Supplementary Materials for

Synthesis of many different types of organic small molecules using one automated process

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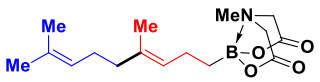
1. General materials and methods

Commercial reagents were purchased from Sigma-Aldrich, EMD Millipore, Fisher Scientific, Alfa Aesar, Frontier Scientific, Oakwood Products, or Strem and were used without further purification unless otherwise noted. Most of the building blocks used in these studies are available from commercial sources. The following MIDA boronates were purchased from Sigma-Aldrich: **20** (697311), **21** (700231), **22** (721573), **23** (710032), **24** (MIDA071), **25** (698229), **26** (697494), **27** (698164), **28** (698016), **29** (698148), **30** (704547), **31** (MIDA032), **32** (736600), **33** (748714), **34** (723711), **35** (738514), **36** (699861), **37** (MIDA020), **38** (MIDA076), **39** (704873), **88a** (730335), **88b** (733539), **88c** (703710), **90** (698083), **93a** (RNI00021), **93b** (698067), **1-1** (MIDA034), **2-2** (MIDA013), **3-1** (698032), **43** (701831), **44** (MIDA039), **45** (MIDA014), **50** (MIDA017), **5-1** (MIDA083), **5-2** (MIDA084), **6-1** (MIDA080), **6-2** (701092), **7-1** (723711), **7-2** (MIDA081), **8-2** (MIDA085), 2-furanyl MIDA boronate (701017).

Unless otherwise noted, manual building block syntheses were carried out in oven- or flame-dried glassware under a dry inert atmosphere. Unless otherwise noted: Celite™ refers to Celite™ 545 filter aid (not acid washed); Darco® refers to activated carbon, Darco® G-60, -100 mesh, powder; and K_3PO_4 and K_2CO_3 were both anhydrous and were freshly and finely ground in a 120 °C mortar and pestle. XPhos 2nd generation palladacycle refers to chloro(2-dicyclohexylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)[2-(2′-amino-1,1′-biphenyl)]palladium(II) (**741825, Sigma-Aldrich)**. Solvents were purified via passage through packed columns as described by Pangborn and coworkers (*34*) (THF, Et_2O, CH_3CN, CH_2Cl_2: dry neutral alumina; hexanes, benzene, toluene: dry neutral alumina and Q5 reactant; DMSO, DMF: activated molecular sieves. Water was deionized.

Thin layer chromatography (TLC) was performed using the indicated eluent on E. Merck silica gel 60 F254 plates (0.25 mm). Compounds were visualized by exposure to a UV lamp (λ = 254 and/or 366 nm) and/or a basic solution of $KMnO_4$ followed by brief heating with a Varitemp® heat gun. Flash chromatography was performed as described by Still and coworkers (*35*) using EM Merck silica gel 60 (230-400 mesh). ^{1}H NMR spectra were recorded at room temperature on one of the following instruments: Varian Unity 500, Varian VXR 500, or Varian Unity Inova 500NB. Chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane and referenced to residual protium in the NMR solvent ($CDCl_3$, δ = 7.26; $(CD_3)_2CO$, δ = 2.05, center line; CD_2Cl_2, δ = 5.32, center line; $(CD_3)_2SO$, δ = 2.50, center line). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sept = septet, m = multiplet, br = broad, app = apparent, dd = doublet of doublets, dt = doublet of triplets, dq = doublet of quartets), coupling constant (*J*) in Hertz (Hz), and integration. ^{13}C NMR spectra were recorded at room temperature on one of the following instruments: Varian Unity 500 or Varian VXR 500. Chemical shifts (δ) are reported in ppm downfield from tetramethylsilane and referenced to carbon resonances in the NMR solvent ($CDCl_3$, δ = 77.16, center line; $(CD_3)_2CO$, δ = 29.84, center line; CD_2Cl_2, δ = 53.84; $(CD_3)_2SO$, δ = 39.52, center line). Carbons bearing boron substituents are sometimes not observed due to quadrupolar relaxation. High resolution mass spectra (HRMS) were performed by Furong Sun and Elizabeth Eves at the University of Illinois School of Chemical Sciences Mass Spectrometry Laboratory.

2. Manual synthesis of 14



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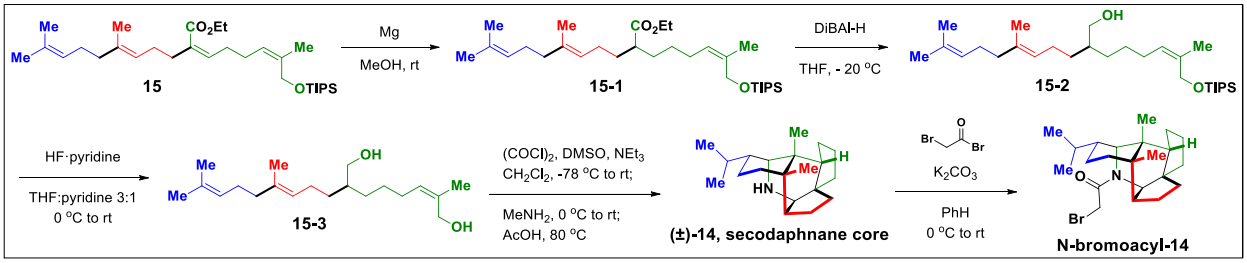
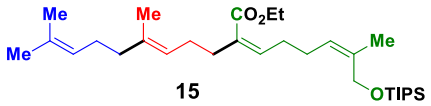
To a flame-dried 7 mL vial cooled under Argon and equipped was added zinc dust (248.1 mg, 3.79 mmol, 1.5 equiv.) and iodine (32.3 mg, 0.127 mmol, 0.5 equiv.). The vial was sealed with a PTFE-lined cap, purged twice with argon, and charged with DMF (1.0 mL, 2.5 M). After stirring at room temperature for 5 min until I_2 color disappeared, 5-bromo-2-methyl-2-pentene (0.34 mL, 413.8 mg, 2.54 mmol, 1.0 equiv.) was added to the reaction vial via syringe under a positive pressure of argon. The vial was sealed with Teflon tape and parafilm after the gas inlet needle was removed. The reaction mixture was then placed in an 80 °C aluminum heat block and maintained at that temperature with stirring for 4 h. The reaction mixture was then allowed to cool to room temperature and was taken into the glovebox. There the reaction mixture was passed through a 0.2 µm filter to afford a bright yellow solution, which was used immediately. To a flame-dried 40 mL vial was added vinyl iodide **17** (351 mg, 1.0 mmol, 1.0 equiv.), $PdCl_2(PPh_3)_2$ (21.0 mg, 0.03 mmol, 0.03 equiv.), and LiBr (452 mg; 5.2 mmol; 5.2 equiv.) followed by THF (9 mL, 0.1 M total). The resulting mixture was allowed to stir at room temperature for 5 min as a yellow suspension. After 5 min, alkyl zinc **16** solution in DMF (1.0 mL, 2.5 M, 2.5 equiv.) was added to the reaction mixture rinsing with THF for quantitative transfer, causing the reaction mixture to turn orange. The vial was sealed with a PTFE-lined cap and removed from the glovebox. The vials were placed in a 60 °C aluminum heat block and maintained at that temperature with stirring for 6 h. The reaction mixture was then cooled to room temperature and quenched with saturated aqueous NH_4Cl (10 mL). The mixture was transferred into a separatory funnel rinsing with EtOAc (10 mL) and H_2O (10 mL) was added. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine:H_2O (1:1) (3 x 20 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford an orange brown oil. The crude material was adsorbed onto Celite from an acetone slurry and purified by silica gel chromatography (Hexanes:Acetone 4:1 to Hexanes:Acetone 1:1) to afford a pale yellow solid. The solid was triturated with Et_2O:Hexanes (1:1) to give the product **19** as a white solid after filtration and drying (182 mg, 59%). TLC (EtOAc): R_f = 0.41, visualized by UV, stained with $KMnO_4$; ^{1}H-NMR (500 MHz, acetone-d_6): δ 5.22 (tq, J = 7.2, 1.4 Hz, 1H), 5.11 (tquint, J = 7.1, 1.4 Hz, 1H), 4.18 (d, J = 16.9 Hz, 2H), 4.02 (d, J = 16.9 Hz, 2H), 3.10 (s, 3H), 2.11 – 2.00 (m, 4H), 1.96 (dd, J = 8.4, 7.0 Hz, 2H), 1.66 – 1.64 (m, 3H), 1.61 – 1.58 (m, 6H), 0.71 – 0.63 (m, 2H); ^{13}C-NMR (125 MHz, acetone-d_6): δ 168.8, 133.6, 131.5, 128.5, 125.1, 62.6, 46.2, 40.4, 27.4, 25.8, 23.2, 17.7, 15.9; HRMS (ESI+) calculated for $C_{16}H_{26}BNO_4Na$ $[M+H]^+$ *m/z* 330.1853, found 330.1852.





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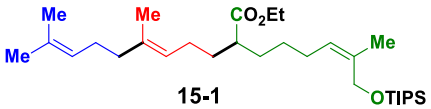
To a solution of MIDA boronate **19** (307 mg, 1 mmol, 1 equiv) in THF (5 mL) was added 1N NaOH (aq) (5 mL, 5 mmol, 5 equiv) under ambient atmosphere and temperature. The reaction was stirred at room temperature for 20 min. The reaction was concentrated *in vacuo* to remove THF. With vigorous stirring, saturated NH_4Cl (aq.) (5mL) was added. The mixture was extracted with Et_2O (3 × 5 mL). The organic extracts were dried over Na_2SO_4, filtered and concentrated to 1 mL. This solution was then transferred to a 7 mL vial, rinsing with THF (1mL). The vial was sealed with a septum cap and the solution concentrated to 1 mL under a stream of N_2. THF (2 mL) was added under N_2, and the solution concentrated to 1.25 mL under a stream of N_2. This solution of the boronic acid (75% yield) was then taken into the glovebox for the subsequent coupling reaction. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.28 (br s, 1H), 5.08-4.95 (m, 2H), 1.94 (q, *J* = 7.4 Hz, 4H), 1.83 (dd, J = 8.7, 6.2 Hz, 2H), 1.56 (dd, *J* = 6.3 Hz, 3H), 1.48 (s, 6H), 0.58 (dd, *J* = 9.1, 7.0 Hz, 2H); ^{11}B-NMR (128 MHz, DMSO-d_6): δ 32.5. Note: over-concentration of the boronic acid solution will cause boroxine formation. NMR data for boroxine: ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.28 (br s, 1H), 5.12 (app t, J = 7.5 Hz, 1H), 5.03 (dt, J = 8.9, 1.5 Hz, 1H), 1.99-1.84 (m, 6H), 1.59 (s, 3H), 1.51 (s, 3H), 1.50 (s, 3H), 0.49 (t, J = 7.7 Hz, 2H); ^{11}B-NMR (128 MHz, DMSO-d_6): δ 24.1.

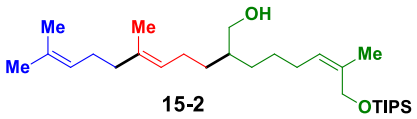
In the glovebox, a flame-dried 7 mL vial was charged with vinyl bromide **18** (108 mg, 0.25 mmol, 1 equiv), Ag_2O (261 mg, 1.125 mmol, 4.5 equiv), and a stir bar. The boronic acid solution prepared above was then added, rinsing with THF (1.25 mL). Pd[P(*o*-tol)$_3$]$_2$ (17.8 mg, 0.025 mmol, 1 equiv) was then added. The vial was sealed with a PTFE-lined cap, brought out of the glovebox and stirred at 60 °C in a heating block for 13.5 h. The reaction was then cooled to room temperature and filtered through celite, eluting with Et_2O. The filtrate was concentrated *in vacuo*, azeotroping once with CH_2Cl_2. The crude product was purified by silica gel column chromatography (20% to 30% CH_2Cl_2/hexanes) to give the product **15** as a slightly yellow oil (73.2 mg, 58% yield). TLC (40% CH_2Cl_2/hexanes): R_f = 0.47, visualized by UV, stained with $KMnO_4$; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.83 (t, *J* = 7.5 Hz, 1H), 5.18 (dt, *J* = 7.0, 1.0 Hz, 1H), 5.12-5.08 (m, 2H), 4.23 (s, 2H), 4.20 (q, J = 7.3 Hz, 2H), 2.44 (q, J = 7.5 Hz, 2H), 2.26 (t, *J* = 7.0 Hz, 1H), 2.14-2.04 (m, 6H), 1.97 (app t, *J* = 8.5 Hz, 2H), 1.77 (d, *J* = 1.0 Hz, 3H), 1.68 (s, 3H), 1.60 (s, 3H), 1.58 (s, 3H), 1.30 (t, *J* = 7.2 Hz, 3H), 1.14-1.05 (m, 21H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 168.0, 141.1, 135.9, 135.7, 132.2, 131.3, 125.0, 124.3, 123.3, 62.0, 60.0, 39.7, 34.7, 29.8, 27.7, 27.4, 26.7, 25.7, 18.3, 17.7, 16.0, 14.3, 12.0 ; HRMS (ESI+) calculated for $C_{31}H_{57}O_3Si$ $[M+H]^+$ *m/z* 505.4077, found 505.4077.



15-1

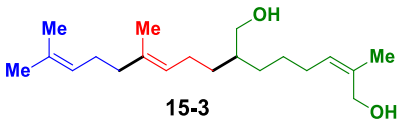
In the glovebox, the 40 mL vial containing **15** (214 mg, 0.424 mmol, 1 equiv) and a stir bar was charged with Mg turnings (412 mg, 16.96 mmol, 40 equiv). The vial was sealed with a septum cap and brought out of the glovebox and placed under N_2. MeOH (8 mL) was added via syringe

and the mixture was sonicated for 2 min, then stirred at rt with an N_2 inlet needle. An exotherm formed as the Mg turnings dissolved. The reaction was cooled in an ice/water bath. The reaction was then stirred for 16 h, gradually warming to room temperature. The reaction was cooled to 0 °C in an ice/water bath, then quenched with the addition of saturated aq. NH_4Cl (8 mL), forming a gelatinous mixture which was agitated manually. A small amount of H_2O was added to dissolve the inorganic salts. The mixture was transferred to a separatory funnel, rinsing with Et_2O. After mixing and phase separation, the aqueous layer was extracted with Et_2O (15 mL). The aqueous layer was concentrated *in vacuo* to remove most of the MeOH. The resulting aqueous phase was extracted with Et_2O (2 x 15 mL). The combined organics were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was diluted with benzene (5 mL) and the mixture further dried with Na_2SO_4, filtered into a 40 mL vial and concentrated and dried under high vacuum to give the product **15-1** as a mixture of the ethyl ester and methyl ester in the ratio 7.7 : 1 (200.8 mg, 0.397 mmol, 94% yield). This material was used without further purification. TLC (40% CH_2Cl_2/hexanes): R_f = 0.47, stained by $KMnO_4$; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.15 (t, *J* = 7.0 Hz, 1H), 5.10-5.07 (m, 2H), 4.21 (s, 2H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.66 (s, 3H for methyl ester), 2.31 (tt, *J* = 9.0. 5.55 Hz, 1H), 2.08-2.04 (m, 2H), 2.01 (m, 6H), 1.76 (app s, 3H), 1.68 (app s, 3H), 1.68-1.60 (m, 1H), 1.60 (s, 3H), 1.57 (s, 3H), 1.58-1.55 (m, 1H), 1.48-1.40 (m, 2H), 1.30 (quint, *J* = 7.8 Hz, 2H), 1.26 (t, *J* = 7.0 Hz, 3H), 1.14-1.05 (m, 21H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 176.3, 135.8 (Me), 135.7, 135.5, 131.3, 125.6, 125.5 (Me), 124.3, 123.6, 123.5 (Me), 61.9, 60.0, 51.3 (Me), 45.2, 45.1 (Me), 39.7, 32.4, 32.1, 27.8 (Me), 27.7, 26.6, 25.8, 25.7, 21.0, 18.0, 17.7, 15.9, 14.3, 12.0; HRMS (ESI+) calculated for $C_{31}H_{59}O_3Si$ $[M+H]^+$ *m/z* 507.4233, found 507.4231. Note: (Me) = peaks corresponding to the methyl ester.



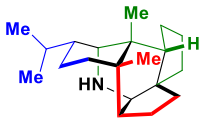
15-2

The 40 mL vial containing **15-1** (200.8 mg, 0.0544 mmol, 1 equiv) was charged with a stir bar and sealed with a septum cap. The vial was vac-filled with N_2 (× 3). THF (8 mL) was added via syringe and the solution cooled to -20 °C in a dry ice/ethylene glycol/ethanol bath. DIBAl-H (1M in hexanes, 2 mL, 2 mmol, 5.04 equiv) was added dropwise. The reaction was stirred at -20 °C for 2 h. The reaction was quenched by adding saturated Rochelle's salt solution (10 mL) was dropwise at -20 °C. Et_2O (5 mL) was then added. The mixture was warmed to room temperature and stirred for 1 h. The mixture was transferred to a separatory funnel, rinsing with H_2O and Et_2O (10 mL). After mixing and phase separation, the aqueous layer was extracted with Et_2O (2 x 5 mL). The combined organics were washed with 1:1 H_2O/brine (20 mL), brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (5% to 10% to 20% Et_2O/hexanes) to give the product **15-2** as a colorless oil (169.9 mg, 90% yield). TLC (20% Et_2O/hexanes): R_f = 0.24, stained by $KMnO_4$; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.19 (app dt, = 7.0, 1.0 Hz, 1H), 5.11-5.07 (m, 2H), 4.22 (d, J = 12.5 Hz, 1H), 4.21 (d, J = 12.5 Hz, 1H), 3.54 (dd, J = 5.5, 1.5 Hz, 2H), 2.11-1.94 (m, 8H), 1.77 (d, = 1.0 Hz, 3H), 1.68 (s, 3H), 1.60 (s, 6H), 1.50-1.25 (m, 7H), 1.15-1.06 (m, 21H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 135.3, 135.1, 131.3, 126.0, 124.5, 124.3, 65.6, 62.0, 40.1, 39.7, 30.9, 30.5, 27.9, 27.2, 26.7, 25.7, 25.2, 21.0, 21.0, 18.0, 17.7, 16.0; HRMS (ESI+) calculated for $C_{29}H_{57}O_2Si$ $[M+H]^+$ *m/z* 465.4128, found 465.4126.



15-3

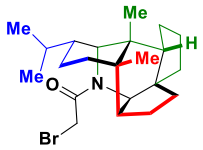
To a solution of **15-2** (165.3 mg, 0.356 mmol) in THF (3.6 mL) and pyridine (1.2 mL) in a polyethylene vial equipped with a stir bar was added HF·pyridine (0.4 mL) dropwise at 0 °C. The vial was purged with N_2, and sealed with a screw cap. The reaction was gradually warmed to rt. After 3.5 h, another portion of HF·pyridine (0.4 mL) was added to the reaction at rt. The reaction was then stirred for another 3 h. The reaction was added portionwise to a stirring solution of saturated aqueous $NaHCO_3$ (10 mL). Et_2O (10 mL) was added. The mixture was transferred to a separatory funnel and another 10 mL saturated aqueous $NaHCO_3$ was added. After phase separation, the aqueous layer was extracted with Et_2O (2 × 10 mL). The combined organics were washed with H_2O, brine, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by silica gel chromatography (20% to 30% to 40% EtOAc/hexanes) to give the pure product **15-3** as a colorless oil (98.2 mg, 89% yield). TLC (40% EtOAc/hexanes): R_f = 0.25, stained by $KMnO_4$; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.29 (app t, J = 7.5 Hz, 1H), 5.12-5.07 (m, 2H), 4.16 (d, J = 11.5 Hz, 1H), 4.10 (d, J = 11.5 Hz, 1H), 3.58 (dd, J = 10.5, 5.0 Hz, 1H), 3.51 (dd, J = 11.0, 6.0 Hz, 1H), 2.10-1.97 (m, 8 H), 1.80 (d, J = 1.3 Hz, 3H), 1.68 (d, J = 1.0 Hz, 3H), 1.60 (s, 6H), 1.50-1.25 (m, 9H) ^{13}C-NMR (125 MHz, $CDCl_3$): δ 135.2, 134.4, 131.3, 128.5, 124.4, 124.3, 65.5, 61.5, 39.7 (2C), 30.9, 30.2, 27.6, 26.9, 26.7, 25.7, 25.2, 21.3, 17.7, 16.0; HRMS (ESI+) calculated for $C_{20}H_{37}O_2$ $[M+H]^+$ *m/z* 309.2794, found 309.2794.



(±)-14, secodaphnane core

To a Schlenk tube (1 cm diameter) sealed with a rubber septum and vac-filled with N_2 (×3) was added CH_2Cl_2 (0.2 mL) followed by DMSO (0.015 mL, 0.211 mmol, 8.7 equiv). The solution was cooled to -78 °C in a dry ice/acetone bath. Oxalyl chloride (2.0 M in CH_2Cl_2, 0.05 mL, 0.1 mmol, 4.1 equiv) was added dropwise via syringe. The resulting solution was stirred at -78 °C for 30 min. A solution of diol **15-3** (7.5 mg, 0.0243 mmol, 1.0 equiv) in CH_2Cl_2 (0.2 mL) in a 7 mL vial was added dropwise to the reaction flask via syringe, rinsing with CH_2Cl_2 (0.2 mL). The solution was stirred for 30 min at – 78 °C, then NEt_3 (0.030 mL, 0.215 mmol, 8.8 equiv) was added into the reaction dropwise. The reaction was stirred for 5 min at the same temperature, then the cold bath was removed and the reaction stirred at room temperature for another 45 min. TLC showed complete conversion of the diol. The reaction was cooled to 0 °C in an ice/water bath. Dry $MeNH_2$ gas was then passed above the reaction solution over 3 min via an inlet needle with an outlet needle, causing an increase in reaction volume and dissolution of the solids. The reaction was stirred for 3.5 h, gradually warming to room temperature in the ice/water bath. The flask was then opened to the Schlenk line, causing evaporation of the dissolved $MeNH_2$. The solvent was removed under a stream of N_2, giving an off-white oily solid. The rubber septum was quickly replaced with a new septum under positive N_2 flow. The Schlenk tube was evacuated and filled with N_2, then evacuated again, and the residue was dried under high vacuum overnight. The flask was filled with N_2. Dry AcOH (0.4 mL) was added to dissolve the brown residue. The solution was stirred at 80 °C (oil bath temperature) for 8.5 h. The reaction was cooled to 0 °C in an ice/water bath. CH_2Cl_2 (2 mL) and 3N NaOH were added with stirring until pH>10. The mixture was transferred to a separatory funnel and the layers separated. The aqueous

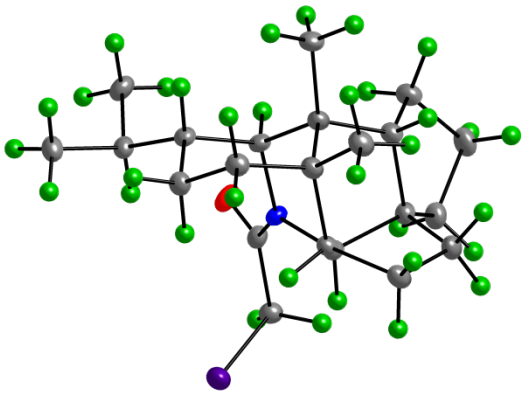
layer was then extracted with CH_2Cl_2 (2 × 2 mL). The organics were dried over Na_2SO_4, filtered and concentrated *in vacuo*. ^{1}H-NMR showed the crude product as the ammonium salt. The brown residue was taken up in CH_2Cl_2 (5 mL) and added to the aqueous layers were from the extraction which were re-adjusted to pH=14 with 6N NaOH. After mixing and phase separation, the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organics were washed with brine, dried over Na_2SO_4 and concentrated. The crude product was purified by silica gel column chromatography (20% to 50% EtOAc/pentane) to give the product **14** as a colorless oil (2.7 mg, 39% yield). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.89 (s, 1H), 2.54 (d, *J* = 4.5, 1H), 1.89 (t, *J* = 5.0 Hz, 1H), 1.74-1.38 (m, 15H), 1.17 (dd, *J* = 9.5, 3.0, 1H) 0.98-0.92 (m, 1H), 0.88 (d, *J* = 6.5, 3H), 0.87 (d, *J* = 7.0, 3H), 0.74 (s, 3H), 0.70 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 60.3, 54.8, 50.4, 49.7, 47.3, 43.4, 39.4, 38.6, 36.4, 35.6, 34.5, 28.6, 27.8, 26.6, 22.8, 21.1 (2C), 21.0, 18.4, 21.1 (3C), 21.0; HRMS (ESI+) calculated for $C_{20}H_{34}N$ $[M+H]^+$ *m/z* 288.2691, found 288.2697.



N-bromoacyl-14

In an unoptimized procedure, anhydrous K_2CO_3 (36.5 mg, 0.264 mmol, 4 equiv) was weighed into a flame-dried 7 mL vial equipped with a stir bar. The vial was sealed with a septum cap, evacuated and filled with N_2 (×3). Amine **14** (19 mg, 0.066 mmol, 1 equiv) was dissolved in PhH (0.75 mL) and added to the vial. The suspension was cooled to 0 °C, then bromoacetyl bromide (11.5 µL, 0.132 mmol, 2 equiv) was added via syringe and the reaction was warmed to room temperature. After 1 h, another portion of bromoacetyl bromide (11.5 µL, 0.132 mmol, 2 equiv) was added. The reaction was left to stir for another 15 h at room temperature. The reaction was filtered through celite and silica gel, eluting with CH_2Cl_2. The brown filtrate was treated with Darco and filtered through celite. The filtrate was concentrated *in vacuo*, giving a brown residue, which was purified by silica gel chromatography (10-20% EtOAc/hexanes) to give a white solid as the pure product (6.7 mg, 25%). The solid was taken up in EtOH (~ 1 mL) and H_2O was added, causing the solution to become cloudy. The precipitate was re-dissolved in a minimal amount of EtOH and the solution filtered through a 0.2 µM filter into a 7 mL vial. The solution was then left to slowly evaporate, giving crystals for X-ray analysis. TLC (20% EtOAc/hexanes): R_f = 0.59, visualized by UV; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 4.11 (br s, 1H), 4.08 (d, *J* = 11.5 Hz, 1H), 3.80, (d, *J* = 11.5 Hz, 1H), 3.50 (d, J = 4.7 Hz, 1H), 2.20 (t, *J* = 5.3 Hz, 1H), 1.77-1.13 (m, 17H), 1.09 (d, *J* = 6.2 Hz, 3H), 0.87 (s, 3H), 0.80 (s, 3H), 0.78 (d, J = 6.5 Hz, 3H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ 169.9, 61.9, 55.4, 53.3, 51.4, 46.6, 45.3, 39.5, 38.4, 36.6, 36.0, 35.6, 28.8, 27.4, 26.0, 23.1, 21.3, 20.6, 20.4, 19.5; HRMS (ESI+) calculated for $C_{22}H_{35}NOBr$ $[M+H]^+$ *m/z* 408.1902, found 408.1906.

X-ray Crystal Structure Data for ***N-bromoacyl-14***



N-bromoacyl-14

Table S1. Crystal data and structure refinement for

Identification code	cd70mas	
Empirical formula	C22 H34 Br N O	
Formula weight	408.41	
Temperature	104(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	Pbca	
Unit cell dimensions	a = 8.8647(3) Å	α= 90°.
	b = 17.0519(6) Å	β= 90°.
	c = 25.7965(9) Å	γ = 90°.
Volume	3899.4(2) $Å^3$	
Z	8	
Density (calculated)	1.391 Mg/m^3	
Absorption coefficient	2.119 mm^{-1}	
F(000)	1728	
Crystal size	0.754 x 0.099 x 0.026 mm^3	
Theta range for data collection	2.389 to 26.429°.	
Index ranges	-11<=h<=11, -21<=k<=21, -32<=l<=32	
Reflections collected	50900	
Independent reflections	4005 [R(int) = 0.0712]	
Completeness to theta = 25.242°	100.0 %	

Absorption correction	Integration
Max. and min. transmission	0.9626 and 0.5182
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4005 / 0 / 230
Goodness-of-fit on F^2	1.077
Final R indices [I>2sigma(I)]	R1 = 0.0262, wR2 = 0.0704
R indices (all data)	R1 = 0.0334, wR2 = 0.0721
Extinction coefficient	n/a
Largest diff. peak and hole	0.691 and -0.467 e.$Å^{-3}$

3. The automated small molecule synthesis platform

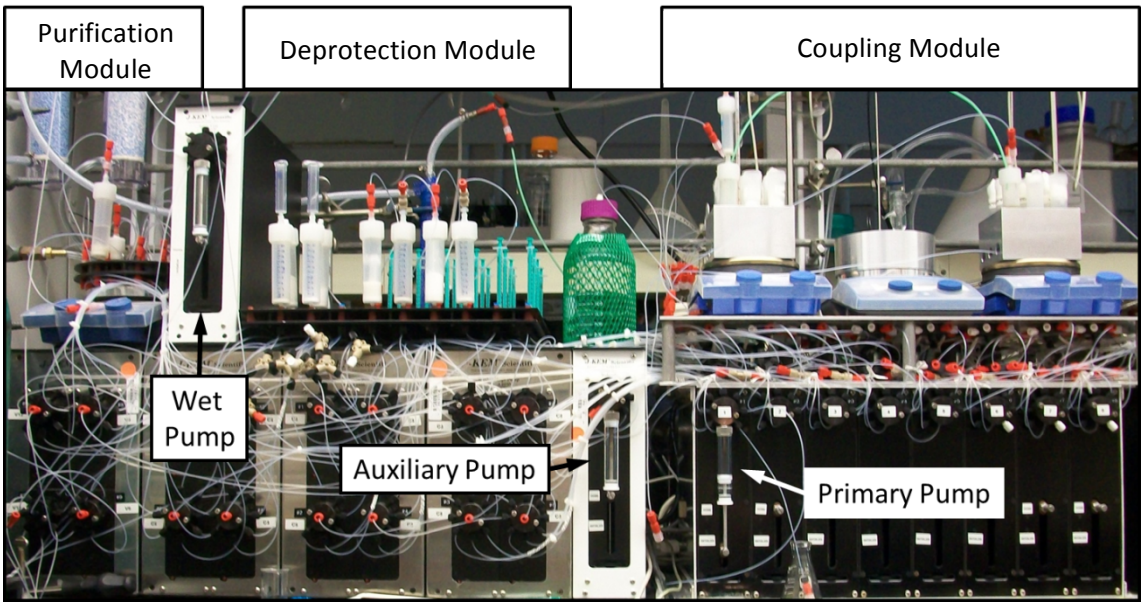


Figure S1. Photograph of the small molecule synthesizer.

Design of the deprotection module

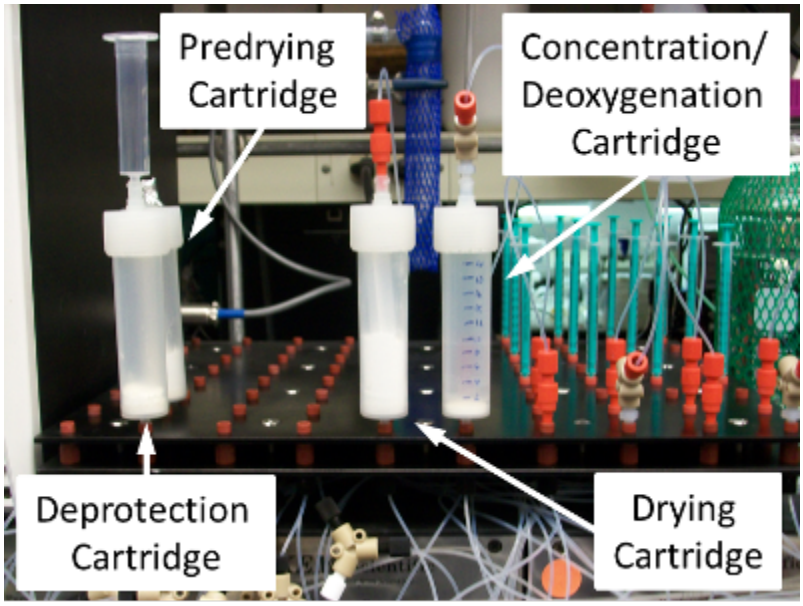


Figure S2. The deprotection module

The deprotection module consists of two J-KEM® Scientific V6 programmable syringe pumps (part # SYR-1400PC). Both are fitted with a 10-mL glass/PTFE syringe (part # SPGS-10000) and an 8-port distribution valve (part # SPDV-8). One pump (the Primary Pump) is utilized as the organic liquid handling pump and the other (the Wet Pump) is used exclusively as the aqueous liquid handling pump. The module utilizes an additional five 8-port distribution

valves (part # SPDV-CS8) housed in four separate quad stack KEM select distribution modules (part # SYR-CS4) for liquid handling. A source of dry nitrogen and dry argon are used for liquid handling and deoxygenation/concentration processes. Connections between valves are made with FEP tubing (1/16'' OD, 0.030'' ID).

To the Deprotection Cartridge, the Primary Pump adds THF and the Wet Pump adds water. The reaction is then agitated with pulses of argon gas. The Wet Pump then adds a quenching reagent (either pH=6 phosphate buffer or saturated NH_4Cl) and the Primary Pump adds Et_2O. The resulting biphasic system is agitated with pulses of nitrogen gas and the aqueous layer is drawn off and disposed of by the Wet Pump. The Wet Pump adds 50% saturated aqueous NaCl. The resulting biphasic system is agitated with pulses of nitrogen and the aqueous layer is drawn off and disposed of by the Wet Pump. The Primary Pump transfers the wet organic solution to a Predrying Cartridge (if applicable), and subsequently Drying Cartridge, containing drying agents and agitates the mixture by repeatedly withdrawing/injecting the solution. The Primary Pump transfers the dried organic solution to a Concentration/Deoxygenation Cartridge and concentrates/deoxygenates the solution with pulses of argon gas.

Design of the coupling module

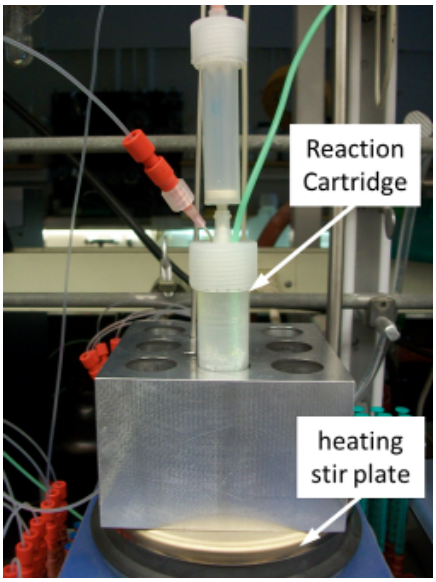


Figure S3. The coupling module

The coupling module consists of one J-KEM® Scientific V6 programmable syringe pump (part # SYR-1400PC), the Primary Pump described above. The module utilizes one additional 8-port distribution valve (part # SPDV-CS8) housed in one separate quad stack KEM select distribution module (part # SYR-CS4) for liquid handling (shared with the deprotection module). A source of dry nitrogen and dry argon are used for liquid handling and deoxygenation processes (shared with the deprotection module). Two IKA® RET control visc IKAMAG® safety control heating stir plates (part # 3364001) and one IKA® RCT basic IKAMAG® safety control heating stir plate (part # 3810001) are used for reaction stirring and temperature control. Connections between valves are made with FEP tubing (1/16'' OD, 0.030'' ID).

The Reaction Cartridge, agitated with a magnetic stir bar, is typically deoxygenated with pulses of argon gas. The Primary Pump adds THF to the reaction cartridge and then slowly adds

the dried/deoxygenated THF solution of boronic acid. After the addition, the reaction is allowed to agitate.

Design of the purification module

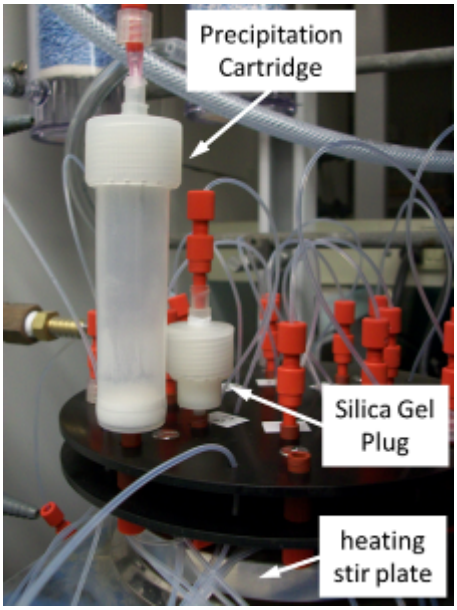


Figure S4. The purification module

The purification module consists of two J-KEM® Scientific V6 programmable syringe pumps (part # SYR-1400PC). One is the Primary Pump described above. The other pump (the Auxillary Pump) is used exclusively as the column eluent and waste handling pump. The module utilizes an additional six 8-port distribution valves (part # SPDV-CS8) housed in three separate quad stack KEM select distribution modules (part # SYR-CS4) for liquid handling. Five of these distribution valves are shared with the deprotection and coupling modules. Two IKA® RET control visc IKAMAG® safety control heating stir plates (part # 3364001), shared with the coupling module, and one IKA® RCT basic IKAMAG® safety control heating stir plate (part # 3810001) are used. Connections between valves are made with FEP tubing (1/16'' OD, 0.030'' ID).

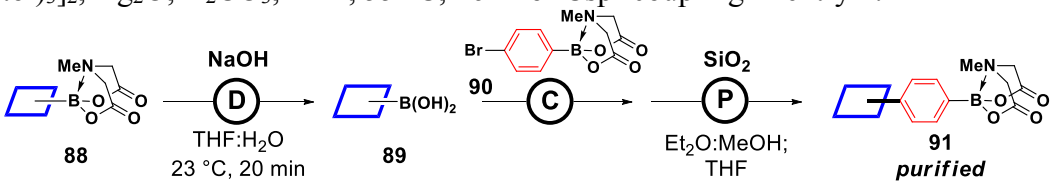
The Auxillary Pump adds hexanes to the Precipitation Cartridge, agitated with a magnetic stir bar. The Primary Pump adds portions of the crude reaction solution to the Precipitation Cartridge. The Auxillary Pump then withdraws the solvent through the Silica gel Plug. This process is repeated until the Reaction Cartridge is empty. The Primary Pump then adds 1.5% MeOH in Et_2O to the Precipitation Cartridge and then the Auxillary Pump withdraws the solvent through the Silica Gel Plug. The Primary Pump then adds Et_2O to the Precipitation Cartridge and then the Auxillary Pump withdraws the solvent through the Silica Gel Plug. The Auxillary Pump then adds THF to the Precipitation Cartridge and the Primary Pump removes the resulting solution and transfers it to the next Deprotection Cartridge.

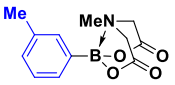
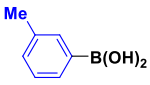
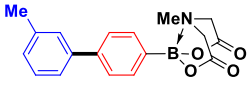
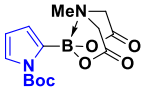
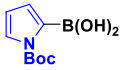
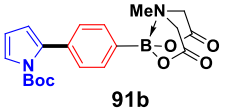
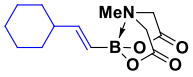
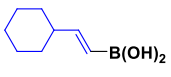
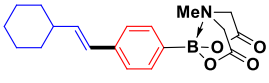
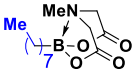
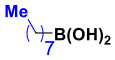
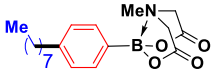
Description of software

The synthesizer is controlled remotely on a Windows-based computer by a custom software program written in VB.NET (based on code written for the J-KEM® Scientific V6 programmable syringe pumps). The software program is designed to interpret instructions to the synthesizer written in a simple custom scripting language. Pre-set series of instructions enable all of the steps required for a synthesis to be executed in a fully automated fashion after the operator simply presses "Start."

4. Single-step C-C bond formation using Automated Procedure I

Table S2. Fully automated cycles of deprotection, coupling, and purification. Coupling conditions: XPhos 2nd generation palladacycle, K_3PO_4, THF, 55 °C, 16 h for entries 1-3, and $Pd[P(o\text{-tol})_3]_2$, Ag_2O, K_2CO_3, THF, 55 °C, 16 h for Csp^3 coupling in entry 4.



entry	MIDA boronate 88	% conversion of 88 to 89	boronic acid 89	% conversion of 90 to 91	MIDA boronate 91	% isolated yield of 91	% purity of 91
1	 **88a**	99	 **89a**	98	 **91a**	61	**>95**
2	 **88b**	99	 **89b**	99	 **91b**	83	**>95**
3	 **88c**	98	 **89c**	99	 **91c**	67	**>95**
4	 **88d**	99	 **89d**	99	 **91d**	59	**80**

Automated Procedure I - *Cartridge Preparation*

Unless otherwise noted, "cartridge" refers to a 12-g Luknova column capped with a 12-g Luknova column screw cap.

- **First Deprotection Cartridges** contain solid NaOH and the starting MIDA boronate.
- **Predrying Cartridges** contain Celite™ (800 mg) and anhydrous $MgSO_4$ (2.1 g). These solids are mixed thoroughly and a plastic 5-mL syringe plunger is placed on top of the mixed solids. This is topped with an aluminum foil cover.

- **Drying Cartridges** contain Celite™ (300 mg) with 4 Å molecular sieves (activated, powder, -325 mesh) (3.6 g) layered on top. A plastic 5-mL syringe plunger is placed on top of the layered solids.
- **Concentration/Deoxygenation Cartridges** are empty.
- **First Reaction Cartridges** contain a PTFE-coated magnetic stir bar, coupling partner, catalyst and ligand, and base. For this cartridge, the factory-supplied fiber frit has been removed and a medium porosity glass frit installed. The cap is pierced with a 1.5-inch 18 G needle and topped with an empty 4-g Luknova column (capped with a 4-g Luknova column screw cap). This cap is tethered to another cap PTFE tubing (1/16-inch I.D., 1/8-inch O.D.). This additional cap, pierced with a 1.5-inch 18 G needle, is attached to the Reaction Filtration Cartridge. The PTFE tubing is adjusted to place the end of the tubing approximately 5 mm above the frit of the First Reaction Cartridge and approximately 20 mm below the screw cap of the Reaction Filtration Cartridge. The luer ports of both screw caps are packed with a small ball of rolled Kimberly-Clark® Kimwipes™.
- **Reaction Filtration Cartridges** contain a PTFE-coated magnetic stir bar and a mixture of Celite™ (2.5 g) and Florisil® (1.25 g). This is tethered to the First Reaction Cartridge as described above.
- **Precipitation Cartridges** contain a PTFE-coated magnetic stir bar, Celite™ (150 mg), and 3-aminopropyl functionalized silica gel (250 mg). Hexanes (10 mL) is added and the cartridge is swirled vigorously to suspend and homogenize the mixture of solids. The stir bar and solids are allowed to settle over 30 seconds and the supernatant hexanes is pushed out of the cartridge with an overhead pressure of air. The stir bar is now embedded in the mixture of solids wet with hexanes.
- **Silica Gel Plugs** contain silica gel, tightly packed, and topped with a 4-g Luknova column frit. This is capped with a 4-g Luknova column screw cap, using four layers of PTFE tape on the sealing insert to ensure a leak-free seal.

Automated Procedure I - *Experimental Details*

- **Deprotection**

In the deprotection module, to a Deprotection Cartridge containing starting MIDA boronate **88** (1.0 mmol) and NaOH (3.0 mmol, 120 mg) is added 12 mL THF followed by 3 mL water. This solution is then agitated by bubbling argon through the solution for 20 minutes at room temperature. After agitation, 3 mL aqueous potassium phosphate buffer (pH=6, 0.5 M) and 5 mL Et_2O are added. The layers are briefly mixed (again, via argon sparging) before being allowed to separate. Then, the Wet Pump disposes of the aqueous layer before adding 3 mL 50% saturated aqueous NaCl, mixing the layers, and allowing them to separate. Again, the Wet Pump disposes of the aqueous layer. The THF/Et_2O solution of boronic acid is then dried using the Predrying and Drying Cartridges. This is accomplished by the repeated injection and withdrawal of the solution into the cartridges (20 repetitions for the Predrying Cartridge, followed by 20 repetitions for the Drying Cartridge). The solution is then passed into the Concentration/Deoxygenation Cartridge before washing the contents of the Predrying and Drying Cartridges with 6 mL THF and adding the wash to the Concentration/Deoxygenation Cartridge. This organic solution is then concentrated to 10 mL (evaporating most of the Et_2O) before washing the drying agents with a further 6 mL THF. The organic solution (now only

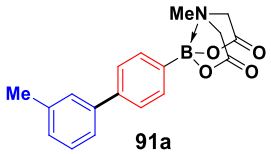
THF) is concentrated to 9 mL. This deoxygenated, dry solution is used directly in the subsequent coupling reaction.

- **Coupling**

In the coupling module, a First Reaction Cartridge is charged with bifunctional MIDA boronate **90** (0.33 mmol), XPhos 2nd generation palladacycle (0.017 mmol, 13.1 mg, 5 mol%), and K_3PO_4 (3.0 mmol, 637 mg) and warmed to 55 °C before being deoxygenated by flushing with argon for 10 minutes. To this cartridge is added 3 mL THF with stirring. The THF solution of boronic acid **89** is added over 4 hours (0.0375 mL/min). At the end of the addition, the reaction is stirred for an additional 12 hours.

- **Purification**

In the purification module, the crude reaction mixture is added to a Reaction Filtration Cartridge and 12 mL hexanes is added to the Precipitation Cartridge/Silica Gel Plug. Then, a 3 mL portion of the filtered crude reaction mixture is added to the Precipitation Cartridge and the solvent is removed from the cartridge, loading any crude reaction product onto the Silica Gel Plug ("catch"). This process is performed a total of 10 times, using 3 mL THF to wash the Reaction and Reaction Filtration Cartridges for each cycle. Then, 12 mL of 1.5% MeOH in Et_2O are added and the solvent is removed three times (36 mL total). Then, 12 mL of Et_2O are added and the solvent is removed 3 times (36 mL total). Finally, 12 mL THF are added and slowly removed (to increase residence time in the column), giving a purified solution of MIDA boronate **91**.



91a

Automated Procedure I was followed using 251.7 mg (1.02 mmol) aryl MIDA boronate **88a** and 104.0 mg (0.333 mmol) bifunctional MIDA boronate **90**. The conversion for the deprotection step was 99% and the conversion for the coupling step was 98%. The desired aryl MIDA boronate **91a** was obtained as a white solid of >95% purity (65.3 mg, 0.202 mmol, 61% yield). TLC (20% MeCN in Et_2O): R_f = 0.37, visualized by UV and $KMnO_4$ stain; ^{1}H-NMR (500 MHz, DMSO-d_6:D_2O, 95:5): δ 7.64 (d, J = 8.5 Hz, 2H), 7.51 (d, J = 8.5 Hz, 2H), 7.48 (s, 1H), 7.45 (dd, J = 7.5, 0.5 Hz, 1H), 7.34 (t, J = 7.5 Hz, 1H), 7.17 (dd, J = 7.5, 0.5 Hz, 1H), 4.34 (d, J = 17.5 Hz, 2H), 4.13 (d, J = 17 Hz, 2H), 2.54 (s, 3H), 2.37 (s, 3H); ^{13}C-NMR (125 MHz, DMSO-d_6:D_2O, 95:5): δ 169.1, 140.7, 140.1, 138.0, 132.9, 128.7, 128.0, 127.2, 125.9, 123.7, 61.8, 47.6, 21.0; HRMS (EI+) calculated for $C_{18}H_{18}BNO_4$ $[M]^+$ m/z 323.13289, found 323.13253.

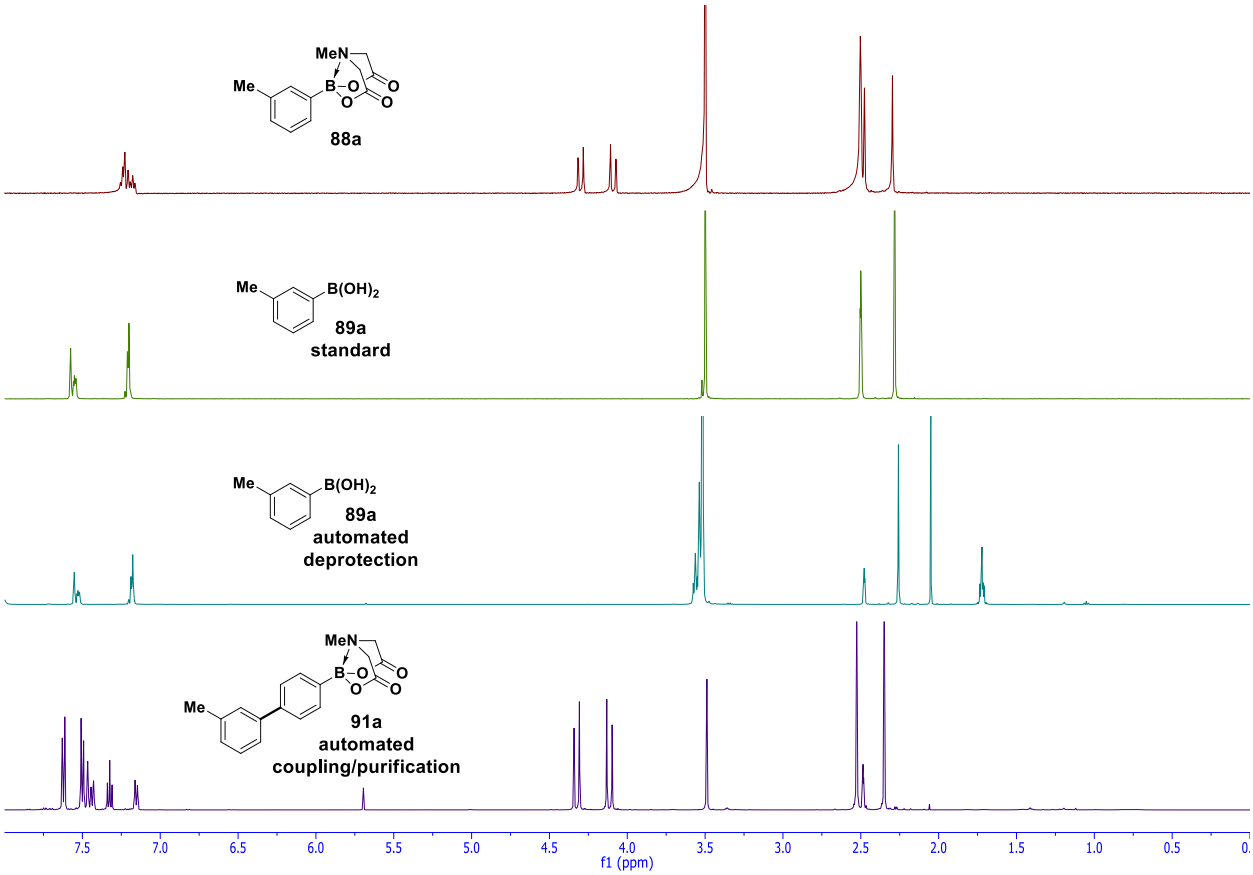
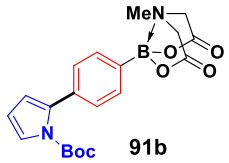


Figure S5. ^{1}H-NMRs for the automated synthesis of **91a**



Automated Procedure I was followed using 325.4 mg (1.01 mmol) aryl MIDA boronate **88b** and 104.4 mg (0.335 mmol) bifunctional MIDA boronate **90**. The conversion for the deprotection step was 99% and the conversion for the coupling step was 99%. The desired aryl MIDA boronate **91b** was obtained as an off-white solid of >95% purity (110.9 mg, 0.278 mmol, 83% yield). TLC (20% MeCN in Et_2O): R_f = 0.46, visualized by UV and $KMnO_4$ stain; ^{1}H-NMR (500 MHz, DMSO-d_6:D_2O, 95:5): δ 7.43 (d, J = 8 Hz, 2H), 7.33 (dd, J = 3, 1.5 Hz, 1H), 7.30 (d, J = 8.5 Hz, 2H), 6.26 (t, J = 3.5 Hz, 1H), 6.23 (dd, J = 3, 1.5 Hz, 1H), 4.34 (d, J = 17 Hz, 2H), 4.13 (d, J = 17 Hz, 2H), 2.54 (s, 3H), 1.28 (s, 9H); ^{13}C-NMR (125 MHz, DMSO-d_6:D_2O, 95:5): δ 169.7, 149.1, 134.7, 134.4, 132.0, 128.2, 123.0, 114.7, 111.2, 83.9, 62.1, 47.9, 27.3; HRMS (ESI+) calculated for $C_{20}H_{24}BN_2O_6$ $[M+H]^+$ *m/z* 399.1727, found 399.1723.

