Supplementary Material

Synthesis of Cyclopropanated [2.2.1] Heterobicycloalkenes: An Improved ProcedureEmily Carlson,[†] Guillaume Duret,[‡] Nicolas Blanchard,[‡] and William Tam^{*,†}

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General Information: All reactions were carried out using a continuous flow apparatus under inert atmosphere. Commercial reagents and catalysts were used without further purification. Column chromatography was performed on 230-400 mesh silica gel following standard flash column chromatography techniques,¹ and analytical thin-layer chromatography (TLC) was performed on pre-coated silica gel 250 μ m 60 F254 aluminum plates, visualized by UV light and *p*-anisaldehyde stain. IR spectra were obtained as NaCl or KBr discs on a Nicolet 380-FTIR spectrometer, or as solids on an ALPHA platinum single reflection diamond ATR spectrophotometer. ¹H, ²H, and ¹³C NMR spectra were recorded on Avance 400 MHz or 600 MHz spectrometers equipped with cryoprobes and are reported in parts per million (ppm) from the solvent as internal standard (CDCl₃: δ 7.24 ppm (¹H at 400/600 MHz) or δ 77.0 ppm (¹³C at 100/125 MHz)). HRMS samples were ionized by electron impact (EI) or electrospray ionization (ESI) as specified and detection of the ions was performed by time of flight (TOF).

General Procedure: HAZARD ALERT! Diazomethane can be fatal if inhaled and capable of detonation if appreciably concentrated. Refer to **Figure S1**: Reactor [C], equipped with a small stir bar, was charged with alkene (1.2 - 17.7 mmol), Pd(OAc)₂ (1 mol% of alkene) and tetrahydrofuran (40 mL) and was capped with septum [E]. To the outlet of reactor [C] was connected in series with Tygon tubing [I] an empty bubbler [J] to serve as a suck-back trap and a glass inlet tube [K] inserted into filter flask [L]. Bubbler [L] was filled prior to setup with a glacial acetic acid-water mixture (1:1). The outlet of bubbler [L] was connected to a piece of Tygon tubing [I_c] directed to the back of the fumehood. Reactor [C] was then securely fitted to the end of tube [H_b] while cooling its contents in an ice bath. Funnel [A] was filled with 25% (12.5M) aqueous sodium hydroxide (100-150 equivalents to alkene) ensuring that stopper [D]

¹ Still, W.C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923-2925.

was tightly shut, and the funnel was capped with septum [E]. Flask [B], equipped with an extra-large stir bar, was charged with Diazald® (2.6-8 equivalents to alkene) and 95% EtOH (50 mL), and the solution was stirred. Flask [B] was then fitted with a stopper [G] containing the inert gas inlet [F], tubing [H_a], and addition funnel [A] assembly. The apparatus was securely clamped at both funnel [A] and flask [B] and a slow stream of argon was passed through the system such that ~3 bubbles per second (bps) were observed from tube [H_a]. Once a constant flow rate of 3-5 bps was established, 25% sodium hydroxide solution was added from funnel [A] into flask [B] at a rate of 1-2 mL/min, maintaining efficient stirring and bubbling. Formation of the light yellow CH_2N_2 gas was observed with the dissolution of Diazald®. Upon complete dissipation of any yellow colour (4-8 hours), the reaction was assessed by TLC for completion. Once the reaction was seen to be complete by TLC, both septa [E] were removed and the apparatus was left to vent any trace CH_2N_2 (8-16 hours). Reactor [C] was removed and its contents were poured over Celite. The filter cake was washed with several portions (4×10 -20 mL) of Et_2O which was then concentrated and purified by column chromatography (hexanes/ethyl acetate mixture).

Figure S1. Experimental apparatus for the cyclopropanation of alkenes 1a-j, 3, and 5a-c.

A: Custom-made dropping funnel (150 mL or 300 mL). B: 500 mL round bottom flask with side arm and wide neck equipped with extra-large stir bar. C: Reactor vessel (50 mL) with small hole at end of inlet tube for bubbles. D: Stopcock. E: Tightly fitted 24/40 rubber septum wired in place. F: Glass nitrogen/argon inlet (9mm OD). G: #12 Rubber stopper with two 9mm bored holes. H: High density polyethylene tubing (7mm ID) with any cut sharp edges smoothed with a heat gun. I: Tygon® tubing. J: Empty bubbler as suck-back trap for AcOH bubbler. K: Glass inlet tube. L: Filter flask with AcOH:H₂O (1:1) (CH₂N₂ trap and bubbler). M: Room temperature water bath. N: 0°C ice-water bath. Note: OD = outer diameter; ID = inner diameter.

