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Efficient synthesis and unit-selective π -extension of π -fused [4.3.3]propellane as chiral building blocks

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A three-dimensional skeleton, π -fused [4.3.3]propellane, was constructed and derivatized by selective π -extension at the two naphthalene units. The obtained propellanes existed as stereoisomers different in spatial arrangement, one of which displayed chiroptical response originating from through-space interactions between 5-azacrysenes in skew position.

Chiroptical properties of organic molecules arise from the electronic transitions in three-dimensional (3D) structures without mirror plane of symmetry.¹ Planar aromatic chromophores are attractive for strong π - π^* transitions from the smoothly conjugated π -systems but need to be contorted into non-planar structures to exhibit circular dichroism (CD) and circularly polarized luminescence (CPL).² Because of such requirement, the synthesis of chiroptical π -conjugated systems is usually difficult as compared with that of planar ones, especially when the fused structures were constructed via multiple bond formation against large strain energy.^{2,3}

Chiral arrangement of two or more π -conjugated planes is an alternative strategy for the development of chiroptical organic compounds.^{4,5} In this scheme, chiroptical molecules can be prepared by simply attaching π -conjugated planes to a chiral 3D core, enabling systematic studies on the structure–properties relationships. These molecules were widely exploited for the development of chiroptical systems responsive to various external stimuli because the chiral information depended on variable non-covalent and through-space interactions between the multiple chromophores.^{5,6} To gain such interactions, π - π stacking configurations were vigorously investigated^{7,8} since a

chiroptical perylene diimide (PDI) dimer reported in 2007 (**1** in Fig. 1).⁷ On the other hand, other structural motifs were rather un-investigated.^{9,10} Use of bicyclic compounds as the rigid 3D cores (**2**) made important contribution to understand exciton chirality in 1976⁹ but the hybrids of such 3D bicyclic skeletons and π -conjugated planes have not attracted great interests on their chiroptical properties. In this work, we used [4.3.3]propellane **3**^{11,12} as a 3D core for the creation of chiroptical molecules, for the first time. Because of the less reactive biphenyl unit,^{13,14b} π -extension was successfully performed in a naphthalene-selective manner, yielding two 5-azachrysene rings in a skew position (**4b**). The chiral arrangement of these photo-responsive segments indeed gave CD and CPL signals with moderate intensity and dissymmetry ($g \sim 10^{-3}$).

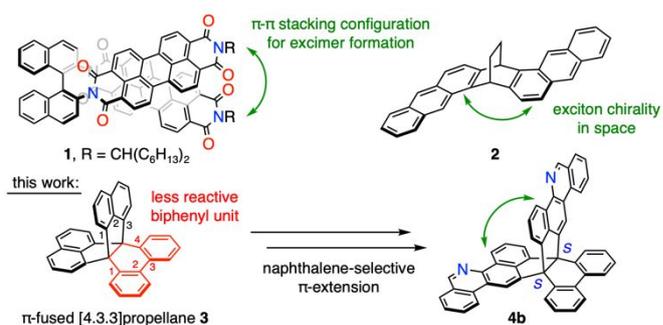


Fig. 1 Chiroptical molecules based on arrangement of two π -conjugated planes (top) and derivatization of a π -fused [4.3.3]propellane (bottom), in which (S,S)-**4b** is displayed from three stereoisomers of **4a,b**.

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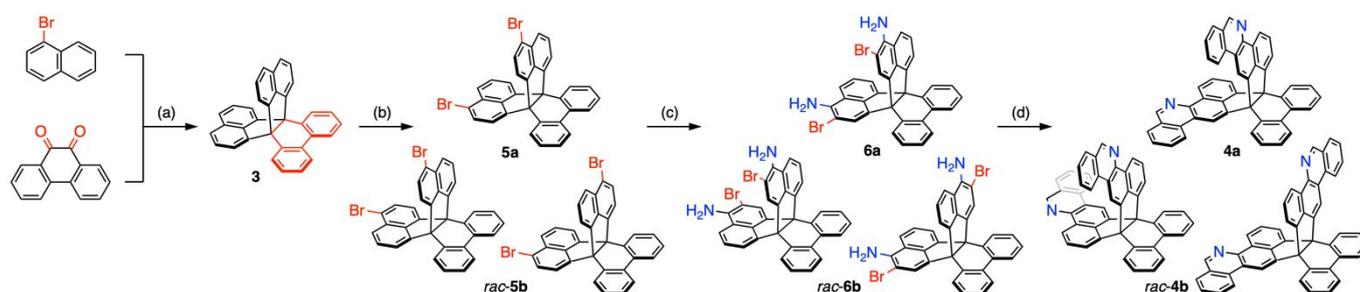
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As the initial attempt, [4.3.3]propellane **3** was synthesized from 9,10-phenanthrenequinone and 1-naphthyl Grignard reagent according to the protocol for a tri-naphthalene-fused [3.3.3]propellane (Scheme 1, step a, see also Scheme S2-1 in the ESI).¹⁴ Although nucleophilic addition of the Grignard reagent in the first step resulted in a lower yield probably because of the increased steric demand at around the 6-membered quinone

