Supporting Information for *Angew. Chem. Int. Ed.* Z17081

SUPPORTING INFORMATION

Asymmetric Catalysis in Diversity-Oriented Organic Synthesis: Enantioselective Synthesis of 4320 Encoded and Spatially Segregated Dihydropyrancarboxamides.

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I. Synthetic Methods

General Methods. Reagents were obtained from commercial sources and used without purification. Reaction solvents (THF, DMF, CH_2Cl_2) were obtained from J. T. Baker (HPLC grade) and purified by passage through two solvent columns prior to use.[1] Triethylamine, diisopropylethylamine, and 2,6-lutidine were distilled from CaH_2. Brominated polystyrene resin (Br-PS, 2 meq/g) was obtained from Polymer Labs, and functionalized with the silicon-based linker according to the reported protocol.[2] 2,2'-Isopropylidenebis[(4*S*)-4-*t*-butyl-2-oxazoline] was purchased from Aldrich, while the enantiomer, 2,2'-Isopropylidenebis[(4*R*)-4-*t*-butyl-2-oxazoline] was prepared as previously described starting for (*R*)-*t*-leucine.[3] Flash chromatography was performed on E. Merck 60 230-400 mesh silica gel. TLC was performed on 0.25 mm E Merck silica gel F_{254} plates and visualized by UV, cerium ammonium molybdate and / or I_2. NMR spectra were recorded on a Varian Mercury400 (400 MHz ^1H, 100 MHz ^{13}C), Varian Unity500 (500 MHz ^1H) or Varian Unity600 (600 MHz ^1H). Chemical shifts are quoted in ppm and reference to TMS or residual protonated solvent. Mass spectra were obtained on a Jeol AX-505H or SX-102A mass spectrometer.

Solid Phase Reactions. All solid phase reactions were conducted in oven dried glass vials under an atmosphere of dry Ar, with mixing provide by a VWR Vortex Genie-2 vortexer. Resin washings were performed in 2 mL fritted polypropylene Bio-Spin® chromatography columns (BioRad) or 10 mL fritted polypropylene PD-10 columns (Pharmacia Biotech) with 360° rotation on a Barnstead-Thermolyne Labquake™ shaker. For cleavage reactions, resin

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(1) The CH_2Cl_2 purification system is composed of one activated alumina (A-2) column and one supported copper redox catalyst (Q-5 reactant) column. The THF purification system is composed of two activated alumina (A-2) columns and the DMF purification system is composed of two activated molecular sieve columns. See: A. B. Pangborn, M. A. Giardello, R. H. Grubbs, R. K. Rosen, F. J. Timmers, *Organometallics* **1996**, *15*, 1518-1520.

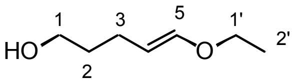
(2) J. A. Tallarico, K. M. Depew, H. E. Pelish, N. J. Westwood, C. W. Lindsley, M. D. Shair, S. L. Schreiber, M. A. Foley, *J. Comb. Chem.* **2001**, *3*, 312-318.

(3) D. A. Evans, G. S. Peterson, J. S. Johnson, D. M. Barnes, K. R. Campos, K. A. Woerpel, *J. Org. Chem.* **1998**, *63*, 4541-4544.

samples were transferred to Eppendorf tubes and a cleavage cocktail comprising 85 / 10 / 5 THF / py / HF-py was added and the samples were vortexed for 1-2 h at rt. The samples were then treated with methoxytrimethylsilane and vortexed for an additional 30 min. The samples were then filtered through a pipette plugged with glass wool, the resin washed with additional THF and the filtrate concentrated.

II. Synthesis of Vinyl Ethers

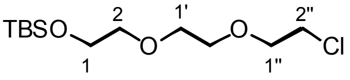
(*E*)-5-Ethoxy-pent-4-en-1-ol



BB1-C

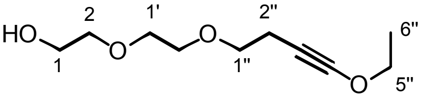
5-Ethoxy-pent-4-yn-1-ol (1.28 g, 10.0 mmol, 1.0 equiv) in THF (2 mL) was added to a suspension $LiAlH_4$ (0.80 g, 21 mmol, 2.1 equiv) in THF (20 mL) and the resulting solution was stirred at rt for 16 h. At this time 0.8 mL of H_2O was added dropwise, followed by 0.8 mL of 15% NaOH, then 2.4 mL of H_2O. Eventually (30 min) white solids formed, the mixture was filtered and the solids were extensively washed with EtOAc. The filtrate and washings were combined, dried (Na_2SO_4), filtered, and the filtrate was concentrated to give and oil which was purified by column chromatography (6/1 hexanes/EtOAc) to give 1.14 g (88%) of the vinyl ether **BB1-C** as a clear colorless oil with better than 19/1 *E* / *Z* selectivity (^1H NMR): ^1H NMR (500 MHz) 6.24 (d, *J* = 12.7, 1 H, HC(5)); 4.76 (dt, *J* = 12.7, 7.3, 1 H, HC(4)); 3.69 (q, *J* = 6.8, 2 H, $H_2C(1')$); 3.65 (q, *J* = 5.3, 2 H, $H_2C(1')$); 2.01 (q, *J* = 7.3, 2 H, $H_2C(3)$); 1.60 (quint , *J* = 7.3, 2 H, $H_2C(2)$); 1.39 (t *J* = 5.4, 1 H, OH); 1.25 (t, *J* = 6.8, 3 H, $H_3C(2')$); ^{13}C NMR (100 MHz) 146.12; 103.26; 64.56; 61.99; 33.46; 24.08; 14.85.

tert-Butyl-{2-[2-(2-chloro-ethoxy)-ethoxy]-ethoxy}-dimethyl-silane



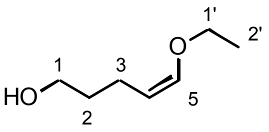
Triethylamine (9.2 mL, 66 mmol, 1.2 equiv), DMAP (0.67 g, 5.5 mmol, 0.1 equiv) and TBSCl (9.1 g, 60.5 mmol, 1.1 equiv) were dissolved in CH_2Cl_2 (60 mL). The 2-chloro(ethoxyethoxy)ethanol (8.0 mL, 55.0 mmol, 1.0 equiv) was added dropwise over 5 min, then the mixture was stirred at rt for 1.5 h. The reaction mixture was poured into H_2O and extracted with EtOAc, the combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated to give a cloudy oil which was passed through a short column of silica gel eluting with 9/1 hexane/EtOAc to give 14.8 g (96%) of the silyl ether as a clear, colorless oil: ^{1}H NMR (500 MHz) 3.74 (q, *J* = 5.4, 4 H, H_2C(1'') and H_2C(2)); 3.64 (s, 4 H, H_2C(1') and H_2C(2')); 3.60 (t, *J* = 5.9, 2 H, H_2CO); 3.54 (t, *J* = 5.9, 2 H, H_2CO)); 0.87 (s, 9 H, H_3CCSi); 0.04 (s, 6 H, H_3CSi) ^{13}C NMR (100 MHz) 72.67; 71.31; 70.68; 70.66; 42.59; 25.86; 18.30; -5.34.

2-[2-(4-Ethoxy-but-3-ynyloxy)-ethoxy]-ethanol



tert-Butyl-{2-[2-(2-chloro-ethoxy)-ethoxy]-ethoxy}-dimethyl-silane was converted to the corresponding iodide by refluxing with 5 equiv of NaI in 2-butanone for 6 h. This was then alkynylated and deprotected by the same process described above to provide *E*-5-Ethoxy-pent-4-en-1-ol: ^{1}H NMR (500 MHz) 4.02 (q, *J* = 6.8, 2 H, H_2C(5'')); 3.74-3.70 (m, 2 H, HCO); 3.68-3.66 (m, 2H, HCO); 3.64-3.60 (m, 4 H, HCO); 3.54 (t, *J* = 7.3, 2 H, H_2CO)); 2.49 (t, *J* = 6.3, 1 H, OH); 2.41 (t, *J* 7.3, 2 H, H_2CO); 1.33 (t, *J* = 7.3, 3 H, H_3C(6'')); ^{13}C NMR (100 MHz) 128.24; 89.89; 73.91; 72.47; 70.56; 70.25; 70.14; 61.66; 18.38; 14.26; MS (CI, NH_3) 220 (M+NH_4); 186.

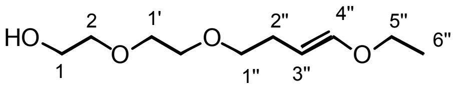
(*Z*)-5-Ethoxy-pent-4-en-1-ol



BB1-D

5-Ethoxy-pent-4-yn-1-ol (1.28 g, 10 mmol) and Lindlar catalyst (400 mg) were combined in EtOAc (20 mL) containing pyridine (1 mL). This mixture was hydrogenated at rt under 1 atm of H_2 for 16 h, then filtered through celite and poured into H_2O. The organic later was washed with sat. $CuSO_4$, H_2O and brine, then dried (Na_2SO_4), filtered, and the filtrate concentrated to give an oil which was purified by column chromatography (6/1 hexanes/EtOAc) to give 0.91 g (70%) of the vinyl ether **BB1-D** as a slightly yellow oil with better than 25 / 1 *Z* / *E* selectivity (^{1}H NMR): ^{1}H NMR (500 MHz) 6.01 (d, *J* = 6.4, 1 H, HC(5)); 4.36 (q, *J* = 7.8, 1 H, HC(4)); 3.79 (q, *J* = 7.3, 2 H, H_2C(1')); 3.63 (t, *J* = 6.3, 2 H, H_2C(1); 2.17 (q, *J* = 7.8, 2 H, H_2C(3)); 2.06 (br s, 1 H, OH); 1.59 (quint, *J* = 6.3, 2 H, H_2C(2)); 1.25 (t, *J* = 7.3, 3 H, H_3C2')); ^{13}C NMR (100 MHz) 145.20; 105.45; 67.55; 61.56; 31.83; 19.71; 15.18.