***exo*-cyclopropanated oxabenzonorbornadiene (2a)** Yield = 2.45 g (90%); clear oil; $R_f = 0.52$ (EtOAc: hexanes = 1:4). FTIR (NaCl, ν , cm^{-1}): 3049, 2999, 1457, 1054, 955, 834, 755, 644. ^1H NMR (CDCl_3 , 400 MHz): δ 7.24 (m, 2H), 7.09 (m, 2H), 5.05 (s, 2H), 1.50 (td, $J = 5.2, 3.6$ Hz, 1H), 1.20 (dd, $J = 6.7, 3.6$ Hz, 2H), 0.86 (td, $J = 6.7, 5.2$, 1H). ^{13}C NMR (JMOD, CDCl_3 , 100 MHz): δ 147.8, 125.8, 119.1, 77.8, 19.9, 14.1. Spectral data are consistent with those previously reported.^[15]

***exo*-cyclopropanated oxabenzonorbornadiene (2b)** Yield = 2.88 g (89 %); white solid; $R_f = 0.65$ (EtOAc: hexanes = 1:4); m.p. = $38\text{--}40^\circ\text{C}$. FTIR (NaCl, ν , cm^{-1}): 3047, 1450, 1381, 1280, 1146, 862, 753. ^1H NMR (CDCl_3 , 400 MHz): δ 7.18 (m, 2H), 7.14 (m, 2H), 1.73 (s, 6H), 1.58 (dt, $J = 5.0, 3.4$ Hz, 1H), 1.22 (dd, $J = 6.6, 3.4$ Hz, 2H), 0.81 (td, $J = 6.6, 5.0$, 1H). ^{13}C NMR (JMOD, CDCl_3 , 100 MHz): δ 151.0, 125.7, 117.7, 83.5, 26.6, 15.5, 13.8. Spectral data are consistent with those previously reported.^[15]

***exo*-cyclopropanated oxabenzonorbornadiene (2c)** Yield = 1.37 g (85 %); white solid; $R_f = 0.59$ (EtOAc: hexanes = 1:4); m.p. = $44\text{--}46^\circ\text{C}$. FTIR (NaCl, ν , cm^{-1}): 3047, 2976, 1459, 1364,

1067, 923, 752. ^1H NMR (CDCl_3 , 400 MHz): δ 7.43 (m, 1H), 7.26 (m, 1H), 7.10 (m, 2H), 5.01 (s, 1H), 1.56 (dt, $J = 5.2, 3.6$, Hz, 1H), 1.26 (s, 9H), 1.24 (td, $J = 6.8, 3.6$ Hz, 1H), 1.16 (td, $J = 6.8, 3.6$ Hz, 1H), 0.96 (td, $J = 6.8, 5.2$ Hz, 1H); ^{13}C NMR (JMOD, CDCl_3 , 100 MHz): δ 149.7, 148.4, 125.4, 125.3, 120.8, 119.1, 93.4, 77.3, 34.0, 26.7, 22.9, 20.0, 16.5. Spectral data are consistent with those previously reported.^[15]

exo-cyclopropanated oxabenzonorbornadiene (2d) Yield = 799 mg (75 %); yellow solid; $R_f = 0.33$ (EtOAc: hexanes = 1:19); m.p. = 35-36 °C. FTIR (KBr, ν , cm^{-1}): 3046, 3001, 2959, 2900, 1454, 1249, 1051, 840, 751; ^1H NMR (400 MHz, CDCl_3): δ 7.35-7.34 (m, 1H), 7.30-7.28 (m, 1H), 7.17-7.14 (m, 2H), 5.16 (s, 1H), 1.50-1.47 (m, 1H), 1.26-1.24 (m, 2H), 0.99-0.94 (m, 1H), 0.36 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3): δ 150.9, 148.8, 125.5, 125.2, 119.2, 119.1, 79.7, 79.1, 22.8, 20.2, 15.0, -2.9; HRMS: Calculated for $\text{C}_{14}\text{H}_{18}\text{SiO}$ $[\text{M}]^+$: 230.1127. Found: 230.1122.

