

Supporting Information

Photochemical Generation of Oxa-Dibenzocyclooctyne (ODIBO) for Metal-Free Click Ligations

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General Methods. All organic solvents were dried and freshly distilled before use, Tetrahydrofuran was distilled from sodium/benzophenone ketyl. Other reagents were obtained from Aldrich or VWR and used as received unless noted. Flash chromatography was performed using 40-63 μm silica gel. All NMR spectra were recorded in CDCl_3 (unless otherwise noted) using 400 MHz instrument. Absorption spectra were recorded on CARY 300 Bio UV-Visible spectrometer. Quantum yield was determined using a ferrioxalate chemical actinometer.¹ Photolyses were conducted in the Rayonet photoreactor equipped with 12 X 4 W 350 nm fluorescent lamps.

Kinetics. Rate measurements in organic solvent were performed using Carry-300 Bio UV-Vis spectrometer, while reactions in aqueous solutions were followed using RX2000 Rapid Kinetics Spectrometer accessory on a Carry-50 Bio UV-Vis spectrometer. The temperature was set to 25.0°C and controlled to 0.1 °C accuracy. Reactions of ODIBO with the excess of azides were monitored by following the decay of the characteristic 322 nm absorbance of ODIBO **2a-c**. Rates of the cycloaddition reaction were measured under pseudo-first order conditions, using 20 fold or higher excess of azides. The experimental data fits the single exponential equation well (Figures 1 and S1). Linear dependence of the observed pseudo-first order rate constants on azide concentration was analyzed by the least squares method to obtain the bimolecular rate constants (Insert in Figures 1 and S1).

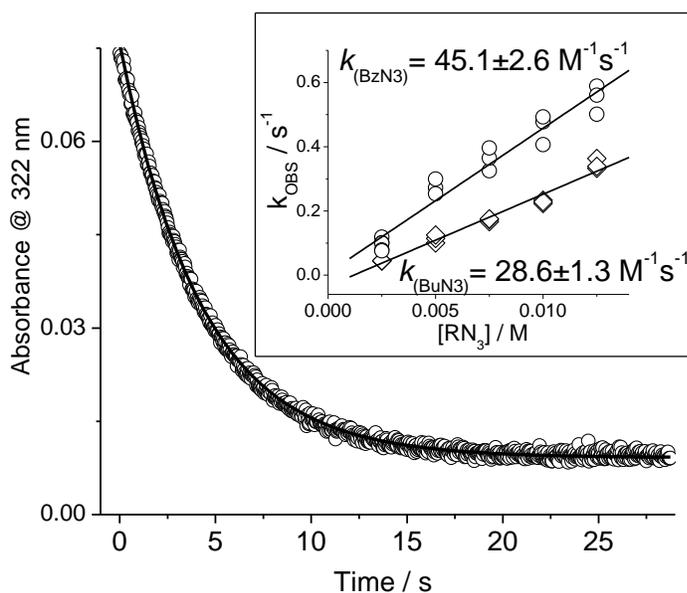
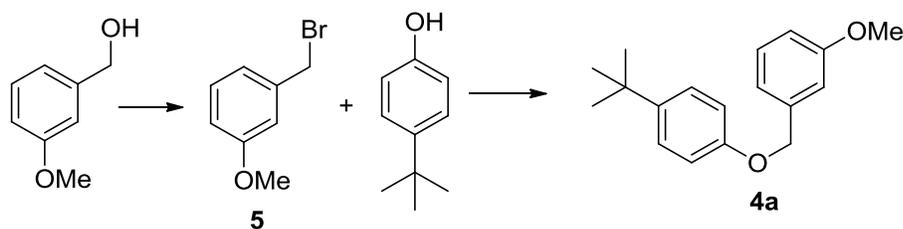


Figure S1. Reaction of 0.115 mM ODIBO with 2.5 mM BzN_3 in Water-MeOH-THF mixture (13 : 4 : 3) at 25°C. The insert illustrates the linear dependence of the observed rates on azide concentration.