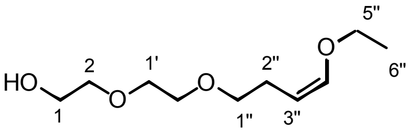
(*E*)-2-[2-(4-Ethoxy-but-3-enyloxy)-ethoxy]-ethanol



BB1-E

The procedure described above for the synthesis of **BB1-C** provided the Z-vinyl ether **BB1-E**: ^{1}H NMR (500 MHz) 6.29 (d, *J* = 12.7, 1 H, HC(4'')); 4.73 (dt, *J* = 12.2, 7.8, 1 H, HC(3'')); 3.76-3.64 (m, 6 H, H_2CO); 3.62-3.59 (m, 4 H, H_2CO); 3.44 (t, *J* = 6.8, 2 H, H_2C(1'')); 2.21 (qd, *J* = 7.3, 1.0, 2 H, H_2C(2'')); 1.25 (t, *J* = 7.3, 3 H, H_3C(6'')); ^{13}C NMR (100 MHz) 147.41; 99.52; 72.44; 71.97; 70.25; 70.05; 64.44; 61.59; 28.13; 14.60; MS (CI, NH_3) 222 (M+NH_4); 176.

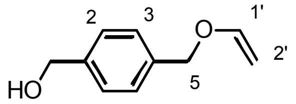
(*Z*)-2-[2-(4-Ethoxy-but-3-enyloxy)-ethoxy]-ethanol



BB1-F

The procedure described above for the synthesis of **BB1-D** provided the Z-vinyl ether **BB1-F**: ^{1}H NMR (400 MHz) 5.99 (dt, *J* = 6.3, 1.5, 1 H, HC(4'')); 4.36 (q, *J* = 6.3, 1 H, HC(3'')); 3.77 (q, *J* = 6.8, 2 H, H_2C(5'')); 3.74-3.70 (m, 2H, HCO); 3.68-3.66 (m, 2 H, HCO); 3.62-3.58 (4 H, m, H_2CO); 3.48 (t, *J* = 7.3, 2 H, H_2C(1'')); 2.56 (br s, 1 H, OH); 2.37 (qd, *J* = 6.8, 1.5, 2 H, H_2C(2'')); 1.23 (t, *J* = 7.3, 3 H, H_3C(6'')); ^{13}C NMR (100 MHz) 146.01; 102.19; 72.45; 71.00; 70.43; 69.95; 67.53; 61.77; 24.50; 15.21; MS (CI, NH_3) 222 (M+NH_4); 176; 159.

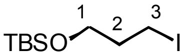
(4-Vinyloxymethyl-phenyl)-methanol



BB1-G

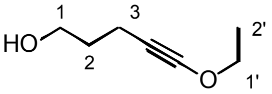
Benzene-1,4-dimethanol (2.76 g, 20.0 mmol, 1.0 equiv) and $Hg(OAc)_2$ (1g, 3.0 mmol, 0.15 equiv) were heated to reflux in butyl vinyl ether (50 mL) for 30 min. The reaction mixture was cooled, poured into sat. $NaHCO_3$ and was extracted with EtOAc. The organic extracts were combined, washed with H_2O and brine, dried (Na_2SO_4), filtered and the filtrate concentrated to give a paste, which contained both mono- and bis-vinyl ethers and starting diol. Column chromatography (4/1 hexanes/EtOAc) provided 1.07 g (33%) of the mono-vinyl ether **BB1-G** as an oil which solidified on standing: ^{1}H NMR (400 MHz) 7.39-7.34 (m, 4 H, HAr); 6.65 (dd, *J* = 14.6, 7.0, 1 H, HC(1')); 4.76 (s, 2 H, H_2C(5)); 4.70 (d, *J* = 5.9, 2 H, H_2COH)); 4.30 (dd, *J* = 14.6, 2.2, 1 H, HC(2')); 4.08 (dd, *J* = 7.0, 2.2, 1 H, HC(2')); 1.62 (t, *J* = 5.9, 1 H, OH); ^{13}C NMR (100 MHz) 151.50; 140.57; 136.13; 127.70; 127.04; 87.39; 69.75; 64.83; MS (CI, NH_3)182 (M+NH_4); 138; 100.

tert-Butyl-(3-iodo-propoxy)-dimethyl-silane



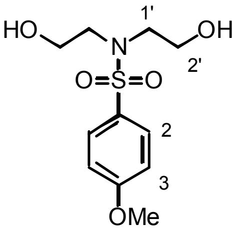
Triethylamine (8.5 mL, 61.0 mmol, 1.2 equiv), DMAP (0.610 g, 5.0 mmol, 0.1 equiv) and TBSCl (8.4 g, 55.5 mmol, 1.1 equiv) were dissolved in CH_2Cl_2 (50 mL). 3-Iodopropanol (9.4 g, 50.5 mmol, 1 equiv) was added and the mixture was allowed to stir at rt for 16 h. The cloudy mixture was then poured into H_2O and extracted with hexane. The combined organic layers were washed with H_2O, sat. $CuSO_4$, H_2O and brine, then dried (Na_2SO_4), filtered and the filtrate was concentrated to give an oil. The crude oil was purified by passed through a short plug of silica gel using 19/1 hexanes/EtOAc as eluent to give 13.9 g (92%) of the silyl ether as a clear, colorless oil: ^1H NMR (500 MHz) 3.67 (t, J = 5.9, 2 H, $H_2C(1)$); 3.28 (t, J = 6.8, 2 H, $H_2C(3)$); 1.99 (quint, J = 5.9, 2 H, $H_2C(2)$); 0.89 (s, 9 H, H_3CCSi)); 0.07 (s, 6 H, H_3CSi). ^{13}C NMR (100 MHz) 62.33; 36.14; 25.90; 18.27; 3.68; -5.33.

5-Ethoxy-pent-4-yn-1-ol



A solution of ethyl alkynyl ether (7.8 g of a 40 % wt. soln. in hexanes, roughly 3.1 g alkynyl ether, 44 mmol, 1.2 equiv) in THF (80 mL) was cooled to –78 °C and nBuLi (16.1 mL of 2.5 M in hexane, 40.3 mmol, 1.1 equiv) was added over 5 min. This solution was allowed to stir for 20 min at –78 °C, then HMPA (14.0 mL, 80.6 mmol, 2.2 equiv) was added and the solution was stirred for a further 20 min, then *tert*-butyl-(3-iodo-propoxy)-dimethyl-silane (11.0 g, 36.6 mmol, 1.0 equiv) was added over 1 min and the mixture was allowed to warm slowly to rt and stir overnight (16 h). The crude reaction mixture was poured into H_2O and extracted with hexane. The organic layers were combined, washed with brine, dried (Na_2SO_4), filtered and the filtrate was concentrated to give a dark oil which was immediately dissolved in THF (35 mL). TBAF (1.0 M in THF, 38 mL, 38 mmol, 1.04 equiv) was then added and the resulting solution was stirred at rt for 1h, the then reaction mixture was poured into H_2O and extracted with EtOAc. The combined extracts were washed with H_2O and brine, dried (Na_2SO_4), filtered and the filtrate was concentrated to give a dark oil which was chromatographed (6/1 hexanes/EtOAc) to give 3.43 g (73%) of the alkynyl ether as a slightly yellow oil: ^1H NMR (500 MHz) 4.02 (q, J = 7.3, 2 H, $H_2C(2')$); 3.73 (q, J = 5.8, 2 H, $H_2C(1)$); 2.24 (t, J = 6.8, 2 H, $H_2C(3)$); 1.70 (quint, J = 6.8, 2 H, $H_2C(2)$); 1.65 (t, J = 5.9, 1 H, OH); 1.33 (t, J = 7.3, 3 H, $H_3C(2')$); ^{13}C NMR (100 MHz) 128.20; 89.55; 73.83; 61.67; 32.11; 14.22; 13.67.

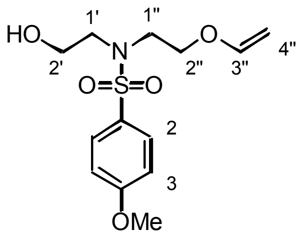
N,*N*-Bis-(2-hydroxy-ethyl)-4-methoxy-benzenesulfonamide



Diethanolamine (8.40 g, 80 mmol, 1.50 equiv) was dissolved in CH_2Cl_2 (30 mL) and pyridine (5.1 mL, 63.6 mmol, 1.2 equiv). A solution of 4-methoxybenzenesulfonyl chloride

(10.9 g, 53 mmol, 1.0 equiv) n CH_2Cl_2 (30 mL) was added quickly and the resulting mixture was stirred at rt overnight, then poured into H_2O and extracted with EtOAc. The organic layers were washed with 1M HCl and brine, dried ($MgSO_4$), filtered, and the filtrate was concentrated to give an oil which was purified by column chromatography (95/5 CH_2Cl_2/MeOH) to give 12 g (83%) of the sulfonamide as an oil which crystallized on standing: ^1H NMR (500 MHz) 7.75 (d, *J* = 8.8, 2 H, HAr); 6.99 (d, *J* = 8.8, 2 H, HAr); 3.87 (a, 3 H, H_3CO); 3.86 (t, *J* = 4.9, 4 H, H_2C(1’); 3.42 (br s, 2 H, OH); 3.26 (t, *J* = 4.9, 4 H, H_2C(2’)). ^{13}C NMR (100 MHz) 163.05; 129.85; 129.37; 114.37; 62.25; 55.61; 52.90.

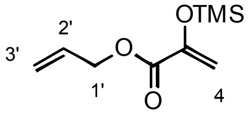
N-(2-Hydroxy-ethyl)-4-methoxy-*N*-(2-vinyloxy-ethyl)-benzenesulfonamide



BB1-H

The general procedure above for the synthesis of monovinyl ether **BB1-G** provided 38% of the desired vinyl ether sulfonamide **BB1-H**: ^1H NMR (500 MHz) 7.76 (d, *J*= 8.8, 2 H, HAr); 6.99 (d, *J* = 8.8, 2 H, HAr); 6.42 (dd, *J* = 14.7, 6.8, 1 H, HC(3’’)); 4.23 (dd, *J* = 14.6, 2.4, 1 H, HC(4’’)); 4.07 (dd, *J* = 6.8, 2.4, 1 H, HC(4’’)); 3.93 (t, *J* = 5.4, 2 H, H_2C(2’’)); 3.87 (s, 3 H, H_3CO); 3.76 (q, *J* = 5.4, 2 H, H_2C(2’)); 3.42 (t, *J* = 5.4, 2 H, H_2C(1’’)); 3.27 (t, *J* = 5.4, 2 H, H_2C(1’)); 2.75 (t, *J* = 6.3, 1 H, OH); ^{13}C NMR (100 MHz) 163.00; 150.83; 130.12; 129.35; 114.31; 87.79; 67.48; 61.26; 55.58; 56.62; 48.87.

