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Synchronized Chiral Induction Between [5]Helicene-Spermine Ligand and B-Z DNA Transition

Kensuke Kawara, Genichiro Tsuji, Yosuke Taniguchi and Shigeki Sasaki*[a]

Dedication ((optional))

Abstract: The 2,13-dimethoxy[5]helicene-spermine ligand **8b** possesses an axial chirality. The racemic **8b** was bound to B-DNA by the accompanying induction of its (*P*)-chirality together with the B-to-Z helicity change of the duplex DNA, $[(dC\text{-}dG)_3]_2$. The (*P*)-chirality of the bound **8b**, in turn, transitioned to the (*M*)-chirality according to the Z-helicity of the DNA. These results have illustrated the chirality synchronization between the DNA and the ligand.

Typical chiral induction systems consist of the combination of a chiral template and an optically flexible molecule. Formation of a chiral molecule can be amplified either by a chiral metal complex or by an organocatalyst.[1,2] Very interesting induction systems have been demonstrated for the helicity of polymers; the helicity of a polymer composed of a chiral unit is switched by light,[3,4] solvent change[5] or pressure changes.[6] The chirality of a non-helical polymer is induced by binding with chiral small molecules[7] or on amorphous silica.[8] Moreover, the chiral-polymer syntheses have been developed by single-handed circularly polarized light.[9] Importantly, the helical polymer may behave as an opposite chiral template depending on the external signal.[10-12] In this context, we became interested in the duplex DNA as a chiral helical polymer.

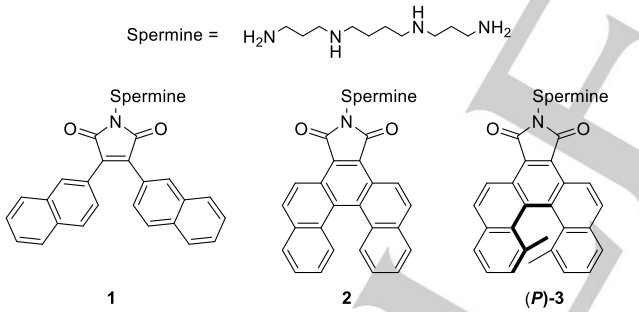

Figure 1. Structures of bis-aryl spermine ligand **1**, [5]helicene ligand **2** and (*P*)-1,14-dimethyl[5]helicene ligand (*P*)-**3**.

The duplex DNA generally adopts right-handed helices under physiological conditions and may change to left-handed helices depending on the sequence and medium conditions (B-Z transition).[13,14] The B-Z transition is supposed to play a role in the gene expression pathway,[15] and is applied to a molecular switch of a nanodevice.[16-22] A variety of ligand has been reported for the B-Z transition,[23-30] the chiral recognition[31-35] and the DNA template-based asymmetric induction.[36-39]

We previously reported that the bisaryl-spermine ligand **1** induced the B-Z transition for the $[(dC\text{-}dG)_3]_2$.[40] It was found that the bisaryl part of **1** was transformed into the [5]helicene **2** *via* the photo-oxidative ring closing reaction. Interestingly, the (*P*)-1,14-dimethyl[5]helicene ligand (*P*)-**3** preferentially binds to B-DNA, whereas its enantiomer (*M*)-**3** shows a higher affinity to Z-DNA.[41] Accordingly, we hypothesized that the chirality of the [5]helicene ligand is induced in a "synchronized" manner with the B- and Z-DNA helicity. A synchronized chiral induction was expected to occur in the following order: (i) the racemic [5]helicene ligand binds to the right-handed B-DNA with induction of the right-handed (*P*)-chirality, (ii) the B-Z transition is induced by further binding of the ligand, and (iii) the chirality of the bound ligand is then changed to the (*M*)-chirality in accord with the B-Z transition (Figure. 2). This synchronized chiral induction system would provide a unique feature in that both the [5]helicene substrate and the DNA template are optically flexible molecules. Allostery is the key process in biological regulation, in which the binding components, such as proteins and nucleic acids, exchange the binding effect with each other.[42] Accordingly, our artificial system would provide a good model for an allosteric system, allowing natural DNA to gain a foothold in asymmetric induction as a ligand-switchable helical polymer.

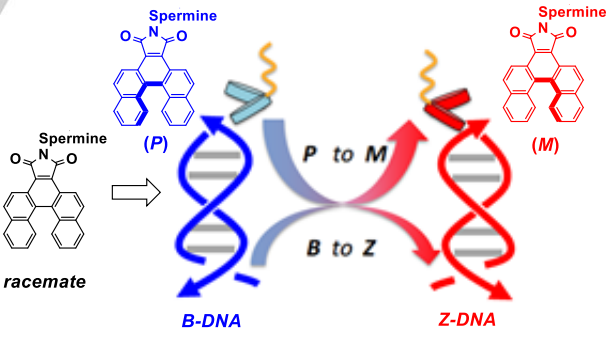

Figure 2. The concept of synchronized chiral induction.

Chiral induction of both the DNA and the [5]helicene ligand is observed by CD measurements. As the CD bands of DNA change in the range of 250-300 nm according to the B-Z transition, the [5]helicene unit was designed to have CD bands at a wavelength longer than 300 nm to avoid overlapping. Among the several synthesized compounds, we adopted the 2,13-dimethoxy-[5]helicene-spermine ligand **8** to check our proposal.

