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Synthesis of unsymmetrically substituted pyrene derivatives through (6-bromo-3,8-dibutylpyren-1-yl)trimethylsilane

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ABSTRACT

A straightforward route to unsymmetrically functionalized pyrene derivatives is described involving the synthesis of key precursor (6-bromo-3,8-dibutylpyren-1-yl)trimethylsilane **1**. In a first step bromide **1** was successful in Suzuki–Miyaura, Sonogashira, and Buchwald–Hartwig cross-coupling reactions. Subsequent transformation of the trimethylsilyl group to bromide enabled the introduction of a second variable functional group onto the pyrene skeleton.

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Multi-functionalization of pyrene ring is attracting significant interest in organic materials science, because it allows manipulation of the spectroscopic and opto-electronic properties of pyrene.^{1,2} Subtle changes in structure or composition of pyrene derivatives can greatly alter their properties as electronic organic devices.³ Among synthetic precursors for a poly-functionalized pyrene, a multi-brominated pyrene is one of the most valuable building blocks on the basis of a transition-metal-catalyzed cross-coupling strategy.^{3–5} For example, 1,3,6,8-tetrabromopyrene⁶ was used as a starting material of cross-coupling reactions to synthesize symmetrical pyrene derivatives for the study of organic electronics⁷ and piezochromic⁸ materials. 1,3-⁹ and 1,8-dibromopyrene³ were also transformed into symmetrical derivatives through Pd-catalyzed cross-coupling reactions to develop the unique radical material¹⁰ and macrocyclic organic device.¹¹ In addition, lithiation also works to activate multi-brominated pyrene,¹² for example, 1,6-dibromopyrene was converted into diester through dilithiation for synthesis of fluorescent brightening polymer.¹³ In contrast to these methods of preparing symmetric pyrenes, there remains a great chemical difficulty in obtaining unsymmetrically functionalized pyrenes.¹⁴

Herein, we report a systematic procedure for the synthesis of unsymmetrically functionalized pyrene derivatives at the 1 and 6 positions (Scheme 1). First, (6-bromo-3,8-dibutylpyren-1-yl)trimethylsilane **1** was prepared and is readily soluble in various organic solvents. Bromide **1** was readily amenable to Suzuki–Miyaura, Sonogashira and Buchwald–Hartwig cross-coupling reactions.

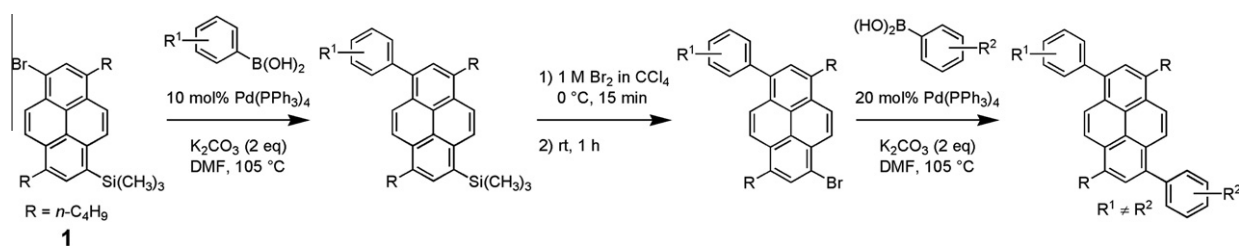
Next, TMS group was converted to bromide and it was readily transformed via Suzuki–Miyaura, Sonogashira and Buchwald–Hartwig reactions. Thus, it provides a convenient access to unsymmetrically functionalized pyrenes.

At the outset of our study the key precursor **1** was designed with three features in mind. The two butyl groups were included to provide solubility in various organic solvents.¹⁵ The Br substituent is the first reactive site, and the TMS group serves as a synthon for a second reactive Br group that can be unveiled after our first cross-coupling. As a minor point the TMS group is also expected to increase solubility.

