Quantitative Self-Sensitized Photooxidation of 1,2-Diarylcyclobutene Derivatives by Singlet Oxygen

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Abstract: Ligands **1** and **2** underwent quantitative photooxidation when they were reacted with singlet oxygen sensitized by methylene blue. However, the quantitative reaction became self-sensitized for the compound **Ru(1)** wherein the ruthenium complex acted as a sensitizer.

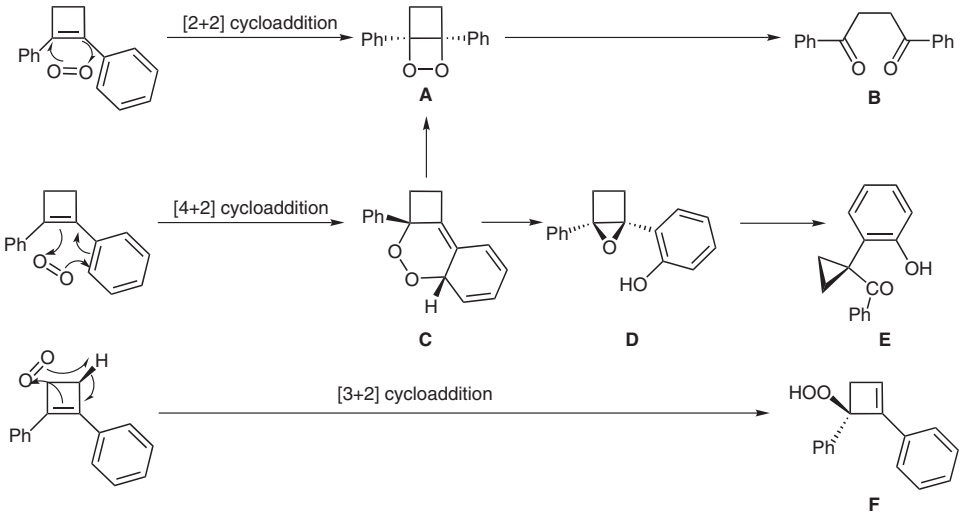
Key words: complexes, heterocycles, ligands, photooxidation, ruthenium

The oxidation of olefins to alcohols or ketones by singlet oxygen has been extensively reported.[1] In this type of reaction, singlet oxygen is produced in situ by a photosensitization process that consists of an energy transfer from the excited state of a sensitizer to the triplet ground state of O_2 ($^3\Sigma_g^-$).[2] Organic molecules as well as coordination compounds like methylene blue[3–5] or ruthenium complexes[6], respectively, are usually used as photosensitizers. However, the reaction becomes self-sensitized if the substrate acts as its own sensitizer.[7] This principle has been employed in the photodynamic treatment of malignant tumors.[8]

Photooxidation reaction between 1,2-diphenylcyclobutene and singlet oxygen can take place in three different modes[5,9] (Scheme 1). The first involves a [2+2] cycloaddition reaction between singlet oxygen and the double bond in the cyclobutene moiety. The resulting dioxetane **A** is easily cleaved either thermally or photochemically to form the diketone **B**. The second type of photooxidation is a [4+2] cycloaddition reaction producing the endoperoxide molecule **C** which rearranges either to dioxetane **A** to yield **B** or to phenol-epoxide **D** to form **E** (Scheme 1). The last type of photooxidation process requires an allylic hydrogen to perform a [3+2] cycloaddition reaction to obtain the allylic hydroperoxide **F**.

Previously reported photooxidation reactions of 1,2-diarylcyclobutene derivatives with singlet oxygen yielded the product with two-carbonyl functions (**B** in the case of 1,2-diphenylcyclobutene) in poor to moderate yields (14–40%).[3,5,9]

Here, we report quantitative photooxidation reactions of non-coordinated ligands **1** and **2** (Scheme 2) sensitized by methylene blue and also, a self-sensitized reaction involving the transformation of the coordinated ligands in complex Ru-**1** (Schemes 3 and 5) to give products with two ketone functionalities (Schemes 4 and 5). These quantitative yields can be explained as follows. Firstly, ligands **1** and **2** and complex Ru-**1** rearrange exclusively to bis-ketone compounds after the [4+2] cycloaddition reaction be-



Scheme 1 Different mechanisms of photooxidation reaction between singlet oxygen and 1,2-diphenylcyclobutene

