Supporting Information

Modular Quadruplex-Duplex Hybrids as Biomolecular Scaffolds for Asymmetric Michael Addition Reactions

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Materials

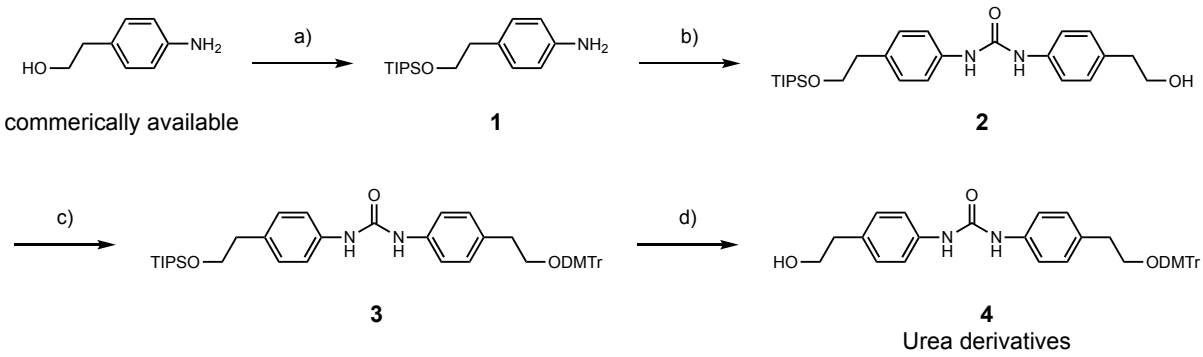
N,N-Dimethylformamide dimethyl acetal, potassium phthalimide, 4,4'-dimethoxytrityl chloride, triethylamine, *N,N*-dimethyl-4-aminopyridine, 3-chloro-1-propanol, 3-amino-1-propanol were received from Wako Chemicals and used without further purification. 2-cyanoethyl *N,N*-diisopropylchloro phosphoramidite, hydrazine monohydrate, 2,2'-bipyridine-5,5'-dicarboxylic acid, 4-amino-1-butanol were purchased from Sigma-Aldrich Chemicals Co. and used as received. *N,N*-Diisopropylethylamine was purchased from Nacalai and used as received. 6-Amino-1-hexanol, 6-chloro-1-hexanol were obtained from TCI. Glen-Pak™ DNA and RNA cartridges columns are purchased at Glen research and used. All other chemicals and solvents were purchased from Sigma-Aldrich Chemicals Co., Wako Pure Chemical Ind. Ltd., TCI, or Kanto Chemical Co. Inc. and used without further purification and synthetic oligonucleotides were obtained from Sigma Genosys. Water was deionized (specific resistance of > 18.0 MW cm at 25^{o}C) by a Milli-Q system (Millipore Corp.).

Methods and Equipment

NMR spectra were obtained on a JEOL JNM ECA-600 spectrometer operating at 600 MHz for ^{1}H NMR and 150 MHz for ^{13}C NMR in $CDCl_3$ unless otherwise noted. Flash column chromatography was performed employing Silica Gel 60 (70–230 mesh, Merck Chemicals). Silica-gel preparative thin-layer chromatography (PTLC) was performed using plates from Silica gel 70 PF_{254} (Wako Pure Chemical Ind. Ltd.). Enantiomeric excess (*ee*) determinations were performed by HPLC analysis (Chiralcel AD-H) using UV-detection. DNA concentrations were measured by Nanodrop ND-1000 spectrophotometer. Rotary mixing of reaction suspension was performed by Intelli-Mixer RM-2 (Elmi).

Synthetic routes for intrastrand bipyridine ligands and non-binding steric moieties

Synthesis of bi-linker conjugated bipyridine ligand derivatives (**^{n}X**, n=3, 4, 6) and biphenyl moieties (**P**) were followed by previous reported papers[1-3]



Scheme S1. Synthesis urea analogue (**U**). Reagents and conditions: (a) 1.0 equiv. of Triisopropylsilyl chloride (TCI, d. 0.901 g/mL), 1.0 equiv. of Imidazole (Sigma Aldrich), DMF, rt, 12 h, 90% yield (ref. Diethylenetriamine-Mediated Direct Cleavage of Unactivated Carbamates and Ureas); (b) 0.53 equiv. of Triphosgene (Sigma Aldrich), 1.5 equiv. of 2-(4-Aminophenyl)ethanol (TCI), 2.4 equiv. of Triethylamine (Nacalai tesque, d. 0.750 g/mL), toluene, rt, 24 h, 90% yield. The reaction mixture was concentrated under reduced pressure. Purify the crude product by silica gel column chromatography (ethyl acetate/hexane = 1:2 to 1:1, v/v) to give of product **2**.; (c) 1.0 equiv. of 4,4'-Dimethoxytrityl Chloride (Wako), 1.5 equiv. of Triethylamine (Nacalai tesque, d. 0.750 g/mL), DCM, rt, 12 h, 60% yield. After adding mQ to reaction mixture, washed with brine, dried over with Na_2SO_4, filtered, and concentrated under reduced pressure. Purify the crude product by silica gel column chromatography (ethyl acetate/hexane = 1:5 to 1:3, v/v) to give of product **3**.; (d) 2.0 equiv. of Tetrabutylammonium fluoride solution 1.0 M in THF (TCI), THF, 0 ^{o}C to rt, 3 h, 60% yield. The reaction mixture was concentrated under reduced pressure and diluted with ethyl acetate, washed with aq. $NaHCO_3$ and aq. NH_4Cl, dried over with $MgSO_4$, filtered, and concentrated. Purify the crude product by silica gel column chromatography (ethyl acetate/hexane = 1:3 to ethyl acetate only, v/v) to give of product **4**.

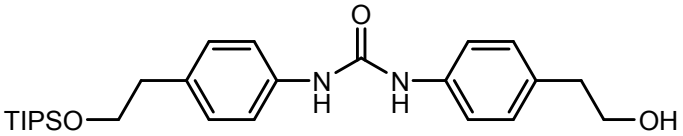


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Figure S1. 1-(4-{2-hydroxyethyl}-phenyl))-3-(4-{2-([triisopropylsilyl]-oxyethyl}-phenyl)-urea

^{1}H NMR ($CDCl_3$): δ 7.49 (d, J_{HH} = 9.5 Hz, 1H), 7.41 (d, J_{HH} = 8.1 Hz, 1H), 7.19 (d, J_{HH} = 8.1 Hz, 2H), 7.09 (quart, J_{HH} = 4.1 Hz, 4H), 6.98 (d, J_{HH} = 8.2 Hz, 2H), 3.82 (t, J_{HH} = 7.1 Hz, 2H), 3.70 (t, J_{HH} = 6.9 Hz, 2H), 2.77 (t, J_{HH} = 6.9 Hz, 2H), 2.68 (t, J_{HH} = 5.9 Hz, 2H), 1.09-1.02 (m, 21H). ^{13}C NMR ($CDCl_3$): δ 154.5, 136.5, 136.4, 134.3, 133.8, 129.6, 129.3, 120.9, 120.3, 64.8, 63.2, 39.0, 38.3, 17.9, 11.9. HRMS (ESI-TOF) calculated for $C_{26}H_{40}N_2SiNaO_3$ $[M+Na]^+$ 479.2701, found 479.2701.

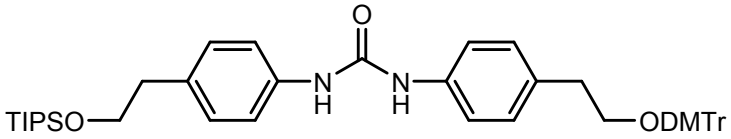

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Figure S2. 1-(4-(2-{[4,4'-dimethoxytrityl]-oxy}-ethyl)-phenyl)-3-(4-{2-([triisopropylsilyl]-oxyethyl}-phenyl)urea

^{1}H NMR ($CDCl_3$): δ 7.35 (d, J_{HH} = 7.7 Hz, 2H), 7.23-7.21 (m, 5H), 7.18-7.15 (m, 4H), 7.12 (t, J_{HH} = 4.1 Hz, 2H), 6.78 (d, J_{HH} = 8.9 Hz, 4H), 6.71 (d, J_{HH} = 8.9 Hz, 2H), 3.84 (quint, J_{HH} = 3.5 Hz, 2H), 3.77 (s, 6H), 3.24 (t, J_{HH} = 6.8 Hz, 2H), 2.84-2.77 (m, 4H), 1.09-1.02 (m, 21H). ^{13}C NMR ($CDCl_3$): δ 158.3, 153.9, 145.1, 136.4, 136.1, 136.0, 135.2, 134.1, 129.94, 129.87, 129.6, 128.1, 127.7, 126.6, 121.2, 120.9, 112.9, 85.9, 64.7, 63.4, 55.2, 39.1, 38.5, 17.9, 11.9. HRMS (ESI-TOF) calculated for $C_{47}H_{58}N_2SiNaO_5$ $[M+Na]^+$ 781.4008, found 781.4008.

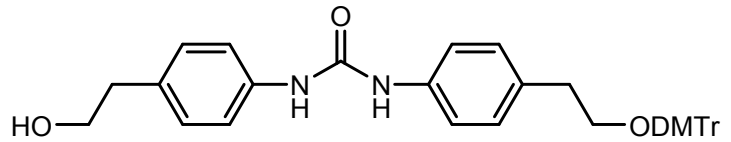

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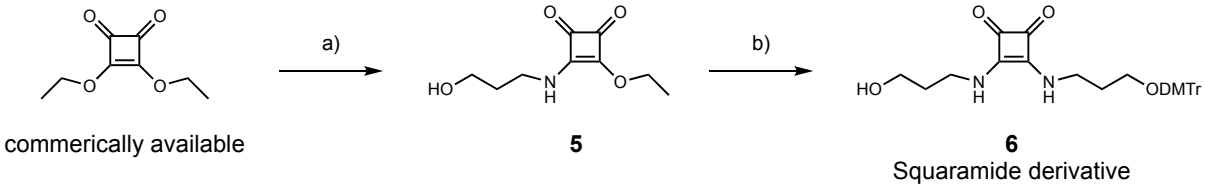
Figure S3. 1-(4-(2-{[4,4'-dimethoxytrityl]-oxy}-ethyl)-phenyl)-3-(4-{2-hydroxyethyl}-phenyl)urea

^{1}H NMR ($CDCl_3$): δ 7.35 (d, J_{HH} = 7.8 Hz, 2H), 7.26-7.23 (m, 11H), 7.17 (quart, J_{HH} = 7.7 Hz, 4H), 6.79 (d, J_{HH} = 8.9 Hz, 4H), 6.53 (d, J_{HH} = 4.4 Hz, 2H), 3.82 (quart, J_{HH} = 3.8 Hz, 2H), 3.77 (s, 6H), 3.26 (t, J_{HH} = 6.8 Hz, 2H), 2.83 (dt, J_{HH} = 18.4 Hz, 6.6 Hz, 4H), 2.15 (s,

1H). ^{13}C NMR ($CDCl_3$): δ 158.3, 153.8, 145.1, 136.43, 136.36, 136.1, 135.4, 134.2, 129.96, 129.93, 129.6, 128.1, 127.7, 126.6, 121.2, 121.0, 112.99, 85.97, 64.7, 63.4, 55.2, 38.4, 36.1. HRMS (ESI-TOF) calculated for $C_{38}H_{38}N_2NaO_5$ $[M+Na]^+$ 625.7208, found 625.2675.



Scheme S2. Synthesis bi(propyl)-linker conjugated squaramide derivative (**Q**). Reagents and conditions: one pot reaction (a) 1.0 equiv. of 3-Amino-1-propanol (Wako, d. 0.990 g/mL), EtOH, rt, 20 min; (b) 1.1 equiv. of 3-(Bis(4-methoxyphenyl)(phenyl)methoxy)propan-1-ol,[1,2] 3.0 equiv. of Triethylamine (Nacalai tesque, d. 0.750 g/mL), EtOH/MeOH=2/1, rt, 12 h, 70% yield. The reaction mixture was concentrated under reduced pressure and diluted with ethyl acetate, washed with aq. $NaHCO_3$, dried over with Na_2SO_4, filtered, and concentrated. Purify the crude product by alumina column chromatography (DCM only to DCM/MeOH=5/1, v/v) to give of product **6**.