The ligands **8** were synthesized according to a previously described method (Scheme 1). The dibromomaleimide

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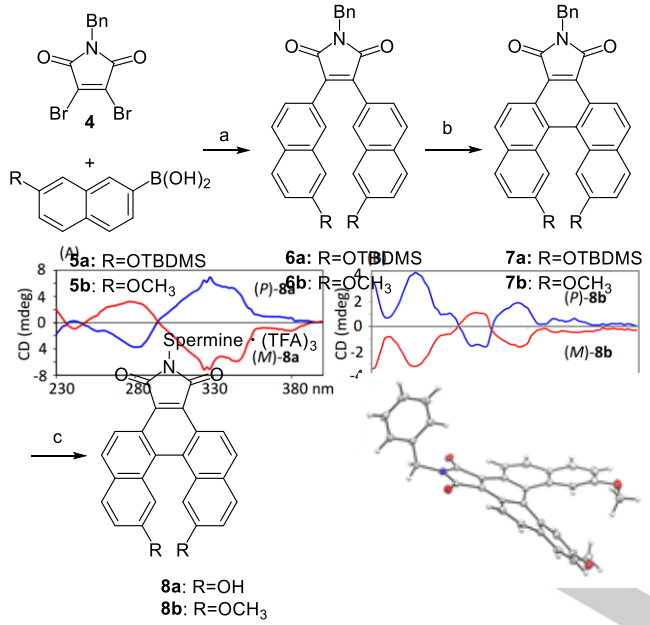
derivatives **4** were coupled with 7-methoxy-2-borate derivatives **5** by the Suzuki-Miyaura cross-coupling reaction to produce the bisaryl derivatives **6**. The [5]helicene compounds **7** were obtained by photocyclization under visible light and oxidation in the presence of iodine. When this photocylization was performed in THF, acetone, or toluene,[43,44] the benzo[a]tetraphene isomer was formed as the major isomer. In contrast, the reaction in methanol produced the [5]helicene derivatives **7** as the predominant isomer in 96% isolated yield. The crystal structure of the 2,13-dimethoxy[5]helicene derivatives **7b** were analyzed by X-ray analysis to show that the methyl groups are in close contact with each other. The [5]helicene derivatives **7** were transformed into the spermine conjugates **8** by a sequence of reactions including hydrolysis of the maleimide, formation of the anhydride, conjugation of the tri-*N*-Boc spermine, and finally, deprotection of the Boc groups.

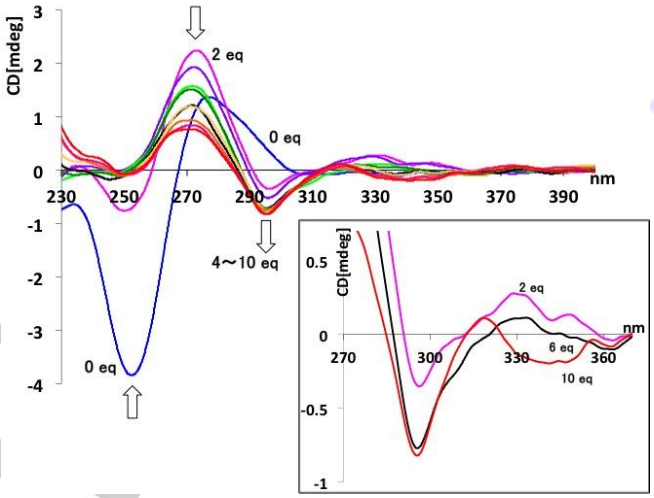


Scheme 1. Synthesis of the 2,13-disubstituted[5]helicene **8** and X ray structure of the [5]helicene skeleton **7b**. a) [1,1-Bis(diphenylphosphino)-ferrocene]dichloropalladium (II), K_3PO_4, 1,4-Dioxane-H_2O, 90 °C, 12 h. b) I_2, THF, MeOH-toluene, r.t., 40 min irradiation. C) (1) 5 M aqueous KOH, 55 °C, 18 h, then 6 M aqueous HCl aq. rt, 1.5 h, 2) TriBoc-spermine, DMF, toluene, at 110°C, 15h. 3) TFA, CH_2Cl_2, rt. 30 min.

Figure 3. A) CD spectra of (*P*)- and (*M*)-**8a**. B) CD spectra of (*P*)- and (*M*)-**8b**. Enantiomers were separated by HPLC equipped with a chiral column, and the separated peaks were transferred to a CD detector.

The enantiomers of the [5]helicene-spermine ligands **8a** and **8b** were separated using an HPLC system equipped with a chiral column and CD detector. The CD spectrum of (*P*)-**8a** shows positive bands at around 325 nm and negative bands at around 280 nm with 296 nm as the changing point. In contrast, the CD of (*P*)-**8b** represents two positive bands at around 340 nm and 280 nm and negative bands at around 320 nm, with two changing points at 327 nm and 306 nm (Figure. 3). The difference in the CD spectra between **8a** and **8b** may arise from the difference in their UV spectra, in which **8b** shows a UV absorbance at a wavelength longer than **8a** (Figure. S4).

Figure 4. CD spectral changes induced by the titration of **8b** into a solution of 20 μM $[(dC\text{-}dG)_3]_2$ in the buffer containing 5 mM sodium cacodylate, 100 mM NaCl at pH 7.0 and 25°C. The arrows represent the direction of the changes by the addition of the ligand **8b**. The inset shows the expanded CD spectra after smoothing the raw data.



