Visible Light Activated Benzimidazolequinone Alkoxyamines of 1,1,3,3-Tetramethylisoindolin-2-yloxyl (TMIO)

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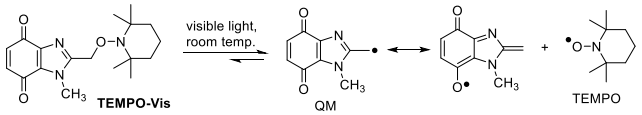
Supporting information (NMR spectra and Figures S1 & S2)

Abstract: 1,1,3,3-Tetramethylisoindolin-2-yloxyl (TMIO) is a well-known stable isoindoline aminoxyl radical, which is thermally generated (at >100 °C) from literature alkoxyamine derivatives. Herein is the synthesis of visible light activated benzimidazolequinone alkoxyamines of TMIO using oxidative methods and the first room temperature nitroxide-exchange experiments with 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) analogues. For the alkoxyamine **TMIO-Vis** dissociation rate constants are provided using TEMPO and oxygen as radical traps.

Introduction

Traditionally bioreductive activation or enzymatic reduction of heterocyclic quinones (prodrugs) gives cytotoxic quinone methides (QMs). Bioreductives include the clinical drug mitomycin C (MMC)[1] and synthetic benzimidazolequinone alternatives.[2] More recently, we introduced alkoxyamines of benzimidazolequinones, the simplest being **TEMPO-Vis**, with visible light induced homolysis providing an alternative to Nature's bioreduction for forming the QM (Scheme 1).[3] This is exceptional, since alkoxyamines of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) normally require temperatures of 80-130 °C for homolysis.[4,5] The driving force for the room temperature homolysis is the release of bench-stable aminoxyl radical (nitroxide) TEMPO, and extensive delocalization of the QM radical (Scheme 1).



Scheme 1. Visible light activated alkoxyamine (**TEMPO-Vis**)[3]

Researchers at Australia's QUT heralded derivatives of the isoindoline nitroxide, 1,1,3,3-tetramethylisoindolin-2-yloxyl (TMIO, Figure 1), as profluorescent probes,[6] with applications that include the monitoring of cellular oxidative stress,[7] polymer degradation,[8] biodiesel exhaust waste,[9] and the dynamic structure of RNA and DNA.[10] Functionalization at the benzene-ring of TMIO gives bioactive antioxidants,[11] with dual anti-inflammatory effects,[12] and TMIO decorated polymers for high tech materials,[13] and organic batteries.[14]

TMIO is a more effective trap for carbon-centred radicals than TEMPO due to the lesser steric influence of the fused five-membered ring on the aminoxyl radical.[15] Traditionally, the dissociation rate constant (k_d) is obtained by heating the alkoxyamine in the presence of excess TEMPO or TMIO,[16] which ensures the rate of radical recombination to the original alkoxyamine is insignificant.

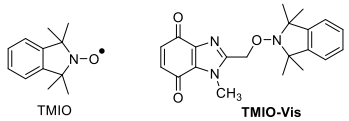


Figure 1. The isoindoline nitroxide (TMIO) and new visible light-activate alkoxyamine (**TMIO-Vis**).

Room temperature photolytic cleavage of alkoxyamines has been exploited as a strategy to achieve nitroxide-mediated living polymerization (so-called photo-NMP).[17-20] Photo-NMP uses high energy UV-irradiation, and there is a requirement for alkoxyamines containing a nitroxide fragment elaborated with a chromophoric group.[19] Alternatively, Guillaneuf and co-workers achieved dissociation with visible-light using alkoxyamines of 4-HO-TEMPO and *N-tert*-butyl-*N*-[1-diethylphosphono(2,2-dimethylpropyl)]oxy (SG1), where the carbon-centred radical fragment is comprised of a highly

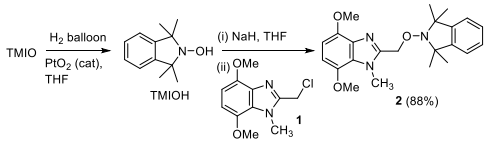
conjugated benzylic derivative.[21] Herein, we describe new benzimidazolequinone alkoxyamines of simple, non-functionalized TMIO, including **TMIO-Vis** (Figure 1), and describe the first nitroxide-exchange experiments activated by visible light. These new alkoxyamines provide a mild room temperature alternative to Nature's reductive activation for the release of the potentially chemotherapeutic QM.