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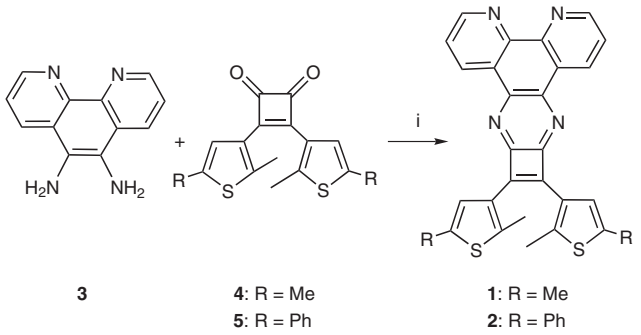
cause of the absence of protons at position 2 in the thiophene moieties. Secondly, ligands **1** and **2** as well as complex Ru-**1** do not have allylic protons at positions 3 and 4 in the cyclobutene fragment. Therefore, the [2+3] cycloaddition reaction cannot take place and hence, the allylic hydroperoxide derivatives are not formed. Additionally, singlet oxygen can react with ligands **1** and **2** and also with complex Ru-**1**. For both forms of the ligands, non-coordinated and complexed, either [2+2] or [4+2] cycloaddition reaction is accessible. In both cases, compounds with two carbonyl functions are obtained.

Ligand **1** was synthesized in a one-step reaction by double condensation between **3**[10] and **4**[11] (Scheme 2).

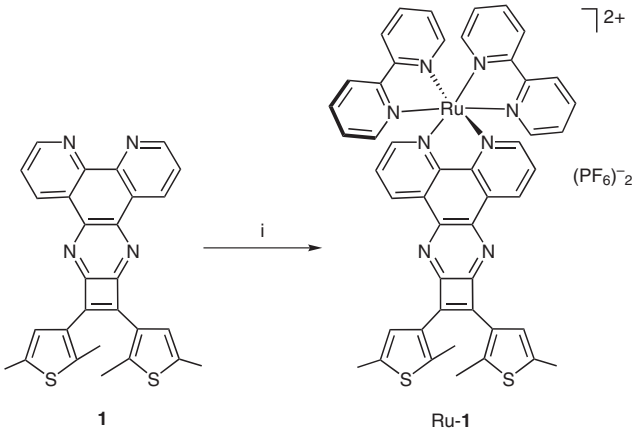


Scheme 2 *Reagents and conditions*: i) Dean–Stark assembly, toluene–AcOH 5:1, reflux, 72 h.

We have optimized the boundary conditions for the synthesis of ligand **1** (Table 1). By refluxing in ethanol (entry 1), methanol (entry 3) or acetic acid (entry 4), only traces of ligand **1** were detected. By heating at 400–500 °C without any solvent, **4** decomposed completely (entry 2). In deaerated acetic acid at boiling point, ligand **1** was formed in 5% yield (entry 5). With a Dean–Stark assembly to remove water, ligand **1** was formed in 13% yield in deaerated toluene–acetic acid (15:2) (entry 6) and 29% yield in deaerated toluene–acetic acid 5:1 (entry 7); both with a reaction time of 24 hours. Finally, we found the best conditions in deaerated toluene–acetic acid (5:1) with a reaction time of 72 hours (entry 8) giving 32% yield.

Ligand **2** was synthesized under the same conditions but the double condensation reaction occurring between **3**[10] and **5**[12] gave a moderate yield of 22%.

The synthesis of the metal complex Ru-**1** (Scheme 3) was performed under argon in an AtmosBag$_{TM}$ (Aldrich: Z112828-1EA). Ru(bpy)$_2$Cl$_2$·2H$_2$O and ligand **1** were heated under reflux in ethanol–water (3:1) overnight. Solvents were removed and the residue was dissolved in water. The complex Ru-**1** was precipitated with NH_4PF_6 and purified on a silica gel preparative plate. Ru-**1** was obtained in a yield of 58%. Any kind of manipulation will have to be carried out under oxygen free atmosphere to avoid the photooxidation of Ru-**1** to Ru-**1**(O) (Scheme 5). This complexation reaction was also performed in solvents like methoxyethanol or 1,2-dichloromethane/water