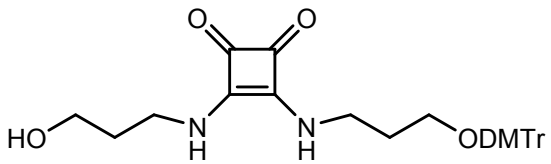


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Figure S4. 3-(3-{[4,4'-dimethoxytrityl]-oxy}-amino-propyl)-4-(3-{hydroxy}-amino-propyl)-cyclobut-3-ene-1,2-dione

^{1}H NMR ($CDCl_3$): δ 9.09 (d, J_{HH} = 2.2 Hz, 1H), 8.72 (d, J_{HH} = 4.8 Hz, 1H), 8.53 (d, J_{HH} = 8.1 Hz, 1H), 8.48 (d, J_{HH} = 7.8 Hz, 1H), 8.21 (dd, J_{HH} = 8.3, 2.2 Hz, 1H), 7.86 (td, J_{HH} = 7.6, 1.7 Hz, 1H), 7.39 (dd, J_{HH} = 8.5, 1.0 Hz, 2H), 7.36 (m, 1H), 7.28 (m, 5H), 7.20 (t, J_{HH} = 7.3 Hz, 1H), 6.85 (d, J_{HH} = 8.9 Hz, 1H), 6.81 (t, J_{HH}= 8.7, 4H), 4.25 (qd, J_{HH} = 6.3, 1.8 Hz, 1H), 4.15 (m, 1H), 3.764 (s, 3H), 3.756 (s, 3H), 3.60 (dd, J_{HH} = 9.7, 4.2 Hz, 1H), 3.43 (dd, J_{HH} = 9.9, 3.4 Hz, 1H), 3.10 (s, 1H), 1.23 (d, J_{HH} = 6.5 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 165.9, 158.8, 158.7, 155.2, 149.5, 147.9, 144.4, 137.2, 135.9, 135.5, 135.3, 130.04, 130.00, 129.7, 128.1, 128.0, 127.2, 124.5, 121.8, 120.8, 113.5, 87.1, 68.8, 65.5, 55.3, 54.1, 20.3. HRMS (ESI-TOF) calculated for $C_{36}H_{35}N_3NaO_5$ $[M+Na]^+$ 612.2469, found 612.2455.

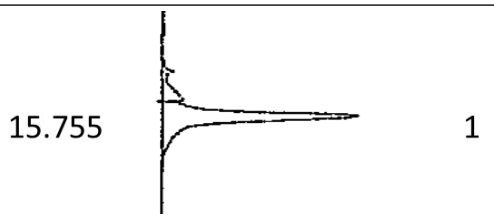
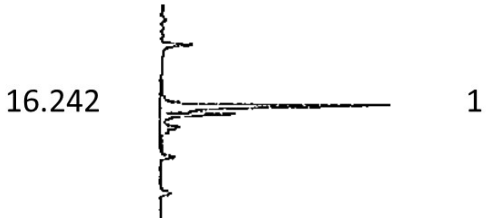
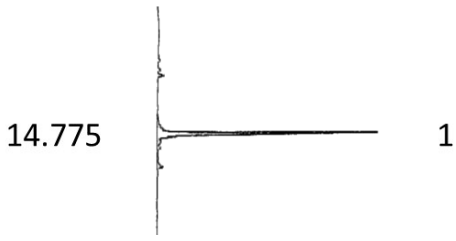
ODN No.	Analytical HPLC profile
ODN1	
ODN2	
ODN3	
ODN7	

Table S1. Analytical HPLC profile of representative oligonucleotides (**ODN 1, ODN 2, ODN 3, ODN 7)**; For HPLC column chromatography, COSMOSIL 5C18 AR-II (Nacalai Tesque, Inc., Kyoto, 150 × 10 mm id), a linear gradient of 3 to 30% acetonitrile over 30 min at a flow rate of 3.0 mL/min. 50 mM TEAA (pH 7.0) was used as a buffer on 254 nm.

DNA oligomer	Calcd.	Found.
5’-GG^{3}**X**GGCGCGAAGCATTCGCGGG^{3}**X**GG-3’	8052.4113	8050.719
5’-GG^{4}**X**GGCGCGAAGCATTCGCGGG^{4}**X**GG-3’	8108.5293	8104.056
5’-GG^{6}**X**GGCGCGAAGCATTCGCGGG^{6}**X**GG-3’	8220.7353	8218.953
5'-GG^{3}**X**GGCGCGAAG-3'	3867.6464	3863.950
5'-GG^{4}**X**GGCGCGAAG-3'	3895.7004	3891.967
5'-GG^{6}**X**GGCGCGAAG-3'	3951.8084	3951.791
5’-CATTCGCGGG^{3}**X**GG-3’	3809.5914	3806.840
5’-CATTCGCGGG^{4}**X**GG-3’	3837.6465	3833.809
5’-CATTCGCGGG^{6}**X**GG-3’	3893.7534	3892.615
5’-GG^{3}**X**GGCGCGAAGCATTCGCGGG**P**GG-3’	8050.4353	8048.239
5’-GG^{3}**X**GGCGCGAAGCATTCGCGGG**U**GG-3’	7994.3713	7993.497
5’-GG^{3}**X**GGCGCGAAGCATTCGCGGG**Q**GG-3’	7922.2613	7908.970
5'-GG**P**GGCGCGAAG-3'	3865.6704	3866.125
5'-GG**U**GGCGCGAAG-3'	3809.6064	3749.517
5'-GG**Q**GGCGCGAAG-3'	3793.5614	3783.581
5’-CATTCGCGGG**P**GG-3’	3807.6154	3806.813
5’-CATTCGCGGG**U**GG-3’	3751.5514	3750.654
5’-CATTCGCGGG**Q**GG-3’	3735.4614	3722.569
5’-GG^{3}**X**GG-3’	1675.2330	1673.732
5’-GG^{4}**X**GG-3’	1703.2870	1701.290
5’-GG^{6}**X**GG-3’	1759.3950	1758.973

Table S2. MALDI-TOF-Mass data of newly synthesized ODNs.

Other DNA oligomers were purchased from Sigma Genosys or JBios.

Enantioselective Michael addition reaction

The *ee* of the product was determined on a Daicel Chiralcel AD-H column with a solvent mixture of suitable polarity. Various ratios of Hexane and 2-propanol mixed solution was used with a flow rate of 1.0 mL/min or 0.5 mL/min. The conversion of the chiral products was calculated based on the below formula.

$$\text{conversion (\%)} = \frac{A(\text{v.s.})_{pd}}{\frac{A(\text{v.s.})_{sm}}{C} + A(\text{v.s.})_{pd}} \times 100$$

Here, $A(\text{v.s.})_{pd}$ is the total peak area of the product of the reaction, $A(\text{v.s.})_{sm}$ is the peak area of the starting material and ***C*** is the correction factor determined from a calibration curve.

The enantiomeric excess (*ee*) of the chiral products was determined via the below equations. Based on the chiral HPLC peak analysis; peak 1 and peak 2 according to Figure S7-Figure S10.

$$\text{enantiomeric excess (\%)} = \frac{A_{norm}(2) - A_{norm}(1)}{A_{norm}(2) + A_{norm}(1)} \times 100$$

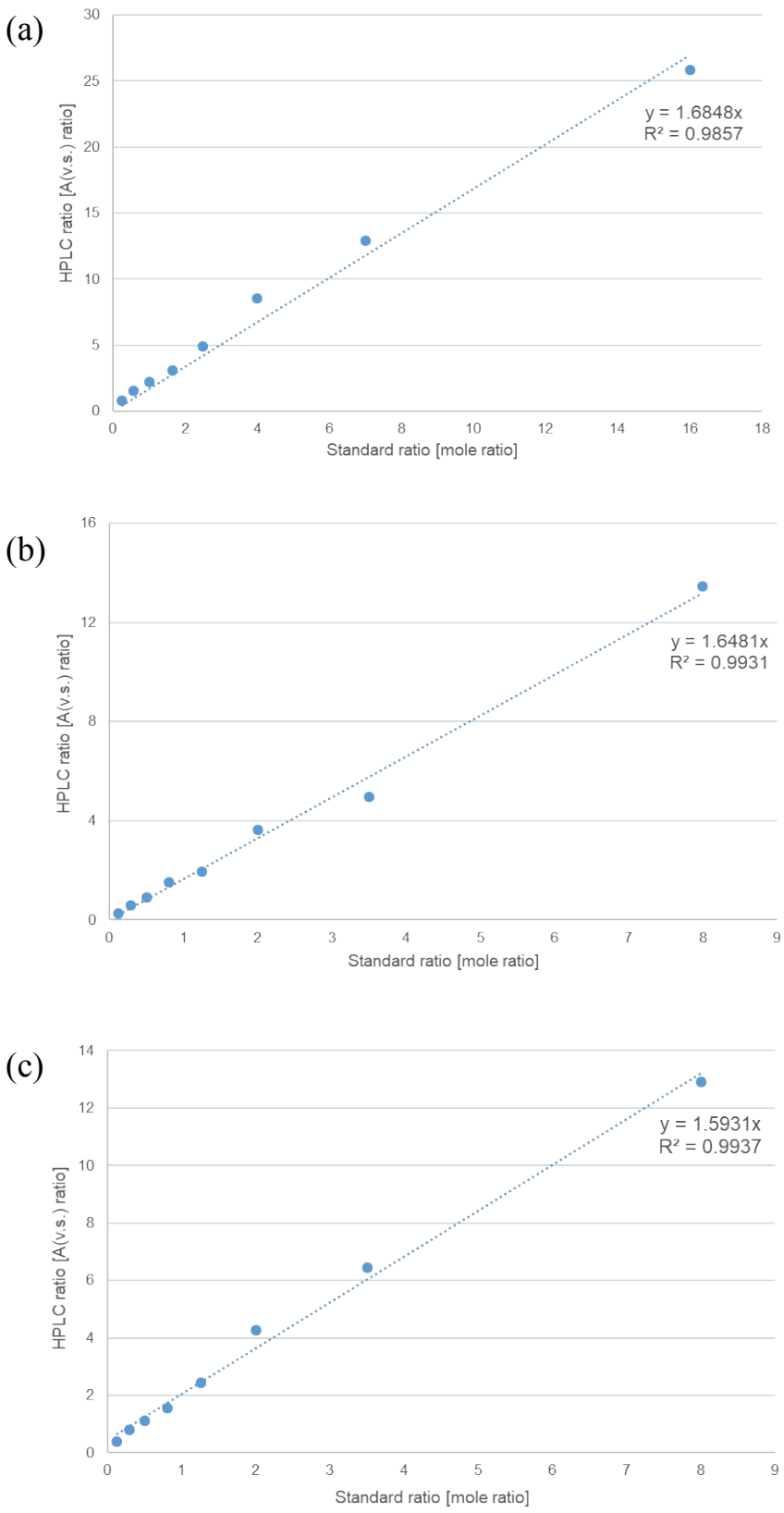


Figure S5. Calibration curves for the determination of the correction factor of **3aa-3ac**
(a) Calibration curve of **3aa**; (b) Calibration curve of **3ab**; (c) Calibration curve of **3ac**