Results and Discussion

Synthesis of Benzimidazolequinone-TMIO Alkoxyamines

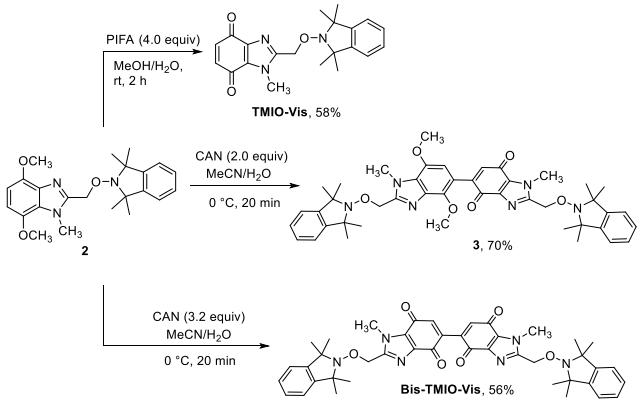
(a) via Oxidation

The parent 4,7-dimethoxybenzimidazole alkoxyamine **2** was prepared in 88% yield by substitution onto methylene chloride **1** using TMIOH; generated by hydrogenation of TMIO over Adams' catalyst (PtO_2) (Scheme 2).[22]



Scheme 2. Synthesis of 4,7-dimethoxy-1-methyl-{[1,1,3,3-tetramethyl-1,3-dihydro-2*H*-isoindol-2-yl)oxy]methyl}-1*H*-benzimidazole **(2)**.

Oxidative demethylations to the quinone were in the absence of light to minimize visible light-induced alkoxyamine degradation (Scheme 3). Analogous to the TEMPO alkoxyamine,[3] PIFA [$(CF_3CO_2)_2IPh$] converted alkoxyamine **2** to **TMIO-Vis** in 58% yield. Oxidative dimerization of the dimethoxybenzimidazole **2** occurred in the presence of CAN [$Ce(NH_4)_2(NO_3)_6$] to give dimethoxybenzimidazole-benzimidazolequinone **3** in 70% yield and increased amounts of the oxidant gave the fully oxidized derivative **Bis-TMIO-Vis** in 56% yield. The regioselectivity of oxidative coupling is independent of the remote nitroxide moiety and was confirmed using X-ray crystal structures of **Bis-TEMPO-Vis**,[3] and dimethoxybenzimidazole-benzimidazolequinone (DMBBQ).[23]



Scheme 3. Oxidations to TMIO-based benzimidazolequinone alkoxyamines.

(a) via Visible Light Activated Nitroxide Exchange

Nitroxide-release experiments confirm radical character and provide an alternative means for accessing the TMIO alkoxyamines. **Bis-TEMPO-Vis** has two labile alkoxyamine moieties for TEMPO release with identical rates of dissociation observed from both moieties using blue LED.[3] This bis-alkoxyamine in acetonitrile was photolyzed with blue LED in the presence of TMIO (20 equiv) at various times (Table 1). Preparative HPLC allowed the isolation of the mixed bis-alkoxyamine **4** in 44% yield after 85 minutes, while 720 minutes were required for isolation of **Bis-TMIO-Vis** in 76% yield.

Kinetics of Homolysis for TMIO-Vis

Alkoxyamine dissociation in blue LED was initially studied in the presence of an excess of TEMPO as radical trap (Figure 2). Nitroxide exchange is traditionally used to obtain thermal alkoxyamine k_d.[16] Analytical HPLC quantified the room temperature **TMIO-Vis** decay in the presence of 10 and 100 equiv of TEMPO. The decay of **TMIO-Vis** is first order (Figure 3), but decreased by more than six times (from k_d = 0.334 to 0.0532 min^{-1}, Table 2) with the ten-fold increase in TEMPO.

