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SUPPORTING INFORMATION

Title: Ruthenium(II)-Catalyzed Cyclization of Oxabenzonorbornenes with Propargylic Alcohols: Formation of Isochromenes

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General Information

All reactions were carried out in an atmosphere of dry nitrogen at ambient temperature unless otherwise stated. Standard column chromatography was performed on 230-400 mesh silica gel (obtained from Silicycle) using flash column chromatography techniques.[1] Analytical thin-layer chromatography (TLC) was performed on Silicycle precoated silica gel F_{254} plates. All glassware was flame dried under an inert atmosphere of dry nitrogen. Infrared spectra were taken on a Bomem MB-100 FTIR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance-300 and 400 spectrometers. Chemical shifts for ^{1}H NMR spectra are reported in parts per million (ppm) from tetramethylsilane with the solvent resonance as the internal standard (chloroform: δ 7.26 ppm). Chemical shifts for ^{13}C NMR spectra are reported in parts per million (ppm) from tetramethylsilane with the solvent as the internal standard (deuterochloroform: δ 77.0 ppm). Chemical shifts for ^{2}H NMR spectra are reported in parts per million (ppm) from tetramethylsilane with the solvent as the internal standard (deuterochloroform: δ 7.26 ppm). High resolution mass spectra were done by McMaster Regional Centre for Mass Spectrometry at McMaster University, Hamilton, Ontario. Elemental analyses were performed by Canadian Microanalytical Service Ltd., British Columbia or by Quantitative Technologies Inc., New Jersey.

Reagents: Unless stated otherwise, commercial reagents were used without purification. Solvents were purified by distillation under dry nitrogen: from magnesium/iodine (MeOH) and from potassium/benzophenone (THF). Alkene **2f** was bought from *Sigma-Aldrich Co.* and used without further purification. $[Cp^*Ru(CH_3CN)]PF_6$ was bought from *Strem Chemicals*. Alkynes **4a**,[2] **4a**-*d*,[3] bicyclic alkenes **2a**,[4] **2b**,[5] **2c**,[5] **2e**,[6] **2g**,[7] and Cp*Ru(COD)Cl[8] were prepared according to literature procedures.

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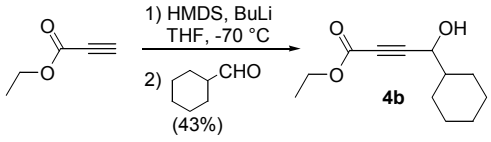
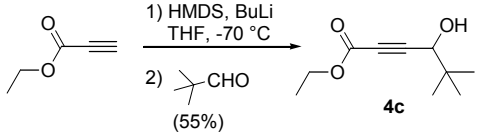
Part A: Synthesis of Alkynes

General procedure (A) for the preparation of alkynes. To a cold solution (-70 °C) of hexamethyldisilazane (HMDS, 1.2 equiv.) in THF (0.6 M versus ethyl propiolate) was added dropwise a solution of butyllithium in hexanes (BuLi, 2.5 M, 1.2 equiv.). The reaction was stirred for 15 min then ethyl propiolate (1.0 equiv.) was added dropwise. The resulting mixture was allowed to stir at –70 °C for 20 min prior to add the electrophile (1.4 equiv.). The reaction was monitored by TLC and upon completion, quenched with water and allowed to warm to room temperature. The reaction mixture was diluted with ethyl acetate the layers were separated. The aqueous layer was extracted three times with ethyl acetate, and the combined organic extracts were then washed with brine, dried over anhydrous magnesium sulfate, filtrated and concentrated to dryness. The crude product was the purified by column chromatography.

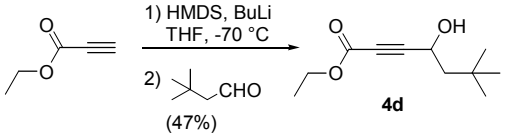


Propargylic alcohol 4b: Following the above general procedure (A) with HMDS (0.75 mL, 3.6 mmol), THF (5.0 mL), BuLi (1.40 mL, 3.54 mmol), ethyl propiolate (0.30 mL, 3.0 mmol) and cyclohexylcarboxaldehyde (0.60 mL, 4.0 mmol). The crude product was purified by column chromatography (gradient EtOAc/hexanes = 1: 9 to 3:7) to give **4b** (269.7 mg, 1.283 mmol, 43 %) as a colorless oil. R_f 0.23 (EtOAc/hexanes = 1:9); IR (neat) 3417, 2930, 2855, 2234, 1714, 1630, 1451, 1241 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.26 (app t, J = 6.1 Hz, 1 H), 4.22 (q, J = 7.1 Hz, 2 H), 2.44 (d, J = 6.0 Hz, 1 H), 1.84-1.87 (m, 2 H), 1.75-1.78 (m, 2 H), 1.58-1.68 (m, 2 H), 1.30 (t, J = 7.1 Hz, 3 H), 1.00-1.26 (m, 5 H); ^{13}C NMR (APT, $CDCl_3$, 100 MHz) δ 153.5, 87.2, 77.3, 66.8, 62.1, 43.6, 28.3, 28.1, 26.1, 25.7, 13.9; HRMS (CI) calcd. for $C_{12}H_{18}O_3$ ($(M+H)^+$): 211.1336; found: 211.1334.