exo-cyclopropanated oxabenzonorbornadiene (2e) Yield = 1.74 g (82 %); beige solid; $R_f = 0.25$ (EtOAc: hexanes = 1:9); m.p. = 132-134 °C. FTIR (KBr, ν , cm^{-1}): 3005, 2983, 2937, 2834, 1495, 1436, 1259, 1043, 809; ^1H NMR (400 MHz, CDCl_3): δ 6.68 (ABq, $J_{AB} = 8.8$ Hz, $\Delta\delta_{AB} = 9.8$ Hz, 2H), 5.19 (s, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 1.86 (s, 3H), 1.52-1.49 (m, 1H), 1.38-1.33 (m, 1H), 1.28-1.24 (m, 1H), 0.86-0.82 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 147.8, 146.9,

138.2, 137.9, 111.2, 111.0, 85.4, 75.1, 56.1, 56.0, 23.9, 22.6, 16.8, 14.0; HRMS: Calculated for $C_{14}H_{16}O_3$ $[M]^+$: 232.1099. Found: 232.1092.

exo-cyclopropanated oxabenzonorbornadiene (2f) Yield = 1.28 g (81 %); yellow oil; R_f = 0.23 (EtOAc: hexanes = 1:9); FTIR (KBr, ν , cm^{-1}): 3048, 2984, 2932, 1732, 1314, 1053, 1034; 1H NMR (400 MHz, $CDCl_3$): δ 7.28-7.27 (m, 1H), 7.23-7.22 (m, 1H), 7.16-7.14 (m, 2H), 5.04 (d, $J=2.3$ Hz, 1H), 4.21-4.15 (qd, $J=7.2$ Hz, 1.1 Hz, 2H), 2.67-2.51 (m, 4H), 1.58-1.55 (m, 1H), 1.31-1.27 (m, 4H), 1.12-1.09 (m, 1H), 0.94-0.90 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.63, 148.9, 148.6, 125.9, 119.3, 118.2, 86.3, 77.5, 60.4, 29.5, 25.2, 22.5, 22.3, 14.7, 14.3; HRMS: Calculated for $C_{16}H_{18}O_3$ $[M]^+$: 258.1256. Found: 258.1251.

exo-cyclopropanated oxabenzonorbornadiene (2g) Yield = 930 mg (85 %); colorless oil; R_f = 0.24 (EtOAc: hexanes = 1:19); FTIR (KBr, ν , cm^{-1}): 3075, 3053, 3003, 2246, 1457, 1448, 1193, 1161, 1044, 952, 735; 1H NMR (400 MHz, $CDCl_3$): δ 7.38-7.36 (m, 2H), 7.23-7.21 (m, 2H), 1.61 (m, 1H), 0.98 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.0, 126.0, 119.3, 77.3 (t, $J=32$ Hz), 19.6 (t, $J=26$ Hz), 14.1; 2H NMR (61.4 MHz, $CDCl_3$): 5.15 (br s, 2H), 1.29 (br s, 2H); HRMS: Calculated for $C_{11}H_6D_4O$ $[M]^+$: 162.0983. Found: 162.0986.

exo-cyclopropanated oxabenzonorbornadiene (2h) Yield = 510 mg (94%); clear oil; $R_f = 0.23$ (EtOAc: hexanes = 1:19). FTIR (NaCl, ν , cm^{-1}): 3069, 2973, 2932, 1453, 1435, 1385, 1169, 1132, 1006. ^1H NMR (CDCl_3 , 400 MHz): δ 7.38-7.35 (m, 1H), 7.32-7.30 (m, 1H), 7.27-7.21 (m, 2H), 5.05 (s, 1H), 1.79-1.77 (m, 1H), 1.78 (s, 3H), 1.11-1.08 (m, 1H), 1.05 (s, 3H), 0.83-0.80 (m, 1H); ^{13}C NMR (JMOD, CDCl_3 , 100 MHz): δ 149.2, 148.4, 125.7, 125.4, 119.4, 119.0, 86.6, 77.1, 28.9, 28.4, 18.7, 14.6, 13.0. HRMS: Found: Calculated for $\text{C}_{13}\text{H}_{15}\text{O}$ $[\text{M}+\text{H}]^+$: 187.1117. Found: 187.1112.