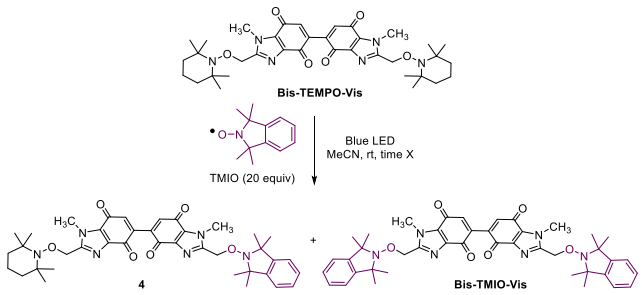


Table 1. Blue LED mediated nitroxide exchange[a]: Conversions[b] and yields.

Time X (min)	**Bis-TEMPO-Vis** (%)	**4** (%)	**Bis-TMIO-Vis** (%)
20	72	25	3
85	26	47 (44)[c]	27
720	1	19	80 (76)[c]

[a] Performed using one 9 W blue LED bulb (420-520 nm) under Ar. [b] Conversion determined by HPLC. [c] Isolated yield after preparative HPLC.

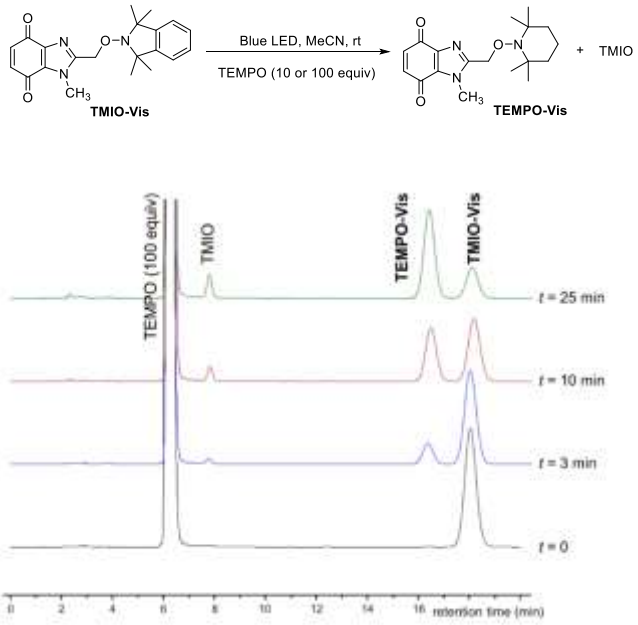


Figure 2. Measuring the rate of **TMIO-Vis** homolysis using TEMPO as a radical trap, studied by HPLC monitoring at 254 nm. The chromatogram is for homolysis in the presence of TEMPO (100 equiv).

The retardation in alkoxyamine homolysis caused by free TEMPO can be attributed to the well-known effects of nitroxide quenching of excited triplet states.[17,20,24] Further, the UV-Vis absorption spectrum shows strong absorbance of TEMPO in the blue region (Figure 4), thus competitive absorption plays a significant role in **TMIO-Vis** homolysis rates, particularly when TEMPO is present at 100-fold excess.

Nitroxide-exchange is therefore unsuitable for obtaining k_d under visible light. O_2 is the preferred radical trap,[18,21,25] and visible light activated alkoxyamine homolysis was carried out under an O_2 atmosphere, while monitoring alkoxyamine decay by HPLC. The obtained k_d for **TMIO-Vis** (0.725 min^{-1}) within experimental error is the same as **TEMPO-Vis** (0.730 min^{-1}) (Figure S1, Table 2). There is no significant absorption from the liberated TMIO (1 equiv, Figure 4) with alkoxyamine decay following first-order kinetics for the duration of the experiment. The almost identical k_d values are supported by comparable DFT-derived bond dissociation energies (BDEs) and lowest triplet energy level (E_T) values (Table 2), with ΔG_d = BDE – E_T = -118.6 and -122.3 $kJmol^{-1}$ for **TMIO-Vis** and **TEMPO-Vis**, respectively. The similarities in homolysis parameters are supported by superimposable alkoxyamine UV-Vis spectra with light absorption occurring at the analogous benzimidazolequinone chromophore (Figure 4).