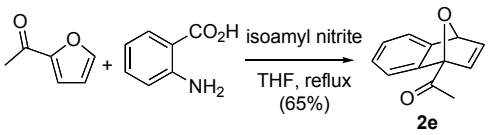
Propargylic alcohol 4c: Following the above general procedure (A) with HMDS (0.75 mL, 3.6 mmol), THF (5.0 mL), BuLi (1.40 mL, 3.54 mmol), ethyl propiolate (0.30 mL, 3.0 mmol) and trimethylacetaldehyde (0.45 mL, 4.1 mmol). The crude product was purified by column

chromatography (gradient EtOAc/hexanes = 1:9 to 1:4) to give **4c** (298.5 mg, 1.620 mmol, 55 %) as a colorless oil. R_f 0.21 (EtOAc/hexanes = 1:9); IR (neat) 3457, 2967, 2872, 2234, 1716, 1254 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.22 (q, *J* = 7.1 Hz, 2 H), 4.12 (s, 1 H), 2.36 (br s, 1 H), 1.30 (t, *J* = 7.1 Hz, 3 H), 1.01 (s, 9 H); ^{13}C NMR (APT, $CDCl_3$, 100 MHz) δ 153.4, 86.9, 77.5, 71.0, 62.1, 36.0, 26.2, 25.2, 14.0; HRMS (CI) calcd. for $C_{10}H_{16}O_3$ ($(M+H)^+$): 185.1178; found: 185.1184.

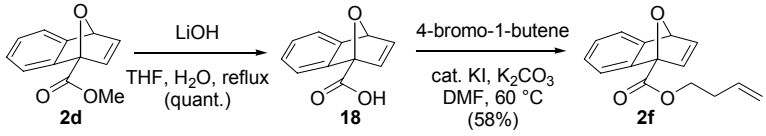


Propargylic alcohol 4d: Following the above general procedure (A) with HMDS (0.75 mL, 3.6 mmol), THF (5.0 mL), BuLi (1.40 mL, 3.54 mmol), ethyl propiolate (0.30 mL, 3.0 mmol) and 3,3-dimethylbutaldehyde (0.50 mL, 4.0 mmol). The crude product was purified by column chromatography (gradient EtOAc/hexanes = 1:19 to 1:4) to give **4d** (276.8 mg, 1.396 mmol, 47 %) as a colorless oil. R_f 0.26 (EtOAc/hexanes = 1:9); IR (neat) 3432, 2956, 2907, 2871, 2235, 1714, 1245 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.55-4.60 (m, 1H), 4.22 (q, *J* = 7.1 Hz, 2 H), 2.05 (m, 1 H), 2.01-2.08 (m, 2 H), 1.30 (t, *J* = 7.1 Hz, 3 H), 0.98 (s, 9 H); ^{13}C NMR (APT, $CDCl_3$, 100 MHz) δ 153.5, 88.8, 76.4, 62.1, 59.9, 50.5, 30.2, 29.8, 14.0; HRMS (EI) calcd. for $C_{11}H_{18}O_3$ (M^+): 198.1256; found: 198.1262.

Part B: Synthesis of Alkenes



Alkene 2e: To a stirring solution of isoamyl nitrite (14.5 mL, 109 mmol) and 2-acetylfuran (7.3 ml, 73 mmol) in dry THF (100 mL) under N_2, a solution of anthranilic acid (5.0 g, 37 mmol) in dry THF (25 mL) was added slowly by drop funnel. The solution was warmed up to 65-70 °C during the addition of anthranilic acid and refluxed for 2 h following the addition. The resulting mixture was concentrated and purified by column chromatography (EtOAc/hexanes = 1.5:8.5) to afford alkene **2e** as a pale yellow oil (4.57 g, 24.5 mmol, 65%). R_f 0.53 (EtOAc/hexanes = 3:7); IR (neat) 3070, 3016, 1715, 1454, 1441, 1417, 1365, 1320, 1274, 1234 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz) δ 7.26 (m, 2 H), 7.04 (m, 4 H), 5.82 (br. s, 1 H), 2.42 (br s, 3 H); ^{13}C NMR (APT, $CDCl_3$, 100MHz) δ 205.2, 148.0, 147.5, 143.4, 142.3, 125.6, 125.2, 120.6, 119.5, 114.5, 95.7, 82.3, 26.8. HRMS (EI) calcd. for $C_{12}H_{10}O_2$ (M^+): 186.0681; found: 186.0688.



Alkene 18: In a round-bottomed flask equipped with a condenser were successively loaded **2d** (0.5012 g, 2.479 mmol), THF (7.5 mL), H_2O (2.5 mL) and LiOH (1.24 g, 29.6 mmol). The biphasic reaction mixture was allowed to gently refluxed for 30 min, prior to be cooled to 0 ºC. The mixture was acidified with conc. H_2SO_4 to ca. pH = 3. The solid was filtrated and washed with cold water, then dissolved in EtOAc, dried over magnesium sulfate and concentrated to dryness to give **18** as a beige solid (463.2 mg, 2.461 mmol, quantitative yield). ^1H NMR ($CDCl_3$, 400 MHz) δ 7.43-7.47 (m, 1 H), 7.28-7.31 (m, 1 H), 7.01-7.14 (m, 4 H), 5.87 (d, J = 1.5 Hz, 1 H); ^{13}C NMR (APT, $CDCl_3$, 100 MHz) δ 172.7, 147.4, 146.6, 143.7, 142.1, 125.9, 125.4, 120.7, 120.0, 90.1, 82.6. HRMS (CI) calcd. for $C_{11}H_8O_3$ ($(M+H)^+$): 189.0552; found: 189.0560. Acid **18** was used for the next step without further purification.

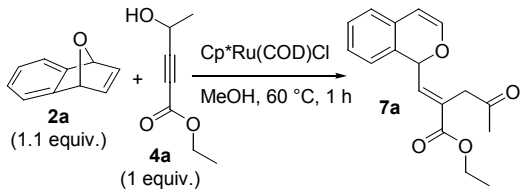
Alkene 2f: To a mixture of **18** (152.8 mg, 0.8077 mmol) and K_2CO_3 (181.2 mg, 1.311 mmol) in DMF (3.0 mL) was added potassium iodide (ca. 10 mg). The flask was then equipped with a condenser and purged with nitrogen prior to slowly add 4-bromo-1-butene (0.40 mL, 3.9 mmol). The reaction was heated at 60 ºC for 24 h then allowed to cool to room temperature.

