 124.7, 124.4, 122.9, 122.5, 122.2, 121.9, 121.3, 121.0, 120.80, 120.72, 120.2, 120.1, 119.8, 117.9, 61.4, 61.28, 61.25, 61.15, 34.4, 29.9, 29.1; HRMS (ESI) calculated for $C_{42}H_{31}O_{10}F_6S_2$ ($[M+H]^+$) *m/z* = 873.1263, found 873.1262.

Alkene **20**: Grubbs first-generation catalyst (0.003 g, 0.003 mmol) was added to a stirred 40 °C solution of **13** (0.047 g, 0.10 mmol) in dichloromethane (0.8 mL). After 12 h, the reaction mixture was cooled to room temperature and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (1.3 × 15 cm; 30% dichloromethane/hexanes) to afford **20** (light yellow solid, 0.031 g, 67%, 2.7:1 *d.r.*) as an inseparable mixture of diastereomers: R_f = 0.38 (30% dichloromethane/hexanes); ^1H NMR (600 MHz, $CDCl_3$ δ 8.54 (d, *J* = 7.7 Hz, 4H), 8.20 (d, *J* = 7.5 Hz, 3H), 8.16 (d, *J* = 7.6 Hz, 1H), 8.12 – 8.04 (m, 10H), 7.99 (d, *J* = 9.0 Hz, 5H), 7.81 (d, *J* = 8.8 Hz, 1H), 6.12 – 6.08 (m, 1H), 6.02 – 5.97 (m, 3H), 4.32 – 4.27 (m, 12H), 4.18 – 4.14 (m, 2H), 4.04 – 3.98 (m, 6H), 3.95 (s, 3H), 3.89 (s, 9H); $^{13}C\{^1H\}$NMR (151 MHz, $CDCl_3$) δ 148.44, 148.41, 143.1, 140.12, 140.09, 131.9, 131.0, 130.9, 130.8, 130.6, 129.6, 128.87, 128.80, 128.06, 128.04, 126.9, 126.71, 126.5, 126.26, 126.20, 126.18, 125.9, 123.4, 122.34, 122.29, 121.53, 121.46, 120.51, 120.50, 120.1, 118.0, 61.9, 61.02, 60.99, 33.6, 28.3; HRMS (ESI) calculated for $C_{42}H_{31}O_{10}F_6S_2$ ($[M+H]^+$) *m/z* = 873.1263, found 873.1257.

8-Bromo-4,5-dimethoxypyren-1-ol (**25**): SeO_2 (0.009 g, 0.08 mmol) and a 30% solution (w/w) of hydrogen peroxide in water (1.0 mL, 12 mmol) were added to a stirred 50 °C solution of **6** (0.89 g, 2.9 mmol) in *t*-BuOH (12 mL). After 3 days, the reaction mixture was cooled to room temperature, poured into water (30 mL) and further diluted with dichloromethane (15 mL). The layers were separated, and the aqueous phase was extracted with dichloromethane (3 × 15 mL). The combined organic extracts were washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (2.5 × 18 cm, 80% dichloromethane/hexane) to afford **24** (0.533 g, 57%): R_f = 0.48 (80% dichloromethane/hexanes); ^1H NMR (600 MHz, $CDCl_3$) δ 8.53 (d, *J* = 8.5 Hz, 1H), 8.47 (d, *J* = 9.4 Hz, 1H), 8.35 (d, *J* = 8.4 Hz, 1H), 8.27 (d, *J* = 8.4 Hz, 1H), 8.17 (d, *J* = 9.3 Hz, 1H), 7.85 (d, *J* = 8.5 Hz, 1H), 4.21 (s, 3H), 4.19 (s, 3H), 2.58 (s, 3H); $^{13}C\{^1H\}$NMR (151 MHz, $CDCl_3$) δ 170.0, 144.7, 144.4, 144.2, 130.7, 129.4, 128.2, 126.8, 123.9, 123.2, 123.1, 121.8, 120.7, 120.5, 120.4, 119.8, 61.30, 61.27, 21.3; HRMS (ESI) calculated for **24** $C_{20}H_{16}BrO_4$ ($[M+H]^+$) *m/z* = 399.0232, found 399.0215. Compound **24** was dissolved in MeOH (20 mL) and K_2CO_3 (0.641 g, 4.64 mmol) was added, the resulting mixture was stirred for 30 min. The reaction mixture was directly poured into ice water (50 mL) and neutralized with 1 M HCl (40 mL), the layers were separated and the aqueous phase was extracted with dichloromethane (3 × 30 mL). The combined organic extracts were washed with a saturated solution of $NaHCO_3$ (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford **25** as a light brown solid (0.393 g, 82%): R_f = 0.24 (dichloromethane); HRMS (ESI) calculated for $C_{18}H_{13}BrO_3$ ($[M]^+$) *m/z* = 356.0048, found 356.0041. The ^1H and ^{13}C NMR spectra for **25** were poorly resolved. As such it was subjected to allylation and characterized at a later stage – see below.