exo-cyclopropanated oxabenzonorbornadiene (2i) Yield = 380 mg (72%); yellow solid; $R_f = 0.49$ (EtOAc: hexanes = 1:1); m.p. = 60-62 $^\circ\text{C}$. FTIR (NaCl, ν , cm^{-1}): 3052, 2983, 2934, 1721, 1374, 1279, 1241, 1140, 759; ^1H NMR (CDCl_3 , 400 MHz): δ 7.45-7.44 (m, 1H), 7.32-7.31 (m, 1H), 7.19-7.12 (m, 2H), 5.29 (s, 1H), 5.11 (s, 1H), 4.10-3.99 (m, 2H), 2.14 (t, $J=4.7$ Hz, 1H), 1.96-1.93 (m, 1H), 1.80-1.77 (m, 1H), 1.23 (t, $J=7.1$ Hz, 3H); ^{13}C NMR (JMOD, CDCl_3 , 100 MHz): δ 172.0, 147.0, 146.9, 126.2, 126.1, 122.0, 119.4, 78.4, 77.6, 60.6, 34.4, 33.1, 22.7, 14.2; HRMS: Calculated for $\text{C}_{14}\text{H}_{14}\text{O}_3$ $[\text{M}]^+$: 230.0943. Found: 230.0940.

exo-cyclopropanated oxabenzonorbornadiene (2j) Yield = 140 mg (65%); beige solid; $R_f = 0.28$ (EtOAc: hexanes = 1:1); m.p. = 45-47 °C. FTIR (NaCl, ν , cm^{-1}): 3054, 3043, 3002, 2927, 1578, 1400, 1258, 952, 830, 642; ^1H NMR (CDCl_3 , 400 MHz): δ 8.20 (dd, $J=10.6$ Hz, 1.2 Hz, 1H), 7.52 (dd, $J=14.6$ Hz, 1.1 Hz, 1H), 7.01 (dd, $J=14.6$ Hz, 5.3 Hz, 1H), 5.11 (s, 1H), 5.06 (s, 1H), 1.61-1.59 (m, 1H), 1.41-1.7 (m, 1H), 1.32-1.28 (m, 1H), 1.01-0.97 (m, 1H); ^{13}C NMR (JMOD, CDCl_3 , 100 MHz): δ 169.3, 145.4, 141.0, 126.5, 120.5, 77.8, 77.1, 20.4, 18.4, 14.3; HRMS: Calculated for $\text{C}_{10}\text{H}_9\text{NO}$ $[\text{M}]^+$: 159.0684. Found: 159.0689.

exo-6-oxa-7-N-butoxycarbonyltricyclo[3.2.1.0^{2,4}]oxazine (4) Yield = 907 mg (97%); white solid; $R_f = 0.25$ (EtOAc: hexanes = 1:4); m.p. = 72-74 °C (lit. 83-85 °C); FTIR (KBr, ν , cm^{-1}): 2982, 2252, 1722 (C=O), 1478, 1393, 1163, 909, 734; ^1H NMR (400 MHz, CDCl_3): δ 4.78 (m, 1H), 4.56 (m, 1H), 1.56 (d, $J = 18.3$ Hz, 1H), 1.50 (s, 9H), 1.45-1.38 (m, 3H), 0.39-0.33 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 157.8, 81.9, 80.7, 60.8, 28.3, 27.7, 13.9, 12.9, 4.1; Spectral data are consistent with those previously reported.^[13]

***exo*-6-oxa-7-N-butoxycarbonyltricyclo[3.2.1.0^{2,4}]hydrazine (6a)** Yield = 516 mg (95 %); white solid; R_f = 0.08 (EtOAc: hexanes = 1:9); m.p. = 117-119 °C. FTIR (KBr, ν , cm^{-1}): 2977, 2932, 1737, 1694 (C=O), 1367, 1339, 1164, 1111; ^1H NMR (400 MHz, CDCl_3): 4.68 (br s, 1H), 4.42 (br s, 1H), 1.59 (m, 1H), 1.43 (s, 18H), 1.31 (d, J =11.3 Hz, 1H), 1.20-1.06 (m, 2H), 0.42-0.39 (m, 1H), 0.33-0.28 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3): δ [156.9, 156.3, 155.3] (C=O; peaks appear split due to relative orientation about nitrogen in different invertomers),^[31] [80.2, 80.0], [61.3, 60.4, 59.6], 27.1, 25.8, [13.4, 13.0, 11.6, 11.1], 3.6; HRMS: Calculated for $\text{C}_{16}\text{H}_{26}\text{N}_2\text{O}_4$ $[\text{M}]^+$: 310.1893. Found: 310.1890.