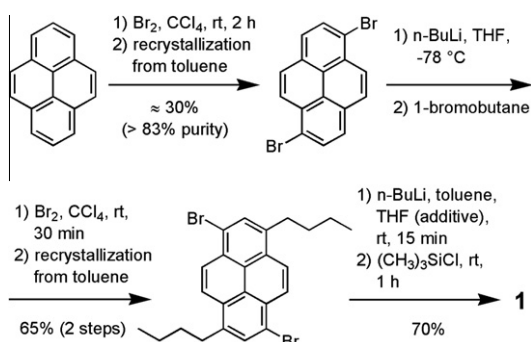
The key intermediate **1** was synthesized from pyrene as shown in Scheme 2. The reaction of pyrene with bromine in CCl₄¹⁶ gave an isomeric mixture of 1,6- and 1,8-dibromopyrene,¹⁷ and the single operation of recrystallization from toluene afforded 1,6-dibromopyrene in ca. 30% yield with >83% purity.^{18,19} Initial efforts to convert 1,6-dibromopyrene to the corresponding 1,6-dioctylpyrene or 1,6-didodecylpyrene proved difficult due to the numerous amounts of *n*-butylated pyrene byproducts. Presumably the 1,6-dilithiated pyrene immediately reacted with 1-bromobutane that was produced by lithium-halogen exchange between *n*-BuLi and 1,6-dibromopyrene. Thus, dialkylation reaction was performed with 1-bromobutane, and it was followed by dibromination at the 3,8-positions, giving 1,6-dibromo-3,8-dibutylpyrene in 65% (two steps). Lithiation of 1,6-dibromo-3,8-dibutylpyrene smoothly proceeded with THF as an additive, and the reaction with chlorotrimethylsilane gave **1** in 70% yield.²⁰ According to this process, ca. 25 g of **1** was prepared in all. The direct *mono*-lithiation of 1,6-dibromopyrene was not successful even though the amount of *n*-BuLi was controlled, presumably due to the low solubility into

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Scheme 1. The outline of synthetic route to unsymmetrically substituted pyrene via **1**.



Scheme 2. Synthesis of **1**.

organic solvents. Compound **1** proved to be quite soluble in CHCl_3 , CH_2Cl_2 , benzene, toluene, THF, EtOAc, CH_3CN , $\text{CH}_3\text{CH}_2\text{CN}$, acetone and even hexane.²¹

The scope of reactivity of **1** was examined on cross-coupling reactions, by preparing a 1-substituted (3,8-dibutylpyren-6-yl)trimethylsilane **2–13** (Fig. 1). The results are summarized in Table 1.²² Suzuki–Miyaura reactions (entries 1–10) were conducted with 0.5 mmol (233 mg) of **1** and 2 mL of DMF at 105 °C, in the presence of 10 mol % $\text{Pd}(\text{PPh}_3)_4$ and 2 equiv K_2CO_3 .²³ The reactions in entries 1–6 proved to be initially very clean as confirmed by TLC. For entry 7, reaction of *ortho*-methoxyphenylboronic acid was sluggish presumably due to the steric hindrance,²⁴ and the alternative catalyst system of $\text{Pd}_2(\text{dba})_3$ (dba = dibenzylideneacetone) and $\text{P}(\text{C}_6\text{H}_{11})_3$ completed the reaction in 8 h with 93% yield. For entries 8–10, the arylboronic acids containing bromine and nitrogen were examined, and bromide **9**,²⁵ benzamide **10**,²⁶ and pyridine **11** were obtained in 90%, 95% and 47% yield, respectively. Sonogashira cross-coupling²⁷ was carried out with trimethylsilylacetylene, and compound **12** was given in 91% yield (entry 11). Buchwald–Hartwig amination reaction with pyrrolidine¹⁰ also proceeded to yield **13** in 70% (entry 12).