To evaluate the B-Z transition by the ligand, The CD spectrum was measured using 20 μM $[(dC\text{-}dG)_3]_2$ as the B-DNA in 5 mM sodium cacodylate buffer containing 100 mM NaCl at 25 °C and pH 7.0. (Figure. 4. Arrows represent the direction of the changes). The CD of $[(dC\text{-}dG)_3]_2$ alone indicated a positive band at 278 nm and a negative band at 250 nm, representing a typical right-handed B-DNA. By the addition of *rac.***8b,** the negative bands at 250 nm decreased and the positive bands at 278 nm shifted to a shorter wavelength, and the negative bands at 295 nm appeared. The negative bands at 295 nm are suggestive of the B-Z transition, because **8b** has a small induced CD band around 300 nm. In contrast, **8a** did not induce the B-Z transition, meaning that the methyl groups of **8b** are important for induction of the Z-DNA due to the hydrophobicity. The inset in Figure. 4 shows the selected CD spectra in the range of 270-370 nm observed by the addition of 2, 6 and 10 equivalences of **8b**. Noteworthy, the positive bands around 340 nm appeared by the low equivalences of **8b** in the complexes with B-DNA, and the further addition of **8b** induced the negative bands around 340 nm. These induced CD bands suggest a chirality change from (*P*)- to (*M*)-**8b**. These spectra are slightly different from the CD spectra shown in Figure. 3B.

The UV absorbance of **8b** at 320 nm decreased to 16% with the accompanying red-shifts by the DNA binding (Figure S6, A), which are suggestive of the stacking interactions between the [5]helicene part of the ligand and the base pair at the terminal of the B-DNA or Z-DNA duplex. This hypochromism might affect

the induced CD spectra in this region. To clarify the relationship between the binding stoichiometry and the chiral induction, the CD changes at 295 nm and 340 nm are plotted versus the added equivalence of the ligand to DNA. The former changes indicate the B-Z transition (Figure. 5A) and the latter changes imply that the positive values are due to the (*P*)-chirality and the negative ones are the (*M*)-chirality of the ligand (Figure. 5B). Figure. 5A indicates that the B-Z transition is complete by the addition of 4 equivalences of **8b**. Figure. 5B shows a remarkable contrast; the positive bands initially increased, then the negative bands increased in intensity by the addition of more than 3 equivalences of **8b**. In the UV-titration experiments when B-DNA was added to a solution of **8b**, the UV absorbance of **8b** decreased until the **8b**:B-DNA=1:1 (Figure. S6, B). Accordingly, these results have clearly indicated that the (*P*)-chirality of **8b** is initially induced by binding with B-DNA, and that further binding of **8b** induced the B-Z transition, then the (*M*)-chirality of **8b** is induced by the influence of the Z-DNA. The further bound ligand may bind around the DNA and contribute to dehydration of the DNA.

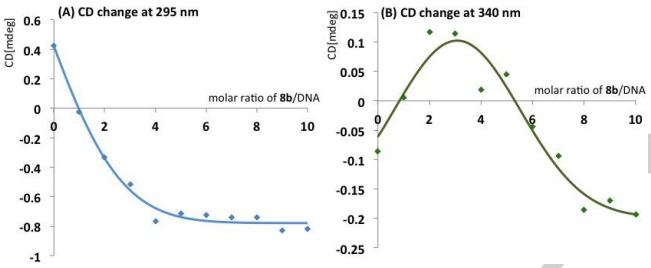


Figure 5. Plot of CD band intensity versus ligand **8b** equivalence to DNA [(dC-dG)$_3$]$_2$. (A) Plot of CD values at 295 nm, an indication of Z-DNA. (B) Plot of CD values at 295 nm, indicating (*P*)- to (*M*)-chirality shift.

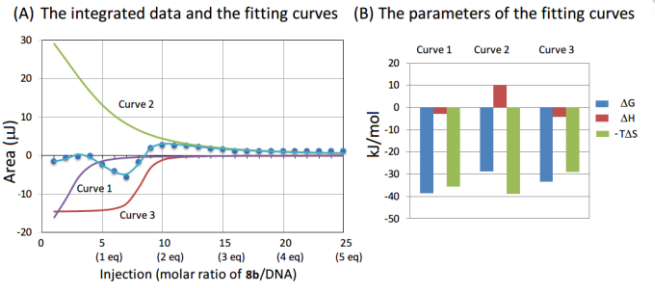


Figure 6. (A) The integrated data and the fitting curves. (B) The thermodynamic data of the fitting curves. A solution of **8b** was added to a solution of 17.8 μM [(dC-dG)$_3$]$_2$ in the buffer containing 5 mM Na cacodylate and 100 mM NaCl at pH 7.0 and 20 °C. The concentration of **8b** was increased by 3.56 μM (0.2 equivalences to DNA) after each addition.