The mixture was partitioned between 1N aqueous HCl and diethyl ether. Layers were separated; aqueous phase was extracted three times with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (gradient EtOAc/hexanes = 1:19 to 1:9) to provide **2f** (112.3 mg, 0.4635 mmol, 58%) as a pale yellow oil. R_f 0.29 (EtOAc/hexanes = 1:4); IR (CH_2Cl_2) 3134, 3076, 3052, 3015, 2980, 2961, 2902, 1737 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.40-7.43 (m, 1 H), 7.30-7.32 (m, 1 H), 7.03-7.13 (m, 4 H), 5.84-5.95 (m, 1 H), 5.85 (s, 1 H), 5.22 (dm, *J* = 17.2 Hz, 1 H), 5.17 (dm, *J* = 10.2 Hz, 1 H), 4.51 (t, *J* = 7.8 Hz, 1 H), 2.59 (app qt, *J* = 6.8, 1.3 Hz, 2 H); ^{13}C NMR (APT, $CDCl_3$, 100 MHz) δ 167.6, 147.7, 147.2, 143.5, 142.5, 133.3, 125.6, 125.1, 120.5, 119.9, 117.8, 90.3, 82.4, 64.7, 33.0. HRMS (EI) calcd. for $C_{15}H_{14}O_3$ (M^+): 242.0943; found: 242.0942.

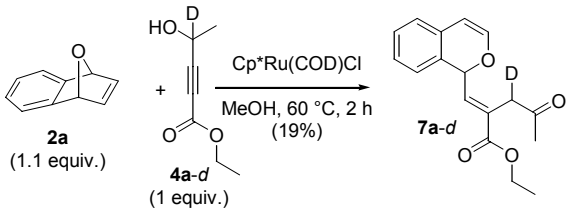
Part C: Ruthenium-Catalyzed Reactions

General procedure (B) for ruthenium-catalyzed formation of cyclobutene, cyclopropane and/or isochromene products. A mixture of alkene **2** (1.1-1.4 equiv.), acetylene **4** (1.0 equiv.) and MeOH (0.5 M versus acetylene) in an oven-dried vial was added via a cannula to an oven-dried screw-cap vial containing Cp*Ru(COD)Cl (weighed out from a dry box, 5-6 mol%) under nitrogen. The reaction mixture was stirred at 60 °C for 1 h. The solvent was evaporated and the crude product was purified by column chromatography.

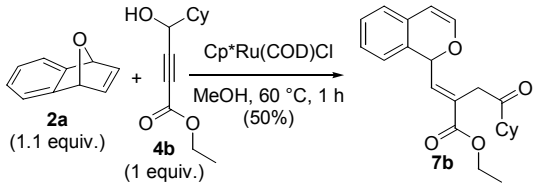
General procedure (C) for ruthenium-catalyzed formation of isochromene or cyclopropane products from ethyl diazoacetate. A solution of alkene **2** (1 equiv.) in THF (0.5 M) in an oven-dried vial was added via cannula to an oven-dried vial containing $[Cp^*Ru(NCCH_3)_3]PF_6$ (weighed out from a dry box, 5-6 mol%) under nitrogen. The reaction mixture was stirred at 60 °C, then a solution of ethyl diazoacetate (2-3 equiv.) in THF (1.1 M) was added over 30-45 min using a syringe. The reaction was monitored by ^{1}H NMR and upon completion, the solvent was evaporated and the crude product was purified by column chromatography.



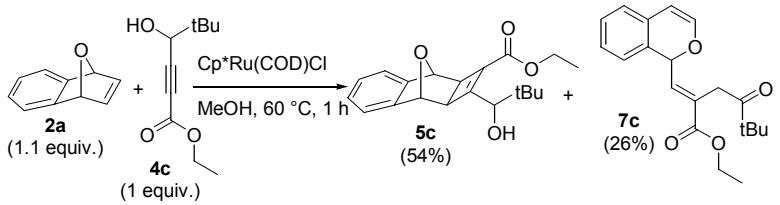
Isochromene 7a: Following the above general procedure (B) with alkene **2a** (204.9 mg, 1.421 mmol), alkyne **4a** (180.0 mg, 1.266 mmol), MeOH (1.6 mL), and Cp*Ru(COD)Cl (17.2 mg, 0.0453 mmol). The reaction mixture was stirred at 60 ºC for 1 h. The crude product was purified by column chromatography (gradient EtOAc/hexanes= 1:19 to 1:4) to provide **7a** (181.2 mg, 0.6330 mmol, 50%) as a white solid (mp = 60-62 ^{o}C, Et_2O/hexanes). R_f 0.33 (EtOAc/hexanes = 1:4); IR (neat) 3070, 2985, 2955, 2936, 1720, 1713, 1622 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.22-7.26 (m, 2 H), 7.17 (app t, *J* = 7.5 Hz, 1 H), 6.99 (app t, *J* = 7.5 Hz, 2 H), 6.53 (d, *J* = 5.7 Hz, 1 H), 5.84 (d, *J* = 5.7 Hz, 1 H), 5.73 (d, *J* = 8.8 Hz, 1 H), 4.17-4.23 (m, 2 H), 3.63 (d, *J* = 17.1 Hz, 1 H), 3.53 (d, *J* = 17.1 Hz, 1 H), 2.23 (s, 3 H), 1.29 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (APT, $CDCl_3$, 100 MHz) δ 204.5, 166.5, 144.5, 139.5, 129.6, 129.4, 128.7, 128.0, 127.2, 124.4, 123.5, 105.5, 73.7, 61.4, 41.8, 29.9,14.1. HRMS (EI) calcd. for $C_{17}H_{18}O_4$ (M^+): 286.1205; found: 286.1207.