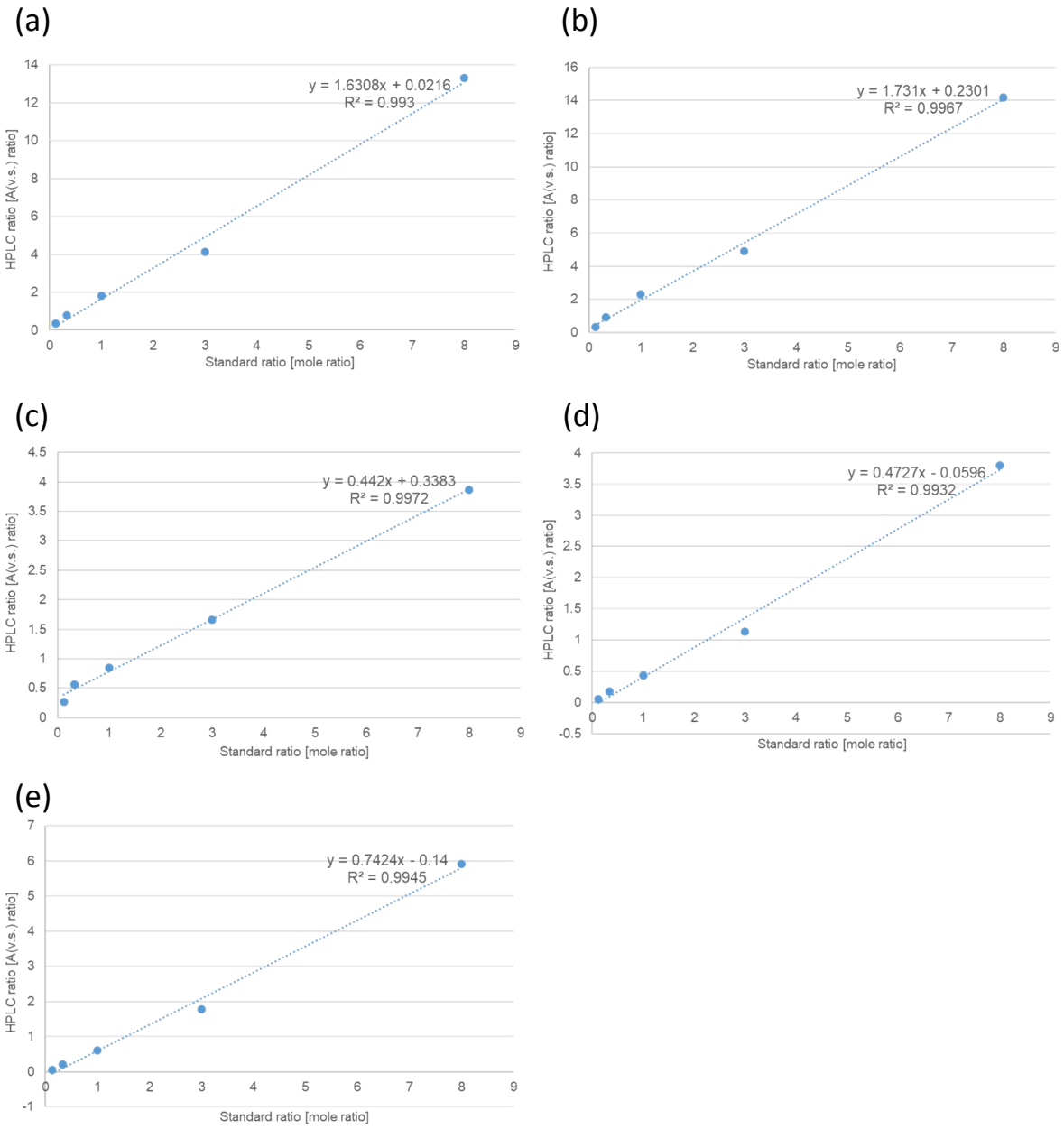
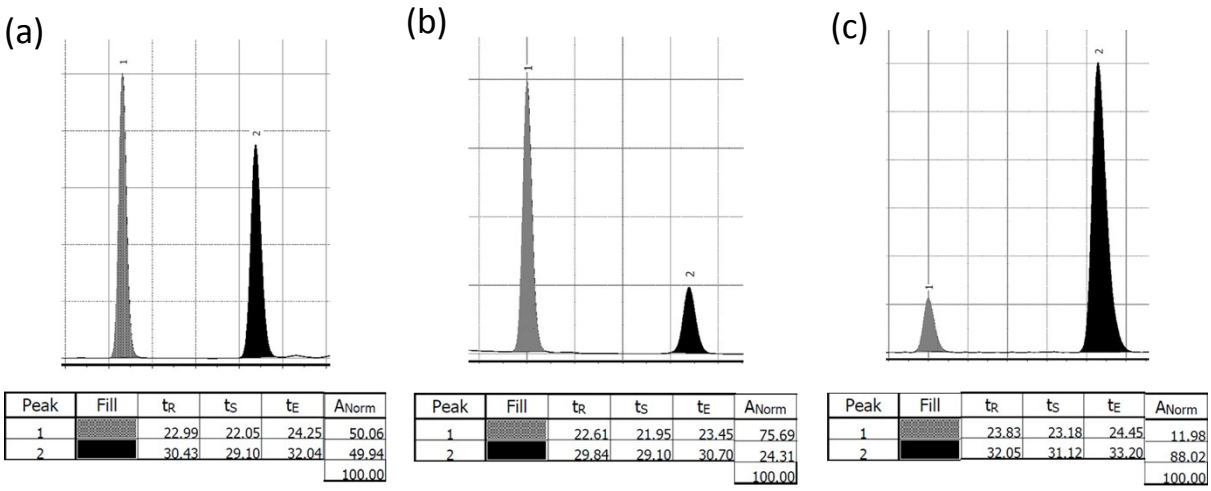


Figure S6. Calibration curves for the determination of the correction factor of **3ba-3fa**
(a) Calibration curve of **3ba**; (b) Calibration curve of **3ca**; (c) Calibration curve of **3da**; (d) Calibration curve of **3ea**; (e) Calibration curve of **3fa**



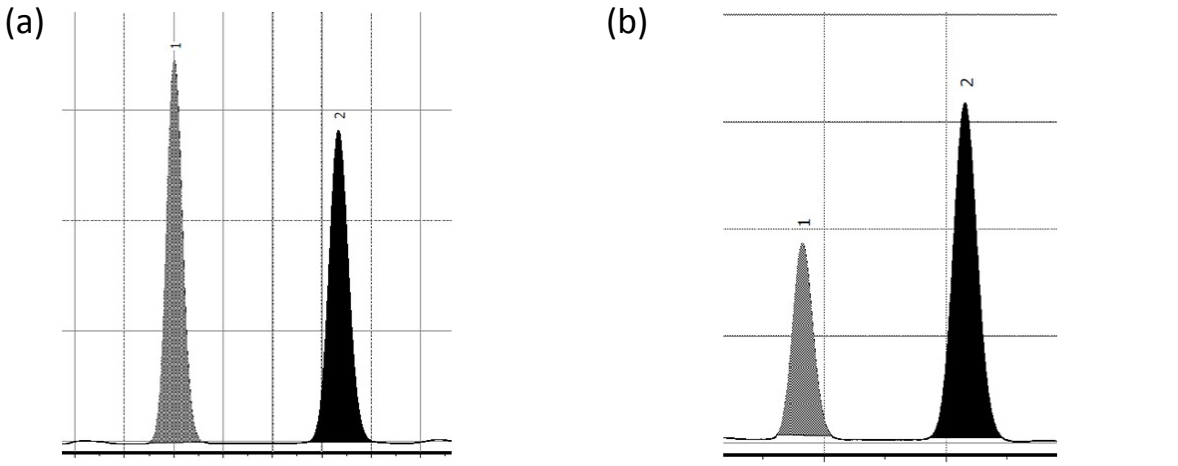
Peak	Fill	t_R	t_S	t_E	ANorm
1		22.99	22.05	24.25	50.06
2		30.43	29.10	32.04	49.94
					100.00

Peak	Fill	t_R	t_S	t_E	ANorm
1		22.61	21.95	23.45	75.69
2		29.84	29.10	30.70	24.31
					100.00

Peak	Fill	t_R	t_S	t_E	ANorm
1		23.83	23.18	24.45	11.98
2		32.05	31.12	33.20	88.02
					100.00

Figure S7. HPLC analysis of nitromethane added **3aa** product.

(a) Racemic mixture of **3a** (Coefficient *C*= 1.68), (b) Enantioenriched **3a** by **ODN2** (**^{3}X**)/**ODN6** (**U**) (GG**^{3}X**GG-/-GG**U**GG) (entry 9 in **Table 2**)., (c) Enantioenriched **3a** by **ODN2** (**^{3}X**)/**ODN6** (**Q**) (GG**^{3}X**GG-/-GG**Q**GG), (entry 10 in **Table 2**). For chiral HPLC column analysis, CHIRALPAK® AD-H (DAICEL Corporation, 4.6 × 250 mm, 5 μm particle size), Hexane/2-propanol=90/10 mixed solution at a flow rate of 1.0 mL/min, rt, 254 nm.



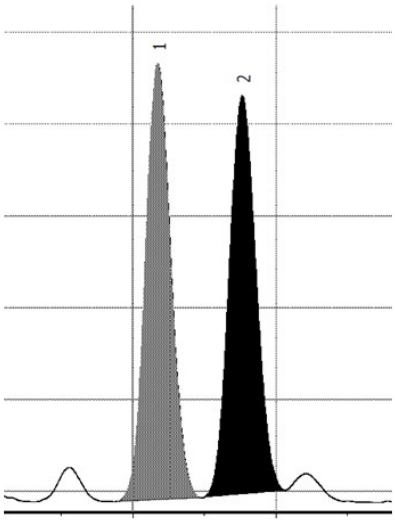
Peak	Fill	t_R	t_S	t_E	ANorm
1		17.00	16.27	17.77	50.03
2		20.20	19.32	21.49	49.97
					100.00

Peak	Fill	t_R	t_S	t_E	ANorm
1		15.89	15.30	16.70	32.29
2		18.67	17.98	19.60	67.71
					100.00

Figure S8. HPLC analysis of dimethylmalonate added **3ab** product.

(a) Racemic mixture of **3b** (Coefficient *C*= 1.65), (b) Enantioenriched **3b** by **ODN1** (**^{3}X**) (GG**^{3}X**GG-····-GG**^{3}X**GG) (entry 2 in **Table S3**). For chiral HPLC column analysis, CHIRALPAK® AD-H (DAICEL Corporation, 4.6 × 250 mm, 5 μm particle size), Hexane/2-propanol=90/10 mixed solution at a flow rate of 1.0 mL/min, rt, 254 nm.

(a)

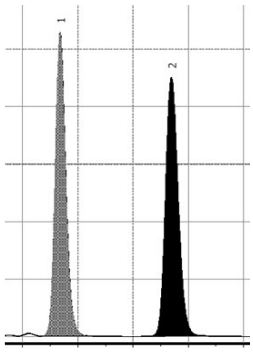


Peak	Fill	t_R	t_S	t_E	ANorm
1		40.87	39.45	42.40	50.92
2		43.82	42.50	45.30	49.08
					100.00

Figure S9. HPLC analysis of diethylmalonate added **3ac** product.

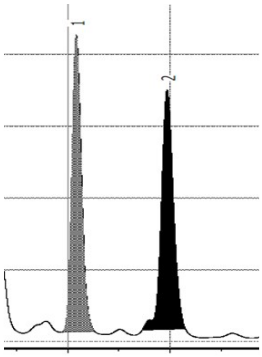
(a) Racemic mixture of **3c** (Coefficient *C*= 1.59), b) Enantioenriched **3c** by **ODN1** (**^{3}X**) (GG**^{3}X**GG-····-GG**^{3}X**GG) (entry 3 in **Table S3**). For chiral HPLC column analysis, CHIRALPAK® AD-H (DAICEL Corporation, 4.6 × 250 mm, 5 μm particle size), Hexane/2-propanol=90/10 mixed solution at a flow rate of 1.0 mL/min, rt, 254 nm.

(a)



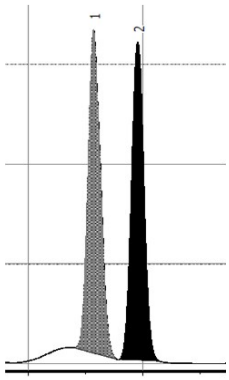
Peak	Fill	t_R	t_S	t_E	A_{Norm}
1		9.68	9.32	10.28	49.41
2		11.69	11.32	12.32	50.59
					100.00

(b)



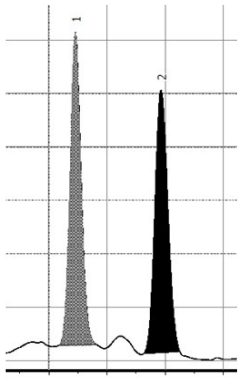
Peak	Fill	t_R	t_S	t_E	A_{Norm}
1		8.16	7.85	8.53	49.99
2		9.94	9.65	10.25	50.01
					100.00

(c)



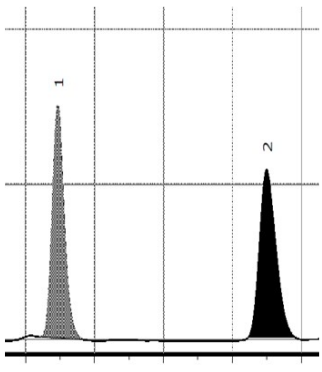
Peak	Fill	t_R	t_S	t_E	H_{Norm}
1		32.84	32.00	33.85	50.45
2		34.77	33.98	35.70	49.55
					100.00

(d)



Peak	Fill	t_R	t_S	t_E	A_{Norm}
1		20.91	20.32	21.65	50.44
2		23.85	23.25	24.50	49.56
					100.00

(e)



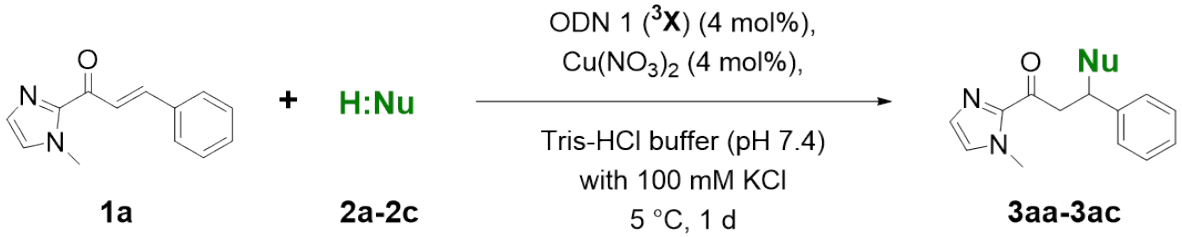
Peak	Fill	t_R	t_S	t_E	A_{Norm}
1		16.93	16.43	17.68	50.38
2		22.98	22.45	23.80	49.62
					100.00

Figure S10. HPLC analysis of nitromethane added **3ba-3fa** product.