To obtain further insight into the relationship between the ligand binding, chirality change and the B-Z transition, the thermodynamic parameters were obtained by isothermal calorimetric titration (ITC). The solution of **8b** was added to a solution containing [(dC-dG)$_3$]$_2$. The observed heat areas were well fitted with the simulated curve method using three independent fitting curves, which include one endothermic and two exothermic processes (Figure. 6A). These processes were interpreted and compared to the CD titration data in Figure. 5. Curve 1 may represent the first binding step with an approximate ligand:DNA=1:1 ratio. Curve 2 continued until the addition of 2 equivalences of **8b**, which is different from the CD change at 295 nm due to the B-Z transition (Figure. 5A). In our previous study, an endothermic process associated with the ligand binding to B-DNA was assigned to an *intermediate*-DNA conformation prior to the transit to the Z-DNA. In a similar sense, curve 2 may imply the formation of the *intermediate*-DNA associated with the **8b** binding. The change in curve 3 was completed before the addition of 2 equivalences of **8b**. In the meantime, the (*P*)-chirality induction of **8b** reached a maximum at around 2 equivalences (Figure. 5B). Curve 3 arose after the end of curve 1, indicating that the second binding of **8b** takes place with the *intermediate*-DNA. As the CD change at 295 nm reached a plateau by the addition of more than 4 equivalences of the **8b** (Figure. 5A), excess binding of **8b** is needed for the full transition to the Z-DNA from an *intermediate*-DNA. Interestingly, the (*M*)-chirality induction took place by excess ligand binding after a full transition to the Z-DNA. Based on the CD and ITC experiments, binding phenomena are interpreted as follows. Curve 1 indicates a process of 1:1 ligand:DNA binding, probably at the end of the duplex. The initial 1:1 binding induces the conformational change of B-DNA to an *intermediate*-DNA, which is reflected in curve 2. The second binding of **8b** occurs with the *intermediate*-DNA, which is shown by curve 3. During the binding to the B-DNA duplex, the (*P*)-chirality of **8b** is induced. No thermodynamic behavior was observed for more than 2 equivalences of **8b** by the ITC experiments, although the full B-Z transition of the DNA was achieved at about 4 equivalences of **8b** (Figure. 5A). As the ITC method is applicable for the rapid reaction, the transition from the *intermediate*-DNA to the Z-DNA is too slow to be detected by ITC analysis. After the B-DNA was fully transformed into the Z-DNA, the induction of the (*M*)-chirality of **8b** increased depending on the amount of **8b** (Figure. 5B). Similar to preferences of (*P*)-**3** for the B-DNA and that of (*M*)-**3** for the Z-DNA, it is conceivable that (*P*)-**8b** preferentially binds the B-DNA and (*M*)-**8b** binds the Z-DNA.

Attempts for isolation of **8b** from the DNA complex to directly determine the (*P*)- or (*M*)-chirality were unsuccessful. It is of particular interest that (*P*)- and (*M*)-**8b**, which were isolated by a chiral column, and racemized at different rates depending on the concentrations and the B- or Z-chirality of the bound DNA. (*P*)-**8b** more rapidly racemized in the presence of the B-DNA than the absence or in the presence of the Z-DNA (Figure. 7A, red marks). On the other hand, the racemization rates of (*M*)-**8b** in the presence of either the B-DNA or Z-DNA were almost the same, although they were faster than that in the absence of DNA (Figure. 7A, blue marks). Figure. 7B shows that the CD intensity of (*P*)- and (*M*)-**8b** did not significantly change at their high concentrations.

Figure 7. Racemization rates of (*P*)- and (*M*)-**8b** in the presence or the absence of 10 μM of DNA. (A) 5 μM **8b**, (B) 40 μM **8b** in the buffer containing 1 mM Na cacodylate and 100 mM NaCl at pH 7.0 and 25°C.

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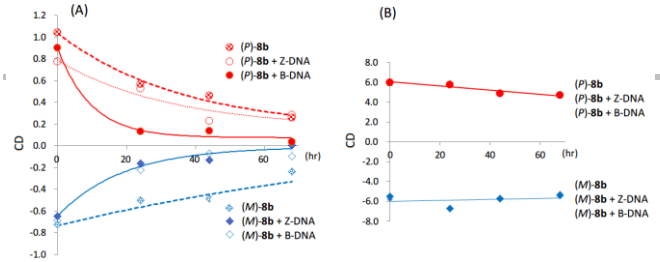

It was shown in our previous study that the (*P*)- or (*M*)-[5]helicene ligand was preferentially bound to the B- or Z-DNA, respectively. Figure. 7 suggests that **8b** rapidly racemizes only in the complex with the DNA and that the ligand with the preferable chirality for the corresponding B- or Z-DNA would become relatively dominant. Most probably, the orientation of the methoxy groups, which should be a major racemization barrier of **8b** as shown in the X-ray structure (Scheme 1), may be aligned in a different direction in the complex with the DNA, resulting in a decreased racemization barrier. Accordingly, the chirality induction observed in the CD changes shown in Figure. 4 can be interpreted as the result of the chiral induction of part of the ligand bound to the DNA.

In conclusion, we have successfully demonstrated a synchronized chiral induction system using the 2,13-dimethoxy [5]helicene-spermine ligand **8b** and the template DNA duplex. This synchronized chiral induction system provides a unique feature in that the chirality of both the ligand and template is mutually induced by their binding, and would draw attention to the natural DNA as a ligand-switchable helical polymer.

