

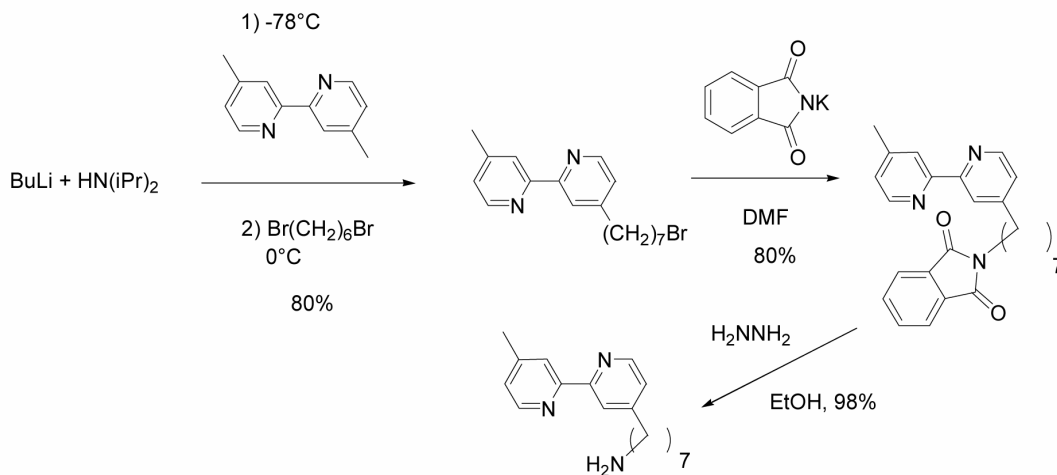
Supporting information

- 1. Synthesis of conjugate 1.**
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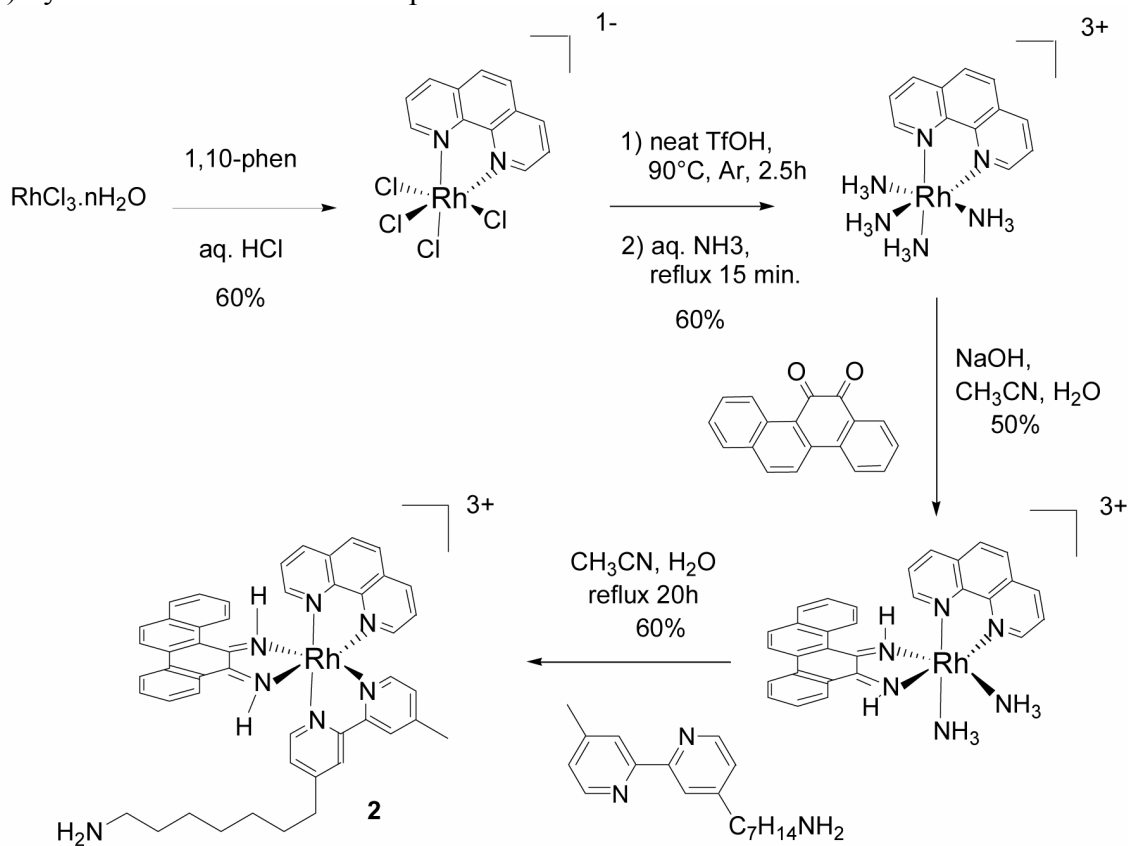
1. Synthesis of conjugate 1.