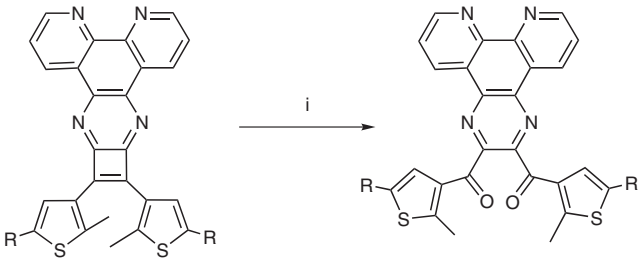


Scheme 3 *Reagents and conditions*: i) Ru(bpy)$_2$Cl$_2$·2H$_2$O, EtOH–H$_2$O (3:1), argon atmosphere, reflux, 24 h.

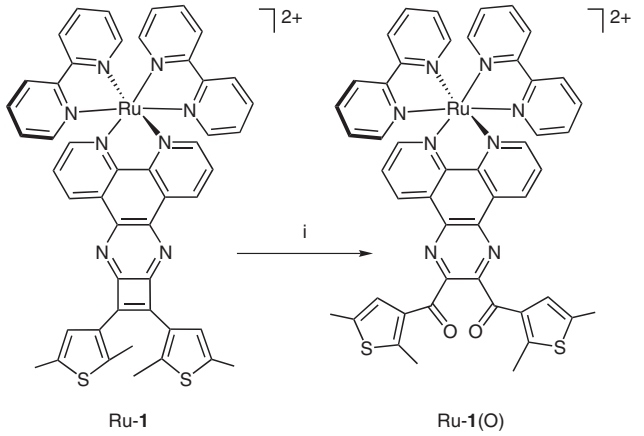
Table 1 Double Condensation Reaction of 5,6-Diaminophenanthroline (**3**)[10] with 3,4-Bis(2,5-dimethylthien-3-yl)cyclobutenedione (**4**)[11] (Scheme 2)

Entry	**3** (mmol)	**4** (equiv)	Solvent (mL)	Acetic acid (mL)	Temp (°C)	Time (h)	Recovered **4** (%)	Yield (%)
1	1.8	0.66	EtOH (40)	0.4	79	22	79	traces
2	0.1	1	–	–	400–500	0.25	0	0
3[a]	0.5	1	MeOH (15)	0.15	65	17	86	traces
4[a]	1.5	0.9	AcOH	40	118	24	87	traces
5[c]	0.5	1	AcOH	10	118	24	66	5
6[b,c]	0.5	1	toluene (15)	2	111	24	53	13
7[b,c]	0.6	1	toluene (10)	2	111	24	55	29
8[b,c]	1.2	1	toluene (20)	4	111	72	47	32

[a] Addition of $MgSO_4$.
[b] Dean–Stark assembly to remove water was used.
[c] Argon was bubbled for 20 min.



Scheme 4 *Reagents and conditions*: i) Oxygen bubbling in deuterated chloroform with methylene blue as photosensitizer; irradiation with a 300 W lamp.



Scheme 5 *Reagents and conditions*: i) Oxygen bubbling in deuterated acetonitrile; irradiation with a 300 W lamp.

(1:1) but were unsuccessful due to the decomposition of ligand **1** to unknown products under such conditions.

Photooxidation of ligands **1** and **2** were performed in the same way (Scheme 4). In an NMR tube, the ligand was dissolved in deuterated chloroform containing methylene blue as photosensitizer. The reaction mixture was irradiated under oxygen bubbling with a 300 W incandescent lamp for 3 hours. Methylene blue was removed by extraction. Ligands **1**(O) and **2**(O) were obtained pure and hence isolated in quantitative yield without any purification.

Photooxidation of complex Ru-**1** was performed in deuterated acetonitrile (Scheme 5) in an NMR tube. The reaction mixture was irradiated under oxygen bubbling with a 300 W incandescent lamp for 15 minutes. The solvent was removed to give complex Ru-**1**(O) and isolated in quantitative yield without any purification.

Analytical data are consistent with the given structures of photooxidized products. The number of peaks in ^{1}H NMR and ^{13}C NMR before and after photooxidation were identical meaning the symmetry of the compounds did not change during the photooxidation process. Mass spectrum and high-resolution mass spectrum of photooxidized products showed an increase in molecular weight by 32 g/mol corresponding to the incorporation of two atoms of oxygen. A new band around 1650 cm^{-1} in the IR spectrum allows an attribution of these oxygen atoms to carbonyl functions.