Experimental Section

tert-Butyldimethyl((7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-yl)oxy)silane (**5a**)

tert-Butyldimethylsilyl chloride (2.19 g, 14.5 mmol), imidazole (1.97 g, 28.9 mmol), and *N,N*-dimethyl-4-aminopyridine (60.2 mg, 0.48 mmol) were added to a solution of 7-bromo-2-naphthol (2.2 g, 9.86 mmol) in DMF (40 mL), then the mixture was stirred at room temperature for 30 min. The reaction mixture was diluted and extracted with AcOEt. The organic layers were washed with brine and dried over Na_2SO_4, then evaporated. The residue was chromatographed (silica gel, *n*-hexane:AcOEt = 20:1) to give the TBDMS-protected 7-bromo-2-naphthol (3.32 g, 99 %) as a white powder. ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm, 7.84 (1H, s), 7.67 (1H, d, *J*=8.6 Hz), 7.60 (1H, d, *J*=8.9 Hz), 7.39 (1H, d, *J*=8.9 Hz), 7.08 (1H, s), 7.05 (1H, d, *J*=9.2 Hz), 1.01 (9H, s), 0.24 (6H, s); IR (cm^{-1}) 2955, 2929, 1625; ESI-MS (m/z) 338.36 ([M+H]$^+$). This compound (888.4 mg, 2.63 mmol), bis(pinacolato)diboron (1.00 g, 3.95 mmol) and [1,1′-bis (diphenylphosphino)ferrocene]dichloro-palladium(II) (107.8 mg, 0.132 mmol) and KOAc (907.3 mg, 9.21 mmol) were dissolved in degassed 1,4-dioxane (26.3 mL). The mixture was stirred at 80 °C for 12 h. The reaction mixture was diluted with AcOEt and filtered using celite, then saturated aqueous NH_4Cl was added to the filtrate and extracted with AcOEt. The organic layers were washed with water, brine, and dried over Na_2SO_4, then evaporated. The residue was chromatographed (silica gel, *n*-hexane:AcOEt = gradient 100:1 to 50:1) to give **5a** (861.3 g, 85 %) as a white powder. ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm, 8.21 (1H, s), 7.66-7.41 (3H, m), 7.22 (1H, d, *J*=2.1 Hz), 7.09 (1H, dd, *J*=2.4 Hz, 8.6 Hz), 1.37 (12H, s), 1.00 (9H, s), 0.22 (6H, s); ^{13}C-NMR (500 MHz, ($CDCl_3$) δ ppm, 153.50, 153.13, 134.06, 130.98, 129.23, 128.50, 126.84, 123.45, 115.56, 84.01, 25.87, 25.15, 25.05, -4.23; IR (cm^{-1}) 2977, 1602, 1510, 1460, 1380, 1126; ESI-HRMS (m/z) Calcd. for 385.2369 ([M+H]$^+$), Found 385.2391.

2-(7-Methoxynaphthalen-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**5b**)

CH_3I (2.1 mL, 33.7 mmol) was added to a solution of 7-bromo-2-naphthol (1 g, 4.48 mmol) and K_2CO_3 (2.22 g, 13.4 mmol) in DMF (300 mL), then the mixture was stirred at room temperature for 3 h. The reaction was quenched with saturated aqueous NH_4Cl and extracted with AcOEt. The organic layers were washed with brine and dried over Na_2SO_4, then evaporated. The residue was chromatographed (silica gel, *n*-hexane only) to give 2-bromo-7-methoxy naphthalene (1.01 g, 95 %) as a white powder. ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm, 7.88 (1H, d, *J*=1.5 Hz), 7.67 (1H, d, *J*=9.2 Hz), 7.60 (1H, d, *J*=8.9 Hz), 7.38 (1H, dd, *J*=1.8 Hz, 8.5 Hz), 7.13 (1H, dd, *J*=2.4 Hz, 8.9 Hz), 7.01 (1H, d, *J*=2.4 Hz), 3.90 (3H, s); IR (cm^{-1}) 1623; ESI-MS (m/z) 236.04 ([M+H]$^+$). This compound (81.3 mg, 0.343 mmol), bis(pinacolato)diboron (130.8 mg, 0.515 mmol) and [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (33.6 mg, 0.0412 mmol) and KOAc (117.8 mg, 1.20 mmol) were dissolved in degassed 1,4-dioxane (3.4 mL). The mixture was stirred at 90 °C for 15 h. The reaction mixture was diluted with AcOEt and filtered using celite, then saturated aqueous NH_4Cl was added to the filtrate and extracted with AcOEt. The organic layers were washed with water, brine, and dried over Na_2SO_4, then evaporated. The residue was chromatographed (silica gel, *n*-hexane:AcOEt = gradient 50:1 to 20:1) to give **5b** (83.0 mg, 85 %) as a pale brown powder. ^{1}H-NMR (500 MHz, $CDCl_3$) δ ppm, 8.29 (1H, s), 7.77-7.71 (3H, m), 7.20-7.17 (2H, m), 3.91 (3H, s), 1.38 (12H, s); ^{13}C-NMR (500 MHz, $CDCl_3$) δ ppm, 157.60, 135.16, 134.03, 130.75, 129.31, 128.44, 126.88, 119.94, 106.52, 84.00, 55.38, 25.06; IR (cm^{-1}) 2978, 1605, 1463; ESI-HRMS (m/z) Calcd. for 285.1660 ([M+H]$^+$), Found 285.1640.