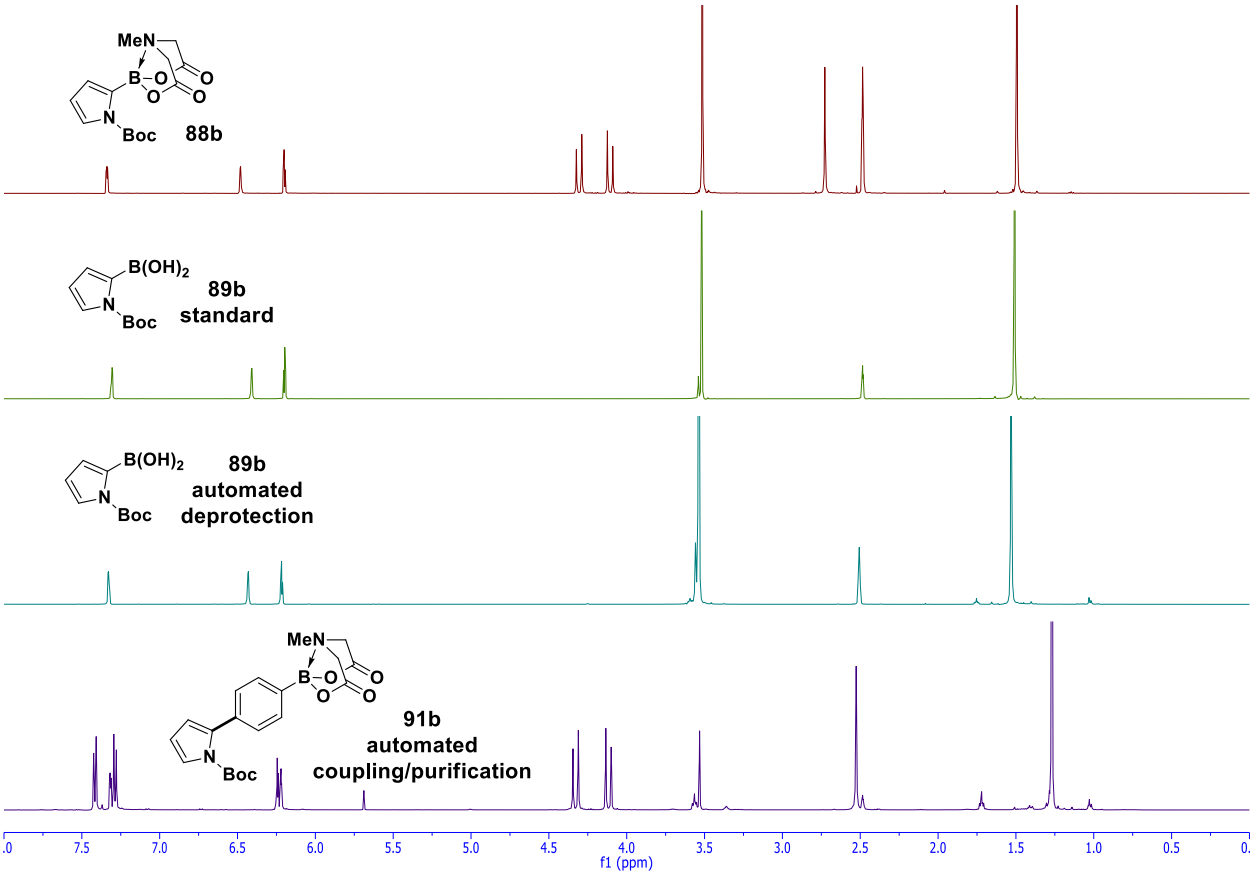
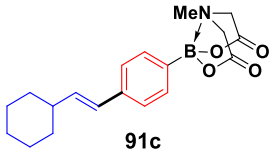


Figure S6. ^{1}H-NMRs for the automated synthesis of **91b**



91c

Automated Procedure I was followed using 265.9 mg (1.00 mmol) aryl MIDA boronate **88c** and 105.6 mg (0.339 mmol) bifunctional MIDA boronate **90**. The conversion for the deprotection step was 98% and the conversion for the coupling step was 99%. The desired aryl MIDA boronate **91c** was obtained as an off-white solid of >95% purity (77.7 mg, 0.228 mmol, 67% yield). TLC (20% MeCN in Et_2O): R_f = 0.44, visualized by UV and $KMnO_4$ stain; ^{1}H-NMR (500 MHz, DMSO-d_6:D_2O, 95:5): δ 7.35 (s, 4H), 6.34 (d, J = 16.5 Hz, 1H), 6.25 (dd, J = 16.5, 7 Hz, 1H), 4.31 (d, J = 17 Hz, 2H), 4.08 (d, J = 17 Hz, 2H), 2.47 (s, 3H), 2.13-2.06 (m, 1H), 1.74-1.68 (m, 4H), 1.63-1.60 (m, 1H), 1.31-1.23 (m, 2H), 1.18-1.11 (m, 3H); ^{13}C-NMR (125 MHz, DMSO-d_6:D_2O, 95:5): δ 169.6, 138.1, 136.8, 132.7, 127.3, 125.4, 61.9, 47.7, 40.6, 32.6, 25.8, 25.6; HRMS (EI+) calculated for $C_{19}H_{24}BNO_4$ $[M]^+$ *m/z* 341.17984, found 341.18030.

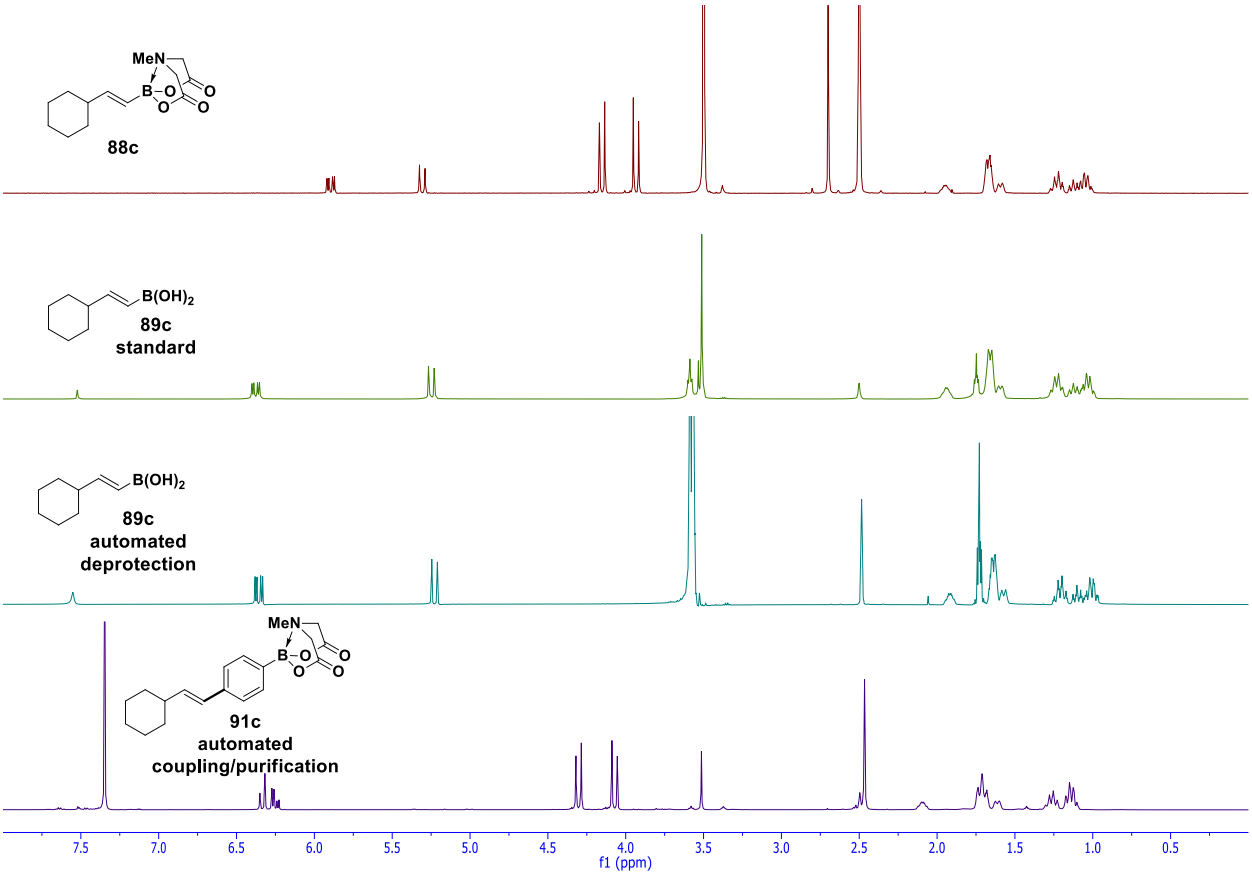
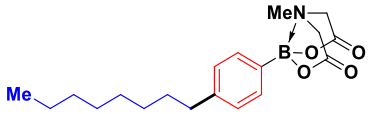


Figure S7. ^{1}H-NMRs for the automated synthesis of **91c**



91d

Automated Procedure I was followed with modifications: 268.4 mg (0.997 mmol) octyl MIDA boronate **88d**, 105.2 mg (0.337 mmol) *p*-bromophenyl MIDA boronate **90**, an increased catalyst loading of 25.6 mg (10 mol%) Pd[P(*o*-tol)$_3$]$_2$, and 237.6 mg Ag_2O (1.03 mmol) and 277.7 mg K_2CO_3 (2.01 mmol) were used. The conversion for the deprotection step was 99% and the conversion for the coupling step was 99%. The desired aryl MIDA boronate **91d** was obtained as an off-white solid of 80% purity (68.9 mg, 0.200 mmol, 59% yield). TLC (50% acetone/hexanes) R_f = 0.48, visualized by UV and $KMnO_4$ stain; ^{1}H-NMR (500 MHz, DMSO-d_6:D_2O, 95:5): δ 7.32 (d, J = 7.6 Hz, 2H), 7.16 (d, J = 7.7 Hz, 2H), 4.29 (d, J = 17.3 Hz, 2H), 4.07 (d, J = 17.3 Hz, 2H), 2.57-2.52 (m, 2H), 2.47 (s, 3H), 1.54 (quint, J = 7.4 Hz, 2H), 1.29-1.19 (m, 10H), 0.83 (t, J = 6.8 Hz, 3H); ^{13}C-NMR (125 MHz, DMSO-d_6:D_2O, 95:5): δ 169.8, 134.8, 132.9, 128.4, 128.1, 62.3, 57.5, 42.6, 35.8, 31.9, 31.4, 29.4, 29.3, 22.7, 14.6.; HRMS (ESI+) calculated for $C_{19}H_{29}BNO_4$ $[M+H]^+$ *m/z* 346.2190, found 346.2180.

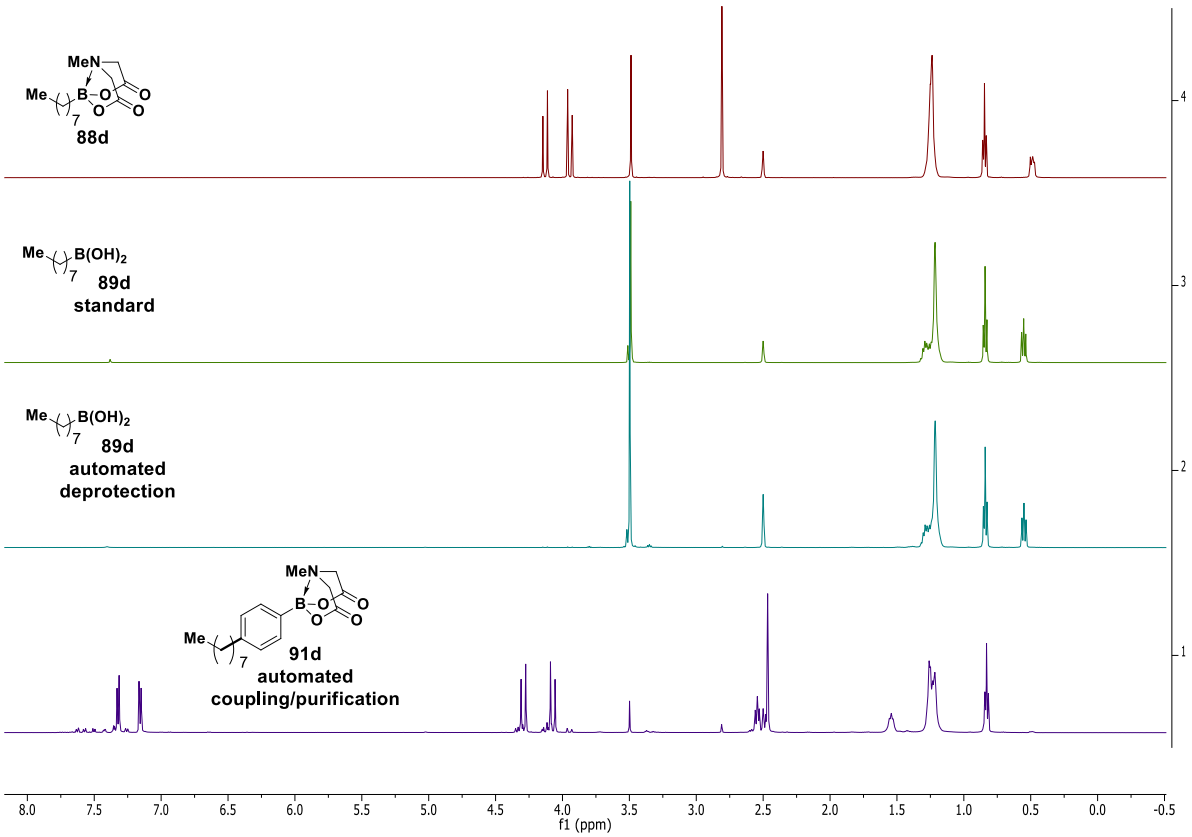
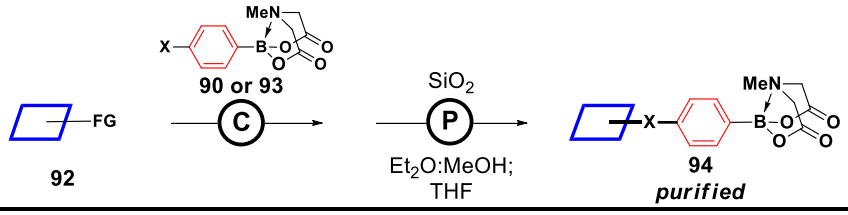
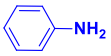
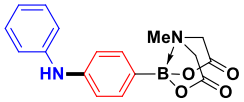
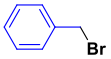
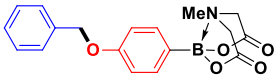
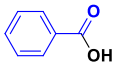
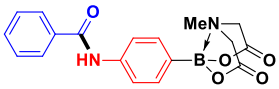
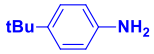
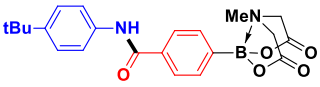


Figure S8. ^{1}H-NMRs for the automated synthesis of **91d**

5. Single-step C-X bond formation using Automated Procedure II

Table S3. Fully automated cycles of deprotection, coupling, and purification for carbon-heteroatom bond formation.



entry	48	MIDA boronate	conditions	MIDA boronate 50	% isolated yield of 50	% purity of 50
1	 **92a**	**X** = Br **90**	PdXPhos K_3PO_4, THF 55 °C, 16 h	 **94a**	75	**88**
2	 **92b**	**X** = OH **93a**	K_2CO_3 30% MeCN/THF 60 °C, 16 h	 **94b**	83	**>95**
3	 **92c**	**X** = NH_2 **93b**	TATU, DIPEA 30% MeCN/THF 40 °C, 13 h	 **94c**	80	**90**
4	 **92d**	**X** = CO_2H **93c**	TATU, DIPEA 30% MeCN/THF 23 °C, 1h	 **94d**	88	**90**

Automated Procedure II - *Cartridge Preparation*

Unless otherwise noted, "cartridge" refers to a 12-g Luknova column capped with a 12-g Luknova column screw cap.

- **Drying Cartridges** contain 4.2 g Na_2SO_4, topped with the plunger from a 5 mL syringe.
- **Concentration/Deoxygenation Cartridges** are empty.
- **First Reaction Cartridges** are the 40 mL reaction vials described above, and contain a PTFE-coated magnetic stir bar, coupling partner, coupling reagent (where applicable) and base. These cartridges have no frit at their base. The Luer port at the bottom is packed with a small piece of Kimwipe (so that solids are retained in the vial during weighing). The top of the vial is capped with a screw-top rubber septum cap. This septum is pierced with a 1.5 inch 18 G needle which is connected to an empty 4 g Luknova column (capped with a 4 g Luknova column screw cap connected to a source of dry nitrogen). Additionally, the cap is tethered to the screw cap topping the Reaction Filtration Cartridge via PTFE tubing (1/16-inch I.D., 1/8-inch O.D.) This tubing is adjusted in such a way to be ~5 mm above the base of the reaction vessel, and is used to transfer the crude reaction mixture to the Reaction Filtration Cartridge.
- **Reaction Filtration Cartridges** contain 1.0 g Celite™ and 0.5 g Florisil® which have been thoroughly mixed. This is tethered to the First Reaction Cartridge as described above.

- **Precipitation Cartridges** contain a PTFE-coated magnetic stir bar, Celite™ (150 mg), and 3-aminopropyl functionalized silica gel (250 mg). Hexanes (10 mL) is added and the cartridge is swirled vigorously to suspend and homogenize the mixture of solids. The stir bar and solids are allowed to settle over 30 seconds and the supernatant hexanes is pushed out of the cartridge with an overhead pressure of air. The stir bar is now embedded in the mixture of solids wet with hexanes.
- **Silica Gel Plugs** contain silica gel, tightly packed, and topped with a 4-g Luknova column frit. This is capped with a 4-g Luknova column screw cap, using four layers of PTFE tape on the sealing insert to ensure a leak-free seal.

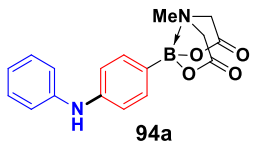
Automated Procedure II - *Experimental Details*

- **Coupling**

The First Reaction Cartridge is charged with all solid reagents (MIDA boronates, coupling reagents, etc.) before sealing, placing into an appropriately warmed heating block, and flushing with argon (10 minutes). To this is added THF (12 mL, unless otherwise noted) with stirring. After stirring briefly, any necessary liquid reagents are added via syringe through the septum cap. The reaction is then stirred in an appropriately warmed heating block until complete, at which point it is transferred to the Reaction Filtration Cartridge before workup/purification.

- **Purification**

After filtration, the crude reaction mixture is added to the Extraction/Workup Cartridge. To this cartridge is then added 5 mL 50% saturated aqueous NaCl. The layers are mixed via argon sparging (60 seconds) before removing and disposing of the aqueous layer. This is repeated twice more, for a total of three aqueous washes before the organic layer is dried in the Predrying Cartridge. This is accomplished through the repeated injection and withdrawal of the solution into the cartridge (20 repetitions). Then, a 3 mL portion of the filtered and washed crude reaction mixture is added to the Precipitation Cartridge and the solvent is removed from the Precipitation Cartridge, loading any crude reaction product onto the Silica Gel Plug ("catch"). This process is performed a total of 10 times, washing the Predrying Cartridge with 2 mL THF for the final two repetitions. Then, 12 mL of 1.5% MeOH in Et_2O are added and the solvent is removed 3 times (36 mL total). Then, 12 mL of Et_2O are added and the solvent is removed 3 times (36 mL total). Finally, 12 mL THF are added and slowly removed (to increase residence time in the column), giving a purified solution of the product MIDA boronate. In the case of a single-step coupling experiment this solution is added to an empty Deprotection Cartridge where it can be retrieved for analysis or further use. In the case of multi-step experiments, the solution is moved to a Deprotection Cartridge containing NaOH, concentrated to 10 mL, and another cycle of deprotection begins.



94a

Automated Procedure II was followed using 95 µL aniline **92a** (1.04 mmol), 105.2 mg (0.337 mmol) *p*-bromophenyl MIDA boronate **90**, 638.4 mg K_3PO_4 (3.01 mmol), and 13.5 mg (5 mol%) 2nd generation XPhos palladacycle. The reaction was run at 55°C for 16 h. The desired aryl

MIDA boronate **94a** was obtained as an off-white solid (82.3 mg, 0.254 mmol, 75% yield) of 88% purity. ^{1}H-NMR (500 MHz, DMSO-d_6:D_2O, 95:5): δ 7.27 (d, J = 8.3 Hz, 2H), 7.22 (dd, J = 8.5 and 7.2 Hz, 2H), 7.08 (d, J = 7.3 Hz, 2H), 7.05 (d, J = 8.5 Hz, 2H), 6.82 (t, J = 7.2 Hz, 1H), 4.27 (d, J = 17.2 Hz, 2H), 4.05 (d, J = 17.2 Hz, 2H), 2.50 (s, 3H). ^{13}C-NMR (125 MHz, DMSO-d_6:D_2O, 95:5): δ 169.6, 144.3, 143.1, 133.5, 129.3, 120.1, 117.2, 115.8, 61.7, 47.6; HRMS (ESI+) calculated for $C_{17}H_{18}BN_2O_4$ $[M+H]^+$ *m/z* 325.1360, found 325.1358.

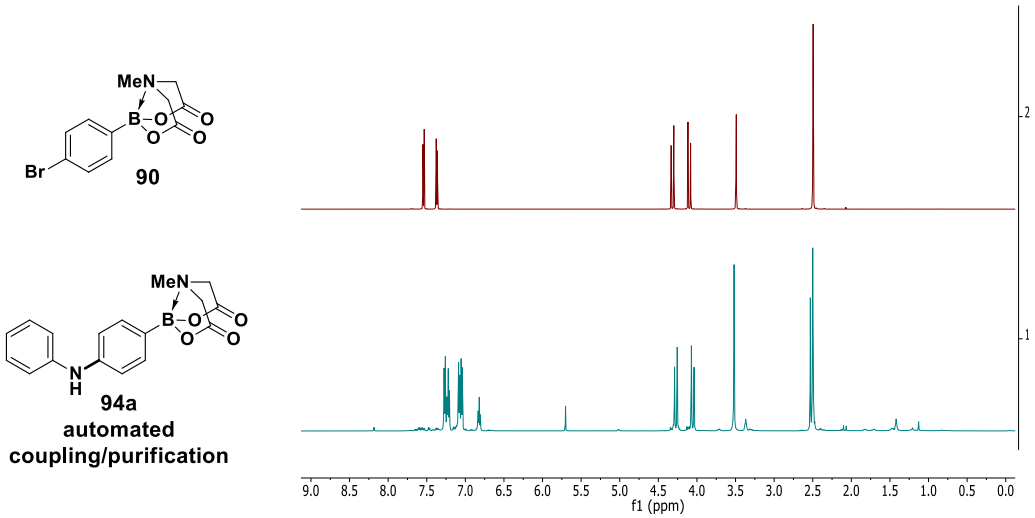
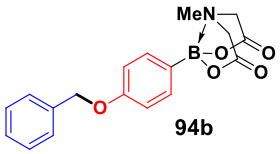


Figure S9. ^{1}H-NMRs for the automated synthesis of **94a**



Automated Procedure II was followed using 82.9 mg (0.333 mmol) *p*-hydroxyphenyl MIDA boronate **93a**, 120 µL benzyl bromide **92b** (1.01 mmol), and 416.4 mg (3.01 mmol) K_2CO_3. After automated addition of THF (8.4 mL), MeCN (3.6 mL) was added as a co-solvent. The reaction was run at 60 °C for 16 h. The desired aryl MIDA boronate **94b** was obtained as a solid (93.5 mg, 0.276 mmol, 83% yield) of >95% purity. ^{1}H-NMR (500 MHz, DMSO-d_6:D_2O, 95:5): δ 7.46 – 7.42 (m, 2H), 7.41 – 7.36 (m, 2H), 7.36 – 7.30 (m, 3H), 6.99 (d, J = 8.4 Hz, 2H), 5.08 (s, 2H), 4.28 (d, J = 17.2 Hz, 2H), 4.06 (d, J = 17.2 Hz, 2H), 2.47 (s, 3H); ^{13}C-NMR (125 MHz, DMSO-d_6:D_2O, 95:5): δ 169.7, 159.3, 137.3, 134.0, 128.7, 128.1, 127.9, 114.4, 69.2, 61.8, 47.7; HRMS (ESI+) calculated for $C_{18}H_{19}NO_5B$ $[M+H]^+$ *m/z* 340.1356, found 340.1355.

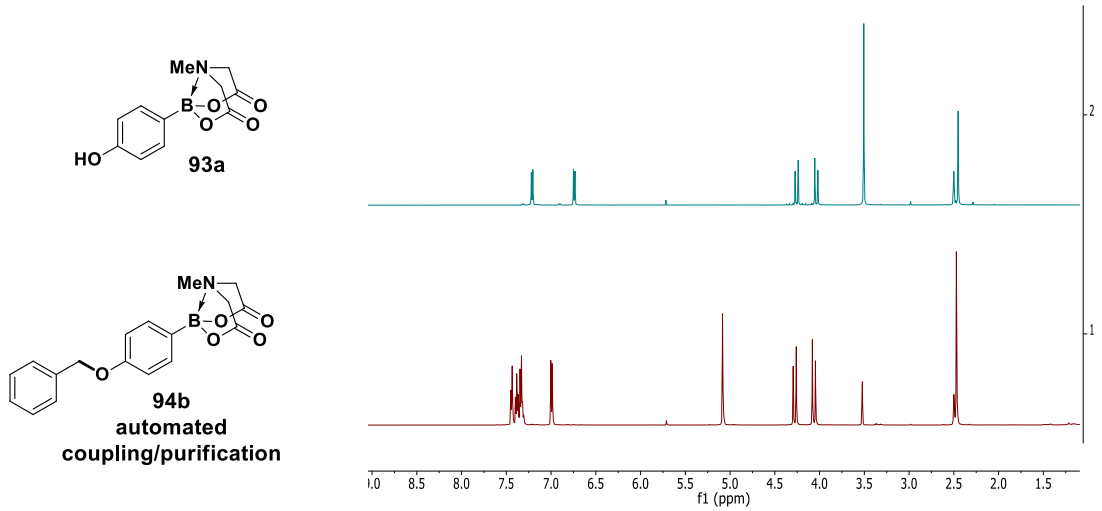
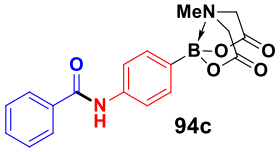


Figure S10. ^{1}H-NMRs for the automated synthesis of **94b**.



Automated Procedure II was followed using 82.2 mg (0.331 mmol) *p*-aminophenyl MIDA boronate **93b**, 60.7 mg (0.497 mmol) benzoic acid **92c**, 170.7 mg (0.532 mmol) TATU, and 90 µL (0.517 mmol) DIPEA. After automated addition of THF (8.4 mL), MeCN (3.6 mL) was added as a co-solvent. The reaction was run at 40 °C for 13 h. The desired aryl MIDA boronate **94c** was obtained as an off-white solid (93.7 mg, 0.266 mmol, 80% yield) of 90% purity. ^{1}H-NMR (500 MHz, DMSO-d_6:D_2O, 95:5): δ 10.27 (s, 1H), 7.96 – 7.92 (m, 2H), 7.78 – 7.74 (m, 2H), 7.62 – 7.57 (m, 1H), 7.55 – 7.50 (m, 2H), 7.40 (d, J = 8.3 Hz, 2H), 4.31 (d, J = 17.2 Hz, 2H), 4.10 (d, J = 17.2 Hz, 2H), 2.51 (s, 3H); ^{13}C-NMR (125 MHz, DMSO-d_6:D_2O, 95:5): δ169.6, 165.8, 139.8, 135.0, 132.9, 131.8, 128.6, 127.8, 119.7, 61.9, 47.7; HRMS (ESI+) calculated for $C_{18}H_{18}N_2O_5B$ $[M+H]^+$ *m/z* 353.1309, found 353.1310.

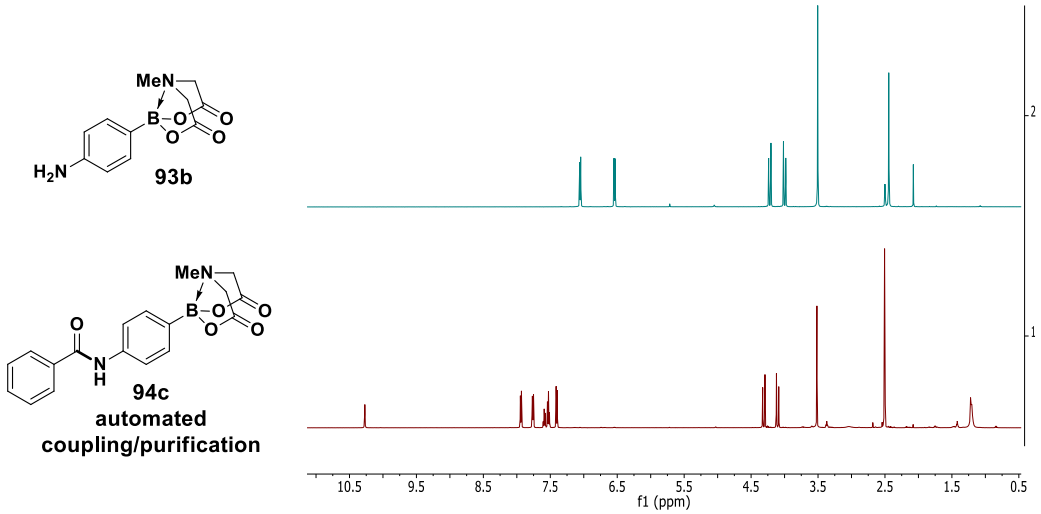
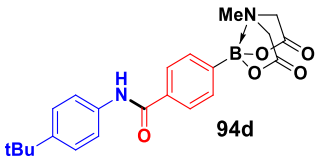


Figure S11. ^{1}H-NMRs for the automated synthesis of **94c**.



Automated Procedure II was followed using 91.7 mg (0.331 mmol) *p*-carboxyphenyl MIDA boronate **93c**, 55 µL (0.345 mmol) *p*-(*tert*-butyl)aniline, 118.3 mg (0.367 mmol) TATU, and 60 µL (0.344 mmol) DIPEA. After automated addition of THF (8.4 mL), MeCN (3.6 mL) was added as a co-solvent. The reaction was run at room temperature for 1 h. The desired aryl MIDA boronate **94d** was obtained as an off-white solid (118.7 mg, 0.291 mmol, 88% yield) of 90% purity. ^{1}H-NMR (500 MHz, DMSO-d_6:D_2O, 95:5): δ 10.19 (s, 1H), 7.92 (d, J = 8.2 Hz, 2H), 7.66 (d, J = 8.7 Hz, 2H), 7.57 (d, J = 8.1 Hz, 2H), 7.36 (d, J = 8.7 Hz, 2H), 4.35 (d, J = 17.3 Hz, 2H), 4.14 (d, J = 17.2 Hz, 2H), 2.52 (s, 3H), 1.27 (s, 9H); ^{13}C-NMR (125 MHz, DMSO-d_6:D_2O, 95:5): δ169.6, 165.7, 146.4, 136.7, 135.5, 134.2, 132.6, 127.0, 125.4, 120.5, 62.1, 47.9, 34.3, 31.4; HRMS (ESI+) calculated for $C_{22}H_{26}BN_2O_5$ $[M+H]^+$ *m/z* 409.1935, found: 409.1931.

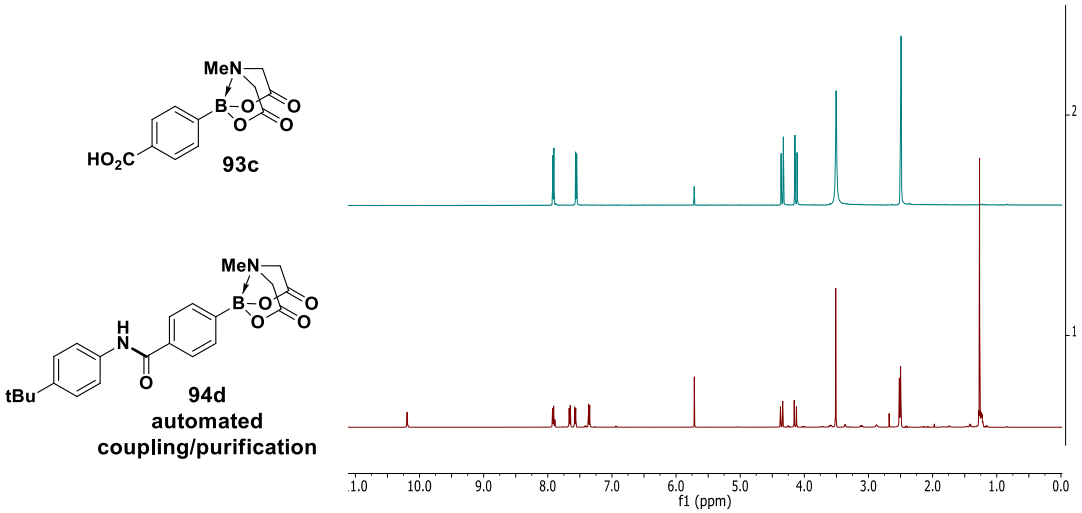


Figure S12. ^{1}H-NMRs for the automated synthesis of **94d**.

6. Syntheses involving multiple ICC cycles (Figure 2C) using Automated Procedure III

Automated Procedure III - *Cartridge Preparation*

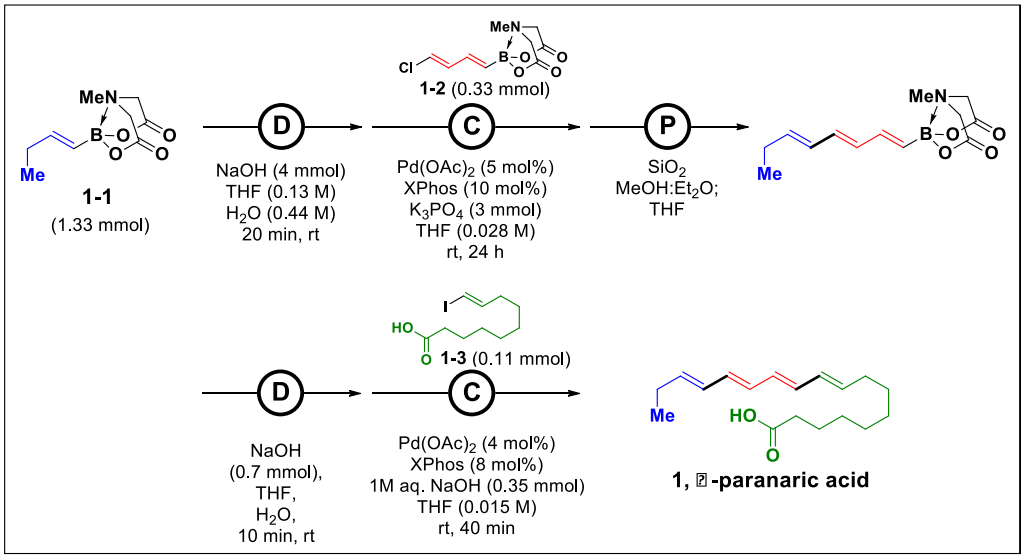
For multi-step syntheses, cartridges are prepared in the same manner as outlined in **Automated Procedure I** (for C-C coupling reactions) and **Automated Procedure II** (for C-X bond forming reactions). Each ICC cycle requires one set of the above described cartridges.

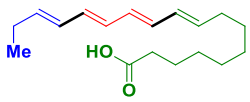
Automated Procedure III - *Experimental Details*

Automated Procedures I and **II** are followed with the following addendums:

- For two-step syntheses, after eluting the product from the Silica Gel Plug with 12 mL THF, the purified MIDA boronate solution is added to the Second Deprotection Cartridge which already contains solid NaOH (1.0 mmol, 40 mg). The Second Reaction Cartridge contains the capping building block (0.11 mmol), XPhos 2nd generation palladacycle (0.0056 mmol, 4.4 mg, 5 mol%), and K_3PO_4 (1.0 mmol, 212 mg). The coupling reactions are run at the concentrations noted in the following procedures. This cartridge is identical to a First Reaction Cartridge, but is not tethered to a Reaction Filtration Cartridge.
- For three-step syntheses, the Third Deprotection Cartridge contains NaOH (0.33 mmol, 13.3 mg) and no Drying Cartridge is used for the third reaction. The Third Reaction Cartridge is a 7-mL glass vial containing a PTFE-coated magnetic stir, the capping building block (0.037 mmol), XPhos 2nd generation palladacycle (0.00185 mmol, 1.5 mg, 5 mol%), and K_3PO_4 (0.33 mmol, 71 mg). The coupling reactions are run at the concentrations noted in the following procedures. The vial is sealed under argon with a septum-top screw cap.

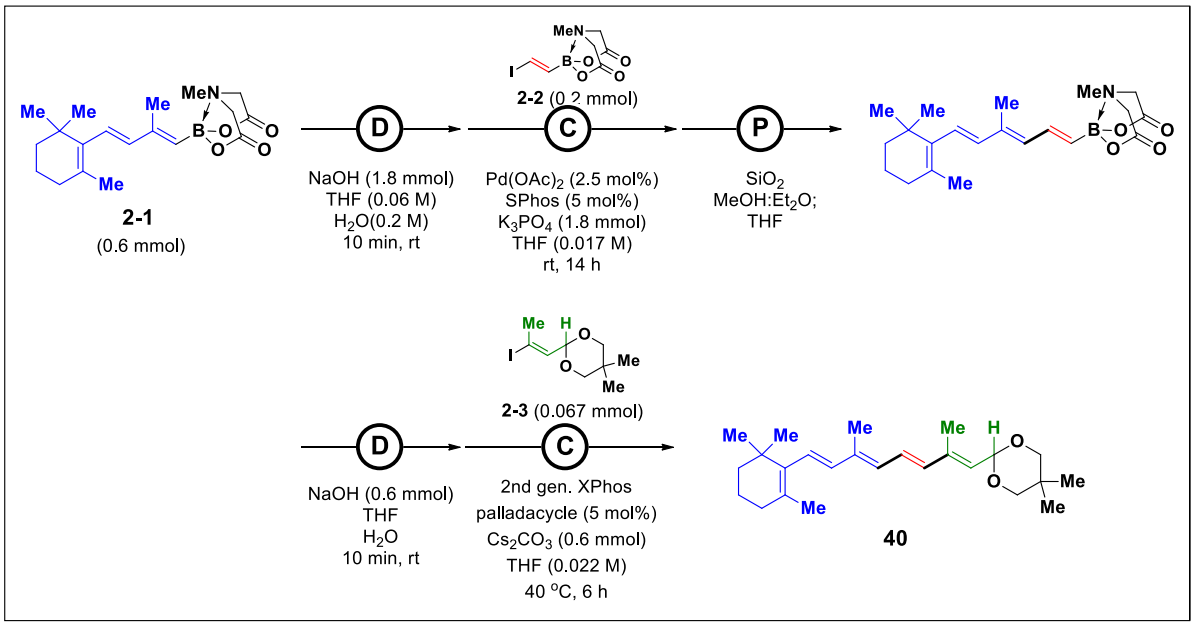
At the end of the synthesis, the crude reaction mixture is purified by either silica gel chromatography or preparative HPLC.

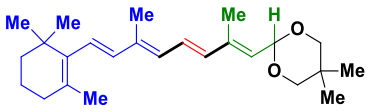




1, β-paranaric acid

Automated Procedure III was followed with the following modifications: The first coupling reaction was run at room temperature for 24 hours. The second deprotection reaction was run for 10 minutes, and the second coupling reaction was run in a 20-mL glass vial at room temperature using aqueous NaOH as the base for 40 minutes. The procedure was also conducted under subdued light conditions to protect against isomerization of the polyene framework. **1** was afforded as a fluorescent solid (18.3 mg, 0.0662 mmol, 56% yield). ^{1}H NMR indicated a 10:1 mixture of the desired β-parinaric acid (**1**):9-(*Z*)-parinaric acid (arising from 10:1 *E*:*Z* mixture of starting material vinyl iodide **1-3**). TLC (50% Et_2O in hexanes): R_f = 0.13, visualized by UV; HPLC (Agilent Prep-C18, 10 µm, 30 x 150 mm (product number: 413910-302), 25 mL/min, gradient: A = water, B = acetonitrile, 0 min: 95% A, 5% B; 2 min: 95% A, 5% B; 15 min: 0% A, 100% B; 30 min: 0% A, 100% B): 23.7 min; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.21-6.05 (m, 6H), 5.76-5.63 (m, 2H), 2.34 (t, *J* = 7 Hz, 2H), 2.15-2.07 (m, 4H), 1.66-1.60 (m, 2H), 1.43-1.26 (m, 8H), 1.01 (t, *J* = 7.5 Hz, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 179.2, 136.7, 135.1, 132.6, 132.6, 131.0, 131.0, 130.8, 129.8, 34.0, 33.0, 29.4, 29.2, 29.1, 29.1, 26.0, 24.8, 13.7; HRMS (ESI+) calculated for $C_{18}H_{29}O_2$ $[M+H]^+$ *m/z* 277.2168, found 277.2175.

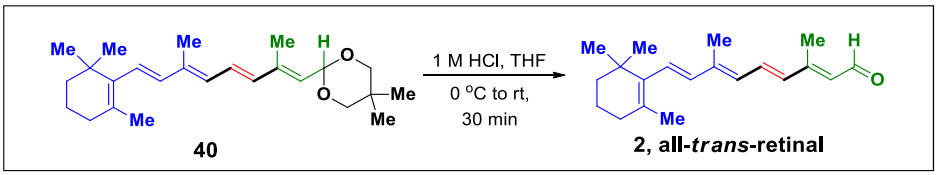


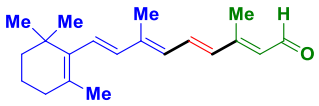


40

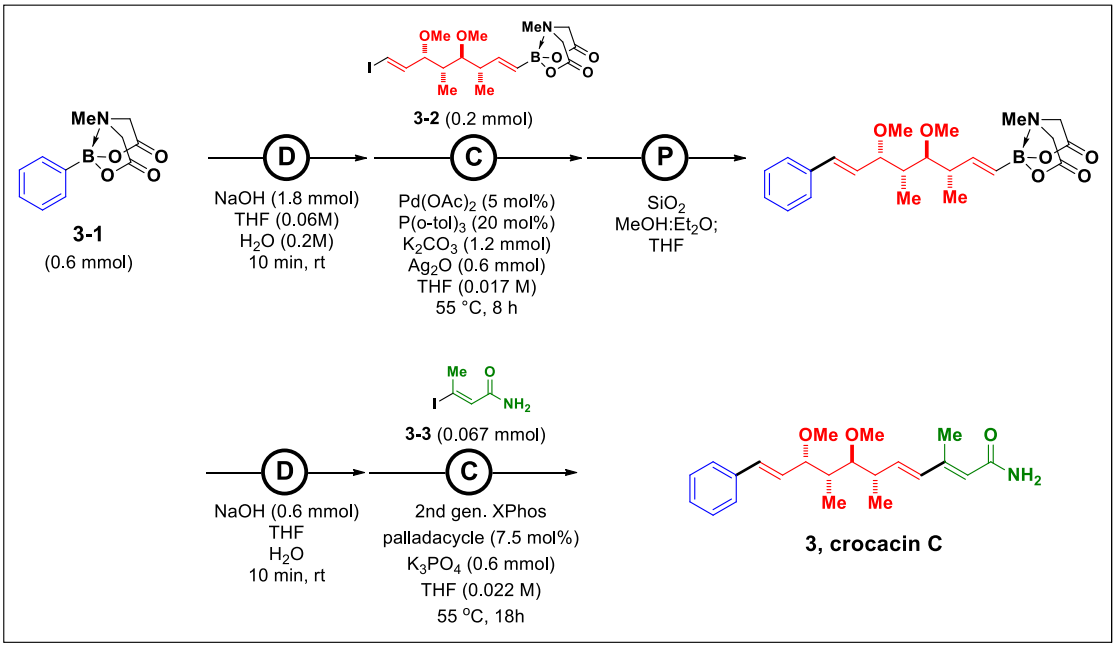
Automated Procedure III was followed with the following modifications: In the first coupling reaction, SPhos was used as the ligand and the reaction was run for 14 hours at room temperature. Both deprotection reactions were run for 10 minutes. The second coupling reaction was run in a 7-mL glass vial at 40 °C for 6 hours using Cs_2CO_3 as the base. The procedure was also conducted under subdued light conditions to protect against isomerization of the polyene

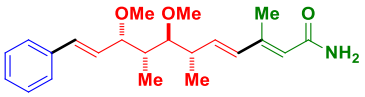
framework. Crude **40** was purified via silica gel chromatography (100% hexanes to 30% EtOAc in hexanes) to afford **40** as a single stereoisomer and a yellow oil (18.2 mg, 0.0491 mmol, 74% yield). TLC (petroleum ether: ether 4:1): R_f = 0.86, stained by $KMnO_4$; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.66 (dd, *J* = 14.8, 11.2 Hz, 1H), 6.27 (d, *J* = 15.2 Hz, 1H), 6.19-6.08 (m, 3H), 5.54 (d, *J* = 6 Hz, 1H), 5.21 (d, *J* = 6.4 Hz, 1H), 3.66 (d, *J* = 11.2 Hz, 2H), 3.53 (d, *J* = 10.8 Hz, 2H), 2.01 (t, *J* = 6.4 Hz, 2H), 1.95 (s, 3H), 1.91 (s, 3H), 1.70 (s, 3H), 1.62-1.59 (m, 2H), 1.47-1.44 (m, 2H), 1.23 (s, 3H), 1.01 (s, 6H), 0.75 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$):δ 139.3, 137.8, 137.6, 136.6, 135.8, 130.0, 129.3, 127.2, 127.0, 126.2, 109.8, 98.8, 39.6, 34.2, 33.0, 30.0, 28.9, 23.0, 22.0, 21.7, 19.2, 13.4, 12.7; HRMS (ESI+) calculated for $C_{25}H_{39}O_2$ $[M+H]^+$ *m/z* 371.2950, found 371.2950.





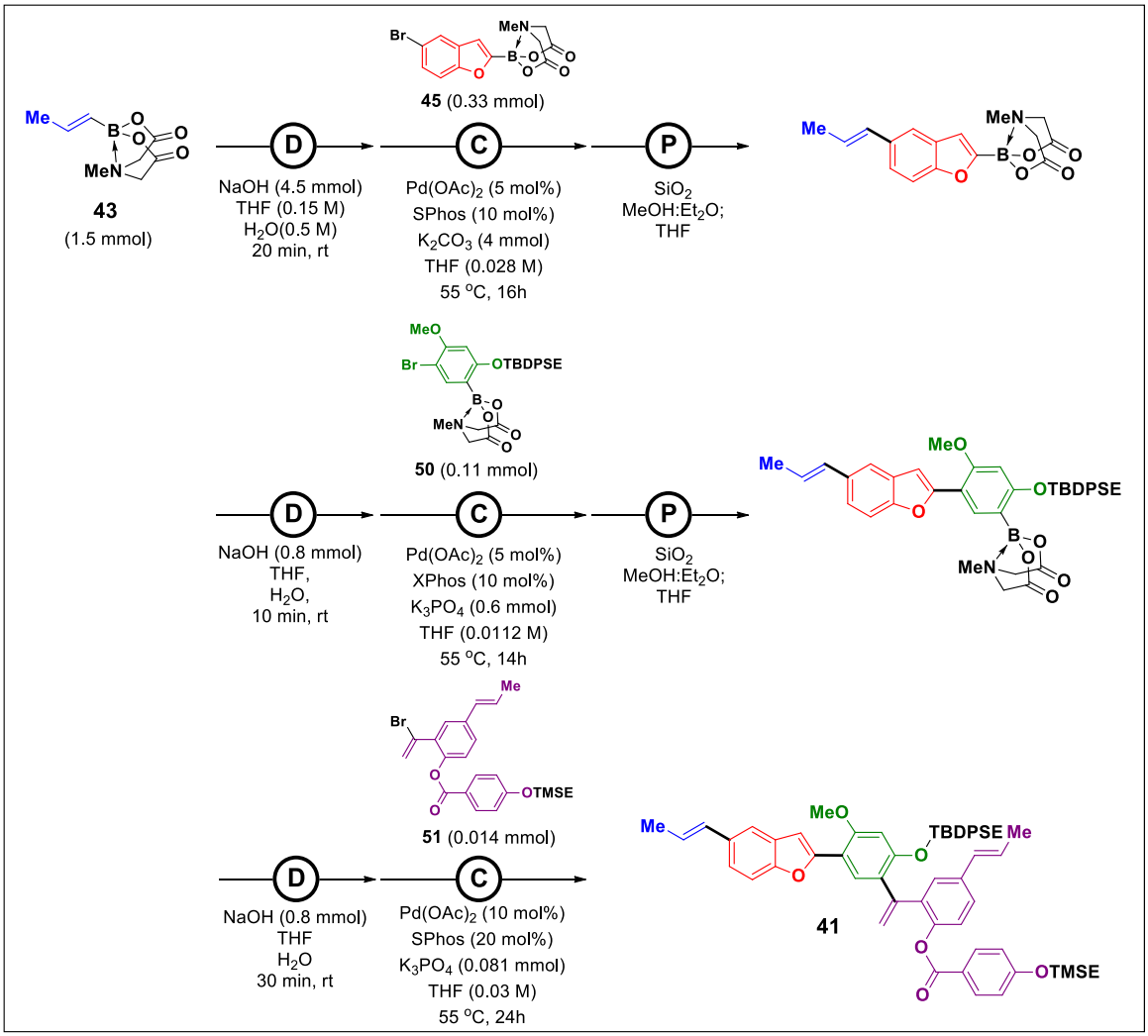
A 7-mL vial charged with **40** (18.2 mg, 0.049 mmol, 1.0 equiv.) was sealed with a PTFE-lined cap and purged with N_2 and THF (1.0 mL, 0.05M) was added to afford a clear yellow solution. The vial was cooled to 0 °C in an ice bath for 5 minutes. Aqueous HCl (1M, 0.5 mL) was added dropwise to the reaction vial and the reaction mixture was allowed to warm to 23 °C with stirring over 30 minutes. After 30 minutes, the reaction mixture was transferred to a separatory funnel containing aqueous saturated $NaHCO_3$ (5 mL), rinsing with diethyl ether (10 mL) and the phases were separated. The aqueous layer was back-extracted with diethyl ether (5 mL) and the combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to afford a yellow-orange oil. The resulting crude material (4:1 ratio of all-*trans* retinal (**2**):13-*cis*-retinal) was adsorbed onto Celite™ from an acetone solution and purified by silica gel chromatography (32:1 hexanes: EtOAc) to afford **2** as an orange solid (8.9 mg, 0.0313 mmol, 64% yield). ^{1}H-NMR (500 MHz, $CDCl_3$):δ 10.11 (d, *J* = 8 Hz, 1H), 7.14 (dd, *J* = 15, 11.5 Hz, 1H), 6.37 (d, *J* =15 Hz, 1H), 6.34 (d, *J* = 15 Hz, 1H), 6.19 (d, *J* = 9.5 Hz, 1H), 6.16 (d, *J* = 16 Hz, 1H), 5.97 (d, *J* = 8.5 Hz, 1H), 2.33 (d, *J* = 1 Hz, 3H), 2.04-2.02 (m, 2H), 2.03 (s, 3H), 1.72 (s, 3H), 1.63-1.60 (m, 2H), 1.49-1.46 (m, 2H), 1.03 (s, 6H).