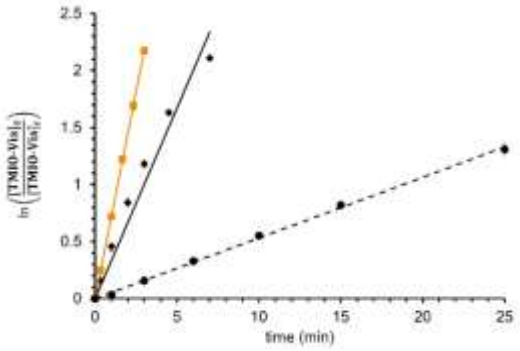


Figure 3. Rate plots for room temperature blue LED induced **TMIO-Vis** alkoxyamine (5 mM) homolysis in MeCN under oxygenated conditions in the absence of TEMPO (squares, orange line), and in the presence of free TEMPO (10 equiv, diamonds, solid black line and 100 equiv, circles, dashed line). Experiments were performed in triplicate.

Table 2. Kinetics of alkoxyamine homolysis using visible light[a] and DFT-calculated homolysis parameters.

Alkoxyamine	Radical Trap	k_d (min^{-1})[b]	BDE ($kJ \cdot mol^{-1}$)[c]	E_T ($kJ \cdot mol^{-1}$)[c]
TMIO-Vis	TEMPO (10 equiv)	0.334±0.004	-	-
TMIO-Vis	TEMPO (100 equiv)	0.0532±0.0012	-	-
TMIO-Vis	O_2	0.725 ± 0.012	89.1	207.7
TEMPO-Vis[d]	O_2	0.730 ± 0.011	85.1	207.4

[a] Performed with alkoxyamine (5 mM) in MeCN using one 9 W blue LED bulb (420-520 nm). [b] Derived from the slope of the first order plots (Figures S1 and 3). [c] M06-2X/6-311++G (d,p).

Bis-alkoxyamine **3** is photolytically stable, which is supported by the long wavelength absorbance band at λ_{max} = 486 nm (Figure 4), and is rationalized by a low energy charge-transfer state.[3] Given the similarity between **TMIO-Vis** and **TEMPO-Vis**, the kinetics of **Bis-TMIO-Vis** were not investigated and are expected to mirror **Bis-TEMPO-Vis** with identical rates of fragmentation from both alkoxyamine moieties.[3]

Conclusion

In summary, we have described the first alkoxyamines of TMIO with remarkable dissociation under visible light and established room temperature nitroxide exchange experiments with TEMPO. Significant TEMPO absorption occurs in the visible region and oxygen is a more effective trap for measurement of k_d. Facile alkoxyamine homolysis is due to the stability of QM. The identical benzimidazolequinone chromophore for **TMIO-Vis** and **TEMPO-Vis** leads to similar rates of nitroxide release, *i.e.* both alkoxyamines have approximately the same stability under visible light. **Bis-TMIO-Vis** is prepared at room temperature by nitroxide exchange or oxidation of monomeric 4,7-dimethoxybenzimidazole alkoxyamine **2** using CAN.

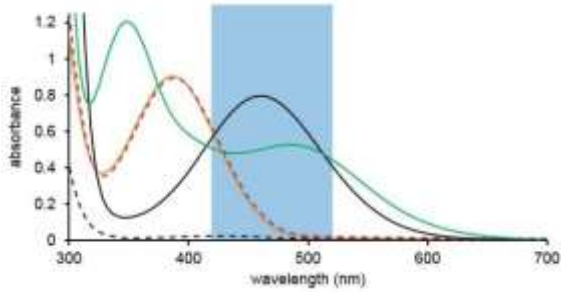


Figure 4. UV-Vis absorbance spectra in MeCN of dimethoxybenzimidazole-benzimidazolequinone **3** (green continuous, 0.375 mM), **TMIO-Vis** (orange continuous, 0.75 mM), **TEMPO-Vis** (purple dash, 0.75 mM), TEMPO (black continuous, 75.0 mM), and TMIO (black dashed, 9.4 mM). The shaded area is the blue LED emission region (420–520 nm).

