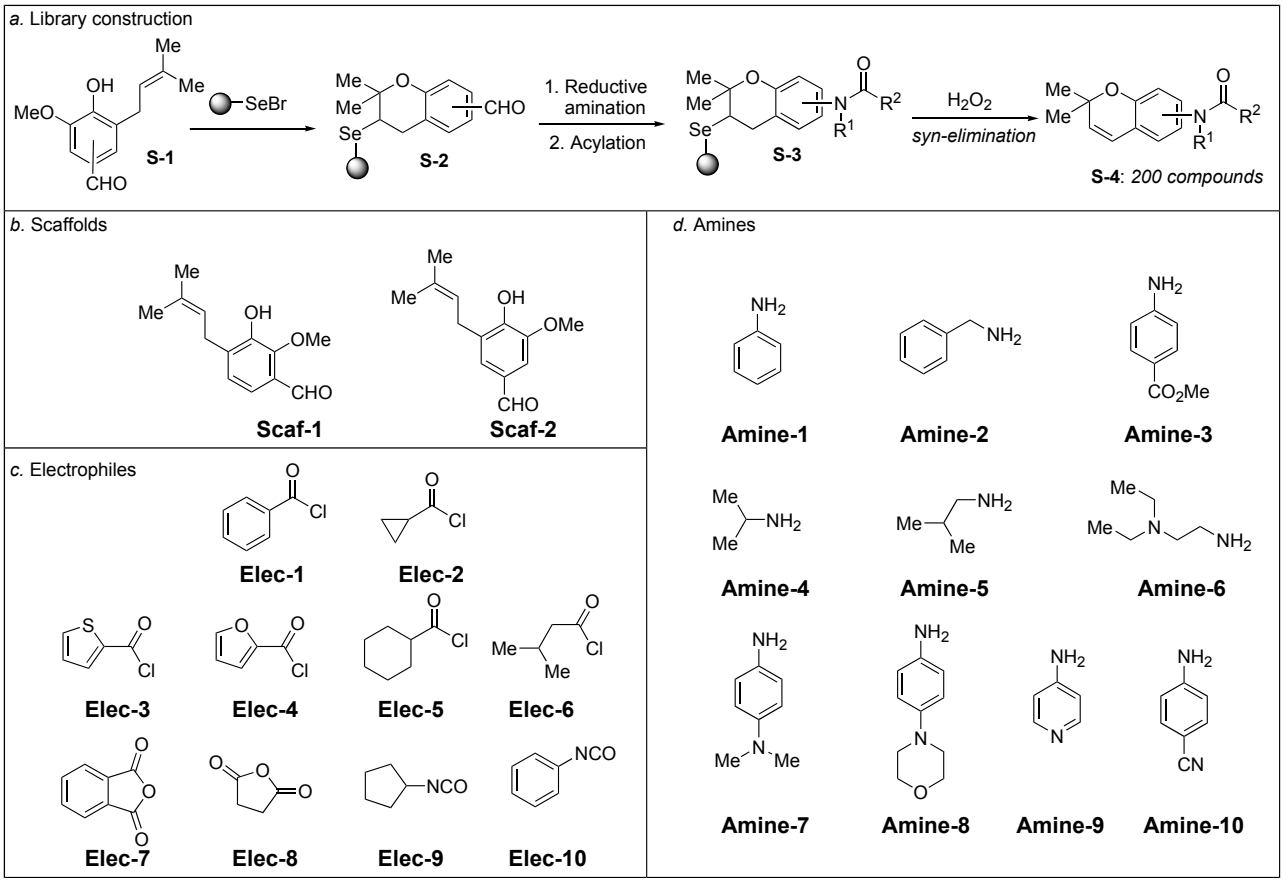
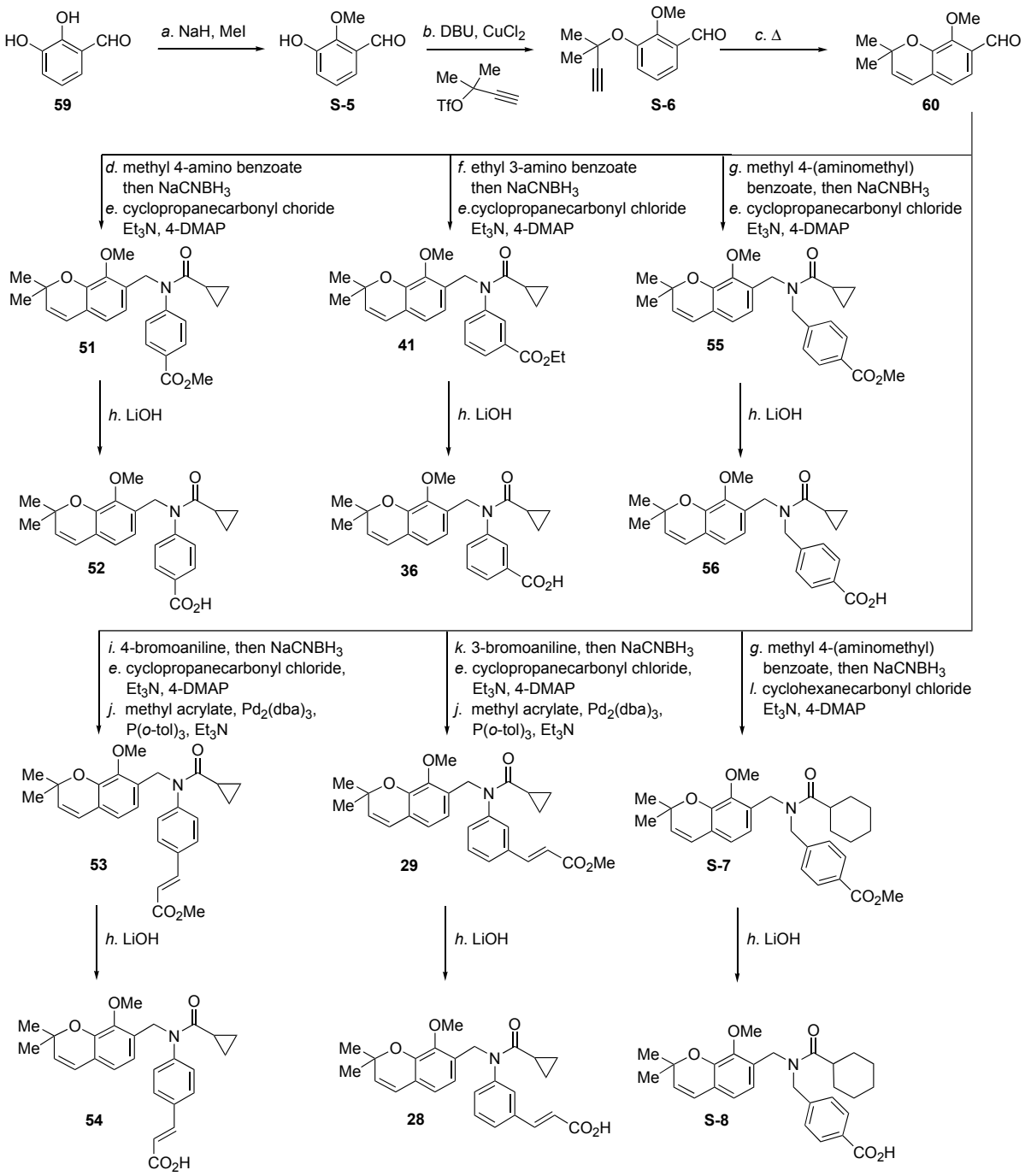
Scheme S-1. Solid-phase synthesis of a focused library of benzopyran containing small molecules as potential FXR agonists.[a]