The procedure for rate measurements described above is usually more accurate than NMR techniques. NMR measurements are conducted under second order conditions at only one concentration or limited range of concentrations. The consumption of the reagents is usually followed to 60-75% conversion due to the difficulties in reliable integration of low intensity signals. Using pseudo-first order conditions, broad range of reagent concentrations, and following reaction to > 98% conversion allows for more accurate rate measurements. Thus, rate constant for the reaction of DIBO with benzyl azide was reported at $0.17 \text{ M}^{-1}\text{s}^{-1}$ by NMR method,² while the actual value is significantly lower,³ $k = 0.057 \text{ M}^{-1}\text{s}^{-1}$; For ADIBO (DIBAC) the difference is less pronounced: $0.29 - 0.31 \text{ M}^{-1}\text{s}^{-1}$ by NMR⁴ and $0.42 \text{ M}^{-1}\text{s}^{-1}$ by UV.⁵

Materials.

Scheme S1. Preparation of 1-((4-(*t*-butyl)phenoxy)methyl)-3-methoxybenzene (**4a**)



1-(Bromomethyl)-3-methoxybenzene (5)⁶ was prepared using standard protocol for the bromination of alcohols. PBr_3 (4.31 mL, 15.92 mmol) was added to a solution of 3-methoxybenzyl alcohol (3.143 g, 22.75 mmol) in DCM (40 mL) at 0°C and the solution was stirred for 30 minutes at 0°C . The reaction mixture was diluted with ether (150 mL), worked up with sodium thiosulfate solution, brine, and dried over MgSO_4 . The solvents were removed in vacuo to provide 1-(bromomethyl)-3-methoxybenzene (3.33 g, 73%) as a colorless oil. $^1\text{H-NMR}$: 7.23-7.27 (t, $J = 8 \text{ Hz}$, 1H), 6.97-6.99 (d, $J = 7.6 \text{ Hz}$, 1H), 6.93-6.93 (d, $J = 2 \text{ Hz}$, 1H), 6.83-6.85 (d, 8, 2.4 Hz, 1H), 4.47 (s, 2H), 3.81 (s, 3H).

1-((4-(*tert*-Butyl)phenoxy)methyl)-3-methoxybenzene (4a). 1-(Bromomethyl)-3-methoxybenzene (**5**, 2.87 g, 14.27 mmol, 5 mL DMF) was added to a solution of 4-(*tert*-butyl)phenol (2.144 g, 14.27 mmol) in DMF (100 mL), followed by K_2CO_3 (1.973 g, 14.27 mmol). The solution was stirred at 70°C for 4h. The reaction mixture was cooled to room temperature, diluted with ether (200 mL), washed with water (100 mL x 5), brine and dried with MgSO_4 . Solvents were

removed in vacuum and the residue was purified by chromatography (Hexanes : Ethyl Acetate 10:2) to provide (2.31 g, 60%) **4a** as a colorless oil. $^1\text{H-NMR}$: 7.30-7.32 (d, $J = 9.2$ Hz, 2H), 7.28 (s, 1H), 6.99-7.02 (m, 2H), 6.99-6.93 (d, $J = 8.8$ Hz, 2H), 6.85-6.87 (dd, $J = 8$, 2 Hz, 1H), 5.02 (s, 2H), 1.30 (s, 9H). $^{13}\text{C-NMR}$: 160.06, 156.78, 143.86, 139.16, 129.82, 126.47, 119.87, 114.51, 113.66, 113.11, 70.14, 55.46, 34.31, 31.75. HRMS calcd. ($\text{M}+\text{H}^+$): $\text{C}_{18}\text{H}_{22}\text{O}_2$ 271.1693, found: 271.1698