Isochromene 7a-*d*: Following the above general procedure (B) with alkene **2a** (60.5 mg, 0.420 mmol), alkyne **4a**-*d* (49.9 mg, 0.349 mmol), MeOH (0.6 mL), and Cp*Ru(COD)Cl (6.3 mg, 0.017 mmol). The reaction mixture was stirred at 60 ºC for 2.5 h. The crude product was purified by column chromatography (gradient EtOAc/hexanes = 1:9 to 1:4) to provide **7a**-*d* (19.5 mg, 0.0678 mmol, 19%). **7a**-*d* (major diastereomer) R_f 0.33 (EtOAc/hexanes = 1:4); IR (CH_2Cl_2) 3066, 2981, 2906, 1713, 1252 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.13-7.25 (m, 3 H), 6.97-7.01 (m, 2 H), 6.53 (d, J = 5.7 Hz, 1 H), 5.84 (d, J = 5.7 Hz, 1 H), 5.73 (d, J = 8.8 Hz, 1 H), 4.17-4.23 (m, 2 H), 3.61 (br s, 1 H), 2.23 (s, 3 H), 1.29 (t, J = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 204.5, 166.5, 144.5, 139.5, 129.7, 129.4, 128.7, 128.1, 127.2, 124.4, 123.5, 105.5, 73.7, 61.4, 41.6 (t, J = 20 Hz), 29.9,14.1. ^2H NMR ($CHCl_3$, 61 MHz) δ 3.57. HRMS (EI) calcd. for $C_{17}H_{17}{}^2HO_4$ (M^+): 287.1267; found: 287.1281.



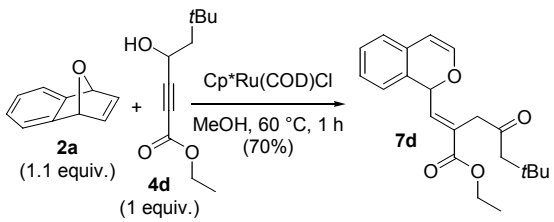
Isochromene 7b: Following the above general procedure (B) with alkene **2a** (50.8 mg, 0.352 mmol), alkyne **4b** (52.7 mg, 0.252 mmol), MeOH (0.7 mL), and Cp*Ru(COD)Cl (6.4 mg, 0.017 mmol). The reaction mixture was stirred at 60 ºC for 1 h. The crude product was purified by column chromatography (gradient Et_2O/hexanes = 1:9 to 1:4) to provide **7b** (44.2 mg, 0.125 mmol, 50%) as a white solid (mp = 60-62 ºC, uncrist.). R_f 0.49 (EtOAc/hexanes = 3:7); IR (CH_2Cl_2) 2981, 2929, 2853, 1709 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.21-7.25 (m, 2 H), 7.17 (app td, J = 7.6, 1.3 Hz, 1 H), 6.99 (d, J = 7.5 Hz, 2 H), 6.53 (d, J = 5.7 Hz, 1 H), 5.84 (d, J = 5.7 Hz, 1 H), 5.70 (d, J = 8.8 Hz, 1 H), 4.24-4.15 (m, 2 H), 3.67 (d, J = 17.2 Hz, 1 H), 3.54 (d, J = 17.2 Hz, 1 H), 2.46 (tt, J = 11.2, 3.4 Hz, 1 H), 1.88-1.91 (m, 2 H), 1.77-1.80 (m, 2 H), 1.65-1.68 (m, 1 H), 1.27 (t, J = 7.1 Hz, 3 H), 1.17-1.40 (m, 5 H); ^{13}C NMR (APT, $CDCl_3$, 100 MHz) δ 209.5, 166.6, 144.6, 139.3, 129.8, 129.7, 128.6, 128.1, 127.2, 124.5, 123.4, 105.4, 73.8, 61.2, 50.8, 39.0, 28.5, 28.4, 25.8, 25.61, 25.55, 14.1. HRMS (CI) calcd. for $C_{22}H_{26}O_4$ ($(M+H)^+$): 355.1909; found: 355.1915.



Cyclobutene 5c and isochromene 7c: Following the above general procedure (B) with alkene **2a** (42.1 mg, 0.292 mmol), alkyne **4c** (42.0 mg, 0.228 mmol), MeOH (0.6 mL), and Cp*Ru(COD)Cl (6.2 mg, 0.016 mmol). The reaction mixture was stirred at 60 ºC for 1 h. The crude product was purified by column chromatography (gradient Et_2O/hexanes = 1:9 to 2:3) to provide cycloadduct **5c** (40.7 mg, 0.124 mmol, 54%) and **7c** (19.5 mg, 0.0593 mmol, 26%).

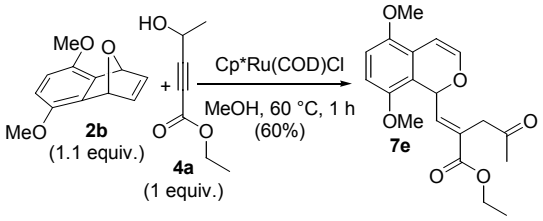
5c (major diastereomer): white solid (mp = 88-89 ºC, uncrist.); R_f 0.25 (EtOAc/hexanes = 2:3); IR (CH_2Cl_2) 3408, 3058, 2963, 2906, 2869, 1712, 1682 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.28-7.35 (m, 2 H), 7.17-7.19 (m, 2 H), 5.17 (d, J = 8.9 Hz, 1 H), 5.09 (s, 1 H), 5.08 (s, 1 H), 4.27-4.31 (m, 2 H), 4.01 (br d, J = 8.9 Hz, 1 H), 2.86 (br d, J = 3.2 Hz, 1 H), 2.70 (br d, J = 3.4 Hz, 1 H), 1.37 (t, J = 7.1 Hz, 3 H), 1.00 (s, 9 H); ^{13}C NMR (APT, $CDCl_3$, 100 MHz) δ 166.3, 163.5, 144.3, 143.9, 132.1, 126.9, 126.8, 120.0, 119.7, 78.4, 75.5, 75.2, 61.2, 49.0, 44.8, 37.4, 26.1, 14.2. HRMS (EI) calcd. for $C_{20}H_{24}O_4$ (M^+): 328.1675; found: 328.1670.