To conclude, we have developed synthetic methods involving a double condensation reaction to get ligands **1** and **2**. Ligand **1** was coordinated to a ruthenium center giving Ru-**1** under mild conditions. We have performed quantitative photooxidation reactions of ligands **1** and **2** with singlet oxygen, produced by a photosensitized process using methylene blue as sensitizer, as well as a self-sensitized photooxidation reaction for complex Ru-**1**.

Column chromatography was performed using silica gel (230–400 or 400–600 mesh size) from Chemie Brunschweig AG. Preparative plates (20 × 20 cm) with silica gel 60 F_{254}, having a layer thickness of 2 mm (for preparative plate chromatography) and aluminum sheets coated with silica gel 60 F_{254} (for TLC) were purchased from Merck. A mixture of MeCN, MeOH and 10% aq KNO_3 in a volume ratio of 40:10:1 respectively, was used as the eluent. All products were characterized by ^{1}H NMR and ^{13}C NMR, on Bruker Avance DRX-400 (400.13 MHz, for ^{1}H NMR and 100.62 MHz for ^{13}C NMR) and on Bruker Avance DRX-360 (360 MHz, for ^{1}H NMR and 90.55 MHz for ^{13}C NMR spectrometer). Chemical shifts are given in ppm using the solvent itself as internal standard. The chemical shifts are expressed as δ values and the coupling constants (*J*) are given in Hertz. Mass spectra were recorded on HP 5988A Quadrupole (EI ionization, 70 eV) mass spectrometer. ESI and high-resolution mass spectra were recorded on a Bruker FTMS 4.7T BioAPEXII spectrometer. GC-MS analyses were done on ThermeQuest Finnigan VOYAGER GS/MS Trace GC 2000 Series equipped with an Optima-5-MS column (0.25 μm, 25 m × 0.32 mm; Marcherey-Nagel). UV/vis spectra were recorded with a Perkin-Elmer Lambda 40. The wavelength maxima are reported in nm.

Ligand 1

In a Dean-Stark assembly, the corresponding 1,2-diketone **4** (362 mg, 1.2 mmol, 1.0 equiv) and phenanthroline-5,6-diamine **3** (252 mg, 1.2 mmol, 1.0 equiv) were dissolved in deaerated toluene (20 mL) and AcOH (4 mL) under argon. The mixture was stirred for 24 h under reflux (130 °C). Solvents were removed by distillation. The residue was chromatographed on silica gel using CH_2Cl_2–Et_3N (100:1) as eluent to give **1**; yield: 182 mg (32%).

IR (KBr): 2914, 2852, 1664, 1522, 1484, 1430, 1364, 1298, 1214, 1188, 1144, 922, 804, 736 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.44 (s, 6 H), 2.84 (s, 6 H), 6.88 (s, 2 H), 7.66 (dd, *J* = 4.3, 8.4 Hz, 2 H), 9.14 (dd, *J* = 4.3, 1.6 Hz, 2 H), 9.24 (dd, *J* = 1.8, 8.2 Hz, 2 H).

^{13}C NMR ($CDCl_3$): δ = 174.2, 153.1, 146.5, 144.0, 137.7, 135.9, 135.1, 131.9, 125.6, 123.1, 15.8, 14.9.

MS (EI): *m*/*z* = 477.12 (M^+ + 1).

HRMS: *m*/*z* calcd for $C_{28}H_{21}N_4S_2$ (M^+ + 1): 477.1202; found: 477.1197.

UV/vis ($CHCl_3$): λ_{max} (ε) = 288 (30700), 315 (33900), 450 nm (3400).

Ligand 2

In a Dean–Stark assembly, the corresponding 1,2-diketone **5** (511 mg, 1.2 mmol, 1.0 equiv) and phenanthroline-5,6-diamine **3** (252 mg, 1.2 mmol, 1.0 equiv) were dissolved in deaerated toluene (20 mL) and AcOH (4 mL) under argon. The mixture was stirred for 24 h under reflux (130 °C). Solvents were removed by distillation.

The residue was chromatographed on silica gel using CH_2Cl_2–Et_3N (100:1) as eluent to give **2**; yield: 160 mg (22%).