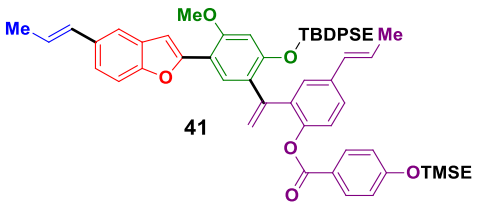




3, crocacin C

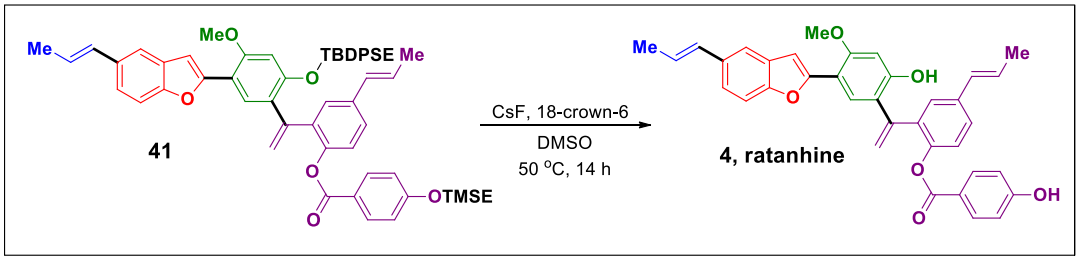
Automated Procedure III was followed with the following modifications: In the first coupling reaction, P(*o*-tol)$_3$ was used as the ligand and K_2CO_3 and Ag_2O were used as the base and the reaction was run for 8 hours. Both deprotection reactions were run for 10 minutes. The second coupling reaction was run for 18 hours in a 7-mL glass vial. Crude **3** was purified via silica gel chromatography (40% EtOAc in hexanes to 50% EtOAc in hexanes) to afford **3** as an off-white solid (14.5 mg, 0.0406 mmol, 61% yield). TLC (20% EtOAc in hexanes): R_f = 0.08, visualized by UV; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.39 (d, *J* = 7.5 Hz, 2H), 7.32 (t, *J* = 7 Hz, 2H), 7.23 (t, *J* = 7 Hz, 1H), 6.56 (d, *J* = 16.5 Hz, 1H), 6.17-6.01 (m, 3H), 5.63 (s, 1H), 5.38 (br s, 2H), 4.08 (dd, *J* = 7.5, 1 Hz, 1H), 3.54 (s, 3H), 3.32 (s, 3H), 3.19 (dd, *J* = 10, 2 Hz, 1H), 2.56-2.53 (m, 1H), 2.25 (d, *J* = 1 Hz, 3H), 1.56-1.52 (m, 1H), 1.19 (d, *J* = 7 Hz, 3H), 0.84 (d, *J* = 7 Hz, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 169.4, 149.7, 137.2, 136.8, 134.1, 132.1, 129.3, 128.7, 127.7, 126.5, 119.7, 86.5, 81.1, 61.6, 56.6, 42.7, 40.2, 18.9, 13.9, 9.8; HRMS (ESI+) calculated for $C_{22}H_{32}NO_3$ $[M+H]^+$ *m/z* 358.2382, found 358.2392.

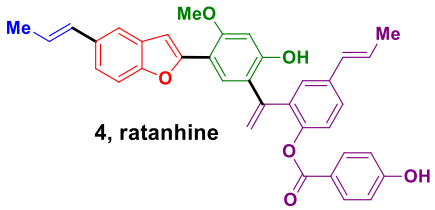




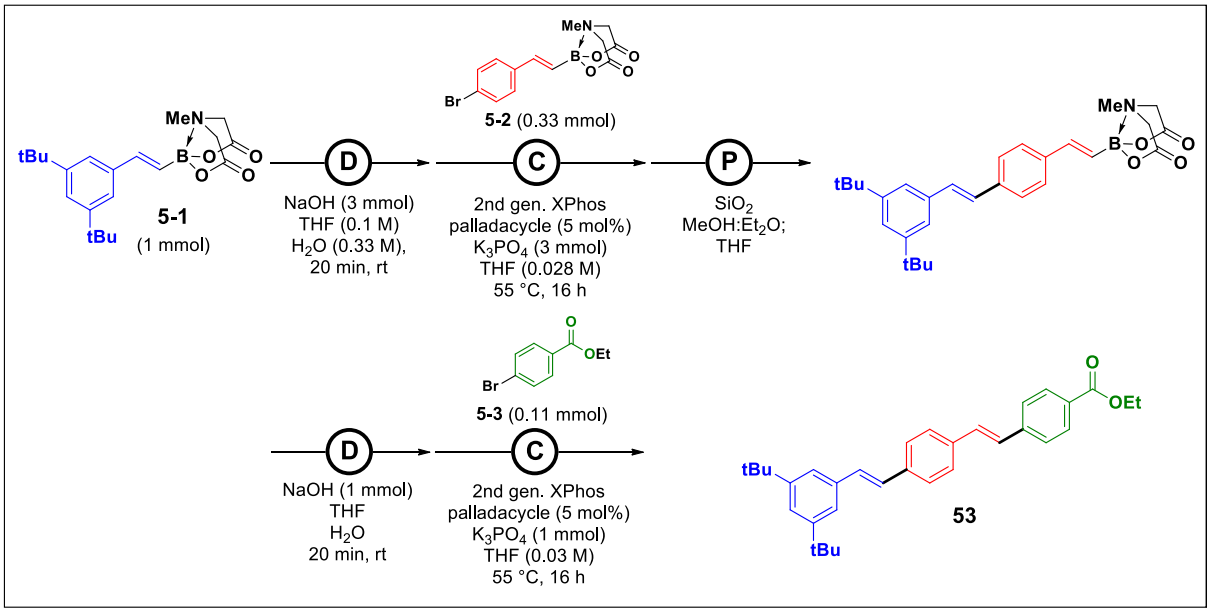
Automated Procedure III was followed with the following modifications: The first coupling reaction was run using SPhos (10 mol%), $Pd(OAc)_2$ (5 mol%) and K_2CO_3 as the base. The second and third deprotection reactions were run for 10 and 30 minutes, respectively. The second coupling reaction was run for 14 hours and the third coupling reaction was run for 24 hours using SPhos as the ligand. **41** was isolated as a colorless oil (4.7 mg, 36% yield), the ^{1}H NMR of which contained small amounts of hydrocarbon impurities presumed to represent some leaching from the HPLC column. HPLC (Agilent Prep-C18, 10 µm, 30 x 150 mm (product number: 413910-302), 25 mL/min, gradient: A = water, B = 20% THF in MeCN, 0 min: 80% A, 20% B; 5 min: 0% A, 100% B; 50 min: 0% A, 100% B): 13.4 min; ^{1}H-NMR (500 MHz, acetone-d_6): δ 7.67 (s, 1H), 7.64-7.62 (m, 4H), 7.54 (d, J = 9 Hz, 2H), 7.50 (s, 1H), 7.45-7.43 (m, 8H), 7.25 (d, J = 2 Hz, 1H), 7.21 (d, J = 8.5 Hz, 1H), 7.10 (d, J = 8.5 Hz, 1H), 6.95 (d, J = 1 Hz, 1H), 6.56 (dd, J =

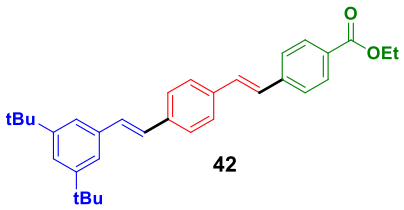
16, 2 Hz, 1H), 6.51-6.46 (m, 3H), 6.38 (dq, *J* = 15.5, 6.5 Hz, 1H), 6.35 (s, 1H), 6.26 (dq, *J* = 15.5, 6.5 Hz, 1H), 5.46 (s, 2H), 3.86-3.83 (m, 2H), 3.81 (s, 3H), 3.57-3.54 (m, 2H), 1.91 (dd, *J* = 6.5, 1.5 Hz, 3H), 1.88 (dd, *J* = 5, 1.5 Hz, 3H), 1.20-1.17 (m, 2H), 0.99 (s, 9H), 0.89-0.86 (m, 2H), 0.02 (s, 9H); HRMS (ESI+) calculated for $C_{59}H_{65}O_6Si_2$ $[M+H]^+$ *m/z* 925.4320, found 925.4316.



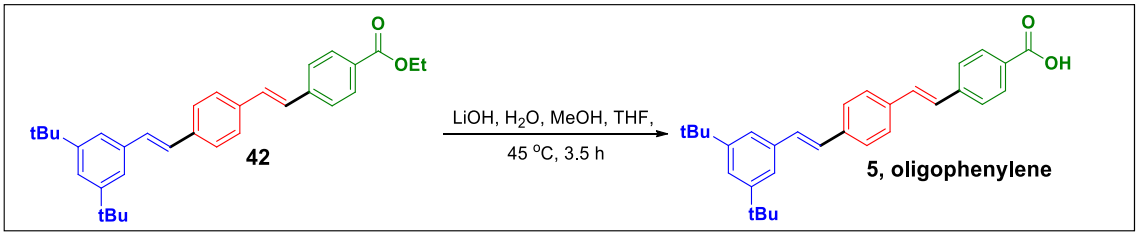


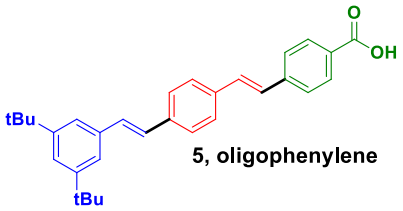
To a 1-mL Reacti-vial™ containing **41** and a PTFE-coated magnetic stir bar was added CsF (8.2 mg, 0.054 mmol) and 18-crown-6 (1.1 mg, 0.00416) followed by DMSO (0.15 mL) in a glovebox. The vial was sealed with a cap and stirred at 50 °C for 14 hours. The reaction was then cooled to room temperature, diluted with 8 mL EtOAc and washed with a solution of 1:1 saturated aqueous NH_4Cl/H_2O (8 mL). The aqueous layer was extracted with 4 mL EtOAc. The combined organic layers were washed with H_2O (2 × 4 mL), then with brine (8 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography to afford **4** as an off-white solid (0.2 mg, 0.00036 mmol, 7% yield). TLC (40% EtOAc/pentane): R_f = 0.44, visualized by shortwave UV; ^{1}H-NMR (500 MHz, acetone-d_6): δ 7.83 (dt, *J* = 9.0, 2.0 H, 2H), 7.77 (s, 1H), 7.53 (s, 1H), 7.43 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.37 (d, *J* = 8.5 Hz, 1H), 7.34 (d, *J* = 2.5 Hz, 1H), 7.28 (d, *J* = 8.0, 1.0 Hz, 1H), 7.17 (d, *J* = 8.5 Hz, 1H), 7.14 (s, 1H), 6.83 (dt, *J* = 8.5, 2.0 Hz, 2H), 6.55 (s, 1H), 6.50 (dd, *J* = 15.5, 1.5 Hz, 1H), 6.44 (dd, *J* = 16.0, 1.5 Hz, 1H), 6.31-6.21 (m, 2H), 5.61 (d, *J* = 1.5 Hz, 1H), 5.57 (d, *J* = 2.0 Hz, 1H), 3.96 (s, 3H), 1.87 (dd, *J* = 6.5, 1.5 Hz, 3H), 1.84 (dd, *J* = 6.5, 1.5 Hz, 3H); HRMS (ESI+) calculated for $C_{36}H_{31}O_6$ $[M+H]^+$ *m/z* 559.2121, found 559.2128.





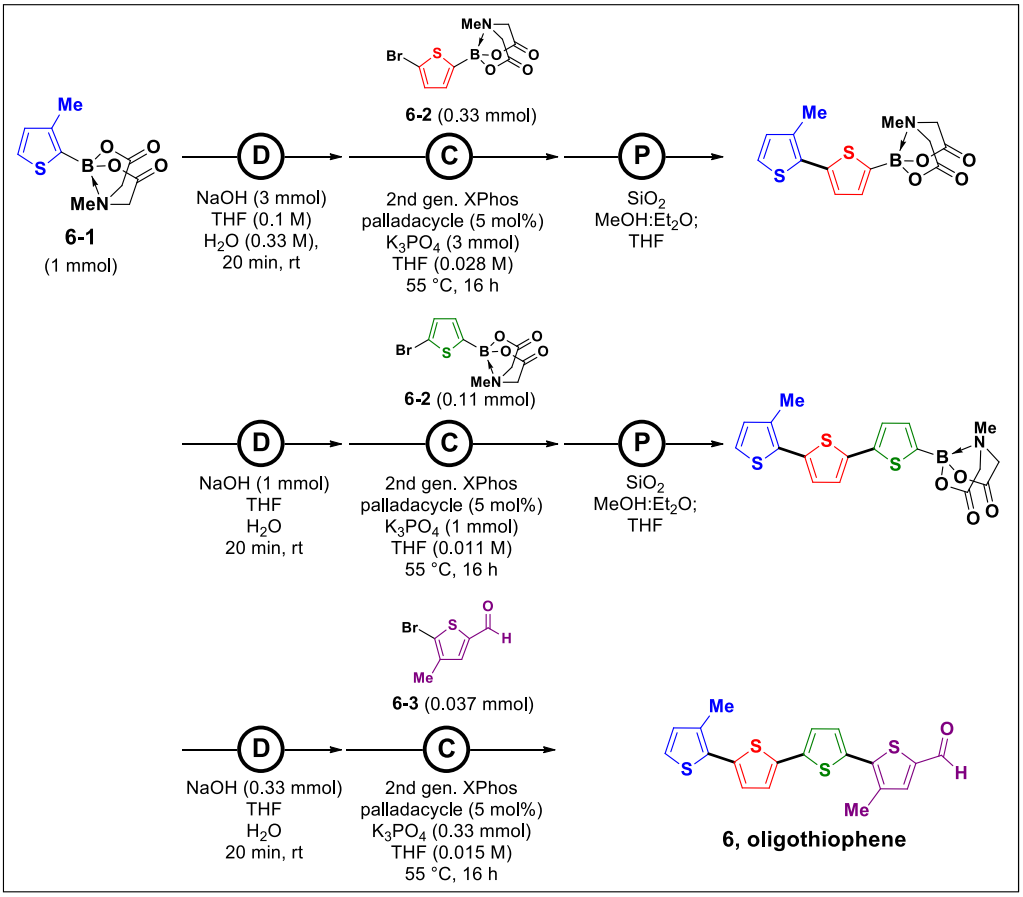
Automated Procedure III was followed with the following modifications: In the second coupling reaction, the addition of the boronic acid was performed over 1 minute and the coupling was run in a 7-mL glass vial. **42** was afforded as a yellow solid (44.1 mg, 0.0945 mmol, 84% yield). TLC (40% DCM in hexanes): R_f = 0.31, visualized by UV; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.06 (d, J = 8 Hz, 2H), 7.59-7.54 (m, 6H), 7.41-7.39 (m, 3H), 7.23 (d, J = 16.5 Hz, 1H), 7.22 (d, J = 16 Hz, 1H), 7.15 (d, J = 15.5 Hz, 1H), 7.12 (d, J = 16 Hz, 1H), 4.40 (q, J = 7 Hz, 2H), 1.42 (t, J = 7.5 Hz, 3H), 1.40 (s, 18H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 166.5, 151.2, 141.9, 137.8, 136.5, 136.0, 130.9, 130.2, 130.1, 129.3, 127.5, 127.4, 127.3, 127.0, 126.4, 122.4, 121.0, 61.0, 35.0, 31.6, 14.5; HRMS (ESI+) calculated for $C_{33}H_{39}O_2$ $[M+H]^+$ *m/z* 467.2950, found 467.2943.

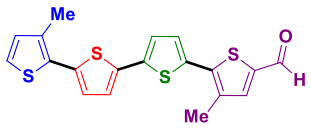




5, oligophenylene

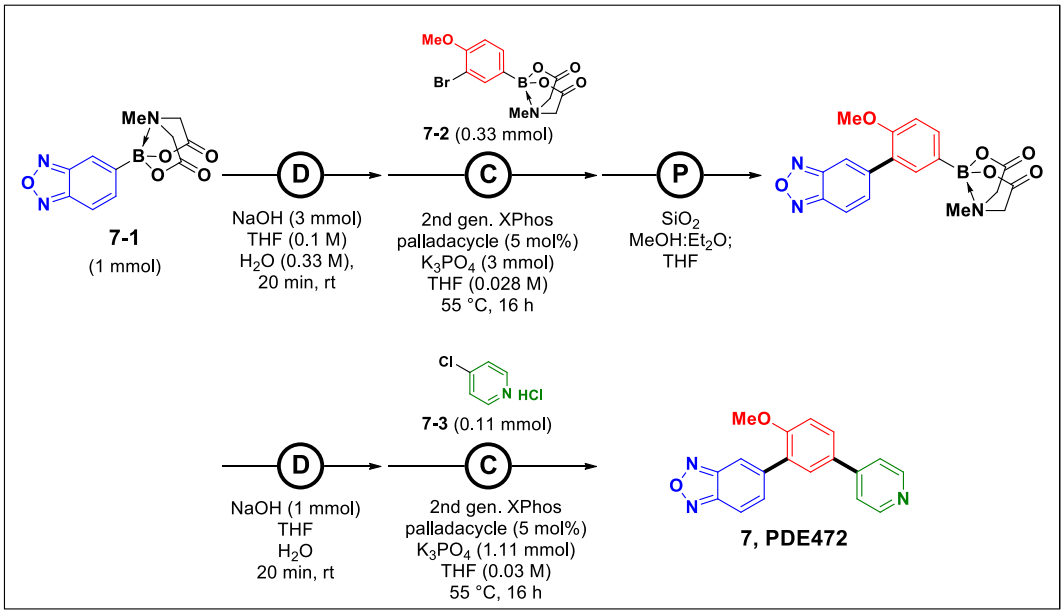
To a solution of ethyl ester **42** (44.1 mg, 0.0945 mmol) in MeOH/THF 1:1 (2 mL) was added LiOH solution (18 mg, 0.752 mmol in 0.4 mL H_2O) in one portion. The mixture was stirred vigorously at 45 °C for 3.5 hours. The reaction was cooled briefly in an ice-water bath and 0.2 mL of 2 N HCl was added. The mixture was diluted with 5 mL H_2O and extracted with EtOAc (10 mL, then 2 × 5 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by recrystallization from hot toluene. A second crop was obtained by precipitation from toluene/hexanes and combined with the first crop to afford **5** as a bright yellow solid (20.5 mg, 0.047 mmol, 50% yield). ^{1}H-NMR (500 MHz, DMSO-d_6): δ 12.88 (s, 1H), 7.92 (d, J = 8 Hz, 2H), 7.70 (d, J = 8.5 Hz, 2H), 7.64 (s, 3H), 7.43 (d, J = 1.5 Hz, 2H), 7.40 (d, J = 16.5 Hz, 1H), 7.34 (d, J = 16.5 Hz, 1H), 7.32 (d, J = 17 Hz, 1H), 7.30 (s, 2H), 7.26 (d, J = 16.5 Hz, 1H), 1.31 (s, 18 H); ^{13}C-NMR (125 MHz, DMSO-d_6): δ 167.0, 150.5, 141.5, 137.2, 136.2, 135.7, 130.6, 129.7 (2C), 129.4, 127.2, 127.1, 126.8, 126.4, 121.6, 120.8, 34.5, 31.2; HRMS (EI+) calculated for $C_{31}H_{34}O_2$ $[M]^+$ *m/z* 438.25588, found: 438.25538.

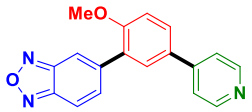




6, oligothiophene

Automated Procedure III was followed. Crude **6** was purified via silica gel chromatography (100% hexanes to 20% EtOAc in hexanes) to afford **6** as a red/orange solid (7.5 mg, 0.0194 mmol, 50% yield). TLC (20% EtOAc in hexanes): R_f = 0.29, visualized by longwave UV; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 9.81 (s, 1H), 7.54 (s, 1H), 7.24 (d, *J* = 3.5 Hz, 1H), 7.17 (m, 3H), 7.06 (d, *J* = 3.5 Hz, 1H), 6.90 (d, *J* = 5.0 Hz, 1H), 2.48 (s, 3H), 2.43 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 182.6, 141.6, 140.6, 139.7, 139.2, 136.7, 135.8, 134.8, 134.5, 134.2, 131.7, 130.7, 128.2, 126.2, 124.8, 124.2, 123.8, 16.1, 15.7; HRMS (EI+) calculated for $C_{19}H_{14}OS_4$ $[M]^+$ *m/z* 385.99277, found 385.99217.

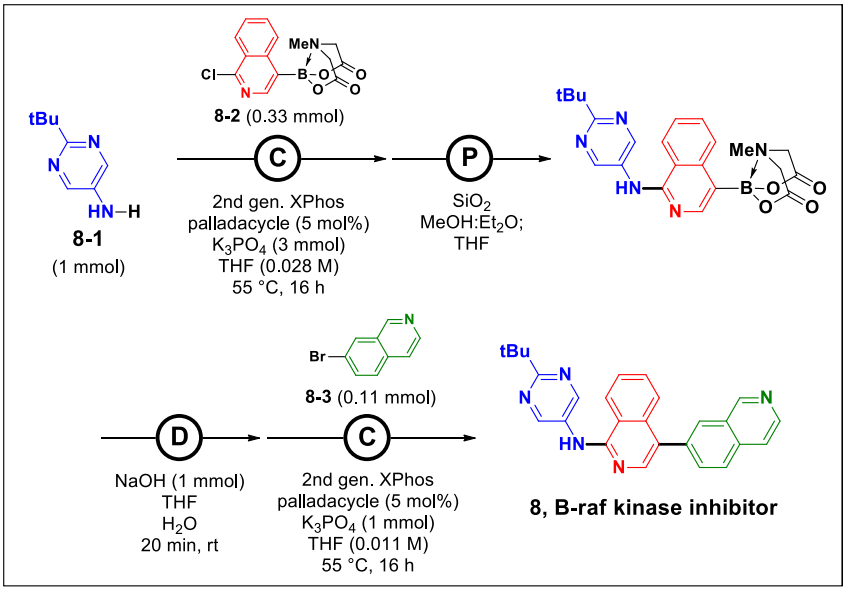


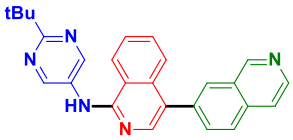


7, PDE472

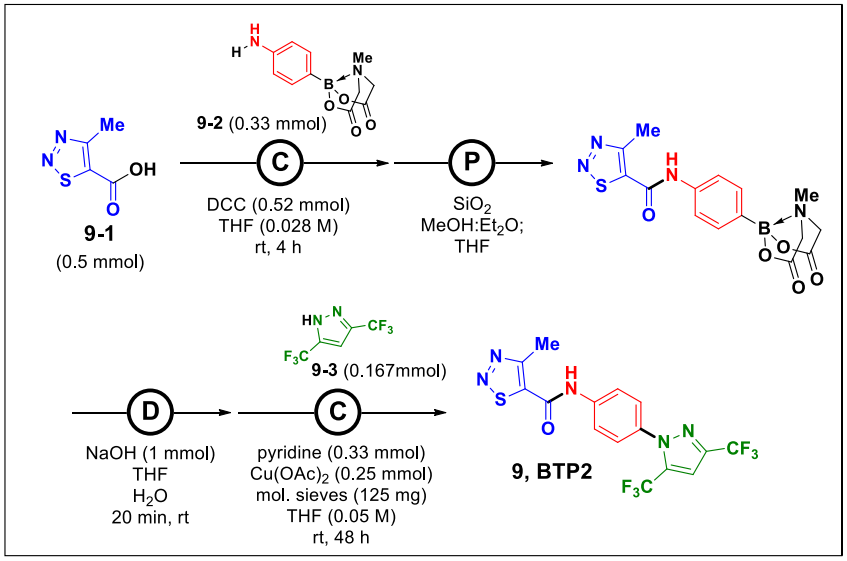
Automated Procedure III was followed with the following modifications: In the second coupling reaction: 1.11 mmol of K_3PO_4 were used, the addition of the boronic acid was performed over 1 minute, and the coupling was run in a 7-mL glass vial. **7** was afforded as a colorless solid (6.6 mg, 0.0218 mmol, 20% yield). TLC (EtOAc): R_f = 0.30, visualized by UV; HPLC (Agilent Prep-C18, 10 µm, 30 x 150 mm (product number: 413910-302), 25 mL/min, gradient: A = water, B = acetonitrile, 0 min: 95% A, 5% B; 20 min: 5% A, 95% B): 17.5 min; ^{1}H-NMR (500 MHz, acetone-d_6): δ 8.63 (br s, 2H), 8.12 (t, *J* = 1 Hz, 1H), 7.97 (dd, *J* = 9.5, 1 Hz, 1H), 7.96 (d, *J* = 2.5 Hz, 1H), 7.93 (dd, *J* = 9, 2.5 Hz, 1H), 7.87 (dd, *J* = 9.5, 1.5 Hz, 1H), 7.74 (app d, *J* = 6 Hz, 2H), 7.35 (d, *J* = 9 Hz, 1H), 3.98 (s, 3H); ^{13}C-NMR (125 MHz, DMSO-

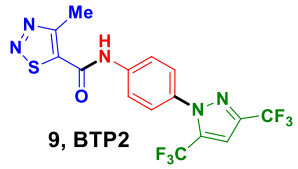
d_6): δ 157.3, 150.1, 149.3, 148.1, 146.1, 142.2, 135.8, 129.8, 129.1, 129.0, 128.2, 120.9, 114.9 (2C), 112.7, 56.1; HRMS (ESI+) calculated for $C_{18}H_{14}N_3O_2$ $[M+H]^+$ *m/z* 304.1086, found 304.1081.





Automated Procedure III was followed. Crude **8** was purified via silica gel chromatography (50% hexanes in EtOAc to 100% EtOAc) to afford **8** as a tan-orange solid (12.9 mg, 0.0318 mmol, 28% yield). TLC (EtOAc): R_f = 0.25, visualized by UV; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 9.31 (br s, 1H), 9.19 (s, 2H), 8.58 (d, *J* = 5 Hz, 1H), 8.16 (d, *J* = 8 Hz, 1H), 8.10 (s, 1H), 8.05 (s, 1H), 7.95 (d, *J* = 8.5 Hz, 1H), 7.87-7.81 (m, 2H), 7.74 (d, *J* = 5.5 Hz, 1H), 7.68-7.60 (m, 2H), 7.56 (br s, 1H), 1.44 (s, 9H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 171.2, 152.5, 151.6, 148.5, 143.2, 140.9, 136.9, 135.9, 135.2, 133.2, 132.7, 130.8, 128.9, 128.6, 127.2, 126.8, 126.3, 125.6, 121.9, 120.6, 118.2, 39.0, 29.9; HRMS (ESI+) calculated for $C_{26}H_{24}N_5$ $[M+H]^+$ *m/z* 406.2032, found 406.2031.





Automated Procedure III was followed with the following modifications: In the first coupling reaction, *N*,*N*'-dicyclohexylcarbodiimide (DCC) was used as a coupling agent. The DCC, carboxylic acid **9-1**, and amine MIDA boronate **9-2** all began in the First Reaction Cartridge and the coupling was run at room temperature for 4 hours. In the second coupling reaction, 0.167 mmol of pyrazole **9-3**, 0.33 mmol of pyridine, 0.25 mmol of $Cu(OAc)_2$, and 125 mg of activated 4 Å powdered molecular sieves were used, the addition of the boronic acid was performed over 1 minute, and the coupling was run at room temperature for 48 hours in a 7-mL glass vial. **9** was afforded a colorless solid (6.7 mg, 0.0159 mmol, 9% yield). TLC (20% EtOAc in hexanes): R_f = 0.22, visualized by UV; HPLC (Agilent Prep-C18, 10 µm, 30 x 150 mm (product number: 413910-302), 25 mL/min, gradient: A = water, B = MeCN, 0 min: 95% A, 5% B; 10 min: 5% A, 95% B; 15 min: 5% A, 95% B; 15.5 min: 95% A, 5% B; 20.5 min: 95% A, 5% B): 11.6 min; NMR matches data of product from manual synthesis (Section 1).

7. Library synthesis (Figure 3)

a. Automated assembly of building blocks

General Scheme for Automated Synthesis of Library Members 53-64

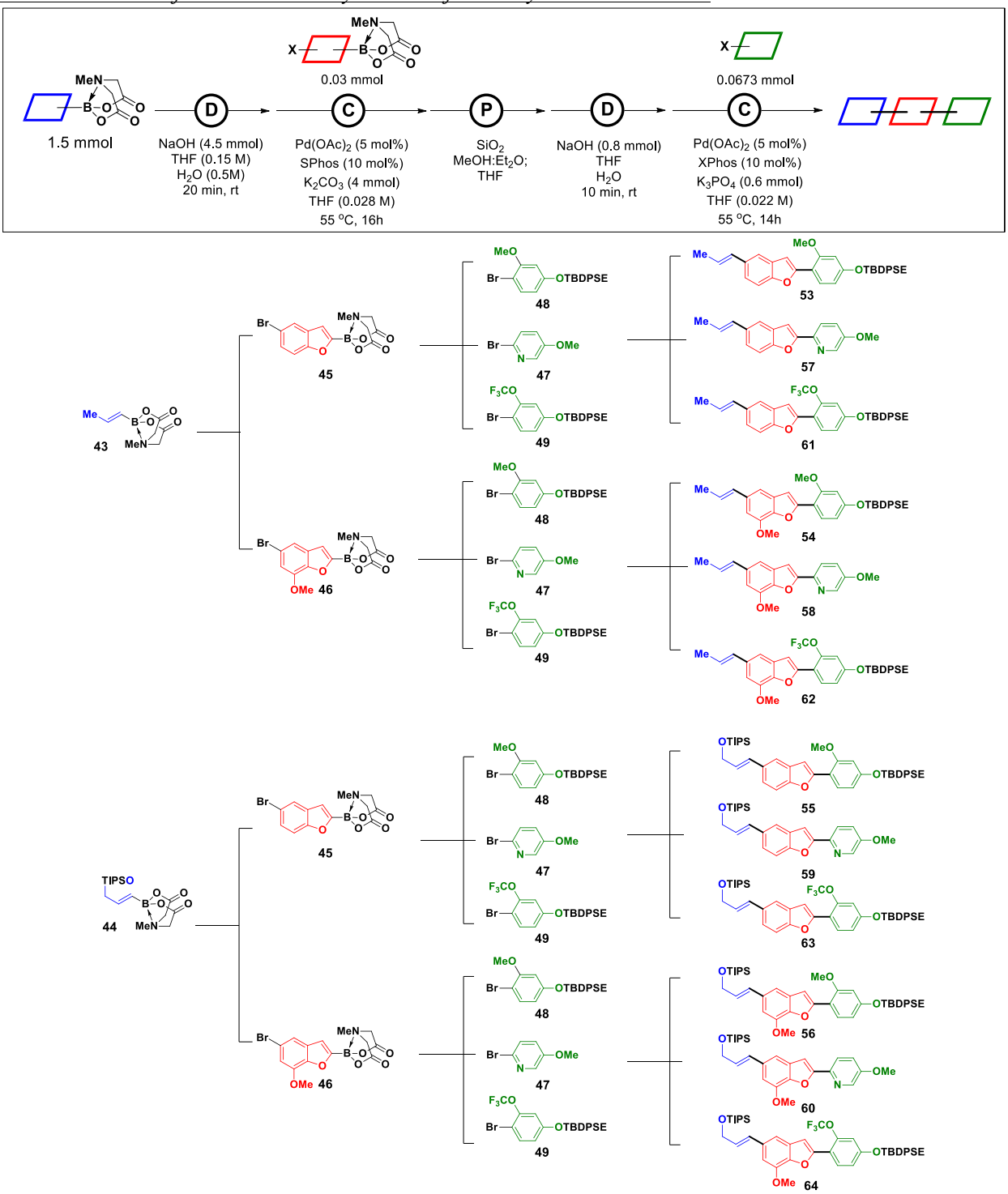
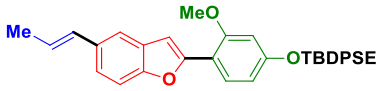
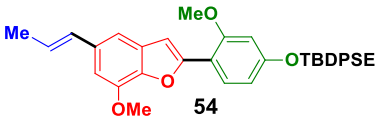


Figure S13. Building blocks used in the synthesis of library members **53-64**



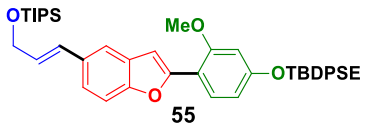
protected ratanhiaphenol III (53)
(27.8 mg, 75% yield)

Automated Procedure III as modified for **41** was followed to give **53** (27.8 mg, 75% yield). TLC (50% DCM in hexanes): R_f = 0.51, stained by $KMnO_4$; ^{1}H-NMR (500 MHz, acetone-d_6): δ 7.82 (d, J = 8.5 Hz, 1H), 7.74-7.71 (m, 4H), 7.53 (d, J = 1.5 Hz, 1H), 7.47-7.42 (m, 6H), 7.39 (d, J = 8.5 Hz, 1H), 7.29 (dd, J = 8.5, 1.5 Hz, 1H), 7.17 (d, J = 1 Hz, 1H), 6.52-6.46 (m, 3H), 6.24 (dq, J = 15.5, 6.5 Hz, 1H), 4.14-4.11 (m, 2H), 3.93 (s, 3H), 1.88-1.84 (m, 5H), 1.09 (s, 9H); ^{13}C-NMR (125 MHz, acetone-d_6): δ 161.3, 158.8, 153.8 (2C), 136.7, 134.8, 134.0, 132.2, 131.2, 130.3, 128.7, 128.3, 124.5, 122.8, 118.7, 112.8, 111.2, 106.6, 105.0, 100.0, 66.2, 55.9, 28.1, 18.6, 18.5, 12.6; HRMS (ESI+) calculated for $C_{36}H_{39}O_3Si$ $[M+H]^+$ *m/z* 547.2668, found 547.2673.



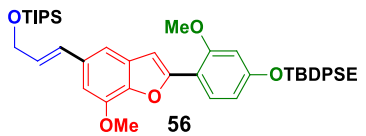
54
(27.9 mg, 72% yield)

Automated Procedure III as modified for **41** was followed to give **54** (27.9 mg, 72% yield). TLC (50% DCM in hexanes): R_f = 0.23, visualized by UV; ^{1}H-NMR (500 MHz, acetone-d_6): δ 7.84 (dd, J = 8, 0.5 Hz, 1H), 7.74-7.72 (m, 4H), 7.47-7.43 (m, 6H), 7.14 (s, 1H), 7.10 (d, J = 1.5 Hz, 1H), 6.93 (d, J = 1.5 Hz, 1H), 6.50-6.45 (m, 3H), 6.24 (dq, J = 15.5, 6.5 Hz, 1H), 4.14-4.10 (m, 2H), 4.01 (s, 3H), 3.93 (s, 3H), 1.87-1.84 (m, 5H), 1.09 (s, 9H); ^{13}C-NMR (125 MHz, acetone-d_6): δ 161.3, 158.7, 153.7, 145.9, 143.0, 136.7, 135.0, 134.8, 132.6, 132.5, 130.3, 128.7, 128.3, 124.6, 112.8, 111.6, 106.6, 105.2 (2C), 100.0, 66.2, 56.3, 56.0, 28.1, 18.5 (2C) 12.6; HRMS (ESI+) calculated for $C_{37}H_{41}O_4Si$ $[M+H]^+$ *m/z* 577.2774, found 577.2767.



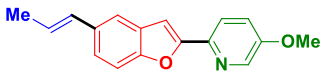
55
(25.9 mg, 54% yield)

Automated Procedure III as modified for **41** was followed to give **55** (25.9 mg, 54% yield). TLC (50% DCM in hexanes): R_f = 0.49, stained by $KMnO_4$; ^{1}H-NMR (500 MHz, acetone-d_6): δ 7.83 (d, J = 8.5 Hz, 1H), 7.74-7.72 (m, 4H), 7.61 (d, J = 1.5 Hz, 1H), 7.47-7.42 (m, 7H), 7.35 (dd, J = 8.5, 2 Hz, 1H), 7.19 (d, J = 0.5 Hz, 1H), 6.77 (dt, J = 16, 1.5 Hz, 1H), 6.51-6.47 (m, 2H), 6.35 (dt, J = 15.5, 5 Hz, 1H), 4.47 (dd, J = 4.5, 1.5 Hz, 2H), 4.14-4.11 (m, 2H), 3.94 (s, 3H), 1.88-1.84 (m, 2H), 1.22-1.08 (m, 30H); ^{13}C-NMR (125 MHz, acetone-d_6):δ 161.4, 158.8, 154.1, 154.0, 136.7, 134.8, 133.2, 131.3, 130.3, 130.2, 128.8, 128.7, 128.3, 123.3, 119.3, 112.8, 111.3, 106.7, 105.0, 100.0, 66.2, 64.8, 56.0, 28.1, 18.6, 18.4, 12.8, 12.6; HRMS (ESI+) calculated for $C_{45}H_{59}O_4Si_2$ $[M+H]^+$ *m/z* 719.3952, found 719.3925.



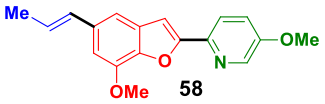
56
(29.2 mg, 57% yield)

Automated Procedure III as modified for **41** was followed to give **56** (29.2 mg, 57% yield). TLC (50% DCM in hexanes): R_f = 0.40, visualized by UV; ^{1}H-NMR (500 MHz, acetone-d_6):δ 7.84 (app d, J = 9 Hz, 1H), 7.74-7.71 (m, 4H), 7.48-7.43 (m, 6H), 7.17 (d, J = 1 Hz, 1H), 7.16 (s, 1H), 7.00 (d, J = 1.5 Hz, 1H), 6.73 (dt, J = 15.5, 1.5 Hz, 1H), 6.50 (s, 1H), 6.50--6.48 (m, 1H), 6.36 (dt, J = 16, 4.5 Hz, 1H), 4.47 (dd, J = 5, 1.5 Hz, 2H), 4.14-4.11 (m, 2H), 4.02 (s, 3H), 3.93 (s, 3H), 1.88-1.84 (m, 2H), 1.20-1.09 (m, 30H); ^{13}C-NMR (125 MHz, acetone-d_6): δ 161.3, 158.7, 153.8, 146.0, 143.2, 136.7, 143.7, 134.2, 132.7, 130.5, 130.3, 128.8, 128.7, 128.3, 112.8, 112.3, 106.6, 105.5, 105.2, 100.0, 66.2, 64.8, 56.3, 55.9, 28.1, 18.6, 18.4, 12.8, 12.6; HRMS (ESI+) calculated for $C_{46}H_{61}O_5Si_2$: $[M+H]^+$ *m/z* 749.4058, found 749.4056.



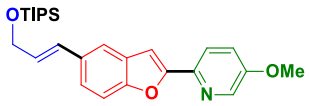
57
(9.9 mg, 56% yield)

Automated Procedure III as modified for **41** was followed to give **57** (9.9 mg, 56% yield). TLC (20% EtOAc in hexanes): R_f = 0.28, stained by $KMnO_4$; ^{1}H-NMR (500 MHz, acetone-d_6): δ 8.37 (dd, J = 3, 0.5 Hz, 1H), 7.89 (dd, J = 8.5, 0.5 Hz, 1H), 7.63 (dd, J = 2 Hz, 1H), 7.50 – 7.48 (m, 2H), 7.39 (dd, J = 8.5, 2 Hz, 1H), 7.31 (d, J = 1 Hz, 1H), 6.53 (dd, J = 16, 1.5 Hz, 1H), 6.29 (dq, 15.5, 6.5 Hz, 1H), 3.95 (s, 3H), 1.87 (dd, J = 6.5, 1.5 Hz, 3H); ^{13}C-NMR (125 MHz, acetone-d_6):δ 157.0, 156.6, 155.2, 142.5, 139.2, 134.5, 132.0, 130.4, 125.1, 123.7, 121.2, 120.9, 119.3, 111.9, 103.6, 56.2, 18.6; HRMS (ESI+) calculated for $C_{17}H_{16}NO_2$ $[M+H]^+$ *m/z* 266.1181, found 266.1180.



58
(6.9 mg, 35% yield)

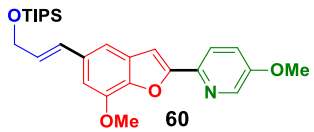
Automated Procedure III as modified for **41** was followed to give **58** (6.9 mg, 35% yield). TLC (20% EtOAc in hexanes): R_f = 0.23, stained by $KMnO_4$; ^{1}H-NMR (500 MHz, acetone-d_6): δ 8.36 (dd, J = 3, 0.5 Hz, 1H), 7.89 (dd, J = 8.5, 0.5 Hz, 1H), 7.49 (dd, J = 8.5, 3.0 Hz, 1H), 7.28 (s, 1H), 7.19 (d, J = 1.5 Hz, 1H), 7.01 (d, J = 1.5 Hz, 1H), 6.50 (d, J = 15.5, 1.5 Hz, 1H), 6.29 (dq, J = 16, 6.5 Hz, 1H), 4.05 (s, 3H), 3.95 (s, 3H), 1.87 (dd, J = 6.5, 1.5 Hz, 3H); ^{13}C-NMR (125 MHz, acetone-d_6): δ 156.9, 156.6, 146.3, 144.5, 142.5, 139.2, 135.5, 132.3, 131.8, 125.1, 121.2, 120.8, 112.0, 105.8, 103.9, 56.3, 56.2, 18.5; HRMS (ESI+) calculated for $C_{18}H_{18}NO_3$ $[M+H]^+$ *m/z* 296.1287, found 296.1282.



59
(5.6 mg, 19% yield)

Automated Procedure III as modified for **41** was followed to give **59** (5.6 mg, 19% yield). Library member **70** was isolated as an off-white solid containing **70** (5.6 mg, 19% yield) and a small amount of a byproduct and was carried on to the manual deprotection without further purification. TLC (20% EtOAc in hexanes): R_f = 0.33, visualized by UV; ^{1}H-NMR (500 MHz, acetone-d_6): δ 8.37 (dd, J = 3, 1 Hz, 1H), 7.89 (dd, J = 9, 1 Hz, 1H), 7.71 (d, J = 1.5 Hz, 1H), 7.52 (d, J = 8.5, 1H), 7.49 (dd, J = 8.5, 3 Hz, 1H), 7.46 (dd, J = 8.5, 1H), 7.34 (d, J = 1 Hz, 1H), 6.80 (dt, J = 15.5, 2 Hz, 1H), 6.40 (dt, J = 15.5, 5 Hz, 1H), 4.50 (dd, J = 4.5, 2 Hz, 2H), 3.96 (s,

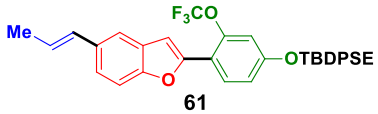
3H), 1.22-1.10 (m, 21H); HRMS (ESI+) calculated for $C_{26}H_{36}NO_3Si$ $[M+H]^+$ *m/z* 438.2464, found 438.2468.



60

(8.5 mg, 26% yield)

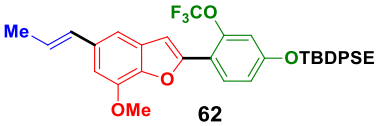
Automated Procedure III as modified for **41** was followed to give **60** (8.5 mg, 26% yield). TLC (20% EtOAc in hexanes): R_f = 0.26, visualized by UV; ^{1}H-NMR (500 MHz, acetone-d_6): δ 8.36 (dd, *J*= 3, 0.5 Hz, 1H), 7.90 (dd, *J* = 9, 0.5 Hz, 1H), 7.49 (dd, *J* = 8.5, 3 Hz, 1H), 7.30 (s, 1H), 7.26 (d, *J* = 1.5 Hz, 1H), 7.08 (d, *J* = 1.5 Hz, 1H), 6.76 (dt, *J* = 15.5, 2 Hz, 1H), 6.41 (dt, *J* = 16, 4.5 Hz, 1H), 4.49 (dd, *J* = 5, 2 Hz, 2H), 4.06 (s, 3H), 3.95 (s, 3H), 1.21-1.11 (m, 21H); ^{13}C-NMR (125 MHz, acetone-d_6):δ 157.0, 156.6, 146.4, 144.7, 142.5, 139.2, 134.8, 131.9, 130.2, 129.3, 121.2, 120.8, 112.8, 106.0, 103.9, 64.7, 56.4, 56.2, 18.4, 12.8; HRMS (ESI+) calculated for $C_{27}H_{38}NO_4Si$ $[M+H]^+$ *m/z* 468.2570, found 468.2572.



61

(27.8 mg, 69% yield)

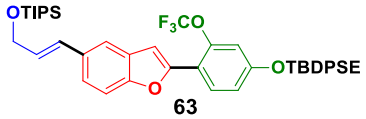
Automated Procedure III as modified for **41** was followed to give **61** (27.8 mg, 69% yield). TLC (20% DCM in hexanes): R_f = 0.27, visualized by UV; ^{1}H-NMR (500 MHz, acetone-d_6): δ 7.94 (d, *J* = 9 Hz, 1H), 7.74-7.72 (m, 4H), 7.62 (d, *J* = 1.5 Hz, 1H), 7.48-7.42 (m, 7H), 7.37 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.10 (d, *J* = 0.5 Hz, 1H), 6.91 (dd, *J* = 9, 2.5 Hz, 1H), 6.82 (quint, *J* = 1.5 Hz, 1H), 6.51 (dd, *J* = 16, 2 Hz, 1H), 6.27 (dq, *J* = 16, 7 Hz, 1H), 4.17-4.14 (m, 2H), 1.90-1.87 (m, 2H), 1.86 (dd, *J* = 6.5, 1.5 Hz, 3H), 1.10 (s, 9H); ^{13}C-NMR (125 MHz, acetone-d_6): δ 160.7, 154.2, 151.7, 147.0, 136.7, 134.6, 134.5, 132.0, 130.4, 130.3, 129.8, 128.7, 125.1, 123.8, 121.5 ($J_{C\text{-}F}$ = 257 Hz), 119.2, 116.8, 114.2, 111.6, 109.0, 105.7, 67.0, 28.1, 18.6 (2C), 12.4; HRMS (ESI+) calculated for $C_{36}H_{36}F_3O_3Si$ $[M+H]^+$ *m/z* 601.2386, found 601.2386.



62

(32.2 mg, 76% yield)

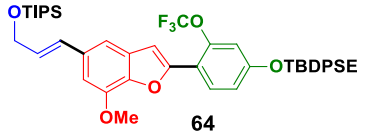
Automated Procedure III as modified for **41** was followed to give **62** (32.2 mg, 76% yield). TLC (20% DCM in hexanes): R_f = 0.09, visualized by UV; ^{1}H-NMR (500 MHz, acetone-d_6): δ 7.94 (d, *J* = 9 Hz, 1H), 7.74-7.72 (m, 4H), 7.48-7.42 (m, 6H), 7.18 (d, *J* = 1.5 Hz, 1H), 7.07 (s, 1H), 7.00 (d, *J* = 1.5 Hz, 1H), 6.92 (dd, *J* = 9, 2.5 Hz, 1H), 6.81 (quint, *J* = 2 Hz, 1H), 6.48 (dd, *J* = 16, 2 Hz, 1H), 6.27 (dq, *J* = 16, 6.5 Hz, 1H), 4.17-4.14 (m, 2H), 4.03 (s, 3H), 1.90-1.86 (m, 2H), 1.86 (dd, *J* = 6.5, 1.5 Hz, 3H), 1.09 (s, 9H); ^{13}C-NMR (125 MHz, acetone-d_6): δ 160.7, 151.5, 146.9, 146.1, 143.6, 136.7, 135.5, 134.6, 132.3, 131.9, 130.3, 129.7, 128.7, 125.1, 121.5 ($J_{C\text{-}F}$ = 257 Hz), 116.8, 114.2, 111.8, 109.0, 105.9 (2C), 67.0, 56.4, 28.1, 18.6, 18.5, 12.4; HRMS (ESI+) calculated for $C_{37}H_{38}O_4F_3Si$ $[M+H]^+$ *m/z* 631.2491, found 631.2488.



63

(21.6 mg, 42% yield)

Automated Procedure III as modified for **41** was followed to give **63** (21.6 mg, 42% yield). Library member **63** was isolated as a colorless oil containing **63** (21.6 mg, 42% yield) and a small amount of a byproduct and was carried on to the manual deprotection without further purification. TLC (10% DCM in hexanes): R_f = 0.11, visualized by UV; ^{1}H-NMR (500 MHz, acetone-d_6): δ 7.95 (d, J = 9 Hz, 1H), 7.74-7.70 (m, 5H), 7.50-7.41 (m, 8H), 7.13 (d, J = 0.5 Hz, 1H), 6.92 (dd, J = 9, 2.5 Hz, 1H), 6.82 (quint, J = 1.5 Hz, 1H), 6.79 (dt, J = 16, 1.5 Hz, 1H), 6.39 (dt, J = 16, 4.5 Hz, 1H), 4.48 (dd, J = 5, 2 Hz, 2H), 4.18-4.14 (m, 2H), 1.90-1.87 (m, 2H), 1.21-1.08 (m, 30H); HRMS (ESI+) calculated for $C_{45}H_{54}F_3O_4Si_2$ $[M+H]^+$ *m/z* 771.3513, found 771.3550.