1-Allyloxy-8-bromo-4,5-dimethoxypyrene (**26**): NaH (0.031 g, 1.3 mmol) and allyl bromide (0.17 g, 1.4 mmol) were added to a stirred solution of **25** (0.29 g, 0.82 mmol) in DMF (22 mL) at room temperature. After 30 min., the reaction mixture was poured into water (20 mL) and neutralized with 1 M HCl (20 mL). The resulting mixture was extracted with dichloromethane (3 × 15 mL), the combined organic extracts were washed with water (40 mL) and a saturated solution of $NaHCO_3$ (40 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (2.5 × 18 cm; dichloromethane) to afford **26** as a yellow solid (0.30 g, 91%): R_f = 0.70 (dichloromethane); ^1H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, *J* = 9.4 Hz, 1H), 8.43 (d, *J* = 8.7 Hz, 1H), 8.38 (d, *J* = 9.4 Hz, 1H), 8.25 – 8.20 (m, 2H), 7.58 (d, *J* = 8.7 Hz, 1H), 6.26 (ddt, *J* = 17.3, 10.4, 5.1 Hz, 1H), 5.60 (dd, *J* = 17.3, 1.6 Hz, 1H), 5.41 (dd, *J* = 10.6, Hz, 1H), 4.95 – 4.88 (m, 2H), 4.22 (s, 3H), 4.16 (s, 3H); $^{13}C\{^1H\}$NMR (151 MHz, $CDCl_3$) δ 152.8, 144.9, 142.4, 133.2, 130.4, 130.0, 128.7, 124.9, 124.2, 123.6, 122.9, 122.2, 120.8, 120.6, 119.3, 118.6, 117.8, 110.0, 69.7, 61.2, 61.1; HRMS (ESI) calculated for $C_{21}H_{18}BrO_3$ ($[M+H]^+$) *m/z* = 397.0439, found 397.0422.

ASSOCIATED CONTENT

Supporting Information

^1H and ^{13}C NMR spectra for all new compounds, and crystallographic data, including CIFs. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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REFERENCES

1. Figueira-Duarte, T. M.; Müllen, K. Pyrene-Based Materials for Organic Electronics. *Chem. Rev.* **2011**, *111*, 7260-7314.