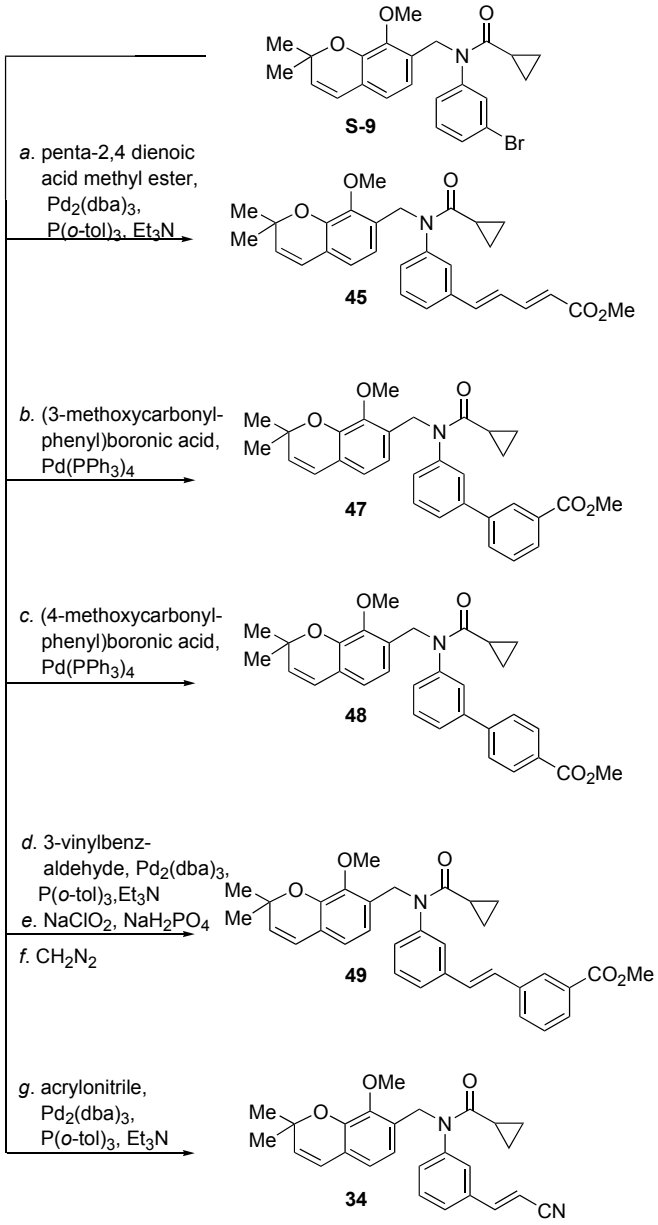
[a]Panel a) solid-phase protocol. Panel b) *o*-prenylated phenols employed as scaffolds. Panel c) Electrophiles employed. Panel d) Amines employed. Reagents and conditions: See reference 21.