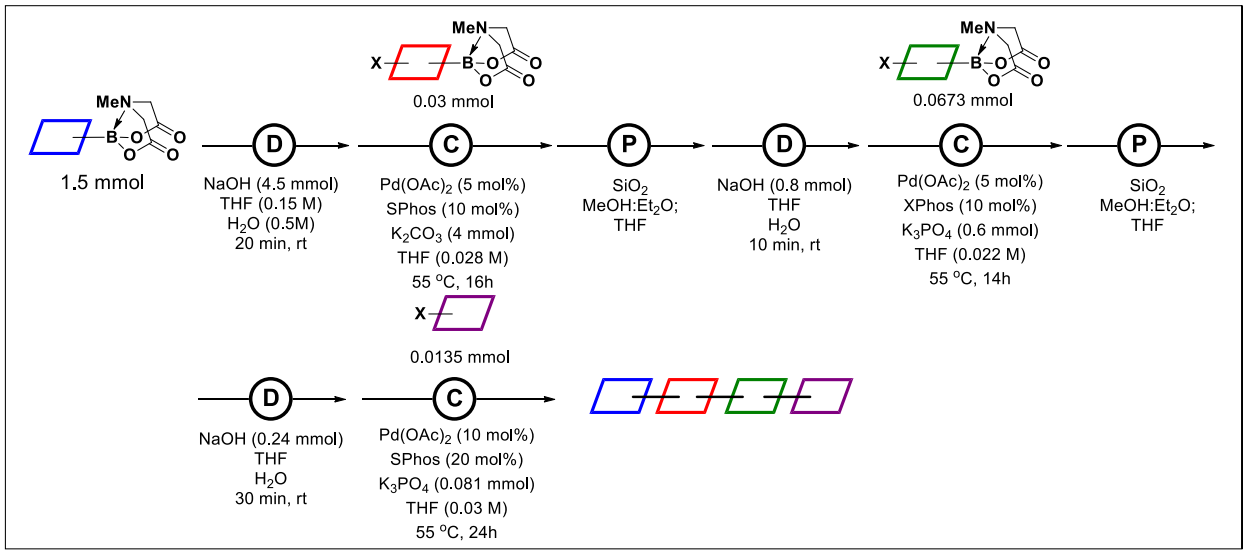


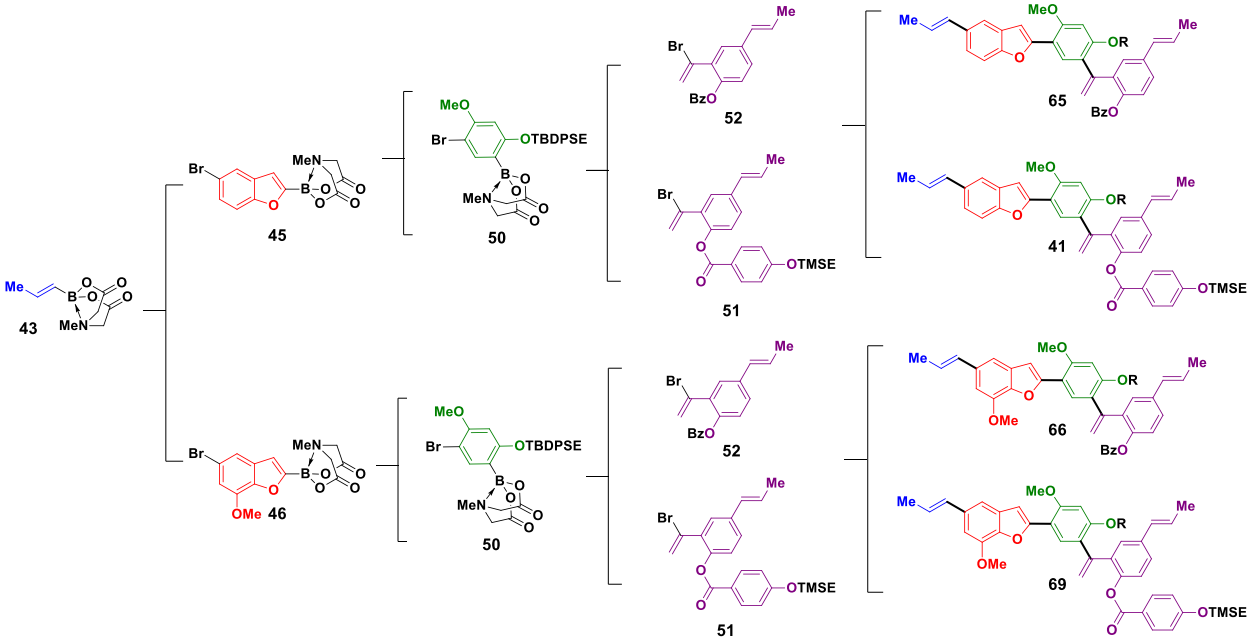
64

(35.7 mg, 65% yield)

Automated Procedure III as modified for **41** was followed to give **64** (35.7 mg, 65% yield). TLC (20% DCM in hexanes): R_f = 0.11, visualized by UV; ^{1}H-NMR (500 MHz, acetone-d_6): δ 7.95 (d, J = 8.5 Hz, 1H), 7.74-7.72 (m, 4H), 7.46-7.42 (m, 6H), 7.26 (d, J = 1.5 Hz, 1H), 7.09 (s, 1H), 7.06 (d, J = 1 Hz, 1H), 6.93 (dd, J = 8.5, 2.5 Hz, 1H), 6.81 (quint, J = 1.5 Hz, 1H), 6.79 (dt, J = 15.5, 2 Hz, 1H), 6.39 (dq, J = 16, 4.5 Hz, 1H), 4.47 (dd, J = 4.5, 1.5 Hz, 2H), 4.17-4.14 (m, 2H), 4.04 (s, 3H), 1.90-1.86 (m, 2H), 1.20-1.09 (m, 30H); ^{13}C-NMR (125 MHz, acetone-d_6): δ 160.7, 151.6, 146.9, 146.2, 143.8, 136.7, 134.8, 134.6, 132.0, 130.3, 130.2, 129.8, 129.3, 128.7, 121.5 ($J_{C\text{-}F}$ = 257 Hz), 116.8, 114.2, 112.6, 109.0, 106.2, 106.0, 67.0, 64.7, 56.4, 28.1, 18.5, 18.4, 12.8, 12.4; HRMS (ESI+) calculated for $C_{46}H_{57}F_3O_5Si_2Na$ $[M+H]^+$ *m/z* 825.3594, found 825.3600.

General Scheme for Automated Synthesis of Library Members 41 and 65-71





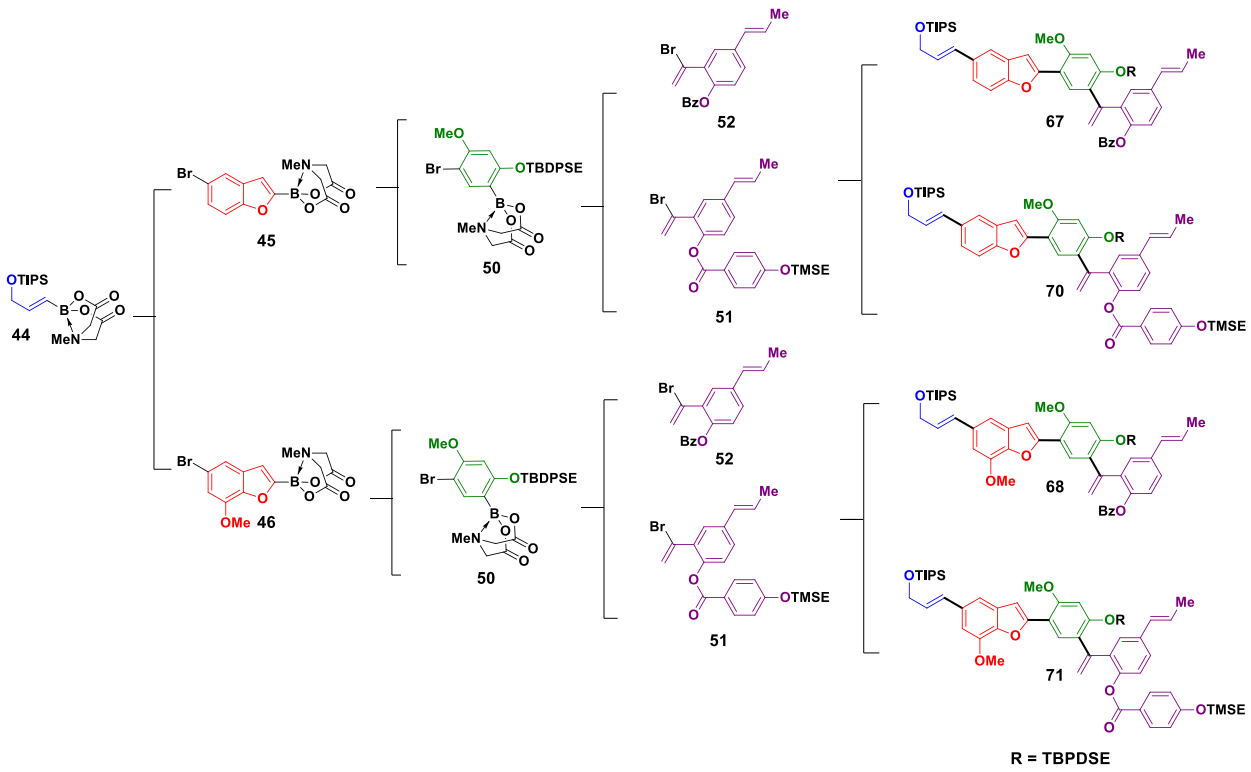
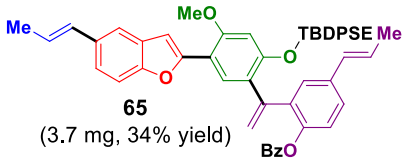
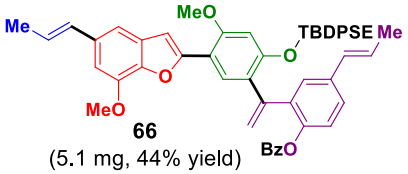


Figure S14. Building blocks used in the synthesis of library members **41** and **65-71**

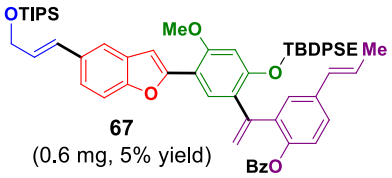


Automated Procedure III as modified for **41** was followed to give **65** (3.7 mg, 34% yield). HPLC (Agilent Prep-C18, 10 µm, 30 x 150 mm (product number: 413910-302), 25 mL/min, gradient: A = water, B = 10% THF in MeCN, 0 min: 80% A, 20% B; 5 min: 0% A, 100% B; 50 min: 0% A, 100% B): 17.1 min; ^{1}H-NMR (500 MHz, acetone-d_6): δ 7.71 (s, 1H), 7.68-7.61 (m, 6H), 7.60 (d, J = 2.5 Hz, 1H), 7.50 (d, J = 1.5 Hz, 1H), 7.47-7.41 (m, 7H), 7.36 (d, J = 8.5 Hz, 1H), 7.29 (dd, J = 8.5, 1.5 Hz, 1H), 7.17-7.13 (m, 2H), 7.10-7.06 (m, 2H), 6.95 (d, J = 1 Hz, 1H), 6.56 (dd, J = 16, 2 Hz, 1H), 6.51 (dd, J = 16, 1.5 Hz, 1H), 6.38 (dq, J = 16, 6.5 Hz, 1H), 6.34 (s, 1H), 6.25 (dq, J = 15.5, 7 Hz, 1H), 5.50 (d, J = 1.5 Hz, 1H), 5.49 (d, J = 2 Hz, 1H), 3.88-3.86 (m, 2H), 3.79 (s, 3H), 1.90 (dd, J = 6.5, 1.5 Hz, 3H), 1.87 (dd, J = 6.5, 1.5 Hz, 3H), 1.27-1.23 (m, 2H), 0.99 (s, 9H); HRMS (ESI+) calculated for $C_{54}H_{53}O_5Si$ $[M+H]^+$ *m/z* 809.3662, found 809.3658.



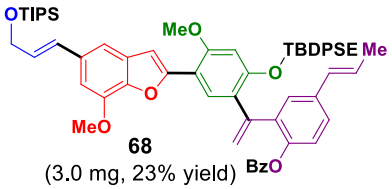
Automated Procedure III as modified for **41** was followed to give **66** (5.1 mg, 44% yield). HPLC (Agilent Prep-C18, 10 µm, 30 x 150 mm (product number: 413910-302), 25 mL/min,

gradient: A = water, B = 10% THF in MeCN, 0 min: 80% A, 20% B; 5 min: 0% A, 100% B; 50 min: 0% A, 100% B): 14.3 min; TLC (70% DCM in hexanes): R_f = 0.5, visualized by UV; ^{1}H-NMR (500 MHz, acetone-d_6): δ 7.75 (s, 1H), 7.68-7.63 (m, 6H), 7.59 (d, J = 2.5 Hz, 1H), 7.47-7.41 (m, 8H), 7.17-7.14 (m, 2H), 7.10-7.07 (m, 3H), 6.93 (s, 1H), 6.55 (dd, J = 16, 1.5 Hz, 1H), 6.48 (dd, J = 16, 1.5 Hz, 1H), 6.38 (dq, J = 16, 6.5 Hz, 1H), 6.34 (s, 1H), 6.26 (dq, J = 15.5, 6.5 Hz, 1H), 5.51 (d, J = 2 Hz, 1H), 5.50 (d, J = 2 Hz, 1H), 4.00 (s, 3H), 3.88-3.85 (m, 2H), 3.78 (s, 3H), 1.90 (dd, J = 6.5, 1.5 Hz, 3H), 1.87 (dd, J = 6.5, 1.5 Hz, 3H), 1.27-1.23 (m, 2H), 0.99 (s, 9H); HRMS (ESI+) calculated for $C_{55}H_{55}O_6Si$ $[M+H]^+$ *m/z* 839.3768, found 839.3772.



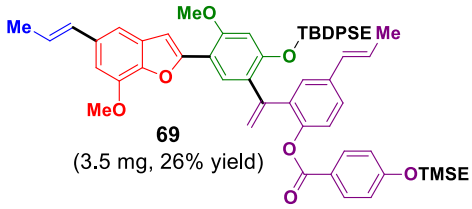
67
(0.6 mg, 5% yield)

Automated Procedure III as modified for **41** was followed to give **67** (0.6 mg, 5% yield). HPLC (Agilent Prep-C18, 10 µm, 30 x 150 mm (product number: 413910-302), 25 mL/min, gradient: A = water, B = 10% THF in MeCN, 0 min: 80% A, 20% B; 5 min: 0% A, 100% B; 50 min: 0% A, 100% B): 48.3 min; ^{1}H-NMR (500 MHz, acetone-d_6): δ 7.71 (s, 1H), 7.67-7.58 (m, 7H), 7.47-7.37 (m, 10H), 7.16-7.14 (m, 2H), 7.10-7.07 (m, 2H), 6.97 (s, 1H), 6.78 (app d, J = 16 Hz, 1H), 6.56 (dd, J = 15.5, 1.5 Hz, 1H), 6.41-6.36 (m, 2H), 6.35 (s, 1H), 5.51 (d, J = 1.5 Hz, 1H), 5.50 (d, J = 1.5 Hz, 1H), 4.50 (dd, J = 5, 2 Hz, 2H), 3.88-3.85 (m, 2H), 3.79 (s, 3H), 1.91 (dd, J = 6.5, 1.5 Hz, 3H), 1.29-1.07 (m, 23H), 0.94 (s, 9H); HRMS (ESI+) calculated for $C_{63}H_{73}O_6Si_2$ $[M+H]^+$ *m/z* 981.4946, found 981.4949.



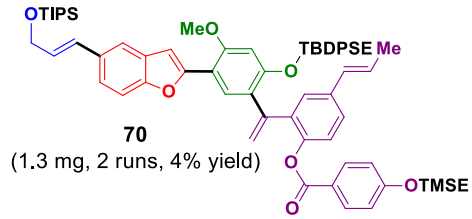
68
(3.0 mg, 23% yield)

Automated Procedure III as modified for **41** was followed to give **68** (3.0 mg, 23% yield). Library member **68** was isolated as a colorless oil (3.0 mg), the ^{1}H NMR of which contained small amounts of hydrocarbon impurities presumed to represent some leaching from the HPLC column. HPLC (Agilent Prep-C18, 10 µm, 30 x 150 mm (product number: 413910-302), 25 mL/min, gradient: A = water, B = 10% THF in MeCN, 0 min: 80% A, 20% B; 5 min: 0% A, 100% B; 50 min: 0% A, 100% B): 33.4 min; TLC (50% DCM in hexanes): R_f = 0.18, visualized by UV; ^{1}H-NMR (500 MHz, acetone-d_6):δ 7.75 (s, 1H), 7.69-7.62 (m, 6H), 7.60 (d, J = 2.5 Hz, 1H), 7.47-7.40 (m, 7H), 7.17-7.13 (m, 3H), 7.10-7.06 (m, 2H), 7.00 (d, J = 1.5 Hz, 1H), 6.95 (s, 1H), 6.76 (dt, J = 15.5, 1.5 Hz, 1H), 6.56 (dd, J = 15.5, 1.5 Hz, 1H), 6.40-6.35 (m, 2H), 6.34 (s, 1H), 5.52 (d, J = 1.5 Hz, 1H), 5.50 (d, J = 1.5 Hz, 1H), 4.49 (dd, J = 5, 2 Hz, 2H), 4.02 (s, 3H), 3.88-3.85 (m, 2H), 3.78 (s, 3H), 1.90 (dd, J = 6.5, 2.5 Hz, 3H), 1.29-1.23 (m, 2H), 1.23-1.08 (m, 21H), 0.99 (s, 9H); HRMS (ESI+) calculated for $C_{64}H_{74}O_7Si_2Na$ $[M+Na]^+$ *m/z* 1033.4871, found 1033.4895.



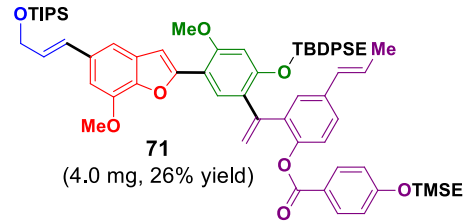
69
(3.5 mg, 26% yield)

Automated Procedure III as modified for **41** was followed to give **69** (3.5 mg, 26% yield). HPLC (Agilent Prep-C18, 10 µm, 30 x 150 mm (product number: 413910-302), 25 mL/min, gradient: A = water, B = 20% THF in MeCN, 0 min: 80% A, 20% B; 5 min: 0% A, 100% B; 50 min: 0% A, 100% B): 12.2 min; ^{1}H-NMR (500 MHz, acetone-d_6): δ 7.71 (s, 1H), 7.64-7.62 (m, 4H), 7.56-7.53 (m, 2H), 7.46-7.41 (m, 8H), 7.10 (d, J = 8 Hz, 1H), 7.08 (d, J = 1 Hz, 1H), 6.94 (d, J = 1.5 Hz, 1H), 6.93 (s, 1H), 6.56 (dd, J = 15.5, 1.5 Hz, 1H), 6.51-6.47 (m, 3H), 6.38 (dq, J = 15.5, 6.5 Hz, 1H), 6.34 (s, 1H), 6.27 (dq, J = 15.5, 6.5 Hz, 1H), 5.46 (s, 2H), 4.02 (s, 3H), 3.87-3.84 (m, 2H), 3.80 (s, 3H), 3.56 (app t, J = 8 Hz, 2H), 1.90 (dd, J = 6.5, 1.5 Hz, 3H), 1.88 (dd, J = 6.5, 1.5 Hz, 3H), 1.23-1.20 (m, 2H), 0.98 (s, 9H), 0.91-0.88 (m, 2H), 0.03 (s, 9H); HRMS (ESI+) calculated for $C_{60}H_{67}O_7Si_2$ $[M+H]^+$ *m/z* 955.4425, found 955.4437.



70
(1.3 mg, 2 runs, 4% yield)

Automated Procedure III as modified for **41** was followed to give **70** (1.3 mg, 4% yield). HPLC (Agilent Prep-C18, 10 µm, 30 x 150 mm (product number: 413910-302), 25 mL/min, gradient: A = water, B = 20% THF in MeCN, 0 min: 80% A, 20% B; 5 min: 0% A, 100% B; 50 min: 0% A, 100% B): 26.8 min; ^{1}H-NMR (500 MHz, acetone-d_6): δ 7.69 (s, 1H), 7.64-7.61 (m, 5H), 7.57 (s, 1H), 7.55 (d, J = 9 Hz, 2H), 7.46-7.34 (m, 9H), 7.10 (d, J = 8.5 Hz, 1H), 6.97 (s, 1H), 6.80 (dt, J = 16, 1.5 Hz, 1H), 6.56 (dd, J = 15.5, 1.5 Hz, 1H), 6.49 (d, J = 7 Hz, 2H), 6.41-6.34 (m, 3H), 5.46 (s, 2H), 4.51 (dd, J = 5, 2 Hz, 2H), 3.90-3.85 (m, 2H), 3.81 (s, 3H), 3.58 (app t, J = 8 Hz, 2H), 1.91 (dd, J = 6.5, 1 Hz, 3H), 1.24-1.17 (m, 5H), 1.15-1.12 (m, 18H), 0.99 (s, 9H), 0.88 (m, 2H), 0.03 (s, 9H); HRMS (ESI+) calculated for $C_{68}H_{85}O_7Si_3$ $[M+H]^+$ *m/z* 1097.5603, found 1097.5591



71
(4.0 mg, 26% yield)

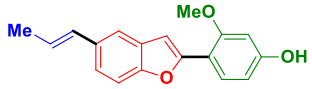
Automated Procedure III as modified for **41** was followed to give **71** (4.0 mg, 26% yield). Library member **71** was isolated as a colorless oil (4.0 mg), the ^{1}H NMR of which contained small amounts of hydrocarbon impurities presumed to represent some leaching from the HPLC column. HPLC (Agilent Prep-C18, 10 µm, 30 x 150 mm (product number: 413910-302), 25 mL/min, gradient: A = water, B = 20% THF in MeCN, 0 min: 80% A, 20% B; 5 min: 0% A, 100% B; 50 min: 0% A, 100% B): 22.3 min; ^{1}H-NMR (500 MHz, acetone-d_6): δ 7.72 (s, 1H), 7.64-7.62 (m, 5H), 7.55 (d, J = 8.5 Hz, 2H), 7.46-7.41 (m, 7H), 7.14 (d, J = 1 Hz, 1H), 7.10 (d, J

= 8 Hz, 1H), 7.00 (d, *J* = 1.5 Hz, 1H), 6.95 (s, 1H), 6.76 (dt, *J* = 15.5, 1.5 Hz, 1H), 6.56 (dd, *J* = 16, 2 Hz, 1H), 6.49 (d, *J* = 8.5 Hz, 2H), 6.42-6.34 (m, 3H), 5.44 (d, *J* = 2 Hz, 1H), 5.43 (d, *J* = 2 Hz, 1H), 4.50 (dd, *J* = 5, 2 Hz, 2H), 4.03 (s, 3H), 3.88-3.82 (m, 2H), 3.80 (s, 3H), 3.59 (app t, *J* = 8 Hz, 2H), 1.91 (dd, *J* = 6.5, 1.5 Hz, 3H), 1.24-1.17 (m, 5H), 1.15-1.13 (m, 18H), 0.99 (s, 9H), 0.91-0.88 (m, 2H), 0.03 (s, 9H); HRMS (ESI+) calculated for $C_{69}H_{86}O_8Si_3Na$ $[M+Na]^+$ *m/z* 1149.5528, found 1149.5552.

b. **Manual deprotections**

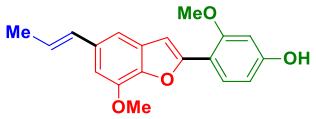
Deprotection condition 1 (for library members **53-56** and **59-64**)

To a 7-mL vial containing the protected library member and a PTFE-coated magnetic stir bar was added TBAF·$3H_2O$ (2.2–15 equiv) followed by 1:1 DMSO/DMPU under ambient atmosphere. The vial was sealed with a Teflon-lined cap and stirred at 50 °C for 30 minutes–6 hours. The reaction was then cooled to room temperature and diluted with a solution of 1:1 saturated NH_4Cl/H_2O (1.5–2 mL). The layers were mixed and the aqueous layer was removed. The organic layer was washed with H_2O (2 × 1.5 mL). The combined aqueous phase was extracted with EtOAc (3 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography to give the pure product as a white or off-white solid.



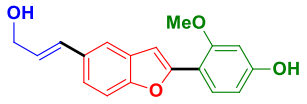
ratanhiaphenol III (deprotected 53)
(7.1 mg, 50% yield)

Deprotection condition 1 was followed to give **deprotected 53** (7.1 mg, 50% yield). TLC (20% EtOAc/hexanes): R_f = 0.14, visualized by shortwave UV; ^{1}H-NMR (500 MHz, acetone-d_6): δ 8.77 (br s, 1H), 7.83 (d, *J* = 8.5 Hz, 1H), 7.54 (d, *J* = 2.0 Hz, 1H), 7.41 (d, *J* = 8.5 Hz, 1H), 7.29 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.16 (d, *J* = 1.0 Hz, 1H), 6.64 (d, *J* = 2.0 Hz, 1H), 6.60 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.51 (d, *J* = 16, 1.5 Hz, 1H), 6.25 (dq, *J* = 15.5, 7 Hz, 1H), 3.99 (s, 3H), 1.86 (dd, *J* = 7.0, 2.0 Hz, 3H); ^{13}C-NMR (125 MHz, acetone-d_6): δ 160.2, 159.2, 154.2, 153.8, 134.0, 132.3, 131.3, 128.5, 124.5, 122.7, 118.7, 111.9, 111.2, 108.5, 104.6, 100.2, 55.9, 18.6; HRMS (ESI+) calculated for $C_{18}H_{17}O_3$ $[M+H]^+$ *m/z* 281.1178, found 281.1181.



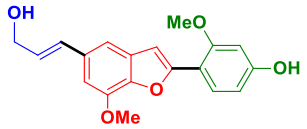
deprotected 54
11.7 mg, 78% yield

Deprotection condition 1 was followed to give **deprotected 54** (11.7 mg, 78% yield). TLC (30% EtOAc/hexanes): R_f = 0.3, visualized by shortwave UV; ^{1}H-NMR (500 MHz, acetone-d_6): δ 8.73 (br s, 1H), 7.84 (d, *J* = 8.5 Hz, 1H), 7.13 (s, 1H), 7.11 (d, *J* = 1.0 Hz, 1H), 6.93 (d, *J* = 1.0 Hz, 1H), 6.64 (d, *J* = 2.0 Hz, 1H), 6.60 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.48 (dd, *J* = 16, 1.5 Hz, 1H), 6.25 (dq, *J* = 16, 6.5 Hz, 1H), 4.03 (s, 3H), 3.98 (s, 3H), 1.86 (dd, *J* = 6.5, 1.5 Hz, 3H); ^{13}C-NMR (125 MHz, acetone-d_6): δ 160.2, 159.1, 154.0, 145.9, 142.9, 135.0, 132.7, 132.6, 128.5, 124.6, 111.9, 111.6, 108.5, 105.1, 104.8, 100.2, 56.4, 55.9, 18.6; HRMS (ESI+) calculated for $C_{19}H_{19}O_4$ $[M+H]^+$ *m/z* 311.1283, found 311.1277.



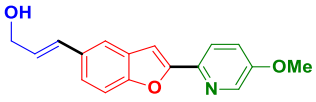
deprotected 55
(6.0 mg, 56% yield)

Deprotection condition 1 was followed to give **deprotected 55** (6.0 mg, 56% yield). TLC (50% EtOAc/hexanes): R_f = 0.27, visualized by shortwave UV; ^{1}H-NMR (500 MHz, acetone-d_6): δ 8.78 (br s, 1H), 7.83 (d, J = 8.5 Hz, 1H), 7.61 (d, J = 1.5 Hz, 1H), 7.43 (d, J = 8.5 Hz, 1H), 7.36 (dd, J = 9.0, 2.0 Hz, 1H), 7.18 (d, J = 0.5 Hz, 1H), 6.70 (d, J = 16.0 Hz, 1H), 6.64 (d, J = 2.5 Hz, 1H), 6.60 (dd, J = 8.5, 2.5 Hz, 1H), 6.38 (dt, J = 16, 5.5 Hz, 1H), 4.25 (t, J = 5.5 Hz, 2H), 3.99 (s, 3H), 3.84 (t, J = 5.5 Hz, 1H); ^{13}C-NMR (125 MHz, acetone-d_6): δ 160.2, 159.1, 154.2, 153.9, 133.3, 131.3, 130.5, 129.6, 128.5, 123.0, 119.2, 111.8, 111.2, 108.4, 104.5, 100.2, 63.4, 55.8; HRMS (ESI+) calculated for $C_{18}H_{17}O_4$ $[M+H]^+$ *m/z* 297.1127, found 297.1128.



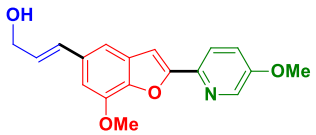
deprotected 56
(7.4 mg, 35% yield)

Deprotection condition 1 was followed to give **deprotected 56** (7.4 mg, 35% yield). TLC (60% EtOAc/hexanes): R_f = 0.22, visualized by shortwave UV; ^{1}H-NMR (500 MHz, acetone-d_6): δ 8.75 (br s, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.18 (d, J = 1.5 Hz, 1H), 7.15 (s, 1H), 6.99 (d, J = 1.0 Hz, 1H), 6.66 (dt, J = 17, 1.5 Hz, 1H), 6.64 (d, J = 2.0 Hz, 1H), 6.60 (dd, J = 8.5, 2.5 Hz, 1H), 6.38 (dt, J = 16, 5.5 Hz, 1H), 4.25 – 4.24 (m, 2H), 4.04 (s, 3H), 3.99 (s, 3H), 3.84 (br s, 1H); ^{13}C-NMR (125 MHz, acetone-d_6): δ 160.2, 159.1, 154.2, 146.0, 143.2, 134.4, 132.8, 130.9, 129.7, 128.5, 112.3, 111.9, 108.5, 105.4, 104.8, 100.2, 63.4, 56.4, 55.9; HRMS (ESI+) calculated for $C_{19}H_{19}O_5$ $[M+H]^+$ *m/z* 327.1232, found 327.1223.



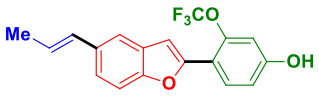
deprotected 59
(3.1 mg, 63% yield)

Deprotection condition 1 was followed to give **deprotected 59** (3.1 mg, 63% yield). TLC (60% EtOAc/hexanes): R_f = 0.36, visualized by shortwave UV; ^{1}H-NMR (500 MHz, acetone-d_6): δ 8.37 (dd, J = 2.5, 0.5 Hz, 1H), 7.90 (d, J = 8.5 Hz, 1H), 7.70 (d, J = 1.5 Hz, 1H), 7.52 (d, J = 8.5 Hz, 1H), 7.50 (dd, J = 9.0, 3.0 Hz, 1H), 7.45 (dd, J = 8.5, 1.5 Hz, 1H), 7.33 (d, J = 1 Hz, 1H), 6.72 (dt, J = 15.5, 1.5 Hz, 1H), 6.41 (dt, J = 16.0, 5.5 Hz, 1H), 4.26 (t, J = 8.0 Hz, 2H), 3.96 (s, 3H), 3.87 (br t, J = 5.0 Hz, 1H); ^{13}C-NMR (125 MHz, acetone-d_6): δ 157.1, 156.6, 155.4, 142.4, 139.2, 133.8, 130.4, 130.2, 130.1, 124.1, 121.2, 120.9, 119.8, 111.9, 103.5, 63.3, 56.2; HRMS (ESI+) calculated for $C_{17}H_{16}NO_3$ $[M+H]^+$ *m/z* 282.1130, found 282.1132.



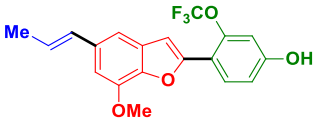
deprotected 60
(3.9 mg, 67% yield)

Deprotection condition 1 was followed to give **deprotected 60** (3.9 mg, 67% yield). TLC (60% EtOAc/hexanes): R_f = 0.27, visualized by shortwave UV; ^{1}H-NMR (500 MHz, acetone-d_6): δ 8.36 (dd, J = 2.5, 0.5 Hz, 1H), 7.90 (d, J = 8.5 Hz, 1H), 7.49 (dd, J = 9.0, 3.0 Hz, 1H), 7.30 (s, 1H), 7.25 (d, J = 1.0 Hz, 1H), 7.08 (d, J = 1.5 Hz, 1H), 6.68 (app d, J = 15.5 Hz, 1H), 6.41 (dt, J = 16, 5.5 Hz, 1H), 4.25 (t, J = 5.5 Hz, 2H), 4.06 (s, 3H), 3.95 (s, 3H), 3.86 (br t, J = 5.5 Hz, 1H); ^{13}C-NMR (125 MHz, acetone-d_6): δ 159.9, 156.5, 146.3, 144.6, 142.4, 139.2, 134.8, 131.8, 130.4, 130.2, 121.2, 120.8, 112.6, 105.9, 103.8, 63.3, 56.3, 56.2; HRMS (ESI+) calculated for $C_{18}H_{18}NO_4$ $[M+H]^+$ *m/z* 312.1236, found 312.1239.



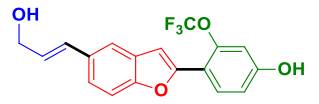
deprotected 61
(12.6 mg, 81% yield)

Deprotection condition 1 was followed to give **deprotected 61** (12.6 mg, 81% yield). TLC (20% EtOAc/hexanes): R_f = 0.36, visualized by shortwave UV; ^{1}H-NMR (500 MHz, acetone-d_6): δ 9.30 (br s, 1H), 7.96 (d, J = 8.5 Hz, 1H), 7.63 (d, J = 1.0 Hz, 1H), 7.47 (d, J = 8.5 Hz, 1H), 7.38 (dd, J = 8.5, 1.5 Hz, 1H), 7.10 (s, 1H), 7.03 (dd, J = 8.5, 2.0 Hz, 1H), 6.98 (m, 1H), 6.52 (dd, J = 15.5, 1.5 Hz, 1H), 6.28 (dq, J = 15.5, 6.5 Hz, 1H), 1.87 (dd, J = 6.5, 1.5 Hz, 3H); ^{13}C-NMR (125 MHz, acetone-d_6): δ 159.7, 154.2, 152.0, 147.2, 134.4, 131.9, 130.5, 130.0, 125.0, 123.7, 121.5 (J_{C-F} = 257 Hz), 119.1, 115.9, 115.7, 111.5, 109.3, 105.3, 18.5; HRMS (ESI+) calculated for $C_{18}H_{14}O_3F_3$ $[M+H]^+$ *m/z* 335.0895, found 335.0889.



deprotected 62
(14.3 mg, 77% yield)

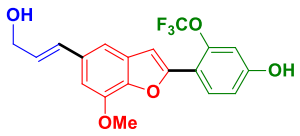
Deprotection condition 1 was followed to give **deprotected 62** (14.3 mg, 77% yield). TLC (20% EtOAc/hexanes): R_f = 0.27, visualized by shortwave UV; ^{1}H-NMR (500 MHz, acetone-d_6): δ 9.33 (br s, 1H), 7.96 (d, J = 9.0 Hz, 1H), 7.19 (d, J = 0.5 Hz, 1H), 7.07 (s, 1H), 7.03 (dd, J = 8.5, 2.0 Hz, 1H), 7.00 (d, J = 1.5 Hz, 1H), 6.97 (m, 1H), 6.49 (dd, J = 15.5, 1.5 Hz, 1H), 6.28 (dq, J = 16.0, 6.5 Hz, 1H), 4.04 (s, 3H), 1.86 (dd, J = 6.5, 3.0 Hz, 3H); ^{13}C-NMR (125 MHz, acetone-d_6): δ 159.7, 151.7, 147.1, 146.0, 143.5, 135.4, 132.2, 131.9, 129.9, 125.0, 121.5 (J_{C-F} = 256 Hz), 115.9, 115.7, 111.8, 109.2, 105.8, 105.6, 56.3, 18.5; HRMS (ESI+) calculated for $C_{19}H_{16}O_4F_3$ $[M+H]^+$ *m/z* 365.1001, found 365.0997.



deprotected 63
(7.1 mg, 73% yield)

Deprotection condition 1 was followed to give **deprotected 63** (7.1 mg, 73% yield). TLC (40% EtOAc/hexanes): R_f = 0.21, visualized by shortwave UV; ^{1}H-NMR (500 MHz, acetone-d_6): δ 9.30 (br s, 1H), 7.97 (d, J = 8.5 Hz, 1H), 7.10 (d, J = 1.5 Hz, 1H), 7.50 (d, J = 8.5 Hz, 1H), 7.44 (dd, J = 8.5, 2.0 Hz, 1H), 7.12 (d, J = 0.5 Hz, 1H), 7.04 (dd, J = 8.5, 2.5 Hz, 1H), 6.98 (quint, J = 2 Hz, 1H), 6.72 (d, J = 16 Hz, 1H), 6.41 (dt, J = 16.0, 5.0 Hz, 1H), 4.26 (d, J = 5.0 Hz, 2H), 3.84 (br s, 1H); ^{13}C-NMR (125 MHz, acetone-d_6): δ 159.8, 154.4, 152.1, 147.2, 133.8, 130.6, 130.1,

130.0 (2C), 124.0, 121.5 ($J_{C\text{-}F}$ = 256 Hz), 119.7, 115.9, 115.7, 111.6, 109.3, 105.3, 63.3; HRMS (ESI+) calculated for $C_{18}H_{14}O_4F_3$ $[M+H]^+$ *m/z* 351.0844, found 351.0849.

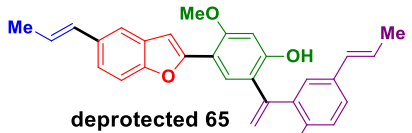


deprotected 64
(11.4 mg, 67% yield)

Deprotection condition 1 was followed to give **deprotected 64** (11.4 mg, 67% yield). TLC (40% EtOAc/hexanes): R_f = 0.13, visualized by shortwave UV; ^{1}H-NMR (500 MHz, acetone-d_6): δ 9.30 (br s, 1H), 7.97 (d, *J* = 8.5 Hz, 1H), 7.26 (d, *J* = 0.5 Hz, 1H), 7.09 (s, 1H), 7.06 (d, *J* = 1.0 Hz, 1H), 7.04 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.97 (m, 1H), 6.68 (d, *J* = 15.5 Hz, 1H), 6.41 (dt, *J* = 16.0, 5.0 Hz, 1H), 4.26 (d, *J* = 5.0 Hz, 2H), 4.06 (s, 3H), 3.85 (br s, 1H); ^{13}C-NMR (125 MHz, acetone-d_6): δ 159.7, 151.8, 147.1, 146.1, 143.7, 134.8, 131.9, 130.4, 130.1, 129.9, 121.5 ($J_{C\text{-}F}$ = 256 Hz), 115.9, 115.7, 112.4, 109.2, 106.0, 105.6, 63.3, 56.4; HRMS (ESI+) calculated for $C_{19}H_{16}O_5F_3$ $[M+H]^+$ *m/z* 381.0950, found 381.0946.

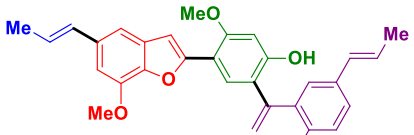
Deprotection condition 2 (for library members **65-68**)

To a 1-mL Reacti-vial™ containing the protected tetramer library member and a PTFE-coated magnetic stir bar was added TBAF·3H_2O (15-20 equiv) followed by DMSO under ambient atmosphere. The vial was sealed with a cap and stirred at 50 °C for 5 hours. The reaction was then cooled to room temperature, diluted with 8 mL Et_2O and washed with a solution of 1:1 saturated NH_4Cl/H_2O (4 mL). The aqueous layer was extracted with 4 mL Et_2O. The combined organic layers were washed with H_2O (2 × 4 mL), then with brine (4 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography.



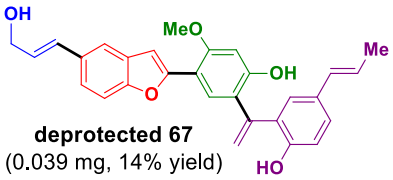
deprotected 65
(1.0 mg, 48% yield)

Deprotection condition 2 was followed to give **deprotected 65** (1.0 mg, 48% yield). TLC (40% EtOAc/pentane): R_f = 0.49, visualized by shortwave UV; ^{1}H-NMR (500 MHz, acetone-d_6): δ 7.77 (s, 1H), 7.53 (d, *J* = 1.5 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.27 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.18-7.17 (m, 3H), 6.82 (dd, *J* = 6.5, 3.0 Hz, 1H), 6.68 (s, 1H), 6.50 (dd, *J* = 16.0, 1.5 Hz, 1H), 6.31 (dd, *J* = 15.5, 1.5 Hz, 1H), 6.24 (dq, *J* = 16.0, 6.5 Hz, 1H), 6.05 (dq, *J* = 15.5, 7.0 Hz, 1H), 5.69 (d, *J* = 2.5 Hz, 1H), 5.66 (d, *J* = 2.5 Hz, 1H), 3.99 (s, 3H), 1.85 (dd, *J* = 6.5, 1.5 Hz, 1H), 1.78 (dd, *J* = 6.5, 1.5 Hz, 1H); HRMS (ESI+) calculated for $C_{29}H_{27}O_4$ $[M+H]^+$ *m/z* 439.1909, found 439.1904.



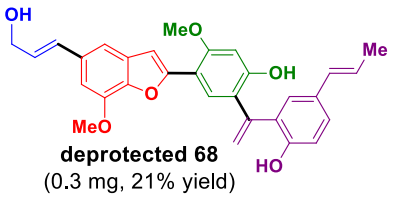
deprotected 66
(1.1 mg, 38% yield)

Deprotection condition 2 was followed to give **deprotected 66** (1.1 mg, 38% yield). TLC (40% EtOAc/pentane): R_f = 0.46, visualized by shortwave UV; ^{1}H-NMR (500 MHz, acetone-d_6): δ 7.81 (s, 1H), 7.18-7.14 (m, 3H), 7.10 (d, J = 1.0 Hz, 1H), 6.90 (d, J = 1.0 Hz, 1H), 6.82 (dd, J = 7.5, 1.5 Hz, 1H), 6.67 (s, 1H), 6.46 (dd, J = 16, 1.5 Hz, 1H), 6.30 (dd, J = 15.5, 1.0 Hz, 1H), 6.24 (dq, J = 15.5, 6.5 Hz, 1H), 6.04 (dq, J = 15.5, 6.5 Hz, 1H), 5.70 (d, J = 1.5 Hz, 1H), 5.67 (d, J = 2.0 Hz, 1H), 3.98 (s, 3H), 3.96 (s, 3H), 1.85 (dd, J = 7.0. 2.0 Hz, 3H), 1.78 (dd, J = 6.5, 1.5 Hz, 3H); HRMS (ESI+) calculated for $C_{30}H_{29}O_5[M+H]^+$ *m/z* 469.2015, found 469.2014.



deprotected 67
(0.039 mg, 14% yield)

Deprotection condition 2 was followed to give **deprotected 67** (0.039 mg, 14% yield). The yield of the deprotection of **78** was determined by ^{1}H-NMR using an internal standard. ^{1}H-NMR (500 MHz, acetone-d_6): δ 7.78 (s, 1H), 7.60 (d, J = 1 Hz, 1H), 7.40 (d, J = 8 Hz, 1H), 7.33 (dd, J = 8.5, 1.5 Hz, 1H), 7.19-7.17 (m, 3H), 6.82 (d, J = 9 Hz, 1H), 6.70-6.68 (m, 2H), 6.37 (dt, J = 16, 5.5 Hz, 1H), 6.31 (dd, J = 15.5, 1 Hz, 1H), 6.05 (dq, J = 15.5, 6.5 Hz, 1H), 5.69 (d, J = 2 Hz, 1H), 5.66 (d, J = 2 Hz, 1H), 4.24 (dd, J = 5, 2 Hz, 2H), 3.99 (s, 3H), 1.78 (dd, J = 6.5, 1.5 Hz, 3H); HRMS (ESI+) calculated for $C_{29}H_{27}O_5$ $[M+H]^+$ *m/z* 455.1858, found 455.1866.

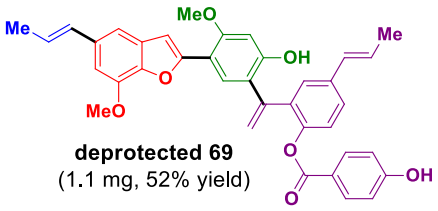


deprotected 68
(0.3 mg, 21% yield)

Deprotection condition 2 was followed to give **deprotected 68** (0.3 mg, 21% yield). TLC (40% EtOAc/pentane): R_f = 0.48, visualized by shortwave UV; ^{1}H-NMR (500 MHz, acetone-d_6): δ 7.81 (s, 1H), 7.18 – 7.14 (m, 4H), 6.97 (d, J = 1.0 Hz, 1H), 6.82 (dd, J = 7.0, 1.5 Hz, 1H), 6.67 – 6.63 (m, 2H), 6.37 (dt, J = 16, 5.5 Hz, 1H), 6.30 (dd, J = 15.5, 1.5 Hz, 1H), 6.04 (dq, J = 16.0, 7.0 Hz, 1H), 5.69 (d, J = 2.0 Hz, 1H), 5.66 (d, J = 2.0 Hz, 1H), 4.23 (d, J = 4.5 Hz, 2H), 3.98 (s, 3H), 3.98 (s, 3H), 1.78 (dd, J = 6.5, 2.0 Hz, 3H); HRMS (ESI+) calculated for $C_{30}H_{29}O_6$ $[M+H]^+$ *m/z* 485.1964, found 485.1952.

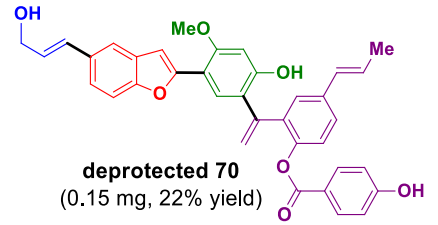
Deprotection condition 3 (for library members **69-71**)

To a 1-mL Reacti-vial™ containing the protected library member and a PTFE-coated magnetic stir bar was added CsF (25-30 equiv) and 18-crown-6 (2 equiv) followed by DMSO in a glovebox. The vial was sealed with a cap and stirred at 50 °C for 14 hours. The reaction was then cooled to room temperature, diluted with 8 mL EtOAc and washed with a solution of 1:1 saturated NH_4Cl/H_2O (8 mL). The aqueous layer was extracted with 4 mL EtOAc. The combined organic layers were washed with H_2O (2 × 4 mL), then with brine (8 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography.



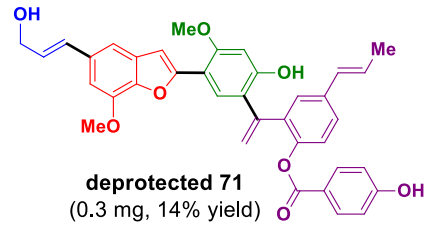
deprotected 69
(1.1 mg, 52% yield)

Deprotection condition 3 was followed to give **deprotected 69** (1.1 mg, 52% yield). TLC (40% EtOAc/pentane): R_f = 0.39, visualized by shortwave UV; ^{1}H-NMR (500 MHz, acetone-d_6): δ 7.85 (app d, J = 9.0 Hz, 2H), 7.81 (s, 1H), 7.43 (dd, J = 8.5, 2.5 Hz, 1H), 7.33 (d, J = 2.5 Hz, 1H), 7.18 (d, J = 8.5 Hz, 1H), 7.12 – 7.10 (m, 2H), 6.92 (d, J = 1.5 Hz, 1H), 6.84 (app d, J = 9.0 Hz, 2H), 6.55 (s, 1H), 6.49 – 6.42 (m, 2H), 6.30 – 6.21 (m, 2H), 5.62 (d, J = 2.0 Hz, 1H), 5.58 (d, J = 1.5 Hz, 1H), 3.97 (s, 3H), 3.96 (s, 3H), 1.86 (dd, J = 6.5, 1.5 Hz, 3H), 1.83 (dd, J = 7.0, 2.0 Hz, 3H); HRMS (ESI+) calculated for $C_{37}H_{33}O_7$ $[M+H]^+$ *m/z* 589.2226, found 589.2224.



deprotected 70
(0.15 mg, 22% yield)

Deprotection condition 3 was followed to give **deprotected 70** (0.15 mg, 22% yield). TLC (60% EtOAc/pentane): R_f = 0.24, visualized by shortwave UV; ^{1}H-NMR (500 MHz, acetone-d_6): δ 7.82 (app d, J = 8.5 Hz, 2H), 7.77 (s, 1H), 7.60 (d, J = 1.5 Hz, 1H), 7.43 (dd, J = 8.0, 2.0 Hz, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.35-7.33 (m, 2H), 7.17 (d, J = 8.5 Hz, 1H), 7.15 (d, J = 1.0 Hz, 1H), 6.83 (app d, J = 9.0 Hz, 2H), 6.69 (app d, J = 16.0 Hz, 1H), 6.56 (s, 1H), 6.44 (d, J = 16 Hz, 1H), 6.38 (dt, J = 16.0, 5.5 Hz, 1H), 6.27 (dq, J = 16, 6.5 Hz, 1H), 5.61 (d, J = 1.5 Hz, 1H), 5.58 (d, J = 2.0 Hz, 1H), 4.25-4.24 (m, 2H), 3.97 (s, 3H), 1.84 (dd, J = 6.5, 1.5 Hz, 3H); HRMS (ESI+) calculated for $C_{36}H_{31}O_7$ $[M+H]^+$ *m/z* 575.2070, found 575.2070.



deprotected 71
(0.3 mg, 14% yield)

Deprotection condition 3 was followed to give **deprotected 71** (0.3 mg, 14% yield). TLC (60% EtOAc/pentane): R_f = 0.23, visualized by shortwave UV; ^{1}H-NMR (500 MHz, acetone-d_6): δ 7.85 (dt, J = 8.5, 2.0 Hz, 2H), 7.81 (s, 1H), 7.43 (dd, J = 8.0, 2.0 Hz, 1H), 7.33 (d, J = 2.0 Hz, 1H), 7.18-7.17 (m, 2H), 7.13 (s, 1H), 6.98 (s, 1H), 6.84 (dt, J = 9.0, 2.0 Hz, 2H), 6.66 (app d, J = 16.0 Hz, 1H), 6.55 (s, 1H), 6.44 (dd, J = 16.5, 1.5 Hz, 1H), 6.37 (dt, J = 16.0, 5.5 Hz, 1H), 6.27 (dq, J = 16.0, 6.5 Hz, 1H), 5.62 (d, J = 1.5 Hz, 1H), 5.58 (d, J = 1.5 Hz, 1H), 4.25-4.24 (m, 2H), 3.99 (s, 3H), 3.96 (s, 3H), 1.83 (dd, J = 6.5, 1.5 Hz, 3H); HRMS (ESI+) calculated for $C_{37}H_{33}O_8$ $[M+H]^+$ *m/z* 605.2175, found 605.2167.

8. Synthesis of cyclic targets 10-14 (Figure 4) using Automated Procedures III and IV

Automated Procedure IV - *Cartridge Preparation*

Unless otherwise noted, "cartridge" refers to a 12-g Luknova column capped with a 12-g Luknova column screw cap. Additionally, the Second-Generation procedure makes use of custom 40 mL reaction vials which are fitted at their bottom with ground-glass joints designed to fit into a Luer lock and at their tops with threads to allow for sealing with septum-top screw caps.

- **First Deprotection Cartridges** are the 40 mL reaction vials described above. They contain solid starting MIDA boronate and solid NaOH.
- **Second and Third Deprotection Cartridges** are the 40 mL reaction vials described above. They contain solid NaOH.
- **Predrying Cartridges** are not used in **Automated Procedure IV**.
- **Drying Cartridges** contain 4.2 g Na_2SO_4, topped with the plunger from a 5 mL syringe.
- **Concentration/Deoxygenation Cartridges** are empty.
- **First Reaction Cartridges** are the 40 mL reaction vials described above, and contain a PTFE-coated magnetic stir bar, coupling partner, catalyst, ligand, and base. These cartridges have no frit at their base. The Luer port at the bottom is packed with a small piece of Kimwipe (so that solids are retained in the vial during weighing). The top of the vial is capped with a screw-top rubber septum cap. This septum is pierced with a 1.5 inch 18 G needle which is connected to an empty 4 g Luknova column (capped with a 4 g Luknova column screw cap connected to a source of dry nitrogen). Additionally, the cap is tethered to the screw cap topping the Reaction Filtration Cartridge via PTFE tubing (1/16-inch I.D., 1/8-inch O.D.) This tubing is adjusted in such a way to be ~5 mm above the base of the reaction vessel, and is used to transfer the crude reaction mixture to the Reaction Filtration Cartridge.
- **Reaction Filtration Cartridges** contain 1.0 g Celite™ and 0.5 g Florisil® which have been thoroughly mixed. This is tethered to the First Reaction Cartridge as described above.
- **Second and Third Reaction Cartridges** contain a PTFE-coated magnetic stir bar, coupling partner, catalyst and ligand, and base.
- **Precipitation Cartridges** contain a PTFE-coated magnetic stir bar, Celite™ (150 mg), and 3-aminopropyl functionalized silica gel (250 mg). Hexanes (10 mL) is added and the cartridge is swirled vigorously to suspend and homogenize the mixture of solids. The stir bar and solids are allowed to settle over 30 seconds and the supernatant hexanes is pushed out of the cartridge with an overhead pressure of air. The stir bar is now embedded in the mixture of solids wet with hexanes.
- **Silica Gel Plugs** contain silica gel, tightly packed, and topped with a 4-g Luknova column frit. This is capped with a 4-g Luknova column screw cap, using four layers of PTFE tape on the sealing insert to ensure a leak-free seal.