2. Feng, X.; Hu, J. Y.; Redshaw, C.; Yamato, T. Functionalization of Pyrene to Prepare Luminescent Materials – Typical Examples of Synthetic Methodology. *Chem. Eur. J.* **2016**, *22*, 11898-11916.
3. Casas-Solvas, J. M.; Howgego, J. D.; Davis, A. P. Synthesis of Substituted Pyrenes by Indirect Methods. *Org. Biomol. Chem.* **2014**, *12*, 212-232.
4. Tashiro, M.; Yamato, T.; Kobayashi, K.; Arimura, T. Metacyclophanes and Related Compounds. 19. Reaction of 8-Methoxy[2.2]Metacyclophanes with Iodine in Benzene Solution. A Preparative Route of Pyrenes. *J. Org. Chem.* **1987**, *52*, 3196-3199.
5. Musa, A.; Sridharan, B.; Lee, H.; Mattern, D. L. 7-Amino-2-Pyrenecarboxylic Acid. *J. Org. Chem.* **1996**, *61*, 5481-5484.
6. (a) Yang, W.; Monteiro, J. H. S. K.; de Bettencourt-Dias, A.; Catalano, V. J.; Chalifoux, W. A. Pyrenes, Peropyrenes, and Teropyrenes: Synthesis, Structures, and Photophysical Properties. *Angew. Chem. Int. Ed.* **2016**, *55,* 10427-10430; (b) Walker, D. B.; Howgego, J.; Davis, A. P. Synthesis of Regioselectively Functionalized Pyrenes via Transition-Metal-Catalyzed Electrocyclization. *Synthesis* **2010**, *21*, 3686–3692.
7. For examples, see: (a) Merner, B. L.; Dawe, L. N.; Bodwell, G. Tetramethyl[8](2,11)Teropyrenophane: Half of an Aromatic Belt and a Segment of an (8,8) Single-Walled Carbon Nanotube. *Angew. Chem. Int. Ed.* **2009**, *48*, 5487-5491; (b) Merner, B. L.; Unikela, K. S.; Dawe, L. N.; Thompson, D. W.; Bodwell, G. J. 1,1,*n*,*n*-Tetramethyl[*n*](2,11)Teropyrenophanes (*n* = 7–9): A Series of Armchair SWCNT Segments. *Chem Commun.* **2013**, *49*, 5930-5932; (c) Figueira-Duarte, T. M.; Del Rosso, P. G.; Trattnig, R.; Sax, S.; List, E. J. W.; Mullen, K. Designed Suppression of Aggregation in Polypyrene: Toward High-Performance Blue-Light-Emitting Diodes. *Adv. Mater.* **2010**, *22*, 990-993; (d) Yamato, T.; Miyazawa, A.; Tashiro, M. Medium-Sized Cyclophanes. Part 31. l Synthesis and Electrophilic Substitution of 8-Substituted [2]Metacyclo[2](1,3)pyrenophanes. *J. Chem. Soc. Perkin Trans 1*. **1993**, 3127-3137.
8. Coventry, D. N.; Batsanov, A. S.; Goeta, A. E.; Howard, J. A. K.; Marder, T. B.; Perutz, R. N. Selective Ir-Catalysed Borylation of Polycyclic Aromatic Hydrocarbons: Structures of Naphthalene-2,6-Bis(Boronate), Pyrene-2,7-Bis(Boronate) and Perylene-2,5,8,11-Tetra(Boronate) Esters. *Chem Commun.* **2005**, *41*, 2172-2174.
9. Venkataramana, G.; Dongare, P.; Dawe, L. N.; Thompson, D. W.; Zhao, Y.; Bodwell, G. J. 1,8-Pyrenylene-Ethynylene Macrocycles. *Org. Lett.* **2011**, *13*, 2240-2243.
10. Keller, S. N.; Veltri, N. L.; Sutherland, T. C. Tuning Light Absorption in Pyrene: Synthesis and Substitution Effects of Regioisomeric Donor-Acceptor Chromophores. *Org. Lett.* **2013**, *15*, 4798-4801.
11. Zöphel, L.; Beckmann, D.; Enkelmann, V.; Chercka, D.; Rieger, R.; Müllen, K. Asymmetric Pyrene Derivatives for Organic Field-Effect Transistors. *Chem. Commun.* **2011**, *47*, 6960-6962.
12. Tintel, C.; Terheijden, J.; Lugtenburg, J.; Cornelisse, J. Photoreduction and Photoaddition Reactions of Pyrenediones. *Tetrahedron Lett.* **1987**, *28*, 2057-2060.
13. For details on the syntheses of **1b** and **1c**, see the Supporting Information file.
14. Lee, H.; Harvey, R. G. Synthesis of 2,7-Dibromopyrene. *J. Org. Chem.* **1986**, *51*, 2847-2848.
15. Asakawa, T.; Hiza, A.; Nakayama, M.; Inai, M.; Oyama, D.; Koide, H.; Shimizu, K.; Wakimoto, T.; Harada, N.; Tsukada, H.; Oku, N.; Kan, T. PET Imaging of Nobiletin Based on a Practical Total Synthesis. *Chem Commun.* **2011**, *47*, 2868-2870.
16. (a) Connolly, T.; Wang, Z.; Walker, M. A.; McDonald, I. M.; Peese, K. M. Tandem Ring-Closing Metathesis/Transfer Hydrogenation: Practical Chemoselective Hydrogenation of Alkenes. *Org. Lett.* **2014**, *16*, 4444-4447; (b) Mitra, N. K.; Meudom, R.; Corzo, H. H.; Gorden, J. D.; Merner, B. L. Overcoming Strain-Induced Rearrangement Reactions: A Mild Dehydrative Aromatization Protocol for Synthesis of Highly Distorted *p*-Phenylenes. *J. Am. Chem. Soc.* **2016**, *138*, 3235-3240.
17. Wang, C. Z.; Feng, X.; Kowser, Z.; Wu, C.; Akther, T.; Elsegood, M. R. J.; Redshaw, C.; Yamato, T. Pyrene-Based Color-Tunable Dipolar Molecules: Synthesis, Characterization and Optical Properties. *Dyes Pigments* **2018**, *153*, 125–131.
18. Mitra, N. K.; Meudom, R.; Gorden J. D.; Merner, B. L. A Non-Cross-Coupling Approach to Arene-Bridged Macrocycles: Synthesis, Structure and Direct, Regioselective Functionalization of a Cycloparaphenylene Fragment. *Org. Lett.* **2015**, *17*, 2700-2703.