Scheme S-2. Solution phase synthesis of ester and acid containing compounds (SAR region I).[a]



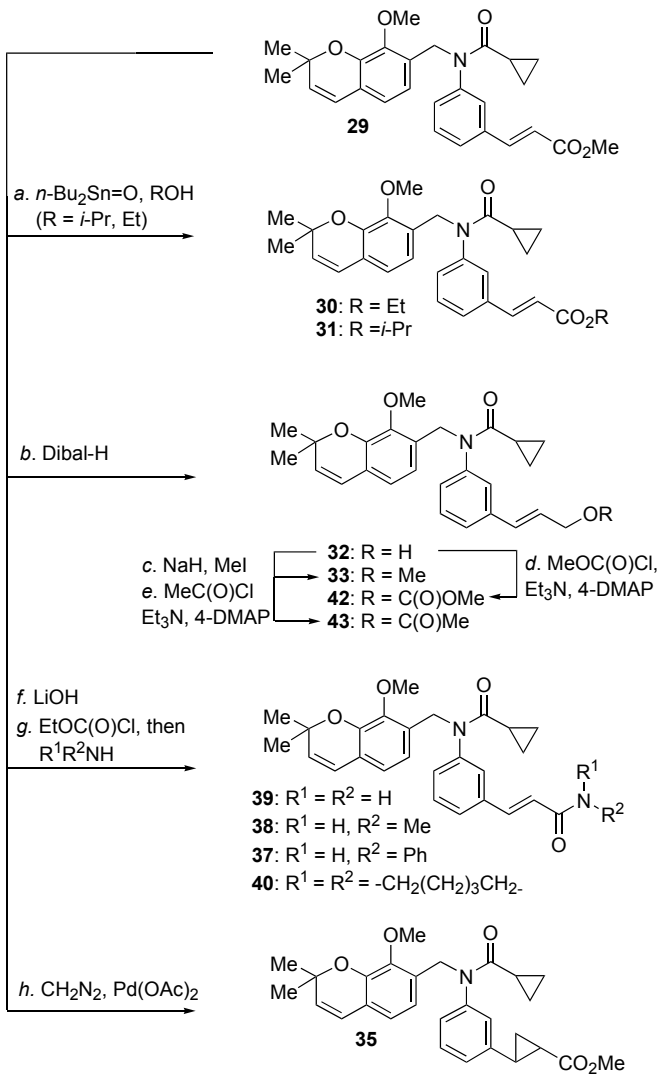
[a](a) see reference 28; (b) 1.5 equiv of 2-methyl-3-butyn-2-ol, 1.5 equiv of DBU, 1.7 equiv of trifluoroacetic anhydride, 0.1 equiv of $CuCl_2$, CH_3CN, 0 $\rightarrow$ 25°C,12 h, 75%; (c) *N,N*-diethylaniline, 190°C, 0.5 h, 90%; (d) 1.5 equiv of methyl 4-aminobenzoate, THF, 70°C,4 h; then 2.0 equiv of $NaCNBH_3$, 10% MeOH, 70°C, 4 h, 82%; (e) 1.3 equiv of cyclopropanecarbonyl chloride, 1.3 equiv of Et_3N, 0.1 equiv of 4-DMAP, CH_2Cl_2, 25°C, 12 h, 85-95%; (f) 1.5 equiv of ethyl 3-aminobenzoate, THF , 70°C, 4 h; then 2.0 equiv of $NaCNBH_3$, 10% MeOH, 70°C, 4h, 77%; (g) 1.5 equiv of methyl 4-(aminomethyl)benzoate,THF, 70°C, 4h; then 2.0 equiv of $NaCNBH_3$,10% MeOH, 70°C, 4h, 80% ; (h) 4.0 equiv of LiOH, THF:H_2O (10:1), 25°C, 12 h, 75-98%; (i) 1.5 equiv of 4-bromoaniline, THF, 70°C, 4h; then 2.0 equiv of $NaCNBH_3$, 10% MeOH, 70°C, 4h, 78%; (j) 4.0 equiv of methyl acrylate, 0.2 equiv of $Pd_2(dba)_3$, 0.5 equiv of P(*o*-tol)$_3$, 5.0 equiv of Et_3N, DMF, 90°C, 24 h, 71-80%; (k) 1.5 equiv of 3-bromoaniline, THF, 70°C, 4h; then 2.0 equiv of $NaCNBH_3$, 10% MeOH, 70°C, 4h, 83%; (l) 1.3 equiv of cyclohexanecarbonyl chloride, 1.3 equiv of Et_3N, 0.1 equiv of 4-DMAP, CH_2Cl_2, 25°C, 12 h, 95%.