Automated Procedure IV - *Experimental Details*

- **Deprotection**

In the deprotection module, to a Deprotection Cartridge containing starting MIDA boronate (1.0 mmol) and NaOH (3.0 mmol, 120 mg) is added 3 mL THF followed by 3 mL water. This solution is then agitated by bubbling argon through the solution for 20 minutes at room temperature while open to the air. After the reaction is completed, argon is then continually

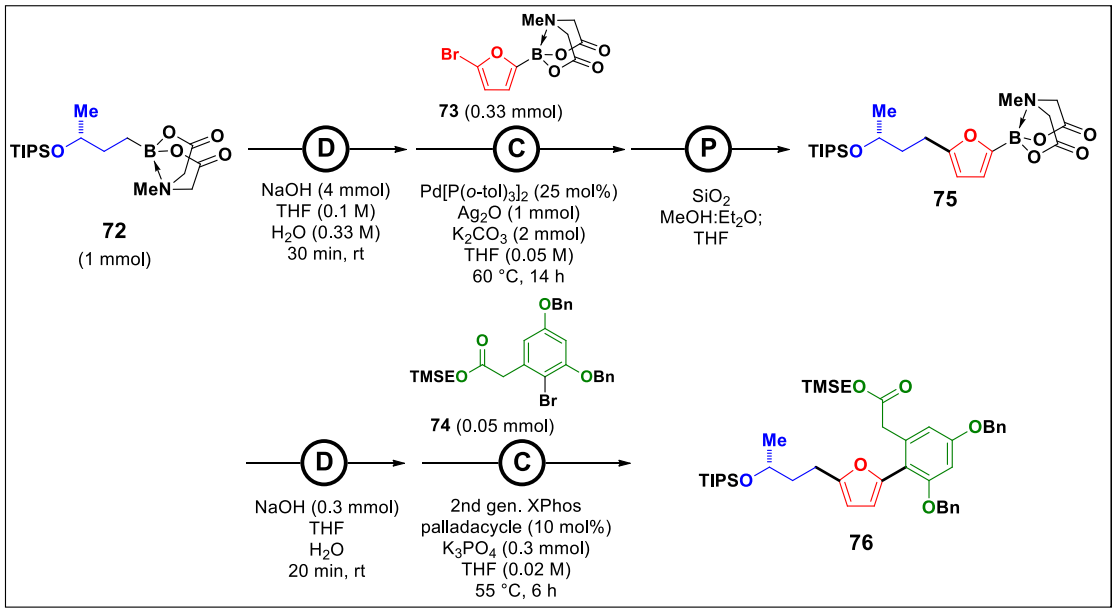
bubbled through the solution for 1 hour to remove THF, leaving a primarily aqueous solution of what is presumed to be the trihydroxyborate salt. After concentration, sat. NH_4Cl (3 mL) is added to quench the reaction, causing a white precipitate to form. After briefly agitating, diethyl ether (4 mL) is added to extract the boronic acid from the aqueous layer. This biphasic mixture is then agitated via argon sparging (60 seconds) before removing the aqueous layer from the Deprotection Cartridge. The organic layer is then moved to the Drying Cartridge via the primary pump. The aqueous layer is then replaced into the Deprotection Cartridge. The ether extraction procedure is repeated twice more (12 mL total) before disposing of the aqueous layer. The ethereal boronic acid solution is then dried in the Drying Cartridge via the repeated injection and withdrawal of the solution (20 repetitions). The solution is then passed into the Concentration/Deoxygenation Cartridge before washing the contents of the Drying Cartridge with 2 mL diethyl ether. The solution is then concentrated to ~2 mL before solvent switching by adding THF (4 mL) and then concentrating to ~2 mL. Another portion of THF (4 mL) is added before concentrating to the volume required for the subsequent coupling reaction.

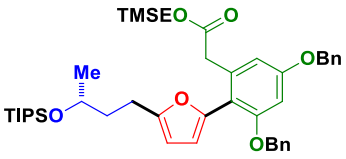
- **Coupling**

In the coupling module, a Reaction Cartridge is charged with bifunctional halo-MIDA boronate or capping halide building block, ligand and/or catalyst in a glovebox. The Cartridge is warmed to the appropriate temperature before having the THF solution of boronic acid added in a single portion.

- **Purification**

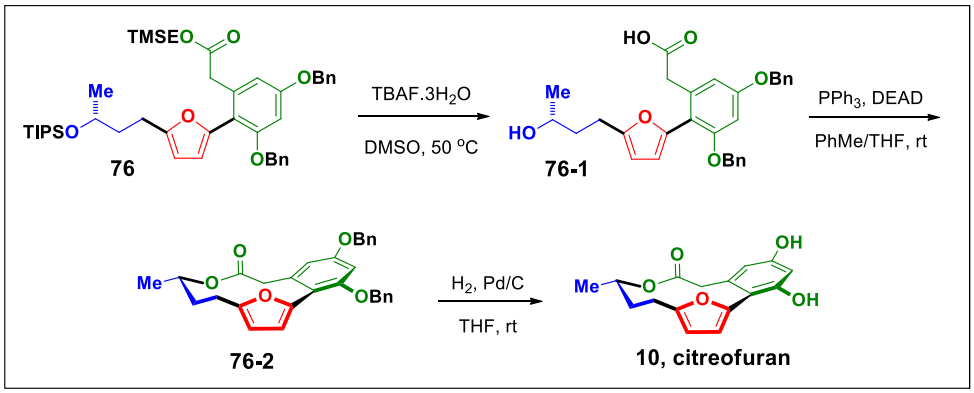
In the purification module, the crude reaction mixture is added to a Reaction Filtration Cartridge and 12 mL hexanes is added to the Precipitation Cartridge/Silica Gel Plug. Then, a 3 mL portion of the filtered crude reaction mixture is added to the Precipitation Cartridge and the solvent is removed from the cartridge, loading any crude reaction product onto the Silica Gel Plug ("catch"). This process is performed a total of ten times, using 3 mL THF to wash the Reaction and Reaction Filtration Cartridges for each cycle. Then, 12 mL of 1.5% MeOH in Et_2O are added and the solvent is removed three times (36 mL total). Then, 12 mL of Et_2O are added and the solvent is removed three times (36 mL total). Finally, 12 mL THF are added and slowly removed (to increase residence time in the column), giving a purified solution of MIDA boronate **4**. The solution is then moved to an empty Concentration/Deoxygenation Cartridge and concentrated to 3 mL before being added to the next Deprotection Cartridge.

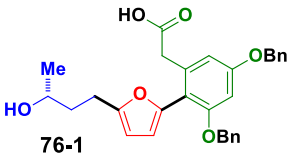




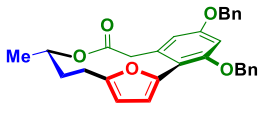
76

Automated Procedure III was followed with the following modifications: In the first deprotection reaction, 4 mmol of NaOH were used and the reaction was run for 30 minutes. In the first coupling reaction, the concentration was 0.05 M with respect to **73**, 1 mmol of Ag_2O, 2 mmol of K_2CO_3, and 25 mol% of $Pd[P(o\text{-tol})_3]_2$ were used, the addition of the boronic acid was performed over 1 minute, and the reaction was run at 60 °C for 14 hours. In the second deprotection reaction, 0.3 mmol of NaOH were used. In the second coupling reaction, the concentration was 0.02 M with respect to **74**, 0.3 mmol of K_3PO_4 and 10 mol% of 2nd generation XPhos palladacycle were used, and the reaction was run for 6 hours in a 7-mL glass vial. For the purification steps, the Et_2O:MeOH eluent (1.5% MeOH in Et_2O) was diluted 50% with hexanes. This automated cycle was performed 6 times to accumulate **76** as a slightly yellow residue (88.4 mg total; average of 14.7 mg, 0.020 mmol, 39% yield). HPLC (Agilent Prep-C18, 10 µm, 30 x 150 mm (product number: 413910-302), 25 mL/min, gradient: A = MeCN, B = EtOAc, 0 min: 100% A, 0% B; 1 min: 100% A, 0% B; 10 min: 90% A, 10% B; 25 min: 90% A, 10% B; 25.5 min: 100% A, 0% B): 18.5 min; ^{1}H-NMR (500 MHz, acetone-d_6): δ 7.50-7.48 (m, 2H), 7.43-7.39 (m, 4H), 7.37-7.32 (m, 3H), 7.31-7.28 (m, 1H), 6.77 (d, J = 2.5 Hz, 1H), 6.68 (d, J = 2.5 Hz, 1H), 6.37 (d, J = 3.0 Hz, 1H), 6.10 (d, J = 3.0 Hz, 1H), 5.14 (s, 2H), 5.13 (s, 2H), 4.14-4.08 (m, 3H), 3.64 (d, J = 1.5 Hz, 2H), 2.75 (t, J = 8.0 Hz, 2H), 1.92-1.80 (m, 2H), 1.24 (d, J = 6.5 Hz, 3H), 1.09-1.08 (m, 21H), 0.98-0.95 (m, 2H), 0.03 (s, 9H); ^{13}C-NMR (125 MHz, acetone-d_6): δ171.6, 160.2, 158.8, 155.8, 148.1, 138.2, 138.1, 137.1, 129.3, 129.1, 128.7, 128.5, 128.4, 128.0, 115.4, 112.0, 110.2, 106.6, 100.3, 70.9, 70.6, 68.7, 63.0, 40.9, 38.8, 24.5, 23.8, 18.6, 18.5, 17.9, 13.2, -1.5 ; HRMS (ESI+) calculated for $C_{44}H_{63}O_6Si_2$ $[M+H]^+$ *m/z* 743.4163, found 743.4166.





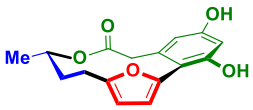
A 7 mL vial containing protected seco acid **76** (85.6 mmol, 0.115 mmol, 1 equiv) and a stir bar was charged with TBAF·3H_2O (185 mg, 0.586 mmol, 5.1 equiv) in the glovebox. The vial was sealed with a septum cap and brought out of the glovebox. DMSO (2.3 mL) was added via syringe and the reaction was stirred at 50 °C for 70 min in a heating block. The reaction was cooled to room temperature, then partitioned between H_2O (20 mL) and Et_2O (20 mL). After mixing thoroughly and separating the phases (both phases should become clear), the aqueous layer was extracted with Et_2O (20 mL, then with 10 mL). The combined organics were washed with brine, dried over $MgSO_4$, filtered and concentrated to ~ 5mL. Celite was added to the solution and the crude product was adsorbed onto celite *in vacuo*. The celite pad was loaded onto a florisil column (5 cm length, 2 cm diameter) equilibrated with 60% EtOAc/hexanes. The impurities were eluted with 80% EtOAc/hexanes + 0.1% AcOH. The product was eluted with 80% EtOAc/hexanes + 0.2% AcOH. The fractions containing the product were concentrated to ~ 5 mL and then azeotroped with n-heptane to remove residual AcOH. After complete removal of solvent, the residue was triturated with 1:5 DCM:pentane, causing an off-white solid to precipitate. The suspension was then concentrated *in vacuo* and dried under high vacuum to give an off-white fluffy solid as the product **76-1** (41 mg, 73%). ^{1}H-NMR matches literature data (*29*).



76-2

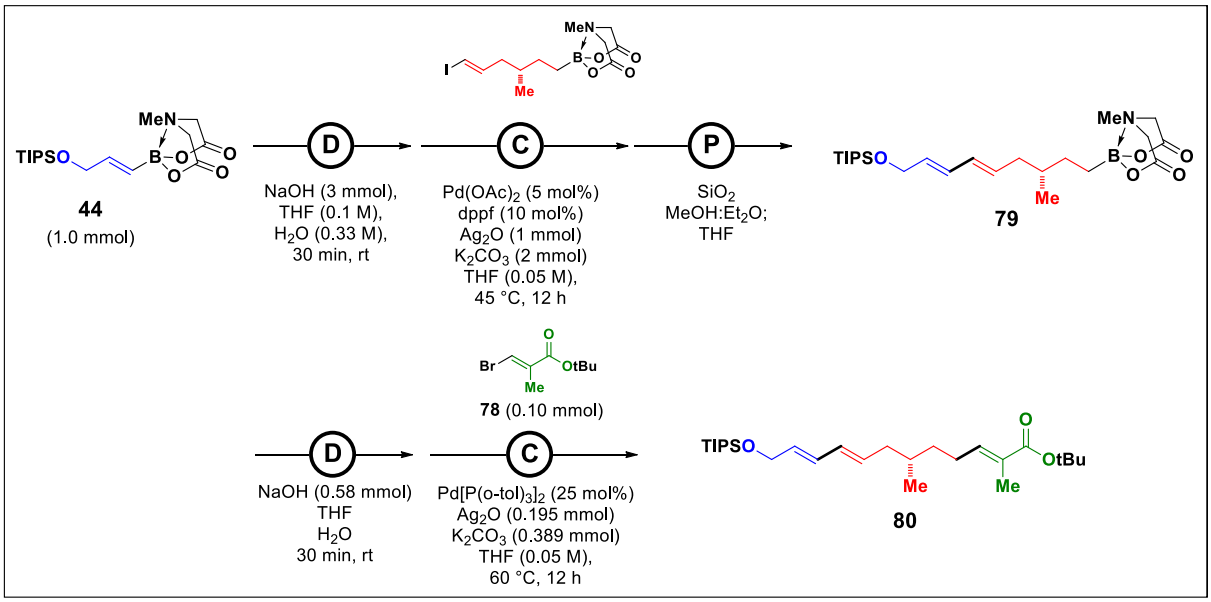
The following procedure is modified from a known literature procedure (*29*). A dry 40 mL vial equipped with a stir bar was charged with PPh_3 (99.2 mg, 0.378 mmol, 5.05 equiv). The vial was sealed with a septum cap, evacuated and filled with N_2 (×3). THF (2.5 mL) was added, followed by PhMe (5 mL). A dry 7 mL vial was charged with seco acid **76-1** (36.4 mg, 0.0748 mmol, 1 equiv), sealed with a septum cap, evacuated and filled with N_2 (×3). THF (0.4 mL) and PhMe (2 mL) was added. Diethyl azodicarboxylate solution (40 wt% in PhMe, 0.17 mL, 0.374 mmol, 5 equiv) was then added to the 40 mL vial via syringe, giving a very light yellow solution. A 3 mL syringe was charged with 1.2 mL of the seco acid solution, which was added to the 40 mL vial

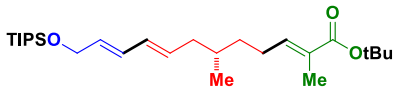
over 6 h with the aid of a syringe pump. The reaction was then stirred for another 1 h. Another portion of PPh_3 (99.2 mg, 0.378 mmol, 5.05 equiv) was added as a solid. The vial was flushed briefly with N_2 and re-sealed with a septum cap. Another portion of diethyl azodicarboxylate solution (40 wt% in PhMe, 0.17 mL, 0.374 mmol, 5 equiv) was added. The 3 mL syringe was then charged with the remaining seco acid solution and added to the reaction over 5 h. The reaction was then stirred for another 5 h. THF (0.3 mL) was used to rinse out the 7 mL vial, adding the rinse to the reaction over 1h. The reaction was stirred for another 3.5 h, then transferred to a recovery flask, rinsing with EtOAc. Celite was added and the crude product adsorbed *in vacuo*. The crude product was purified by silica gel column (hexanes to 5% to 10% to 15% EtOAc/hexanes) to give an off-white solid as the pure product **76-2** (12.4 mg, 35%). TLC (30% Et_2O/hexanes): R_f = 0.28, visualized by short wave UV; ^{1}H-NMR matches literature data (*29*). Supplementary ^{1}H-NMR: (500 MHz, $CDCl_3$): δ 7.43-7.38 (m, 4H), 7.35-7.31 (m, 4H), 7.29-7.27 (m, 2H), 6.55 (d, *J* = 2.5 Hz, 1H), 6.57 (d, *J* = 2.0 Hz, 1H), 6.31 (d, *J* = 3.0 Hz, 1H), 6.09 (d, *J* = 3.0 Hz, 1H), 5.30-5.24 (m, 1H), 5.09 (d, *J* = 11.5 Hz, 1H), 5.05 (d, *J* = 12.5 Hz, 1H), 5.04 (d, *J* = 11.5 Hz, 1H), 5.00 (d, *J* = 12.0 Hz, 1H), 3.28 (dd, *J* = 17.0, 14.5 Hz, 2H), 2.83 (ddd, *J* = 15.5, 6.5, 2.5 Hz, 1H), 2.73 (ddd, *J* = 15, 11.5, 2.5 Hz, 1H), 2.07-2.03 (m, 1H), 1.86-1.79 (m, 1H), 1.27 (d, J = 6.5 Hz, 3H).



10, citreofuran

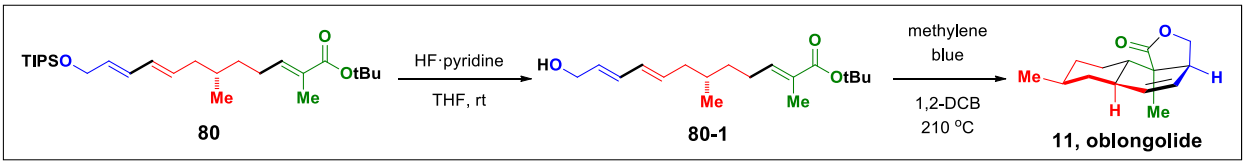
In an unoptimized procedure, a solution of the dibenzyl ether **76-2** (12.1 mg, 0.0258 mmol) in a 7 mL vial was charged with 10% Pd/C (2 mg) The vial was sealed with a septum cap and H_2 gas was bubbled through the stirring suspension for 8 min from a balloon. The outlet needle was removed and the reaction was stirred under H_2 atmosphere at room temperature. After 1 h, another portion of 10% Pd/C (1.4 mg) was added to the reaction. The vial was flushed with H_2 for 3 min, then left to stir. After another 2 h, a third portion of 10% Pd/C (5 mg) was added and the reaction was left to stir for another 25 min. The reaction was then purged with N_2 for 5 min, then filtered through celite, rinsing with EtOAc. The filtrate was concentrated in vacuo, azeotroping once with CH_2Cl_2. The crude product was purified by silica gel chromatography (20% to 30% to 40% EtOAc/pentane) to give a mixture of citreofuran and the tetrahydrofuran side product arising from reduction of the furan ring. The pure product **10** (0.99 mg, 13%) was obtained after HPLC purification (Agilent Prep-C18, 10 µm, 30 x 150 mm, product number: 413910-302, 25 mL/min, gradient: 40% to 70% EtOH/H_2O in 25 min) ^{1}H-NMR matches literature data (*29*).

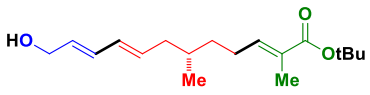




80

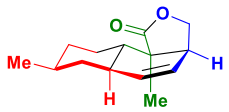
Automated Procedure III was followed with the following details/modifications: In the first coupling reaction, the concentration was 0.05 M with respect to building block **77** (0.33 mmol), 5 mol% of $Pd(OAc)_2$, 10 mol% of dppf, 1 mmol of Ag_2O, and 2 mmol of K_2CO_3 were used, the addition of the boronic acid was performed over 1 minute, and the reaction was run at 45 °C for 12 hours. In the second deprotection reaction, 0.58 mmol of NaOH was used and the reaction was run for 30 minutes. In the second coupling reaction, 25 mol% of $Pd[P(o\text{-}tol)_3]_2$, 0.195 mmol of Ag_2O, and 0.389 mmol of K_2CO_3 were used. The addition of the boronic acid was performed over <1 minute, and the reaction was run at 60 °C for 12 hours. The crude reaction mixture was purified by two rounds of column chromatography (10% Et_2O/hexanes; 20% to 30% to 35% to 45% DCM/hexanes). This automated procedure was performed 2 times to accumulate **80** as a slightly yellow residue (19.4 mg total, average 9.7 mg, 0.022 mmol, 21% average yield). TLC (40% CH_2Cl_2/hexanes): R_f = 0.25, visualized by UV, stained by $KMnO_4$; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.64 (dt, J = 7.5, 1.5 Hz, 1H), 6.32-6.27 (m, 1H), 6.13-6.08 (m, 1H), 5.72-5.64 (m, 2H), 4.31 (app d, J = 4.5 Hz, 2H), 2.25-2.10 (m, 3H), 2.01-1.95 (m, 1H), 1.76 (d, J = 1.5 Hz, 3H), 1.57 (sextet, J = 6.5 Hz, 1H), 1.50-1.43 (m, 10 H), 1.30-1.24 (m, 1H), 1.14-1.06 (m, 21H), 0.92 (d, J = 7.0 Hz, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 167.6, 141.2, 132.3, 131.2, 130.5, 129.7, 129.0, 79.9, 63.7, 40.0, 35.2, 33.0, 28.1, 26.3, 19.4, 18.0, 12.3, 12.0; HRMS (ESI+) calculated for $C_{27}H_{50}O_3SiNa$ $[M+Na]^+$ m/z 473.3427, found 473.3430.





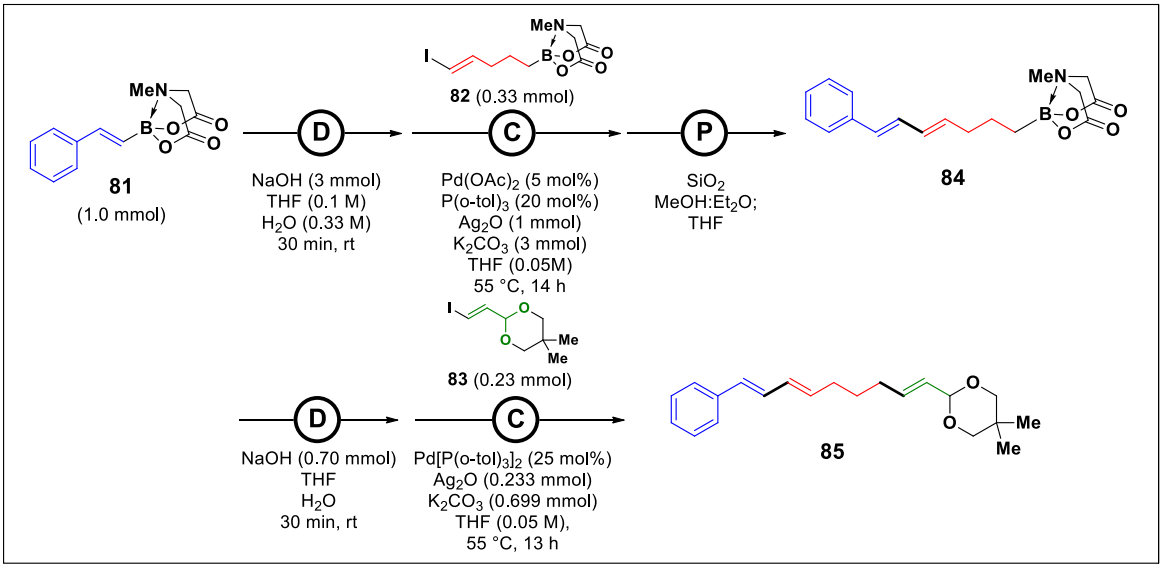
80-1

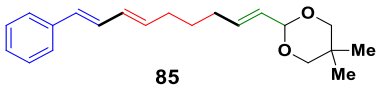
To a polyethylene vial containing a solution of **80** in THF (0.4 mL) was added HF·pyridine (0.09 mL), followed by THF (0.3 mL). The vial was capped and stirred at room temperature for 3 h. The reaction was quenched with the dropwise addition of saturated aqueous $NaHCO_3$ (5 mL). The mixture was stirred for 5 min, then transferred to a separatory funnel saturated aqueous $NaHCO_3$ (3 mL), rinsing with Et_2O (8 mL). After mixing and phase separation, the aqueous layer was extracted with Et_2O (4 mL × 2). The combined organics were washed with H_2O, brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*, azeotroping once with CH_2Cl_2. The crude product was purified by silica gel chromatography (30% to 40% Et_2O/pentane) to give a colorless liquid as the product **80-1** (7.3 mg, 60%). TLC (50% Et_2O/hexanes): R_f = 0.32, visualized by UV, stained by $KMnO_4$; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.63 (td, *J* = 7.5, 1.5 Hz, 1H), 6.23 (dd, *J* = 15.0, 10.0 Hz, 1H), 6.04 (dd, *J* = 15.0 Hz, 10.5 Hz, 1H), 5.73 (dt, *J* = 15.5 Hz, 6.0 Hz, 1H), 5.67 (dt, *J* = 15.0, 7.5 Hz, 1H), 4.17 (app d, *J* = 5.5 Hz, 1H), 2.20-2.08 (m, 3H), 1.99-1.93 (m, 1H), 1.78 (d, *J* = 1.0 Hz, 3H), 1.56-1.41 (m, 11H), 1.33 (t, *J* = 9.5 Hz, 1H), 1.27-1.21 (m, 1H), 0.89 (d, *J* = 6.5 Hz, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 167.6, 141.2, 133.7, 131.9, 130.8, 129.6, 129.0, 79.9, 63.5, 40.0, 35.2, 32.9, 28.1, 26.3, 19.4, 12.3; HRMS (ESI+) calculated for $C_{18}H_{30}O_3Na$ $[M+Na]^+$ *m/z* 317.2093, found 317.2096.



11, oblongolide

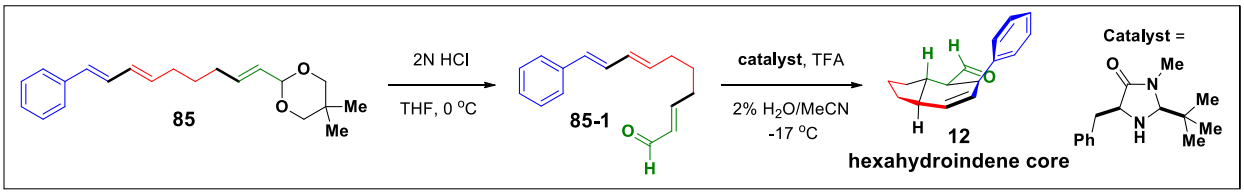
The following procedure is modified from a known literature procedure (*30*): A Schlenk bomb containing alcohol **80-1** (7.3 mg, 0.0248 mmol) and a stir bar was charged with 1,2-dichlorobenzene (2.5 mL) under a stream of N_2. Methlyene blue (~ 1 mg) was added, forming a blue solution. The solution was degassed with 6 freeze-pump-thaw cycles. The flask was sealed under vacuum, then warmed to room temperature and placed in a sand bath and warmed to ~150 °C. The reaction temperature was allowed to equilibrate for another 15 min before introducing N_2 gently into the reaction vessel. The vessel was sealed again and stirred at 200-210 °C (bath temperature). The reaction was stirred for a total of 68 h at that temperature. The reaction was cooled to room temperature, then transferred to a 15 mL rbf, rinsing with CH_2Cl_2. The CH_2Cl_2 was removed by rotary evaporation. The remaining solvent was removed by distillation under vacuum, giving a blue residue. The crude product was loaded onto a silica gel column equilibrated with 10% Et_2O/pentane. The product was eluted with 20% Et_2O/pentane. This semi-purified product was purified on a second silica gel column (100% CH_2Cl_2) to give oblongolide **11** as a white solid (1.3 mg, 24%) in 85-90% purity. ^{1}H-NMR matches literature data (*30*). Supplementary data: ^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.61 (d, *J* = 10.0 Hz, 1H), 5.55 (ddd, *J* = 10.0, 4.5, 2.5 Hz, 1H), 4.39 (t, *J* = 9.0 Hz, 1H), 3.83 (dd, *J* = 11.0, 8.5 Hz, 1H), 2.75-2.70 (m, 1H), 1.96-1.74 (m, 3H), 1.52-1.45 (m, 1H), 1.35-1.21 (m, 3H), 1.14 (s, 3H), 0.97-0.84 (m, 4H), 0.79 (q, *J* = 12.3 Hz, 1H)

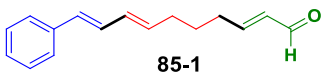




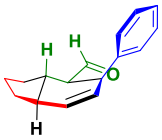
85

Automated Procedure III was followed with the following modifications: In the first coupling reaction, the concentration was 0.05 M with respect to **82**, 1 mmol of Ag_2O, 3 mmol of K_2CO_3, 5 mol% of $Pd(OAc)_2$, and 20 mol% of P(*o*-tol)$_3$ were used, the addition of the boronic acid was performed over 1 minute, and the reaction was run at 55 °C for 14 hours. In the second deprotection reaction, 0.7 mmol NaOH were used and the reaction was run for 30 minutes. In the second coupling reaction, vinyl iodide **83** was weighed into a clean, dry 7 mL vial in a glove box, sealed and removed immediately prior to the reaction, and was then washed into the reaction vial using THF (1 mL) in an automated fashion. The concentration was 0.05 M with respect to **83** (0.233 mmol), 0.233 mmol of Ag_2O, 0.699 mmol of K_2CO_3, and 25 mol% of $Pd[P(o\text{-tol})_3]_2$ were used, the addition of the boronic acid was performed over <1 minute, and the reaction was run at 55 °C for 13 hours in a 7-mL glass vial. For the purification steps, the Et_2O:MeOH eluent (1.5% MeOH in Et_2O) was diluted 50% with hexanes. This automated cycle was performed 9 times to give 48.9 mg of crude linear precursor **85** as a slightly yellow residue. This was purified by two rounds of column chromatography (5% to 10% to 20% Et_2O/hexanes; 5% acetone/hexanes) to yield 18.8 mg of linear precursor **85**. TLC (80% CH_2Cl_2/hexanes): R_f = 0.35, visualized by UV, stained by $KMnO_4$; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.37 (app d, J = 8 Hz, 2H), 7.30 (app t, J = 7.5 Hz, 2H), 7.19 (t, J = 7.0 Hz, 1H), 6.74 (dd, J = 15.5, 10.5 Hz, 1H), 6.44 (d, J = 16 Hz, 1H), 6.21 (dd, J = 15, 10.5 Hz, 1H), 5.93 (dt, J = 15.5, 7.0 Hz, 1H), 5.80 (dt, J = 15.5, 7.0 Hz, 1H), 5.59 (ddt, J = 16.0, 5.5, 1.0 Hz, 1H), 4.85 (d, J = 5.0 Hz, 1H), 3.65 (d, J = 11.5 Hz, 2H), 3.50 (d, J = 10.5 Hz, 2H), 2.17 (q, J = 7.0 Hz, 2H), 2.12 (q, J = 7.0 Hz, 2H), 1.55 (quint, J = 7.5 Hz, 2H), 1.22 (s, 3H), 0.74 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 137.8, 135.6, 135.3, 131.0, 130.3, 129.5, 128.7, 127.3, 127.2, 126.3, 101.4, 77.4, 32.4, 31.7, 30.2, 28.3, 23.1 22.1; HRMS (ESI+) calculated for $C_{21}H_{29}O_2$ $[M+H]^+$ *m/z* 313.2168, found 313.2156.



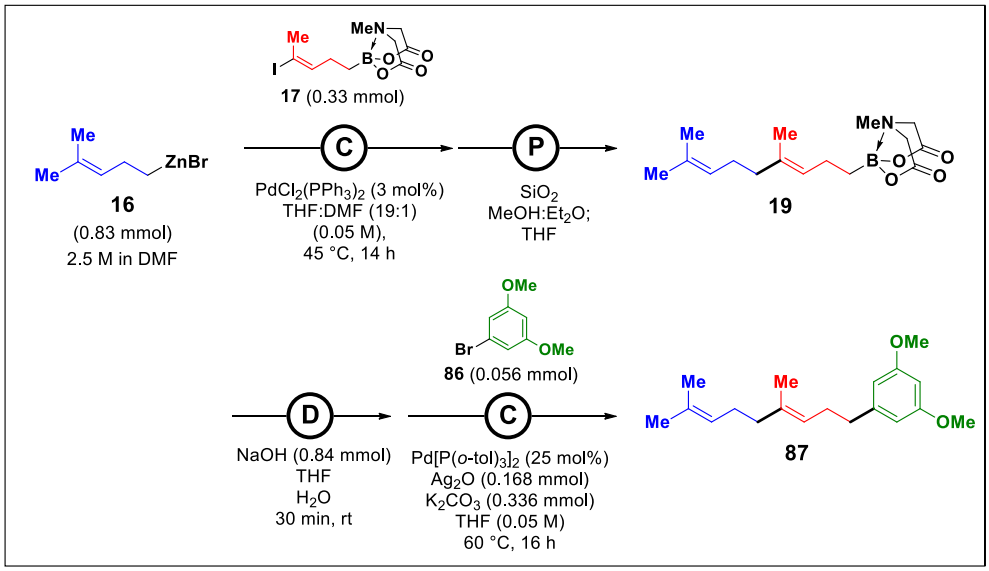


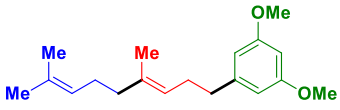
To a solution of ketal **85** (18.8 mg, 0.0602 mmol) in THF (2 mL) in a 7 mL vial was added 2N HCl (1 mL) dropwise under ambient atm at 0 °C. The addition was completed in less than 1 min. The vial was capped with a PTFE-lined cap and stirred at 0 °C for 2 h 10 min. The reaction was quenched with the slow addition of saturated aqueous $NaHCO_3$ (2 mL) at the same temperature. The mixture was stirred vigorously until bubbling ceased. The mixture was then transferred to a separatory funnel containing saturated aqueous $NaHCO_3$ (5 mL) and Et_2O (5 mL), rinsing with Et_2O (5 mL). After mixing and phase separation, the aqueous layer was extracted with Et_2O (2 × 5 mL). The combined organics were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* at room temperature. The crude product was taken up in a minimum amount of 60% DCM/pentane and loaded onto a silica gel column equilibrated with 60% DCM/pentane. The crude product was purified by silica gel chromatography (60% to 70% DCM/pentane) to afford the product **85-1** as a single isomer (8.5 mg, 62%). ^{1}H-NMR matches literature data (*32*). Supplementary ^{1}H-NMR (500 MHz, $CDCl_3$): δ 9.52 (d, J = 8.0 Hz, 1H), 7.38 (app d, J = 8.0 Hz, 2H), 7.31 (app t, J = 7.5 Hz, 2H), 7.21 (d, J = 7.5 Hz, 1H), 6.86 (dt, J = 15.5, 6.5 Hz, 1H), 6.75 (dd, J = 15.5, 10.0 Hz, 1H), 6.47 (d, J = 15.5 Hz, 1H), 6.23 (dd, J = 15.0, 10.5 Hz, 1H), 6.14 (ddt, J = 15.5, 6.5, 1.0 Hz, 1H), 5.79 (dt, J = 15.0, 7.5 Hz, 1H), 2.38 (app q, J = 7.0 Hz, 2H), 2.22 (app q, J = 8.0 Hz, 2H), 1.67 (quint, J = 7.5 Hz, 1H).



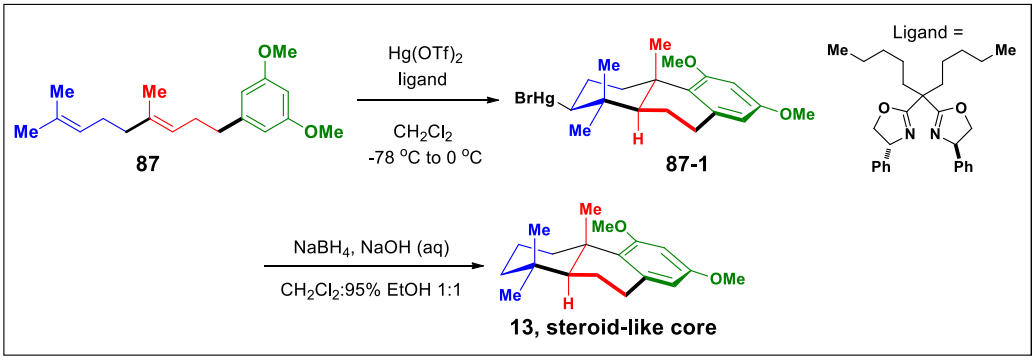
12, hexahydroindene core

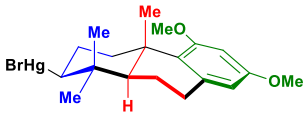
The following procedure is modified from a published procedure (*32*): A solution of imidazolidinone catalyst (29.4 mg, 0.118 mmol) in MeCN (1.2 mL) in a 7 mL vial was cooled to -35 °C in a dry ice/ethylene glycol/EtOH bath with stirring. TFA (9 µL, 0.118 mmol) and H_2O (24 µL) were added. The solution was stirred for 5 min at the same temperature. 75 µL of this solution was then added to the 2 mL vial containing aldehyde **85-1**. The vial was capped with a PTFE-lined cap and left to stand in a -18 °C freezer for 39 h. The reaction was then warmed to room temperature and loaded directly onto a silica gel column equilibrated with 5% EtOAc/pentane, rinsing with a small amount of the same solvent mixture. The product was eluted with 5% EtOAc/pentane. The fractions containing the product were concentrated *in vacuo* at room temperature to give the product **12** as a crystalline solid (6.7 mg, 79% yield). The d.r. was determined to be 17:1 ^{1}H-NMR. The e.r. was determined to be 95.5:4.5 by chiral HPLC (Chiralcel-OD-H, 15% IPA/hexane isocratic elution, flow rate = 0.75 mL/min, t_r (minor) = 5.33 min, t_r (major) = 5.85 min). ^{1}H-NMR matches reported literature data (*32*).





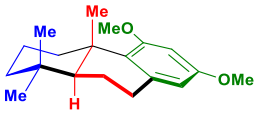
Automated Procedure III was followed with the following modifications: In the first coupling reaction, 0.33 mL of a freshly prepared solution of **16** in DMF (~2.5 M) was added manually to the First Reaction Cartridge, the concentration was 0.05 M with respect to **17**, 3 mol% of $PdCl_2(PPh_3)_2$ was used, and the reaction was run at 45 °C for 14 hours. Furthermore, the Reaction Filtration Cartridge contained only 300 mg of Celite™ and after filtration, the crude reaction underwent an automated aqueous quench (6 mL saturated aqueous NH_4Cl + 1 mL water) followed by an automated drying process before being purified. In the second deprotection reaction, 0.84 mmol of NaOH were used and the reaction was run for 30 minutes. In the second coupling reaction, 0.168 mmol of Ag_2O, 0.336 mmol of K_2CO_3, and 25 mol% of $Pd[P(o\text{-tol})_3]_2$ were used, the addition of the boronic acid was performed over 1 minute, and the reaction was run at 60 °C in a 7-mL glass vial. For the purification steps, the Et_2O:MeOH eluent (1.5% MeOH in Et_2O) was diluted 50% with hexanes. This automated cycle was performed 4 times to accumulate **87** as a slightly yellow residue (14.8 mg total; average of 3.7 mg, 0.013 mmol, 23% yield). TLC (hexanes): R_f = 0.31, visualized by UV, stained with $KMnO_4$; HPLC (Sunfire Prep-C18, 5 µm, 30 x 150 mm (product number: 186002797), 25 mL/min, gradient: A = water, B = MeCN, 0 min: 50% A, 50% B; 15 min: 5% A, 95% B; 25 min: 5% A, 95% B; 25.5 min: 50% A, 50% B): 19.5 min; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.36 (d, J = 2.5 Hz, 2H), 6.30 (t, J = 2.5 Hz, 1H), 5.18 (tq, J = 7.0, 1.5 Hz, 1H), 5.09 (tdt, J = 6.0, 1.9, 1.0 Hz, 1H), 3.78 (s, 6H), 2.58 (dd, J = 9.1, 6.7 Hz, 2H), 2.29 (q, J = 8.0 Hz, 2H), 2.09-1.96 (m, 4H), 1.68 (d, J = 1.0 Hz, 3H), 1.60 (s, 3H), 1.58 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 160.8, 145.0, 135.9 131.5, 124.4, 123.7, 106.6, 97.8, 55.4, 39.9, 36.6, 29.9, 26.9, 25.8, 17.8, 16.2; HRMS (ESI+) calculated for $C_{19}H_{29}O_2$ $[M+H]^+$ m/z 289.2168, found 289.2175.





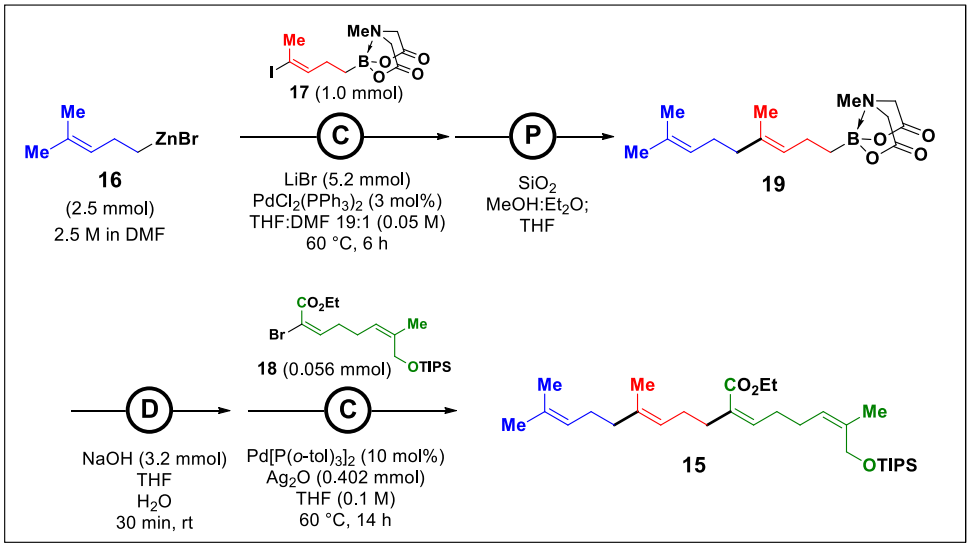
87-1

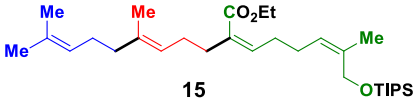
To an oven-dried 20 mL vial equipped with a magnetic stir bar was added $Hg(OTf)_2$ (28.2 mg, 0.057 mmol, 1.1 equiv.) and ligand (*33*) (28.2 mg, 0.063 mmol, 1.2 equiv.). The vial was purged with Ar thrice and charged with CH_2Cl_2 (4.7 mL). The catalyst solution was then allowed to stir vigorously at room temperature for 20 min at which point it was cooled to -78 °C in an IPA/dry ice bath. After 7 min, linear precursor **87** (14.8 mg, 0.051 mmol, 1.0 equiv.) in CH_2Cl_2 (0.5 mL) was added to the reaction mixture dropwise via syringe over 3 min, giving a bright yellow solution. The reaction mixture was allowed to stir at -78 °C for 1 h at which point the IPA/dry ice bath was replaced with a water/ice bath. The reaction mixture was allowed to slowly warm to 0 °C with stirring over 2 h then quenched with the addition of a pre-mixed solution of sat. NaBr (aq): sat. $NaHCO_3$ (aq) : H_2O (5 mL, 1:2:2) at 0 °C. The ice bath and Ar inlet were removed and reaction mixture was allowed to warm to room temperature with stirring over 45 min. The mixture was transferred to a 40 mL vial, rinsing with CH_2Cl_2 and H_2O. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford a pale yellow solid which was loaded onto Celite as a CH_2Cl_2 slurry and purified by SiO_2 chromatography (hexanes to 4:1 hexanes:EtOAc) to afford organomercury bromide **87-1** as a white crystalline solid (23.1 mg; 79% yield). Enhancement of ee by recrystallization was achieved by dissolving the solid organomercury bromide in warm EtOAc (5 mL) and diluting with warn hexanes (50 mL), and storing at -20 °C for 24 h. The resulting mother liquor was concentrated *in vacuo* to afford enantioenriched **87-1** (16.7 mg; 57% yield). TLC (4:1 Hexanes:EtOAc): $R_f = 0.50$, visualized by UV, stained with CAM; ^{1}H-NMR matches literature data (*33*). Supplementary ^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.27 (d, J = 2.7 Hz, 1H), 6.18 (d, J = 2.7 Hz, 1H), 3.75 (s, 6H), 3.18 (dt, J = 13.5, 3.6 Hz, 1H), 2.92 – 2.78 (m, 3H), 2.27 (qd, J = 13.7, 3.4 Hz, 1H), 1.97 (dq, J = 14.0, 3.8 Hz, 1H), 1.81 (dd, J = 12.9, 5.7 Hz, 1H), 1.67 – 1.57 (m, 1H), 1.38 (d, J = 11.6 Hz, 1H), 1.31 (s, 3H), 1.20 (td, J = 13.4, 3.7 Hz, 1H), 1.15 (s, 3H), 1.13 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 159.6, 158.1, 138.7, 129.2, 104.8, 97.7, 56.5, 55.3, 55.1, 40.2, 39.8, 38.9, 37.2, 33.6, 29.9, 27.6, 26.5, 20.9, 19.9; HRMS (ESI+) calculated for $C_{19}H_{28}O_2BrHg$ $[M+H]^+$ *m/z* 569.0979, found 569.0980.



13, steroid-like core

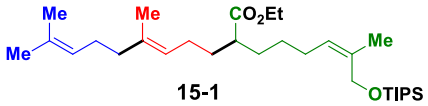
To an oven-dried 2 mL vial containing organomercury bromide **87-1** (16.7 mg, 29.5 μmol, 1.0 equiv), equipped with a magnetic stir bar, and purged with Argon thrice was added CH_2Cl_2 (147 μL) and EtOH (147 μL). $NaBH_4$ (4.4M in 14M NaOH, 33.4 μL; 5.0 equiv) was added dropwise via syringe at room temperature causing the reaction mixture to turn dark gray. The reaction mixture was allowed to stir at room temperature for 2 hours at which point it was diluted with Et_2O and transferred to a 40 mL vial rinsing with H_2O and Et_2O. The layers were separated and aqueous layers extracted with Et_2O (2 × 10 mL). The combined organics were washed with brine (2 × 10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford a yellow oil with white precipitate. This crude material was loaded onto Celite as a CH_2Cl_2 slurry and purified by SiO_2 chromatography (hexanes to 2.5% EtOAc in hexanes) to afford **13** as a white solid (3.5 mg; 41% yield, 90:10 e.r.) (*36*). The e.r. was determined by chiral HPLC (Chiralcel OD-H, t_r = 17.70 min (major); 18.97 min (minor); flow rate = 0.3 mL/min, 0.3% IPA in Hexanes for 30 min. Detected at λ= 254 nm.). TLC (5% EtOAc in hexanes): R_f = 0.31, visualized by UV, stained with CAM; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.28 (d, J = 2.6 Hz, 1H), 6.19 (d, J = 2.6 Hz, 1H), 3.75 (s, 6H), 3.09 – 3.01 (app dt, J = 13.2, 3.2 Hz, 1H), 2.89 – 2.77 (m, 2H), 1.79 (app dd, J = 6.0, 13.2 Hz, 1H), 1.70 (qt, J = 13.5, 3.6 Hz, 1H), 1.60 – 1.40 (m, 3H), 1.27 (s, 3H), 1.33-1.25 (m, 1H), 1.18 (dtd, J = 30.0, 13.0, 3.9 Hz, 2H), 0.95 (s, 3H), 0.92 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 159.8, 157.9, 139.0, 130.5, 104.9, 97.7, 55.2 (2C), 53.5, 41.7, 39.2, 36.9, 34.0, 33.9, 33.7, 22.3, 20.2, 19.6, 19.1; HRMS (ESI+) calculated for $C_{19}H_{29}O_2$ $[M+H]^+$ *m/z* 289.2162, found 289.2168.





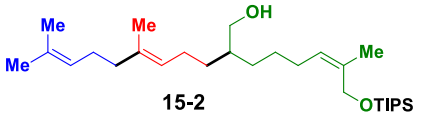
Automated Procedure IV was followed with the following modifications: In the first coupling reaction, 1.0 mL of a freshly prepared solution of **16** in DMF (2.5 M, 2.5 mmol) was added manually to the First Reaction Cartridge, the concentration was 0.05 M with respect to **17** (1 mmol), 3 mol% of $PdCl_2(PPh_3)_2$ and 5.2 eq LiBr was used, and the reaction was run at 60 °C for

6 hours. Furthermore, the Reaction Filtration Cartridge contained only 300 mg of Celite™ and after filtration, the crude reaction underwent an automated aqueous quench (6 mL saturated aqueous NH_4Cl + 1 mL water) followed by an automated drying process before being purified. In the second deprotection reaction, 3 mmol of NaOH were used and the reaction was run for 30 minutes. In the second coupling reaction, 0.402 mmol of Ag_2O and 10 mol% of $Pd[P(o\text{-tol})_3]_2$ were used, the addition of the boronic acid was performed over 1 minute, and the reaction was run at 60 °C for 14 hours in a 7-mL glass vial. This automated cycle was performed 3 times to accumulate **15** as a slightly yellow residue (37.5 mg total; average of 12.5 mg, 0.025 mmol, 28% yield). NMR and MS data matches that of product from manual synthesis (Section 1).



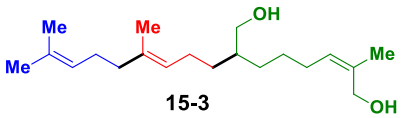
15-1

In the glovebox, the 7 mL vial containing **15** (34.6 mg, 0.0685 mmol, 1 equiv) and a stir bar was charged with Mg turnings (70.5 mg, 2.90 mmol, 42.3 equiv). The vial was sealed with a septum cap and brought out of the glovebox and placed under N_2. MeOH (1.4 mL) was added via syringe and the mixture was sonicated for 2 min, then stirred at rt with an N_2 inlet needle. Note: an exotherm formed as the Mg turnings dissolved, but the reaction was not cooled. The reaction was stirred for 16 h, then quenched with the addition of sat. aq. NH_4Cl (2 mL). The mixture was transferred to a separatory funnel, rinsing with Et_2O (10 mL) and H_2O (5 mL). After mixing and phase separation, the aqueous layer was extracted with Et_2O (2 x 5 mL). The combined organics were washed with H_2O (10 mL), brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was taken up in CH_2Cl_2, filtered through a pad of Na_2SO_4 and concentrated *in vacuo*. After drying under high vacuum, the material was re-subjected to the above reaction conditions to consume the remaining starting material. After the same work-up procedure described above, the desired reduced product **15-1** was obtained as a 4:1 mixture of ethyl:methyl ester (29.1 mg, 84% yield). This material was used without further purification. NMR data matches that of product from manual synthesis (Section 1).



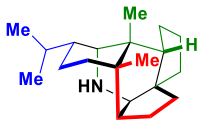
15-2

The 7 mL vial containing ester **15-1** (27.6 mg, 0.0544 mmol, 1 equiv) was charged with a stir bar and sealed with a septum cap. The vial was vac-filled with N_2 (× 3). THF (1.1 mL) was added via syringe and the solution cooled to -25 °C in a dry ice/ethylene glycol/ethanol bath. DIBAl-H (1M in hexanes, 0.27 mL, 0.27 mmol, 4.96 equiv) was added dropwise. The reaction was stirred at – 20 °C for 2 h. The reaction was quenched by adding sat. Rochelle's salt solution (1.5 mL) was dropwise at -20 °C. Et_2O (1.5 mL) was then added. The mixture was stirred vigorously for 10 min, then H_2O (1 mL) and Et_2O (1mL) were added. After stirring for another 10 min, the mixture was transferred to a separatory funnel, rinsing with H_2O (8mL) and Et_2O (8 mL). After mixing and phase separation, the aqueous layer was extracted with Et_2O (2 x 5 mL). The combined organics were washed with H_2O, brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (5% to 10% to 20% Et_2O/hexanes) to give the product **15-2** as a colorless oil (22.5 mg, 89% yield). NMR data matches that of product from manual synthesis (Section 1).



15-3

To a solution of **15-2** (22.3 mg, 0.048 mmol) in THF (0.75 mL) and pyridine (0.25 mL) in a polyethylene vial equipped with a stir bar was added HF·pyridine (0.18 mL) dropwise at 0 °C. The vial was purged with N_2, and sealed with a screw cap. The reaction was gradually warmed to rt. After 5 h, another portion of HF·pyridine (0.05 mL) was added to the reaction at rt. The reaction was then stirred for another 1.5 h, then quenched by the slow addition of sat. aqueous $NaHCO_3$ (3 mL). The mixture was transferred to a separatory funnel containing sat. aq. $NaHCO_3$ (10 mL), rinsing with Et_2O (10 mL). After mixing and phase separation, the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organics were washed with H_2O, brine, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by silica gel chromatography (20% to 30% to 40% EtOAc/hexanes) to give the pure product **15-3** as a colorless oil (13.7 mg, 93% yield). NMR data matches that of product from manual synthesis (Section 1).