ring, the second acid-mediated cyclization of resulting diol intermediates was successful. The two-step synthesis did not rely on a Pd catalyst^{11a} and could be conducted in a gram scale,^{11d} providing 3.77 g of **3** in total 22% yield. Then, 2.1 equiv. of bromine was employed for two-fold naphthalene-selective functionalization (step b), which was highly difficult in a tri-naphthalene-fused [3.3.3]propellane.^{14b,15} A stereomixture of dibromo[4.3.3]propellanes **5a** and *rac*-**5b** was selectively obtained in 95% yield with almost no mono- and tribrominated side products, because of lower reactivity of the biphenyl unit.^{13,14b} The dibrominated mixture was converted into tetra-functionalized precursors **6a,b** via a three-reaction sequence (step c). Coupling reaction with benzophenoneimine replaced bromo groups with imine ones, which were hydrolysed into

amino groups in a mixture of 3 M aqueous hydrochloric acid and THF. The following two-fold bromination proceeded in a highly site-selective manner because of the amino groups. During the reaction sequence, the biphenyl rings were intact, enabling unit-selective modifications. Lastly, (2-formylphenyl)boronic acid was coupled with **6a,b** via Suzuki–Miyaura coupling reactions and the crude mixture was directly refluxed after the addition of 2 M HCl (aq) in one pot, to complete the formation of carbon–nitrogen double bonds (step d).¹⁶ The target 5-azachrysene derivatives were obtained in 85% combined yield as a stereomixture of an achiral C_s-isomer **4a** and a pair of enantiomers **4b** with C₂ symmetry.



Scheme 1 Construction and naphthalene-selective modification of π -fused [4.3.3]propellane. Reagents and conditions: (a) (i) 1-bromonaphthalene (1.0 equiv.), Mg (1.0 equiv.), THF, RT, 1 h, then 9,10-phenanthrenequinone (0.40 equiv.), 50 °C, 45 h, 33%; (ii) CF₃SO₃H (2.0 equiv.), toluene, reflux, 14 h, 66%; (b) Br₂ (2.1 equiv.), CH₂Cl₂, RT, 3 d, 95%; (c) (i) Ph₂C=NH (4.0 equiv.), Pd₂(dba)₃ (5.0 mol%), *rac*-BINAP (15 mol%), *t*-BuONa (4.0 equiv.), toluene, reflux, 15 h, 68%; (ii) 3 M HCl (aq), THF, RT, 2 h, then NH₃ (aq), 94%; (iii) NBS (2.0 equiv.), CH₂Cl₂, 0 °C, 4 h, 55%; (d) (2-formylphenyl)boronic acid (2.5 equiv.), Pd(PPh₃)₄ (6 mol%), Na₂CO₃ (6.0 equiv.), DME, reflux, 15 h, then 2 M HCl (aq), DME, reflux, 2 h, 85%. Pd₂(dba)₃: tris(dibenzylideneacetone)dipalladium(0), BINAP: 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, NBS = *N*-bromosuccinimide, DME = 1,2-dimethoxyethane.

The three stereoisomers of **4a,b** were separated using a chiral high-performance liquid chromatography (HPLC) apparatus (Fig. S6-1). The second fraction showed eight ¹H NMR peaks for the biphenyl protons and was identified as C_s-isomer **4a** (Fig. S3-13 and S3-17a). In contrast, the first and third fractions displayed four signals with the double integral values, enabling the confirmation of the different chemical structures and the assignment to C₂-symmetric enantiomers **4b** (Fig. S3-15 and S3-17a). Ultraviolet/visible (UV/vis) absorption spectra of **4a** and **4b** are plotted as almost the identical shapes in Fig. 2. The lowest-energy peak was observed at around 370 nm for both **4a** and **4b**, which was red-shifted from the peak of pristine 5-azacrysene at 360 nm¹⁷ owing to the through-space interactions. The absorption spectra had clear split structures in the low-energy region and became complicated due to overlapping as the transition energy increased.