2-(Trimethylsilanyloxy)-acrylic acid allyl ester



Triethylamine (33 mL, 235 mmol, 1.1 equiv) was added to a solution of TMSOTf (50 g, 225 mmol, 1.05 equiv) in benzene (225 mL) and the resulting solution was cooled to 0 °C. Allyl pyruvate (27.4 g, 214 mmol, 1.0 equiv) was added over 30 min and the resulting two phase mixture was stirred at 0 oC for another 2h, then poured into ice cold H_2O and extracted with hexane. The hexane extracts were washed with H_2O, sat. $CuSO_4$, H_2O and brine, then dried (Na_2SO_4), filtered, and the filtrate was concentrated to give 30.4 g (68%) of the silyl enol ether as a yellow oil which was used without further purification: ^{1}H NMR (500 MHz) 5.86 (ddd, J = 171, 10.7, 1.4, 1 H, HC(2')); 5.55 (d, J = 1.0, 1 H, HC(4)); 5.35 (dd, J = 17.1, 1.3, 1 H, HC(3')); 5.26 (dd, J = 10.7, 1.5, 1 H, HC(3')); 4.9 (d, J = 1.0, 1 H, HC(4)); 4.74-4.72 (m, 2 H, H_2C(1')); 0.06 (s, 9 H, H_3CSi); ^{13}C NMR (100 MHz) 164.01; 146.88; 131.79; 118.39; 104.24; 65.75; -0.08. MS (EI) 200 (M+); 185; 157; 141; 115.

III. General Synthesis of β,γ-unsaturated ketoesters[4]

Borontrifluoride etherate (2.2 equiv) was added over 5 min to a solution of aldehyde (1.0 equiv) in CH_2Cl_2 (0.5 M) at –78 °C. The resulting solution was stirred for 30 min, then 2-(Trimethylsilanyloxy)-acrylic acid allyl ester (1.1 equiv) was added dropwise over 5 min. The solution was allowed to stir at –78 °C for 10 min, then warmed slowly to rt and stirred overnight. The mixture was poured into sat. $NaHCO_3$ and extracted with EtOAc, the organic layers were combined, dried (Na_2SO_4), filtered and the filtrate concentrated to give an oil which was dissolved in benzene (0.2 M) and silica gel (1 g per mmol) added). This mixture was heated to reflux for 2-4 h, cooled, filtered, the filter pad washed with EtOAc and the combined filtrates were concentrated to give the crude unsatruated esters. Purification by column chromatography then provided the pure unsaturated esters.

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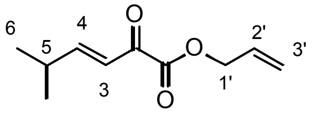
(4) (a) H. Sugimura, K. Yoshida, *Bull. Chem. Soc. Jpn.* **1992**, *65*, 3209-3211. (b) D. A. Evans, J. S. Johnson, E. J. Olhava, *J. Am. Chem. Soc.* **2000**, *122*, 1635-1649.

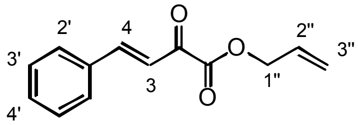
5-Methyl-2-oxo-hex-3-enoic acid allyl ester



BB2-A

^{1}H NMR (400 MHz) 7.14 (dd, *J* = 15.6, 6.3, 1 H, HC(4)); 6.60 (dd, *J* = 15.6, 1.5, 1 H, HC(3)); 5.98 (ddt, *J* = 17.6, 10.7; 5.9, 1 H, HC(2’)); 5.41 (d, *J* = 17.1, 1 H, HC(3’)); 5.31 (d, *J* = 10.7, 1 H, HC(3)); 4.76 (dt, *J* = 5.6, 1.5, 2 H, H_2C(1’)); 2.55 (m, 1 H, HC(5)); 1.10 (d, *J* = 6.8, 6 H, H_3C(6)); ^{13}C NMR (100 MHz) 183.22; 161.85; 160.67; 130.70; 122.25; 66.51; 31.76; 20.90; MS (EI) 182 (M+); 109; 97; 87.

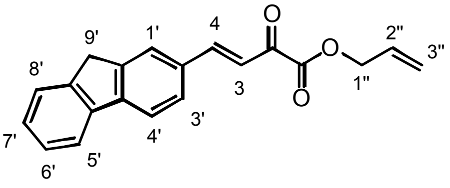
2-Oxo-4-phenyl-but-3-enoic acid allyl ester



BB2-B

^{1}H NMR (500 MHz) 7.87 (d *J* = 16.1, 1 H, HC(4)); 7.66 (d, *J* = 8.3, 2 H, HC(2’)); 7.45 (m, 3 H, HAr); 7.36 (d, *J* = 16.1, 1 H, HC(3)); 6.02 (ddt, *J* = 17.1, 10.8, 3.9, 1 H, HC(2’’)); 5.44 (dd, *J* = 17.1, 1.5, 1 H, HC(3’’)); 5.35 (dd, *J* = 10.7, 1.2, 1 H, HC(3’’)); 4.83 (d, *J* = 5.9, 2 H, H_2C(1’’)); ^{13}C NMR (100 MHz) 182.44; 161.72; 148.48; 133.86; 131.59; 130.78; 128.99; 128.95; 120.43; 119.83; 66.74; MS (EI) 216 (M+); 131; 103.

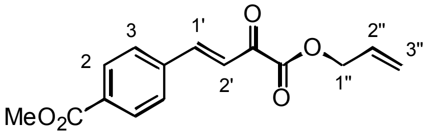
4-(9*H*-Fluoren-2-yl)-2-oxo-but-3-enoic acid allyl ester



BB2-C

^{1}H NMR (500 MHz) 7.96 (d, *J* = 16.1, 1 H, HC(4)); 7.82 (m, 2 H, HC(1’ and 8’)); 7.67 (m, 1 H, HAr); 7.59 (m, 1 H, HAr); 7.43 (d, *J* = 16.1, 1H, HC(3)); 7.44-7.35 (m, 3 H, HAr); 6.05 (ddt, *J* = 17.1, 10.3, 5.9, 1 H, HC(2’’)); 5.46 (d, *J* = 17.1, 1H, HC(3’’)); 5.36 (d, *J* = 10.2, 1 H, HC(3’’)); 4.84 (dt, *J* = 5.9, 1.5, 2 H, H_2C(1’’)); 3.95 (s, 2 H, H_2C(9’)); ^{13}C NMR (100 MHz) 182.17; 161.85; 148.92; 145.40; 143.98; 143.76; 140.44; 132.36; 130.82; 128.63; 127.83; 127.00; 125.26; 125.10; 120.53; 120.23; 119.79; 119.38; 66.79; 36.75; MS (EI) 304 (M+); 220; 219; 191; 189.

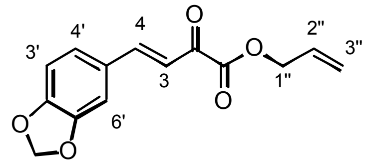
4-(3-Allyloxycarbonyl-3-oxo-propenyl)-benzoic acid methyl ester



BB2-D

^{1}H NMR (500 MHz) 8.08 (d, *J* = 8.8, 2 H, HC(2)); 7.87 (d, *J* = 16.1, 1 H, HC(1’)); 7.69 (d, *J* = 8.3, 2 H, HC(3)); 7.43 (d, *J* = 16.1, 1 H, HC(2’)); 6.07 (ddt, *J* = 17.1, 10.3, 6.3, 1 H, HC(2’’)); 5.44 (dd, *J* = 17.1, 1.0, 1 H, HC(3’’)); 5.35 (dd, *J* = 10.7, 1.3, 1 H, HC(3’’)); 4.82 (d, *J* = 5.9, 2 H, H_2C(1’’)); 3.94 (s, 3 H, H_3CO_2)); ^{13}C NMR (100 MHz) 182.03; 166.00; 161.31; 146.59; 137.86; 132.31; 130.61; 130.06; 128.66; 122.33; 119.97; 66.95; 52.36; MS (EI) 274 (M+); 243; 189.

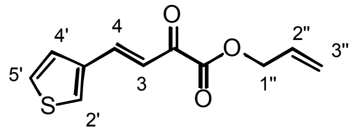
4-Benzo[1,3]dioxol-5-yl-2-oxo-but-3-enoic acid allyl ester



BB2-E

^{1}H NMR (500 MHz) 7.78)(d, 16.1, 1 H, HC(4)); 7.14 (d, *J* = 17.1, 1 H, HC(3)); 6.85 (d, *J* = 7.1, 1 H, Har)); 7.14 (s, 1 H, HC(6’)); 7.13 (d, *J* = 7.2, 1 H, Har)); 6.04 (s, 2 H, H_2CO_2); 6.01 (ddt, *J* = 17.1, 10.7, 5.9, 1 H, HC(2’’)); 5.43 (dd, *J* = 17.1, 1.0, 1 H, HC(3’’)); 5.33 (d, *J* = 10.6, 1.0, 1 H, HC(3’’)); 4.81 (dt, *J* = 5.9, 1.5, 2 H, H_2C(1’’)); ^{13}C NMR (100 MHz) 182.01; 161.82; 150.83; 148.43; 148.22; 130.80; 128.42; 126.49; 119.77; 118.39; 108.68; 106.80; 101.79; 66.76; MS (EI) 260 (M+); 175.

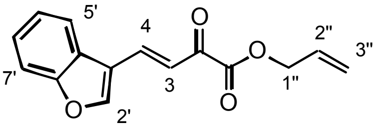
2-Oxo-4-thiophen-3-yl-but-3-enoic acid allyl ester



BB2-F

^{1}H NMR (500 MHz) 7.86 (d, *J* = 16.1, 1 H, HC(4)); 7.69 (m, 1 H, HAr); 7.40 (m, 1 H, HAr); 7.36 (s, 1 H, HC(2’)); 7.16 (d, *J* = 16.1, 1 H, HC(3); 6.04 (ddt, *J* = 17.1, 10.7, 5.9, 1 H, HC(2’’)); 5.44, (dd, *J* = 17.1, 1.5, 1 H, HC(3’’)); 5.34 (dd, *J* = 10.6, 1.4, 1 H, HC(3’’)); 4.81 (dt, *J* = 6.3, 1.0, 2 H, H_2C(1’’)); ^{13}C NMR (100 MHz) 182.38; 161.56; 131.23; 130.66; 129.59; 127.64; 127.23; 125.07; 120.08; 119.62; 66.12; MS (EI) 222 (M+); 137; 109.