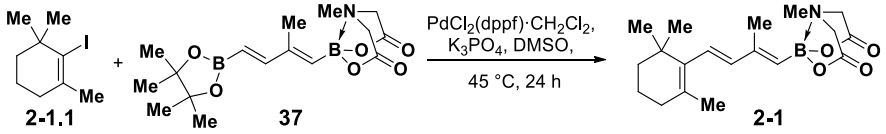
(±)-14, secodaphnane core

The following procedure was modified from a published procedure: To a Schlenk tube sealed with a rubber septum and vac-filled with N_2 (3×) was added CH_2Cl_2 (0.3 mL) followed by DMSO (30 µL, 0.386 mmol, 8.7 equiv). The solution was cooled to -78 °C in a dry ice/acetone bath. Oxalyl chloride (2.0 M in CH_2Cl_2, 90 µL, 0.18 mmol, 4.05 equiv) was added dropwise via syringe. The resulting solution was stirred at -78 °C for 30 min. A solution of diol **15-3** (13.7 mg, 0.0444 mmol, 1.0 equiv) in CH_2Cl_2 (0.3 mL) in a 7 mL vial was added dropwise to the reaction flask via syringe, rinsing with CH_2Cl_2 (0.3 mL). The solution was stirred for 20 min at – 78 °C, then NEt_3 (45 µL, 0.32 mmol, 7.25 equiv) was added into the reaction dropwise. The reaction was stirred for 5 min at the same temperature, then the cold bath was removed and the reaction stirred at room temperature for another 45 min. TLC showed complete conversion of the diol. The reaction was cooled to 0 °C in an ice/water bath. Dry $MeNH_2$ gas was then passed above the reaction solution over 4 min via an inlet needle with an outlet needle, causing an increase in reaction volume and dissolution of the solids. The reaction was stirred for 4 h, gradually warming to room temperature in the ice/water bath. The flask was then opened to the Schlenk line, causing evaporation of the dissolved $MeNH_2$. The solvent was removed under a stream of N_2, giving a yellow oily solid. The rubber septum was quickly replaced with a new septum under positive N_2 flow, and the residue was dried under high vacuum overnight. The flask was filled with N_2. Dry AcOH (0.7 mL) was added to dissolve the brown residue. The solution was stirred at 80 °C (oil bath temperature) for 8.5 h. The reaction was cooled to room temperature and transferred to an Erlenmeyer flask equipped with a stir bar, rinsing with CH_2Cl_2 (10 mL). The solution was cooled to 0 °C in an ice/water bath. 3N NaOH was added dropwise with stirring until pH>10 (approx. 4.4 mL). The mixture was transferred to a separatory funnel, rinsing with CH_2Cl_2 (5 mL). After phase separation the pH was adjusted to 14 with 2 drops of 3N NaOH. The aqueous phase was then extracted with CH_2Cl_2 (2 × 3 mL). The combined organics were washed with saturated $NaHCO_3$ (aq), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (20-40% EtOAc/pentane) to give the

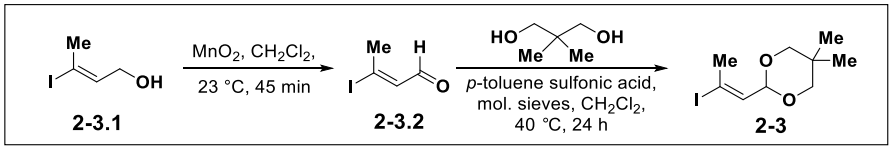
product as a colorless oil (6.0 mg, 47% yield). NMR data matches that of product from manual synthesis (Section 1).

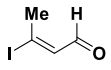
9. Synthesis of building blocks

a. Synthesis of building blocks for **2**



The following reaction was run in duplicate. In a glovebox, to a 40-mL vial charged with vinyl iodide **2-1.1** (*37*) (914 mg, 3.66 mmol, 1.2 equiv.) and bisborylated diene **37** (*38*) (1064 mg, 3.05 mmol, 1.0 equiv.) was added $PdCl_2(dppf)\cdot CH_2Cl_2$ (125 mg, 0.153 mmol, 5 mol%), K_3PO_4 (3884 mg, 18.3 mmol, 6.0 equiv.), and DMSO (20 mL, 0.15 M). The vial was sealed with a PTFE-lined cap and removed from the glovebox. The vial was placed in a 45 °C aluminum heat block and maintained at that temperature with stirring for 24 hours. The reaction was cooled to 23 °C and transferred to a separatory funnel, diluting with EtOAc (50 mL). The organic layer was washed with brine:H_2O (1:1, 2 x 50 mL) to remove DMSO, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude material was adsorbed onto Celite™ from an acetone solution and purified by silica gel chromatography (hexanes:EtOAc 1:1 → EtOAc) to afford **2-1** as a pale yellow solid (1.0 g, 48% yield). TLC (EtOAc): R_f = 0.45, stained by $KMnO_4$; ^{1}H-NMR (500 MHz, acetone-d_6): δ 6.17 (d, J = 16.5 Hz, 1H), 6.11 (d, J = 16.5 Hz, 1H), 5.34 (s, 1H), 4.21 (d, J = 16.5 Hz, 2H), 4.04 (d, J = 17.0 Hz, 2H), 3.03 (s, 3H), 1.98 (s, 3H), 1.98-2.01 (m, 2H), 1.67 (s, 3H), 1.58-1.62 (m, 2H), 1.45-1.47 (m, 2H), 1.00 (s, 6H); ^{11}B-NMR (128 MHz, acetone-d_6): δ 15.8; ^{13}C-NMR (125 MHz, acetone-d_6): δ 169.0, 148.7, 141.2, 138.3, 129.3, 127.1, 62.3, 47.3, 40.2, 34.7, 33.4, 29.2, 21.8, 19.8, 15.4; HRMS (ESI+) calculated for $C_{19}H_{29}O_4NB$ $[M+H]^+$ *m/z* 346.2190, found 346.2192.

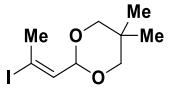




2-3.2

2-3.2 is known, but synthesized via a different method and characterization has not been reported. **2-3.2** was thus synthesized using the following procedure: Crotyl alcohol **2-3.1** (*39,40)* (1.08 g, 5.54 mmol, 1.0 equiv.) and activated MnO_2 (14 g, 30 equiv.) was weighed into a 100-mL round-bottom flask equipped with a PTFE-coated magnetic stir bar and topped with a rubber septum and purged with N_2. Dichloromethane (50 mL, 0.11 M) was added to the round-bottom flask and the resulting reaction mixture was stirred at 23 °C for 45 minutes. After 45 minutes, the reaction mixture was filtered through a plug of silica gel and Celite™ and concentrated *in vacuo* to afford **2-3.2** as a yellow oil (*41*) (500 mg, 46% yield). TLC (petroleum ether:diethyl ether

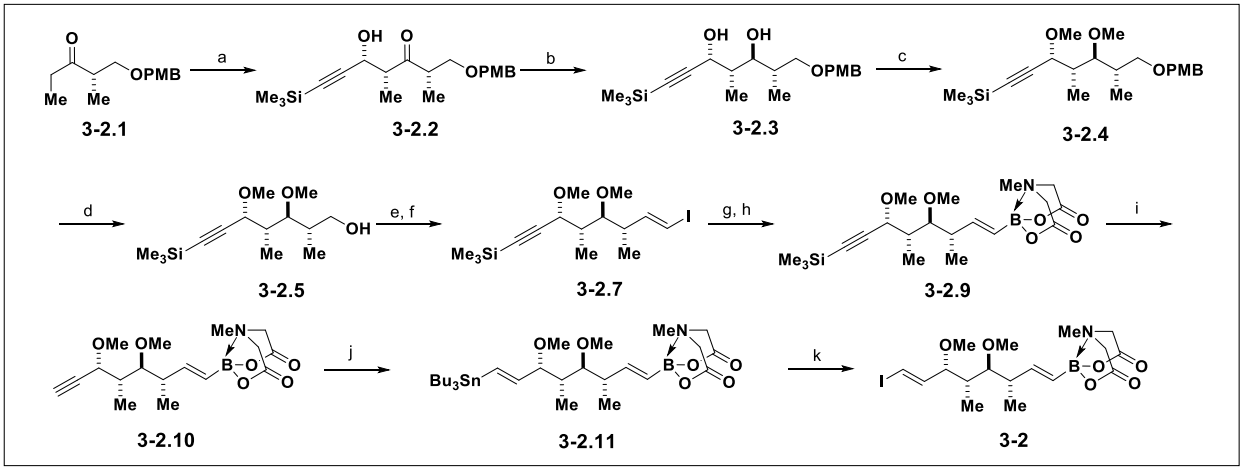
4:1): R_f = 0.51, stained by $KMnO_4$; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 9.79 (d, *J* = 6.5 Hz, 1H), 6.84-6.86 (m, 1H), 3.00 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 185.9, 141.8, 126.1, 29.9; HRMS (ESI+) calculated for C_4H_6OI $[M+H]^+$ *m/z* 196.9463, found, 196.9468.



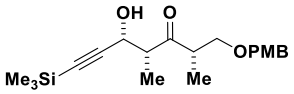
2-3

2-3.2 (150 mg, 0.77 mmol, 1.0 equiv.), neopentyl glycol (797 mg, 7.7 mmol, 10.0 equiv.), and *p*-toluene sulfonic acid (15 mg, 0.08 mmol, 0.1 equiv.) was charged in a 40-mL vial equipped with a PTFE-coated magnetic stir bar. The vial was sealed with a PTFE-lined cap and purged with N_2. Dichloromethane (15 mL, 0.05 M) was added to the vial and the resulting mixture was stirred for 1 minutes until homogeneous. Activated 4 Å powdered molecular sieves (300 mg, 2:1 weight ratio to aldehyde) were added to the vial to afford a cloudy white solution. The resulting reaction mixture was stirred at 40 °C for 24 hours. After 24 hours, the reaction mixture was filtered through a filter funnel and concentrated *in vacuo*. The resulting white solid was adsorbed onto Celite™ from an acetone solution and purified by silica gel chromatography (4:1 petroleum ether:ether) to afford **2-3** as a pale yellow oil (150 mg, 69% yield). TLC (petroleum ether:diethyl ether 4:1): R_f = 0.71, stained by $KMnO_4$; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.27 (d, *J* = 6.0 Hz, 1H), 5.02 (d, *J* = 6.0 Hz, 1H), 3.64 (d, *J* = 11.5 Hz, 2H), 3.88 (d, *J* = 11.0 Hz, 2H), 2.51 (s, 3H), 1.20 (s, 3H), 0.74 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$); δ 138.0, 102.0, 97.9, 30.0, 29.1, 22.9, 21.9; HRMS (ESI+) calculated for $C_9H_{16}O_2I$ $[M+H]^+$ *m/z* 283.0195, found 283.0200.

b. Synthesis of building blocks for **3**

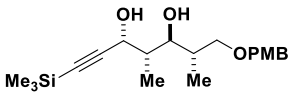


Conditions: (a) 3-(trimethylsilyl)propiolaldehyde, $Sn(OTf)_2$, NEt_3, CH_2Cl_2, -78 °C, 2 h; (b) $Me_4NBH(OAc)_3$, MeCN/AcOH 2:1, -25 °C, 16 h; (c) Me_3OBF_4, proton sponge, CH_2Cl_2, 23 °C, 2.5 h; (d) $(NH_4)_2Ce(NO_3)_6$, MeCN/H_2O, 10:1, 23 °C, 1 h; (e) Dess-Martin periodinane, CH_2Cl_2, 0 °C to 23 °C, 1.5 h; (f) CHI_3, $CrCl_2$, THF, 0 °C to 23 °C, 3 h. (g) n-BuLi, THF, $B(OMe)_3$, -78 °C; 1N HCl; (h) N-methyliminodiacetic acid, benzene/DMSO 10:1, 80 °C, 2 h; (i) $AgNO_3$, 2,6-lutidine, acetone/H_2O 1:1, 0 °C, 2.5 h; (j) $HSnBu_3$, Pd_2dba_3, RuPhos, CH_2Cl_2, 23 °C; (k) I_2, CH_2Cl_2, 23 °C.



3-2.2

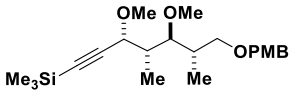
To a 500-mL Schlenk flask charged with $Sn(OTf)_2$ (112.5 mmol, 46.9 g) was added CH_2Cl_2 (500 mL) and triethylamine (120 mmol, 16.7 mL) dropwise. The resulting orange-brown suspension was cooled to -78 °C. To the stirred mixture was added (S)-1-(p-methoxybenzyloxy)-2-methylpentan-3-one (**3-2.1**) (75.0 mmol, 17.8 g, 2.00 mL) as a neat liquid over 15 minutes. The mixture was stirred for 2 hours at -78 °C. To the mixture was added 3-(trimethylsilyl)propiolaldehyde (*42*) (112.5 mmol, 14.2 g) as a neat liquid over 20 minutes. The mixture was stirred for an additional 3 hours at -78 °C. The reaction was quenched by pouring the mixture slowly into saturated aqueous NH_4Cl (300 mL) cooled in an ice bath, rinsing with additional CH_2Cl_2. The mixture was stirred vigorously for 10 minutes, then filtered through Celite™ to remove the tin(II) salts. The filtrate was transferred to a 2-L separatory funnel and the phases separated. The organic phase was washed with saturated aqueous NH_4Cl (200 mL). The combined aqueous phases were extracted with CH_2Cl_2 (200 mL). The combined organic phases were washed with H_2O (200 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford a yellow-brown oil. This residue was subjected to flash chromatography on silica gel (EtOAc:hexanes 8:100 → 20:100) to afford **3-2.2** as a colorless oil (36.71 g, 73% yield). TLC (20% EtOAc/hexanes): R_f = 0.22, stained by $KMnO_4$; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.5 (app d, *J* = 8.5 Hz, 2H), 6.87 (app d, *J* = 8.5 Hz, 2H), 4.78 (d, *J* = 3.5 Hz, 1H), 4.43 (d, *J* = 11.5 Hz, 1H), 4.36 (d, *J* = 11.5 Hz, 1H), 3.79, (s, 3H), 3.58 (app t, *J* = 9 Hz, 1H), 3.41 (dd, *J* = 9, 5 Hz, 1H), 3.14 (m, 1H), 2.92, (dq, *J* = 7.5, 3 Hz, 1H), 1.26 (d, *J* = 7.5 Hz, 3H), 1.01 (d, *J* = 7 Hz, 3H), 0.17 (s, 9H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 216.1, 159.3, 129.5, 129.3, 113.8, 104.0, 90.2, 73.1, 63.3, 55.2, 51.7, 44.7, 13.5, 10.5, -0.2; HRMS (ESI+) calculated for $C_{20}H_{30}O_4NaSi$ $[M+Na]^+$ *m/z* 385.1811, found 385.1808.



3-2.3

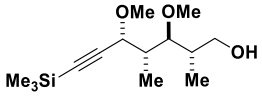
To a 1-L, 3-neck, round-bottom flask charged with tetramethylammonium triacetoxyborohydride (298 mmol, 78.30 g) was added dry acetic acid (240 mL) and MeCN (400 mL). The resulting homogeneous solution was cooled to -30 °C and stirred for 30 minutes. To the stirred solution was added **3-2.2** (71.6 mmol, 25.95 g), dropwise over 1 minute, as a solution in MeCN (50 mL + 50 mL rinse). The solution was stirred and allowed to slowly warm to 0 °C over 13 h. The reaction was then poured into aqueous dibasic sodium tartrate solution (0.5 M, 400 mL) and stirred for 1 hour. The solution was transferred into a separatory funnel, and Et_2O was added. After mixing and phase separation, the aqueous layer was extracted with Et_2O. The combined organic phase was washed with saturated aqueous $NaHCO_3$ (2 × 200 mL), then brine (20 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Toluene was added to azeotrope most of the remaining acetic acid prior to silica gel purification. The residue obtained after concentration was subjected to flash chromatography on silica gel (EtOAc:hexanes:AcOH 10:90:2 → 20:80:2) to afford **3-2.3** as a pale yellow oil (18.51 g, 71% yield). Chromatographic purification was carried out again to obtain an analytically pure sample (colorless oil). TLC (30% EtOAc/hexanes): R_f = 0.39, stained by $KMnO_4$; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.22 (app d, *J* = 8.5 Hz, 2H), 6.87 (app d, *J* = 8.5 Hz, 2H), 4.65 (d, *J* = 2.5 Hz, 1H),

4.46 (d, J = 11 Hz, 1H), 4.45 (d, J = 11.5 Hz, 1H), 3.80, (s, 3H), 3.73-3.68 (m, 2H), 3.45 (dd, J = 9.5, 5.5 Hz, 1H), 2.00-1.94, (m, 2H), 1.03 (t, J = 7 Hz, 6H), 0.17 (s, 9H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 159.4, 129.4, 129.3, 113.9, 105.6, 89.6, 80.1, 73.6, 73.4, 66.0, 55.2, 40.6, 34.9, 14.8, 12.8, -0.1; HRMS (ESI+) calculated for $C_{20}H_{33}O_4Si$ $[M+H]^+$ *m/z* 365.2148, found 365.2152.



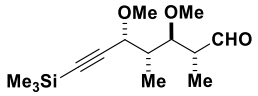
3-2.4

To a 1-L Schlenk flask charged with **3-2.3** (25.8 mmol, 9.40 g) was added CH_2Cl_2 (450 mL). To the stirred solution was added Proton Sponge (141.9 mmol, 38.70 g) as a solid in one portion, then trimethyloxonium tetrafluoroborate (180.6 mmol, 38.70 g) as a solid in one portion. The mixture was stirred at 23 °C for 16 hours. The orange mixture was filtered and the solid was rinsed with additional CH_2Cl_2 (100 mL). The filtrate was concentrated *in vacuo* to ~50 mL, during which a solid precipitated. To this suspension was added Et_2O (300 mL), mixed and filtered, rinsing with 150 mL Et_2O. The filtrate was transferred to a 1-L separatory funnel and washed with 0.5 M HCl (2 × 250 mL). The aqueous phase was extracted with 100 mL Et_2O. The combined organics were neutralized with saturated aqueous $NaHCO_3$ (200 mL) and washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to give a yellow oil. The oil was subjected to flash chromatography on silica gel (EtOAc:hexanes 1:20 → 1:10) to afford **3-2.4** as a colorless oil (5.37 g, 53% yield). TLC (10% EtOAc/hexanes): R_f = 0.33, stained by $KMnO_4$; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.25 (app d, J = 8.5 Hz, 2H), 6.89 (app d, J = 8.5 Hz, 2H), 4.44 (d, J = 11.5 Hz, 1H), 4.38 (d, J = 11.5 Hz, 1H), 4.21 (d, J = 3 Hz, 1H), 3.80, (s, 3H), 3.57 (dd, J = 9.5, 5 Hz, 1H), 3.41 (s, 3H), 3.39, (s, 3H), 3.27 (dd, J = 9.0, 8.0 H, 1H), 3.13 (dd, J = 10.0, 2.5 Hz, 1H), 2.10 – 2.04, (m, 1H), 1.94 – 1.88 (m, 1H), 1.09 (d, J = 7.0 Hz, 3H), 1.01 (d, J = 7.5 Hz, 3H), 0.18 (s, 9H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 160.0, 130.8, 129.0, 113.7, 104.7, 90.9, 85.1, 72.7, 72.0, 71.3, 61.2, 56.5 (2C), 55.2, 41.7, 35.7, 16.4, 11.3, 0.0; HRMS (ESI+) calculated for $C_{22}H_{36}O_4NaSi$ $[M+Na]^+$ *m/z* 415.2281, found 415.2272.



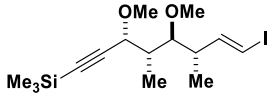
3-2.5

To a stirred solution of **3-2.4** in MeCN and H_2O was added ceric ammonium nitrate (1.844 mmol, 1.011 g) portion wise over 15 minutes under ambient atmosphere and temperature. The solution was stirred for 60 min at 23 °C, then diluted with Et_2O (100 mL) and washed H_2O (150 mL) and saturated $NaHSO_3$ (2 × 150 mL). The combined aqueous layer was extracted with Et_2O (100 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated. The resulting oil was subjected to flash chromatography on silica gel (EtOAc:CH_2Cl_2 0:100 → 20:100) to afford **3-2.5** as a colorless oil (202 mg, 77% yield). TLC (20% EtOAc/hexanes): R_f = 0.37, stained by $KMnO_4$; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 4.23 (d, J = 3 Hz, 1H), 3.86 (d, J = 11, 3 Hz, 1H), 3.53 (dd, J = 11.5, 4.5 Hz, 1H), 3.46, (s, 3H), 3.40 (s, 3H), 3.24 (dd, J = 10, 2 Hz, 1H), 2.01-1.95 (m, 1H), 1.88-1.82, (m, 1H), 1.18 (d, J = 7.5 Hz, 3H), 0.99 (d, J = 7 Hz, 3H), 0.18 (s, 9H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 104.3, 91.4, 87.7, 71.8, 64.4, 61.4, 56.4, 42.1, 35.6, 16.1, 11.2, -0.1; HRMS (ESI+) calculated for $C_{14}H_{28}O_3NaSi$ $[M+Na]^+$ *m/z* 295.1705, found 295.1708.



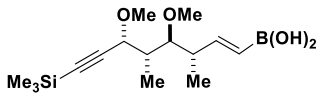
3-2.6

To a solution of **3-2.5** (15.15 mmol, 4.13 g) in CH_2Cl_2 (150 mL) in a 300-mL round-bottom flask cooled to 0 °C was added Dess-Martin Periodinane (30.3 mmol, 12.86 g) portionwise over 5 minutes, under ambient atmosphere. The reaction was stirred for 10 minutes after the addition was complete, then the ice/water bath was removed. The reaction was stirred for another 75 minutes, and then transferred to a separatory funnel. The mixture was extracted with 1:1 saturated $NaHCO_3$/1.5 M $Na_2S_2O_3$ (6 × 50 mL) until TLC indicated that all byproducts have been removed. The aqueous phase was then extracted with CH_2Cl_2 (100 mL), and the combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated at 27 °C. The resulting oil (**3-2.6**) was dried briefly under high vacuum (~15 minutes), then used immediately for the next reaction.



3-2.7

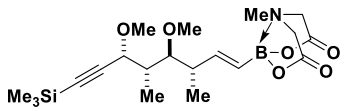
To a 500-mL Schlenk flask charged with anhydrous $CrCl_2$ (242.4 mmol, 29.81 g) was added THF (250 mL) and cooled to 10 °C in an ice/water bath. With the exclusion of light, to the stirred suspension was added slowly over 15 minutes via cannula a solution of **3-2.6** (assumed 15.15 mmol) and CHI_3 (75.75 mmol, 29.83 g) in THF (80 mL). The resulting red mixture was stirred at 23 °C for 2 hours. The mixture was filtered through Celite™ and washed with Et_2O (300 mL). The dark-colored solution was transferred to a separatory funnel and washed with H_2O (2 x 200 mL), brine, then dried over anhydrous $MgSO_4$, filtered and concentrated to give a black residue. The residue was absorbed onto Celite™ *in vacuo* from an acetone solution. The resulting powder was subjected to flash chromatography on silica gel (hexanes:EtOAc 100:0 → 20:100). The product obtained after chromatography was stirred with saturated Na_2SO_3 and passed through a pad of Darco® to remove residual iodine to afford **3-2.7** as a pale yellow oil (4.06 g, 68% yield over 2 steps). TLC (20% EtOAc/hexanes): R_f = 0.52, stained by $KMnO_4$; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.55 (dd, *J* = 15, 9.5 Hz, 1H), 6.02 (dd, *J* = 15, 1 Hz, 1H), 4.23 (d, *J* = 2 Hz, 1H), 3.43, (s, 3H), 3.39 (s, 3H), 3.04 (dd, *J* = 10, 2 Hz, 1H), 2.49-2.43 (m, 1H), 1.72-1.65 (m, 1H), 1.13 (d, *J* = 6.5 Hz, 3H), 0.94 (d, *J* = 7 Hz, 3H), 0.19 (s, 9H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 147.3, 104.3, 91.3, 85.1, 75.1, 71.8, 61.3, 56.4, 43.2, 42.1, 18.1, 10.8, -0.0; HRMS (ESI+) calculated for $C_{15}H_{27}O_2NaISi$ $[M+Na]^+$ *m/z* 417.0723, found 417.0741.



3-2.8

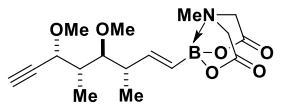
In an unoptimized procedure, a dry 200-mL Schlenk flask was charged with THF (46 mL) and **3-2.7** in 10 mL THF. The solution was cooled to -78 °C and *n*-BuLi (1.6 M in hexanes, 12.3 mmol, 7.7 mL) was added dropwise via cannula over 15 minutes, during which the reaction turned yellow. The reaction was stirred at -78 °C for 25 minutes, then trimethylborate (13.45 mmol, 1.5 mL) was added neat in one portion. Stirring was continued at -78 °C for 20 minutes, then the cooling bath was removed. The reaction was slowly warmed to 23 °C over 2 hours. The reaction

was poured into a 1 N HCl solution (200 mL) pre-cooled to 0 °C and stirred for 15 minutes. The mixture was transferred to a separatory funnel, rinsing with 100 mL Et_2O. The mixture was shaken and the phases were separated. The aqueous phase was extracted with Et_2O (2 × 50 mL). The combined organics were washed with H_2O (50 mL), brine, dried over anhydrous $MgSO_4$, filtered and concentrated to give a yellow oil (**3-2.8**), which was diluted with toluene (30 mL) and used directly in the next step.



3-2.9

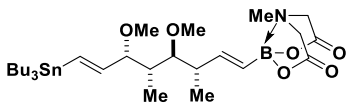
To a solution of **3-2.8** in toluene (50 mL) and DMSO (5 mL) was added N-methyliminodiacetic acid (1.45 g, 9.84 mmol). The round-bottom flask was fitted with a Dean-Stark trap and a reflux condenser and refluxed for 4 hours. The reaction was cooled to 23 °C and transferred into 1:1 saturated NaCl/H_2O (50 mL). The organic phase was washed with another 50 mL 1:1 saturated NaCl/H_2O. The combined aqueous phase was washed with Et_2O (2 × 50 mL), and the organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (Et_2O:acetone 100:0 → 1:2) to give **3-2.9** as a white solid (1.74 g, 50% yield over 2 steps). TLC (acetone/hexane 1:1): R_f = 0.47, stained by $KMnO_4$; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.24 (dd, *J* = 18, 8 Hz, 1H), 5.41 (dd, *J* = 18, 1 Hz, 1H), 4.21 (d, *J* = 3 Hz, 1H), 3.82 (d, *J* = 16.5 Hz, 2H), 3.66 (dd, *J* = 16.5, 3 Hz, 2H), 3.40 (s, 3H), 3.38 (s, 3H), 3.08 (dd, *J* = 10, 2 Hz, 1H), 2.80, (s, 3H), 2.52-2.49 (m, 1H), 1.68-1.61 (m, 1H), 1.13 (d, *J* = 7 Hz, 3H), 0.95 (d, *J* = 7 Hz, 3H), 0.17 (s, 9H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 167.6, 167.5, 148.9, 104.8, 91.3, 85.6, 72.1, 61.6, 61.2, 56.8, 46.9, 42.8, 42.1, 18.2, 11.2, 0.2; HRMS (ESI+) calculated for $C_{20}H_{35}BNO_6Si$ $[M+H]^+$ *m/z* 424.2327, found 424.2329.



3-2.10

To a solution of **3-2.9** (1.69 g, 3.99 mmol) in acetone/H_2O/lutidine (10:10:1, 84 mL) at 0 °C was added $AgNO_3$ (3.39 g, 20.0 mmol) in one portion. The reaction was gradually allowed to warm to 23 °C over 2.5 hours. The reaction was quenched by transferring the mixture into saturated aqueous NH_4Cl (100 mL) and diluted with EtOAc (50 mL). The mixture was filtered to remove the insoluble salts. The filtrate was transferred to a separatory funnel and the phases were separated. The organic phase was washed with 0.5 M HCl (2 × 50 mL) and the aqueous phase extracted with EtOAc (50 mL). The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to afford a white foam. The foam was dissolved in Et_2O (~10 mL), then 20% Et_2O/hexane (30 mL) was added and the suspension was filtered, washing with additional 20% Et_2O/hexane (20 mL). The filtrate was concentrated *in vacuo* to give **3-2.10** as a white solid (1.22 g, 87% yield). TLC (acetone/hexane 1:1): R_f = 0.34, stained by $KMnO_4$; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.24 (dd, *J* = 17.5, 8 Hz, 1H), 5.41 (dd, *J* = 17.5, 1 Hz, 1H), 4.23 (t, *J* = 2 Hz, 1H), 3.79 (d, *J* = 16 Hz, 2H), 3.66 (dd, *J* = 16, 1.5 Hz, 2H), 3.42 (s, 3H), 3.40 (s, 3H), 3.09 (dd, *J* = 10, 2.5 Hz, 1H), 2.81, (s, 3H), 2.55-2.47 (m, 1H), 2.40 (d, *J* = 2 Hz, 1H), 1.69-1.61 (m, 1H), 1.14 (d, *J* = 7 Hz, 3H), 0.96 (d, *J* = 7 Hz, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 168.1,

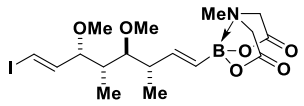
168.0, 148.1, 85.3, 82.6, 74.3, 71.2, 61.4, 61.0, 56.6, 46.9, 42.5, 41.9, 18.0, 10.7; HRMS (ESI+) calculated for $C_{17}H_{27}BNO_6$ $[M+H]^+$ *m/z* 352.1931, found 352.1933.



3-2.11

Preparation of catalyst stock solution. A dry 7-mL vial equipped with a PTFE-coated magnetic stir bar was charged with RuPhos (9.3 mg, 0.02 mmol). The vial was brought into the glovebox, and Pd_2dba_3 (4.6 mg, 0.005 mmol) was added. CH_2Cl_2 (3 mL) was added, and the mixture was stirred at 23 °C for 25 minutes.

The freshly prepared catalyst stock solution was used immediately for the preparation of **3-2.11**: A dry 20-mL vial equipped with a PTFE-coated magnetic stir bar was charged with **3-2.10** (176 mg, 0.5 mmol). The vial was evacuated and filled with argon (x 3), then CH_2Cl_2 (5 mL) was then added, followed by the catalyst stock solution, rinsing with CH_2Cl_2 (2 mL). Tributyltin hydride (0.27 mL, 1.00 mmol) was added neat dropwise to the reaction under argon at 23 °C, over 1 hour 25 minutes. The reaction was stirred at 23 °C for 2 hours after the addition was complete. The reaction was concentrated *in vacuo* and purified by silica gel chromatography (10% to 50% acetone/hexanes). The yellow solid obtained after concentration was dissolved in 10% acetone/hexanes and passed through a pad of Darco® and Celite™ to give a colorless solution. The solution was concentrated *in vacuo* to give **3-2.11** as an off-white solid (255 mg, 79% yield). TLC (acetone/hexane 1:1): R_f = 0.47, stained by $KMnO_4$; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.27 (dd, *J* = 18, 7.5 Hz, 1H), 6.12, (d, *J* = 19 Hz, 1H), 5.84, (dd, *J* = 19, 6 Hz, 1H), 5.38 (d, *J* = 18 Hz, 1H), 3.83-3.82 (m, 1H), 3.79 (dd, *J* = 16.5, 3 Hz, 2H), 3.65 (d, *J* = 16.5 Hz, 2H), 3.46-3.44 (m, 1H), 3.44 (s, 3H), 3.26 (s, 3H), 3.11 (dd, *J* = 9.5, 2.5 Hz, 1H), 2.78, (s, 3H), 2.55-2.47 (m, 1H), 1.53-1.47 (m, 6H), 1.31 (sext, *J* = 7.5 Hz, 6H), 1.13 (d, *J* = 6.5 Hz, 3H), 0.91-0.87 (m, 15H), 0.77 (d, *J* = 7.5 Hz, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 167.4, 149.1, 147.5, 130.4, 86.1, 84.0, 61.4, 60.8, 56.4, 46.6, 42.0, 41.7, 29.1, 27.2, 18.1, 13.7, 9.8, 9.4; LRMS (ESI+) calculated for $C_{29}H_{55}BNO_6Sn$ $[M+H]^+$ *m/z* 644.3, found 644.3.

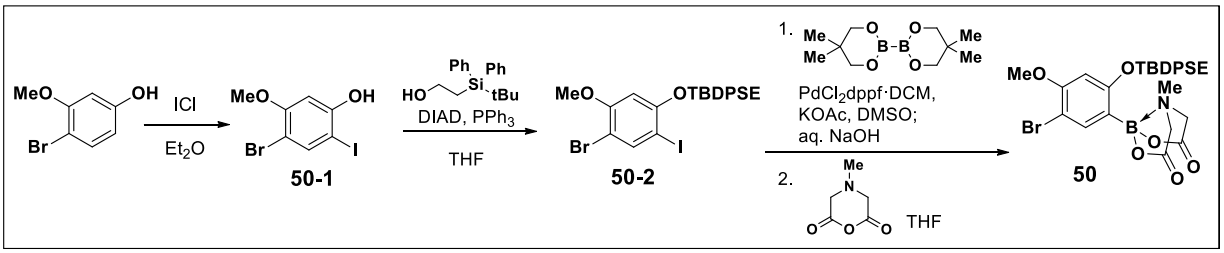


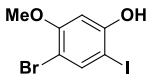
3-2

To a solution of **3-2.11** (1.387 g, 2.16 mmol) in CH_2Cl_2 (20 mL) in a 50-mL round-bottom flask was added dropwise a solution of I_2 (0.576 g, 2.27 mmol) in CH_2Cl_2 (30 mL) via a pressure-equalizing funnel at 0 °C under ambient atmosphere over 1 hour. The funnel was rinsed with CH_2Cl_2 (10 mL) and the solution added portion wise to the reaction. The ice bath was removed and the reaction was allowed to gradually warm to 23 °C over 1 hour. The reaction was transferred into a 250-mL separatory funnel, rinsing with additional CH_2Cl_2. The organic layer was washed with 2 × 30 mL 1 M $Na_2S_2O_5$ solution, then with 2 × 25 mL 3 M KF solution. The combined aqueous layer was extracted with 25 mL CH_2Cl_2. The organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (1:6 to 2:3 acetone/hexanes) to give **3-2** as a white solid (0.827 g, 80%). TLC (acetone/hexane 1:1): R_f = 0.32, stained by $KMnO_4$; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.46 (dd, *J* = 14.5, 7 Hz, 1H), 6.26, (d, *J* = 14.5 Hz, 1H), 6.19, (dd, *J* = 17.5, 7.5 Hz, 1H), 5.39 (d, *J* =

17.5 Hz, 1H), 3.94 (d, *J* = 16.5 Hz, 2H), 3.88-3.87 (m, 1H), 3.68 (dd, *J* = 16.5, 4.5 Hz, 2H), 3.42 (s, 3H), 3.26 (s, 3H), 3.07 (dd, *J* = 9.5, 1.5 Hz, 1H), 2.80, (s, 3H), 2.55-2.47 (m, 1H), 1.12 (d, *J* = 7.0 Hz, 3H), 1.50-1.45 (m, 1H), 0.76 (d, *J* = 7.0 Hz, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 167.7, 167.6, 148.5, 145.8, 85.8, 82.8, 61.4, 61.0, 56.7, 46.8, 41.8, 41.6, 18.0, 9.8; HRMS (ESI+) calculated for $C_{17}H_{28}BNO_6I$ $[M+H]^+$ *m/z* 480.1054, found 480.1053.

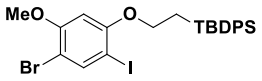
c. Synthesis of building blocks for **4** and the library





50-1

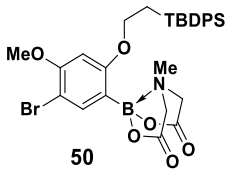
A 100-mL round-bottom flask charged with 4-bromo-3-methoxyphenol (5000 mg, 24.63 mmol, 1.0 equiv.) was sealed with a septum and purged with N_2 and diethyl ether (25 mL, 1.0 M) was added to afford a clear solution. The flask was cooled to 0 °C in an ice bath for 10 minutes. Iodine monochloride (1.3 mL, 1.05 equiv.) was added dropwise to the reaction flask and the reaction mixture was allowed to warm to 23 °C with stirring over 1.5 hours. After 1.5 hours, the reaction mixture was transferred to a separatory funnel containing aqueous saturated $Na_2S_2O_3$ (50 mL), rinsing with diethyl ether (50 mL) and the phases were separated. The aqueous layer was back-extracted with diethyl ether (50 mL × 3) and the combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to afford crude **50-1** as a yellow-brown oil (7.86 g, 97% crude yield). This oil was used for the next step without further purification. TLC (hexanes:diethyl ether 2:3): R_f = 0.32, stained by $KMnO_4$; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.73 (s, 1H), 6.62 (s, 1H), 5.23 (s, 1H), 3.86 (s, 3H); HRMS (EI+) calculated for $C_7H_6O_2IBr$ $[M+H]^+$ *m/z* 327.85961, found 327.85939.



50-2

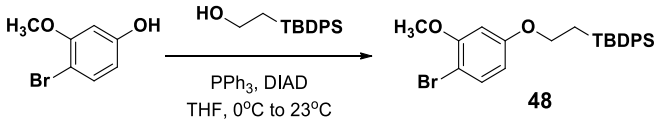
Triphenylphosphine (PPh_3, 5054 mg, 19.3 mmol, 1.8 equiv.) was charged in a 100-mL Schlenk flask equipped with a PTFE-coated magnetic stir bar and back-filled with N_2. THF (57 mL) was added and the reaction mixture was cooled to 0 °C for 10 minutes. Diisopropyl azodicarboxylate (DIAD, 3.8 mL, 1.8 equiv.) was added dropwise to the reaction flask affording a white precipitate. This heterogeneous mixture was stirred at 0 °C for 10 minutes. 2-(*tert*-butyldiphenylsilyl)ethanol (*43*) (5482 mg, 19.3 mmol, 1.8 equiv.) was added to the reaction flask and THF (4 mL) was added to dissolve all reagents and the resulting mixture was stirred at 0 °C for 10 minutes. Separately, **50-1** (3511 mg, 10.7 mmol, 1.0 equiv.) was charged in a 20-mL vial, back-filled with N_2, and THF (6 mL) was added. This solution was added to the reaction flask at

0 °C and stirred at that temperature for 10 minutes. After 10 minutes, the reaction mixture was warmed to 23 °C with stirring for 16 hours. After 16 hours, the reaction mixture was transferred to a 200-mL round-bottom flask, rinsing with diethyl ether (20 mL), and concentrated *in vacuo* to afford an orange oil. The crude material was adsorbed onto Celite™ from an acetone solution and purified by SiO_2 chromatography (20% DCM:hexanes → 30% DCM:hexanes) to afford **50-2** as a white solid (5.23 g, 82% yield). TLC (hexanes:diethyl ether 2:3): R_f = 0.68, stained by $KMnO_4$; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.81 (s, 1H), 7.65 (d, *J* = 7.0 Hz, 4H), 7.43 – 1.38 (m, 6H), 6.09 (s, 1H), 4.02 – 3.98 (m, 2H), 3.68 (s, 3H), 1.86 – 1.83 (m, 2H), 1.07 (s, 9H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 157.8, 156.8, 141.2, 135.8, 133.5, 129.5, 127.9, 103.0, 98.0, 75.6, 67.6, 56.2, 27.6, 18.0, 11.7; HRMS (ESI+) calculated for $C_{25}H_{28}O_2SiBrINa$ $[M+Na]^+$ *m/z* 616.9984, found 616.9979.



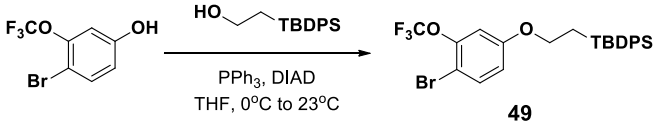
50

In a glove box, to a 100-mL round-bottom flask equipped with a PTFE-coated magnetic stir bar and containing **50-2** (3572 mg, 6.0 mmol, 1.0 equiv.) was added potassium acetate (1767 mg, 18.0 mmol, 3.0 equiv.), bis(neopentylglycolato)diboron (1355 mg, 6.0 mmol, 1.0 equiv.) and $PdCl_2$dppf•CH_2Cl_2 (147 mg, 0.18 mmol, 3 mol%). The flask was sealed with a septum cap and removed from the glove box. Outside the glovebox, DMSO (50 mL, 0.12 M) was added to the reaction flask under N_2 atmosphere and the reaction mixture was placed in an 80 °C oil bath and stirred at that temperature for 18 hours. After 18 hours, the reaction mixture was cooled to 23 °C and 1 M aqueous NaOH (18.0 mL, 3.0 equiv) was added dropwise and the resulting heterogeneous mixture was stirred vigorously for 30 minutes at 23 °C. The reaction mixture was transferred to a separatory funnel with EtOAc (100 mL) and water (100 mL). The layers were separated and the aqueous phase was extracted with water (3 x 100 mL). Combined organic layers were dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to afford the crude boronic acid This crude boronic acid was concentrated in a 40-mL I-Chem vial and charged with *N*-methyliminodiacetic acid (MIDA) anhydride (*44*) (3873 mg, 30 mmol, 5.0 equiv.) and equipped with a PTFE-coated magnetic stir bar. The vial was flushed with N_2 and THF (20 mL, 0.3 M) was added and the reaction mixture was placed in a 70 °C aluminum heat block and stirred at that temperature for 24 hours. After 24 hours, the reaction mixture was cooled to 23 °C and transferred to a separatory funnel with EtOAc (100 mL) followed by deionized water (100 mL). The phases were separated and the aqueous layer was extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to afford an off-white solid. The crude material was adsorbed onto Celite™ from an acetone solution and purified by SiO_2 chromatography (hexanes:EtOAc 1:1 → EtOAc) and recrystallized from DCM/hexanes to afford **50** as a white solid (1.707 g, 46% yield over three steps). TLC (EtOAc): R_f = 0.66, stained by $KMnO_4$; ^{1}H-NMR (500 MHz, acetone-d_6): δ 7.70 (d, *J* = 8.0 Hz, 2H), 7.63 (s, 1H), 7.42-7.45 (m, 6H), 6.45 (s, 1H), 4.35 (d, *J* = 17.0 Hz, 2H), 4.20 (d, *J* = 17.0 Hz, 2H), 4.11-4.14 (m, 2H), 3.72 (s, 3H), 2.84 (s, 3H), 1.91 – 1.88 (m, 2H), 1.05 (s, 9H); ^{13}C-NMR (125 MHz, acetone-d_6): δ 169.3, 163.1, 158.5, 138.9, 136.5, 134.5, 130.3, 128.7, 98.5, 70.1, 67.2, 64.5, 56.3, 48.2, 27.9, 21.7, 18.5, 11.8; HRMS (ESI+) calculated for $C_{30}H_{36}O_6BNSiBr$ $[M+H]^+$ *m/z* 624.1588, found 624.1602.



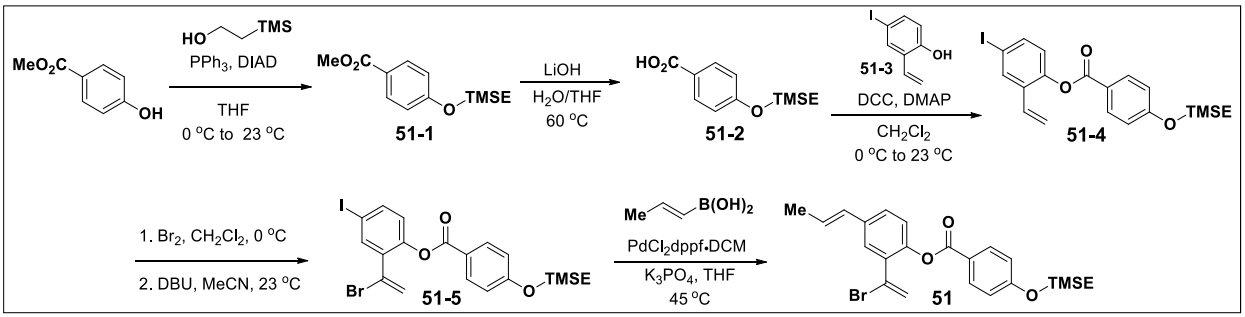
48

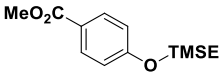
To a stirred solution of triphenylphosphine (1.10 g, 4.2 mmol, 1.2 equiv) in THF (10 mL) at 0 °C was added dropwise diisopropylazodicarboxylate (DIAD; 830 µL, 4.2 mmol, 1.2 equiv) to generate a yellow suspension. In one portion, 4-bromo-3-methoxyphenol (711 mg, 3.5 mmol, 1 equiv) and 2-(*tert*-butyldiphenylsilyl)ethanol (1.19 g, 4.2 mmol, 1.2 equiv) were added. The mixture was stirred for 15 minutes, after which the ice bath was then removed and the reaction warmed to ambient temperature. After stirring for 1 hour, the reaction was diluted with diethyl ether and adsorbed onto Celite™ *in vacuo*. The Celite™ pad was loaded onto a silica gel column and eluted with hexanes/DCM gradient (4:1 to 3:7). Fractions containing a minor impurity were re-adsorbed on Celite™ and eluted from a silica gel column using a hexanes/DCM gradient (4:1 to 3:1). Purified fractions were combined to afford **48** as a colorless amorphous solid (1.19g, 72% yield). ^{1}H-NMR (500 MHz, acetone-d_6): δ 7.74 – 7.72 (m, 4H), 7.50 – 7.44 (m, 6H), 7.34 (d, J = 8.5 Hz, 1H), 6.43 (d, J = 2.5 Hz, 1H), 6.27 (dd, J = 9.0, 3.0 Hz, 1H), 4.08 – 4.05 (m, 2H), 3.81 (s, 3H) 1.86 – 1.83 (m, 2H), 1.11 (s, 9H); ^{13}C-NMR (125 MHz, acetone-d_6): δ 160.5, 157.5, 136.6, 134.7, 133.8, 130.3, 128.7, 107.7, 102.4, 101.3, 66.3, 56.4, 28.1, 18.5, 12.5; HRMS (EI+) calculated for $C_{25}H_{29}O_2SiBr$ $[M]^+$ *m/z* 468.11202, found 468.11118.



49

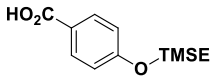
To a stirred solution of triphenylphosphine (765 mg, 3.0 mmol, 1.5 equiv) in THF (7.5 mL) at 0 °C was added dropwise diisopropylazodicarboxylate (DIAD; 570 µL, 3.0 mmol, 1.5 equiv) to generate a yellow suspension. In one portion, 4-bromo-3-(trifluoromethoxy)phenol (500 mg, 2.0 mmol, 1 equiv) and 2-(*tert*-butyldiphenylsilyl)ethanol (830 mg, 3.0 mmol, 1.5 equiv) were added. The mixture was stirred for 15 minutes, after which the ice bath was then removed and the reaction warmed to ambient temperature. After stirring for 16 hours, the reaction was diluted with diethyl ether and adsorbed onto Celite™ *in vacuo*. The Celite™ pad was loaded onto a silica gel column and eluted with 4:1 hexanes/DCM. The colorless oil from this column was re-adsorbed onto Celite™, loaded onto silica gel, and eluted with a hexanes/DCM gradient (hexanes to 9:1 hexanes/DCM) to afford **49** as a colorless oil (785 mg, 77% yield). ^{1}H-NMR (500 MHz, acetone-d_6): δ 7.71 – 7.69 (m, 4H), 7.55 (d, J = 8.5 Hz, 1H), 7.47 – 7.41 (m, 6H), 6.82 – 6.81 (m, 1H), 6.75 (dd, J = 8.5, 2.5 Hz, 1H), 4.11 – 4.07 (m, 2H), 1.86 – 1.83 (m, 2H), 1.08 (s, 9H); ^{13}C-NMR (125 MHz, acetone-d_6): δ 160.5, 157.5, 136.6, 134.7, 133.8, 130.3, 128.7, 107.7, 102.4, 101.3, 66.3, 56.4, 28.1, 18.5, 12.5.





51-1

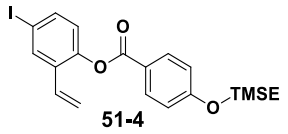
Triphenylphosphine (PPh_3, 7450 mg, 28.4 mmol, 1.8 equiv.) was charged in a 250-mL round-bottom flask equipped with a PTFE-coated magnetic stir bar and back-filled with N_2. THF (70 mL) was added and the reaction mixture was cooled to 0 °C for 10 minutes. Diisopropyl azodicarboxylate (DIAD, 5.6 mL, 28.4 mmol, 1.8 equiv.) was added dropwise to the reaction flask affording a white precipitate. This heterogeneous mixture was stirred at 0 °C for 10 minutes. 2-trimethylsilylethanol (4.1 mL, 28.4 mmol, 1.8 equiv.) was added to the reaction flask and the resulting mixture was stirred at 0 °C for 10 minutes. Methyl *p*-hydroxybenzoate (2400 mg, 15.8 mmol, 1.0 equiv.) was added to the flask in one portion followed by THF (10 mL) and the resulting reaction mixture was and stirred at 0 °C for 10 minutes. After 10 min, the reaction mixture was warmed to 23 °C with stirring for 16 hours. After 16 hours, the reaction mixture was concentrated *in vacuo* to afford a clear oil. This crude oil was dissolved in minimum amount of diethyl ether (5 mL). Hexanes (100 mL) were added and the solution was stirred at 23 °C for 5 minutes until white solid precipitated. The solid was filtered through a fritted filter funnel rinsing with hexanes. The filtrate was concentrated *in vacuo* to afford a clear oil, which was adsorbed onto Celite™ from an acetone solution and purified by SiO_2 chromatography (20% DCM:hexanes → 50% DCM:hexanes) to afford **51-1** as a clear oil (434 mg, 11% yield). TLC (dichloromethane:hexanes 1:1): R_f = 0.28, shortwave UV; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.97 (d, *J* = 9.5 Hz, 2H), 6.88 (d, *J* = 9.0 Hz, 2H), 4.13 (t, *J* = 7.5 Hz, 2H), 3.88 (s, 3H), 1.15 (t, *J* = 8.0 Hz, 2H), 0.09 (s, 9H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 216.4, 172.1, 163.5, 132.3, 121.4, 114.2, 65.8, 17.6, -1.35; HRMS (ESI+) calculated for $C_{13}H_{20}O_3SiNa$ $[M+Na]^+$ *m/z* 275.1079, found 275.1084.



51-2

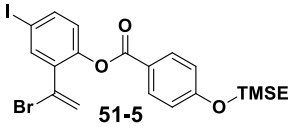
A 40-mL vial equipped with a PTFE-coated magnetic stir bar was charged with $LiOH.H_2O$ (722 mg, 17.2 mmol, 10 equiv.) and H_2O (4 mL). The vial was placed in a 60 °C aluminum heating block and stirred at that temperature for 5 minutes until a clear solution was afforded. The vial was removed from the heating block and a solution of **51-1** (434 mg, 1.72 mmol, 1.0 equiv.) in THF (9 mL, 0.2 M) was added to the reaction vial. The vial was sealed with a PTFE-lined cap and placed in a 60 °C aluminum heating block and stirred at that temperature for 14 hours. The reaction mixture was cooled to 23 °C, then to 0 °C for 10 minutes. 6 N HCl was added dropwise to the crude reaction mixture with stirring until pH ≤ 1. The reaction mixture was transferred to a

separatory funnel with H_2O (20 mL) and EtOAc (40 mL). The phases were separated and the aqueous layer was extracted with EtOAc (40 mL x 2). The combined organic layers were washed with brine (50 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to afford a white solid. The crude solid was adsorbed onto Celite™ from an acetone solution and purified by SiO_2 chromatography (1:4 EtOAc:hexanes → 2:1:7 EtOAc:EtOH:hexanes) to afford **51-2** as a white solid (361 mg, 88% yield). TLC (EtOAc:hexanes 1:4): R_f = 0.22, shortwave UV; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.03 (d, *J* = 9.0 Hz, 2H), 6.91 (d, *J* = 8.5 Hz, 2H), 4.15 (t, *J* = 7.5 Hz, 2H), 1.16 (t, *J* = 8.0 Hz, 2H), 0.09 (s, 9H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 172.2, 163.5, 132.3, 121.4, 114.2, 65.8, 17.6, -1.35; HRMS (ESI+) calculated for $C_{12}H_{18}O_3SiNa$ $[M+Na]^+$ *m/z* 261.0923, found 261.0934.