Scheme S-3. Solution phase synthesis of various ester and vinyl cyanide containing compounds via palladium catalyzed reaction manifolds (SAR region I).[a]



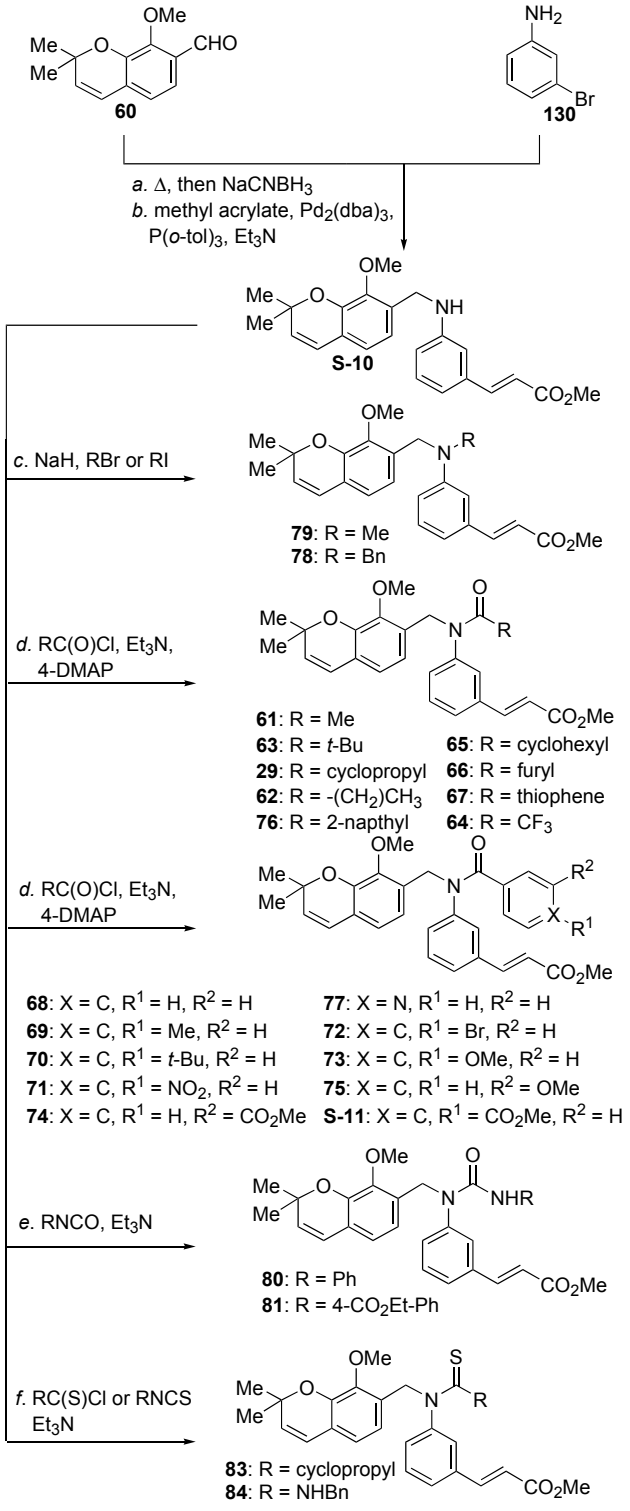
[a](a) 2.0 equiv of penta-2,4dienoic acid methyl ester, 0.2 equiv of $Pd_2(dba)_3$, 0.6 equiv of P(*o*-tol)$_3$, 5.0 equiv of Et_3N, DMF, 90°C, 24 h, 70%; (b) 5.0 equiv of 3-(methoxycarbonylphenyl)boronic acid, toluene:MeOH:1M Na_2CO_3 (10:3:1), 90°C, 24 h, 75%; (c) 5.0 equiv of 4-(methoxycarbonylphenyl)boronic acid, toluene:MeOH:1M Na_2CO_3 (10:3:1), 90°C, 24 h, 78%; (d) 2.0 equiv of 3-vinylbenzaldehyde, 0.2 equiv of $Pd_2(dba)_3$, 0.6 equiv of P(*o*-tol)$_3$, 5.0 equiv of Et_3N, DMF, 90°C, 24 h, 85%; (e) 1.5 equiv of $NaClO_2$, 4.0 equiv of NaH_2PO_4 , 10.0 equiv of 2-methyl-2-butene, THF:*t*-BuOH:H_2O (3:1:1), 25 °C, 3 h, 98% ; (f) 10 equiv of CH_2N_2, Et_2O, 0°C, 1 h, 100%; (g) 2.0 equiv of acrylonitrile, 0.2 equiv of $Pd_2(dba)_3$, 0.6 equiv of P(*o*-tol)$_3$, 5.0 of Et_3N, DMF, 90°C, 24h, 55%.