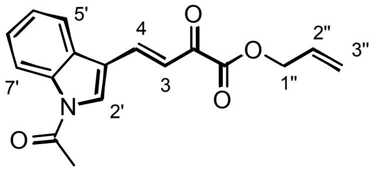
4-(Benzofuran-3-yl)-2-oxo-but-3-enoic acid allyl ester



BB2-G

^{1}H NMR (500 MHz) 7.74 (d, J = 15.6, 1 H, HC(4)); 7.62 (d, J = 7.3, 1 H, HAr); 7.51 (d, J = 8.3, 1 H, HAr); 7.47 (d, J = 15.6, 1 H, HC(3)); 7.42 (td, J = 7.3, 1.0, 1 H, HAr); 7.28 (td, J = 8.3, 1.0, 1 H, HAr)); 7.14 (s, 1 H, HC(2’)); 6.03 (ddt, J = 17.1, 10.3, 5.9, 1 H, HC(2’)); 5.45 (dd, J = 17.1, 1.0, 1 H, HC(3’’)); 5.36 (dd, J = 10.2, 1.0, 1 H, HC(3’’)); 4.83 (dt, J = 5.9, 1.5, 2 H, H$_2$C(1’’)); ^{13}C NMR (100 MHz) 181.69; 161.26; 155.85; 152.04; 133.75; 130.73; 128.19; 127.49; 123.54; 122.07; 120.43; 119.87; 114.69; 111.55; 66.90; MS (EI) 256 (M+); 228; 213; 185; 129.

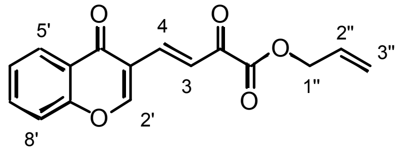
4-(1-Acetyl-1*H*-indol-3-yl)-2-oxo-but-3-enoic acid allyl ester



BB2-H

^{1}H NMR (500 MHz) 8.49 (d, J = 7.8, 1 H, HAr)); 8.03 (d, J = 16.1, 1 H, HC(4)); 7.91 (d, J = 6.8, 1 H, HAr); 7.86 (s, 1 H, HC(2’)); 7.53 (d, J = 16.1, 1 H, HC(3)); 7.48-7.40 (m, 2 H, HAr); 6.21 (ddt, J = 17.1, 10.7, 5.9, 1 H, HC(2’’)); 5.46 (dd, J = 17.1, 1.5, 1 H, HC(3’’)); 5.36 (dd, J = 10.7, 1.5, 1 H, HC(3’’)); 4.84 (dt, J = 5.9, 1.5, 2 H, HC(1’’)); 2.71 (s, 3 H, H$_3$CC(O)); ^{13}C NMR (100 MHz) 181.88; 168.14; 161.75; 139.69; 136.63; 130.77; 130.14; 127.27; 126.35; 124.75; 120.23; 120.13; 119.85; 118.40; 116.87; 66.87; 24.01; MS (EI) 297 (M+); 212; 170.

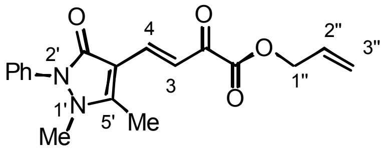
2-Oxo-4-(4-oxo-4*H*-chromen-3-yl)-but-3-enoic acid allyl ester



BB2-I

^{1}H NMR (500 MHz) 8.29 (dd, J = 7.8, 1.5, 1 H, HAr); 8.23 (t, J = 8.8, 2 H, HAr); 7.78 (m, 1 H); 7.57 (d, J = 15.1, 1 H); 7.30 (m, 2 H); 6.02 (ddt, J = 17.1, 10.3, 6.3, 1 H, HC(2’’)); 5.44 (dd, J = 17.1, 1.0, 1 H, HC(3’’)); 5.34 (dd, J = 10.7, 1.5, 1 H, HC(3’’)); 4.82 (dt, J = 5.9, 1.4, 2 H, H$_2$C(1’’)); ^{13}C NMR (100 MHz) 183.08; 175.40; 161.39; 159.31; 155.23; 139.13; 130.72; 126.23; 126.06; 124.01; 123.84; 119.76; 118.99; 118.08; 66.76; MS (EI) 284 (M+); 256; 228; 199; 149.

4-(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-2-oxo-but-3-enoic acid allyl ester



BB2-J

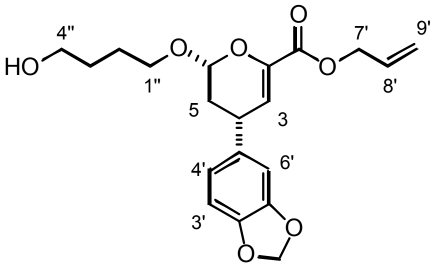
^{1}H NMR (500 MHz) 7.92 (d, *J* = 15.1, 1 H, HC(4)); 7.68 (d, *J* = 15.1, 1 H, HC(3)); 7.50 (t, *J* = 7.3, 2 H, HAr); 7.39 (t, *J* = 6.3, 1 H, HAr); 7.31 (d, *J* = 8.3, 2 H, HAr); 5.96 (ddt, *J* = 17.6, 10.7, 2.9, 1 H, HC(2'')); 5.38 (dd, *J* = 17.1, 1.5, 1 H, HC(3'')); 5.27 (dd, *J* = 10.7, 1.5, 1 H, HC(3'')); 4.76 (d, *J* = 3.0, 2 H, H_2C(1'')); 3.32 (s, 3 H, H_3CN); 2.42 (s, 3 H, H_3CC); ^{13}C NMR (100 MHz) 182.87; 162.68; 162.09; 153.01; 137.21; 133.46; 130.97; 129.36; 128.20; 125.90; 119.34; 116.98; 103.62; 66.36; 34.46; 10.83; MS (EI) 326 (M+); 241.

IV. Building Block Testing

General procedure for test cycloadditions. Vinyl ether resin (prepared as described below) (5 mg, ~1.1 meq / g, ~0.005 mmol, 1 equiv), the appropriate heterodiene (0.015 mmol, 3 equiv) and 5 mg of activated powdered 4A molecular sieves were placed in a dry 4 mL vial, capped with septa and placed under Ar. THF (80 uL) was added, followed by a 0.05 M solution of the appropriate catalyst **1** solution (prepared as described below). The resulting mixture was vortexed gently for 16-24 h then filtered (powdered sieves pass through the filter, thus separating them from the resin beads) and washed with 4 x 1 mL x 20 min THF, then 3 x 1 mL x 15 min CH_2Cl_2 and dried briefly. The resin was then transferred to an Eppendorf tube and treated with cleavage cocktail as described above, after concentration the samples were analyzed by ^{1}H NMR, LCMS and CSP HPLC and/or CSP SFC.

Vinyl ether testing:

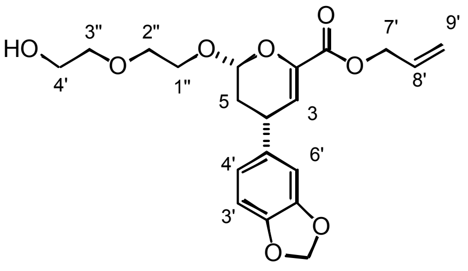
(4*R*,6*R*)-4-Benzo[1,3]dioxol-5-yl-6-(4-hydroxy-butoxy)-5,6-dihydro-4*H*-pyran-2-carboxylic acid allyl ester



7-A-E

^{1}H NMR (600 MHz) 6.74-6.72 (m, 2 H, HAr); 6.67 (dd, *J* = 7.8, 1.5, 1 H, HAr)); 6.14 (d, *J* = 2.9, 1 H, HC(3)); 5.96 (ddt, *J* = 17.1, 10.7, 5.3, 1 H, HC(8’)); 5.93 (d, *J* = 1.5, 2 H, H_2CO_2)); 5.36 (dd, *J* = 17.1, 1.5, 1 H, HC(9’)); 5.26 (dd, *J* = 10.7, 1.5, 1 H, HC(9’)); 5.14 (dd, *J* = 7.3, 2.0, 1 H, HC(6)); 4.71 (ABX, *J* = 14.3, 5.3, 2 H, H_2C(7’)); 4.01 (dt, *J* = 9.8, 5.9, 1 H, HC(1’’)); 3.70-3.60 (m, 4 H, HC(4), HC(1’’), H_2C(4’’)); 2.28 (ddd, *J* = 13.2, 6.8, 1.5, 1 H, HC(5)); 1.93 (dt, *J* = 13.6, 7.8, 1 H, HC(5)); 1.72-1.59 (m, 4 H, H_2C(2’’); H_2C(3’’)); MS (ESI) 400 (M+Na+1); 399 (M+Na); 387; 287; 261; HRMS (ESI) $C_{20}H_{24}O_7$-Na requires 399.1420; found 399.1432.

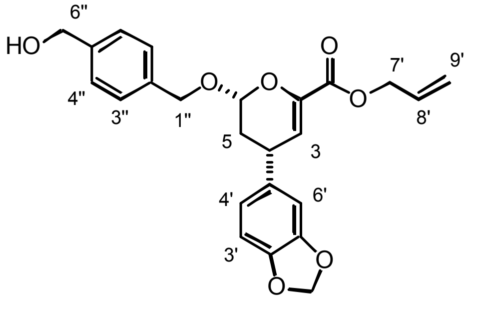
(4*R*,6*R*)-4-Benzo[1,3]dioxol-5-yl-6-[2-(2-hydroxy-ethoxy)-ethoxy]-5,6-dihydro-4*H*-pyran-2-carboxylic acid allyl ester



7-B-E

^{1}H NMR (600 MHz) 6.72-6.69 (m, 3 H, HAr); 6.23 (d, *J* = 4.3, 1 H, HC(3)); 6.0-5.96 (m, 1 H, HC(8’)); 5.93 (d, *J* = 5.4, 2 H, H_2CO_2); 5.35 (dd, *J* = 17.1, 1.0, 1 H, HC(9’)); 5.26 (dd, *J* = 10.3, 1.0, 1 H, HC(9’)); 5.16 (d, *J* = 2.4, 1 H, HC(6)); 4.72 (ABX, J = 18.6, 5.9, 5.9, 2 H, H_2C(7’)); 3.94 (ddd, *J* = 14.1, 9.8, 6.8, 1 H, HC(1’’)); 3.61-3.50 (m, 7 H, HCO); 2.19 (m, 1 H, HC(5). Other low field signals obscurred by plasticizer.