7c: colorless oil; R_f 0.49 (EtOAc/hexanes = 3:7); IR (CH_2Cl_2) 3066, 2981, 2930, 2872, 1711 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.21-7.25 (m, 2 H), 7.18 (app td, J = 7.6, 1.3 Hz, 1 H), 6.99 (d, J = 7.6 Hz, 2 H), 6.54 (d, J = 5.7 Hz, 1 H), 5.85 (d, J = 5.7 Hz, 1 H), 5.67 (d, J = 8.8 Hz, 1 H), 4.24-4.16 (m, 2 H), 3.75 (d, J = 17.6 Hz, 1 H), 3.59 (d, J = 17.6 Hz, 1 H), 1.27 (t, J = 7.1 Hz, 3 H), 1.20 (s, 9 H); ^{13}C NMR (APT, $CDCl_3$, 100 MHz) δ 211.5, 166.6, 144.7, 139.2, 130.3, 129.7, 128.6, 128.2, 127.2, 124.5, 123.4, 105.4, 73.8, 61.2, 44.4, 35.4, 26.6, 14.1. HRMS (CI) calcd. for $C_{20}H_{24}O_4$ ($(M+H)^+$): 329.1753; found: 329.1744.

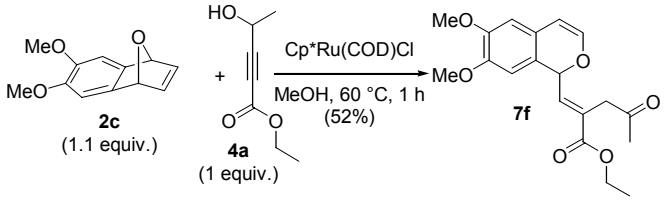


Isochromene 7d: Following the above general procedure (B) with alkene **2a** (58.6 mg, 0.406 mmol), alkyne **4d** (55.8 mg, 0.281 mmol), MeOH (0.6 mL), and Cp*Ru(COD)Cl (6.1 mg, 0.016 mmol). The reaction mixture was stirred at 60 ºC for 1 h. The crude product was purified by column chromatography (gradient Et_2O/hexanes = 1:9 to 2:3) to provide **7d** (67.0

mg, 0.196 mmol, 70%) as a white solid (mp = 52-55 ºC, uncrist.); R_f 0.45 (EtOAc/hexanes = 1:9); IR (CH_2Cl_2) 3065, 2954, 2869, 1713, 1626 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.15-7.25 (m, 3 H), 6.98-7.00 (m, 2 H), 6.53 (d, J = 5.7 Hz, 1 H), 5.84 (d, J = 5.7 Hz, 1 H), 5.71 (d, J = 8.8 Hz, 1 H), 4.26-4.16 (m, 2 H), 3.61 (d, J = 17.3 Hz, 1 H), 3.50 (d, J = 17.0 Hz, 1 H), 2.40 (s, 2 H), 1.28 (t, J = 7.1 Hz, 3 H), 1.03 (s, 9 H); ^{13}C NMR (APT, $CDCl_3$, 100 MHz) δ 206.0, 166.6, 144.6, 139.2, 129.7, 129.6, 128.6, 128.1, 127.2, 124.5, 123.4, 105.4, 73.7, 61.2, 54.8, 43.2, 31.0, 29.6, 14.1. HRMS (CI) calcd. for $C_{21}H_{26}O_4$ ($(M+H)^+$): 343.1909; found: 343.1912.

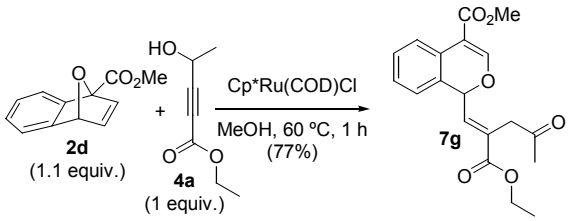


Isochromene 7e: Following the above general procedure (B) with alkene **2b** (112.4 mg, 0.550 mmol), alkyne **4a** (70.5 mg, 0.496 mmol), MeOH (0.9 mL), and Cp*Ru(COD)Cl (13.3 mg, 0.035 mmol). The reaction mixture was stirred at 60 ºC for 1 h. The crude product was purified by column chromatography (gradient Et_2O/hexanes = 1:9 to 1:1) to provide **7e** (103.1 mg, 0.2976 mmol, 60%) as a colorless oil. R_f 0.23 (EtOAc/hexanes = 3:7); IR (CH_2Cl_2) 3098, 3060, 2979, 2959, 2939, 2907, 2836, 1712, 1438, 1261 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.23 (d, J = 9.4 Hz, 1 H), 6.71 (d, J = 8.9 Hz, 1 H), 6.62 (d, J = 8.9 Hz, 1 H), 6.45 (d, J = 5.9 Hz, 1 H), 6.09 (d, J = 9.4 Hz, 1 H), 6.08 (d, J = 5.8 Hz, 1 H), 4.12-4.18 (m, 2 H), 3.78 (s, 3 H), 3.70 (s, 3 H), 3.63-3.74 (m, 2 H), 2.21 (s, 3 H), 1.24 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (APT, $CDCl_3$, 100 MHz) δ 204.9, 167.1, 148.7, 147.5, 143.2, 138.2, 127.0, 119.3, 116.7, 110.8, 109.1, 99.0, 68.1, 61.2, 56.0, 55.5, 41.8, 29.4,14.1. HRMS (CI) calcd. for $C_{19}H_{22}O_6$ ($(M+H)^+$): 347.1495; found: 347.1486.