(a) Racemic mixture of **3ba** (Coefficient *C*= 1.63); For chiral HPLC column analysis, CHIRALPAK® AD-H (DAICEL Corporation, 4.6 × 250 mm, 5 μm particle size), Hexane/2-propanol=90/10 mixed solution at a flow rate of 1.0 mL/min, rt, 254 nm, (b) Racemic mixture of **3ca** (Coefficient *C*= 1.73); For chiral HPLC column analysis, CHIRALPAK® AD-H (DAICEL Corporation, 4.6 × 250 mm, 5 μm particle size), Hexane/2-propanol=70/30 mixed solution at a flow rate of 1.0 mL/min, rt, 254 nm, (c) Racemic mixture of **3da** (Coefficient *C*= 2.26); For chiral HPLC column analysis, CHIRALPAK® AD-H (DAICEL Corporation, 4.6 × 250 mm, 5 μm particle size), Hexane/2-propanol=90/10 mixed solution at a flow rate of 0.5 mL/min, rt, 254 nm, (d) Racemic mixture of **3ea** (Coefficient *C*= 2.12); For chiral HPLC column analysis, CHIRALPAK® AD-H (DAICEL Corporation, 4.6 × 250 mm, 5 μm particle size), Hexane/2-propanol=90/10 mixed solution at a flow rate of 1.0 mL/min, rt, 254 nm, (e) Racemic mixture of **3fa** (Coefficient *C*= 1.38); For chiral HPLC column analysis, CHIRALPAK® AD-H (DAICEL Corporation, 4.6 × 250 mm, 5 μm particle size), Hexane/2-propanol=70/30 mixed solution at a flow rate of 1.0 mL/min, rt, 254 nm.

Table S3. Catalytic results of the enantioselective Michael addition reaction with malonate derivatives.

[a] Experiments were carried out using 3.3 mM α,β-unsaturated 2-acyl imidazole, 66 mM of nucleophiles, 0.13 mM DNA, and 0.13 mM $Cu(NO_3)_2$ at 5 °C in 20 mM Tris-HCl buffer (pH 7.4) for 1 day. The conversion and enantioselectivities were determined by chiral HPLC analysis.



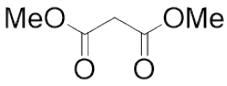
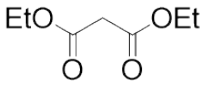
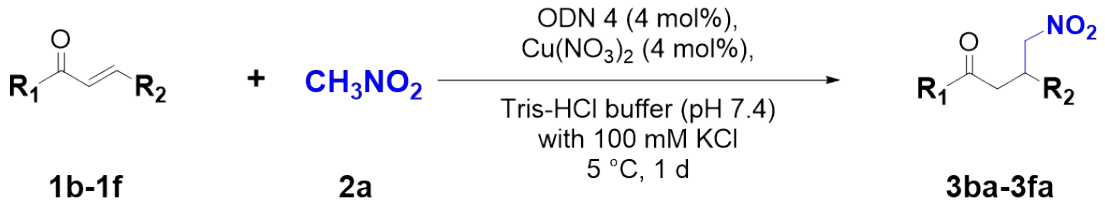
entry	H:Nu	*ee* [conv.]
1	CH_3NO_2	65% [41%]
2		39% [19%]
3		No Reaction

Table S4. Catalytic results of the enantioselective Michael addition reaction with various α,β-unsaturated ketones.

[a] Experiments were carried out using 3.3 mM α,β-unsaturated ketones, 66 mM of nucleophiles, 0.13 mM DNA, and 0.13 mM $Cu(NO_3)_2$ at 5 °C in 20 mM Tris-HCl buffer (pH 7.4) for 1 day. The conversion and enantioselectivities were determined by chiral HPLC analysis.

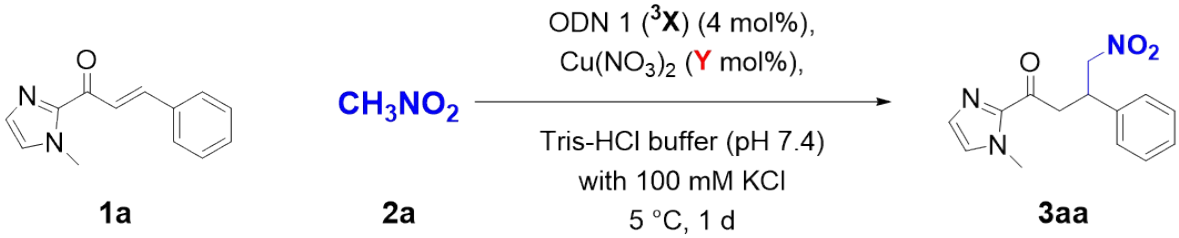


1b-1f **2a** **3ba-3fa**

			ODN 4 (U)	**ODN 4 (Q)**
entry[a]	**R_1**	**R_2**	*ee* [conv.]	*ee* [conv.]
3ba	*N*-imidazoyl	*tert*-butyl	-56% [15%]	28% [15%]
3ca	*N*-imidazoyl	cyclohexyl	23% [41%]	52% [23%]
3da	pyridyl	phenyl	No Reaction	
3ea	pyridyl	*p*-bromophenyl	No Reaction	
3fa	pyridyl	p-nitrophenyl	No Reaction	12% [29%]

Table S5. Catalytic results of the enantioselective Michael addition reaction with various equivalent of catalytic metal.

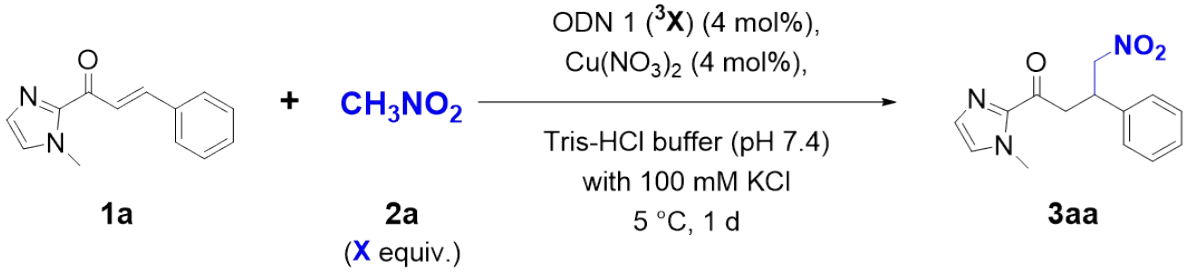
[a] Experiments were carried out using 3.3 mM α,β-unsaturated 2-acyl imidazole, 66 mM of nitromethane, and 0.13 mM DNA at 5 °C in 20 mM Tris-HCl buffer (pH 7.4) for 1 day. The conversion and enantioselectivities were determined by chiral HPLC analysis.



entry[a]	Y mol%	ee [conv.]
1	2 mol%	61% [45%]
2	4 mol%	65% [41%]
3	8 mol%	57% [82%]

Table S6. Catalytic results of the enantioselective Michael addition reaction with various equivalent of nucleophile.

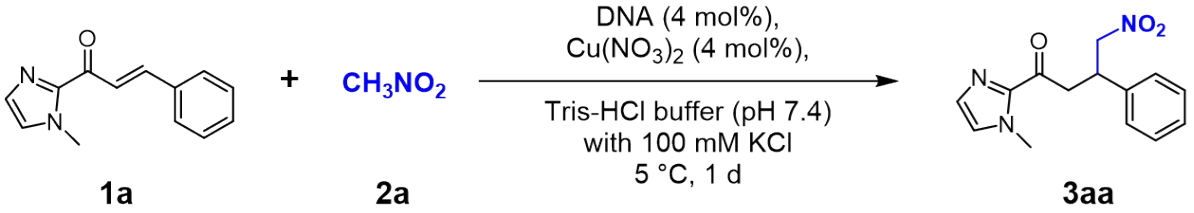
[a] Experiments were carried out using 3.3 mM α,β-unsaturated 2-acyl imidazole, 0.13 mM DNA, and 0.13 mM $Cu(NO_3)_2$ at 5 °C in 20 mM Tris-HCl buffer (pH 7.4) for 1 day. The conversion and enantioselectivities were determined by chiral HPLC analysis. [b] Optimized reaction conditions on room-temperature for 1 day.



entry[a]	X equiv.	*ee* [conv.]
1	10 equiv.	64% [41%]
2	20 equiv.	65% [41%]
3	50 equiv.	61% [45%]
4	100 equiv.	65% [64%]
5[b]	20 equiv.	50% [51%]

Table S7. Catalytic results of the enantioselective Michael addition reaction catalyzed by QD hybrid DNAs.

[a] Experiments were carried out using 3.3 mM α,β-unsaturated 2-acyl imidazole, 66 mM of nucleophiles, 0.13 mM DNA, and 0.13 mM $Cu(NO_3)_2$ at 5 °C in 20 mM Tris-HCl buffer (pH 7.4) for 1 day. The conversion and enantioselectivities were determined by chiral HPLC analysis. [b] Optimized reaction conditions with , 3.3 mM α,β-unsaturated 2-acyl imidazole, 0.33 M of nucleophiles, 0.33 mM DNA, and 0.33 mM $Cu(NO_3)_2$ at 5 °C in 20 mM Tris-HCl buffer (pH 7.4) for 3 day.



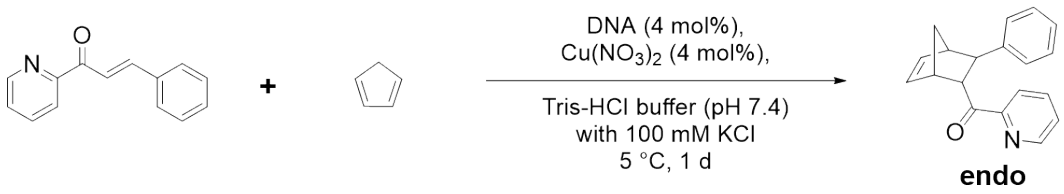
1a **2a** **3aa**

entry[a]	DNA oligomer	ee [conv.]
1	**ODN 1** (**^{3}X**)	65% [41%]
2	**ODN 7** (**^{3}X**)	39% [12%]
3	**ODN 5** (**P**)/**ODN 6** (**P**)	racemate [10%]
4	**ODN 5** (**U**)/**ODN 6** (**U**)	racemate [15%]
5	**ODN 5** (**P**)/**ODN 6** (**Q**)	5% [23%]
6[b]	**ODN 7** (**^{3}X**)	37% [82%]
7[b]	**ODN 7** (**^{4}X**)	44% [71%]
8[b]	**ODN 7** (**^{6}X**)	29% [67%]

Table S8. Catalytic results of other enantioselective reactions catalyzed by the modular DNA hybrid catalysts.

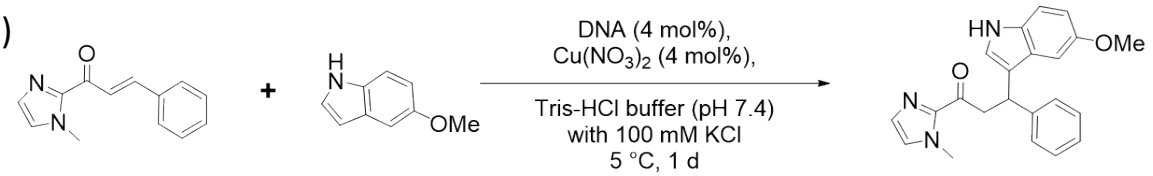
[a] Experiments were carried out using 3.3 mM α,β-unsaturated ketones, 3.3 mM of 5-methoxyindole or 80 mM cyclopentadiene, 0.13 mM DNA, and 0.13 mM $Cu(NO_3)_2$ at 5 °C in 20 mM Tris-HCl buffer (pH 7.4) for 1 day. The conversion and enantioselectivities were determined by chiral HPLC analysis. [b] Chiral HPLC conditions; CHIRALPAK® OD-H (DAICEL Corporation, 4.6 × 250 mm, 5 μm particle size), Hexane/2-propanol=95/5 mixed solution at a flow rate of 0.5 mL/min, rt, 254 nm. [c] Optimized reaction conditions on the room temperature for 1 day. [d] Chiral HPLC conditions; CHIRALPAK® AD-H (DAICEL Corporation, 4.6 × 250 mm, 5 μm particle size), Hexane/2-propanol=80/20 mixed solution at a flow rate of 1.0 mL/min, rt, 254 nm.