Experimental Section

General: 1,1,3,3-Tetramethylisoindolin-2-yloxyl (TMIO) was synthesized in four steps according to the literature,[26,27] starting from phthalic anhydride. 2-(Chloromethyl)-4,7-dimethoxy-1-methyl-1*H*-benzimidazole **1** was prepared by *N*-methylation and chlorination of (4,7-dimethoxy-1*H*-benzimidazol-2-yl)methanol.[3] Thin layer chromatography (TLC) used Merck TLC silica gel 60 F254 plates and a UV lamp (254 nm) for visualization. Flash chromatography used silica gel, pore size 60 Å, 230–400 mesh, and particle size 40–63 μm with EtOAc and hexanes, as solvents. Dry column vacuum chromatography (with Apollo Scientific silica gel ZEOprep 60 and 15–35 μm particle size),[28] was preferable for purification of light-active alkoxyamines, due to the convenience of light exclusion by covering the apparatus with Al-foil during elution.
Photoreactor: Experiments were in a metallic visible light photoreactor of diameter 10 cm and containing 9 W blue LED bulb (Figure S2). A clear glass vial (1.5 mL capacity) or round-bottomed flask (25 mL capacity, for nitroxide-exchange) containing the solution of alkoxyamine was placed in the center of the reactor opposite the bulb. The bulb was air-cooled using 2.5 W fan, which insured an ambient reactor temperature. The emission spectra of the LED was narrow and confined to the visible region (Figures S2 and 4).
HPLC Measurements: Analytical HPLC used the Agilent 1100 Series HPLC equipped with a UV detector operating at 254 nm and a Phenomenex® BondClone™ 10 μm C18, 250 × 4.6 mm column. Calibration curves were generated for [alkoxyamine] for the construction of rate plots. The mobile phase comprised of 55% MeCN in H_2O at a flow rate of 1.5 mL/min for 12 min in the cases of **TEMPO-Vis** and **TMIO-Vis** in the presence of O_2 scavenger, and the mobile phase was 48% MeCN in H_2O at a flow rate of 1.5 mL/min for 22 min in the case of **TMIO-Vis** homolysis in the presence of TEMPO scavenger. Preparative HPLC for purification of compound **4** and **Bis-TMIO-Vis** was performed using the same equipment as above. Solutions of bis-alkoxyamines (30 mg/mL, MeCN) were injected (75 μL) onto the column. MeCN/water was used eluent, according to the following program (all concentrations are %MeCN): time 0 = 70%, 17.5 min = 70%, 18 min = 98%, 23 min = 98%. Flow rate was maintained at 1 mL/min. The eluent was collected at 16.2–18.4 min for compound **4**, and at 13.5–15.8 min for **Bis-TMIO-Bis**. The fractions were combined, extracted using CH_2Cl_2, dried ($MgSO_4$) and evaporated to give the bis-alkoxyamines.
UV-vis Measurements: UV-vis spectra used a Varian (Cary 100) spectrometer (Figure 4). UV-vis spectra for **TMIO-Vis** and **TEMPO-Vis** are at the same concentration (0.75 mM), compound **3** is at half concentration (0.375 mM) due to stronger absorbance, and TEMPO is depicted at 100-fold concentration (75.0 mM) to provide an insight into the **TMIO-Vis** homolysis experiment with added TEMPO (100 equiv).
DFT calculations: Geometry optimizations were performed using Gaussian 16,[29] installed at the Irish Centre for High-End Computing (ICHEC), using an M06-2X functional[30] with a 6-311++G (d,p) basis set. Chemical structures were fully optimized in the gas phase and verified as local minima through frequency calculations. Bond dissociation energies (BDEs) were calculated based on the free energy difference between the starting alkoxyamines and the radical products (thermal free energy correction was added). The lowest triplet energies (E_T) of starting alkoxyamines are relative to the optimized singlet ground state (S_0) energies.