Synthetic scheme:

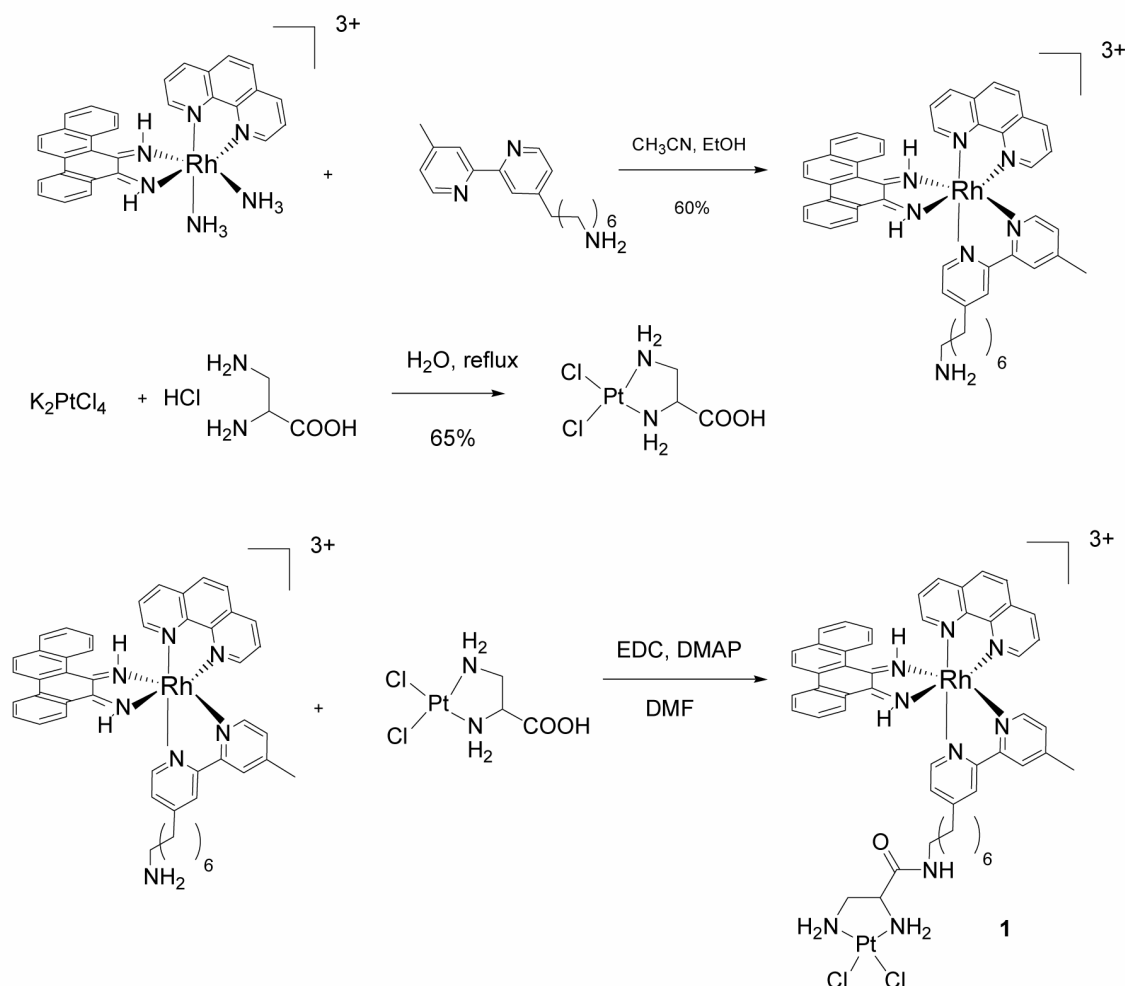
1) Synthesis of the bipyridine ligand precursor:



2) Synthesis of the rhodium complex core:



3) Synthesis of the platinum unit and assembly of the full conjugate:



Scheme S1: Synthetic steps to complexes **1** (conjugate) and **2** (rhodium recognition unit control).