(a)



entry[a,b]	DNA	*ee* [conv.]
1	5'-**GG**-^{3}**X**-**GG**CGCGAAG 3'-**GG**-^{3}**X**-**GG**GCGCTTA C	No Reaction
2[c]	5'-**GG**-^{3}**X**-**GG**CGCGAAG 3'-**GG**-^{3}**X**-**GG**GCGCTTA C	No Reaction

(b)



entry[a,d]	DNA	*ee* [conv.]
1	5'-GCATGG-^{3}**X**-CACGGT-3' 3'-CGTACC-^{3}**X**-GTCCCA-5'	No Reaction
2	5'-**GG**-^{3}**X**-**GG**-3' 3'-**GG**-^{3}**X**-**GG**-5'	33% [15%]
3	5'-**GG**-^{3}**X**-**GG**CGCGAAG 3'-**GG**-^{3}**X**-**GG**GCGCTTA C	26% [40%]

(a) Catalytic results of enantioselective Diels-Alder reactions, (b) Catalytic results of enantioselective Friedel-Crafts alkylations.

CD Spectroscopy.

CD spectra of oligonucleotide solutions collected in 0.5-nm steps from 350 to 220 nm were measured using JASCO J-805LST Spectrometer in a 1-cm quartz cuvette. Ellipticity was recorded in the forward direction at temperatures from 5 to 95 °C at a rate of 1.0 °C/min and each spectrum shown is the average of two individual scans. The melting samples were denatured at 95 °C for 5 min and annealed slowly to RT then stored at 5 °C until experiments were initiated. All melting samples were prepared in a total volume of 150 µl containing 3.3 µM of each strand oligonucleotide, 3.3 µM $Cu(NO_3)_2$, 20 mM Tris-HCl buffer (pH 7.4) and 100 mM KCl. Molar ellipticity was calculated by followed equation.

$$Molar\ Ellipticity\ [\theta] = \frac{\theta}{10 \cdot C \cdot l}[10^3 \cdot deg \cdot M^{-1} \cdot cm^{-1}]$$

where, θ = ellipticity [mdeg], C = molar concentration [mol/L], and l = length of cuvette [cm]

Figure S11. CD spectra of the QD hybrids (ODN 1 (^{3}X) and ODN 2 (^{3}X)/ODN 3 (^{3}X)) in the presence of 100 mM potassium ion.[a]

[a] Solution conditions: 3.3 μM each DNA and 100 mM KCl in 20 mM Tris-HCl buffer (pH 7.4).

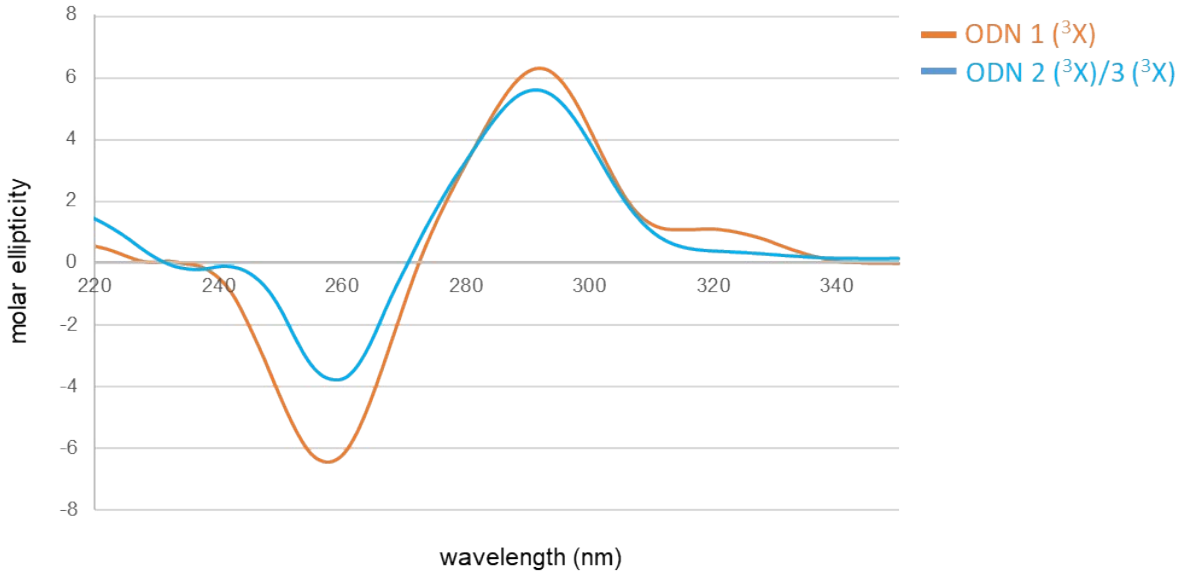


Figure S12. CD spectra of the QD hybrids (ODN 1 (^{3}X)) in the presence/absence of 1 equivalent of the copper ion.[a]

[a] Solution conditions: 3.3 μM each DNA, 1 equiv. of $Cu(NO_3)_2$ and 100 mM KCl in 20 mM Tris-HCl buffer (pH 7.4).

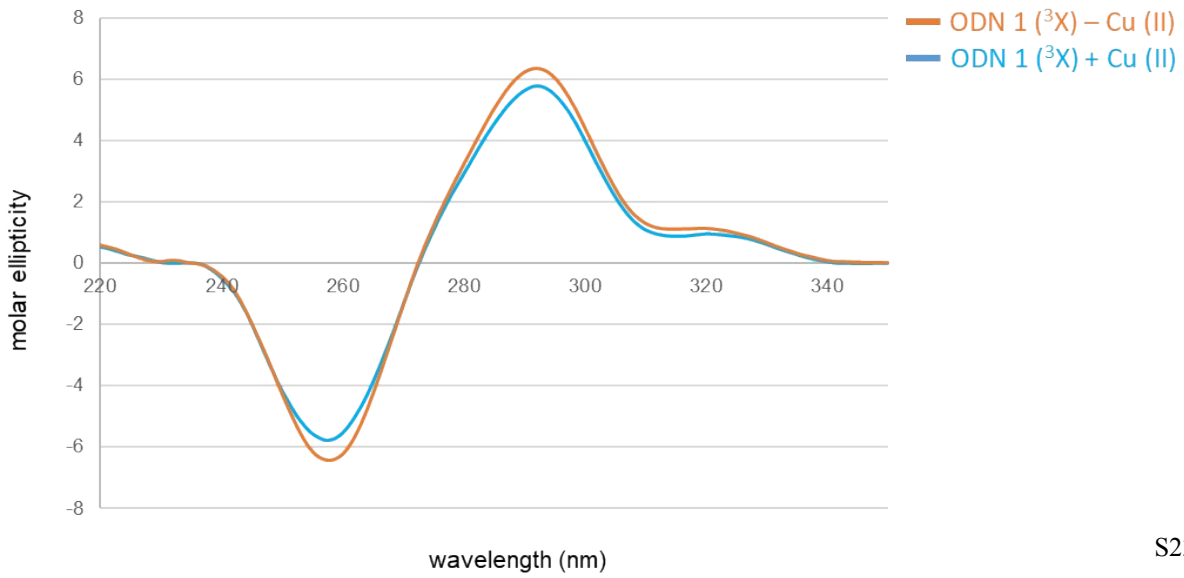


Figure S13. CD spectra of the QD hybrids (ODN 1 (^{3}X)) in the presence/absence of various monovalent ions. [a]

[a] Solution conditions: 3.3 μM each DNA and 100 mM KCl, NH_4Cl, NaCl, and LiCl in 20 mM Tris-HCl buffer (pH 7.4).

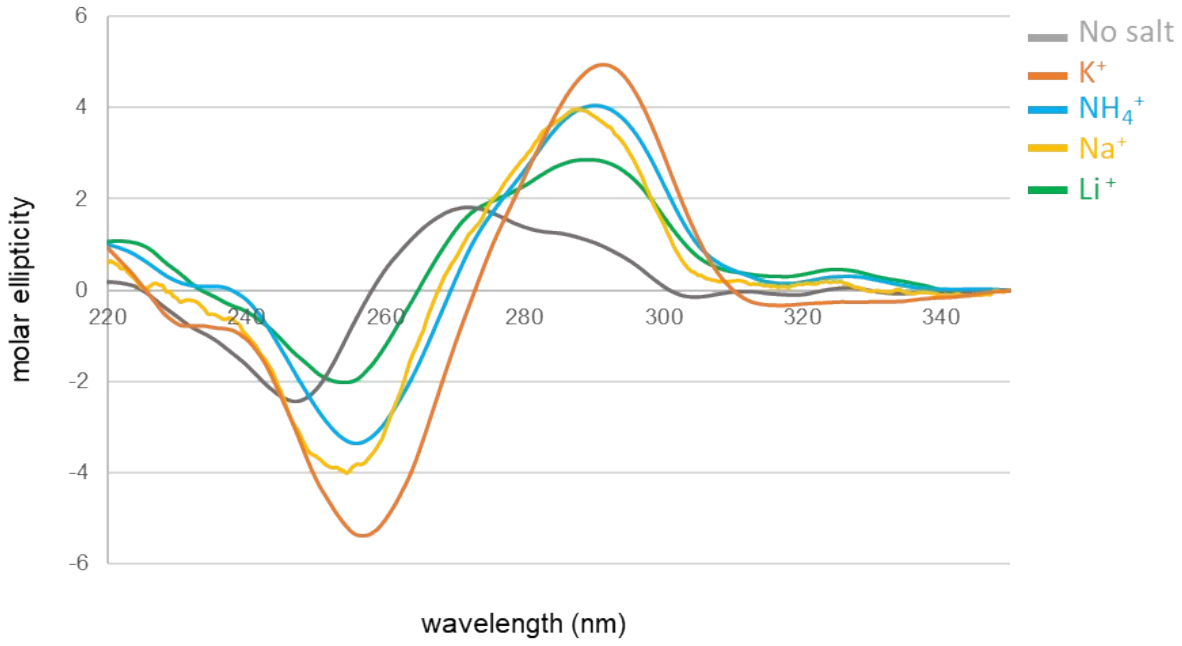


Figure S14. CD spectra of the QD hybrids (ODN 4 (P/U/Q)) in the presence/absence of 1 equivalent of the copper ion.[a]

[a] Solution conditions: 3.3 μM each DNA, 1.0 equiv. of $Cu(NO_3)_2$ and 100 mM KCl in 20 mM Tris-HCl buffer (pH 7.4).

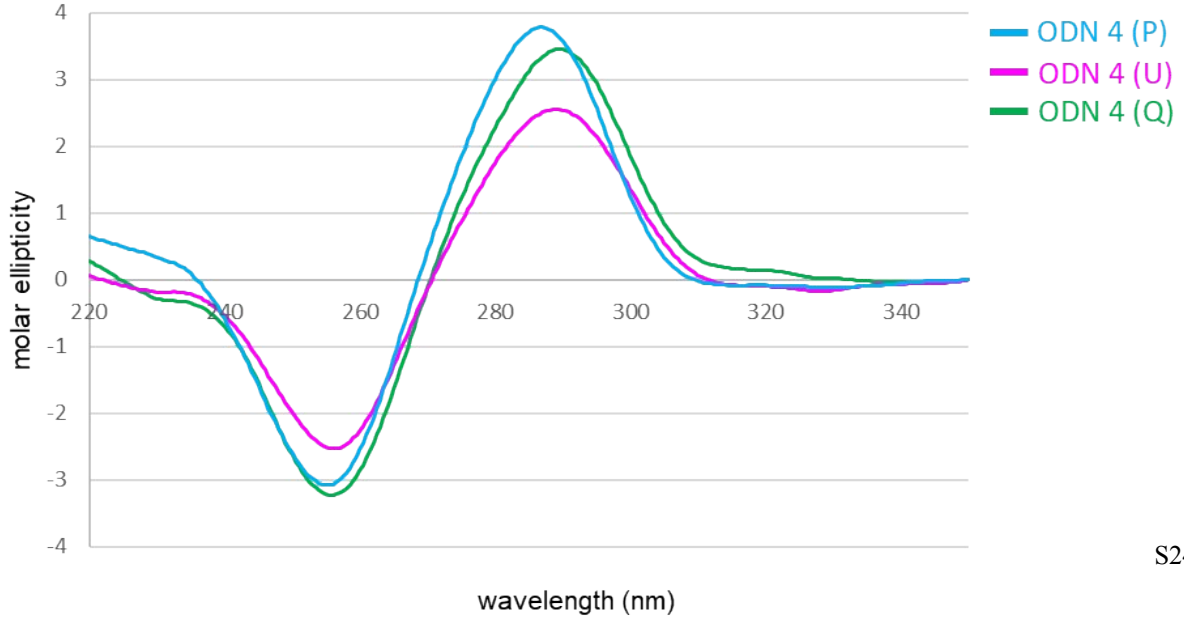


Figure S15. CD spectra of the quadruplex core sequence (ODN 7 (^{n}X, wherein n=3, 4, 6)) in the presence of 1 equivalent of the copper ion.[a]

[a] Solution conditions: 7.0 μM each DNA, 1 equiv. of $Cu(NO_3)_2$ and 100 mM KCl in 20 mM Tris-HCl buffer (pH 7.4).