Compound Characterization: Melting points were on a Stuart Scientific melting point apparatus SMP3. Infrared spectra used a Perkin-Elmer Spec 1 with ATR attached. NMR spectra were on a JEOL 400 MHz or a Varian 500 MHz instrument. The chemical shifts were in ppm relative to TMS. ^{13}C NMR data were at 100 or 125 MHz with complete proton decoupling. NMR assignments used DEPT and ^{1}H-^{1}H (COSY) and ^{1}H-^{13}C correlation. HRMS used ESI time-of-flight mass spectrometer (TOFMS) in positive mode using a Waters LCT mass spectrometry instrument.
4,7-Dimethoxy-1-methyl-2-{[(1,1,3,3-tetramethyl-1,3-dihydro-2*H*-isoindol-2-yl)oxy]methyl}-1*H*-benzimidazole (2): TMIO (0.340 g, 1.79 mmol) and PtO_2 (7 mg, 0.03 mmol) in THF (10 mL) were stirred under a balloon of H_2 at rt, until the mixture turned colorless (~1 h). The mixture was filtered, NaH (27 mg, 0.67 mmol, 60%) added. After stirring for 1 h at rt, chloride **1** (0.143 g, 0.60 mmol) was added, and heated at reflux for 16 h. H_2O (50 mL) was added, extracted using CH_2Cl_2 (3 × 40 mL), dried ($MgSO_4$), and the combined organic layers evaporated. The residue was purified by flash chromatography with EtOAc and hexanes as eluent to give **2** (0.209 g, 88%), as a white solid; mp 162–164 °C; R_f 0.37 (2 : 3 EtOAc : hexanes); ν_{max} (neat,) 1041, 1073, 1100, 1145, 1164, 1190, 1210, 1233, 1264, 1338, 1362, 1392, 1463, 1532, 2223, 2837, 2954 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.19–1.62 (12H, bs), 3.91 (3H, s), 3.97 (3H, s), 4.22 (3H, s, NCH_3), 5.20 (2H, s), 6.51 (1H, d, J = 8.5 Hz), 6.59 (1H, d, J = 8.5 Hz), 7.10 (2H, dd, J = 3.2, 5.3 Hz), 7.24 (2H, dd, J = 3.2, 5.3 Hz) ppm; δ_C (100 MHz, $CDCl_3$) 25.1, 30.1 (both CH_3), 33.2 (NCH_3), 55.8, 56.0 (both OCH_3), 67.6 (C), 71.3 (CH_2), 101.2, 103.5, 121.5 (all CH), 126.9 (C), 127.4 (CH), 134.4, 141.9, 144.9, 146.3, 149.5 (all C) ppm; HRMS (ESI) m/z $[M + H]^+$, $C_{23}H_{30}N_3O_3$ calcd. 396.2284, observed 396.2287.
1-**Methyl-2-{[(1,1,3,3-tetramethyl-1,3-dihydro-2*H*-isoindol-2-yl)oxy]methyl}-1*H*-benzimidazole-4,7-dione (TMIO-Vis):** [Bis(trifluoroacetoxy)iodo]benzene (PIFA, 0.65 g, 1.51 mmol) was added to a suspension of **2** (0.15 g, 0.38 mmol) in aq MeOH (2.5%, 4.5 mL) at rt, and stirred for 2 h in the absence of light. H_2O (10 mL) was added, and the solution extracted with CH_2Cl_2 (3 × 20 mL). The dried ($MgSO_4$) combined organic layers were evaporated, and the residue purified by dry column vacuum chromatography with EtOAc and hexanes as eluent to give **TMIO-Vis** (80 mg, 58%), as a yellow solid; mp 169–170 °C (deg); R_f 0.47 (2 : 3 EtOAc : hexanes); λ_{max} (MeCN) 382 (ε = 1.17 × 103), 248 (ε = 1.82 × 104), 223 nm (ε = 2.36 × 104); ν_{max} (neat) 2977, 2929, 1666 (C=O), 1592, 1515, 1478, 1451, 1376, 1361, 1332, 1273, 1195, 1163, 1104, 1051, 1038 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.20–1.57 (12H, bs), 4.16 (3H, s, NCH_3), 5.13 (2H, s), 6.64 (1H, d, J = 10.4 Hz), 6.71 (1H, d, J = 10.4 Hz), 7.08–7.10 (2H, m), 7.23–7.25 (2H, m) ppm; δ_C (100 MHz, $CDCl_3$) 25.2, 30.0 (both CH_3),