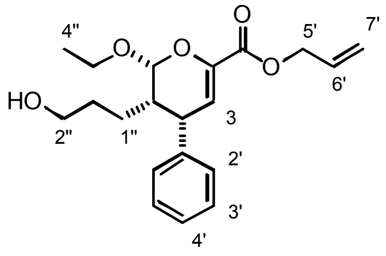
(4*R*,6*R*)-4-Benzo[1,3]dioxol-5-yl-6-(4-hydroxymethyl-benzyloxy)-5,6-dihydro-4*H*-pyran-2-carboxylic acid allyl ester



7-G-E

^{1}H NMR (600 MHz) 7.36-7.30 (m, 4 H, HAr); 6.74-6.70 (m, 2 H, HAr); 6.66 (dd, J = 7.8, 1.5, 1 H, HC(Ar)); 6.15 (d, J = 2.9, 1 H, HC(3)); 6.00-5.93 (m, 1 H, HC(8')); 5.93 (s, 2 H, H_2CO_2)); 5.37 (dd, J = 17.1, 1.5, 1 H, HC(9')); 5.27 (dd, J = 10.7, 1.5, 1 H, HC(9')); 5.20 (dd, J = 7.3, 2.0 , 1 H, HC(6)); 4.96 (d, J = 11.7, 1 H, HC(1'')); 4.78-4.68 (m, 5 H, H_2C(6''); HC(1''); H_2C(7')); 3.62 (ddd, J = 10.7, 8.3, 2.9, 1 H, HC(4)); 2.29 (ddd, J = 14.3, 6.8, 1.5, 1 H, HC(5)); 1.99 (dt, J = 14.2, 7.8, 1 H, HC(5)); MS (ESI) 447 (M+Na); 407; 363; 285; HRMS (ESI) $C_{24}H_{24}O_7$-Na requires 447.1420; found 447.1401.

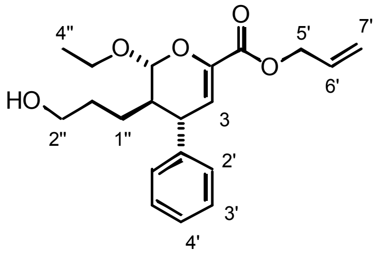
(4*R*,5*S*,6*R*)-6-Ethoxy-5-(3-hydroxy-propyl)-4-phenyl-5,6-dihydro-4*H*-pyran-2-carboxylic acid allyl ester



8-D-E

^{1}H NMR (600 MHz) 7.32-7.20 (m, 5 H, HAr); 6.29 (d, J = 3.9, 1 H, HC(3)); 5.96 (ddt, J = 17.1, 10.6, 5.9, 1 H, HC(6')); 5.36 (dd, J = 17.1, 1.5, 1 H, HC(7')); 5.26 (dd, J = 10.7, 1.5, 1 H, HC(7')); 4.76-4.65 (m, 2 H, H_2C(5')); 3.96 (dq, J = 7.3, 7.1, 1 H, HC(4'')); 3.7-3.5 (m, 3 H, HC(4'') and H_2C(3'')); 3.49 (t, J = 6.3, 1 H, HC(4)); 2.25-2.20 (m, 1 H, HC(5); 1.60-1.22 (m, 4 H, H_2C(1'') and H_2C(2'')); 1.19 (t, J = 7.1, 3 H, H_3C(5'')); MS (ESI) 369 (M+Na); 357; 299; 280; 217; HRMS (ESI) $C_{20}H_{26}O_5$-Na requires 369.1678; found 369.1669.

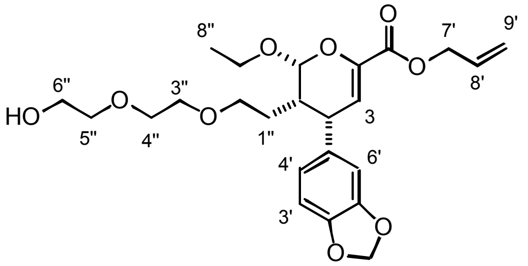
(4*R*,5*R*,6*R*)-6-Ethoxy-5-(3-hydroxy-propyl)-4-phenyl-5,6-dihydro-4*H*-pyran-2-carboxylic acid allyl ester



9-C-B

^{1}H NMR (600 MHz) 7.31-7.20 (m, 5 H, HAr); 6.16 (d, *J* = 3.4, 1 H, HC(3)); 5.95 (ddt, *J* = 17.1, 10.7, 5.9, 1 H, HC(6’)); 5.35 (dd, *J* = 17.1, 1.5, 1 H, HC(7’)); 5.25 (dd, *J* = 10.7, 1.4, 1 H, HC(7’)); 4.92 (d, *J* = 5.9, 1 H, HC(6)); 4.71 (ABX, *J* = 17.6, 5.4, 2 H, $H_2C(5’)$); 4.00 (dq, *J* = 7.3, 6.8, 1 H, HC(4’’)); 3.60-3.52 (m, 3 H, $H_2C(3’’)$ and HC(4’’)); 3.34 (dd, *J* = 6.8, 3.4, 1 H, HC(4)); 2.03 (quint, *J* = 6.9 1 H, HC(5)); 1.62-1.56 (m, 2 H, $H_2C(1’’)$); 1.50-1.46 (m, 2 H, $H_2C(2’’)$); 1.20 (t, *J* = 7.3, 3 H, $H_3C(5’’)$); MS (ESI) 369 (M+Na); 299; 280; 217. HRMS (ESI) $C_{20}H_{26}O_5$-Na requires 369.1678; found 369.1577.

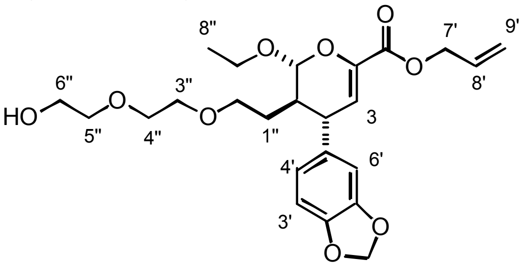
(4*R*,5*S*,6*R*)-4-Benzo[1,3]dioxol-5-yl-6-ethoxy-5-{2-[2-(2-hydroxy-ethoxy)-ethoxy]-ethyl}-5,6-dihydro-4*H*-pyran-2-carboxylic acid allyl ester



8-F-E

^{1}H NMR (600 MHz) 6.75-6.65 (m, 3 H, HAr); 6.24 (d, *J* = 3.9, 1 H, HC(3)); 5.99-5.92 (m, 1 H, HC(8’)); 5.93 (d, *J* = 1.5, 1 H, HCO_2)); 5.91 (d, *J* = 1.5, HCO_2)); 5.35 (dd, *J* = 17.1, 1.5, 1 H, HC(9’)); 5.25 (dd, *J* = 10.7, 1.5, 1 H, HC(9’)); 5.19 (d, *J* = 2.4, 1 H, HC(6)); 4.77-4.66 (m, 2 H, $H_2C(7’)$); 3.93-3.90 (m, 1 H, HC(7’’)); 3.78-3.30 (m, 12 H, H_2CO; HC(7’’); HC(4)); 1.19 (t, *J* = 6.9, 3 H, $H_3C(8’’)$); other signals obscurred; MS (ESI) 487 (M+Na); 419; 417; 261; HRMS (ESI) $C_{24}H_{32}O_9$-Na 487.1944; found 487.1943.

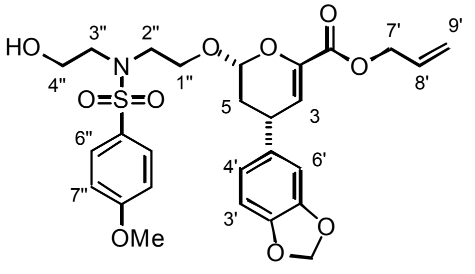
(4*R*,5*R*,6*R*)-4-Benzo[1,3]dioxol-5-yl-6-ethoxy-5-{2-[2-(2-hydroxy-ethoxy)-ethoxy]-ethyl}-5,6-dihydro-4*H*-pyran-2-carboxylic acid allyl ester



9-E-E

^{1}H NMR (600 MHz) 6.75-6.66 (m, 3 H, HAr); 6.11 (d, *J* = 3.4, 1 H, HC(3)); 5.97-5.92 (m, 1 H, HC(8’)); 5.93 (d, *J* = 2.4, 2 H, H_2CO_2)); 5.35 (dd, *J* = 17.6, 1.5, 1 H, HC(9’)); 5.25 (d, *J* 10.3, 1 H, HC(9’)); 4.92 (d, *J* = 5.9, 1 H, HC(6)); 4.70 (ABX, *J* = 13.6, 5.9, 2 H, H_2C(7’)); 3.96 (qd, *J* = 7.3, 6.8, 1 H, HC(7’’)); 3.75-3.43 (m, 11 H, HCO; HC(7’)); 3.33 (dd, *J* = 6.3, 3.4, 1 H, HC(4)); 2.07, quint, *J* = 5.9, 1 H, HC(5)); 1.72-1.63 (m, 2 H, H2C(1’’)); 1.19 (t, *J* = 6.8, 3 H, H_3C(8’’)); MS (ESI) 487 (M+Na); 419; 261; HRMS (ESI) $C_{24}H_{32}O_9$-Na requires 487.1944; found 487.1921.