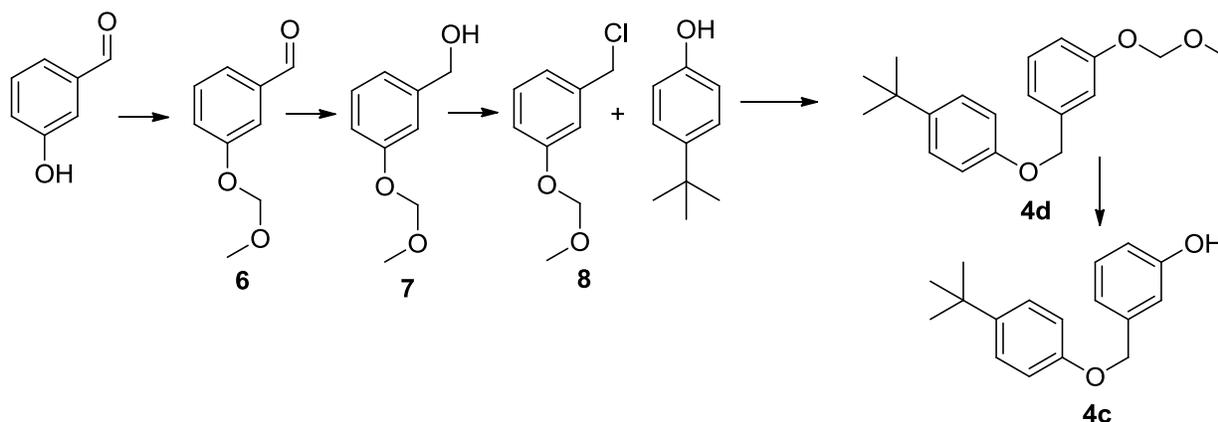
3-(tert-Butyl)-9-methoxydibenzo[b,f]cyclopropa[d]oxocin-1(7H)-one (Photo-ODIBO, 1a). A solution of tetrachlorocyclopropene (0.944 mL, 7.69 mmol) in 5 mL of DCM was added to a suspension of aluminum chloride (1.026 g, 7.69 mmol) in dry DCM (80 mL). The reaction mixture was stirred for 15 minutes, cooled to -78°C , a solution of **4a** (2.08g, 7.69 mmol) in DCM (10 mL) was added dropwise, and stirred for 3 h at -78°C . The reaction mixture was allowed to warm slowly to room temperature and stir for an additional 30 min. The reaction was quenched with 5% HCl solution, organic layer separated, washed with brine, and dried over MgSO_4 . The solvent was removed in vacuo and the residue purified by chromatography (DCM: methanol 30:1) to provide a brown oil, which was then recrystallized from diethyl ether to afford the cyclopropenone **1a** (0.720 g, 29%) as a white powder. M.p. = $160\text{-}163^\circ\text{C}$. $^1\text{H-NMR}$: 7.97-7.93 (m, 2H), 7.49-7.51 (dd, $J = 8.4$, 2.4 Hz, 1H), 7.21-7.19 (d, $J = 8.4$ Hz, 1H), 7.01-7.02 (m, 2H), 5.27-5.29 (d, 1H), 4.78-4.81 (d, 1H), 3.91 (s, 3H), 1.35 (s, 9H). $^{13}\text{C-NMR}$: 162.95, 160.58, 152.87, 148.18, 144.23, 142.38, 140.82, 135.70, 131.27, 130.81, 122.14, 117.96, 117.20, 117.02, 114.18, 78.91, 55.91, 34.78, 31.55. ESI HRMS: calcd ($\text{M}+\text{H}^+$): $\text{C}_{21}\text{H}_{21}\text{O}_3$ 321.1485, found 321.1504

2-(tert-Butyl)-11,12-didehydro-8-methoxy-6H-dibenzo[b,f]oxocine (ODIBO 2a). A solution of cyclo-propenone **2** (0.020 g, 0.0625 mmol) in a DCM : methanol mixture (1 : 29, 60 mL) was irradiated with 350 nm fluorescent lamps (12 x 4W) for 8 min at r.t. The solution was concentrated in vacuo and purified by chromatography (DCM : hexanes 2:1) to provide ODIBO **2a** (0.013 g, 70%) as a yellow oil. $^1\text{H-NMR}$: 7.25-7.22 (m, 3H), 7.11-7.09 (d, 1H), 7.01-7.00 (d, $J = 2.4$ Hz, 1H), 6.90-6.88 (dd, $J = 8.4$, 2.4 Hz, 1H), 5.20-5.17 (dd, $J = 12$ Hz, 0.5H), 4.56-4.53 (dd, $J = 12$ Hz, 0.5H) 1.291 (s, 9H). $^{13}\text{C-NMR}$: 167.19, 159.44, 149.00, 146.80, 126.75, 125.38, 123.54, 121.20, 118.04, 117.56, 117.10, 114.07, 113.74, 110.55, 77.89, 55.50, 31.39. ESI HRMS: calcd. ($\text{M}+\text{H}^+$): $\text{C}_{20}\text{H}_{21}\text{O}_2$ 293.1536, found: 293.1552.