32.9 (NCH_3), 67.8 (C), 69.8 (CH_2), 121.5, 127.6 (both CH), 131.4 (C), 136.3, 136.6 (both CH), 141.0, 144.4, 151.3 (all C), 178.7, 181.0 (both C=O) ppm; HRMS (ESI) *m/z* [M + H]$^+$, $C_{21}H_{24}N_3O_3$ calcd. 366.1818, observed 366.1825.

4',7'-Dimethoxy-1,1'-dimethyl-2,2'-bis{[(1,1,3,3-tetramethyl-1,3-dihydro-2*H*-isoindol-2-yl)oxy]methyl}-1*H*,1'*H*-[5,5'-bibenzimidazole]-4,7-dione (3): Cerium(IV) ammonium nitrate (CAN) (0.194 g, 0.36 mmol) in H_2O (2.5 mL) was added dropwise to **2** (70 mg, 0.18 mmol) in MeCN (10 mL) at 0 °C, and stirred for 20 min in the absence of light. H_2O (10 mL) was added and extracted using CH_2Cl_2 (3 × 15 mL), dried ($MgSO_4$), and the combined organic extracts evaporated. The residue was purified by dry column vacuum chromatography with EtOAc and hexanes as eluent to give **3** (47 mg, 70%), as a deep red oil; R_f 0.21 (2 : 3 EtOAc : hexanes); λ_{max} (MeCN) 486 (ε = 1.41 × 103), 348 (ε = 3.21 × 103), 231 nm (ε = 5.31 × 104); ν_{max} (neat) 2972, 2927, 1682, 1654 (C=O), 1500, 1483, 1459, 1375, 1361, 1279, 1166, 1127, 1104 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.26–1.57 (24H, bs), 3.91 (3H, s, OCH_3), 4.19 (3H, s, NCH_3), 4.20 (6H, s), 5.16 (2H, s), 5.19 (2H, s), 6.51 (1H, s), 6.74 (1H, s), 7.09–7.11 (4H, m), 7.22–7.25 (4H, m) ppm; δ_C (125 MHz, $CDCl_3$) 25.1, 30.0 (both CH_3), 32.8, 33.1 (both NCH_3), 55.9, 61.6 (both OCH_3), 67.6, 67.7 (both C), 70.0, 71.1 (both CH_2), 105.5 (CH), 116.8 (C), 121.5, 127.3, 127.4 (all CH), 128.6, 131.4 (both C), 134.4 (CH), 136.4, 141.3, 142.6, 144.4, 144.5, 144.7, 146.9, 150.4, 151.0 (all C), 178.9, 180.1 (both C=O) ppm; HRMS (ESI) *m/z* [M + H]$^+$,$C_{44}H_{51}N_6O_6$ calcd. 759.3870, observed 759.3873.