Materials and Methods: Commercially available chemicals and dry solvents were purchased from Aldrich, Lancaster, Fluka, Acros and Pressure Chemical Company and used as received. $[\text{Rh}(\text{chrysi})(\text{phen})(\text{NH}_3)_2]\text{Cl}_3$ was prepared as described in Mürner, H.; Jackson, B.A.; Barton, J.K. *Inorg. Chem.* **1998**, 37, 3007-3012. Dichloro[(d,l)-diaminopropionic acid]platinum^{II} was prepared according to a published procedure (Altman, J.; Wilchek, M. *Inorg. Chim. Acta* **1985**, 101, 171-173). ^1H (^{13}C NMR) were run on a 300 MHz (75 MHz) Varian spectrometer in CDCl_3 at room temperature using

the solvent residual signal as a reference relative to TMS. ESI mass spectrometry was performed at the Protein/peptide Micro Analytical Laboratory (California Institute of Technology) while elemental analysis was performed by Desert Analytics Laboratories (Tucson, AZ). Synthesized DNA and DNA adducts were characterized by MALDI spectrometry on a Voyager DE-PRO MALDI-TOF mass spectrometer with a 337 nm nitrogen laser source from Applied Biosystems using a hydropicolinic acid/picolinic acid/ammonium citrate matrix. Infrared spectra were recorded on a Biorad Win-IR pro spectrometer as KBr pellets.

4'-(7-Bromoheptyl)-4-methyl-[2,2']bipyridine: 16 mL of 2.5M *n*BuLi in hexanes (40 mmol; 1.05 equiv.) were added dropwise to a mixture of N,N-diisopropylamine (6.4 mL; 46 mmol; 1.2 equiv.) and dry THF (25 mL) at -78°C under argon. After stirring at that temperature for 15 minutes, 7.05 g of 4,4'-dimethyl-[2,2']bipyridine (38 mmol) solubilized in 150 mL of dry THF were quickly cannulated into the reaction mixture at -78°C under argon. The chocolate brown solution was stirred at -78°C for 1h under argon and warmed up in an ice bath for 5 minutes before 30 mL of 1,6-dibromohexane (0.19 mol; 5.1 equiv.) in 30 mL of dry THF were added all at once. The orange-yellow solution was stirred at 0°C for 1.5h before water (100 mL) was added and the pH adjusted to 7.0 with 2 M HCl. 100 mL of diethyl-ether were added and the aqueous layer extracted with dichloromethane (3x50 mL). The combined organic layers were dried (Na₂SO₄), filtered and concentrated in vacuo, and the pure product obtained as a colorless oil in 80% yield after column chromatography (SiO₂; CH₂Cl₂, Et₂O). ¹H NMR: 8.55 (d, ³J=5.1 Hz, 1H), 8.53 (d, ³J=4.2 Hz, 1H), 8.21 (m, 2H), 7.10-7.15 (m, 2H), 3.39 (t, ³J=7 Hz, 2H), 2.69 (t, ³J=8 Hz, 2H), 2.44 (s, 3H), 1.84 (quint., ³J=6.6 Hz, 2H), 1.70 (quint., ³J=7.3 Hz, 2H),

1.3-1.5 (m, 6H). ^{13}C NMR: 155.8, 155.7, 152.7, 148.8, 148.7, 148.1, 124.5, 123.8, 121.9, 121.2, 35.3, 33.8, 32.6, 30.1 28.9, 28.4, 27.7, 21.1. $R_f(\text{Al}_2\text{O}_3, \text{CH}_2\text{Cl}_2) = 0.68$. ESMS: 349.2 (MH^+), 369.0 (MNa^+).