1-Benzyl-5-(tert-butyl)-11-methoxy-1,9-dihydrodibenzo[2,3:6,7]oxocino[4,5-d][1,2,3] triazole 3a. A solution of ODIBO **2a** (0.013 g, 0.044 mmol) and benzyl azide (0.008 g, 0.066

mmol) in DCM were stirred overnight. The solution was concentrated in vacuo and the residue was purified by chromatography (DCM) to give 0.016 g of triazole **3a** (85 %), as a yellow oil. $^1\text{H-NMR}$: 7.67-7.66 (d, $J = 2.4$ Hz, 1H), 7.30-7.27 (m, 3H), 7.22-7.20 (dd, $J = 8.4, 2.8$ Hz, 1H), 7.14-7.11 (m, 3H), 7.01-7.00 (d, $J = 2.4$ Hz, 1H), 6.92-6.89 (dd, $J = 8.4, 2.4$ Hz, 1H), 6.86-6.83 (d, $J = 8.8$ Hz, 1H), 5.66-5.42 (s, 2H), 5.17-4.89 (d, 2H), 3.84 (s, 3H), 1.29 (s, 9H). $^{13}\text{C-NMR}$: 160.60, 152.15, 145.28, 144.12, 138.33, 135.72, 132.36, 130.23, 129.68, 128.83, 128.16, 127.07, 126.99, 119.85, 119.36, 116.57, 115.68, 115.02, 69.46, 55.46, 52.11, 34.14, 34.14, 31.39. ESI HRMS calcd. (M-H^+): $\text{C}_{27}\text{H}_{26}\text{N}_3\text{O}_2$ 424.2031, found: 424.2024.

Scheme S2. Preparation of 1-((4-(*t*-butyl)phenoxy)methyl)-3-methoxybenzene (**4c**)



3-(Methoxymethoxy)benzaldehyde (6).⁷ Sodium hydride (1.572 g, 39.3 mmol) was added to a solution of 3-hydroxybenzaldehyde (4.0 g, 32.8 mmol) in THF (60 mL) and reaction was stirred for 30 min at r.t. MOMCl (3.09 g, 39.3 mmol) was added dropwise and the reaction mixture was stirred at r.t. for 2 h. The reaction was quenched with water (30 mL), and extracted twice with ether (60 mL). Combined organic layers were washed with 2 M NaOH (30 mL), brine, and dried over MgSO_4 . The solvent was removed in vacuo and the residue was purified by chromatography (Hexanes to Hexanes : Ethyl Acetate 4:1) to provide 2.31 g (13.90 mmol, 85%) of 3-(methoxymethoxy)benzaldehyde as a colorless oil. $^1\text{H-NMR}$: 9.94 (s, 1H), 7.48-7.52 (m, 2H), 7.40-7.44 (t, 1H), 7.25-7.28 (d, $J = 12$ Hz, 1H), 5.20 (s, 2H), 3.46 (s, 3H).

3-(Methoxymethoxy)benzyl alcohol (7).⁸ Sodium borohydride (0.824 g, 21.78 mmol) was added to a solution of 3-(methoxymethoxy)benzaldehyde **6** (3.62 g, 21.78 mmol) in methanol (50 mL) at 0 °C and stirred for 45 min. Reaction mixture was diluted with ethyl acetate (200 mL),

washed with water (75 mL), brine, and dried over MgSO₄. The solvent was removed in vacuo and the residue was purified by chromatography (Hexanes : Ethyl Acetate 4:1) to provide 2.18 g (12.96 mmol, 93%) of 3-(methoxymethoxy)benzyl alcohol **7** as a colorless oil. ¹H-NMR: 7.23-7.27 (t, 1H), 7.027 (s, 1H), 6.92-6.79(m, 2H), 5.15 (s, 2H), 4.61 (s, 2H), 3.45 (s, 3H).