1,1'-Dimethyl-2,2'-bis{[(1,1,3,3-tetramethyl-1,3-dihydro-2*H*-isoindol-2-yl)oxy]methyl}-1*H*,1'*H*-[5,5'-bibenzimidazole]-4,4',7,7'-tetrone (Bis-TMIO-Vis): Using the same procedure to make bis-alkoxyamine **3**, except using CAN (0.310 g, 0.58 mmol) to give **Bis-TMIO-Vis** (37 mg, 56%), yellow solid; mp 135–138 °C (deg); R_f 0.28 (19 : 1 Et_2O : hexanes); ν_{max} (neat) 2974, 2925, 1660 (C=O), 1531, 1483, 1375, 1361, 1275, 1166, 1117, 1098, 1036 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.32–1.52 (24H, bs), 4.17 (6H, s, NCH_3), 5.15 (4H, s), 6.76 (2H, s), 7.08-7.11 (4H, m), 7.23-7.26 (4H, m) ppm; δ_C (125 MHz, $CDCl_3$) 25.1, 30.0, 33.0 (all CH_3), 67.7 (C), 69.8 (CH_2), 121.5, 127.5 (both CH), 131.5 (C), 136.8 (CH), 139.3, 140.9, 144.4, 151.8 (all C), 177.5, 178.2 (both C=O) ppm; HRMS (ESI) *m/z* [M + H]$^+$, $C_{42}H_{45}N_6O_6$ calcd. 729.3401, observed 729.3413.

Nitroxide-Exchange: Bis-TEMPO-Vis (50 mg, 0.076 mmol) and TMIO (0.287 g, 1.51 mmol) were stirred in MeCN (20 mL) at rt under Ar with blue LED illumination for X min (Table 1). The solution evaporated, passed through a plug of silica using Et_2O and hexanes to give the mixture of bis-alkoxyamines. The residue purified by preparative HPLC to give the desired TMIO-coupled bis-alkoxyamine. **1,1'-Dimethyl-2-{[(1,1,3,3-tetramethyl-1,3-dihydro-2*H*-isoindol-2-yl)oxy]methyl}-2'-{[(2,2,6,6-tetramethylpiperidin-1-yl)oxy]methyl}-1*H*,1'*H*-[5,5'-bibenzimidazole]-4,4',7,7'-tetrone (4)**, (after X = 85 min, 23 mg, 44%), as a yellow solid; mp 195–200 °C (deg); R_f 0.40 (Et_2O); ν_{max} (neat) 2964, 2929, 1659 (C=O), 1516, 1482, 1361, 1274, 1168, 1120, 1099 cm^{-1}; δ_H (500 MHz, CD_2Cl_2) 1.11 (6H, s, TEMPO-CH_3), 1.26 (6H, s, TEMPO-CH_3), 1.35–1.38 (12H, m, TMIO-CH_3), 1.50–1.55 (6H, m), 4.09 (3H, s, NCH_3), 4.15 (3H, s, NCH_3), 5.02 (2H, s), 5.14 (2H, s), 6.71 (1H, s), 6.72 (1H, s), 7.12 (2H, dd, *J* = 3.2, 5.6 Hz), 7.25 (2H, dd, *J* = 3.2, 5.6 Hz) ppm; δ_C (125 MHz, CD_2Cl_2) 17.0 (CH_2), 19.8 (TEMPO-CH_3), 24.8, 29.7 (both TMIO-CH_3), 32.7, 32.8 (both NCH_3), 33.0 (TEMPO-CH_3), 39.7 (CH_2), 60.1, 67.7 (both C), 69.7, 70.8 (both OCH_2), 121.4, 127.4 (both CH), 131.6, 131.7 (both C), 136.16, 136.17 (both CH), 140.2, 140.3, 140.7, 140.8, 144.5, 151.8, 151.9 (all C), 177.41, 177.44, 178.47, 178.51 (all C=O) ppm; HRMS (ESI) *m/z* [M + H]+, $C_{39}H_{47}N_6O_6$ calcd. 695.3557, observed 695.3552. **Bis-TMIO-Vis**, (after X = 12 h, 42 mg, 76%), compound data same as above.

Homolysis rate (k_d): A solution of **TMIO-Vis** in MeCN (1 mL, 5 mM) in a 1.5 mL clear glass vial was prepared in the absence of light. For time = 0, a sample was analyzed by HPLC. Photolysis was under an O_2 balloon and samples were taken to measure [**TMIO-Vis**] by HPLC. Placing the solution in the dark stopped the reaction, as demonstrated by the on/off experiment for **TEMPO-Vis**.[3] Illumination of the solution was resumed, with continued sampling over time. The rate constant (k_d) was derived using the first-order plot describing the decay of [**TMIO-Vis**] over time.

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