Bisnaphthol-benzylmaleimide intermediate (**6a**)

1-Benzyl-3,4-dibromopyrrole-2,5-dione **4** (8.6 mg, 0.0248 mmol), **5a** (20.0 g, 0.0520 mmol) and bis(triphenylphosphine)palladium(II)dichloride (5.2 mg, 0.00744 mmol), benzyltriethylammonium chloride (2.8 mg, 0.0124 mmol) and Cs_2CO_3 (40.4 mg, 0.124 mmol) were dissolved in degassed toluene (1.5 mL) and H_2O (0.5 mL). The mixture was stirred at 85 °C for 4 h. The reaction mixture was diluted with AcOEt and filtered using celite, then saturated aqueous NH_4Cl was added to the filtrate and extracted with AcOEt. The combined organic layers were dried over Na_2SO_4, evaporated. The residue was chromatographed (silica gel, *n*-hexane:AcOEt = gradient 50:1 to 20:1) to give **6a** (13.6 mg, 78%) as a yellow amorphous form. ^{1}H-NMR (500 MHz, $CDCl_3$) δ ppm, 8.08 (2H, s), 7.65 (2H, d, *J*=8.9 Hz), 7.57 (2H, d, *J*=8.5 Hz), 7.48 (2H, d, *J*=8.5 Hz), 7.27-7.36 (5H, m), 7.18 (2H, s), 7.09 (2H, d, *J*=8.9 Hz), 4.85 (2H, s), 1.00 (18H, s), 0.22 (12H, s); ^{13}C-NMR (500 MHz, $(CD_3)_2CO$) δ ppm, 171.23, 154.98, 138.10, 137.22, 135.32, 130.39, 130.32, 130.26, 129.48, 128.90, 128.44, 128.42, 127.87, 125.53, 124.31, 116.47, 42.49, 26.07, 18.85, -4.25; IR (cm^{-1}) 1705; ESI-HRMS (m/z) Calcd. for 700.3278 ([M+H]$^+$), 722.3098 ([M+Na]$^+$), Found 700.3259, 722.3091.

2,13-Dihydroxy[5]helicene-bemzylmaleimide intermediate (**7a**)

Compound **6a** (650 mg, 0.931 mmol) was added to MeOH (300 mL) and any insoluble residue was filtered off. Iodine (87.7 mg, 0.380 mmol) and THF (3 mL) were added to this saturated MeOH solution and mixture was stirred under irradiation by a high-pressure mercury lamp (500 W) at room temperature for 5 h. The reaction mixture was quenched with 20 % aqueous $Na_2S_2O_3$ and extracted with AcOEt. The organic layers were washed with water, brine and dried over Na_2SO_4, then evaporated. This procedure was repeated twice. The collected residue was chromatographed (silica gel, *n*-hexane:AcOEt = gradient 15:1 to 9:1) to give the TBDMS-protected [5]helicene intermediate (464 mg, 71 %) as a yellow amorphous form. ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm, 8.89 (2H, d, *J*=8.9 Hz), 7.96 (2H, d, *J*=8.9 Hz), 7.81 (2H, d, *J*=8.9 Hz), 7.71 (2H, d,

J=2.4 Hz), 7.48 (2H, d, *J*=7.0 Hz), 7.31-7.25 (3H, m), 7.09 (2H, dd, *J*=2.4, 6.4 Hz), 4.93 (2H, s). 0.83 (18H, s), -0.05, (6H, s), -0.09 (6H, s); IR (cm^{-1}) 1704. This protected intermediate (309 mg, 0.440 mmol) was treated with TBAF (1.5 mL, 1.32 mmol) in a THF (5 mL) solution at room temperature for 1.5 h. Saturated aqueous NH_4Cl was added to the reaction mixture and extracted with AcOEt. The organic layers were washed with water and brine, dried over Na_2SO_4, then evaporated. The residue was chromatographed (silica gel, *n*-hexane:AcOEt = 2:1) to give the TBDMS-deprotected **7a** (199 mg, 97 %) as a yellow amorphous form. ^{1}H-NMR (400 MHz, $(CD_3)_2CO$) δ□ppm, 8.82 (2H, d, *J*=8.5 Hz), 8.05 (2H, d, *J*=8.9 Hz), 7.95 (2H, d, *J*=8.9 Hz), 7.80 (2H, d, *J*=2.4 Hz), 7.47 (2H, d, *J*=7.6 Hz), 7.33 (2H, d, *J*=7.3 Hz), 7.22-7.26 (3H, m), 4.92 (2H, s); ^{13}C-NMR (500 MHz, $(CD_3)_2CO$) δ□ppm, 169.98, 132.61, 131.44, 130.76, 130.50, 129.39, 128.66, 128.46, 128.46, 128.24, 127.57, 127.13, 120.09, 118.86, 117.58, 113.70, 41.87; IR (cm^{-1}) 1735; ESI-MS (m/z) 468.30 ($[M-H]^-$) ESI-HRMS (m/z) Calcd. for 469.1236 ($[M-H]^-$), Found 469.1243.

2,13-Dihydroxy[5]helicene-Spermine ligand (**8a**)