Scheme S-4. Solution phase synthesis of ester modifications (SAR region I).[a]



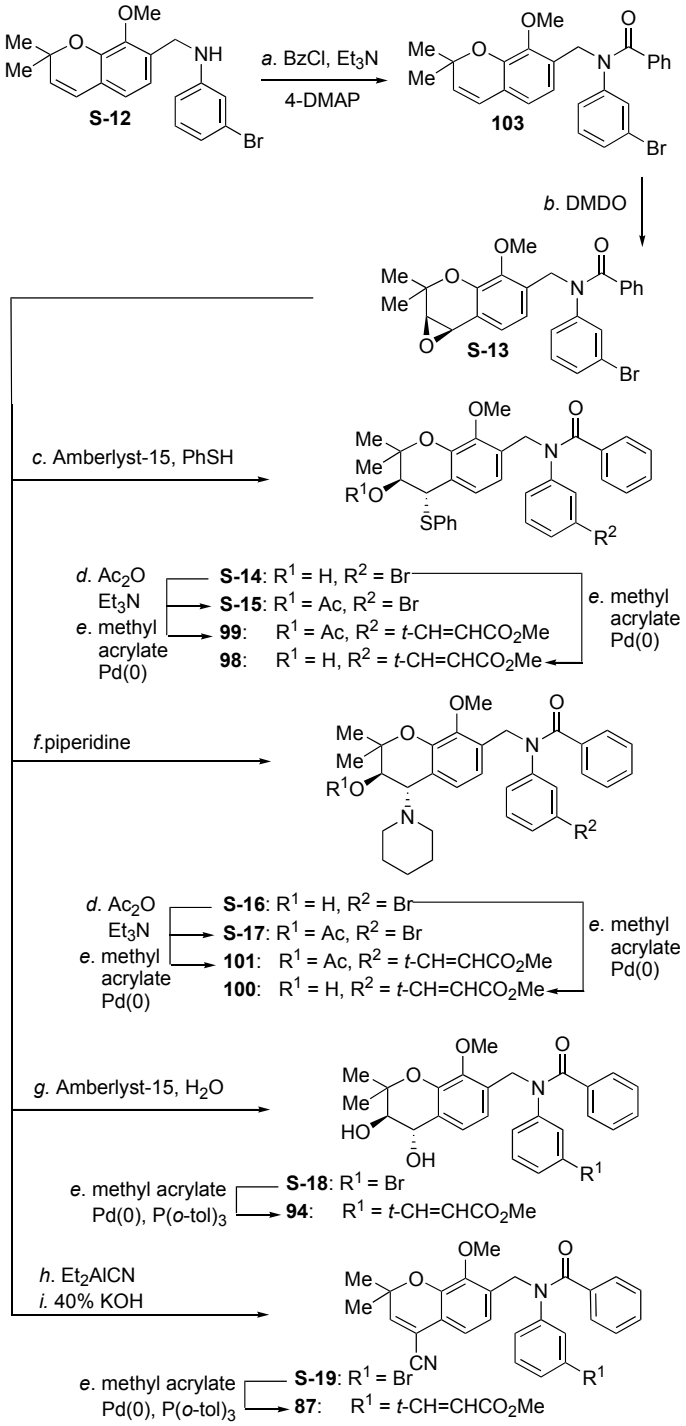
[a](a) 0.5 equiv of *n*-Bu_2Sn=O, EtOH or *i*-PrOH, 25°C, 48 h, 50% and 34%, respectively; (b) 1.2 equiv of diisobutylaluminum hydride, toluene, -78°C, 0.5 h, 52%; (c) 2.0 equiv of NaH, 3.0 equiv of MeI, 0°C, 1 h, 95%; (d) 1.2 equiv of MeOC(O)Cl, 2.0 equiv of Et_3N, 0.1 equiv of 4-DMAP, CH_2Cl_2, 25°C, 24 h, 88%; (e) 1.2 equiv of MeC(O)Cl, 2.0 of equiv Et_3N, 0.1 of equiv 4-DMAP, CH_2Cl_2, 25°C, 24 h, 90%; (f) 4.0 equiv of LiOH, THF:H_2O (10:1), 25°C, 12h, 90%; (g) 1.2 equiv of EtOC(O)Cl, 1.5 equiv of Et_3N, CH_2Cl_2, 25°C,1 h, then 3.0 equiv of amine, CH_2Cl_2, 25°C,12 h, 85-95%; (h) 10.0 equiv of CH_2N_2, 0.2 of equiv $Pd(OAc)_2$, Et_2O, 25°C, 12 h, 95%.