Removal of the trimethylsilyl group with Br_2 was performed to transform **2**, **5**, and **7** into the bromide **14**, **15**, and **16** (Scheme 3). Addition of Br_2 (neat) to CCl_4 solution of **2** proved not to work as confirmed by the multi spots in TLC monitoring. After several attempts, Br_2 as a 1 M CCl_4 was found to convert **2–14** cleanly in

Table 1
Evaluation of the reactivity of **1** on cross-coupling reactions^a

Entry	Product	Yield (%)	Time ^b (h)
1	2	87	23
2	3	88	21
3	4	78	18
4	5	93	22
5	6	89	14
6	7	91	23
7 ^c	8	97	8
8	9	90	11
9	10	95	16
10	11	47	22
11 ^d	12	91	1
12 ^e	13	70	15

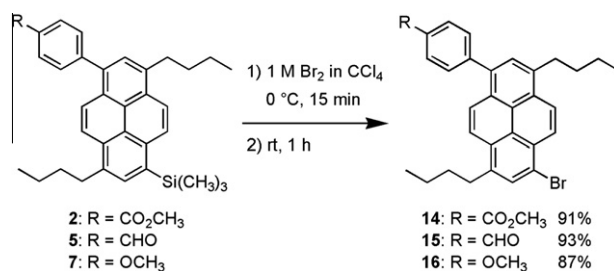
^a All reactions were performed in accordance with the representative procedure in Ref. 22, unless otherwise stated.

^b The reactions were stopped when the complete formation of Pd black was observed and/or when the starting materials disappeared on TLC monitoring.

^c The reaction was carried out in toluene at 110 °C with 5 mol % $\text{Pd}_2(\text{dba})_3$, 15 mol % $\text{P}(\text{C}_6\text{H}_{11})_3$, and K_3PO_4 (2 equiv). dba = dibenzylideneacetone.

^d Reaction at 70 °C was conducted with **1** (0.25 mmol) and TMS acetylene (0.75 mmol) in Et_3N (1.5 mL) and toluene (1.5 mL). A catalyst system of $\text{PdCl}_2(\text{PPh}_3)_2$ (0.0125 mmol) and PPh_3 (0.025 mmol), and CuI (0.025 mmol) was used.

^e Reaction at 90 °C was conducted with **1** (0.25 mmol), pyrrolidine (0.75 mmol) and NaO^tBu (0.75 mmol) in toluene (2.0 mL). A catalyst system of $\text{Pd}_2(\text{dba})_3$ (0.0125 mmol), and BINAP (0.025 mmol) was used.



Scheme 3. Desilylation of **2**, **5**, and **7** with bromine.

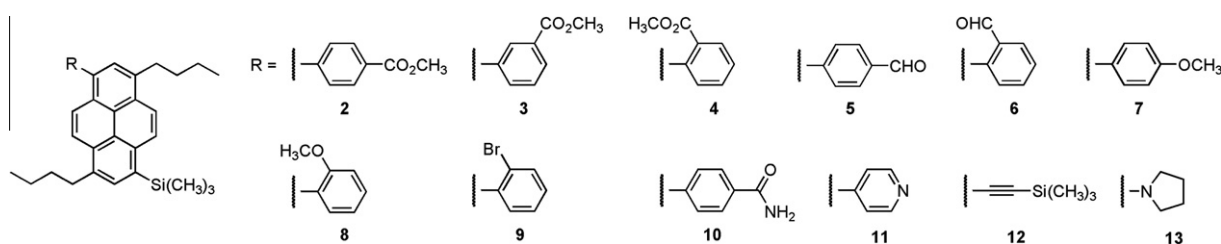


Figure 1. Derivatives from **1** through the cross-coupling reactions.