IR (KBr): 3056, 3020, 2960, 2914, 2848, 1670, 1540, 1486, 1366, 1296, 1262, 1190, 1092, 1018, 804, 738, 686 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.98 (s, 6 H), 7.31 (tt, *J* = 7.33, 1.52 Hz, 2 H), 7.37 (tt, *J* = 7.33, 1.52 Hz, 4 H), 7.53–7.57 (m, 6 H), 7.74 (dd, *J* = 8.21, 4.42 Hz, 2 H), 9.24 (dd, *J* = 4.29, 1.26 Hz, 2 H), 9.31 (dd, *J* = 8.21, 1.64 Hz, 2 H).

^{13}C NMR ($CDCl_3$): δ = 174.8, 153.4, 149.9, 146.2, 142.6, 135.8, 133.9, 133.5, 129.4, 129.3, 129.1, 128.4, 128.1, 125.8, 123.9, 122.8, 16.4.

MS (EI): *m*/*z* = 601.16 (M^+ + 1).

HRMS: *m*/*z* calcd for $C_{38}H_{25}N_4S_2$ (M + 1): 601.1515; found: 601.1524.

UV/Vis ($CHCl_3$): λ_{max} (ε) = 305 (51900), 365 (16200), 483 nm (3000).

Metal Complex Ru-1

The synthesis was performed under argon in an AtmosBag$_{TM}$ (Aldrich: Z112828-1EA). A 25 mL, one-necked, round-bottomed flask was charged with the ligand **1** (20 mg, 44.2 μmol, 1 equiv), $Ru(bpy)_2Cl_2{\cdot}2H_2O$ (25 mg, 48.6 μmol, 1.1 equiv), EtOH (15 mL), and H_2O (5 mL). The solution was refluxed overnight under argon. The organic phase was extracted with H_2O (3 × 20 mL) and the aqueous phase was washed with CH_2Cl_2 (3 × 20 mL). The residual CH_2Cl_2 in the aqueous phase was removed in vacuo followed by the addition of NH_4PF_6 (0.5 g). The precipitate, thus formed, was collected by filtration and purified on a silica gel plate (MeCN–MeOH–10% aq KNO_3, 40:10:1) to afford Ru-**1**; yield: 30 mg (58%).

IR (KBr): 3076, 2917, 2851, 1603, 1526, 1465, 1446, 1370, 839, 762, 730 cm^{-1}.

^1H NMR (CD_3CN): δ = 2.39 (s, 6 H), 2.41 (s, 6 H), 6.63 (s, 2 H), 7.26 (dd, *J* = 6.4, 6.4 Hz, 2 H), 7.47 (dd, *J* = 6.4, 6.4 Hz, 2 H), 7.69 (d, *J* = 5.0 Hz, 2 H), 7.85 (d, *J* = 5.5 Hz, 2 H), 7.87 (d, *J* = 5.5 Hz, 2 H), 8.01 (dd, *J* = 7.7, 7.7 Hz, 2 H), 8.12 (dd, *J* = 7.9, 7.9 Hz, 2 H), 8.17 (d, *J* = 5.0 Hz, 2 H), 8.52 (d, *J* = 8.2 Hz, 2 H), 8.56 (d, *J* = 8.2 Hz, 2 H), 9.51 (d, *J* = 8.2 Hz, 2 H).

MS (ESI): *m*/*z* = 1035.12 ($M^+ - PF_6^-$).

HRMS: *m*/*z* calcd for $C_{48}H_{36}F_6N_8PRuS_2$ ($M^+ - PF_6$): 1035.1184; found: 1035.1179.

UV/vis (MeCN): λ_{max} (ε) = 287 (87100), 420 (19000), 456 nm (23500).

Ligand 1(O)

In an NMR tube, ligand **1** (4 mg, 4.8 mmol, 1.0 equiv) was dissolved in $CHCl_3$ (0.75 mL) containing methylene blue (10^{-4} M). The mixture was irradiated under O_2 bubbling with a 300 W lamp for 3 h. The mixture was then poured into H_2O (1 mL) and extracted with CH_2Cl_2 (3 × 1 mL). The organic extract was dried ($MgSO_4$) and the solvent removed under vacuum to afford ligand **1**(O); yield: 4 mg (ca. 100%).