Scheme S-5. Solution phase synthesis of acyl group variants containing the acrylate moiety (SAR region II).[a]



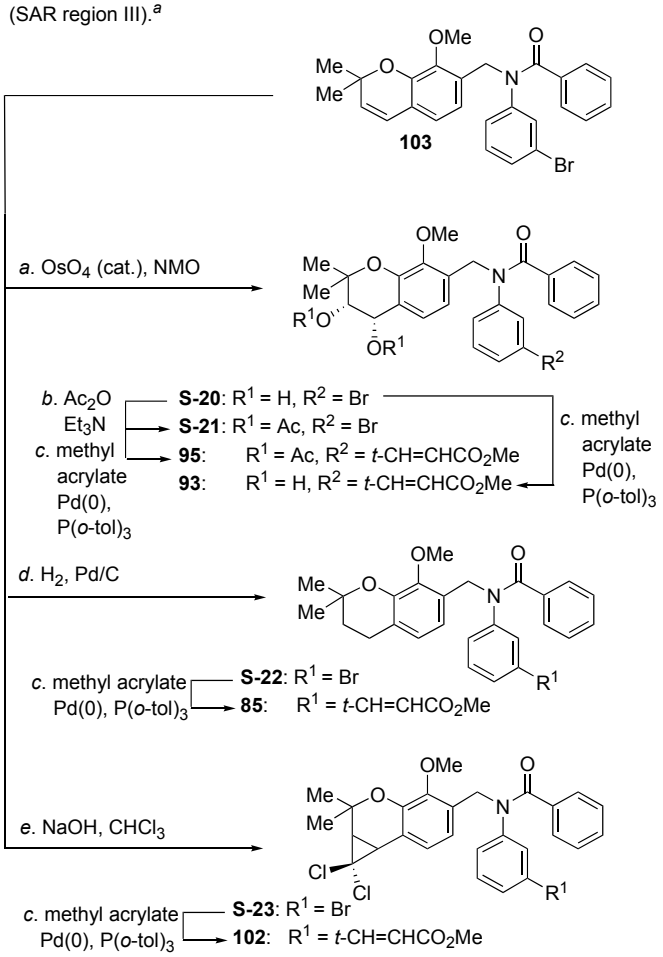
[a](a) 1.0 equiv of **60**, 2.0 equiv of **130**, THF, 70°C, 4 h, then 2.0 equiv of $NaCNBH_3$, 10% MeOH, 70°C, 4 h, 70%; (b) 1.5 equiv of methyl acrylate, 0.2 equiv of $Pd_2(dba)_3$, 0.5 equiv of P(*o*-tol)$_3$, 5.0 equiv of Et_3N, DMF, 90°C, 12 h, 65%; (c) 5.0 equiv of $NaHCO_3$, 5.0 equiv of alkyl halide, EtOH, 80°C, 24 h, 70-85%; (d) 5.0 equiv of acid chloride, 5.0 equiv of Et_3N, 0.2 equiv of 4-DMAP, CH_2Cl_2, 25°C, 24 h, 55-100%; (e) 5.0 equiv of isocyanate, 5.0 equiv of Et_3N, CH_2Cl_2, 25°C, 24 h, 75-85%; (f) 5.0 equiv of thioacid chloride or thioisocyanate, 5.0 equiv of Et_3N, CH_2Cl_2, 25°C, 24h, 50-70%.