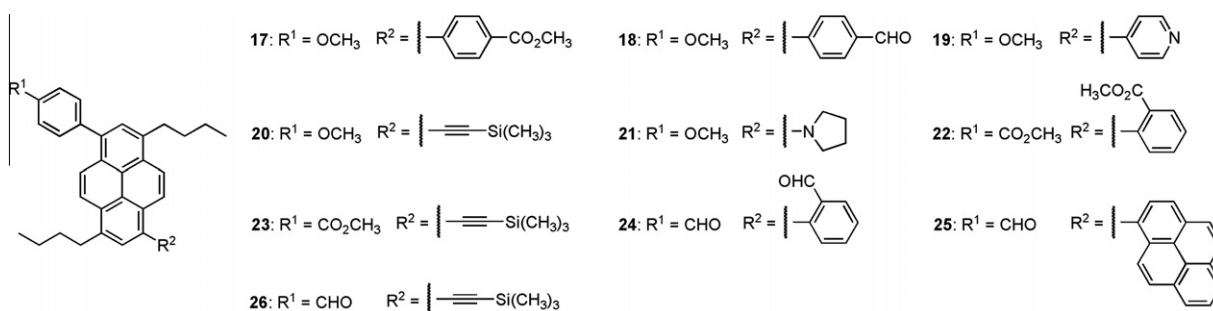


Figure 2. Derivatives from **14**, **15**, and **16** through the cross-coupling reactions.

Table 2

Evaluation of the reactivity of **14**, **15**, and **16** on cross-coupling reactions^a

Entry	Substrate	Product	Yield (%)	Time ^b (h)
1	16	17	81	21
2	16	18	86	21
3	16	19	67	22
4 ^c	16	20	71	21
5 ^d	16	21	80	25
6	14	22	73	22
7 ^c	14	23	74	15
8	15	24	85	17
9 ^c	15	25	97	10
10	15	26	91	15

^a All reactions were performed in accordance with the representative procedure in Ref. 29, unless otherwise stated.

^b The reactions were stopped when the complete formation of Pd black was observed and/or when the starting materials disappeared on TLC monitoring.

^c Reaction at 70 °C was conducted with starting bromide (0.25 mmol) and TMS acetylene (0.75 mmol) in Et₃N (1.5 mL) and toluene (1.5 mL). A catalyst system of PdCl₂(PPh₃)₂ (0.0125 mmol), and PPh₃ (0.025 mmol) and CuI (0.025 mmol) was used.

^d Reaction at 90 °C was conducted with **16** (0.25 mmol), pyrrolidine (0.75 mmol) and NaO^tBu (0.75 mmol) in toluene (2.0 mL). A catalyst system of Pd₂(dba)₃ (0.0125 mmol), and BINAP (0.025 mmol) was used.

91% yield. Similar clean-deprotection by the addition of a 1 M CCl₄ solution of Br₂ were observed in **5** and **7**, giving **15** in 93% yield and **16** in 87% yield, respectively.²⁸

The reactivity of Br substituent of **14**, **15**, and **16** were examined on cross-coupling reactions, by preparing unsymmetrically functionalized pyrenes **17–26** (Fig. 2). The results are summarized in Table 2. Bromide **14** smoothly cross-coupled with arylboronic acids containing methyl ester, formyl, and pyridine groups (entries 1–3). Compound **14** also reacted with trimethylsilylacetylene by Sonogashira cross-coupling in 71% yield (entry 4), and reacted with pyrrolidine in Buchwald–Hartwig amination in 80% yield (entry 5). For entries 6–10, bromide **14** and **15** were also effective to Suzuki–Miyaura and Sonogashira cross-coupling, giving **22–26** in 73–97% yields. In particular, for entries 6 and 8, both **22** and **24** have methyl ester group and formyl group specifically at the *ortho*- and *para*-positions, respectively; thus, these systematic transformations using **1** achieved exact installation of functional groups into pyrene core structure.

In summary, we have developed a systematic procedure for the synthesis of unsymmetrically substituted pyrene derivatives. The synthetic approach, which employs (6-bromo-3,8-dibutylpyren-1-yl)trimethylsilane **1**, accomplished to install varied functional groups into the 1, 6-positions of the pyrene core structure, providing novel functionalized molecules **2–26**. Because of the utility of unsymmetrically functionalized pyrene derivatives, we anticipate that this approach is likely to find widespread use in the field of organic materials science. Furthermore, this strategy should find applications toward other substitution pyrene patterns. We will report this work in due course.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.09.089.