IR (KBr): 2962, 2916, 2600, 2494, 1644, 1472, 1358, 1252, 1124, 190, 742, 634 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.42 (s, 6 H), 2.71 (s, 6 H), 7.10 (s, 2 H), 7.85 (dd, *J* = 8.21, 4.42 Hz, 3 H), 9.37 (dd, *J* = 4.55, 1.77 Hz, 3 H), 9.47 (dd, *J* = 8.08, 1.77 Hz, 2 H).

^{13}C NMR ($CDCl_3$): δ = 15.0, 16.3, 124.4, 126.5, 127.9, 133.9, 134.0, 135.2, 138.2, 151.4, 152.5, 152.9, 187.3.

MS (ESI): *m*/*z* = 509.1 (M^+ + 1).

HRMS: m/z calcd for $C_{28}H_{21}N_4O_2S_2$ (M^+ + 1): 509.1100; found: 509.1101.

UV/Vis ($CHCl_3$): λ_{max} (ε) = 266 (33300), 314 (14800), 357 nm (7800).

Ligand 2(O)

In an NMR tube, ligand **2** (4 mg, 4.8 mmol, 1.0 equiv) was dissolved in $CHCl_3$ (0.75 mL) containing methylene blue (10^{-4} M). The mixture was irradiated under O_2 bubbling with a 300 W lamp for 3 h. Then the mixture was poured into H_2O (1 mL) and extracted with CH_2Cl_2 (3 × 1 mL). The organic phase was dried ($MgSO_4$) and the solvent removed under vacuum to afford ligand **2**(O); yield: 4 mg (ca. 100%).

IR (KBr): 2920, 2854, 1648, 1586, 1534, 1494, 1458, 1362, 1238, 1122, 1026, 948, 758, 688 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.81 (s, 6 H), 7.28 (m, 2 H), 7.34 (m, 4 H), 7.52 (m, 4 H), 7.68 (s, 2 H), 7.86 (dd, *J* = 8.21, 4.42 Hz, 2 H), 9.40 (dd, *J* = 4.55, 1.77 Hz, 2 H), 9.51 (dd, *J* = 8.08, 1.77 Hz, 2 H).

^{13}C NMR: Could not be measured owing to extreme low solubility.

MS (ESI): *m*/*z* = 633.1 (M^+ + 1).

HRMS: *m*/*z* calcd for $C_{38}H_{25}N_4O_2S_2$ (M + 1): 633.1413; found: 633.1400.

UV/vis ($CHCl_3$): λ_{max} (ε) = 269 (43800), 361 nm (8100).

Metal Complex Ru-1(O)

In an NMR tube, metal complex Ru-**1** (4 mg, 3.3 μmol, 1.0 equiv) was dissolved in MeCN (0.75 mL). The solution was irradiated under O_2 bubbling with a 300 W lamp for 15 min. The solvent was removed in vacuo to afford complex Ru-**1**(O); yield: 4 mg (ca. 100%).

IR (KBr): 3082, 2923, 2853, 1653, 1603, 1465, 1447, 1362, 841,764, 731 cm^{-1}.

^1H NMR (CD_3CN): δ = 2.39 (s, 6 H), 2.62 (s, 6 H), 7.14 (d, *J* = 1.01 Hz, 2 H), 7.26 (m, 2 H), 7.47 (m, 2 H), 7.67 (m, 2 H), 7.86 (m, 2 H), 7.89 (dd, *J* = 8.21, 5.43 Hz, 2 H), 8.02 (dt, *J* = 7.96, 1.52 Hz, 2 H), 8.12 (dt, *J* = 7.89, 1.39 Hz, 2 H), 8.24 (dd, *J* = 5.31, 1.26 Hz, 2 H), 8.52 (d, *J* = 7.83 Hz, 2 H), 8.55 (d, *J* = 8.34 Hz, 2 H), 9.41 (dd, *J* = 8.21, 1.39 Hz, 2 H).

MS (ESI): *m*/*z* = 1067.13 ($M^+ - PF_6^-$).

HRMS: *m*/*z* calcd for $C_{48}H_{36}N_8O_2S_2Ru$ (M^{2+} – $2PF_6$): 461.0718; found: 461.0720.

UV/vis (MeCN): λ_{max} (ε) = 285 (67400), 418 (13100), 451 nm (15700).

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