51-4

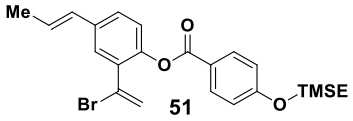
A 100-mL flask equipped with a PTFE-coated magnetic stir bar was charged with **51-2** (361 mg, 1.51 mmol, 1.0 equiv.) and back-filled with N_2. **51-3** (*14*) (447 mg, 1.82 mmol, 1.2 equiv.), DMAP (222 mg, 1.82 mmol, 1.2 equiv.), and dichloromethane (20 mL, 0.08 M) were added to the reaction flask. The clear, colorless solution was cooled to 0 °C and stirred at that temperature for 10 minutes. DCC (375 mg, 1.82 mmol, 1.2 equiv.) was added in one portion at 0 °C under N_2 and stirred at that temperature for 10 minutes. The ice bath was removed after 10 minutes and the reaction flask was allowed to warm to 23 °C with stirring over 15 hours. After 15 hours, the reaction mixture was concentrated *in vacuo* to afford a yellow sludge. The crude material was adsorbed onto Celite™ from an acetone solution and purified by SiO_2 chromatography (30% DCM:hexanes → 40% DCM:hexanes) to afford **51-4** as a clear oil (575 mg, 81% yield). TLC (30% DCM:hexanes): R_f = 0.21, shortwave UV; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.14 (d, *J* = 8.5 Hz, 2H), 7.92 (s, 1H), 7.61 (d, *J* = 8.5 Hz, 1H), 6.96 (d, *J* = 9.0 Hz, 2H), 6.92 (d, *J* = 8.5 Hz, 1H), 6.70 (dd, *J* = 11.0 Hz, *J* = 14.5 Hz, 1H), 5.78 (s, 1H), 5.74 (s, 1H), 5.32 (d, *J* = 11.0 Hz, 1H), 4.17 (t, *J* = 8.0 Hz, 2H), 1.18 (t, *J* = 7.5 Hz, 2H), 0.10 (s, 9H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 164.4, 163.6, 148.2, 137.5, 135.3, 132.8, 132.4, 129.2, 124.9, 120.8, 117.5, 114.4, 90.4, 65.9,17.5, -1.33; HRMS (ESI+) calculated for $C_{20}H_{24}O_3SiI$ $[M+H]^+$ *m/z* 467.0540, found 467.0534.



51-5

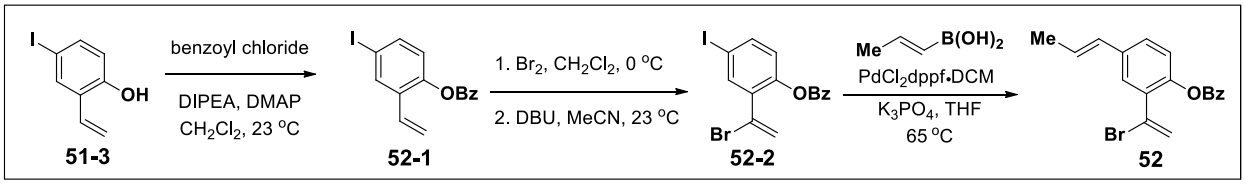
A 50-mL flask equipped with a PTFE-coated magnetic stir bar was charged with **51-4** (575 mg, 1.23 mmol, 1.0 equiv.), sealed with a septum, and back-filled with N_2. Dichloromethane (12 mL, 0.1 M) was added to afford a clear, colorless solution. This solution was cooled to 0 °C and stirred at that temperature for 10 minutes. Bromine (0.14 mL, 2.71 mmol, 2.2 equiv.) was added dropwise to the reaction mixture at 0 °C over the course of 20 minutes until a bright red color persisted. The crude reaction mixture was concentrated *in vacuo* in a 50-mL round-bottom flask and azeotroped with DCM (3 x 15 mL) to afford the dibromide as a yellow foamy solid (721 mg, 93% crude yield). The flask was charged with a PTFE-coated magnetic stir bar, sealed with a septum, and back-filled with N_2. Acetonitrile (11.5 mL, 0.1 M) was added and the reaction mixture was stirred at 23 °C for 5 minutes. DBU (0.2 mL, 1.34 mmol, 1.2 equiv.) was added

dropwise and the resulting mixture was stirred for 10 minutes. After 10 minutes, incomplete conversion was observed by TLC analysis, so another 0.3 mL of DBU was added dropwise. After 20 minutes of stirring at 23 °C, the reaction mixture was cooled to 0 °C and 1 N HCl (10 mL) was added. The reaction mixture was transferred to a separatory funnel with EtOAc (15 mL) and H_2O (15 mL) and the layers were separated. The phases were separated and the aqueous layer was extracted with EtOAc (10 mL x 2). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to afford a clear oil. The crude material was adsorbed onto Celite™ from an acetone solution and purified by SiO_2 chromatography (40% DCM:hexanes) to afford **51-5** as a pale yellow oil (503 mg, 75% yield over two steps). TLC (1:3 DCM:hexanes): R_f = 0.25, shortwave UV; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.13 (d, *J* = 9.0 Hz, 2H), 7.78 (s, 1H), 7.70 (d, *J* = 8.5 Hz, 1H), 6.98 (d, *J* = 8.5 Hz, 1H), 6.96 (d, *J* = 9.0 Hz, 2H), 5.91 (d, *J* = 1.5 Hz, 1H), 5.84 (d, *J* = 2.0 Hz, 1H), 4.17 (t, *J* = 8.0 Hz, 2H), 1.17 (t, *J* = 8.0 Hz, 2H), 0.10 (s, 9H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 164.1, 163.6, 147.8, 138.9, 138.9, 135.4, 132.5, 125.3, 123.0, 122.7, 120.7, 114.4, 89.4, 65.9,17.5, -1.34; HRMS (ESI+) calculated for $C_{20}H_{23}O_3SiBrI$ $[M+H]^+$ *m/z* 544.9645, found 544.9646.

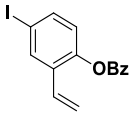


51

In a glove box, to a 7-mL vial equipped with a PTFE-coated magnetic stir bar and containing **51-5** (20 mg, 0.037 mmol, 1.0 equiv.) and *trans*-propenyl boronic acid (4.73 mg, 0.055 mmol, 1.5 equiv.) was added ground potassium phosphate (23 mg, 0.11 mmol, 3.0 equiv.) and $PdCl_2dppf{\cdot}CH_2Cl_2$ (1.5 mg, 0.002 mmol, 5 mol%) followed by THF (0.7 mL, 0.05 M). The vial was sealed with a cap and removed from the glove box. The vial was placed in a 45 °C aluminum heating block and stirred at that temperature for 24 hours. After 24 hours, the reaction mixture was cooled to 23 °C, filtered through a pad of Celite™, and concentrated *in vacuo*. The crude material was adsorbed onto Celite™ from an acetone solution and purified by SiO_2 chromatography (30% DCM:hexanes) to afford **51** as a pale yellow oil (13.5 mg, 80% yield). TLC (1:1 DCM:hexanes): R_f = 0.31, shortwave UV; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.15 (d, *J* = 8.5 Hz, 2H), 7.40 (s, 1H), 7.35 (d, *J* = 8.5 Hz, 1H), 7.13 (d, *J* = 8.5 Hz, 1H), 6.96 (d, *J* = 9.0 Hz, 2H), 6.39 (d, *J* = 16.0 Hz, 1H), (dq, *J* = 15.5 Hz, *J* = 6.5 Hz, 1H), 5.89 (d, *J* = 1.5 Hz, 1H), 5.82 (d, *J* = 1.5 Hz, 1H), 4.17 (t, *J* = 8.0 Hz, 2H), 1.90 (d, *J* = 7.0 Hz, 3H), 1.17 (t, *J* = 8.0 Hz, 2H), 0.10 (s, 9H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 164.6, 163.4, 146.4, 135.8, 133.2, 132.4, 129.6, 127.6, 127.2, 126.8, 124.6, 123.2, 122.1, 121.2, 114.3, 65.9, 18.5, 17.5, -1.33; HRMS (ESI+) calculated for $C_{23}H_{28}O_3SiBr$ $[M+H]^+$ *m/z* 459.0991, found 459.0987.

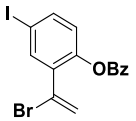


51-3 **52-1** **52-2** **52**



52-1

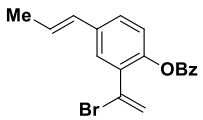
A dry 25-mL Schlenk flask equipped with a PTFE-coated magnetic stir bar was charged with phenol **52-3** (738 mg, 3 mmol) and DMAP (73.3 mg, 0.6 mmol) under N_2. The flask was sealed with a rubber septum and CH_2Cl_2 (15 mL) was added via syringe. To this solution was added DIPEA (2.1 mL, 12.1 mmol) in one portion. Benzoyl chloride (0.7 mL, 6.03 mmol) was then added neat dropwise over 5 minutes. The reaction was stirred for another 19 hours at room temperature, then transferred into a separatory funnel containing 1 N HCl (10 mL). After mixing and phase separation, the organic layer was washed with another portion of 1 N HCl (10 mL) and then with H_2O (20 mL). The combined aqueous layer was extracted with CH_2Cl_2 (20 mL). The organic phase was washed with brine (20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated. The crude product was purified by silica gel chromatography (30 - 35% CH_2Cl_2/hexanes) to afford **52-1** as a colorless viscous oil (643 mg, 61% yield). TLC (50% DCM/hexanes): R_f = 0.44, visualized by shortwave UV; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.21 (d, *J* = 7 Hz, 2H), 7.94 (d, *J* = 2 Hz, 1H), 7.66 (tt, *J* = 7.5, 1.5 Hz, 1H), 7.63 (dd, *J* = 8, 1.5 Hz, 1H), 7.56 (t, *J* = 7.5 Hz, 2H), 6.94 (d, *J* = 8.5 Hz, 1H), 6.71 (dd, *J* = 17.5, 11 Hz, 1H), 5.77 (dd, *J* = 18, 1 Hz, 1H), 5.34 (d, *J* = 11 Hz, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 164.6, 148.0, 137.5, 135.4, 133.9, 132.7, 130.2, 129.0, 128.9, 128.7, 124.7, 117.7, 90.6; HRMS (ESI+) calculated for $C_{15}H_{12}O_2I$ $[M+H]^+$ *m/z* 350.9882, found 350.9890.



52-2

A solution of **52-1** (3.37 g, 9.62 mmol) in CH_2Cl_2 (120 mL) in a 200-mL round-bottom flask was cooled to 0 °C under N_2. Bromine (0.49 mL, 9.62 mmol) was added neat dropwise over 15 minutes. After the addition was complete, the reaction was stirred for a further 5 minutes. The reaction was concentrated *in vacuo* to give an orange solid. Residual bromine was removed by azeotroping the residue with CH_2Cl_2 (15 mL × 2). The round bottom flask containing the crude product and equipped with a PTFE-coated magnetic stir bar was sealed with a rubber septum and back-filled with N_2 twice. MeCN (120 mL) was added to dissolve most of the solid. DBU (1.4 mL, 9.5 mmol) was then added neat dropwise via syringe over 15 minutes. The reaction was stirred for 15 minutes before being charged with another portion of DBU (0.2 mL, 1.34 mmol) added neat dropwise into the reaction. After another 15 minutes, another portion of DBU (0.2 mL, 1.34 mmol) was added. The reaction was poured slowly into 2 N HCl solution (100 mL) cooled to 0 °C with vigorous stirring. EtOAc (50 mL) was added and the mixture stirred. After phase separation, the aqueous layer was extracted with EtOAc (50 mL). The combined organic phase was washed with brine (100 mL), then dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (30-35% CH_2Cl_2/hexanes) to afford **52-2** as an off-white solid (2.67g, 66% yield over 2 steps). TLC (40% CH_2Cl_2/hexanes): R_f = 0.47, visualized by shortwave UV; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.20 (d, *J* = 7.5 Hz, 2H), 7.79 (d, *J* = 2 Hz, 1H), 7.72 (dd, *J* = 8.5, 2 Hz, 1H), 7.66 (t, *J* = 7.5 Hz, 1H), 7.52 (tt, *J* = 8, 1.5 Hz, 2H), 6.99 (d, *J* = 8.5 Hz, 1H), 5.92 (d, *J* = 2 Hz, 1H), 5.85 (d, *J* = 1.5 Hz, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 164.4, 147.6, 138.9, 135.4, 133.9, 130.3, 128.8, 128.6,

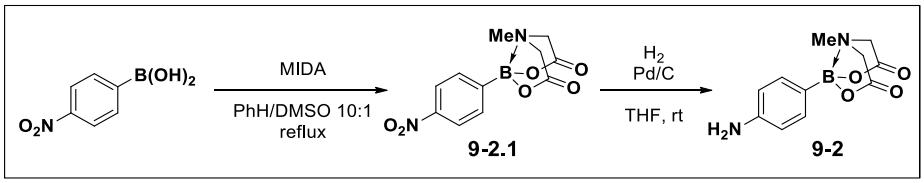
125.1, 123.1, 122.5, 89.7; HRMS (ESI+) calculated for $C_{15}H_{10}O_2BrINa$ $[M+Na]^+$ *m/z* 450.8807, found 450.8809.

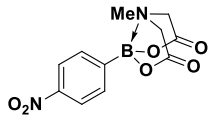


52

A dry 40-mL vial equipped with a PTFE-coated magnetic stir bar was charged with **52-2** (858 mg, 2.0 mmol) and *trans*-propenyl boronic acid (223 mg, 2.6 mmol). The vial was brought into a glovebox and charged with K_3PO_4 (1.27 g, 3 equiv.), $PdCl_2dppf.CH_2Cl_2$ (849 mg, 4 mmol) and THF (20 mL, 0.1 M). The vial was sealed with a Teflon-lined cap and stirred at 60 °C for 18 hours. The reaction was cooled to 23 °C and filtered through a pad of Celite™ and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (30-40% CH_2Cl_2/hexanes) to give **52** as an off-white solid (268 mg, 39% yield). TLC (40% CH_2Cl_2/hexanes): R_f = 0.43, visualized by shortwave UV; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.22 (dd, *J* = 8.0, 1.0 Hz, 2H), 7.65 (t, *J* = 7.5 Hz, 1H), 7.52 (app t, *J* = 8.0 Hz, 2H), 7.41 (d, *J* = 2.0 Hz, 1H), 7.36 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.15 (d, *J* = 8.5 Hz, 1H), 6.40 (dd, *J* = 16.0, 1.5 Hz, 1H), 6.26 (dq, *J* = 15.5, 6.5 Hz, 1H), 5.90 (d, *J* = 1.5 Hz, 1H), 5.83 (d, *J* = 2.0 Hz, 1H), 1.90 (dd, *J* = 7.0, 1.5 Hz, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 164.8, 146.2, 136.0, 133.6, 133.3, 130.3, 129.5, 129.3, 128.6, 127.6, 127.2, 127.0, 124.5, 123.1, 122.2, 18.5; HRMS (ESI+) calculated for $C_{18}H_{16}O_2Br$ $[M+H]^+$ *m/z* 343.0334, found 343.0336.

d. Synthesis of building blocks for **9**

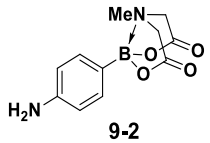




9-2.1

A mixture of *p*-nitrophenyl boronic acid (1.53 g, 9.17 mmol, 1 equiv), N-methyliminodiacetic acid (1.62 g, 11.0 mmol, 1.2 equiv) in toluene (90 mL) and DMSO (9 mL) in a 200 mL rbf fitted with a Dean-Stark trap and a condenser was heated to reflux. The reflux was maintained for 1 h 50 min, emptying the Dean-Stark trap once. The reaction was cooled to room temperature. Toluene was removed *in vacuo* and the residue was partitioned between 1:1 H_2O/brine (100 mL) and 2:1 EtOAc/acetone (2:1). The aqueous layer was extracted with 2:1 EtOAc/acetone (90 mL). The combined organics were washed with brine (~ 50 mL). The organic layer containing grey solids was filtered to separate the solids, rinsing with acetone. The grey solid was washed with H_2O to remove any inorganic salts, then dried under air. The filtrate was dried over $MgSO_4$ and Darco, then filtered through celite and concentrated *in vacuo*. To the solid residue was added ~ 10 mL of acetone. 100 mL Et_2O was layered on top of the mixture and left to stand overnight. The crystals formed were isolated by vacuum filtration, rinsing with Et_2O. The crystals were

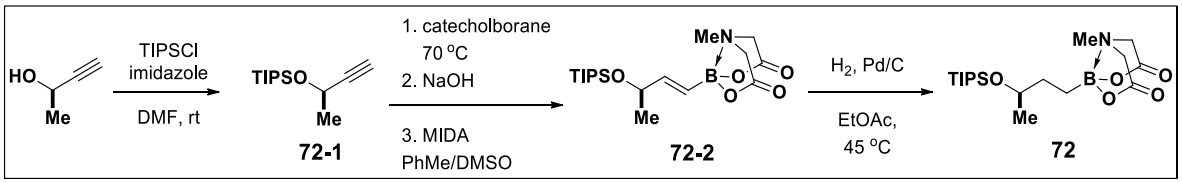
combined with the grey solids to give the desired product **9-2.1** (2.16 g, 85% yield). TLC (50% acetone/hexanes): R_f = 0.35, visualized by UV; ^{1}H-NMR (500 MHz, acetone-d_6): δ 8.28-8.21 (m, 2H), 7.84 (app d, *J* = 8.5 Hz, 2H), 4.45 (d, *J* = 17.1 Hz, 2H), 4.25 (d, *J* = 17.1 Hz, 2H), 2.83 (s, 3H); ^{13}C-NMR (125 MHz, acetone-d_6): δ 169.0, 161.4, 151.4, 134.8, 123.2, 63.1, 48.5; HRMS (EI+) calculated for $C_{11}H_{11}O_6N_2B$ $[M]^+$ *m/z* 278.07103, found 278.07115.

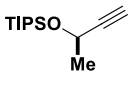


9-2

In an unoptimized procedure, a 100 mL recovery flask was charged with a stir bar, **9-2.1** (500 mg, 1.80 mmol), THF (36 mL) and MeCN (12 mL). The solution was stirred to dissolve the solids. Pd/C (10 wt%, 287 mg) was added. The flask was sealed with a rubber septum and N_2 was bubbled through the mixture for 5 min. The N_2 inlet was replaced with a H_2 balloon. H_2 was bubbled through the solution for 5 min. The outlet needle was removed and the reaction stirred under a H_2 atmosphere at rt for 36 h. The flask was opened briefly to atmosphere and another portion of Pd/C (10 wt%, 63 mg) was added. The flask was re-sealed and H_2 was bubbled through the mixture for 5 min. The outlet needle was removed and the reaction heated to 45 oC for 14 h to consume the remaining starting material. The reaction was cooled to rt, then purged with N_2 for 10 min before filtering through celite, rinsing with MeCN (3 x 10 mL). The filtrate was concentrated in vacuo. The residue was taken up in MeCN (10 mL). Et_2O (50 mL) was layered on top. The mixture was left to stand overnight. The crystals formed were isolated by vacuum filtration and dried under high vac to give **9-2** as a crystalline solid (341 mg, 76% yield). TLC (50% acetone/hexanes): R_f = 0.30, visualized by UV, stained by $KMnO_4$; ^{1}H-NMR (500 MHz, acetone-d_6): δ 7.24-7.18 (m, 2H), 6.69-6.61 (m, 2H), 4.69 (br s, 2H), 4.25 (d, J = 17.0 Hz, 2H), 4.04 (d, J = 2H), 2.69 (s, 3H). ^{13}C-NMR (125 MHz, acetone-d_6): δ ## HRMS (ESI+) calculated for $C_{11}H_{14}N_2O_4B$ $[M+H]^+$ *m/z* 249.1047, found 249.1048.

e. <u>Synthesis of building blocks for **10**</u>

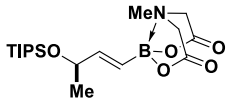




72-1

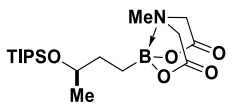
A flame-dried 250 mL Schlenk flask equipped with a stir bar was charged with imidazole (7.28 g, 107.0 mmol, 1.5 equiv). The flask was sealed with a rubber septum, evacuated and back-filled with N_2 (×3). DMF (50 mL) was added via syringe, followed by neat (*R*)-(+)-3-butyn-2-ol (5g, 71.34 mmol, 1.0 equiv). The flask was placed in a water bath at RT. Triisopropylsilyl chloride (23 mL, 107.3 mmol, 1.5 equiv) was then added neat dropwise over 5 min. The reaction was

stirred at rt for 14.5 h, then partitioned between H_2O (250 mL) and Et_2O (200 mL), rinsing with Et_2O (50 mL). The aqueous phase was extracted with Et_2O (150 mL). The combined organics were washed with H_2O (150 mL), brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by SiO_2 column chromatography (100% pentane-5% Et_2O/pentane) to give the pure product **72-1** as a colorless liquid (12.58 g, 78% yield). TLC (100% hexanes): R_f = 0.27, visualized by $KMnO_4$; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 4.59 (dq, *J* = 6.5, 2.0 Hz, 1H), 2.37 (d, *J* = 2.0 Hz, 1H), 1.46 (d, *J* = 6.0 Hz, 3H), 1.15-1.07 (m, 21H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 86.6, 71.0, 58.8, 25.6, 17.9 (2C), 12.1; HRMS (ESI+) calculated for $C_{13}H_{26}OSi$ $[M+H]^+$ *m/z* 226.1753, found 226.1751. $[\alpha]^{23}_D$ +40.3° (c = 0.9, $CHCl_3$).



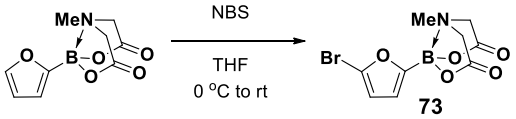
72-2

The following procedure was carried out in quadruplicate. A flame-dried 40 mL vial was charged with alkyne **72-1** (2.63 g, 11.62 mmol, 1.0 equiv) and a stir bar. The vial was flushed with Ar., then sealed with a PTFE septum cap. Catecholborane (1.3 mL, 12.2 mmol, 1.05 equiv) was added via syringe and the reaction stirred for 7 h at 70 °C. The reaction mixtures from the 4 vials were combined into an Erlenmeyer flask, rinsing with THF (140 mL total). The flask was placed in an ice-water bath and cooled to 0 °C. 1N NaOH (100 mL) was added slowly. The mixture was stirred for 15 min at 0 °C, then the ice-water bath was removed and the reaction stirred for another 15 min. The dark brown mixture was then transferred to a separatory funnel and diluted with Et_2O (280 mL). After mixing and phase separation, the aqueous phase was extracted with Et_2O (70 mL). The combined organics were washed with sat. aq. Na_2CO_3 (70 mL × 5), brine (140 mL), dried over $MgSO_4$, filtered and concentrated. The crude boronic acid was diluted with benzene (100 mL) and stored at – 20 °C overnight. After warming the frozen mixture to rt, benzene was removed in vacuo. The residue was transferred to a 500 mL single neck rbf, rinsing with PhMe (250 mL). DMSO (25 mL) was added, followed by MIDA (7.18 g, 48.8 mmol, 1.05 equiv). The mixture was stirred and heated to reflux with a Dean-Stark trap for 4.5 h, then cooled briefly. PhMe was removed in vacuo and the residue was partitioned between EtOAc (250 mL) and H_2O (150 mL). The aqueous layer was extracted with EtOAc (100 mL). The combined organics were washed with 1:1 H_2O/brine (120 mL × 2), brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by SiO_2 column chromatography (100% Et_2O-10% -20% acetone/Et_2O). The colorless fractions containing the product were concentrated to give **72-2** as a white solid (5.79 g, 32% yield). TLC (40% acetone/hexanes): R_f = 0.50, visualized by $KMnO_4$ stain; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.15 (dd, *J* = 18.0, 5.5 Hz, 1H), 5.68 (dd, *J* = 18.0, 1.5 Hz, 1H), 4.52-4.47 (m, 1H), 4.21 (d, *J* = 17.0 Hz, 1H), 4.21 (d, *J* = 16.5 Hz, 1H), 4.01 (d, *J* = 17.0 Hz, 1H), 3.97 (d, *J* = 17.0 Hz, 1H), 3.00 (s, 3H), 1.24 (d, *J* = 6.5 Hz, 3H), 1.12-1.07 (m, 21H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 169.0 (2C), 150.1, 71.5, 62.2 (2C), 47.3, 25.1, 18.5, 18.4, 13.0; HRMS (ESI+) calculated for $C_{18}H_{35}BNO_5Si$ $[M+H]^+$ *m/z* 384.2378, found 384.2383.

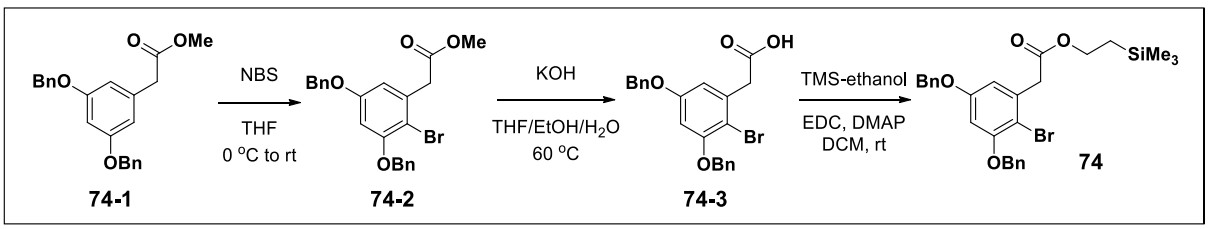


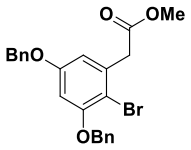
72

A 200 mL single neck rbf was charged with MIDA boronate **72-2** (4.59 g, 11.97 mmol, 1.0 equiv), a stir bar and 10 wt% Pd/C (255 mg, 0.24 mmol, 0.02 equiv). The rbf was sealed with a rubber septum, evacuated and back-filled with N_2 (×3). EtOAc (60 mL) was added via syringe and H_2 was bubbled through the mixture from a balloon for 5 min. The mixture was then stirred under a H_2 atmosphere for 15 min at rt, then at 45 °C for 45 min. The reaction was cooled to rt and purged with N_2, then filtered through celite, rinsing with CH_2Cl_2 (100 mL). The filtrate was concentrated *in vacuo* and the crude product purified on a SiO_2 column (30%-35%-40% acetone/hexanes) to give a white solid as the pure product **72** (3.81 g, 83% yield). TLC (40% acetone/hexanes): R_f = 0.47, visualized by $KMnO_4$ stain; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 4.18 (d, *J* = 17.0 Hz, 1H), 4.18 (d, *J* = 17.0 Hz, 1H), 4.02 (d, *J* = 16.5 Hz, 1H), 4.01 (d, *J* = 16.5 Hz, 1H), 3.96 (dq, *J* = 12.5, 6.5 Hz, 1H), 3.10 (s, 3H), 1.65-1.58 (m, 1H), 1.52-1.45 (m, 1H), 1.17 (d, *J* = 6.0 Hz, 3H), 1.08 (m, 21H), 0.71-0.62 (m, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 168.8, 168.7, 71.3, 62.6 (2C), 46.2, 35.2, 23.4, 18.5 (2C), 13.2; HRMS (ESI+) calculated for $C_{18}H_{37}BNO_5Si$ $[M+H]^+$ *m/z* 386.2534, found 386.2528.



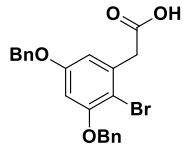
A flame-dried 250 mL Schlenk flask was charged with 2-furanyl MIDA boronate (Aldrich catalog # 701017, 2.00 g, 8.97 mmol, 1.0 equiv) and THF (90 mL). The solution was cooled to 0 °C in an ice-water bath. *N*-bromosuccinimide was added as a solid under a positive pressure of N_2. The reaction was stirred in the cold bath, gradually warming to rt. After 3 h 15 min, the reaction was cooled to 0 °C and another portion of N-bromosuccinimide (239 mg, 1.35 mmol, 0.15 equiv) was added. The reaction was stirred for another 4 h, gradually warming to rt. The reaction mixture was then transferred to a separatory funnel and diluted with EtOAc (100 mL). The organics were washed with sat. aq. Na_2SO_3 (100 mL ×2). The aqueous phase was extracted with EtOAc (100 mL). The combined organics were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by silica gel column (20%-40%-60% EtOAc/Et_2O). The fractions containing product were concentrated and taken up in 10 mL acetone. 1:1 Et_2O/hexanes (100 mL) was layered on top of the acetone solution and the mixture was left to stand at RT. The white solid obtained were filtered and dried *in vacuo* to give the pure product **73** (871 mg, 32% yield). (50% acetone/hexanes): R_f = 0.47, visualized by $KMnO_4$ stain; ^{1}H-NMR (500 MHz, acetone-d_6): δ 6.72 (d, *J* = 3.0 Hz, 1H), 6.44 (d, *J* = 3.5 Hz, 1H), 4.38 (d, *J* = 17.0 Hz, 2H), 4.18 (d, *J* = 17.0 Hz, 2H), 2.92 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 168.7, 125.3, 121.6, 112.4, 62.5, 47.9; HRMS (ESI+) calculated for $C_9H_{10}BNO_5Br$ $[M+H]^+$ *m/z* 301.9835, found 301.9826.





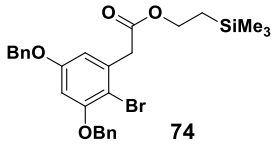
74-2

A 300 mL single neck rbf equipped with a stir bar was charged with methyl ester **74-1** (*45*) (6.43 g, 17.75 mmol, 1.0 equiv) and THF (160 mL) under ambient atmosphere. The solution was cooled to 0 °C in an ice-water bath. *N*-bromosuccinimide (3.22 g, 18.11 mmol, 1.02 equiv) was added as a solid slowly over 2 min. The reaction was stirred at 0 °C for 15 min, then the ice-water bath was removed and the reaction warmed to rt. The reaction was stirred for a total of 2.5 h. The reaction mixture was concentrated *in vacuo*. The residue was taken up in CH_2Cl_2 and the crude product was adsorbed onto celite *in vacuo*. The celite pad was loaded onto a SiO_2 column for purification (50-70% DCM/hexanes). The fractions containing product were concentrated in vacuo to give a white solid, which was dissolved in hot Et_2O/hexanes (approx.. 1:9, 500 mL) and left to cool at RT to allow crystallization overnight. The white solid formed was obtained by vacuum filtration, rinsing with hexanes (60 mL) and dried *in vacuo*, giving the pure product **74-2** (4.75 g, 68% yield). TLC (60% DCM/hexanes): R_f = 0.35, visualized by shortwave UV; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.47-7.45 (m, 2H), 7.40-7.32 (m, 8H), 6.58 (d, J = 3.0 Hz, 1H), 6.55 (d, J = 2.5 Hz, 1H), 5.10 (s, 2H), 5.01 (s, 2H), 3.81 (s, 2H), 3.72 (s, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 170.9, 158.5, 155.9, 136.4, 136.3, 135.9, 128.6, 128.5, 128.1, 127.9, 127.5, 126.9, 109.1, 106.5, 100.9, 70.8, 70.3, 52.2, 42.0; HRMS (ESI+) calculated for $C_{23}H_{22}O_4Br$ $[M+H]^+$ *m/z* 441.0701, found 441.0705.



74-3

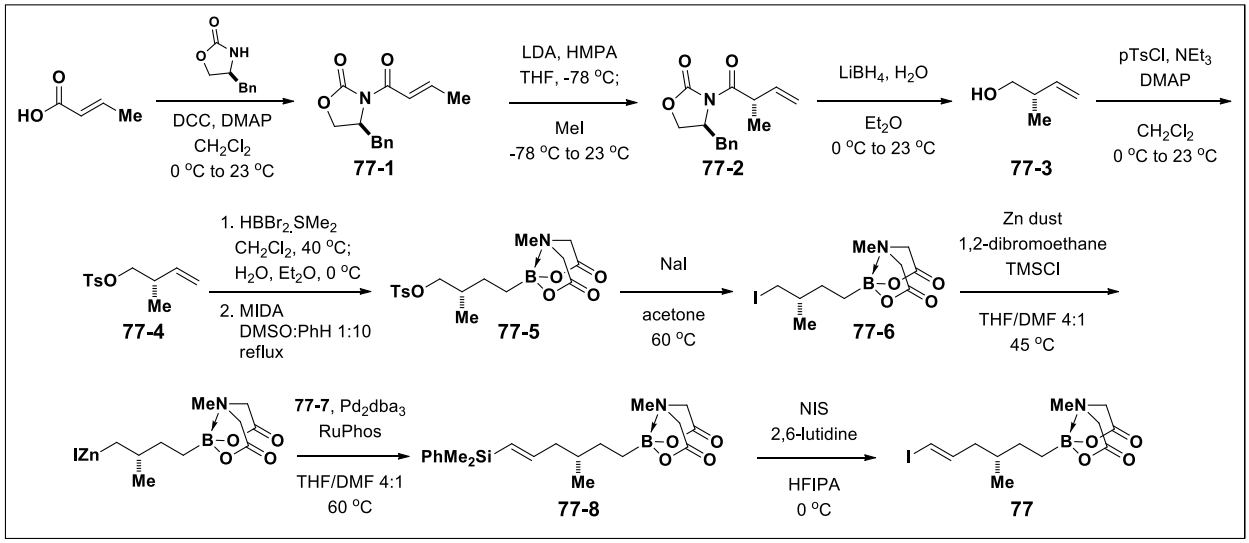
A 40 mL Ichem vial equipped with a stir bar was charged with methyl ester **74-2** (932 mg, 2.11 mmol, 1.0 equiv), followed by EtOH (10 mL) and KOH (2.37 g, 42.24 mmol, 20 equiv), forming a thick suspension. THF (10 mL) was then added. The vial was sealed and stirred vigorously at 60 °C. The solids gradually dissolved to form a clear biphasic mixture. After 2 h 15 min, the reaction was cooled to RT and transferred to a 125 mL Erlenmeyer flask, rinsing with H_2O. With vigorous stirring, the reaction was neutralized to pH 3 with 2N HCl at rt. The mixture was transferred to a separatory funnel, rinsing with Et_2O and H_2O. The organic layer was diluted with EtOAc (50 mL). After mixing and phase separation, the aqueous layer was extracted with EtOAc (50 mL). The combined organics were washed with brine (50 mL × 2), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give **74-3** as a white solid that was used directly for the next step without purification. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.47-7.44 (m, 2H), 7.42-7.30 (m, 8H), 6.59 (d, *J* = 2.5 Hz, 1H), 6.56 (d, *J* = 2.5 Hz, 1H), 5.10 (s, 2H), 5.00 (s, 2H), 3.85 (s, 2H).

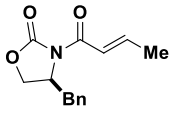


74

A flame-dried 25 mL Schlenk flask equipped with a stir bar was charged with acid **74-3** obtained above, and DMAP (28.2 mg, 0.23 mmol, 0.11 equiv). CH_2Cl_2 (18 mL) was added, followed by trimethylsilylethanol (0.61 mL, 4.26 mmol, 2.0 equiv). EDC.HCl (445 mg, 2.32 mmol, 1.1 equiv) was added as a solid. The reaction was stirred for 18 h at RT, then transferred to a separatory funnel. The organic layer was washed sequentially with H_2O, 1N HCl and sat. $NaHCO_3$, then with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by SiO_2 column chromatography (10-20% EtOAc/hexanes) to give a white cloudy liquid (1.27 g, 71% yield over 2 steps) that turned into a white solid after storage in the freezer. TLC (20% EtOAc/hexanes): R_f = 0.59, visualized by UV; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.54-7.34 (m, 10 H), 6.80 (d, *J* = 2.5 Hz, 1H), 6.75 (d, *J* = 2.5 Hz, 1H), 5.22 (s, 3H), 5.11 (s, 3H), 4.21-4.17 (m, 2H), 3.79 (s, 2H), 1.02-0.98 (m, 2H), 0.04 (s, 9H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 170.6, 158.5, 155.9, 136.4 (2C), 136.2, 128.6, 128.5, 128.1, 127.9, 127.6, 127.0, 109.2, 106.6, 101.0, 70.9, 70.3, 63.3, 42.4, 17.2, -1.5; HRMS (ESI+) calculated for $C_{27}H_{32}O_4SiBr$ $[M+H]^+$ *m/z* 527.1253, found 527.1261.

f. Synthesis of building blocks for **11**

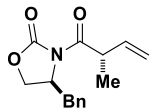




77-1

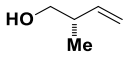
In an oven-dried 3-neck 1000 mL RBF, a solution of (S)-4-benzyloxazolidin-2-one (25.35 g, 143.08 mmol), crotonic acid (24.81 g, 288.2 mmol), and DMAP (2.28 g, 18.67 mmol) in anhydrous CH_2Cl_2 (500 mL) was cooled to 4 °C (internal temp) under N_2 using an ice-water bath. To this was added DCC (59.12 g, 286.55 mmol), causing an exotherm (internal temperature rose to ~10 °C). After approximately 10 min, a precipitate began to form. After 18 h, TLC showed full consumption of the acid while oxazolidinone remained. Another portion of crotonic acid (6.15 g, 71.42 mmol) and DCC (14.52 g, 70.37 mmol) were added at 0 °C and the

reaction was stirred and warmed to RT for a further 3 h. The reaction was filtered through a Buchner funnel, rinsing with CH_2Cl_2 (150 mL). The filtrate was then washed with sat. $NaHCO_3$ (200 mL), 1:1 sat. $NaHCO_3$/water (200 mL), and water (200 mL). The aqueous layer was then extracted with CH_2Cl_2 (200 mL). The combined organics were then dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a thick orange slurry. After storage overnight under nitrogen at 0 °C, the slurry was taken up in a minimum of CH_2Cl_2, loaded onto Celite, and purified by column chromatography (9 cm × 13 cm height, equilibrated with CH_2Cl_2, gradient: 100% DCM to 2.5% EtOAc/DCM to 5% EtOAc/DCM). The resulting product was still impure, so was passed through another silica gel column (9 cm x 8 cm, CH_2Cl_2) before recrystallizing from a minimum of hot EtOAc to yield **77-1** (21.37 g , 61% yield) as a waxy solid. ^{1}H-NMR matches literature data. (*46*) The solid was further dried by azeotroping with toluene (2 × 100mL) and drying under high vacuum (~3 h).



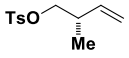
77-2

An oven-dried 1000 mL RBF was fitted with a stir-bar, a cryogenic thermometer, an addition funnel, and an N_2/vacuum inlet. The warm flask was then vac/N_2-filled (3 ×) before adding THF (340 mL) and iPr_2NH (13.5 mL, 96.3 mmol) and cooling to -70 ^{o}C. nBuLi (1.6 M in hexanes, 60.0 mL, 96 mmol) was then added to the addition funnel via syringe before adding to the reaction over ~25 min. After stirring at -70 ^{o}C for a further 25 min, HMPA (16.7 mL, 96.0 mmol) was added in a dropwise fashion (via the addition funnel, over ~10 min). The solution was allowed to stir at -70 °C for approximately 1 h. A separate 500 mL single neck rbf containing imide **77-1** was vac/N_2-filled (3 ×). The white solid was then taken up in THF (120 mL) with stirring. This solution was then added to the addition funnel via syringe and added to LDA solution in a slow, dropwise manner (-68 to -70 °C, over ~50 min) giving a translucent orange solution which was stirred for a further 30 minutes at this temperature before adding neat MeI (16.5 mL, 265 mmol) in a dropwise manner (over ~35 min) at -70 °C. The yellow solution was stirred at -70 °C for 1 h and then the iPrOH/dry ice bath was replaced with an ice/brine bath, allowing it to stir for 45 min before warming to room temperature and stirring for another 30 min. The reaction was then again placed in an ice/brine bath and quenched with sat. NH_4Cl (300 mL). The mixture was then transferred to a separatory funnel, rinsing with Et_2O. After mixing and phase separation, the aqueous layer was extracted with Et_2O (3 × 250 mL). The combined organic layers were washed with brine (200 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a fluorescent yellow oil. Crude ^{1}H NMR showed with a d.r. of 3.6:1 (desired:undesired diastereomer). The desired diastereomer was purified by splitting the crude material into two batches and running two columns on each batch (for four total columns). Gradient: 100% hexanes to 7.5% EtOAc/hexanes, in 2.5% increments. The columns gave **77-2** (9.67 g, 43% yield) as a colorless oil with a d.r. of >20:1 by ^{1}H NMR. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.36 – 7.27 (m, 3H), 7.24 – 7.19 (m, 2H), 5.98 (ddd, J = 17.2, 10.3, 7.7 Hz, 1H), 5.20 (dt, J = 17.3, 1.1 Hz, 1H), 5.14 (dt, J = 10.3, 1.0 Hz, 1H), 4.66 (ddd, J = 10.5, 7.2, 3.7 Hz, 1H), 4.46 (dtd, J = 7.8, 6.9, 5.9 Hz, 2H), 4.23 – 4.15 (m, 1H), 3.29 (dd, J = 13.4, 3.3 Hz, 1H), 2.78 (dd, J = 13.4, 9.6 Hz, 1H), 1.35 (d, J = 6.9 Hz, 3H).



77-3

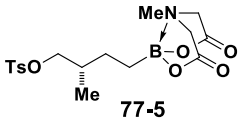
A solution of imide **77-2** (9.67 g, 37.3 mmol) in Et_2O (300 mL) was cooled to ~0 °C in an ice/brine bath, stirring for ~15 minutes before adding H_2O (1.68 mL, 93.3 mmol) via syringe. With vigorous stirring, $LiBH_4$ (2.04 g, 93.7 mmol) was added in four portions in a slow, cautious manner (a vigorous exotherm was noted, with effervescence). After the addition was complete, the flask was fitted with a rubber septum which had already been pierced with a N_2 inlet needle and vent needle. The mixture was stirred in the ice/brine bath for 1.5 h before being warmed to room temperature and stirring for 40 min. TLC analysis (20% EtOAc/hexanes) showed no remaining starting material. The reaction mixture was cooled in an ice/water bath for ~5 min before being quenched with sat. Rochelle's salt (70 mL, added slowly via addition funnel). The biphasic reaction mixture was vigorously stirred for 10 min before being transferred to a separatory funnel. After mixing and phase separation, the organic layer was drained into a RBF containing sat. Rochelle's salt (150 mL) and stirred for 1 hour. The combined aqueous layers were extracted (2 × 100 mL Et_2O). The combined organic layers were then washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated to ~35 mL (house vacuum, room temperature), at which point, oxazolidinone side product had begun crystallizing out. To this solution was added 150 mL pentane, which caused the precipitation of more oxazolidinone. This mixture was filtered, washing the solids with ~50 mL of 30% Et_2O/pentane. The resulting cloudy filtrate was loaded directly atop a silica gel column (5 cm x 7 cm height) and eluted (gradient: 30% Et_2O/pentane to 40% Et_2O/pentane to 50% Et_2O/pentane). The product came off in ~1000 mL of eluent, which was concentrated to give a solution of the product alcohol **77-3** (^{1}H NMR calculation: 2.36 g, 74% yield) in Et_2O/pentane, which was used directly in the next step. A small sample had the solvents fully removed to give enough pure alcohol to obtain an optical rotation which is in agreement with the known literature value.(*47*) ^{1}H-NMR matches literature data. (*47*) $[\alpha]_D^{24}$: -29.8 (c=1.42, $CHCl_3$).



77-4

A flask containing a concentrated solution of alcohol **77-3** (2.36 g, 27.4 mmol) in Et_2O/pentane was charged with a stir bar and CH_2Cl_2 (70 mL). The solution was then stirred in an ice/water bath and cooled for 15 min, during which DMAP (402.8 mg, 3.3 mmol) and Et_3N (11.5 mL, 82.5 mmol) were added. After cooling, *p*TsCl (6.28 g, 32.9 mmol) was added under ambient atmosphere, rinsing the funnel with another portion of CH_2Cl_2 (20 mL). The flask was then fitted with a rubber septum, purged with N_2 for ~5 minutes, and then allowed to stir under N_2 for 15 h, gradually warming to room temperature. TLC showed no remaining starting material (20% EtOAc/hexanes). The reaction was then quenched with water (50 mL). The biphasic mixture was stirred rapidly for 10 min before transferring to a separatory funnel. After mixing and phase separation, the aqueous layer was extracted with CH_2Cl_2 (2 × 75 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to ~20 mL. To this solution was added several scoops of Celite, and the solvent was removed *in vacuo* to give the crude product loaded on Celite. This was loaded atop a silica gel column equilibrated with 5% Et_2O/hexanes. Gradient: 5% Et_2O/hexanes to 7.5% Et_2O/hexanes to 10% Et_2O/hexanes. The fractions containing product were concentrated to give **77-4** (5.06 g, 77% yield) as a colorless oil. TLC (10% EtOAc/hexanes): R_f = 0.34, visualized by UV, stained by $KMnO_4$; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.76 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 7.9 Hz, 2H), 5.60 (ddd, *J* = 17.3, 10.4, 7.0

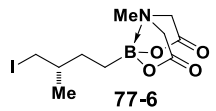
Hz, 1H), 5.05 – 4.98 (m, 2H), 3.89 (dd, *J* = 9.4 and 6.4 Hz, 1H), 3.82 (dd, *J* = 9.4 and 6.8 Hz, 1H), 2.53 – 2.45 (m, 1H), 2.42 (s, 3H), 0.98 (d, *J* = 6.8 Hz, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 144.8, 138.4, 133.0, 129.9, 127.9, 116.0, 74.0, 37.0, 21.7, 16.0; HRMS (ESI+) calculated for $NaC_{12}H_{16}O_3S$ $[M+Na]^+$ *m/z* 263.0718 found 263.0716.



77-5

Note: this reaction was done in duplicate, and the two vials were combined for workup. An oven-dried 40 mL vial was charged with tosylate **77-4** (1.01 g, 4.19 mmol), sealed with a septum cap, and then vac/filled with N_2 (×3). CH_2Cl_2 (10.0 mL) was then added via syringe, followed by a solution of $HBBr_2$▪SMe_2 (1.0 M in CH_2Cl_2, 5.0 mL, 5.0 mmol) at room temperature. The vial was then placed in a 40 °C heating block and allowed to stir for 10 h. ^{1}H NMR of an aliquot of the reaction revealed nearly complete conversion. Separately, a rbf flask containing 100 mL Et_2O and 50 mL water was cooled to 0 °C in an ice bath. The two vials containing the reaction mixtures were cannulated into this rbf in a dropwise fashion with vigorous stirring. After stirring for ~10 min, the biphasic mixture was transferred to a separatory funnel. After mixing and phase separation, the aqueous layer was extracted with Et_2O (2 × 100 mL). The combined organics were washed with brine (100 mL), dried over Na_2SO_4, and vacuum filtered. The solution was then concentrated to ~15 mL of a cloudy mixture and used directly in the next step.

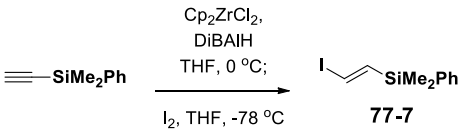
To the solution of the boronic acid in a rbf was added MIDA (1.53 g, 10.4 mmol), and a PhH:DMSO mixture (10:1, 88 mL). The rbf was then fitted with a Dean-Stark trap and a water-cooled condenser. The mixture was stirred and refluxed for 1 h, after which TLC showed complete conversion. The reaction mixture was cooled to room temperature and transferred to a separatory funnel containing 1:1 brine/water (100 mL) and EtOAc (100 mL), rinsing with EtOAc. After mixing and phase separation, the aqueous layer was extracted with EtOAc (100 mL). The combined organics were then washed with 1:1 brine/water (100 mL), brine (100 mL), and then dried over Na_2SO_4. After filtration, the solution was concentrated, giving a viscous oil. This oil was diluted with acetone (~5 mL) before adding hexanes (100 mL) in a slow, dropwise fashion via addition funnel, causing a white powdery solid to precipitate. The white solid was collected by vacuum filtration and then dried under high vacuum to give **77-5** (2.14 g, 64% yield). TLC (50% acetone/hexanes): R_f = 0.31, visualized by UV, stained by $KMnO_4$; ^{1}H-NMR (500 MHz, acetone-d_6): δ 7.81 (d, *J* = 8.3 Hz, 2H), 7.48 (d, *J* = 7.9 Hz, 2H), 4.17 (d, *J* = 16.9 Hz, 2H), 4.00 (d, *J* = 16.9 Hz, 2H), 3.96 (dd, *J* = 9.6, 5.5 Hz, 1H), 3.86 (dd, *J* = 9.5, 6.5 Hz, 1H), 3.06 (s, 3H), 2.46 (s, 3H), 1.74 (dq, *J* = 12.9, 6.5 Hz, 1H), 1.45 – 1.36 (m, 1H), 1.19 (dddd, *J* = 13.8, 12.3, 7.5, 4.8 Hz, 1H), 0.88 (d, *J* = 6.7 Hz, 3H), 0.61 (dt, *J* = 13.2, 4.8 Hz, 1H), 0.51 (dt, *J* = 13.2, 4.9 Hz, 1H); ^{13}C-NMR (125 MHz, acetone-d_6): δ 168.7, 145.7, 134.5, 130.8, 128.7, 75.8, 62.7, 46.3, 35.9, 28.0, 21.5, 16.6.; HRMS (ESI+) calculated for $C_{17}H_{25}BNO_7S$ $[M+H]^+$ *m/z* 398.1445, found 398.1451.



77-6

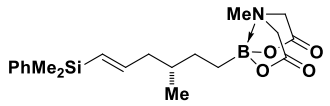
A flame-dried 40 mL vial was charged with MIDA boronate **77-5** (761.8 mg, 1.92 mmol) and NaI (444.6 mg, 2.97 mmol). Acetone (6.0 mL, HPLC grade) was added via syringe under a

positive pressure of N_2. The reaction was then stirred for 13 h in a 60 °C heating block before TLC showed complete conversion. The reaction mixture was then poured into a separatory funnel containing EtOAc (100 mL) and water (100 mL), rinsing once with EtOAc. Upon shaking, a persistent emulsion formed. After adding brine (30 mL) and re-shaking, the aqueous layer was extracted with EtOAc (100 mL). The combined organic layers were then washed with sat. $Na_2S_2O_3$ (2 × 50 mL) and brine (100 mL), dried over Na_2SO_4, filtered and concentrated. The crude product was then taken up in a minimum of acetone and hexanes (100 mL) was added in a slow, dropwise fashion via addition funnel causing the product to precipitate out as a fine white powder. This powder was isolated via vacuum filtration and dried overnight under high vacuum to give **77-6** (550 mg, 81% yield). TLC (50% acetone/hexanes): R_f = 0.41, visualized by UV, stained by $KMnO_4$; ^{1}H-NMR (500 MHz, acetone-d_6): δ 4.20 (d, *J* = 16.9 Hz, 2H), 4.04 (dd, *J* = 16.9 and 1.4 Hz, 2H), 3.39 (dd, *J* = 9.6 and 4.0 Hz, 1H), 3.29 (dd, *J* = 9.6 and 5.7 Hz, 1H), 3.13 (s, 3H), 1.49 – 1.39 (m, 2H), 1.38 – 1.29 (m, 1H), 1.00 (d, *J* = 6.2 Hz, 3H), 0.69 – 0.62 (m, 2H); ^{13}C-NMR (125 MHz, acetone-d_6): δ 168.8, 62.6, 46.3, 37.8, 31.6, 20.7, 18.7; HRMS (ESI+) calculated for $C_{10}H_{18}BNO_4I$ $[M+H]^+$ *m/z* 354.0374, found 354.0372.