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16. The use of CH_2Cl_2 and CHCl_3 in place of CCl_4 was applicable to the bromination, although the chemical yields slightly decreased.
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18. The experiment of dibromination was conducted with 18.2 g of pyrene, and the recrystallization was performed with freshly distilled toluene.
19. The other 17% impurity was mainly 1,8-dibromopyrene. Although the byproduct would be converted to 1,8-dibromo-3,6-dibutylpyrene in the subsequent step, it was removed by the single operation of recrystallization from freshly distilled toluene.
20. *The synthetic procedure of 1*: To a solution of 1,6-dibromo-3,8-dibutylpyrene (7.6 g, 16 mmol) in anhydrous toluene (600 mL) at room temperature was added THF (3.2 mL, 38 mmol), and then *n*-BuLi (11 mL, 1.63 M in hexane) was added dropwise over 3 min. The solution was stirred for 15 min, and chlorotrimethylsilane (9.5 mL, 48 mmol) was added over 1 min. After stirring for 1 h at room temperature, the reaction was quenched with water. The solvent was thoroughly evaporated, and to the mixture was added CHCl_3 and aqueous phase was extracted with CHCl_3 . Combined organic phases were washed with brine, and then dried over Na_2SO_4 , and concentrated to give the crude products. Purification by silica gel column chromatography (hexane only) gave a desired compound **1** (5.2 g, 70%) as white solid materials. ^1H NMR (400 MHz, CDCl_3) δ 8.43 (d, J = 9.5 Hz, 1H), 8.37 (d, J = 9.4 Hz, 1H), 8.30 (d, J = 9.5 Hz, 1H), 8.21 (d, J = 9.4 Hz, 1H), 8.10 (s, 1H), 8.04 (s, 1H), 3.35–3.27 (m, 4H), 1.85–1.83 (m, 4H), 1.56–1.49 (m, 4H), 1.0 (t, J = 7.4, 7.4 Hz, 6H), 0.60 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3) δ 138.3, 136.6, 136.1, 134.5, 134.3, 131.2, 129.9, 128.33, 128.25, 128.1, 127.4, 126.4, 125.2, 124.5, 34.6, 34.11, 34.05, 33.5, 23.3, 23.2, 14.42, 14.38, 1.05. MS (FAB) m/z : 466 (M^+). Anal. Calcd for $\text{C}_{27}\text{H}_{33}\text{BrSi}$: C, 69.66; H, 7.14. Found: C, 69.79; H, 7.10.
21. 6.1 g of **1** was recrystallized from 33 mL of hexane, giving a first crop of 4.1 g in pure form.
22. The typical procedure of cross-coupling reactions (Table 1, entry 1): K_2CO_3 (138 mg, 1 mmol) and *p*-(methoxycarbonyl)phenylboronic acid (135 mg, 0.75 mmol) were dried in vacuo in a Schlenk tube with heating, then bromide **1** (233 mg, 0.5 mmol), and $\text{Pd}(\text{PPh}_3)_4$ (58 mg, 0.05 mmol) were added. The whole system was evacuated and backfilled with argon three times, and 2 mL of DMF was added. The reaction mixture was stirred at room temperature for 1 min, and then conducted at 105 °C for 23 h. After the reaction, the mixture was diluted with 15 mL EtOAc, and filtered through a pad of Celite and florisil. Purification by silica gel column chromatography