(4*R*,6*R*)-4-Benzo[1,3]dioxol-5-yl-6-{2-[(2-hydroxy-ethyl)-(4-methoxy-benzenesulfonyl)-amino]-ethoxy}-5,6-dihydro-4*H*-pyran-2-carboxylic acid allyl ester

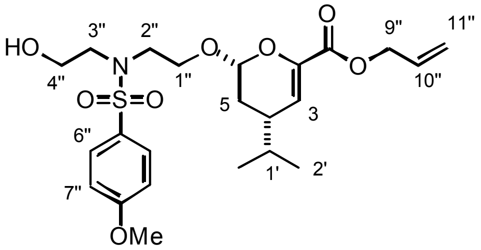


7-H-E

^{1}H NMR (600 MHz) 7.76 (d, *J* = 8.8, 2 H, HAr); 6.97 (d, *J* = 8.8, 2 H, HAr); 6.74 (d, *J* = 7.8, 1 H, HAr)); 6.68-6.64 (m, 2 H, HAr)); 6.13 (d, *J* = 2.9, 1 H, HC(3)); 6.00-5.90 (m, 1 H, HC(8’)); 5.93 (s, 2 H, H_2CO_2)); 5.35 (d, *J* = 17.1, 1.5, 1 H, HC(9’)); 5.26 (dd, *J* = 10.7, 1.5, 1 H, HC(9’)); 5.10 (dd, *J* = 8.3, 2.0, 1 H, HC(6)); 4.77-4.65 (m, 2 H, H_2C(7’)); 4.14-4.10 (m, 1 H); 3.92-3.84 (m, 1 H, 3.86 (s, 3 H, H_3CO); 3.71 –3.68 (m, 2 H); 3.64-3.62 (m, 1 H, HC(4)); 3.48 (dt, *J* = 15.1, 4.4, 1 H); 3.36-3.22 (m, 2 H); 3.08 (dt, *J* = 14.6, 4.9, 1 H); 2.26 (dd, *J* = 12.7, 6.8, 1 H, HC(5)); 1.86 (dt, *J* = 13.2, 8.3, 1 H, HC(5)); MS (ESI) 584 (M+Na); 287; 276. HRMS (ESI) $C_27H_{31}NO_{10}S$-Na requires 584.1566; found 584.1572.

Heterodiene Testing:

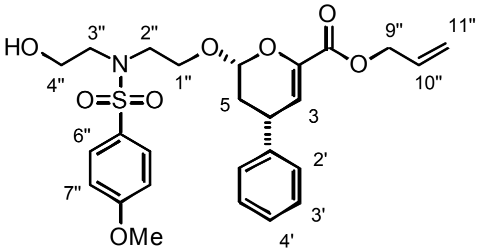
(4*S*,6*R*)-6-{2-[(2-Hydroxy-ethyl)-(4-methoxy-benzenesulfonyl)-amino]-ethoxy}-4-isopropyl-5,6-dihydro-4*H*-pyran-2-carboxylic acid allyl ester



7-H-A

^{1}H NMR (600 MHz) 7.78-7.77 (m, 2 H, HAr); 7.00-6.96 (m, 2 H, HAr); 6.04 (d, *J* = 2.0, 1 H, HC(3)); 5.87 (ddd, *J* = 17.1, 10.7, 1.5, 1 H, HC(10'')); 5.35 (dd, *J* = 17.1, 1.5, 1 H, HC(11'')); 5.25 (dd, *J* = 10.7, 1.5, 1 H, HC(11'')); 4.97 (dd, *J* = 9.3, 1.3, 1 H, HC(6)); 4.72-4.64 (m, 2 H, H_2C(9'')); 4.14-4.10 (m, 1 H); 4.02-3.99 (m, 1 H); 3.96-3.90 (m, 1 H); 3.87 (s, 3 H, H_3CO); 3.80-3.70 (m, 2 H); 3.50-3.32 (m, 2 H); 3.29-3.26 (m, 1 H); 3.18-3.16 (m, 1 H); 2.32-2.26 (m, 1 H, HC(5)); 1.98-1.96 (m, 1 H, HC(5)); 1.74-1.65 (m, 1 H, HC(1')); 0.96 (d, *J* = 7.1, 3 H, H_3C(2')); 0.94 (d, *J* = 7.1, 3 H, H_3C(1')); MS (ESI506 (M+Na); 484 (M+1); 276; 258; HRMS (ESI) $C_{23}H_{33}NO_8S$-Na requires 506.1825; found 506.1847.

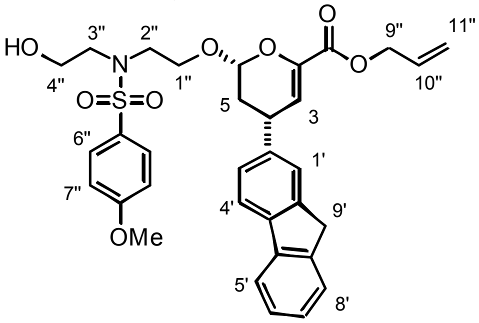
(4*R*,6*R*)-6-{2-[(2-Hydroxy-ethyl)-(4-methoxy-benzenesulfonyl)-amino]-ethoxy}-4-phenyl-5,6-dihydro-4*H*-pyran-2-carboxylic acid allyl ester



7-H-B

^{1}H NMR (600 MHz) 7.76-7.70 (m, 2 H, HAr); 7.31-7.19 (m, 5 H, HAr); 7.00-6.96 (m, 2 H, HAr); 6.20 (d, *J* = 2.9, 1 H, HC(3)); 5.93 (ddd, *J* = 17.1, 10.7, 1.6, 1 H, HC(10'')); 5.36 ()dd, *J* = 17.1, 1.5, 1 H, HC(11'')); 5.26 (dd, *J* = 10.7, 1.5, 1 H, HC(11'')); 5.14 (dd, *J* = 7.8, 2.0, 1 H, HC(6)); 4.77-4.68 (m, 2 H, H_2C(9'')); 4.15-4.10 (m, 1 H); 4.02-3.98 (m, 1 H); 3.91-3.84 (m, 1 H); 3.87 (s,. 3 H, H_3CO); 3.74-3.70 (m, 1 H); 3.65-3.60 (m, 1 H); 3.50-3.40 (m, 1 H); 3.29-3.22 (m, 2 H); 3.08-3.00 (m, 1 H); 2.31 (m, 1 H, HC(5)); 1.93 (dt, *J* = 14.0, 7.5, 1 H, HC(5)); MS (ESI) 540 (M+Na); 518 (M+1); 276; 258; HRMS (ESI) $C_{26}H_{31}N_{O}8S$-Na requires 540.1668; found 540.1644.

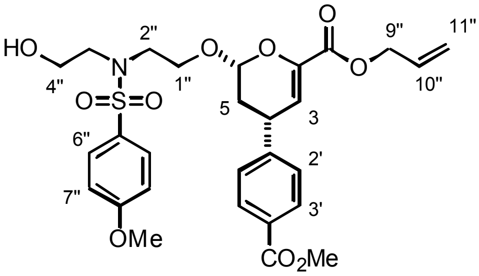
(4*R*,6*R*)-4-(9*H*-Fluoren-2-yl)-6-{2-[(2-hydroxy-ethyl)-(4-methoxy-benzenesulfonyl)-amino]-ethoxy}-5,6-dihydro-4*H*-pyran-2-carboxylic acid allyl ester



7-H-C

^{1}H NMR (600 MHz) 7.77-7.70 (m); 7.55-7.53 (m); 7.38-7.20 (m); 7.70-6.94 (m); 6.24 (d, *J* = 2.9, 1 H, HC(3)); 5.96 (ddd, *J* = 17.1, 10.7, 1.5, 1 H, HC(10'')); 5.36 (dd, *J* = 17.1, 1.5, 1 H, HC(11'')); 5.26 (dd, *J* = 10.7, 1.5, 1 H, HC(11'')); 5.17 (dd, *J* = 7.8, 2.0, 1 H, HC(6)); 4.77-4.68 (m, 2 H, H_2C(9'')); 4.16-4.11 (m, 1 H); 3.95-3.90 (m, 1 H); 3.88-3.82 (m, 1 H); 3.83 (s, 3 H, H_3CO); 3.82-3.80 (m, 1 H, HC(4)); 3.64-3.62 (m, 1 H); 3.51-3.46 (m, 1 H); 3.30-3.22 (m, 2 H); 3.06-3.00 (m, 1 H); 2.36 (dd, *J* = 12.7, 7.3, 1 H, HC(5)); 1.98 (dt, *J* = 13.6, 8.8, 1 H, HC(5)); MS (ESI) 628 (M+Na); 606 (M+1); 536; 478; 276; HRMS (ESI) $C_{33}H_{35}NO_8S$-Na requires 628.1998; found 628.2008.

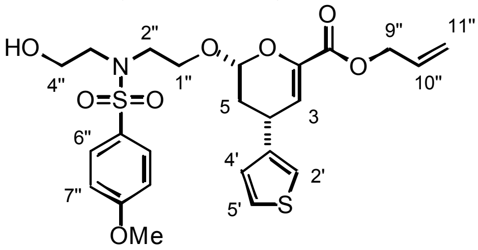
(4*R*,6*R*)-6-{2-[(2-Hydroxy-ethyl)-(4-methoxy-benzenesulfonyl)-amino]-ethoxy}-4-(4-methoxycarbonyl-phenyl)-5,6-dihydro-4*H*-pyran-2-carboxylic acid allyl ester



7-H-D

^{1}H NMR (600 MHz) 7.98 (d, *J* = 8.8, 2 H, HC(3')); 7.76-7.72 (m, 2 H, HAr); 7.28 (d, *J* = 8.8, 2 H, HC(2')); 6.99-6.95 (m, 2 H, HAr)); 6.19 (d, *J* = 2.9, 1 H, HC(3)); 5.86 (ddd, *J* = 17.1, 10.7, 1.5, 1 H, HC(10'')); 5.36 (dd, *J* = 17.1, 1.4, 1 H, HC(11'')); 5.26 (dd, *J* = 10.7, 1.5, 1 H, HC(11'')); 5.17 (dd, *J* = 7.8, 2.0, 1 H, HC(6)); 4.77-4.66 (m, 2 H, H_2C(9'')); 4.14-4.08 (m, 1 H); 3.93-3.85 (m, 2 H); 3.91 (s, 3 H, H_3CO_2C)); 3.86 (s, 3 H, H_3CO); 3.79-3.76 (m, 1 H, HC(4)); 3.62-3.60 (m, 1 H); 3.46-3.42 (dt, *J* = 15.1, 4.9, 1 H); 3.26-3.19 (m, 2 H); 3.01 (dt, *J* = 10.2, 5.9, 1 H); 2.36-2.30 (m, 1 H, HC(5)); 1.96-1.92 (m, 1 H, HC(5)); MS (ESI) 598 (M+Na); 576 (M+1); 276; HRMS (ESI) $C_{28}H_{33}NO_{10}S$-Na requires 598.1723; found 598.1702.