Five M aqueous KOH (8 mL) was added to a solution of **7a** (193 mg, 0.411mmol) in ethanol (5 mL) and the mixture was stirred at 50 °C for 15 h, then the mixture was acidified to pH1 with 10 % aqueous HCl. After 1.5 h, the precipitates were collected and washed with water, then dried under vacuum to give the corresponding anhydrous material as a dark yellow amorphous form. This material was used for the next reaction without further purification. A mixture of this anhydrous material (162 mg, 0.432 mmol) and tri-Boc spermine (256 mg, 0527 mmol) in toluene-DMF was heated at 90 °C for 24 h. The reaction mixture was diluted and extracted with AcOEt. The organic layers were washed with brine and dried over Na_2SO_4, then evaporated. The residue was chromatographed (silica gel, *n*-hexane:AcOEt = 2:1) to give the tri-Boc-spermine-2,13-dihydrioxy[5]helicene conjugate (185 mg, 50 % in 2 steps) as an orange amorphous form. ^{1}H-NMR (400 MHz, $(CD_3)_2CO$) δ ppm, 8.67 (2H, d, *J*=8.9 Hz), 7.88 (2H, d, *J*=8.9 Hz), 7.82 (2H, d, *J*=8.6 Hz), 7.63 (2H, d, *J*=2.1 Hz), 7.12 (2H, dd, *J*=8.5 Hz), 3.70 (2H, t, *J*=6.9 Hz), 3.24-3.14 (8H, m), 2.98-2.95 (2H, m), 1.97 (2H, quint., *J*=7.0 Hz), 1.65-1.56 (2H, m), 1.48-1.42 (4H, m), 1.39 (9H, s), 1.36 (18H, s); IR (cm^{-1}) 3314, 1757, 1697, 1618; ESI-MS (m/z) 866.59 ($[M+H]^+$). This material (24.6 mg, 0.0280 mmol) was treated with 25 % TFA in CH_2Cl_2 (3 mL) at room temperature for 15 min. TFA was removed by NH-silica and the target material was eluted with a $CHCl_3$: MeOH= 5:1 solution. The obtained crude material was purified by HPLC (Nacalai Tesque COSMOSIL $5C_{18}$-AR-II) (Figure S3) to give the 2,13-hydroxy[5]helicene-spermine ligand **8a** (7.53 mg as tri-acetate, 36 %) as a yellow solid. ^{1}H-NMR (500 MHz, CD_3OD) δ ppm, 9.39 (2H, d, *J*=8.5 Hz), 8.83 (2H, d, *J*=8.5 Hz), 8.43 (2H, d, *J*=8.9 Hz), 7.93 (2H, d, *J*=8.6 Hz), 3.97 (2H, t, *J*=6.7 Hz), 3.30-3.02 (10H, m), 2.69 (2H, s), 2.20 (2H, t, *J*=7.9 Hz), 2.06 (2H, t, *J*=7.9 Hz), 1.80 (4H, m); ^{13}C-NMR (500 MHz, $(CD_3)_2SO$) δ ppm, 169.25, 155.59, 131.40, 129.85, 129.71, 126.65, 126.03, 125.69, 119.65, 117.09, 112.49, 48.39, 48.13, 46.23, 45.90, 37.84, 35.71, 27.60, 26.41, 26.10, 22.76; IR (cm^{-1}) 1680; ESI-HRMS (m/z) Calcd. for 563.3129 ($[M+H]^+$), Found 563.3162. The concentration of a stock solution of the ligand was determined by an NMR integration value using maleic acid as the internal standard.

Bismethoxynaphthalene-benzylmaleimide intermediate (**6b**)

1-Benzyl-3,4-dibromopyrrole-2,5-dione **4** (511 mg, 1.48 mmol), **5b** (1.05 g, 3.69 mmol) and [1,1′-bis(diphenylphosphino)ferrocene]dichloro-palladium(II) (400 mg, 0.490 mmol) and K_3PO_4 (1.57 g, 7.40 mmol) were dissolved in degassed 1,4-dioxane (12.9 mL) and H_2O (2.1 mL). The mixture was stirred at 90 °C for 12 h. The reaction mixture was diluted with AcOEt and filtered using celite, then saturated aqueous NH_4Cl was added to the filtrate and extracted with AcOEt. The organic layers were dried over Na_2SO_4, then evaporated. The residue was chromatographed (silica gel, *n*-hexane:AcOEt = gradient 50:1 to 20:1) to give **6b** (435 mg, 59 %) as a yellow amorphous form. ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm, 8.10 (2H, s), 7.67 (2H, d, *J*=8.9 Hz), 7.60 (2H, d, *J*=8.5 Hz), 7.51-7.49 (2H, m), 7.35-7.27 (3H, m), 7.22 (2H, dd, *J*=1.5 Hz, 8.5 Hz), 7.17 (2H, dd, *J*=2.4 Hz, 8.9 Hz), 7.11 (2H, d, *J*=2.4 Hz), 4.85 (2H, s), 3.88 (6H, s); ^{13}C-NMR (500 MHz, $CDCl_3$) δ ppm, 170.80, 158.18, 136.66, 136.10, 135.16, 134.42, 129.61, 129.35, 129.28, 129.01, 128.87, 127.90, 126.80, 124.44, 120.52, 106.80, 55.51, 25.06; IR (cm^{-1}) 2921, 1702, 1217; ESI-HRMS (m/z) Calcd. for 500.1856 ($[M+H]^+$), Found 500.1894.

2,13-Dimethoxy[5]helicene-bemzylmaleimide intermediate (**7b**)

A solution of **6b** (5.3 mg, 0.0106mmol), iodine (3.0 mg, 0.0117 mmol) and THF (100 µL) in toluene (2.6 mL) and MeOH (2.6 mL) was stirred under irradiation of by a high-pressure mercury lamp (500 W) at room temperature for 40 min. The reaction mixture was quenched with 20 % aqueous $Na_2S_2O_3$ and extracted with AcOEt. The organic layers were washed with water, brine and dried over Na_2SO_4, then evaporated. The residue was chromatographed (silica gel, *n*-Hexane:AcOEt = 50:1) to give **7b** (5.1 mg, 96 %) as a yellow amorphous form. ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm, 8.97 (2H, d, *J*=8.9 Hz), 7.99 (2H, d, *J*=8.9 Hz), 7.87 (2H, d, *J*=8.9 Hz), 7.66 (2H, s), 7.50 (2H, d, *J*=7.0 Hz), 7.32-7.20 (5H, m), 4.94 (2H, s), 3.48 (6H, s); ^{13}C-NMR (500 MHz, $CDCl_3$) δ ppm, 169.58, 157.00, 136.90, 131.16, 130.90, 129.93, 129.58, 128.86, 128.68, 128.50, 127.90, 127.05, 126.58, 119.68, 119.57, 110.44, 68.13, 55.10; IR (cm^{-1}) 2921, 1702, 1390, 1261; ESI-HRMS (m/z) Calcd. for 498.1700 ($[M+H]^+$), Found 498.1708.