gave **2** (227 mg, 87%) as pale yellow solid materials. ^1H NMR (400 MHz, CDCl_3) δ 8.39 (d, J = 9.4 Hz, 1H), 8.30 (d, J = 9.4 Hz, 1H), 8.23 (d, J = 8.4 Hz, 2H), 8.16 (d, J = 9.4 Hz, 1H), 8.09 (d, J = 9.4 Hz, 1H), 8.03 (s, 1H), 7.81 (s, 1H), 7.72 (d, J = 8.4 Hz, 2H), 4.01 (s, 3H), 3.37 (t, J = 7.7, 7.7 Hz, 2H), 3.30 (t, J = 7.7, 7.7 Hz, 2H), 1.92–1.78 (m, 4H), 1.59–1.46 (m, 4H), 1.03–0.98 (m, 6H), 0.61 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3) δ 167.3, 146.7, 137.1, 136.0, 135.5, 134.5, 134.1, 131.0, 129.9, 129.8, 129.1, 128.8, 128.6, 128.1, 127.1, 126.5, 126.0, 125.2, 123.4, 122.4, 52.4, 34.4, 34.3, 33.9, 33.8, 23.3, 23.2, 14.34, 14.33, 1.0. MS (FAB) m/z : 520 (M^+). Anal. Calcd for $\text{C}_{35}\text{H}_{40}\text{O}_2\text{Si}$: C, 80.72; H, 7.74. Found: C, 80.76; H, 7.55.
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24. Numerous amounts of compound **1** was observed on TLC analyzing even in 48 h reaction times.
25. The solubility of **9** was very good: 244 mg of **9** dissolved in 0.5 mL hexane.
26. Cross-coupling between **1** and *p*-(aminocarbonyl)phenylboronic acid was carried out in toluene at 110 °C with 5 mol % $\text{Pd}_2(\text{dba})_3$, 15 mol % $\text{P}(\text{C}_6\text{H}_{11})_3$, and 2 equiv K_3PO_4 , however no reaction was observed.
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28. Benzylic bromination of **2**, **5**, and **7** were not observed.
29. The typical procedure of cross-coupling reactions (Table 2, entry 1): K_2CO_3 (83 mg, 0.6 mmol) and *p*-(methoxycarbonyl)phenylboronic acid (81 mg, 0.45 mmol) were dried in vacuo in a Schlenk tube with heating, then bromide **16** (149 mg, 0.3 mmol), and $\text{Pd}(\text{PPh}_3)_4$ (69 mg, 0.06 mmol) were added. The whole system was evacuated and backfilled with argon three times, and 1.2 mL of DMF was added. The reaction mixture was stirred at room temperature for 1 min, and then conducted at 105 °C for 21 h. After the reaction, the mixture was diluted with 15 mL EtOAc, and filtered through a pad of Celite and florisil. Purification by silica gel column chromatography gave **17** (134 mg, 81%) as pale yellow solid materials. ^1H NMR (400 MHz, CDCl_3) δ 8.24–8.17 (m, 5H), 8.10 (d, J = 9.5 Hz, 1H), 7.83 (d, J = 8.4 Hz, 2H), 7.73 (d, J = 8.4 Hz, 2H), 7.58 (d, J = 8.7 Hz, 2H), 7.11 (d, J = 8.7 Hz, 2H), 4.01 (s, 3H), 3.94 (s, 3H), 3.33 (t, J = 7.6, 7.6 Hz, 4H), 1.86–1.81 (m, 4H), 1.54–1.48 (m, 4H), 1.00–0.96 (m, 6H). ^{13}C NMR (100 MHz, CDCl_3) δ 167.4, 159.2, 146.7, 137.4, 136.9, 136.6, 135.9, 134.0, 131.9, 131.0, 129.9, 129.5, 129.1, 129.0, 128.2, 127.5, 127.3, 126.42, 126.39, 125.8, 124.6, 123.2, 122.6, 114.1, 55.6, 52.4, 34.3, 34.2, 33.7, 23.2, 14.3. MS (FAB) m/z : 554 (M^+). Anal. Calcd for $\text{C}_{39}\text{H}_{38}\text{O}_3$: C, 84.44; H, 6.90. Found: C, 84.46; H, 7.01.