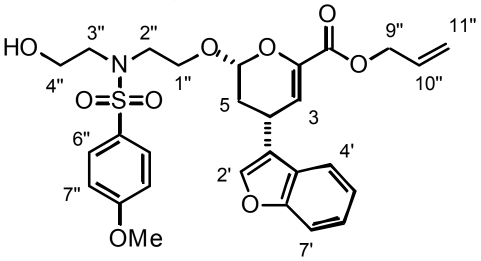
(4*R*,6*R*)-6-{2-[(2-Hydroxy-ethyl)-(4-methoxy-benzenesulfonyl)-amino]-ethoxy}-4-thiophen-3-yl-5,6-dihydro-4*H*-pyran-2-carboxylic acid allyl ester



7-H-F

^{1}H NMR (600 MHz) 7.77-7.74 (m, 2 H, HAr); 7.74-7.72 (m, 1 H, HAr); 7.29 (dd, *J* = 4.9, 2.9, 1 H, HAr); 7.05-6.95 (m, 3 H, HAr); 6.21 (d, *J* = 3.4, 1 H, HC(3)); 5.86 (ddd, *J* = 17.1, 10.7, 1.4, 1 H, HC(10’’)); 5.36 (dd, *J* = 17.1, 1.5, 1 H, HC(11’’)); 5.26 (dd, *J* = 10.7, 1.5, 1 H, HC(11’’)); 5.15 (dd, *J* = 7.8, 2.0, 1 H, HC(6)); 4.75-4.64 (m, 2 H, HC(9’’)); 4.12-4.08 (m, 1 H); 4.02-3.98 (m, 1 H); 3.92-3.80 (m, 2 H); 3.86 (s, 3 H, H_3CO); 3.74-3.70 (m, 1 H); 3.68 (t, *J* = 4.9, 1 H); 3.50-3.40 (m, 1H); 3.32-3.22 (m, 1 H); 3.07-3.02 (m, 1H); 2.34-2.30 (m, 1 H, HC(5)); 2.00-1.95 (m,1 H, HC(5)); MS (ESI) 546 (M+Na); 524 (M+1); 302; 276; 258; 249; HRMS (ESI) $C_{24}H_{29}NO_8S_2$ requires 546.1232; found 546.1230.

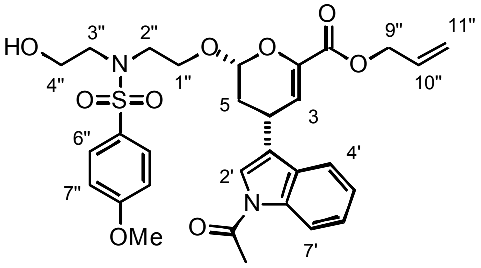
(4*R*,6*R*)-4-Benzofuran-3-yl-6-{2-[(2-hydroxy-ethyl)-(4-methoxy-benzenesulfonyl)-amino]-ethoxy}-5,6-dihydro-4*H*-pyran-2-carboxylic acid allyl ester



7-H-G

^{1}H NMR (600 MHz) 7.74-7.70 (m, 2 H, HAr); 7.48 (d, *J* = 6.8, 1 H, HAr); 7.42 (d, *J* = 8.3, 1 H, Hr); 7.26-7.18 (m, 2 H, HAr); 7.00-6.97 (m, 2 H, HAr); 6.47 (s, 1 H, HC(2’)); 6.34 (d, *J* = 3.9, 1 H, HC(3)); 5.97 (ddd, *J* = 17.1, 10.7, 1.5, 1 H, HC(10’’)); 5.38 (dd, *J* = 17.1, 1.5, 1 H, HC(11’’)); 5.24 (dd, *J* = 10.1, 1.4, 1 H, HC(11’’)); 5.19 (dd, *J* = 6.3, 2.4, 1 H, HC(6)); 4.78-4.68 (m, 2 H, H_2C(9’’)); 4.05-4.00 (m, 1 H); 3.90-3.80 (m, 1 H); 3.86 (s, 3 H, H_3CO); 3.74-3.70 (m, 1 H); 3.50-3.40 (m, 2 H); 3.29-3.24 (m, 1 H); 3.20-3.16 (m, 1 H); 3.13-3.07 (m, 1 H); 2.98-2.90 (m, 1 H); 2.37-2.25 (m, 2 H, H_2C(5)); MS (ESI) 580 (M+Na); 558 (M+1); 258; HRMS (ESI) $C_{28}H_{31}NO_9S$-Na requires 580.1617; found 580.1595.

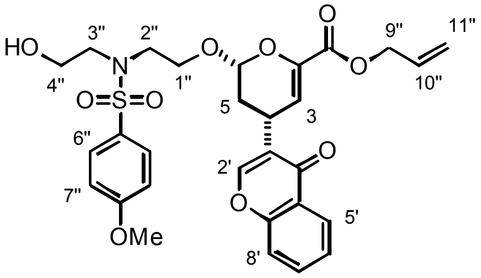
(4*R*,6*R*)-4-(1-Acetyl-1*H*-indol-3-yl)-6-{2-[(2-hydroxy-ethyl)-(4-methoxy-benzenesulfonyl)-amino]-ethoxy}-5,6-dihydro-4*H*-pyran-2-carboxylic acid allyl ester



7-H-H

^{1}H NMR (600 MHz) 7.77-7.75 (m, 2 H, HAr); 7.51-7.49 (m, 1 H); 7.35-7.26 (m, 3 H, HAr); 6.95-6.90 (m, 2 H, HAr); 6.21 (d, *J* = 2.8, 1 H, HC(3)); 5.91 (ddd, *J* = 17.1, 10.7, 1.4, 1 H, HC(10'')); 5.36 (dd, *J* = 17.1, 1.5, 1 H, HC(11'')); 5.25 (dd, *J* = 10.7, 1.5, 1 H, HC(11'')); 5.19 (dd, *J* = 8.4, 1.3, 1 H, HC(6)); 4.68-4.61 (m, 2 H, H_2C(9'')); 4.05-4.00 (m, 1 H); 3.99-3.82 (m, 2 H); 3.85 (s, 3 H, H_3CO); 3.84-3.80 (m, 1 H); 3.60-3.56 (m, 1 H); 3.45-3.20 (m, 3 H); 3.01 (dt, *J* = 14.1, 5.1, 1 H): 2.58 (s, 3 H, $H_3CC(O)$)); 2.38-2.33 (m, 1 H, HC(5)); 2.06-2.00 (m, 1 H, HC(5)); MS (ESI) 621 (M+Na); 599 (M+1); 276; HRMS (ESI) $C_{30}H_{34}N_2O_9S$-Na requires 621.1883; found 621.1860.

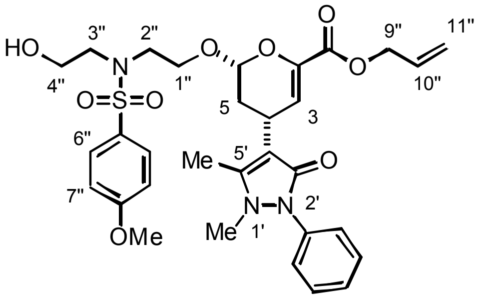
(4*R*,6*R*)-6-{2-[(2-Hydroxy-ethyl)-(4-methoxy-benzenesulfonyl)-amino]-ethoxy}-4-(4-oxo-4*H*-chromen-3-yl)-5,6-dihydro-4*H*-pyran-2-carboxylic acid allyl ester



7-H-I

^{1}H NMR (600 MHz) 8.25 (d, *J* = 7.8, 1.5, 1 HAr); 7.87 (s, 1 H, HC(2')); 7.72 (d, *J* = 9.3, 2 H, HC(6'')); 7.68-7.64 (m, 1 H, HAr); 7.46-7.40 (m, 2 H, HAr); 6.97 (d, *J* = 9.3, 2 H, HC(7'')); 6.19 (d, *J* = 3.9, 1 H, HC(3)); 6.03 (ddd, *J* = 17.1, 10.7, 1.5, 1 H, HC(10'')); 5.37 (dd, *J* = 17.1, 1.5, 1 H, HC(11'')); 5.28 (dd, *J* = 10.7, 1.4, 1 H, HC(11'')); 5.20 (dd, *J* = 4.9, 2.4, 1 H, HC(6)); 4.78-4.69 (m, 2 H, HC(9'')); 4.02-3.98 (m, 1 H, HC(4)); 3.88-3.72 (m, 2 H); 3.86 (s, 3H, H_3CO); 3.58 (t, *J* = 4.8, 1H); 3.36 (dt, *J* = 14.7, 4.9, 1 H); 3.32-3.24 (m, 1 H); 3.17 (dt, *J* = 15.1, 4.9, 1H); 3.10-3.06 (m, 1 H); 2.38-2.34 (m, 1 H, HC(5)); 2.00-1.94 (m, 1 H, HC(5)); MS (ESI) 608 (M+Na); 586 (M+1); 311; HRMS (ESI) $C_{29}H_{31}NO_{10}S$-Na requires 608.1566; found 608.1572.

(4*R*,6*R*)-4-(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-6-{2-[(2-hydroxy-ethyl)-(4-methoxy-benzenesulfonyl)-amino]-ethoxy}-5,6-dihydro-4*H*-pyran-2-carboxylic acid allyl ester

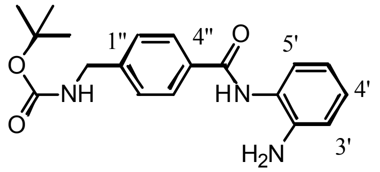


7-H-J

^{1}H NMR (600 MHz) 7.76 (m, 2 H, HAr); 7.46-7.30 (m, 5 H, HAr); 6.99-6.96 (m, 2 H, HAr); 6.11 (d, *J* = 2.9, 1 H, HC(3); 5.96 (ddd, *J* = 17.1, 10.7, 1.5, 1 H, HC(10’’)); 5.35 (dd, *J* = 17.1, 1.5, 1 H, HC(11’’)); 5.26 (dd, *J* = 10.7, 1.5, 1 H, HC(11’’)); 5.11 (dd, *J* = 8.3, 2.0, 1 H, HC(6)); 4.77-4.65 (m, 2 H, H$_2$C(9’’)); 4.04-3.99 (m, 1 H); 3.90-3.85 (m, 1 H); 3.86 (s, 3 H, H$_3$CO); 3.72-3.70 (m, 2 H); 3.44-3.40 (m, 2 H); 3.33-3.20 (m, 3 H); 3.06 (s, 3 H, H$_3$CN); 2.30-2.22 (m, 1 H, HC(5)); 2.22 (s, 3 H, H$_3$CC); 2.02-1.96 (m, 1 H, HC(5)); MS (ESI) 650 (M+Na); 628 (M+1); HRMS (ESI) $C_{31}H_{37}N_3O_9S$-Na requires 628.2329; found 628.2348.