N-[7-(4'-Methyl-[2,2']bipyridinyl-4-yl)-heptyl]-phthalimide:

8.69 g of 4'-(7-bromoheptyl)-4-methyl-[2,2']bipyridine (25 mmol) and 5.13 g of potassium phthalimide (27.7 mmol, 1.11 equiv.) were suspended in 60 mL of dry DMF and heated at 50°C for 16h. The mixture was poured onto ice and dichloromethane (200 mL) added. After separation, the aqueous layer was extracted with dichloromethane (3x 40 mL) and the combined organic layers dried (Na_2SO_4), filtered and concentrated in vacuo. The pure product was obtained as a white solid in 80% yield after digestion in ethanol. ^1H NMR: 8.53 (d, $^3J=5.1$ Hz, 1H), 8.52 (d, $^3J=5.4$ Hz, 1H), 8.20 (m, 2H), 7.80-7.84 (m, 2H), 7.67-7.70 (m, 2H), 7.10-7.15 (br d, 2H), 3.66 (t, $^3J=7.3$ Hz, 2H), 2.67 (t, $^3J=8$ Hz, 2H), 2.42 (s, 3H), 1.62-1.72 (m, 4H), 1.3-1.4 (m, 6H). ^{13}C NMR: 168.4, 156.1, 156.0, 152.7, 148.9, 148.8, 148.0, 133.8, 132.0, 124.6, 123.9, 123.1, 122.0, 121.2, 37.9, 35.4, 30.3, 29.1, 28.9, 28.5, 26.7, 21.1. $R_f(\text{Al}_2\text{O}_3, \text{CH}_2\text{Cl}_2) = 0.51$. ESMS: 414.2 (MH^+), 436.2 (MNa^+). EA: $\text{C}_{26}\text{H}_{27}\text{N}_3\text{O}_2$ *calc.* %C 75.52, %H 6.58, %N 10.16, *obs.* %C 75.24, %H 6.67, %N 9.85.

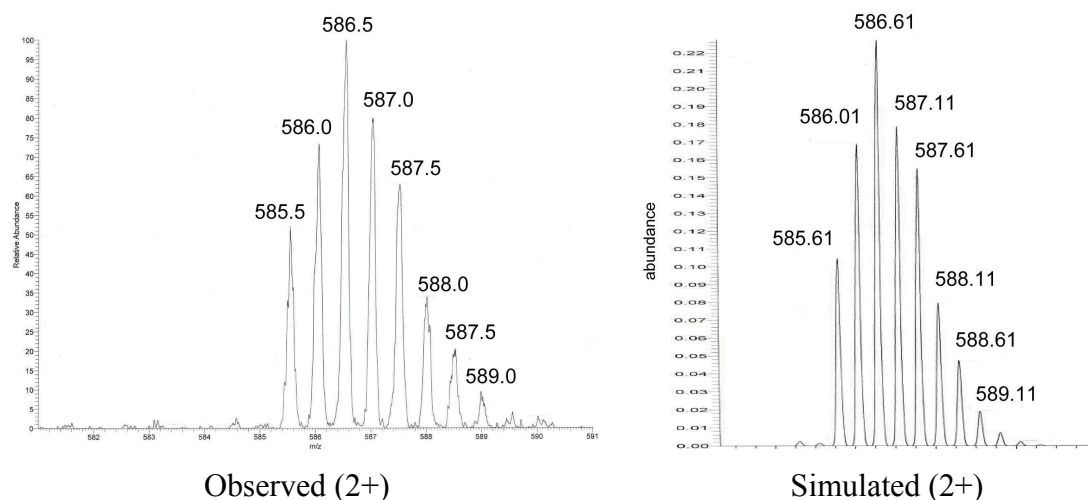
7-(4'-Methyl-[2,2']bipyridinyl-4-yl)-heptylamine (bpy-NH₂): 1.3 mL of hydrazine hydrate (27 mmol, 5.2 equiv.) were added to a suspension of N-[7-(4'-methyl-[2,2']bipyridinyl-4-yl)-heptyl]-phthalimide (2.1 g, 5.08 mmol) in ethanol (40 mL), and the mixture heated at 40°C under argon for 12h. The white precipitate was filtered, washed with ethanol (60 mL) and the filtrate concentrated in vacuo. The residue was taken up in chloroform (50 mL), filtered once more and extracted with 1 M HCl (4x30