2,13-Dimethoxy[5]helicene-Spermine ligand (**8b**)

Five M aqueous KOH (124 mL) was added to a solution of **7b** (125 mg, 0.252 mmol) in THF (125 mL) stirred at 60 °C for 17 h, then the mixture was acidified to pH 1 with 6 M aqueous HCl. After 1.5 h, Et_2O was added to the reaction mixture and extracted with Et_2O. The organic layers were washed with water, brine and dried over Na_2SO_4, then evaporated to give the corresponding anhydrous material as orange amorphous form. This material was used for the next reaction without further purification. A mixture of this anhydrous material and tri-Boc spermine (152 mg, 0.302 mmol) in toluene-DMF was heated at 110 °C for 13 h. The reaction mixture was diluted with AcOEt and extracted with AcOEt. The organic layers were washed with brine and dried over Na_2SO_4, then evaporated. The residue was chromatographed (silica gel, *n*-hexane:AcOEt = gradient 10:1 to 3:1) to give the Tri-Boc-spermine-2,13-dimethoxy [5]helicene conjugate (199 mg, 88% in 2 steps) as a yellow amorphous form. ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm, 8.97 (2H, d, *J*=8.9 Hz), 8.01 (2H, d, *J*=8.9 Hz), 7.88 (2H, d, *J*=8.5 Hz), 7.68 (2H, s), 7.22-7.20 (2H, m), 3.49 (6H, s), 3.78 (2H, t, *J*=7.0 Hz), 3.26-3.04 (10H, m), 2.61 (1H, s), 2.08-1.96 (2H, m), 1.24 (27H, s), 0.99-0.78 (6H, m); IR (cm^{-1}) 2932, 1695 1368, 1171; ESI-MS (m/z) 893.42 ($[M+H]^+$). This material (25 mg, 0.0280 mmol) was treated with 25 % TFA in CH_2Cl_2 (4 mL) at room temperature for 30 min. The crude material was purified by HPLC (Nacalai Tesque COSMOSIL $5C_{18}$-AR-II) (Figure S3) to give the 2,13-dimethoxy[5]helicene-spermine ligand **8b** (22.3 mg as tri-trifluoroacetate, 85 %) as a yellow solids. ^{1}H-NMR (400 MHz, CD_3OD) δ ppm, 8.91 (2H, d *J*=8.9 Hz), 8.08 (2H, d, *J*=8.2 Hz), 7.99 (2H, d, *J*=8.9 Hz), 7.65 (2H, s), 7.29 (2H, d, *J*=9.5 Hz), 3.96-3.90 (2H, m), 3.50 (6H, s), 3.15-2.98 (10H, m), 2.21-2.12 (2H, m), 2.11-2.02 (2H, m), 1.87-1.74 (4H, m); ^{13}C-NMR (500 MHz, $(CD_3)_2SO$) δ ppm, 169.32, 158.16, 156.68, 130.45, 130.26, 129.83, 129.71, 127.87, 126.23, 119.27, 118.43, 110.11, 54.68, 46.14, 44.63, 43.90, 36.21, 34.87, 25.09, 23.79, 22.74, 22.67; IR (cm^{-1}) 1679, 1207, 1136; ESI-HRMS (m/z) Calcd. for 593.3122 ($[M+H]^+$), Found 593.3131. The concentration of a stock solution of the ligand was determined by an NMR integration value using maleic acid as the internal standard.

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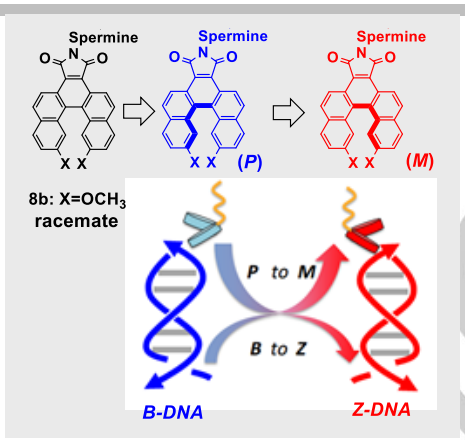
The 2,13-dimethoxy[5]helicene-spermine ligand **8b** possesses an axial chirality. The racemic **8b** was bound to the B-DNA with accompanying induction of its (*P*)-chirality together with the B-to-Z helicity change of the duplex DNA, $[(dC\text{-}dG)_3]_2$. The (*P*)-chirality of the bound **8b**, in turn, transitioned to the (*M*)-chirality according to the Z-helicity of DNA. These results have illustrated the chirality synchronization between the DNA and ligand.



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Synchronized Chiral Induction Between [5]Helicene-Ligand and B-Z DNA Transition