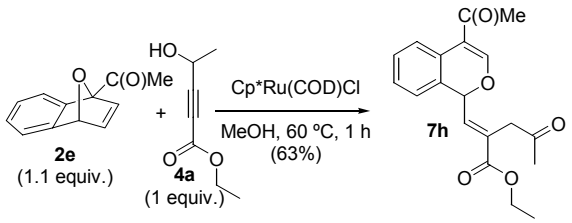


Isochromene 7f: Following the above general procedure (B) with alkene **2c** (69.2 mg, 0.339 mmol), alkyne **4a** (41.6 mg, 0.293 mmol), MeOH (1.2 mL), and Cp*Ru(COD)Cl (6.1 mg, 0.016 mmol). The reaction mixture was stirred at 60 ºC for 1 h. The crude product was

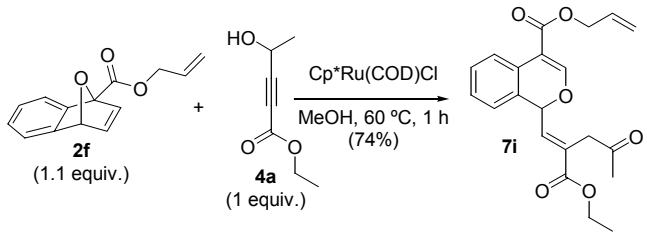
purified by column chromatography (gradient EtOAc/hexanes = 1:9 to 2:3) to provide **7f** (52.8 mg, 0.155 mmol, 52%) as a colorless oil. R_f 0.50 (EtOAc/hexanes = 1:1); IR (CH_2Cl_2) 2984, 2937, 2836, 1713, 1513, 1269 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.20 (d, J = 8.8 Hz, 1 H), 6.60 (s, 1 H), 6.55 (s, 1 H), 6.47 (d, J = 5.7 Hz, 1 H), 5.76 (d, J = 5.7 Hz, 1 H), 5.69 (d, J = 8.8 Hz, 1 H), 4.18-4.24 (m, 2 H), 3.861 (s, 3 H), 3.858 (s, 3 H), 3.70 (d, J = 17.0 Hz, 1 H), 3.45 (d, J = 17.0 Hz, 1 H), 2.23 (s, 3 H), 1.28 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (APT, $CDCl_3$, 100 MHz) δ 204.7, 166.5, 149.0, 148.2, 142.8, 139.8, 128.9, 122.6, 120.0, 108.4, 107.2, 105.1, 73.5, 61.3, 56.2, 56.0, 41.8, 30.1,14.1. HRMS (CI) calcd. for $C_{19}H_{22}O_6$ ($(M+H)^+$): 347.1495; found: 347.1485.



Isochromene 7g: Following the above general procedure (B) with alkene **2d** (55.9 mg, 0.276 mmol), alkyne **4a** (38.6 mg, 0.272 mmol), MeOH (0.6 mL), and Cp*Ru(COD)Cl (5.8 mg, 0.015 mmol). The reaction mixture was stirred at 60 ºC for 1 h. The crude product was purified by column chromatography (gradient Et_2O/hexanes= 1:4 to 1:1) to provide **7g** (72.1 mg, 0.209 mmol, 77%) as a white solid (mp = 100-101 ºC, Et_2O/hexanes). R_f 0.24 (EtOAc/hexanes = 1:4); IR (CH_2Cl_2) 3064, 2982, 2952, 1721, 1717, 1210 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.26-7.32 (m, 2 H), 7.15-7.18 (m, 2 H), 7.08-7.10 (m, 1 H), 6.97 (s, 1 H), 5.87 (d, J = 8.6 Hz, 1 H), 4.23-4.14 (m, 2 H), 3.83 (s, 3 H), 3.71 (d, J = 17.1 Hz, 1 H), 3.52 (d, J = 17.1 Hz, 1 H), 2.23 (s, 3 H), 1.26 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (APT, $CDCl_3$, 100 MHz) δ 204.5, 166.2, 162.9, 142.5, 138.4, 130.1, 129.7, 129.4, 128.9, 128.7, 125.8, 124.7, 113.0, 74.8, 61.3, 52.3, 41.8, 30.0,14.0. HRMS (CI) calcd. for $C_{19}H_{20}O_6$ ($(M+H)^+$): 345.1338; found: 345.1326. Anal. calcd. for $C_{19}H_{20}O_6$: C, 66.27%, H, 5.85%; found: C, 66.40%; H, 5.72%.

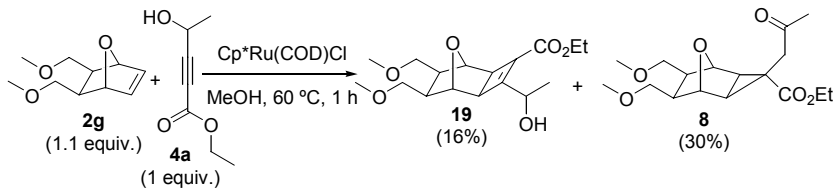


Isochromene 7h: Following the above general procedure (B) with alkene **2e** (73.4 mg, 0.394 mmol), alkyne **4a** (42.3 mg, 0.298 mmol), MeOH (0.8 mL), and Cp*Ru(COD)Cl (6.7 mg, 0.018 mmol). The reaction mixture was stirred at 60 ºC for 1 h. The crude product was purified by column chromatography (gradient EtOAc/hexanes = 1:9 to 2:3) to provide **7h** (61.6 mg, 0.188 mmol, 63%) as a white solid (m.p. = 99-102 ºC, Et_2O/hexanes). R_f 0.30 (EtOAc/hexanes = 3:7); IR (CH_2Cl_2) 3079, 2981, 2933, 1714, 1681, 1256 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.27-7.31 (m, 2 H), 7.19-7.21 (m, 1 H), 7.16 (d, 1 H, J = 8.8 Hz), 7.07-7.09 (m, 1 H), 6.85 (s, 1 H), 5.84 (d, J = 8.8 Hz, 1 H), 4.24-4.15 (m, 2 H), 3.68 (d, J = 17.1 Hz, 1 H), 3.53 (d, J = 17.1 Hz, 1 H), 2.34 (s, 3 H), 2.24 (s, 3 H), 1.27 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (APT, $CDCl_3$, 100 MHz) δ 204.4, 193.9, 166.3, 149.0, 138.6, 130.0, 129.9, 129.6, 129.0, 128.8, 126.4, 124.6, 111.0, 74.5, 61.4, 41.8, 30.0, 25.7, 14.0. Anal. calcd. for $C_{19}H_{20}O_5$: C, 69.50%, H, 6.14%; found: C, 69.67%; H, 6.01%.