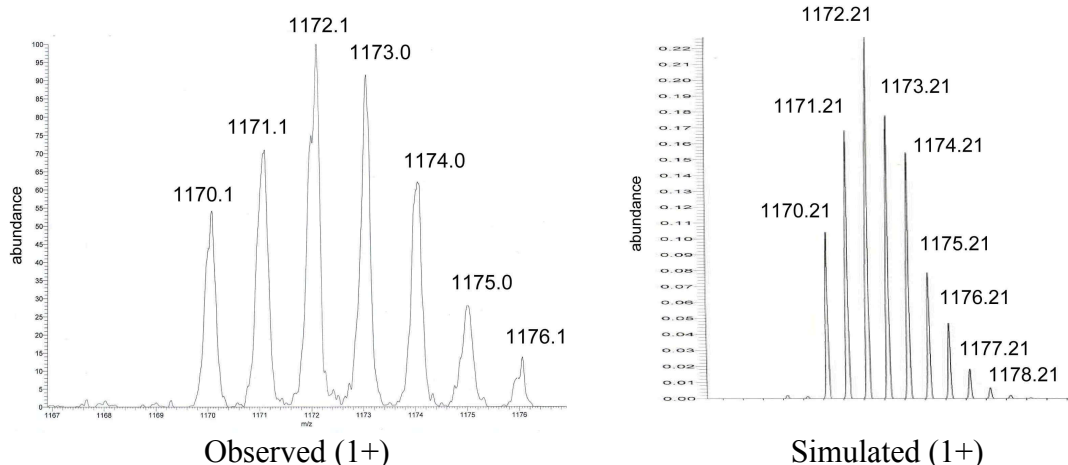
mL). After washing with chloroform (3x30 mL), the combined aqueous layers were basified to pH~10 with NaHCO₃ (s) and 4 M aq. KOH. The mixture was extracted with 5x50 mL CHCl₃ and the combined organic layers dried (Na₂SO₄), filtered and concentrated in vacuo to yield the desired product as a white solid in 98%. ¹H NMR: 8.55 (d, ³J=4.5 Hz, 1H), 8.53 (d, ³J=4.2 Hz, 1H), 8.2s (s, 2H), 7.12 (d, ³J=5.2 Hz, 2H), 2.6-2.75 (m, 4H), 2.43 (s, 3H), 1.69 (quint., ³J=7 Hz, 2H), 1.3-1.5 (m, 8H). ¹³C NMR: 156.1, 156.0, 152.7, 148.9, 148.8, 148.1, 124.6, 123.9, 122.0, 121.2, 41.4, 35.4, 32.0, 30.3, 29.1, 29.0, 26.6, 21.1. ESMS: 284.2 (MH⁺). EA: C₁₈H₂₅N₃·0.19 CHCl₃ *calc.* %C 71.38, %H 8.29, %N 13.73, *obs.* %C 71.40, %H 8.07, %N 13.70.

[Rh(chrysi)(phen)(bpyNH₂)]Cl₃ (2): A solution of [Rh(chrysi)(phen)(NH₃)₂]Cl₃ (103 mg) and 7-(4'-methyl-[2,2']bipyridinyl-4-yl)-heptylamine (55 mg, 1.94 mmol, 1.5 equiv.) in a mixture of acetonitrile (25 mL) and ethanol (1 mL) was refluxed for 16h. After evaporation of the solvents, the brown red residue was taken up in water and loaded on a Sephadex SPC25 cation exchange column (chloride form) and eluted with a gradient of MgCl₂ in water (0-0.5 M). The brown band was desalted by adsorption onto a SepPak C18 Cartridge (Waters), washed with copious water and eluted with a mixture of H₂O/CH₃CN/TFA (0.5:0.5:0.001). 67 mg of a dark red hygroscopic solid were obtained after lyophilization (60%). ESMS: 410.2 (**2**-3Cl-H)²⁺, 431.2 [**2**-3Cl-H+CH₃CN]²⁺, 820.2 (**2**-3Cl-2H)⁺. UV-vis (H₂O) λ_{max} (nm) (log₁₀ε): 207 (4.9), 267 (4.7), 288 (sh), 300 (4.4), 312 (sh), 396 (3.8), 459 (3.6). IR (KBr, cm⁻¹): 3460 (br), 3090, 2941, 2860, 1677, 1620 (sh), 1516, 1432, 1202, 1136, 834, 718. EA: C₄₈H₄₅N₇RhCl₃·CF₃CO₂H·2.7 H₂O *calc.* %C 54.99, %H 4.75, %N 8.98, *obs.* %C 54.99, %H 4.75, %N 8.77.