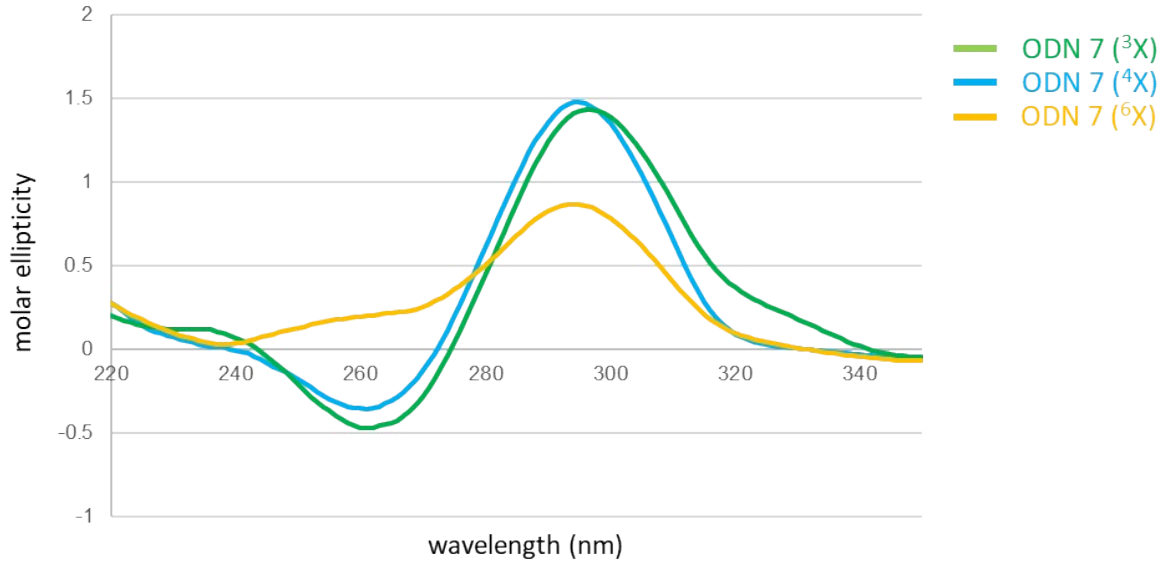


Figure S16. CD spectra of the quadruplex core sequence (ODN 7 (^{n}X, wherein n=3, 4, 6)) in the presence/absence of various monovalent ions.[a]

[a] Solution conditions: 7.0 μM of DNA and 100 mM KCl, NH_4Cl, NaCl, and LiCl in 20 mM Tris-HCl buffer (pH 7.4).

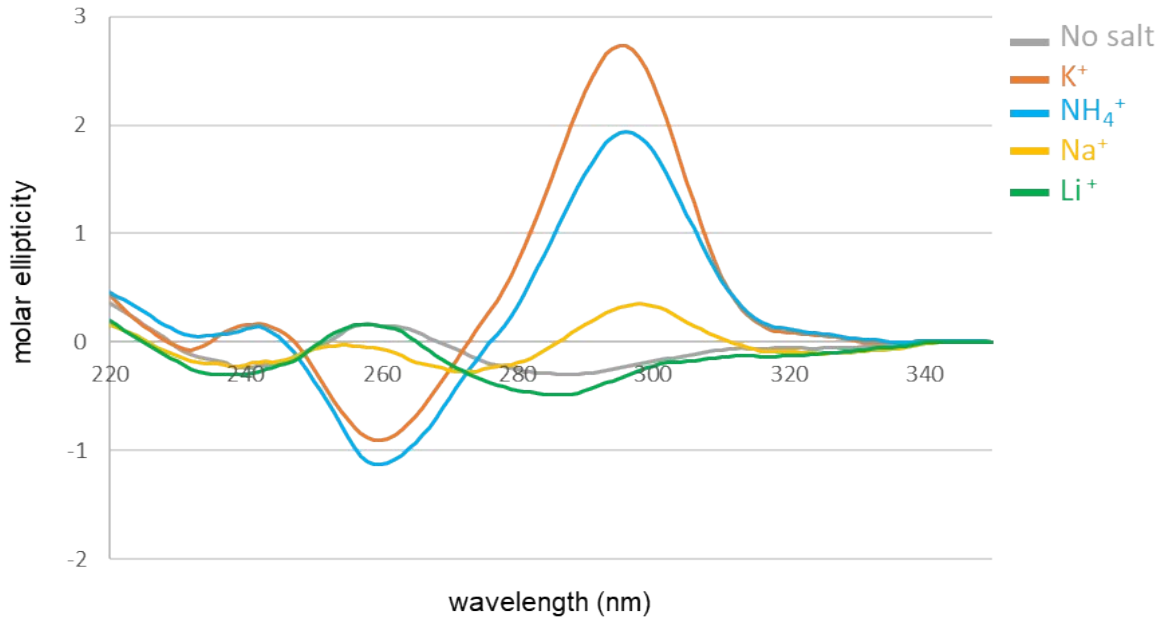


Figure S17. CD spectra of the duplex forming sequence (ODN 8/ ODN 9) in the presence/absence of 1 equivalent of the copper ion.[a]

[a] Solution conditions: 3.3 μM each DNA, 1 equiv. of $Cu(NO_3)_2$ and 100 mM KCl in 20 mM Tris-HCl buffer (pH 7.4).

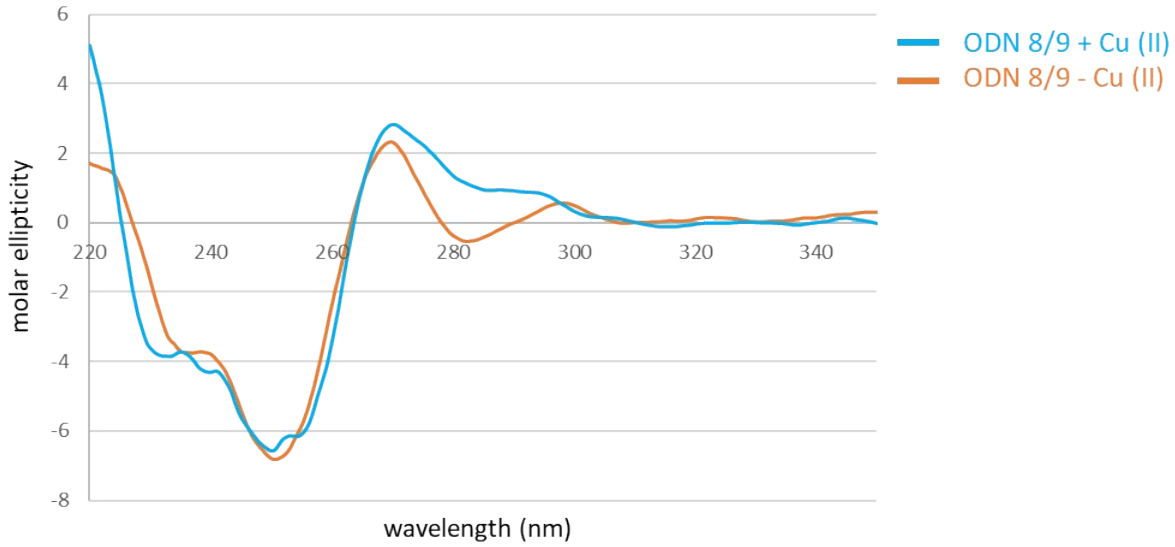
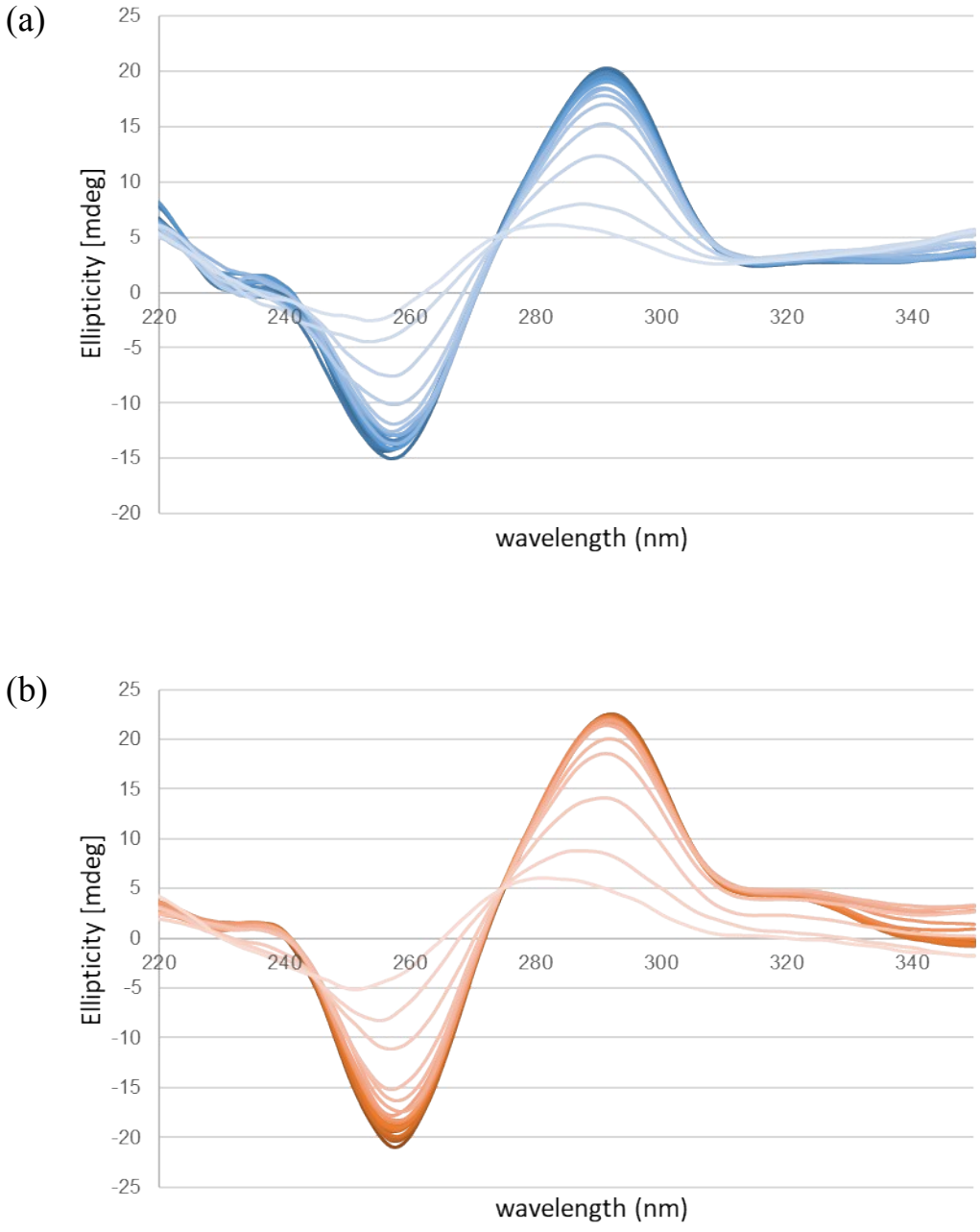


Figure S18. CD spectra on various temperature and melting curve of ODN 1 (^{3}X) in the presence/absence of 1 equivalent of the copper ion.[a]

(a) CD spectra of ODN 1 (^{3}X) on various temperature in the presence of Cu^{2+}, (b) CD spectra of ODN 1 (^{3}X) on various temperature in the absence of Cu^{2+}, (c) Melting curve of ODN 1 (^{3}X) normalized ellipticity on 295 nm.

[a] Solution conditions: 3.3 μM DNA and 1 equiv. of $Cu(NO_3)_2$ and 100 mM KCl in 20 mM Tris-HCl buffer (pH 7.4).