Isochromene 7i: Following the above general procedure (B) with alkene **2f** (50.9 mg, 0.210 mmol), alkyne **4a** (27.1 mg, 0.191 mmol), MeOH (0.5 mL), and Cp*Ru(COD)Cl (5.2 mg, 0.0137 mmol). The reaction mixture was stirred at 60 ºC for 1 h. The crude product was purified by column chromatography (gradient Et_2O/hexanes = 1:9 to 2:3) to provide **7i** (51.9 mg, 0.141 mmol, 74%) as a white solid (mp = 55-57 ºC, Et_2O/hexanes). R_f 0.39 (EtOAc/hexanes = 1:4); IR (CH_2Cl_2) 3076, 2981, 2904, 1722, 1714 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.30-7.32 (m, 2 H), 7.16-7.19 (m, 2 H), 7.09-7.11 (m, 1 H), 6.95 (s, 1 H), 5.88 (d, J = 8.6 Hz, 1 H), 5.79-5.87 (m, 1 H), 5.16 (dd, J = 17.1, 1.6 Hz, 1 H), 5.11 (dd, J = 10.3, 1.5 Hz, 1 H), 4.81 (t, J = 6.8 Hz, 2 H), 4.17-4.24 (m, 2 H), 3.73 (d, J = 17.1 Hz, 1 H), 3.54 (d, J = 17.1 Hz, 1 H), 2.49 (app qt, J = 6.8, 1.2 Hz, 2 H), 2.25 (s, 3 H), 1.28 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (APT, $CDCl_3$, 100 MHz) δ 204.6, 166.3, 162.4, 142.6, 138.6, 133.6, 130.0, 129.7,

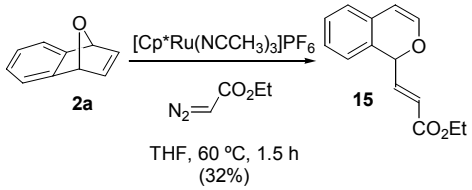
129.5, 128.9, 128.7, 125.8, 124.7, 117.5, 112.9, 74.8, 64.4, 61.4, 41.9, 33.0, 30.0, 14.1. HRMS (CI) calcd. for $C_{22}H_{24}O_6$ ($(M+H)^+$): 385.1651; found: 385.1665.



Cyclobutene 19 and cyclopropane 8: Following the above general procedure (B) with alkene **2g** (58.3 mg, 0.316 mmol), alkyne **4a** (45.0 mg, 0.317 mmol), MeOH (0.8 mL), and Cp*Ru(COD)Cl (6.1 mg, 0.016 mmol). The reaction mixture was stirred at 60 ºC for 1 h. The crude product was purified by column chromatography (gradient Et_2O/hexanes = 1:9 to 1:1) to provide cycloadduct **19** (16.1 mg, 0.0493 mmol, 16%) and **8** (31.0 mg, 0.0950 mmol, 30%).

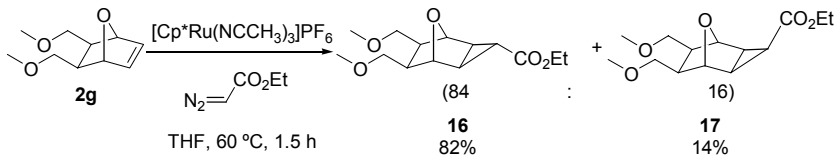
19 (major diastereomer): pale yellow oil; R_f 0.13 (EtOAc/hexanes = 3:2); IR (CH_2Cl_2) 3435, 2978, 2930, 2893, 2879, 2813, 1712, 1205, 1102 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.86 (br d, J = 3.7 Hz, 1 H), 4.54-4.56 (m, 1 H), 4.15-4.25 (m, 2 H), 4.17 (s, 1 H), 4.11 (s, 1 H), 3.13-3.38 (m, 4 H), 3.31 (s, 6 H), 2.83-2.84 (m, 1 H), 2.73 (br d, J = 3.3 Hz, 1 H), 1.93-2.14 (m, 2 H), 1.30 (d, J = 6.8 Hz, 3 H), 1.28 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (APT, $CDCl_3$, 100 MHz) δ 166.5, 163.4, 128.4, 75.9, 75.3, 70.8, 70.5, 65.2, 60.9, 58.8, 47.3, 46.8, 45.6, 44.9, 44.5, 21.2, 14.2. HRMS (EI) calcd. for $C_{17}H_{26}O_6$ (M^+): 326.1729; found: 326.1732.

8: pale yellow oil; R_f 0.35 (EtOAc/hexanes = 2:3); IR (CH_2Cl_2) 2981, 2928, 2892, 2812, 1723, 1714, 1203 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.37 (s, 2 H), 4.04 (q, J = 7.1 Hz, 2 H), 3.28-3.32 (m, 2 H), 3.29 (s, 6 H), 3.18 (s, 2 H), 3.16-3.21 (m, 2 H), 2.25-2.27 (m, 2 H), 2.11 (s, 3 H), 1.81 (s, 2 H), 1.17 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (APT, $CDCl_3$, 100 MHz) δ 207.1, 173.1, 78.4, 70.4, 61.1, 58.7, 46.1, 38.9, 29.8, 29.7, 25.4,14.0. HRMS (EI) calcd. for $C_{17}H_{26}O_6$ (M^+): 326.1729; found: 326.1735.