1-(Chloromethyl)-3-(methoxymethoxy)benzene (8).⁹ A solution of thionyl chloride (1.47 mL, 20.19 mmol) in DCM, (15 mL) was added dropwise to a solution of **7** (3.143 g, 22.75 mmol), and pyridine (2.72 mL, 33.7 mmol) in DCM (20 mL) at 0°C. The reaction mixture was warmed to room temperature and stirred for 2 h. The reaction mixture was diluted with ether (150 mL), washed with water (50 mL), brine, and dried over MgSO₄. The solvents were removed in vacuo and the residue was purified by chromatography (Hexanes : Ethyl Acetate 4:1) to provide 1.74 g (6.76 mmol, 55%) of 1-(chloromethyl)-3-(methoxymethoxy)benzene **8** as a colorless oil. ¹H-NMR: 7.26-7.30 (t, 1H), 7.09 (s, 1H), 7.00-7.052 (m, 2H), 5.19 (s, 2H), 4.56 (s, 2H), 3.49 (s, 3H). ¹³C-NMR: 157.75, 139.22, 130.03, 122.23, 116.65, 116.51, 94.69, 56.23, 46.28.

1-((4-(tert-butyl)phenoxy)methyl)-3-(methoxymethoxy)benzene (4d). A solution of **8** (1.64 g, 8.79 mmol) in DMF (5 mL) was added to a solution of 4-(tert-butyl)phenol (2.144 g, 14.27 mmol) in DMF (60 mL), followed by K₂CO₃ (1.973 g, 14.27 mmol). The reaction mixture was stirred overnight at 85°C, cooled to room temperature, diluted with ether (200 mL), washed with water (100 mL x 5), brine, and dried over MgSO₄. Solvents were removed in vacuo and the residue was purified by chromatography (Hexanes : Ethyl Acetate 10:2) to provide 2.03 g (5.73 mmol, 77%) of **4d** as a colorless oil. ¹H-NMR: 7.36-7.43 (m, 3H), 7.24 (s, 1H), 7.16-7.18 (d, J = 7.6 Hz, 1H), 7.09-7.12 (d, J = 10.4 Hz, 1H), 7.02-7.04 (m, 2H), 5.27 (s, 2H), 5.10 (s, 2H), 3.56 (s, 3H), 1.41 (s, 9H). ¹³C-NMR: 157.87, 156.92, 143.91, 139.34, 129.53, 126.55, 121.17, 115.95, 115.66, 114.67, 94.76, 70.12, 56.24, 34.39, 31.87. ESI HRMS: calcd (M+Na⁺): C₁₉H₂₄O₃ 323.1618, found 323.1614

3-((4-(tert-butyl)phenoxy)methyl)phenol (4c).¹⁰ Amberlyst[®] cation exchange resin (in H⁺ form, 1.9 g) was added to a solution of **4d** (1.90 g, 6.33 mmol) in aqueous methanol (60 mL, 9:1) and stirred for 48 h at 60 °C. The reaction mixture was cooled, filtered, and the solvent was removed in vacuo. The residue was re-dissolved with ethyl acetate (200 mL), washed with water (50 mL), brine, and dried over MgSO₄. The organic solvent was removed in vacuo to provide 1.47 g (5.73 mmol, 91%) of pure **4c** as a yellow oil. ¹H-NMR: 7.29-7.314 (m, 2H), 7.22-7.25 (m, 1H), 6.69-6.98(d, J = 7.6 Hz, 1H), 6.89-913 (m, 3H), 6.76-6.78 (d, J = 10.4 Hz, 1H), 5.00 (s, 1H), 4.94 (s, 1H), 1.29 (s, 9H). ¹³C-NMR: 156.71, 155.99, 143.97, 139.49, 130.06, 126.49, 119.87,

115.02, 114.55, 144.21, 69.90, 34.30, 31.73. ESI HRMS: calcd (M-H⁺): C₁₇H₁₉O₂ 255.1391, found 255.1405.