(c)

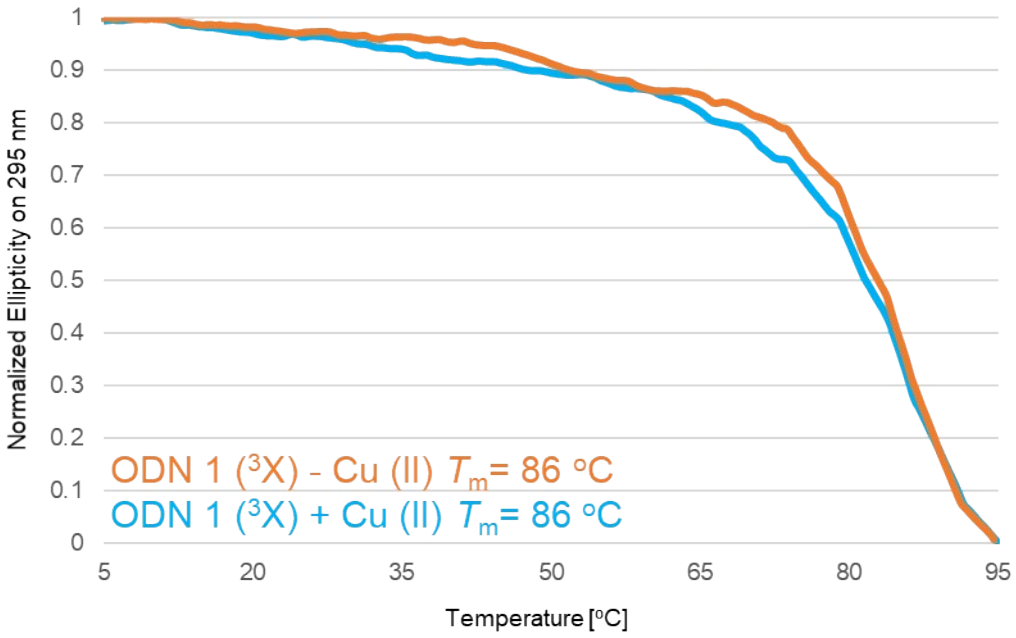

Normalized Ellipticity on 295 nm
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
5
20
35
50
65
80
95
Temperature [°C]
ODN 1 (^{3}X) - Cu (II) T_m= 86 °C
ODN 1 (^{3}X) + Cu (II) T_m= 86 °C

Figure S19. CD spectra on various temperature and melting curve of ODN 2 (^{3}X) and ODN 3 (^{3}X) in the presence of 1 equivalent of the copper ion.[a]

(a) CD spectra of **(**ODN 2 (^{3}X)/ODN 3 (^{3}X)) on various temperature in the presence of Cu^{2+}, (b) Melting curve of (ODN 2 (^{3}X)/ODN 3 (^{3}X)) normalized ellipticity on 295 nm.

[a] Solution conditions: 3.3 μM of each DNA and 1 equiv. of $Cu(NO_3)_2$ and 100 mM KCl in 20 mM Tris-HCl buffer (pH 7.4).

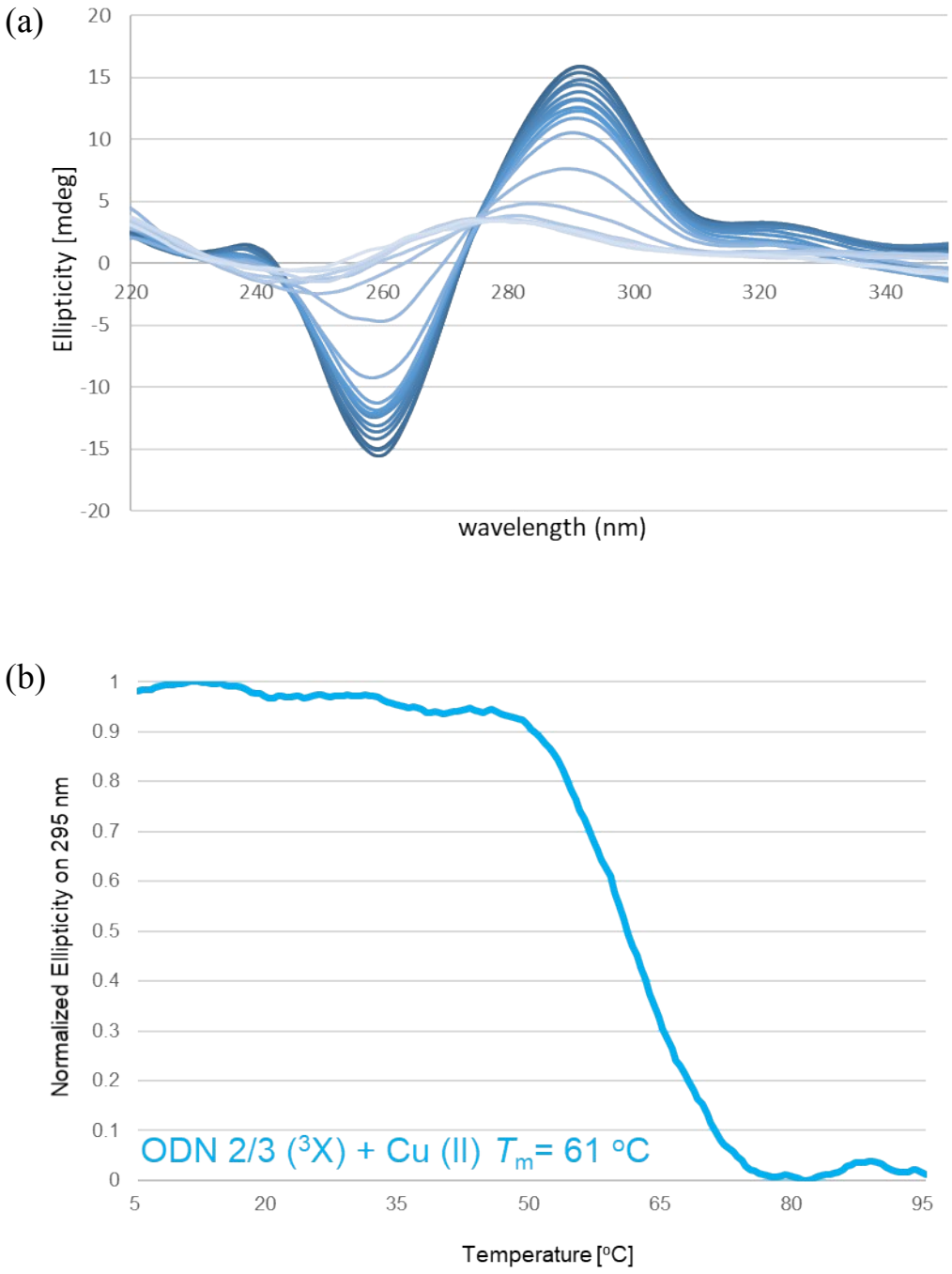
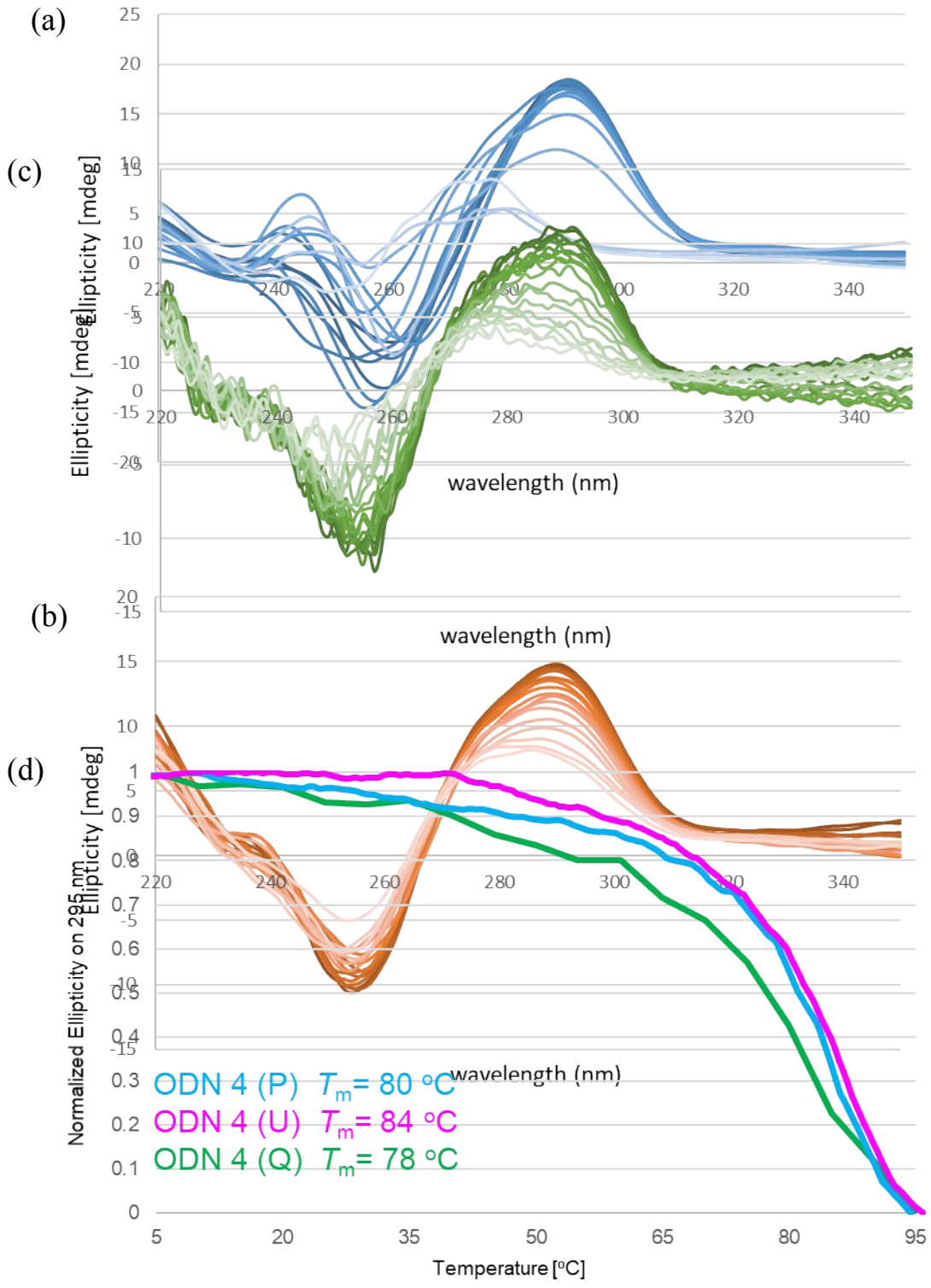


Figure S20. CD spectra on various temperature and melting curve of ODN 4 (P/U/Q) in the presence of 100 mM potassium ions.[a]

(a) CD spectra of ODN 4 (P) on various temperature, (b) CD spectra of ODN 4 (U) on various temperature, (c) CD spectra of ODN 4 (U) on various temperature, (d) Melting curve of ODN 4 (P/U/Q) normalized ellipticity on 295 nm.

[a] Solution conditions: 3.3 μM of each DNA and 100 mM KCl in 20 mM Tris-HCl buffer (pH 7.4).



UV-vis spectroscopy

Catalytic metal binding assay was performed by measuring the absorbance steps from 360 to 220 nm with JASCO V-650 UV/VIS spectrophotometer in micro auto eight-cell holder. Absorbance recorded on room-temperature and averaged based on average of two individual scans. The samples were denatured at 95 °C for 5 min and annealed slowly to RT experiments were initiated. All melting samples were prepared in a total volume of 150 µl containing 7.0 or 10 µM of each strand oligonucleotide, 3.3 µM $Cu(NO_3)_2$, 20 mM Tris-HCl buffer (pH 7.4) and 100 mM KCl.

Melting temperature was determined by measuring changes in absorbance at 260 nm as a function of temperature using a JASCO V-650 UV/VIS spectrophotometer. JASCO PAC-743R equipped with a high performance temperature controller and micro auto eight-cell holder. Absorbance was recorded in the forward and reverse direction at temperatures from 5 to 95 °C at a rate of 0.5 °C/min. The melting samples were denatured at 95 °C for 5 min and annealed slowly to RT then stored at 5 °C until experiments were initiated. All melting samples were prepared in a total volume of 150 µl containing 3.3 µM of each strand oligonucleotide, 3.3 µM $Cu(NO_3)_2$, 20 mM Tris-HCl buffer (pH 7.4) and 100 mM KCl.

Figure S21. UV-vis spectra of the quadruplex core sequence ODN 7 (^{3}X) in the presence of 1 equivalent of the copper ions [a]

[a] Solution conditions: 10 µM DNA , 1 equiv. of $Cu(NO_3)_2$ and 100 mM KCl in 20 mM Tris-HCl buffer (pH 7.4).