Isochromene 15: Following the above general procedure (C) with alkene **2a** (151.3 mg, 1.049 mmol), THF (1.0 mL), $[Cp^*Ru(NCCH_3)_3]PF_6$ (30.2 mg, 0.0599 mmol), ethyl diazoacetate (250 μL, 2.41 mmol) and THF (2.1 mL). The addition was done over 45 min and the reaction

mixture was stirred at 60 ºC for 1.5 h. The crude product was purified by column chromatography (gradient Et_2O/hexanes = 1:19 to 1:9) to provide **15** (76.7 mg, 0.333 mmol, 32%) as a colorless oil. If diethyl fumarate and/or diethyl maleate were still present at this stage, they were distilled off under reduced pressure (kugelrohr distillation). R_f 0.45 (EtOAc/hexanes = 1:9); IR (neat) 3070, 2981, 2937, 2903, 1720, 1628, 1274 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.16-7.27 (m, 2 H), 7.06 (dd, *J* = 1.5, 5.2 Hz, 1 H), 6.97-7.01 (m, 2 H), 6.54 (d, *J* = 5.7 Hz, 1 H), 5.96 (d, *J* = 15.7 Hz, 1 H), 5.78 (d, *J* = 5.7 Hz, 1 H), 5.72 (d, *J* = 5.0 Hz, 1 H), 4.19 (q, *J* = 7.1 Hz, 2 H), 1.28 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (APT, $CDCl_3$, 100 MHz) δ 166.0, 144.2, 144.0, 129.3, 128.7, 127.9, 127.1, 124.7, 123.7, 122.3, 104.9, 75.9, 60.6, 14.2. HRMS (CI) calcd. for $C_{14}H_{14}O_3$ ($(M+H)^+$): 231.1021; found: 231.1025.



Cyclopropanes 16 and 17: Following the above general procedure (C) with alkene **2g** (115.9 mg, 0.629 mmol), THF (0.5 mL), $[Cp^*Ru(NCCH_3)_3]PF_6$ (34.1 mg, 0.0676 mmol), ethyl diazoacetate (170 μL, 1.64 mmol) and THF (1.1 mL). The addition was done over 30 min and the reaction mixture was stirred at 60 ºC for 1.5 h. The crude product was purified by column chromatography (gradient Et_2O/hexanes = 1:19 to 1:1) to provide **16** (139.5 mg, 0.5161 mmol, 82%) and **17** (23.8 mg, 0.0866 mmol, 14%) as colorless oils. Assignment of structures to these 2 epimers was based on the close analogies between these systems and that described by Sauers and co-workers,[9] and Takahashi *et al*.[10]

16: R_f 0.35 (EtOAc/hexanes = 2:3); IR (neat) 2974, 2926, 2893, 2813, 1729, 1407, 1267 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.26 (s, 2 H), 4.04 (q, *J* = 7.1 Hz, 2 H), 3.24-3.28 (m, 2 H), 3.26 (s, 6 H), 3.14-3.18 (m, 2 H), 2.17-2.20 (m, 2 H), 1.62-1.65 (m, 3 H), 1.18 (t, *J* = 7.1 Hz, 3 H); ^1H NMR (C_6D_6, 400 MHz) δ 4.28 (s, 2 H), 3.93 (q, *J* = 7.1 Hz, 2 H), 3.08 (dd, *J* = 8.8, 5.4 Hz, 2 H), 3.00-3.05 (m, 2 H), 3.00 (s, 6 H), 2.01-2.05 (m, 2 H), 1.98 (t, *J* = 2.6 Hz, 1 H), 1.57 (d, *J* = 2.6 Hz, 2 H), 0.93 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (APT, $CDCl_3$, 100 MHz) δ 172.9, 78.2, 70.5, 60.5, 58.8, 45.8, 25.2, 16.4, 14.2. HRMS (EI) calcd. for $C_{14}H_{22}O_5$ (M^+): 270.1467; found: 270.1464.

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[9] (a) R. R. Sauers, P. E. Sonnet *Tetrahedron* **1964**, *20*, 1029; (b) R. R. Sauers, S. B. Schlosberg, P. E. Pfeffer *J. Org. Chem.* **1968**, *33*, 2175.

[10] Y. Matsushima, H. Kikuchi, M. Uno, S. Takahashi *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2475.

17: R_f 0.17 (EtOAc/hexanes = 2:3); IR (CH_2Cl_2) 2980, 2930, 2811, 1729, 1219, 1126 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.42 (s, 2 H), 4.09 (q, *J* = 7.1 Hz, 2 H), 3.30-3.34 (m, 2 H), 3.30 (s, 6 H), 3.20-3.24 (m, 2 H), 2.23-2.26 (m, 2 H), 1.42-1.45 (m, 3 H), 1.24 (t, *J* = 7.1 Hz, 3 H); ^1H NMR (C_6D_6, 400 MHz) δ 4.60 (s, 2 H), 4.08 (q, *J* = 7.1 Hz, 2 H), 3.14 (dd, *J* = 8.8, 5.4 Hz, 2 H), 3.03-3.09 (m, 2 H), 3.00 (s, 6 H), 2.05-2.09 (m, 2 H), 1.06 (t, *J* = 7.2 Hz, 1 H), 1.02 (t, *J* = 7.1 Hz, 3 H), 0.87 (d, *J* = 7.2 Hz, 2 H); ^{13}C NMR (APT, $CDCl_3$, 100 MHz) δ 170.6, 78.5, 70.6, 60.3, 58.8, 46.3, 21.0, 19.5, 14.2. HRMS (EI) calcd. for $C_{14}H_{22}O_5(M^+)$: 270.1467; found: 270.1470.