3-(tert-Butyl)-9-hydroxydibenzo[b,f]cyclopropa[d]oxocin-1(7H)-one (Photo-ODIBO, 1c). A solution of tetrachlorocyclopropene (0.66 mL, 5.39 mmol) in 5 mL of DCM was added to a suspension of aluminum chloride (1.07 g, 8.08 mmol) in dry DCM (80 mL). The reaction mixture was stirred for 15 minutes, cooled to -78°C, a solution **4c** (1.38 g, 7.69 mmol) in DCM (10 mL) was added dropwise, and stirred for 3 h at -78°C. The reaction mixture was allowed to warm slowly to room temperature and stirred for an additional 30 min. The reaction was quenched with 5% HCl solution, organic layer separated, washed with brine, and dried over MgSO₄. The solvent was removed in vacuo and the residue purified by chromatography (DCM: methanol 30:1) to provide 0.220 g (0.718 mmol, 13%) of **1c** as a white powder. M.p. = 170-173°C). ¹H-NMR DMSO: 10.69 (s, 1H), 7.29-7.57 (m, 3H), 7.23-2.35 (d, J = 7.2 Hz, 1H), 6.93-7.05 (m, 2H), 5.25-5.28 (d, J = 7.6 Hz 1H), 4.7704.80 (d, 1H), 1.29 (s, 9H). ¹³C-NMR DMSO: 162.21, 160.56, 151.59, 147.90, 144.90, 141.93, 135.69, 131.33, 130.13, 122.83, 118.64, 117.57, 116.34, 78.80, 34.88, 31.70. ESI HRMS calcd (M+H⁺): C₂₀H₁₉O₃ 307.1329, found 307.1332

2-(tert-Butyl)-11,12-didehydro-8-hydroxy-6H-dibenzo[b,f]oxocine (ODIBO 2c). A solution of Photo-ODIBO **1c** (0.010 g, 0.0625 mmol) in methanol (30 mL) was irradiated with 350 nm fluorescent lamps (12 x 4W) for 5 min at r.t. The solution was concentrated in vacuo to provide ODIBO **2c** (0.008 g, 88%) as a yellow oil. ¹H-NMR: 7.18-7.19 (m, 3H), 7.02-7.11 (m, 2H), 6.84 (s, 1H), 6.73-6.75 (d, J = 8.4 Hz, 1H), 5.28-5.40 (bs, 1H) 5.06-5.06 (d, J = 12 Hz, 1H), 4.43-4.46 (d, J = 12 Hz, 1H), 1.23 (s, 9H). ¹³C-NMR: 167.22, 155.70, 149.36, 147.14, 127.17, 125.66, 123.79, 121.40, 118.46, 118.39, 117.70, 115.83, 114.10, 110.72, 34.60, 31.73, 31.59. ESI HRMS: calcd. (M-H⁺). C₁₉H₁₇O₂, 277.1234 found 277.1223.

4,9-Dimethoxydibenzo[b,f]cyclopropa[d]oxocin-1(7H)-one (Photo-ODIBO, 1b). A solution of tetrachlorocyclopropene (0.15 mL, 1.22 mmol) in 5 mL of DCM was added to a suspension of aluminum chloride (0.49 g, 3.8 mmol) in dry DCM (80 mL). The reaction mixture was stirred for 15 minutes, cooled to -78°C, a solution of 1-methoxy-3-((3-methoxybenzyl)oxy)benzene (**4b**, 0.30 g, 1.27 mmol) in DCM (10 mL) was added dropwise, and stirred for 3 h at -78°C. The reaction mixture was allowed to warm slowly to room temperature and stirred for an additional 30 min. The reaction was quenched with 5% HCl solution, organic layer separated, washed with brine, and dried over MgSO₄. The solvent was removed in vacuo and the residue purified by chromatography (DCM: methanol 30:1) to provide 0.041 g (0.14 mmol, 12%) of **1b** as a white

powder. M.p.= 222-225°C. ¹H-NMR: 7.92 (d, 1H), 7.87 (d, 1H), 7.02 (d, 2H), 6.80 (s, 2H), 5.26 (d, 1H) 4.85 (d, 1H), 3.90 (s, 1H), 3.87 (s, 1H). ¹³C-NMR: 164.6, 164.2, 162.6, 152.3, 142.0, 140.8, 140.3, 135.6, 135.2, 118.3, 117.2, 114.2, 111.1, 110.5, 108.3, 78.7, 55.97, 55.91. IR: 1854 cm⁻¹ (ν_{C=O}).

11,12-Didehydro-3,8-hydroxy-6H-dibenzo[b,f]oxocine (ODIBO 2b) was prepared by 350 nm irradiation of 115 μM methanol solution of Photo-ODIBO **1b** and used for kinetic measurements without further purification.

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