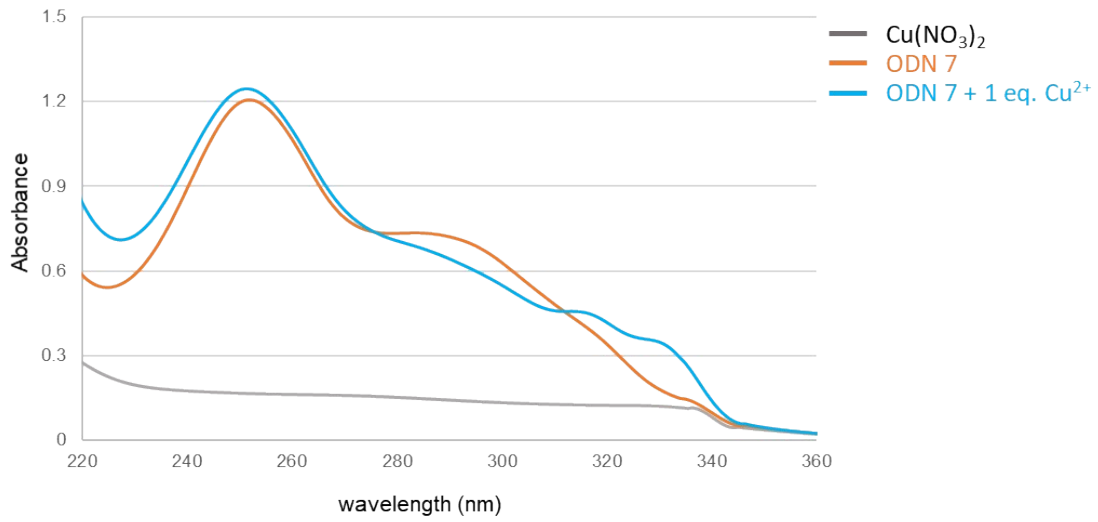


Figure S22 UV-vis spectra of the duplexes ODN 8/ODN 9 in the presence of 1 equivalent of the copper ions [a]

[a] Solution conditions: 7 µM of each DNA, 1 equiv. of $Cu(NO_3)_2$ and 100 mM KCl in 20 mM Tris-HCl buffer (pH 7.4).

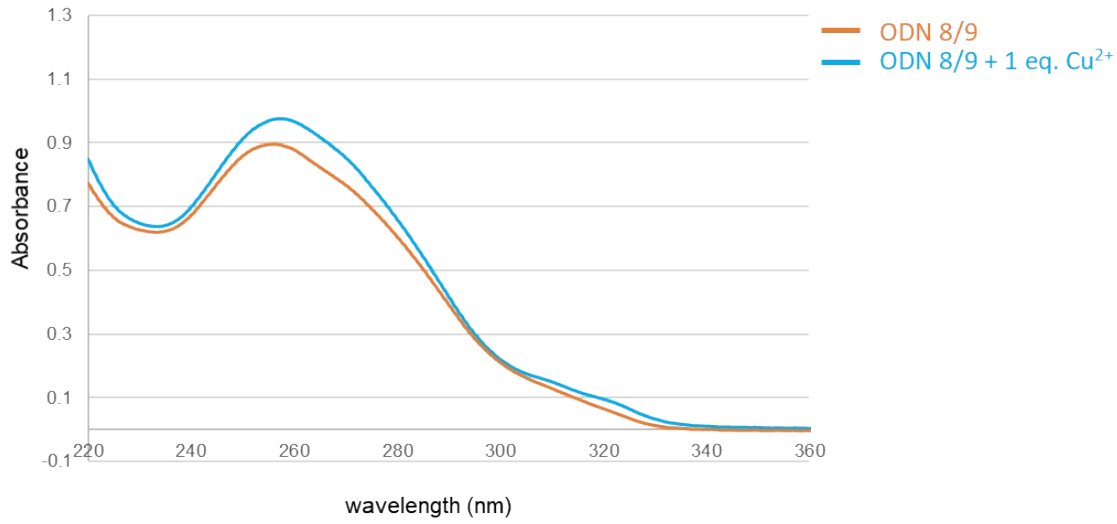
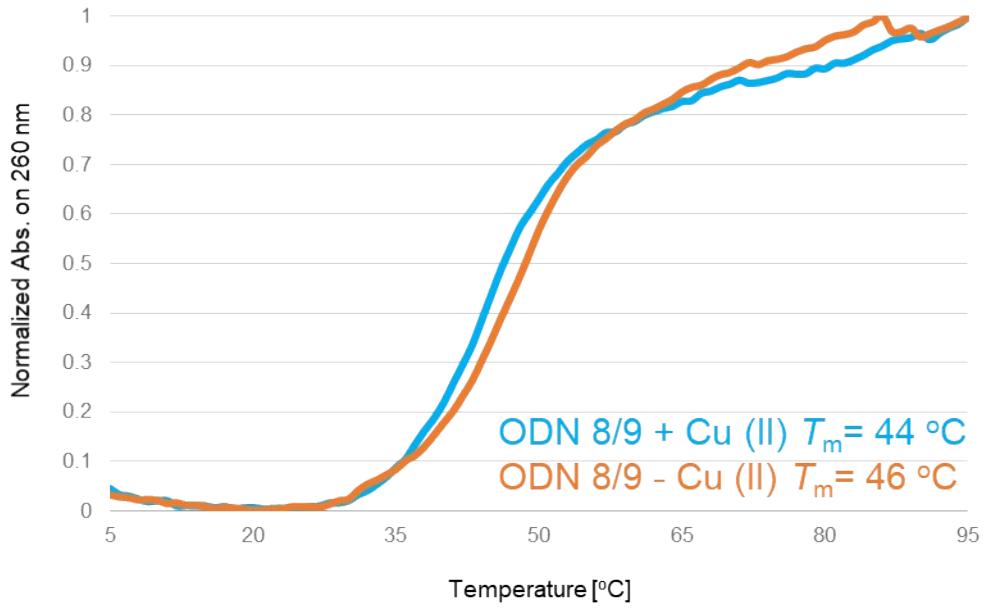


Figure S23. UV melting curve of the duplexes ODN 8/ODN 9 in the presence/absence of 1 equivalent of the copper ions [a,b]

[a] Solution conditions: 3.3 µM of each DNA and 100 mM KCl in 20 mM Tris-HCl buffer (pH 7.4)

[b] Absorbance normalized on 260 nm



Molecular Modeling Studies

Molecular modeling was carried out using the MOE (Molecular Operating Environment) software package. DNA quadruplex-duplex hybrdis containing an intrastrand bipyridine ligand and hydrogen bonding moieties were constructed and minimized with amber force field parameters, a distance-dependent dielectric constant of $\varepsilon = 4r$ (where, r is the distance between two atoms) and convergence criteria having an RMS gradient of less than 0.001 kcal mol^{-1} Å. For energy minimization water molecules were added to produce distance of 10 Å from the solute to droplet sphere boundaries and sodium counter ions were added to neutralize the system.

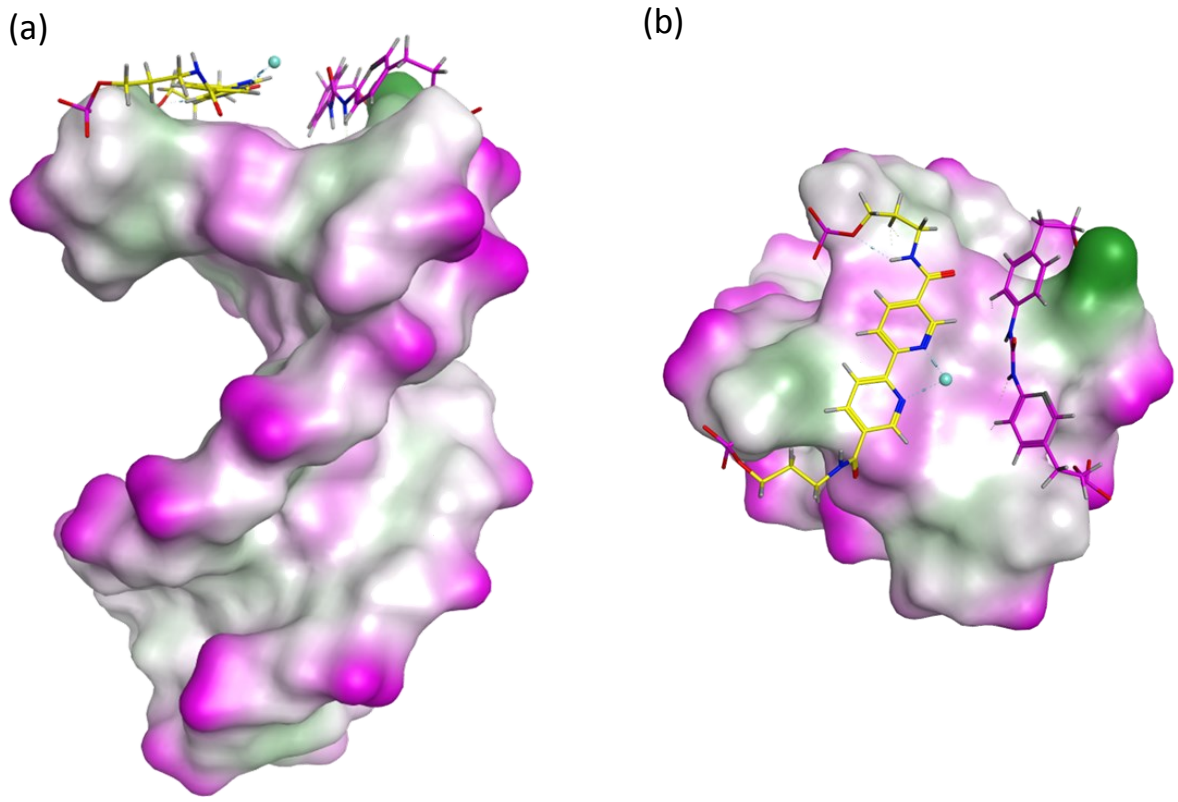


Figure S24. The energy-minimized model of the QD hybrid DNAs.
(a) The side view of **ODN 4** (**U**) in the presence of the copper ion, (b) The top view of **ODN 4** (**U**) in the presence of the copper ion. The yellow structure represents intrastrand bipyridine ligand. The magenta structure means urea derivative (**U**) as the hydrogen bonding moiety in the complementary strand.

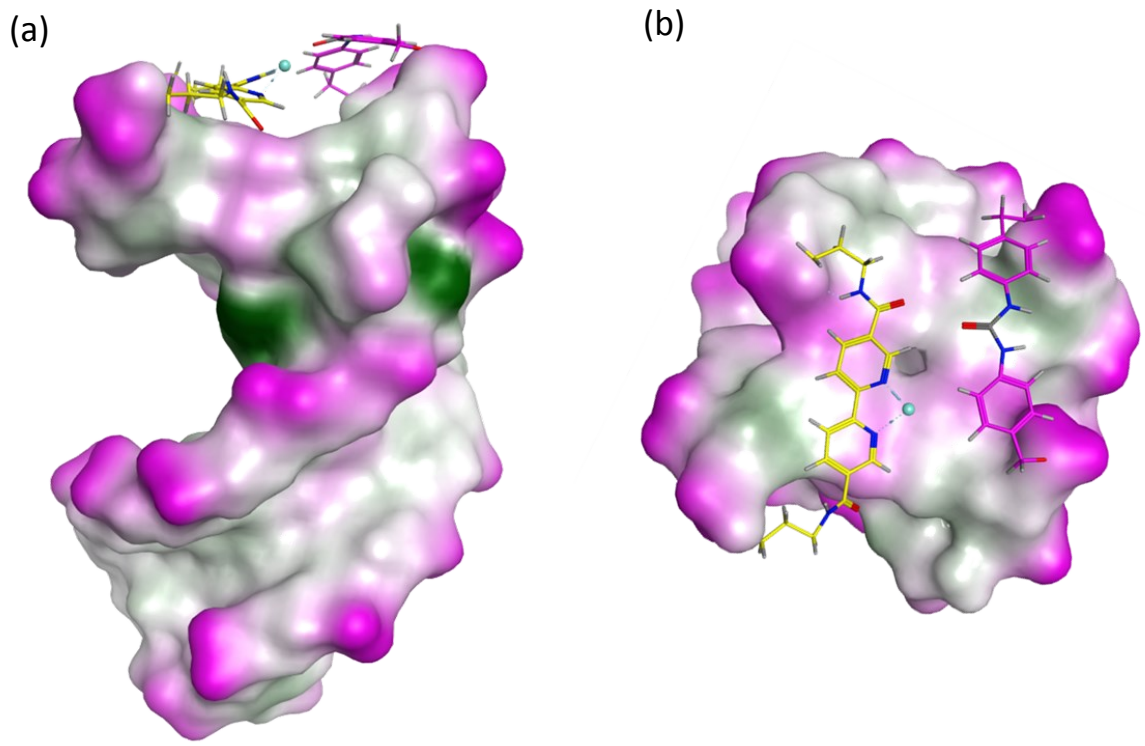


Figure S25. The energy-minimized model of the QD hybrid DNAs.
(a) The side view of **ODN 4** (**Q**) in the presence of the copper ion, (b) The top view of **ODN 4** (**Q**) in the presence of the copper ion. The yellow structure represents intrastrand bipyridine ligand. The green structure means urea derivative (**U**) as the hydrogen bonding moiety in the complementary strand.

Reference

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