***exo*-6-oxa-7-N-isopropoxycarbonyltricyclo[3.2.1.0^{2,4}]hydrazine (6b)** Yield = 803 mg (94 %); white solid; R_f = 0.27 (EtOAc: hexanes = 1:4); m.p. = 55-57 °C; FTIR (KBr, ν , cm^{-1}): 2980, 2938, 1739, 1694, 1468, 1373, 1339, 1104; ^1H NMR (400 MHz, CDCl_3): δ 4.71 (s, 1H), 4.45 (s, 1H), 1.33 (d, J =11.4 Hz, 2H), 1.22 (br s, 12H), 1.08 (d, J = 8.6 Hz, 2H), 0.43-0.40 (m, 1H), 0.34-0.28 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3): δ [157.9, 157.5, 157.2] (C=O; peaks appear split due to relative orientation about nitrogen in different invertomers),^[31] [69.7, 69.5], [62.0, 61.1], 26.5, 21.7, [13.9, 12.2], 4.3; HRMS: Calculated for $\text{C}_{14}\text{H}_{22}\text{N}_2\text{O}_4$ $[\text{M}]^+$: 282.1580. Found: 282.1585.

***exo*-6-oxa-7-N-carboxybenzyltricyclo[3.2.1.0^{2,4}]hydrazine (6c)** Yield = 629 mg (98%); colourless oil; R_f = 0.15 (EtOAc: hexanes = 3:17). FTIR (KBr, ν , cm^{-1}): 3032, 1739, 1703, 1455, 1388, 1321, 1267, 1191, 1111; ^1H NMR (400 MHz, CDCl_3): δ 7.34 (br s, 10H), 5.23 (m, 4H), 4.84 (s, 1H), 4.60 (s, 1H), 1.72-1.18 (m, 4H), 0.47 (br s, 1H), 0.38 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3): δ [158.3, 157.8] (C=O; peaks appear split due to relative orientation about nitrogen in different invertomers),^[31] 135.8, 128.3, 127.9, 127.7, 67.7, [62.6, 61.6], 26.8, [14.1, 12.0], 4.5; HRMS: Calculated for $\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}_4$ $[\text{M}]^+$: 378.1580. Found: 378.1583.

Figure S2. 400 MHz ^1H NMR spectrum of cyclopropane **2d** in CDCl_3

Figure S3. 100 MHz ^{13}C NMR spectrum of cyclopropane **2d** in CDCl_3

Figure S4. 400 MHz ^1H NMR spectrum of cyclopropane **2e** in CDCl_3

Figure S5. 100 MHz ^{13}C NMR spectrum of cyclopropane **2e** in CDCl_3

Figure S6. 400 MHz ^1H NMR spectrum of cyclopropane **2f** in CDCl_3

Figure S7. 100 MHz ^{13}C NMR spectrum of cyclopropane **2f** in CDCl_3

Figure S8. 400 MHz ¹H NMR spectrum of cyclopropane **2g** in CDCl₃

Figure S9. 61.4 MHz ²H NMR spectrum of cyclopropane **2g** in CDCl₃

Figure S10. 100 MHz ^{13}C NMR spectrum of cyclopropane 2g in CDCl_3

Figure S11. 400 MHz ¹H NMR spectrum of cyclopropane **2h** in CDCl₃

Figure S12. 100 MHz ¹³C NMR spectrum of cyclopropane **2h** in CDCl₃

Figure S13. 400 MHz ^1H NMR spectrum of cyclopropane **2i** in CDCl_3

Figure S14. 100 MHz ^{13}C NMR spectrum of cyclopropane **2i** in CDCl_3

Figure S15. 400 MHz ^1H NMR spectrum of cyclopropane **2j** in CDCl_3

Figure S16. 100 MHz ^{13}C NMR spectrum of cyclopropane **2j** in CDCl_3

Figure S17. 600 MHz selective gradient NOE spectrum of 6a in CDCl_3

Figure S18. 400 MHz ^1H NMR spectrum of cyclopropane 6a in CDCl_3

Figure S19. 125 MHz ^{13}C NMR spectrum (JMOD) of cyclopropane 6a in CDCl_3

Figure S20. 125 MHz ^{13}C NMR spectrum of cyclopropane 6a in CDCl_3

Figure S21. 400 MHz ¹H NMR spectrum of cyclopropane 6b in CDCl₃

Figure S22. 100 MHz ¹³C NMR spectrum (JMOD) of cyclopropane 6b in CDCl₃

Figure S23. 125 MHz ^{13}C NMR spectrum of cyclopropane 6b in CDCl_3

Figure S24. 400 MHz ^1H NMR spectrum of cyclopropane 6c in CDCl_3

Figure S25. 100 MHz ^{13}C NMR spectrum (JMOD) of cyclopropane 6c in CDCl_3

Figure S26. 125 MHz ^{13}C NMR spectrum of cyclopropane 6c in CDCl_3