Amine building blocks:

[4-(2-Amino-phenylcarbamoyl)-benzyl]-carbamic acid *tert*-butyl ester



^{1}H NMR (500 MHz, dmso-d_6) 9.60 (s, 1 H, ArNH); 7.91 (d, *J* = 7.8, 2 H, HC(3’’)); 7.48 (t, *J* = 6.4, 1H, CH$_2$N*H*); 7.33 (d, *J* = 6.8, 2 H, HC(2’’)); 7.15 (d, *J* = 7.8, 1 H, HC(6’)); 6.96 (t, *J* = 7.8, 1 H, HC(4’)); 6.76 (d, *J* = 7.8, 1 H, HC(3’)); 6.58 (t, *J* = 7.3, 1 H, HC(5’)); 4.88 (s, 2 H, NH2); 4.17 (d, *J* = 6.4, 2 H, H$_2$Car); 1.39 (s, 9 H, H$_3$C); ^{13}C NMR (100 MHz, dmso-d_6) 165.17; 155.85; 143.78; 143.16; 133.06; 127.83; 127.56; 126.95; 126.66; 126.48; 123.37; 116.28; 116.15; 77.94; 43.19; 28.26; MS (ESI) 342 (M+1); 286.

V. Encoded Split-Pool Library Synthesis

Loading. A potion of the silyl functionalized resin **2** (1.43 meq/g, 2.10 g, 3.0 mmol) was divided into eight equal portions (262 mg, 0.375 mmol, 1.0 equiv), placed under argon in PD-10 tubes and suspended in 3 mL of 3% (vol/vol) TMSCl / CH_2Cl_2 (in PD-10 columns). The swollen beads were allowed to stand for 30 min, then filtered (under argon) and washed with 4 x 3 mL x 2 min CH_2Cl_2. Then, a solution of TfOH (3% in CH2Cl2, 6.6 mL, 2.25 mmol, 6.0 equiv) was added and the resin was allowed to stand (with occasional gentle mixing) for 25 min. The resin was filtered (under argon) and washed with 4 x 3 mL x 2 min CH_2Cl_2. After the final wash an additional 2 mL of CH_2Cl_2 was added to each pool, followed by 2,6-lutidine (350 uL, 3.0 mmol, 8.0 equiv) and the resin was allowed to stand (with occasional gentle mixing) for 15 minutes. At this point each of the vinyl ethers **BB1A-H** were added (0.75 mmol, 2.0 equiv) as solutions in 1 mL of CH_2Cl_2. The tubes were then allowed to stand for 2.5 h (with occasional gentle mixing) then the resin was filtered and washed with 4 x 3 mL x 2 min CH_2Cl_2, then 1 x 5 mL x 15 min THF, then 1 x 5 mL x 15 min CH_2Cl_2 then the resin pools were dried, first by simple suction for 10 min, then under vacuum for 2h and taken to the next step.

First Encoding Step. Each of the eight resin pools from above (0.375 mmol, 1 equiv) was placed in a dry 8 mL vial capped with a septum. To each vial was added the appropriate diazoketone tags (see table below) (0.0672 mmol total tag for each reaction), followed by CH_2Cl_2 (4.0 mL, 16.8 mM total tag concentration) was added to each vial and the vials were gently shaken on a vortexer for 1 h. Then, a solution of $Rh_2(O_2CPh_3)_4$ (4 mL, 2.5 mg / mL) in CH_2Cl_2 was added to each vial and the resulting mixture vortexed for an additional 4 h, then the resin was filtered and washed with 2 x 5 mL x 15 min CH_2Cl_2, then 1 x 5 mL x 5 min THF, then 1 x 5 mL x 8 h THF, then 2 x 5 mL x 10 min THF, then 3 x 5 mL x 15 min CH_2Cl_2. At this point the resin was pooled and rotated/washed in 1 x 15 mL x 30 min THF then 3 x 15 mL x 30 min CH_2Cl_2, and dried as above to give 2.12 g of tagged vinyl ether.

Table S1. Binary tagging scheme for first tagging step.

BB1-	T2B (C4Cl3)	T4B (C6Cl3)	T1A (C3Cl5)	T2A (C4Cl5)
A	29.7 mg	-	-	-
B	-	31.8 mg	-	-
C	-	-	33.5 mg	-
D	-	-	-	34.5 mg
E	14.9 mg	15.9 mg	-	-
F	14.9 mg	-	16.7 mg	-
G	14.9 mg	-	-	17.2 mg
H	-	15.9 mg	16.7 mg	-

Cycloaddition. The resin from above was divided into 20 equal portions (106 mg each, 0.15 mmol (theory), 1.0 equiv) and placed in dry 4 mL vials containing diene building blocks **BB2A-J** (2 vials per building block, 0.45 mmol, 3.0 equiv) and 10 mg of activated powdered 4A molecular sieves. The vials were capped with septa and placed under argon. THF (0.8 mL) was added to each vial, followed by a solution of appropriate catalyst solution (0.8 mL). (Catalyst solutions were prepared by mixing 1 equiv of each 2,2'-Isopropylidenebis[(4*S*)-4-*t*-butyl-2-oxazoline] ligand (141 mg) and Cu(OTf)$_2$ (173 mg) with 4A molecular sieves (50 mg) in THF (12.8 mL) and stirred at rt temp to give a deep green mixture. An identical procedure was used for the (*R*)-enantiomer of catalyst). The resulting mixtures were vortexed gently for 20 h then filtered (powdered sieves pass through the filter, thus separating them from the resin beads) and washed with 4 x 5 mL x 30 min THF, then 3 x 5 mL x 15 min CH_2Cl_2 and dried as above to give 20 pools of partially encoded cycloadducts.

Second Encoding Step. Each of the 20 resin pools (0.15 mmol (theory), 1 equiv) was placed in a dry 8 mL vial capped with a septum. To each pool was added the appropriate combination of tags (0.027 mmol total tag, see table below) followed by 1.6 mL of CH_2Cl_2 and the mixture vortexed gently for 1 h. Then, a solution of $Rh_2(O_2CPh_3)_4$ (1.6 mL, 2.5 mg / mL) in CH_2Cl_2 was added to each vial and the resulting mixture vortexed for an additional 14 h, then the resin was filtered and washed with 2 x 5 mL x 15 min CH_2Cl_2, then 2 x 5 mL x 15 min THF, then 1 x 5 mL x 6 h THF, then 2 x 5 mL x 15 min THF, then 3 x 5 mL x 15 min CH_2Cl_2. At this point the resin pools derived from the (*R*) were combined (likewise the pools from the (*S*) catalyst were combined) and the two pseudo-enantiomeric pools were independently mixed / washed with 2 x 15 mL x 30 min THF and 3 x 15 mL x 15 min CH_2Cl_2, then filtered and dried to give two pseudo-enantiomeric pools of resin, each containing roughly 1.43 g of fully encoded, resin bound cycloadducts. A portion of each pool (1/27) by weight was set aside at this point to provide samples of the initial cycloadducts in the final library collection.

Table S2. Binary tagging scheme for second tagging step.

BB2-	catalyst	T3A (C5Cl5)	T4A (C6Cl5)	T5A (C7Cl5)	T6A (C8Cl5)	T7A (C9Cl5)
A	(S)-1	14.2 mg	-	-	-	-
B	(S)-1	-	14.5 mg	-	-	-
C	(S)-1	-	-	14.9 mg	-	-
D	(S)-1	-	-	-	15.3 mg	-
E	(S)-1	-	-	-	-	15.7 mg
F	(S)-1	7.1 mg	7.3 mg	-	-	-
G	(S)-1	7.1 mg	-	7.5 mg	-	-
H	(S)-1	7.1 mg	-	-	7.6 mg	-
I	(S)-1	7.1 mg	-	-	-	7.9 mg
J	(S)-1	-	7.3 mg	7.5 mg	-	-
A	(R)-1	-	7.3 mg	-	7.6 mg	-
B	(R)-1	-	7.3 mg	-	-	7.9 mg
C	(R)-1	-	-	7.5 mg	7.6 mg	-
D	(R)-1	-	-	7.5 mg	-	7.9 mg
E	(R)-1	-	-	-	7.6 mh	7.9 mg
F	(R)-1	4.7 mg	4.8 mg	5.0 mg	-	-
G	(R)-1	4.7 mg	4.8 mg	-	5.1 mg	-
H	(R)-1	4.7 mg	4.8 mg	-	-	5.2 mg
I	(R)-1	4.7 mg	-	5.0 mg	5.1 mg	-
J	(R)-1	4.7 mg	-	5.0 mg	-	5.2 mg

Deallylation. Each of the two resin pools from above (1.5 mmol (theory) 1.0 equiv) was treated identically. Tetrakis(triphenylphosphine)palladium (1.73 g, 1.5 mmol, 1.0 equiv) was dissolved in 26 mL of THF. The dry resin was then added to this solution followed by thiosalicylic acid (1.62 g, 10.5 mmol, 7 equiv) and the mixture was vortexed gently for 12 h, then the resin pools were filtered and each washed separately with 4 x 15 mL x 1 h THF, then 2 x 15 mL x 15 min DMF, then 1 x 15 mL x 15 min THF, then 1 x 15 mL x 15 min DMF, then 4 x 15 mL x 15 min CH_2Cl_2 then dried to give two pools of resin each weighing roughly 1.34 g. A portion of each pool (1/26 by weight) was set aside at this point to provide samples of the cycloadduct carboxylic acids in the final library collection.

Amide Formation. Each of the two pools from above were split into 25 equal portions (0.056 mmol (theory), 1 equiv), then each set of 25 was treated identically. To each portion of resin in a 4 mL vial was added a stock solution of PyBop (193 mg / mL in CH_2Cl_2, 1.5 mL, 0.55 mmol, 10 equiv) followed by stock solutions of the amine building blocks (1.1 M in DMF, 500 uL, 0.56 mmol, 10 equiv). Then, diisopropylethylamine (100 uL, 0.56 mmol, 10 equiv) was added to each vial and the resulting mixtures were vortexed for 12 h. Each reaction mixture was then filtered and washed with 2 x 1 mL x 30 min CH_2Cl_2, then 2 x 1 mL x 30 min DMF, then 3 x 1 mL x 30 min THF, then 3 x 1 mL x 30 min CH_2Cl_2 then dried as above to give 50 spatially segregated pools of dihydropyrancarboxamides plus the four pools from above for both (*R*) and (*S*)-derived esters and acids. These samples were kept separate to allow for "spatial coding" of the amine building block, in addition to the chemical encoding of the first and second building blocks.