Each enantiomer of **4b** displayed mirror-shaped CD signal with moderate intensity (Table 1), supporting the effective exciton coupling. The first fraction showed positive Cotton effects in ca. 280–370 nm and the third had negative signals. For the assignment of these results, theoretical CD spectra were calculated at the TD-SCF/R ω B97X-D/6-31+G(d,p) level for optimized structures gained at the RB3LYP/6-31G(d) level (Fig. S7-7). In the optimization, two stable configurations for one enantiomer were obtained with a small total energy difference of ca. 1.6 kJ mol⁻¹. They showed opposite torsion around the

central C–C single bonds. The experimental CD spectra of the third fraction could be roughly understood as a mixture of the predicted spectra of these configurations, leading to the assignment to (*S,S*)-isomer.

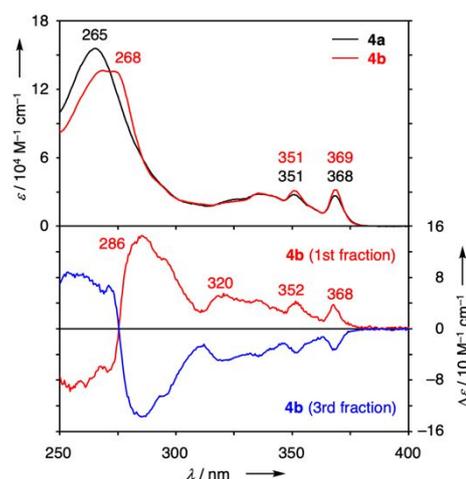


Fig. 2 UV/vis absorption spectra of **4a,b** (top) and CD spectra of **4b** (bottom) in CHCl₃.

Table 1. Chiroptical properties of **4b** in CHCl₃.

λ_{CD} [nm]	$ \Delta\epsilon $ [M ⁻¹ cm ⁻¹]	$ g_{CD} $	Φ_{FL}^a	λ_{CPL}^b [nm]	$ g_{CPL} ^b$
286	1.4×10^2	2.4×10^{-3}	—	—	—
320	5.0×10^1	2.5×10^{-3}	—	—	—
368	3.3×10^1	1.0×10^{-3}	0.36	ca. 380	0.7×10^{-3}

^a λ_{ex} = 335 nm. ^b λ_{ex} = 290 nm.

Fig. 3 represents fluorescence spectra of **4a,b** and CPL spectra of two enantiomers of **4b** in CHCl₃. In line with the UV/vis and CD results, the fluorescence bands also had split features at 373, 393, and 414 nm for **4a** and 373, 392, and 414 nm for **4b**. For both stereoisomers, fluorescence quantum yields (Φ_{FL}) were moderate values of 0.36. Each fraction of **4b** also displayed a mirror-imaged CPL band at around 380 nm. The dissymmetry factor for CPL was 7×10^{-4} , being similar to that for the lowest-energy CD band (Table 1). The dissymmetry factors of helicene derivatives and π - π stacking systems tend to be in the order of 10^{-3} and are sometimes larger than 10^{-2} .^{8b-d,18} Therefore, the observed g values were not high, whereas fluorescence quantum yields of 0.36 were attractive because simple helicenes and some of their derivatives suffer from lower yields (<0.10).^{2b}

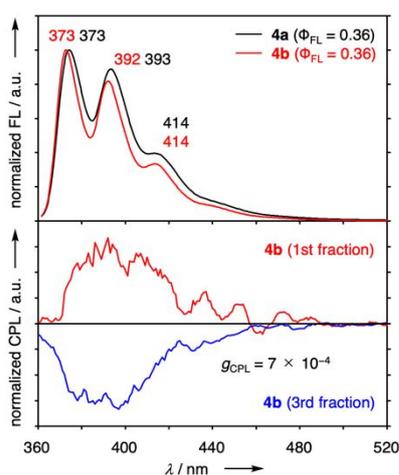


Fig. 3 Fluorescence (FL) spectra of **4a,b** (top, λ_{ex} = 335 nm) and CPL spectra of **4b** (bottom, λ_{ex} = 290 nm) in CHCl₃.

Because the 5-azachrysene units have pyridine-type nitrogen atoms, π -extended propellanes **4a,b** were responsive to an acidic environment. Fig. 4a,b represent the changes of UV/vis absorption and fluorescence spectra of **4b** upon addition of methanesulfonic acid (MSA). The first protonation smoothly occurred with ca. 1 equiv. of MSA and gave new lowest-energy absorption at 401 nm and fluorescence at 480 nm. On the other hand, completion of the second protonation required ca. 20 equiv. of MSA, resulting in two-step spectral changes (Fig. 4c). The stepwise character indicated that the second protonation was less favourable probably because of the charge repulsion and electronic interaction between the two 5-azachrysene segments. In the second step, the new fluorescence band was