77-7

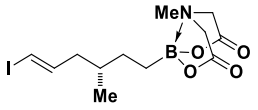
The following procedure was modified from a known literature procedure. (*48*) An oven-dried 1L 3-neck rbf equipped with a thermometer and stir bar was added Cp_2ZrCl_2 (30.56 g, 104.5 mmol, 1.15 equiv). The flask was sealed with rubber septa and evacuated and back-filled with Ar (×3). THF (225 mL) was added via cannula. The solution was cooled to an internal temperature of 4 °C in an ice-water bath. DiBAlH solution (1 M in THF, 100 mL, 100 mmol, 1.1 equiv) was cannulated into the rbf, keeping the internal temperature at 3-4 °C. The addition took 23 min. The reaction was then stirred at 3 °C for 30 min. Phenyldimethylsilylethylene (16.1 mL, 91.1 mmol, 1.0 equiv) was added neat via syringe at the same temperature over 10 min. The reaction was then allowed to warm to 18 °C over 3 h. The reaction was then cooled to -69 °C (internal temperature) in a dry ice/IPA bath. Under air, solid I_2 (30.0 g, 118.18 mmol, 1.3 equiv) was added to a graduated conical flask containing THF (150 mL). The flask was sealed with a rubber septum and stirred to dissolve the I_2. The solution was then cannulated into the reaction flask under Ar, maintain the internal temperature at ≤ -65 °C. The addition took 1 h 15 min. After the addition was complete, the reaction was stirred at – 70 °C for 1.5 h. The dry ice bath was removed and the reaction quenched with 1N HCl (200 mL). The mixture was stirred vigorously, then transferred to a 2L separatory funnel and extracted with Et_2O (100 mL). The aqueous layer was extracted with Et_2O (100 mL). The combined organics were washed with sat. aq. $Na_2S_2O_3$ (200 mL), brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. During solvent removal, a large amount of solids precipitated. To the concentrated residue was added hexanes (150 mL). The suspension was filtered to remove the orange solids, rinsing with hexanes (100 mL). The filtrate was concentrated to a yellow oil. The product was purified by a total of 3 SiO_2 columns (hexanes) to the pure product as a colorless oil **77-7** (15.66 g, 60% yield). TLC (hexanes): R_f = 0.57, visualized by UV; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.52-7.51 (m, 2H), 7.41-7.38 (m, 3H), 7.20 (d, J = 16.5 Hz, 1H), 6.75 (d, J = 16.0 Hz, 1H), 0.38 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 148.3, 136.5, 133.7, 129.5, 128.0, 91.5, -2.9.



77-8

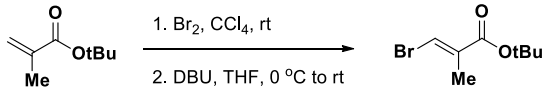
Formation of the organozinc reagent: Iodide **77-6** (1.36 g, 3.85 mmol) was weighed into an oven-dried 40 mL vial. This and another empty vial were taken into the glove box. THF (4.5 mL) and DMF (1.5 mL) were added to dissolve the iodide. The other vial was charged with Zn dust (754.6 mg, 11.54 mmol) and a magnetic stir bar before sealing both vials and removing from the glove box. Under a positive pressure of N_2, TMSCl and 1,2-dibromoethane were added to the vial containing the Zn dust (three drops each from a 25 gauge needle). This was stirred briefly before transferring the iodide **77-6** solution to this vial via syringe. The vial was then rinsed with another portion of THF (1.4 mL). The vial was placed into a 45 ^oC heating block for 2 h. At this point, a small aliquot was removed, quenched with sat. NH_4Cl, and extracted with EtOAc. ^1H NMR of the extract showed full conversion. The reaction vial was then taken into the glove box and filtered through an HPLC iso-disc syringe-tip filter into a dry 40 mL vial. This colorless solution was stored in the glove box for approximately 36 h before use in the next step.

In the glovebox, (*E*)-(2-iodovinyl)dimethyl(phenyl)silane **77-7** (1.12 g, 3.90 mmol) was weighed into the 40 mL vial, followed by the addition of THF (8.6 mL) and DMF (2.1 mL). RuPhos (182 mg, 0.390 mmol) and $Pd_2(dba)_3$ (90.1 mg, 0.0984 mmol) were then added to the solution in that order. The vial was then sealed and removed from the glove box, along with the vial containing the solution of alkylzinc prepared above. The vial containing the catalyst was placed into a 60 ^oC heating block and had a N_2 inlet needled inserted into the septum. The alkylzinc solution was then slowly added to this vial with the assistance of a syringe pump (~75 min). The reaction stirred for a total of 8 h (from the beginning of the addition). The reaction was then cooled to room temperature and transferred to a separatory funnel containing sat. NH_4Cl (80 mL) and EtOAc (60 mL). The vial was rinsed with a further 20 mL EtOAc. After shaking, a persistent emulsion formed which was resolved by adding a small amount (~5 mL) of brine and remixing. After phase separation, the aqueous layer was extracted with EtOAc (80 mL). The combined organic layers were then washed with 1:1 water:brine (100 mL) and brine (100 mL). The organic layers were then stirred over $MgSO_4$ and Darco before filtering through Celite. ^1H NMR of the crude mixture showed product to be the primary component. The crude mixture was dry loaded onto Celite and then purified by column chromatography (silica gel, equilibrated with 20% acetone/hexanes, gradient: 20% to 25% to 30% acetone/hexanes) to give **77-8** (1.003 g, 67% yield) as a slightly off-white foam. TLC (50% acetone/hexanes): R_f = 0.53, visualized by UV, stained by $KMnO_4$; ^1H-NMR (500 MHz, acetone-d_6): δ 7.56 – 7.52 (m, 2H), 7.38 – 7.33 (m, 3H), 6.15 (dt, *J* = 18.5, 6.8 Hz, 1H), 5.79 (dt, *J* = 18.5, 1.4 Hz, 1H), 4.17 (d, *J* = 16.9 Hz, 2H), 4.00 (dd, *J* = 16.8, 3.7 Hz, 2H), 3.07 (s, 3H), 2.25 (dddd, *J* = 13.5, 6.6, 5.3, and 1.6 Hz, 1H), 2.03 – 1.95 (m, 1H), 1.56 – 1.48 (m, 1H), 1.46 – 1.37 (m, 1H), 1.23 (dddd, *J* = 13.6, 12.2, 7.3, 4.8 Hz, 1H), 0.89 (d, *J* = 6.7 Hz, 3H), 0.72 – 0.56 (m, 1H), 0.31 (s, 6H).; ^{13}C-NMR (125 MHz, acetone-d_6): δ 168.8, 149.2, 139.9, 134.6, 129.7, 129.6, 128.6, 62.7, 46.3, 45.0, 36.0, 31.8, 19.7, -2.2.; HRMS (ESI+) calculated for $C_{20}H_{31}NO_4SiB$ $[M+H]^+$ *m/z* 388.2115, found 388.2112.



77

A vial containing vinyl silane **77-8** (176.9 mg, 0.46 mmol) was charged with a stir bar and HFIPA (2.0 mL). The mixture was then sonicated briefly to give a homogenous solution. The vial was then cooled to 0 ^{o}C in an ice-water bath before adding 2,6-lutidine (40 μL, 0.34 mmol) under ambient atmosphere. NIS (156.4 mg, 0.70 mmol) was then added in three portions over about 2 min, yielding a purple/red mixture. The mixture was then stirred in the ice-water bath for 70 min before TLC showed complete conversion. Sat. $Na_2S_2O_3$ (5 mL) was added at 0 ^{o}C and the mixture was stirred for 10 min, after which a faint yellow color remained. The reaction mixture was transferred to a separatory funnel containing EtOAc (10 mL) and sat. $Na_2S_2O_3$ (10 mL). After shaking and phase separation, the aqueous layer was extracted with EtOAc (15 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, and treated with Darco before filtering. This solution was concentrated to give a colorless sticky residue. This residue was taken up into a minimum of acetone (~1 mL) and 50 mL of hexanes was dripped into this solution with vigorous stirring in a slow, dropwise manner via addition funnel, precipitating an off-white powder. This off-white powder was isolated via vacuum filtration and dried under high vacuum to give **77** (104.1 mg, 60% yield). TLC (50% acetone/hexanes): R_f = 0.50, visualized by UV, stained by $KMnO_4$; ^{1}H-NMR (500 MHz, acetone-d_6): δ 6.54 (dt, *J* = 14.9 and 7.6 Hz, 1H), 6.14 (d, *J* = 14.3 Hz, 1H), 4.17 (d, *J* = 16.9 Hz, 2H), 4.01 (dd, *J* = 16.9 and 1.7 Hz, 2H), 3.10 (s, 3H), 2.80 (d, *J* = 16.9 Hz, 3H), 2.18 – 2.11 (m, 1H), 1.96 – 1.89 (m, 1H), 1.56 – 1.46 (m, 1H), 1.44 – 1.34 (m, 1H), 1.26 – 1.17 (m, 1H), 0.88 (d, *J* = 6.7 Hz, 3H), 0.71 – 0.55 (m, 2H); ^{13}C-NMR (125 MHz, acetone-d_6): δ 168.8, 146.7, 75.7, 62.6, 46.2, 43.5, 35.7, 31.5, 19.4; HRMS (ESI+) calculated for $C_{12}H_{20}BNO_4I$ $[M+H]^+$ *m/z* 380.0530, found 380.0527.

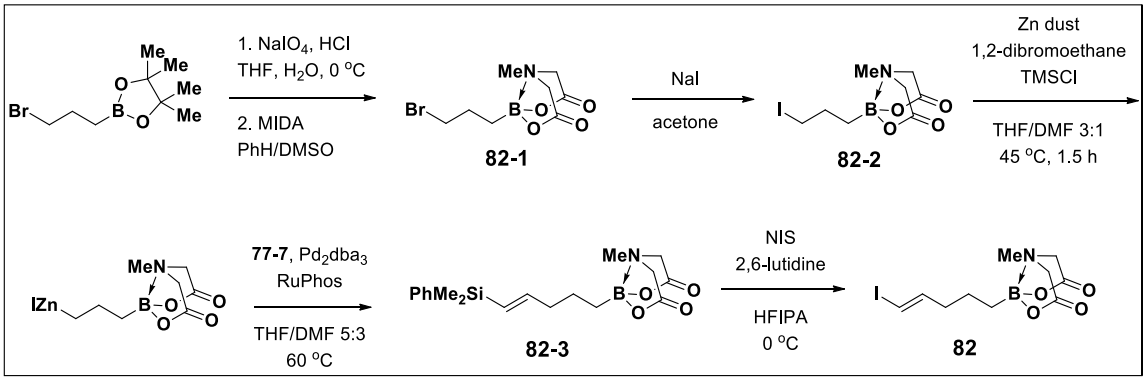


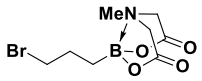
78

In an unoptimized procedure, to a solution of *tert*-butylmethacrylate (5 mL, 30.77 mmol, 1.0 equiv) in CCl_4 (100 mL) was added neat bromine (1.6 mL, 31.38 mmol, 1.02 equiv) slowly over 1 min under ambient atm. The rbf was sealed with a rubber septum and the reaction stirred under an N_2 atm, warming to RT overnight. The reaction was stirred for 17.5 h, then 1M $Na_2S_2O_3$ (50 mL) was added to quench the reaction. The mixture was stirred vigorously until the organic layer turns from red-orange to colorless. The layers were separated and the aqueous phase extracted with CH_2Cl_2 (50 mL × 2). The combined organics were washed with brine, dried over $MgSO_4$, filtered and concentrated to give a colorless liquid, which was a mixture of the dibromide and the starting material in a ratio of 8.5:1. This material was dissolved in THF and cooled to 0 °C. DBU was added neat via syringe under ambient atm over 3 min. The reaction was stirred for 17 h. H_2O (100 mL) and Et_2O (100 mL) was added and the mixture stirred vigorously. The layers were separated and the aqueous layer extracted with Et_2O (50 mL). The combined organics were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo to give an orange liquid which was purified by SiO_2 column chromatography (20%-30% DCM/hexanes), giving a colorless liquid which was a mixture of the desired vinyl bromide and the dibromide in the ratio 12:1. This material was resubjected to the reaction using DBU (0.9 mL, 6 mmol) and THF (100 mL) to consume the remaining dibromide. The reaction was subjected to the same work-up

procedure described above and purified by SiO_2 column chromatography, giving the pure product **78** as a colorless liquid (4.09 g, 60% yield over 2 steps). ^{1}H-NMR matches literature data. (*49*)

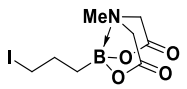
g. Synthesis of building blocks for **12**





82-1

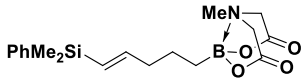
To a solution of 3-bromopropylboronic acid pinacol ester (1.00 g, 4.02 mmol, 1.0 equiv) in a solution of THF (4 mL) and H_2O (3 mL) was added solid $NaIO_4$ (4.30 g, 20.08 mmol, 5.0 equiv) at 0 °C under ambient atm. 1N HCl (8.1 mL, 8.1 mmol, 2.01 equiv) was then added slowly over 3 min. The reaction was stirred in the ice-water bath for 3 h, then transferred to a separatory funnel and diluted with H_2O (25 mL) and Et_2O (25 mL). After mixing and phase separation, the aqueous layer was extracted with Et_2O (25 mL x 2). The combined organics were washed with sat. aq. $Na_2S_2O_3$ (25 mL), brine, dried over $MgSO_4$, filtered and concentrated to 5 mL. Benzene (25 mL) was added and the solution was concentrated to 20 mL. Another portion of benzene (25 mL) was added, followed by DMSO and MIDA (591 mg, 4.02 mmol, 1.0 equiv). The mixture was heated to reflux with a Dean-Stark trap and a water-cooled condenser for 1 h. The reaction was then transferred to a separatory funnel containing H_2O (50 mL) and EtOAc (50 mL). After mixing and phase separation, the aq. layer was extracted with EtOAc (25 mL × 2). The combined organics were washed with H_2O, brine, dried over $MgSO_4$, filtered and concentrated to give a white solid. The solid was washed with Et_2O, filtered and dried in vacuo to give the pure product **82-1** (781 mg, 67% yield). ^{1}H-NMR (500 MHz, acetone-d_6): δ 4.21 (d, J = 17.0 Hz, 2H), 4.06 (d, J = 17.0 Hz, 2H), 3.51 (t, J = 7.0 Hz, 2H), 3.12 (s, 3H), 1.95 – 1.87 (m, 2H), 0.80 – 0.73 (m, 2H); ^{13}C-NMR (125 MHz, acetone-d_6): δ 168.7, 62.7; 46.3, 37.7, 29.1. HRMS (ESI+) calculated for $C_8H_{14}NO_4BrB$ $[M+H]^+$ *m/z* 278.0199, found 278.0195.



82-2

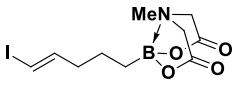
MIDA boronate **82-1** (825 mg, 2.97 mmol, 1.0 equiv) and NaI (1.56 g, 10.39 mmol, 3.5 equiv) were added into a 40 mL Ichem vial equipped with a stir bar. Under ambient atm, acetone (20

mL) was added. The vial was sealed with a PTFE-lined cap and stirred at 60 °C for 4 h. This reaction was carried out in quadruplicate. The reactions were cooled to RT, then combined and filtered through celite, rinsing with EtOAc. The filtrate was concentrated *in vacuo* to give a yellow viscous liquid. EtOAc (100 mL) was added and the solution transferred to a separatory funnel containing H_2O (100 mL), rinsing with EtOAc (100 mL). After mixing and phase separation, the aqueous layer was extracted with EtOAc (60 mL × 2). The combined organics were washed with sat. aq. $Na_2S_2O_3$ (50 mL × 2). The organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated to give a white solid. To the white solid was added acetone (approx. 3 mL), Et_2O (25 mL) and hexanes (50 mL) sequentially. The mixture was stirred for 5 min, then vacuum filtered. The product **82-2** (3.68 g, 95% yield) was obtained as a white solid after drying *in vacuo*. ^{1}H-NMR (500 MHz, acetone-d_6): ^{1}H-NMR δ 4.21 (d, J = 17.0 Hz, 2H), 4.05 (d, J = 17.0 Hz, 2H), 3.31 (t, J = 7.0 Hz, 2H), 3.12 (s, 3H), 1.94 – 1.85 (m, 2H), 0.79 – 0.71 (m, 2H); ^{13}C-NMR (125 MHz, acetone-d_6): δ 168.7, 62.6, 46.3, 30.0, 11.6; HRMS (ESI+) calculated for $C_8H_{14}NO_4IB$ $[M+H]^+$ *m/z* 326.0061, found 326.0061.



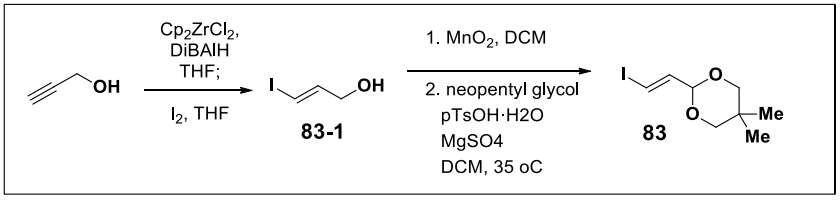
82-3

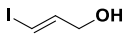
A flame-dried 20 mL vial equipped with a stir bar was charged with Zn dust (588 mg, 9 mmol, 3.0 equiv). A separate flame-dried 7 mL vial equipped with a stir bar was charged with MIDA boronate **82-2** (975 mg, 3.0 mmol, 1.0 equiv). DMF (2 mL) and THF (3.5 mL) were added to dissolve **82-2**. Under Ar, 3 drops of TMSCl followed by 3 drops of 1,2-dibromoethane were added sequentially to the vial containing Zn dust from a syringe with a 25 gauge needle. With stirring, the solution containing **82-2** was transferred to this vial via syringe, rinsing with THF (0.5 mL). The reaction was stirred at 45 °C for 1.5 h. The vial was taken into the glovebox and stored at RT overnight. In the glovebox, a flame-dried 40 mL vial was charged with vinyl iodide **77-7** (1.32 g, 4.13 mmol, 1.5 equiv), RuPhos (128 mg, 0.275 mmol, 0.1 equiv) and Pd_2dba_3 (63 mg, 0.069 mmol, 0.025 equiv), followed by DMF (7 mL). The organozinc solution (5.5 mL) was added, followed by THF (14 mL). The vial was sealed with a PTFE-lined cap, removed from the glovebox and stirred at 60 °C for 7 h. The reaction was cooled to rt and quenched with sat. aq. NH_4Cl (25 mL). The aqueous layer was extracted with EtOAc (25 mL × 2). The combined organics were washed with H_2O, brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by SiO_2 column chromatography (20-30-35% acetone/hexanes). The pure fractions containing product were concentrated *in vacuo* and the resulting solid triturated with acetone/hexanes to give a white solid. The supernatant was combined with mixed fractions from the column and re-subjected to SiO_2 column purification. The solids obtained were combined to give the pure product **82-3** (588 mg, 60% yield). TLC (50% acetone/hexanes): R_f = 0.58, visualized by shortwave UV; ^{1}H-NMR (500 MHz, acetone-d_6) δ 7.56 – 7.51 (m, 2H), 7.37 – 7.30 (m, 3H), 6.18 (dt, J = 18.5, 6.5 Hz, 1H), 5.79 (dt, J = 18.5, 1.5 Hz, 1H), 4.17 (dt, J = 17.0 Hz, 2H), 4.00 (d, J = 16.9 Hz, 2H), 3.07 (s, 3H), 2.25 – 2.16 (m, 2H), 1.53 – 1.45 (m, 2H), 0.68 – 0.63 (m, 2H), 0.30 (s, 6H); ^{13}C-NMR (125 MHz, acetone-d_6): δ 168.8, 150.3, 139.9, 134.5, 129.6, 128.5, 128.0, 62.6, 46.2, 40.7, 24.2, -2.3.; HRMS (ESI+) calculated for $C_{18}H_{27}BNO_4Si$ $[M+H]^+$ *m/z* 360.1802, found 360.1797.



82

A flame-dried 10 mL Schlenk flask equipped with a stir bar was charged with vinyl silane **82-3** (500 mg, 1.39 mmol, 1.0 equiv). HFIPA (5.6 mL) was added via syringe. The solution was cooled in an ice-brine bath. 2,6-lutidine (0.115 mL, 0.97 mmol, 0.7 equiv) was added. After 10 min, N-iodosuccinimide (470 mg, 2.09 mmol, 1.5 equiv) was added as a solid in one portion. The reaction was stirred at the same temperature for 1 h, then quenched with sat. aq. $Na_2S_2O_3$ (5 mL). The mixture was stirred vigorously for 5 min, then partitioned between EtOAc (20 mL) and H_2O (10 mL). The aqueous layer was extracted with EtOAc (20 mL). The combined organics were washed with sat. aq. $Na_2S_2O_3$ (20 mL), brine (× 2), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was azeotroped once with CH_2Cl_2. Et_2O (30 mL) was added to the crude product and the mixture stirred for 5 min. The suspension was filtered and the solid rinsed with Et_2O (10 mL × 2), giving the pure product **82** as a white solid (372 mg, 76% yield). TLC (50% acetone/hexanes): R_f = 0.44, visualized by $KMnO_4$ stain; ^{1}H-NMR (500 MHz, acetone-d_6): δ 6.57 (dt, *J* = 14.5, 7.0 Hz, 1H), 6.13 (dt, *J* = 14.5, 1.5 Hz, 1H), 4.18 (d, *J* = 17.0 Hz, 2H), 4.02 (d, *J* = 17.0 Hz, 2H), 3.09 (s, 3H), 2.12 (dq, *J* = 7.3, 1.5 Hz, 2H), 1.53 – 1.43 (m, 2H), 0.68 – 0.61 (m, 2H).): ^{13}C-NMR (125 MHz, acetone-d_6): δ 168.8, 147.9, 75.1, 62.6, 46.2, 39.5, 24.0; HRMS (ESI+) calculated for $C_{10}H_{16}BNO_4I$ $[M+H]^+$ *m/z* 352.0217, found 352.0229.

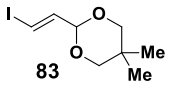




83-1

A dry 500 mL Schlenk flask equipped with a stir bar was charged with $Cp_2Zr_2Cl_2$ (14.86 g, 50.83 mmol, 1.0 equiv) under Ar. The flask was sealed with a rubber septum. THF (120 mL) was cannulated into the flask. The cloudy suspension was cooled to 0 °C. DiBAlH solution (1M in THF, 50 mL, 50 mmol, 1.1 equiv) was added into the reaction over 25 min with the aid of a syringe pump. The reaction mixture was stirred at 0 °C for 45 min. Propargyl alcohol (2.7 mL, 46.21 mmol, 1.0 equiv) was added neat dropwise into the reaction flask over 15 min. After the addition, the cold bath was removed and the reaction stirred at RT for 1.5 h, then cooled to -78 °C. Iodine (15.25 g, 60.07 g, 1.3 equiv) was added to a 100 mL single neck rbf. THF (24 mL) was added via syringe under Ar. The mixture was stirred to dissolve the solids. The solution was then cannulated into the reaction flask over 30 min, rinsing with THF (5 mL). The reaction was then stirred for 45 min at -78 °C. The cold bath was removed and the reaction quenched with the addition of 1N HCl (100 mL). The mixture was transferred to a separatory funnel, rinsing with H_2O (50 mL) and Et_2O (50 mL). After mixing, brine (50 mL) was added to aid separation. The aqueous phase was extracted with Et_2O (100 mL × 2). The combined organics were washed with sat. aq. $Na_2S_2O_3$ (100 mL, then 50 mL). The organics were washed with sat. aq. $NaHCO_3$, brine, dried over $MgSO_4$, filtered through celite and concentrated to 50 mL. Celite was added and the crude product adsorbed onto celite in vacuo for SiO_2 column purification. The fractions

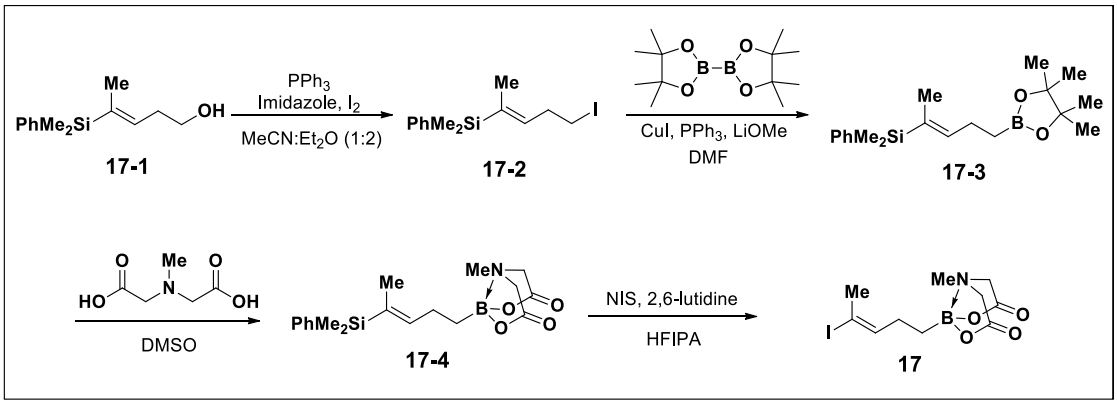
containing **83-1** were concentrated to a small volume (~5 mL) and transferred into a 40 mL vial, rinsing with CH_2Cl_2. The solution (0.95 g, 11% yield based on NMR) was used for the next reaction. ^{1}H-NMR matches literature data. (*48*)

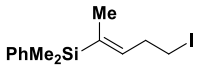


83

To the allylic alcohol **83-1** (0.95g, 5.14 mmol, 1.0 equiv) in CH_2Cl_2 (20 mL) was added MnO_2 (activated, 8.94 g, 102.8 mmol, 20 equiv) in one portion under ambient atmosphere and temperature. The reaction was stirred for 1.5 h, then another portion of MnO_2 (2.23 g, 25.6 mmol, 5 equiv) was added and the reaction stirred for another 15 min. The reaction was filtered through celite, rinsing with additional CH_2Cl_2 (10 mL). To the filtrate was added neopentyl glycol (1.62 g, 15.6 mmol, 3.0 equiv), followed by $MgSO_4$ (3.02 g) and pTsOH.H_2O (25.6 mg, 0.135 mmol, 0.026 equiv). The reaction was stirred at 35 °C for 1.5 h, then cooled to rt. After filtering to remove $MgSO_4$, the filtrate was concentrated in vacuo. The crude product was purified by SiO_2 column chromatography to give **83** (505 mg, 37% yield over 2 steps) as a colorless liquid. TLC (20% EtOAc in Hexanes): R_f = 0.71, visualized with UV, stained with $KMnO_4$; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.69 (dd, J = 14.5, 1.0 Hz, 1H), 6.60 (dd, J = 15.0, 4.0 Hz, 1H), 4.80 (dd, J = 4.0, 1.0 Hz, 1H), 3.64 (dd, J = 10.0, 1.5 Hz, 1H), 3.48 (d, J = 10.5 Hz, 1H), 1.19 (s, 3H), 0.74 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 142.0, 100.6, 82.5, 77.2, 30.2, 22.9, 21.8; HRMS (EI+) calculated for $C_8H_{13}O_2I$ $[M]^+$ *m/z* 267.9960, found 267.9972.

h. Synthesis of building blocks for **13**

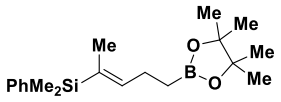




17-2

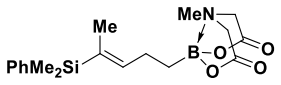
To a flame-dried 250 mL round bottom flask was added triphenylphosphine (4.81 g, 18.35 mmol, 1.1 equiv.) and imidazole (1.71 g, 25 mmol, 1.5 equiv.). The reaction flask was fitted with a septum, purged with N_2, and charged with MeCN (16.8 mL, 1 M) and Et_2O (28.0 mL, 0.6 M). After stirring at room temperature for 5 min as a clear solution, the reaction was cooled to 0 ºC and iodine was added portionwise (4.24 g, 16.7 mmol, 1.0 equiv.). The reaction mixture was allowed to stir at 0 ºC for 15 minutes as a bright yellow, clear solution. Meanwhile, a flame-dried 20 mL vial was charged with alcohol **17-1** (*50*) (3.70 g, 16.8 mmol; 1.0 equiv.). The vial was

sealed with a PTFE-lined cap, purged with N_2 and charged with Et_2O (7 mL, 2.5 M). The solution of alcohol in diethyl ether was added to the reaction flask dropwise via syringe. The reaction mixture was allowed to stir at 0 ºC for 15 minutes as a pale yellow solution at which point the reaction was warmed to room temperature and stirred for 1 h. The reaction was diluted with hexanes (100 mL), filtered through a short silica plug eluting with hexanes, and concentrated *in vacuo* to afford a yellow oil. The crude material was purified by SiO_2 column chromatography on silica gel (hexanes) to afford **17-2** as a yellow oil (4.61 g, 85% yield). Characterization matched what is reported in the literature. (*50*) TLC (hexanes): R_f = 0.19, visualized with UV, stained with $KMnO_4$. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.59 – 7.57 (m, 2H), 7.42 – 7.41 (m, 3H), 5.80 (tq, *J* = 6.8 Hz, *J* = 2.0 Hz, 1H), 3.22 (t, *J* = 7.4 Hz, 2H), 2.79 (q, *J* = 7.4 Hz, 2H), 1.74-1.73 (m, 3H), 0.43 (s, 6H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 139.1, 138.1, 137.5, 134.1, 129.0, 127.8, 32.6, 15.2, 5.1, -3.4.



17-3

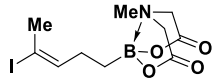
In a glovebox, to a 100 mL recovery equipped with magnetic stir bar and charged with alkyl iodide **17-2** (4.61 g, 13.97 mmol, 1.0 equiv.) and triphenylphosphine (478 mg, 1.82 mmol, 0.13 equiv.) was added bis(pinacolato)diboron (5.32 g, 20.96 mmol, 1.5 equiv.), lithium methoxide (1.06 g, 27.99 mmol, 2.0 equiv.), and copper(I) iodide (287 mg, 1.51 mmol, 0.1 equiv.) The reaction flask was fitted with a septum, removed from the glovebox, and was charged with DMF (28 mL, 0.50 M). The resulting reaction mixture was allowed to stir at room temperature for 18 h, and the reaction mixture was diluted with EtOAc (50 mL), filtered through a short silica plug eluting with EtOAc, and concentrated in vacuo to afford a slurry in residual DMF. Crude mixture was transferred to a separatory funnel and washed with H_2O (slow, dropwise, 200 mL). The aqueous layer was back-extracted with EtOAc (2 x 50 mL). Combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford a pale yellow oil. The crude material was adsorbed onto Celite from an acetone solution and purified by SiO_2 chromatography (hexanes:EtOAc 4:1 to afford **17-3** as a yellow oil (4.13 g, 89% yield). TLC (4:1 hexanes:EtOAc): R_f = 0.69, visualized by UV, stained with $KMnO_4$. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.51-7.49 (m, 2H), 7.36-7.32 (m, 3H), 5.83 (tq, *J* = 6.5 Hz, 2.0 Hz, 1H), 2.25 (q, *J* = 7.5 Hz, 2H), 1.67 (s, 3H), 1.23 (s, 12H), 0.89 (t, *J* = 7.5 Hz, 2H), 0.32 (s, 6H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 143.7, 139.0, 134.1, 133.0, 128.8, 127.7, 83.1, 29.8, 24.9, 23.0, 14.8, -3.3; HRMS (EI+) calculated for $C_{19}H_{31}O_2BSi$ $[M]^+$ *m/z* 330.2186, found 330.2186.



17-4

To a 1 L recovery flask was added pinacol ester **17-3** (7.26 g, 22.0 mmol, 1.0 equiv.) and N-methyliminodiacetic acid (30.0 g, 204 mmol, 9.3 equiv.). The reaction flask was fitted with a septum, purged with N_2, and charged with DMSO (220 mL, 0.1 M). The vial was placed in a 77 °C oil bath and maintained at that temperature with stirring for 15 h. The reaction mixture was diluted with EtOAc (100 mL) and transferred to a separatory funnel rinsing with EtOAc (50 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 75 mL). The combined organic layers were washed with H_2O (slowly dropwise, 600 mL), dried over Na_2SO_4,

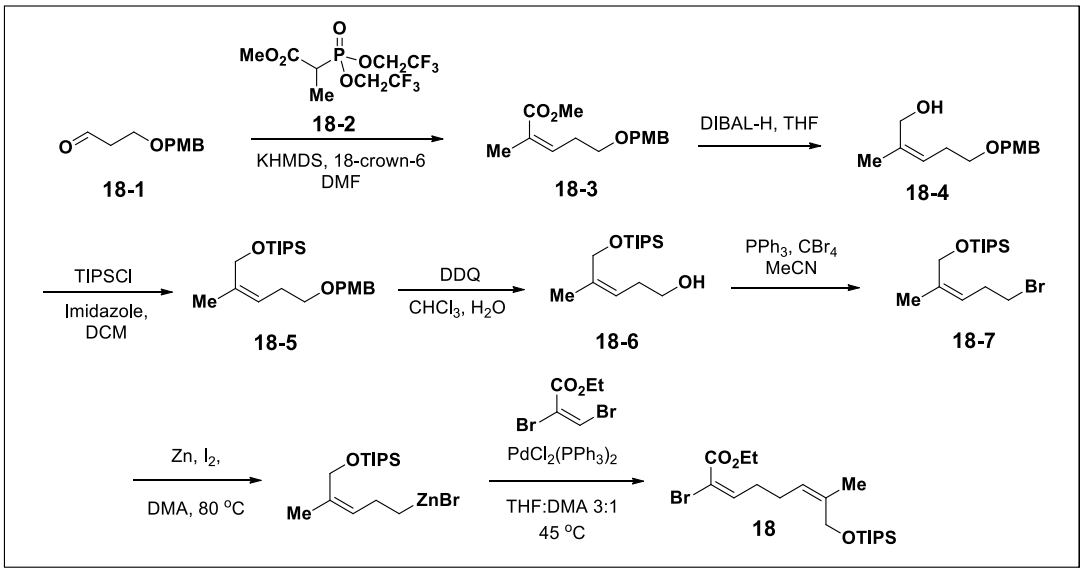
filtered, and concentrated *in vacuo* to afford a yellow oil/off-white solid precipitate. The crude material was adsorbed onto Celite from an acetone solution and purified by SiO_2 chromatography (hexanes:EtOAc 1:1 → EtOAc) to recover **17-3** as a yellow oil (2.62 g, 36% recovery) and afford **17-4** as a white solid (4.29 g, 54% yield).TLC (EtOAc): R_f = 0.26, visualized by UV, stained with KMnO4. ^{1}H-NMR (500 MHz, acetone-d_6): δ 7.53 – 7.51 (m, 2H), 7.37 – 7.31 (m, 3H), 5.94 (tq, *J* = 7.0, 1.5 Hz, 1H), 4.19 (d, *J* = 16.5 Hz, 2H), 4.03 (d, *J* = 16.5 Hz, 2H), 3.10 (s, 3H), 2.23 – 2.17 (m, 2H), 1.66 (s, 3H), 0.75 – 0.69 (m, 2H), 0.31 (s, 6H); ^{13}C-NMR (125 MHz, acetone-d_6) δ 168.8, 145.6, 139.4, 134.7, 132.6, 129.6, 128.5, 62.6, 46.2, 25.2, 23.9, 14.8, -3.2; HRMS (ESI+) calculated for $C_{18}H_{27}BNO_4Si$ $[M+H]^+$ *m/z* 360.1802, found 360.1804.



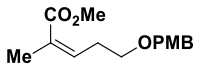
17

To a 100 mL recovery flask equipped with magnetic stir bar was added MIDA boronate **17-4** (1.141 g; 3.18 mmol, 1.0 equiv.), 2,6-lutidine (0.26 mL, 2.22 mmol, 0.7 equiv.) and hexafluoroisopropanol (12.8 mL, 0.25 M). After stirring at room temperature for 5 min as an off-white/pale yellow solution, the reaction was cooled to 0 ºC and NIS (637 mg, 4.76 mmol, 1.5 equiv.) was added in one portion. The reaction mixture was allowed to stir at 0 ºC for 15 minutes as a deep red, clear solution at which point the reaction was warmed to room temperature and stirred for 15 minutes. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ (13 mL) and transferred to a separatory funnel as a pale yellow solution rinsing with EtOAc (20 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 15 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford an off-white solid. The crude material was adsorbed onto Celite from an acetone solution and purified by SiO_2 chromatography (hexanes:acetone 4:1 → hexanes:acetone 3:1 → hexanes:acetone 2:1 → hexanes:acetone 1:1) to afford **17** as an off-white solid. The solid was dissolved in a minimal amount of DCM and layered with hexanes causing a white precipitate to form. The precipitate isolated by vacuum filtration to give the pure product **17** (1.01 g, 91% yield). TLC (EtOAc): R_f = 0.30, visualized by UV, stained with $KMnO_4$; ^{1}H-NMR (500 MHz, acetone-d_6): δ 6.24 (tq, *J* = 7.5, 1.5 Hz, 1H), 4.19 (d, *J* = 17.0 Hz, 2H), 4.02 (d, *J* = 17.0 Hz, 2H), 3.10 (s, 3H), 2.36 (s, 3H), 2.13 – 2.07 (m, 2H), 0.74 – 0.71 (m, 2H); ^{13}C-NMR (125 MHz, acetone-d_6): δ 168.7, 145.0, 92.7, 62.6, 46.3, 27.6, 26.1; HRMS (ESI+) calculated for $C_{10}H_{16}BNO_4I$ $[M+H]^+$ *m/z* 352.0217, found 352.0218.

i. Synthesis of building blocks for **14**



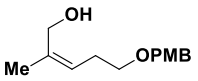
A 100 mL flask was charged with potassium tert-butoxide (5.30 g, 47.2 mmol, 1.2 eq.), fitted with a septum, and vac-filled with nitrogen before adding THF (55 mL). The mixture was cooled to 0 °C and methyl P,P-bis(2,2,2-trifluoroethyl)phosphonoacetate (8.3 mL, 39.3 mmol, 1.0 eq.) was added dropwise over 10 min, giving a clear orange mixture. After 40 min of stirring at 0°C, methyl iodide (12.2 mL, 197 mmol, 5.0 eq.) was added dropwise over 15 min at 0 °C, giving a cloudy orange/white mixture. The reaction was gradually warmed to room temperature and allowed to stir overnight. After 22 h, the reaction mixture was cooled to 0 °C, quenched with saturated NH_4Cl (25 mL), and transferred to a separatory funnel with water (25 mL) and ethyl acetate (25 mL). After mixing and phase separation, the aqueous layer was extracted with ethyl acetate (3 x 50 mL EtOAc). Combined organic layers were dried over Na_2SO_4, filtered, and concentrated to yield a red oil that contained a mixture of starting material, product, and bismethylated byproduct. The crude material was purified by column chromatography (9 cm diameter column, 1L of SiO_2, 4:1 hexanes/EtOAc) to afford **18-2** as a pure colorless oil (5.32 g, 41% yield). ^{1}H-NMR identical to literature. (*51*)



18-3

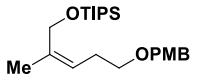
A dry 1 L two neck round bottom flask was charged with 18-crown-6 (30.34 g, 115 mmol, 5.0 equiv.), fitted with a thermometer, sealed with a septum, and vac-filled with N_2. THF (450 mL) was added, and the resulting clear, colorless solution was cooled to -78 °C. Phosphonoacetate **18-2** (7.31 g, 22.0 mmol, 1.0 equiv.) was added, using THF (25 mL) for quantitative transfer. KHMDS (1 M in THF, 22 mL, 1.0 equiv.) was added dropwise to the reaction flask over 10 min, accompanied by a color change to light orange / pink. The resulting solution was stirred at -78 °C for 30 min before adding aldehyde **18-1** (4.28 g, 22.0 mmol, 1.0 equiv.), using 25 mL THF

for quantitative transfer. The resulting reaction mixture was stirred at -78 °C for 2 h 20 min. The reaction was quenched with saturated aqueous NH_4Cl (100 mL). The resulting biphasic mixture was transferred to a 1 L separatory funnel using 100 mL H_2O and 300 mL Et_2O. After mixing and phase separation, the aqueous layer was extracted with diethyl ether (2 × 200 mL Et_2O). The combined organic layers were washed with brine (300 mL), dried over Na_2SO_4, and concentrated *in vacuo* to afford a crude mixture. The same reaction was repeated (23 mmol scale) and crude products were combined for chromatographic purification (10:1 to 8:1 hexanes/EtOAc) to give **18-3** as a clear, colorless oil (6.1 g, 51% yield). TLC (3:1 hexanes/EtOAc): R_f = 0.52, stained by $KMnO_4$; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 6.03 (dt, *J* = 7.5 Hz, *J* = 1.8 Hz, 1H), 4.45 (s, 2H), 3.81 (s, 3H), 3.72 (s, 3H), 3.52 (t, *J* = 6.0 Hz, 2H), 2.77 (m, 2H), 1.91 (m, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 168.5, 159.4, 140.1, 130.7, 129.5, 128.5, 114.0, 72.7, 69.4, 55.5, 53.6, 51.5, 30.4, 20.9; HRMS (ESI+) calculated for $C_{15}H_{21}O_4$ [M+H$^+$] *m/z* 265.1440, found 265.1436.



18-4

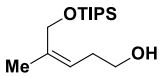
A 1 L two neck round bottom flask was fitted with a thermometer, sealed with a rubber septum, and vac-filled with N_2. THF (280 mL) and the ester **18-3** (6.1 g, 23.1 mmol, 1.0 equiv.) were added to the flask, and the mixture was cooled with to -78 °C in a dry ice / acetone bath. DIBAL-H (1.0 M in hexanes, 69 mL, 3.0 equiv.) was added gradually to the reaction flask over 20 min, and the resulting reaction mixture was stirred at -78 °C for 5 minutes before switching to a -15 °C dry ice / brine cooling bath. After 1.5 h, MeOH (60 mL) was added to quench the reaction at -15 °C. Using Et_2O, the reaction mixture was transferred to a 2 L Erlenmeyer flask, and saturated Rochelle's salt (280 mL) was added. After stirring overnight to complex aluminum salts, the crude mixture was transferred to a 1 L separatory funnel using Et_2O (50 mL) and water (50 mL). After mixing and phase separation, the aqueous layer was extracted (3 × 250 mL EtOAc). The combined organics were washed with brine (400 mL), concentrated *in vacuo* to approximately 50 mL, diluted in Et_2O, dried with Na_2SO_4, vacuum filtered, and concentrated to give a cloudy oil. Chromatographic purification (9 cm diameter column, 500 mL SiO_2, 2:1 hexanes/EtOAc) yielded **18-4** (5.3 g, 97% yield). TLC (2:1 hexanes/EtOAc): R_f = 0.26, stained by $KMnO_4$; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.24 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.32 (td, *J* = 8.0 Hz, *J* = 1.3 Hz, 1H), 4.44 (s, 2H), 4.01 (s, 2H), 3.80 (s, 3H), 3.43 (t, *J* = 6.0, 2H), 2.34 (app. q, 2H), 1.82 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 159.4, 138.2, 130.0, 129.6, 124.7, 114.0, 73.0, 69.0, 61.4, 55.4, 28.6, 22.4; HRMS (ESI+) calculated for $C_{14}H_{21}O_3$ [M+H$^+$] *m/z* 237.1491, found 237.1494.



18-5

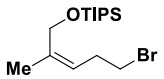
A 500 mL 3-neck round bottom flask was charged with imidazole (3.67 g, 54.0 mmol, 2.4 eq), sealed with three rubber septa, and vac-filled with N_2. Under N_2, CH_2Cl_2 (200 mL) and allylic alcohol **18-4** (5.31 g, 22.5 mmol, 1.0 eq) were added by cannulation with rinsing for quantitative transfer. After cooling to 0 °C in an ice/water bath, TIPSCl (5.8 mL, 27.0 mmol, 1.2 eq) was added dropwise over 7 min. The reaction was allowed to warm to rt with stirring overnight. After 8 h, the reaction mixture was transferred to a 500 mL separatory funnel. The organic layer

was washed (2 × 150 mL water), and combined aqueous layers were extracted (250 mL CH_2Cl_2). The combined organic layers were washed with brine (300 mL), dried with $MgSO_4$, vacuum filtered, and concentrated *in vacuo* to yield the product as an oil. Chromatographic purification (25:3:1 hexanes / DCM / Et_2O to 25:4:1) gave the pure product **18-5** (7.26 g, 82% yield). TLC (10:1 hexanes/EtOAc): R_f = 0.46, stained by $KMnO_4$; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.26, (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 5.20 (dt, *J* = 7.3 Hz, *J* = 1.2 Hz, 1H), 4.43 (s, 2H), 4.23 (s, 2H), 3.80 (s, 3H), 3.41 (t, *J* = 7.2 Hz, 2H), 2.33 (app q, 2H), 1.78 (d, *J* = 1.1 Hz, 3H), 1.14-1.04 (m, 21H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 159.3, 137.5, 130.8, 129.5, 121.8, 114.0, 72.7, 70.1, 62.3, 55.5, 28.5, 21.3, 18.3, 12.2; HRMS (ESI+) calculated for $C_{23}H_{41}O_3Si$ [M+H$^+$] *m/z* 393.2825, found 393.2818.



18-6

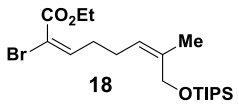
To a 500 mL round bottom flask were added the PMB-protected alcohol **18-5** (7.26 g, 18.5 mmol, 1 eq) chloroform (160 mL), and water (8 mL). The mixture was stirred at room temperature for 10 min before adding 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 12.6 g, 55.5 mmol, 3.0 eq) portionwise over 10 min. After 1 h, the reaction was quenched with the addition of sat. aq. $NaHCO_3$ (100 mL). The mixture was filtered through celite, which was rinsed with EtOAc. The resulting red filtrate was concentrated and then transferred to a 500 mL separatory funnel, rinsing with EtOAc (200 mL) and H_2O (150 mL). Brine (60 mL) was added to improve phase separation, and then the aqueous layer was extracted with EtOAc (2 × 200 mL). The combined organics were washed with brine (250 mL), dried with Na_2SO_4, vacuum filtered, and concentrated to give a dark red oil. Chromatographic purification (8:1 to 5:1 to 3:1 hexanes/Et_2O) gave the pure product **18-6** (4.55 g, 90% yield). TLC (3:1 hexanes/EtOAc): R_f: 0.46; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.26 (t, *J* = 7.7 Hz, 1H), 4.23 (s, 2H), 3.61 (t, *J* = 6.2 Hz, 2H), 2.32 (app. q, 2H), 1.82 (s, 3H), 1.18-1.04 (m, 21H); ^{13}C-NMR (125 MHz, $CDCl_3$): 138.7, 122.6, 62.20, 62.16, 31.3, 21.9, 18.2, 12.2; HRMS (ESI+) calculated for $C_{15}H_{33}O_2Si$ [M+H$^+$] *m/z* 273.2250, found 273.2245.



18-7

A dry 50 mL Schlenk flask was charged with PPh_3 (4.12 g, 15.7 mmol, 1.1 eq), sealed with a rubber septum, and vac-filled with N_2 (×3). CH_2Cl_2 (35 mL) was added. The resulting mixture was stirred and cooled to 0 °C. Br_2 (2.39 g, 15.7 mmol, 1.1 eq) was gradually added until the yellow color persisted, and then several additional crystals of PPh_3 were added until the color vanished. The resulting off-white, opaque mixture was treated with a dropwise addition of pyridine (2.26 g, 28.6 mmol, 2.0 eq), followed by a dropwise addition of **18-6** (3.89 g, 14.29 mmol, 1.0 eq)) as a solution in DCM (5 mL) with rinsing (10 mL DCM) for quantitative transfer. After 1.5 hours TLC showed the reaction was almost complete. The crude mixture was transferred to a rbf and concentrated *in vacuo*, giving an off-white powder. The solid was triturated with pentane and then filtered. (2.65 g, 47% yield). Along with additional crude bromide product from a parallel reaction, chromatographic purification (hexanes to 10:1 Et_2O/hexanes) gave the pure product **18-7** as a colorless oil (5.65 g 93% yield). TLC (hexanes): R_f = 0.25, stained by $KMnO_4$; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.21 (dt, *J* = 7.3 Hz, *J* = 1.2 Hz,

1H), 4.23 (s, 2H), 3.34 (t, J = 7.2 Hz, 2H), 2.60 (app q, 2H), 1.80 (d, J = 1.0 Hz, 3H), 1.16-1.04 (m, 21H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 138.8, 122.4, 62.4, 33.0, 31.5, 21.4, 18.3, 12.2.



18

In an unoptimized procedure, in the glovebox, alkyl bromide **18-7** (2.01 g, 6 mmol, 1 equiv) was weighed into a flame-dried 40 mL vial. Zn dust (1.18 g, 18 mmol, 3 equiv) was weighed into another flame-dried 40 mL vial equipped with a stir bar. 8 mL DMA was added to the vial containing the alkyl bromide to give a colorless solution. The vials were sealed with septum caps and brought out of the glovebox. To the vial containing Zn dust was added I_2 (45.7 mg, 0.18 mmol, 0.03 equiv). The vial was resealed and vac-filled with N_2 (× 3). DMA (2 mL) was added, and the mixture stirred for 2 min during which the brown color of I_2 disappeared. The solution of the alkyl bromide was then cannulated to the Zn dust, rinsing with DMA (2 mL × 2). The mixture was stirred at 80 °C for 14 h, then cooled to rt and taken into the glovebox.

In the glovebox, (E)-ethyl 2,3-dibromoacrylate (*52*) (430 mg, 1.67 mmol) was weighed into a flame-dried 40 mL vial equipped with a stir bar. THF (15 mL) was added, followed by $PdCl_2(PPh_3)_2$ (35.1 mg, 0.05 mmol, 0.03 equiv wrt dibromide). 2 of these reactions were prepared in parallel. The organozinc solution (5 mL) was filtered directly into each of the reaction vial. The reaction were sealed with PTFE-lined caps, brought out of the glovebox and stirred at 45 °C for 6 h, then cooled to rt. The reaction mixtures in the 2 vials were combined into a separatory funnel containing 40 mL saturated aq. NH_4Cl solution, rinsing with H_2O and Et_2O. Et_2O (10 mL) was added and the layers mixed and separated. The aqueous layer was extracted with Et_2O (30 mL × 2). The combined organics were washed with H_2O, brine, dried over $MgSO_4$ and Darco, filtered through celite and concentrated in vacuo. The crude product was purified by silica gel chromatography (20-25-30% CH_2Cl_2/hexanes). The mixed fractions were pooled and re-purified by silica gel chromatography (15-20-25% CH_2Cl_2/hexanes). The fractions containing the pure product were concentrated, then taken up in hexanes and stirred with activated charcoal. The mixture was filtered through celite and concentrated *in vacuo* to give a very slightly brown liquid as the product **18** (526 mg, 36% yield) TLC (30% CH_2Cl_2/hexanes): R_f = 0.41, visualized with UV, stained with $KMnO_4$. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.64 (t, J = 7.7 Hz, 1H), 5.15 (tq, J = 7.3, 1.3 Hz, 1H), 4.26 (q, J = 7.0 Hz, 2H), 4.22 (s, 2H), 2.53 (q, J = 7.5 Hz, 2H), 2.22-2.13 (m, 2H), 1.78 (q, J = 1.3 Hz, 3H), 1.33 (t, J = 7.1 Hz, 3H), 1.22-0.96 (m, 21H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 162.8, 147.8, 137.0, 123.9, 111.6, 62.1, 62.1, 31.6, 26.6, 21.1, 18.0, 14.1, 12.0; HRMS (ESI+) calculated for $C_{20}H_{38}O_3SiBr$ [M+H$^+$] *m/z* 433.1774, found 433.1772.

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