Scheme S-6. Solution phase synthesis of benzopyran olefin modifications (SAR region III).[a]



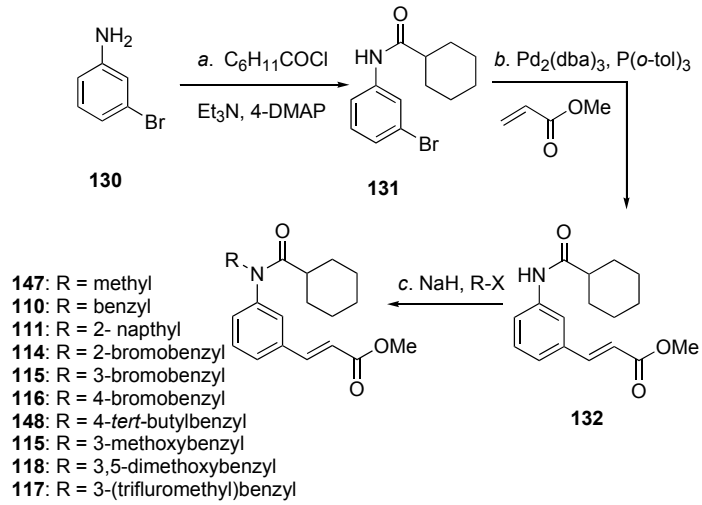
[a](a) 2.0 equiv of benzoyl chloride, 2.0 equiv of Et_3N, 0.2 equiv of 4-DMAP, CH_2Cl_2, 25°C, 24 h, 95%; (b) 10 equiv of DMDO, acetone, 0°C, 1 h, 100%; (c) 5.0 equiv of PhSH, Amberlyst-15 (cat.), CH_2Cl_2 , 25°C, 24 h, 95%; (d) 2.0 equiv of acetic anhydride, 2.0 equiv of Et_3N, 0.2 equiv of 4-DMAP, CH_2Cl_2, 25°C, 24 h, 90%; (e) 2.0 equiv of methyl acrylate, 0.2 equiv of $Pd_2(dba)_3$, 0.6 equiv of P(*o*-tol)$_3$, 5.0 equiv of Et_3N, DMF, 90°C, 24 h, 70-84%; (f) 5.0 equiv of piperidine, CH_2Cl_2, 25°C, 48h, 65%; (g) 5.0 equiv of H_2O, Amberlyst-15 (cat.), THF , 25°C, 24 h, 95%; (h) 2.0 equiv of Et_2AlCN, CH_2Cl_2, 0°C, 1 h, 83%; (i) 40% KOH:MeOH (1:2), 25°C,24 h, 90%. DMDO = dimethyldioxirane.