1: To a solution of **2** (19 mg, 2.0×10^{-5} mol) and dichloro[(d,l)-diaminopropionic-acid]platinum^{II} (18 mg, 4.9×10^{-5} mol, 2.4 equiv.) in 1.0 mL of dry DMF were added 20 mg of EDCI (5 equiv.) and two drops of dry triethylamine under argon. The brown mixture was stirred at room temperature for 20h, adsorbed onto a SepPak C18 Cartridge, washed thoroughly with water, dilute sodium hydroxide and water again, before elution with a mixture of H₂O/CH₃CN/TFA (0.5:0.5:0.001). The desired complex was obtained quantitatively as a hygroscopic brown solid after lyophilization. ESMS: 586.9 (**1**-3Cl-H)²⁺, 1172.1 (**1**-3Cl-2H)⁺. ESI MS MS on peak 1172.1: 1136.0 [(**1**-3Cl-2H)-Cl]⁺, 1099.1 [(**1**-3Cl-2H)-2Cl]⁺. UV-vis (H₂O) λ_{max} (nm) (log₁₀ε): 207 (4.9), 227 (sh), 270 (4.7), 290 (sh), 300 (sh), 310 (sh), 395 (3.8), 459 (3.7) [NB: The spectra of **1** and **2** are very similar and show superimposed signals]. IR (KBr, cm⁻¹): 3440 (br), 3180, 3093, 2936, 2862, 1677, 1625 (sh), 1566, 1523, 1431, 1202, 1133, 833, 801, 719. EA: C₅₁H₅₁N₉ORhPtCl₅.6 CF₃CO₂H.14.5 H₂O *calc.* %C 34.08, %H 3.63, %N 5.68, *obs.* %C 34.01, %H 3.46, %N 5.95.

2. Observed and simulated isotope patterns of conjugate 1 (ESMS).





3. Methods used to study the extent of platination

10 μM of labeled duplex [1] CX_n (X= C, G; n = 0, 3, 9) were prepared by heating a mixture of each strand (same concentration, estimated by UV-vis spectroscopy; one of which contained radiolabeled strands) solubilized in a 20 mM NaCl, 20 mM Na phosphate pH 7 buffer at 90° C for 10 minutes and letting the samples slowly cool down to room temperature (~3h). Duplex CX_n (10 μM in buffer) and complex 1 or 2 (10 μM in water) were then mixed and incubated in the absence of light for up to 24h. 20 μM aliquots were taken out at determined times, diluted to 70 μM by addition of 0.5 M NaCl (to stop the platination reaction [2]), filtered through molecular sieves (to remove free platinum reactant [3]) and dried in vacuo. After quantification of their activity, the dry samples were dissolved in a appropriate volume of loading dye (mixture of formamide, bromophenol and xyleneblue [1]; typically 10 μM) and analyzed by gel electrophoresis under denaturing conditions (0.3 mm thick, 18% acrylamide, TBE buffer, 90W, 2000 V for 90 min). The PtenCl₂ controls were run for about twice as much time, until the fast moving dye was eluted out of the gel, conditions under which the major adducts separates from the parent band well enough to be quantified. The gel was then exposed to phosphor

screens at room temperature for an appropriate amount of time (typically 4-10h) in order to collect a quantifiable signal without saturating the screen (less than 300 000 counts total). Molecular Dynamics phosphorimager was used to collect data from the storage screen and the gel image analyzed using the ImageQuant program.

References:

- [1] Sambrook, J.; Frisch, E.F.; Maniatis, T.; *Molecular Cloning: A Laboratory Manual* 2nd ed.; Cold Spring Harbor Laboratory; New York, **1989**.
- [2] Gonnet, F.; Kozelka, J.; Chottard, J.-C.; *Angew. Chem. Int. Ed. Engl.* **1992**, 31, 1483-1485.
- [3] Micro Bio-spin Chromatography Columns, Bio-Gel P-6 gel, Bio-Rad; 6,000 daltons exclusion limit.

3. Autoradiogram of the denaturing gel revealing the photocleavage pattern within the DNA adducts after cyanide reversal.