high-energy shifted to 447 nm along with the disappearance of original fluorescence at around 380 nm. The blue shift was perhaps ascribed to the loss of charge-transfer character between neutral and protonated 5-azachrysene units. Using the fluorescence intensities at 373, 443, and 490 nm, the acid titration curves of **4b** were fitted as a two-step equilibrium behaviour (Fig. S5-4). The equilibrium constants for the first and second step were determined to be $K_1 = 1.9(2) \times 10^6$ M⁻¹ and $K_2 = 8.6(6) \times 10^4$ M⁻¹, respectively. *C*_s-Symmetric isomer **4a** exhibited similar spectral changes (Fig. S5-2), and the equilibrium constants were $K_1 = 2.1(6) \times 10^6$ M⁻¹ and $K_2 = 4.2(8) \times 10^4$ M⁻¹. Interestingly, the K_1 values of **4a,b** were very similar to each other whereas K_2 of **4b** was almost double of that of **4a**. The difference supported again the larger electronic interaction and charge repulsion between two 5-azachrysene segments in *C*_s-symmetric isomer **4a**.

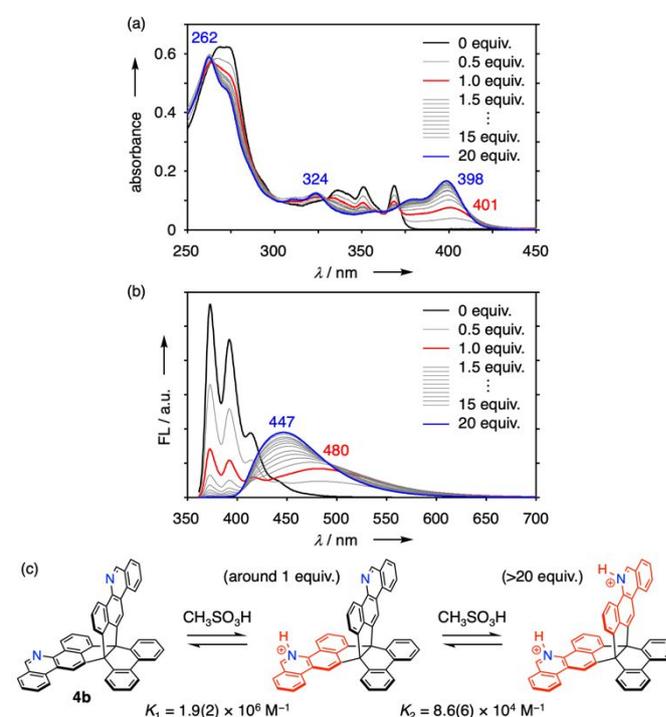


Fig. 4 Changes of (a) UV/vis absorption and (b) fluorescence (FL) spectra (λ_{ex} = 335 nm) of **4b** (6.0×10^{-6} M, 1.0 cm cell) upon addition of varying amount of methanesulfonic acid (MSA, 0–20 equiv.) in CHCl₃. (c) Two-step protonation of (*S,S*)-enantiomer of **4b**.

In summary, π -fused [4.3.3]propellane **3** was constructed from 9,10-phenanthrenequinone and 1-naphthyl Grignard reagents via a two-step procedure in gram scale. Different from tri-naphthalene-fused [3.3.3]propellane,^{14b,15} **3** underwent two-fold bromination selectively at the two naphthalene rings. Further modification provided a set of stereoisomers different in spatial arrangement of 5-azachrysene rings, which were separated on a chiral column. The chiroptical response of chiral isomer **4b** was moderate because of the effective through-space exciton coupling. The pyridine-type nitrogen centres were protonated with MSA to endow both isomers **4a,b** with responsive nature. It is noteworthy that the protonation

processes did not quench fluorescence but gave low-energy bands of UV/vis absorption and fluorescence. Di-functional π -fused [4.3.3]propellanes are potentially useful as 3D building blocks for macrocyclic compounds and linear polymers with free volume and π -electron-derived properties. Therefore, π -fused [4.3.3]propellane derivatives are actively pursued in our group.

K.T. and T.O. supervised and administrated this project. K.K. performed conceptualization. K.K., S.T., and N.S. synthesized and separated the compounds. K.K., S.T., N.S., K.W., M.G., S.F., and S.O. conducted spectroscopic studies and theoretical calculations. K.K., S.T., and N.S. prepared the ESI and K.K. wrote the draft. All authors reviewed and edited the draft and ESI.

There are no conflicts to declare.

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Notes and references

‡ Precisely speaking, compounds are achiral when they possess improper rotation (S_n), including mirror plane (S_1) and inversion centre (S_2).

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