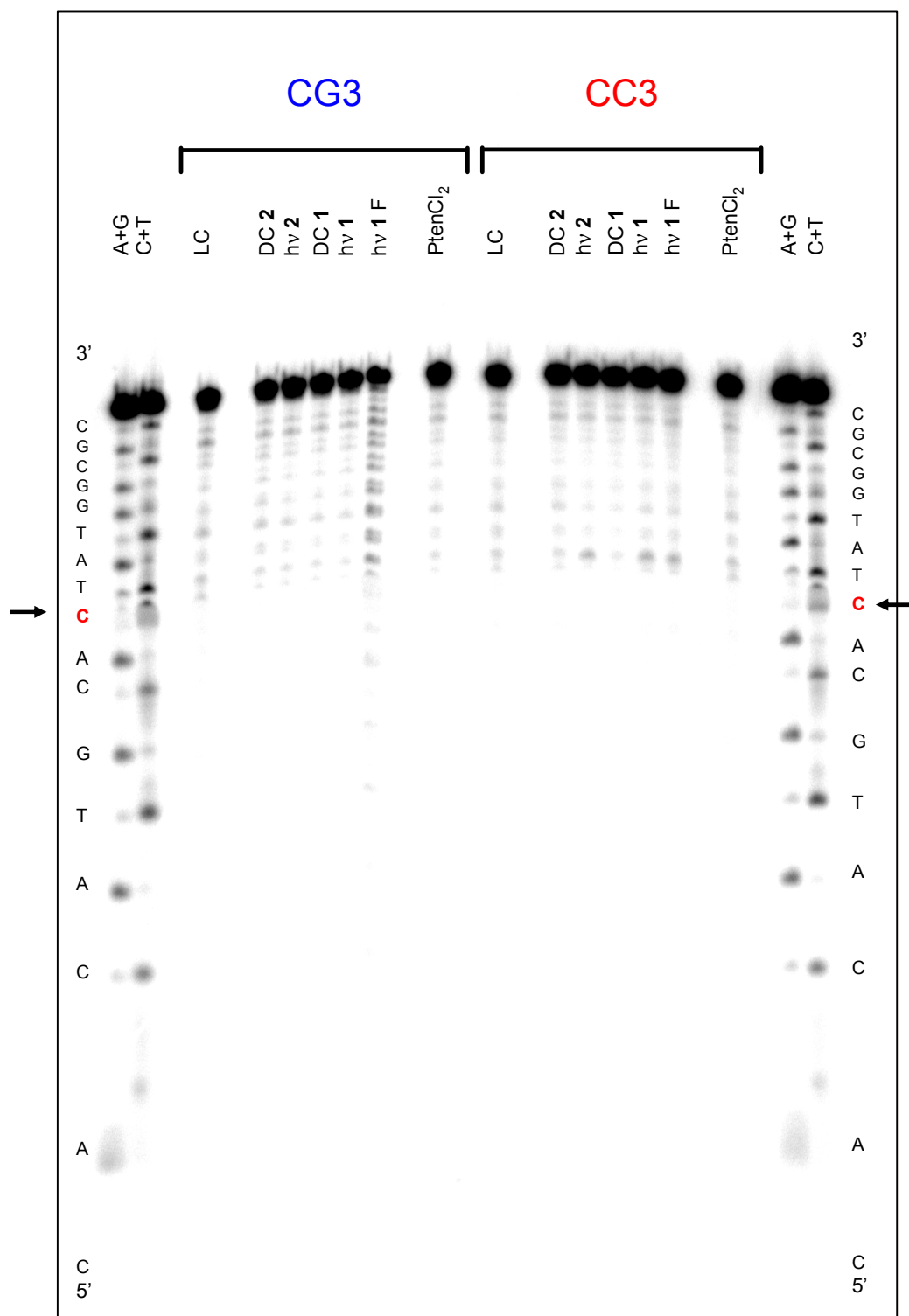


Figure S1: autoradiogram of the gel electrophoresis of products after the following treatments: 1) incubation of duplexes **CG3** and **CC3** (5 μ M) with complexes **1** or **2** (5 μ M) in sodium phosphate buffer pH 7 (10 mM) in the presence of sodium chloride (10 mM) at 37°C for 12h, protected from light; 2) irradiation of the mixture for 15 min. at 442 nm wavelength (HeCd laser; 12.5 mW power); 3) treatment with 0.2 M NaCN (basic) at 60°C for 24h, protected from light (all samples except Maxam Gilbert). DC n: duplex incubated with complex **n** in the absence of light, hv n: irradiation after incubation with complex **n**. hv n F: irradiation after molecular sieve purification of the incubated duplexes. PtenCl₂: duplex incubated with PtenCl₂.