Scheme S-7. Solution phase synthesis of benzopyran olefin modifications (SAR region III).[a]



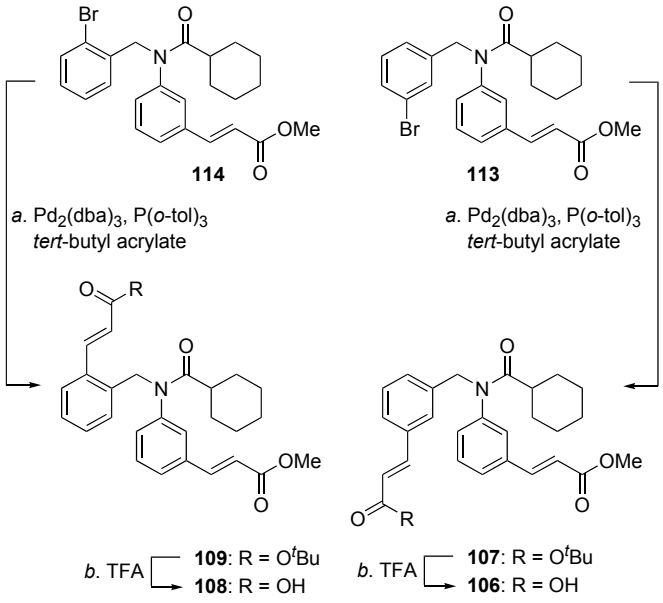
[a](a) 0.02 equiv of OsO_4, 2.0 equiv of NMO, acetone:H_2O (10:1), 25°C, 24 h, 85%; (b) 5.0 of equiv acetic anhydride, 10.0 equiv of Et_3N, 0.2 equiv of 4-DMAP, CH_2Cl_2, 25°C, 24 h, 90%; (c) 2.0 equiv of methyl acrylate, 0.2 equiv of $Pd_2(dba)_3$, 0.6 equiv of P(*o*-tol)$_3$, 5.0 equiv of Et_3N, DMF, 90°C, 24 h, 65-80%; (d) 10% Pd/C, EtOAc, 25°C, 0.5 h, 100% (e) $CHCl_3$: 2.0 N NaOH (7:1), adogen 464 (cat.) 25°C, 6 h, 85%. NMO = 4-methylmorpholine *N*-oxide

Scheme S-8. Solution phase synthesis of region III analogs; replacement of the benzopyran.[a]



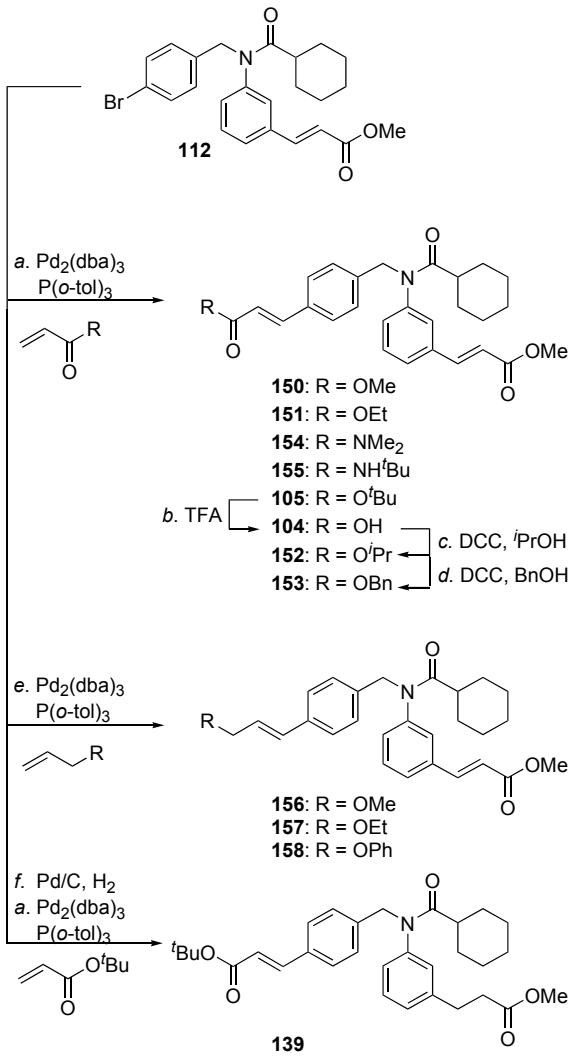
[a](a) 1.1 equiv of $C_6H_{11}COCl$, 1.3 equiv of Et_3N, 0.05 equiv of 4-DMAP, CH_2Cl_2, 25°C, 3 h, 95%; (b) 4.0 equiv of methyl acrylate, 5.0 equiv of Et_3N, 0.2 equiv of $Pd_2(dba)_3$,, 0.6 equiv of P(*o*-tol)$_3$, DMF, 90°C, 12 h, 80% ; (c) 1.1 equiv of NaH, THF, 0 °C, 30 min; then 1.3 equiv of benzyl bromides, THF, 0°C, 2 h, 60 - 90%. R-X = methyl iodide, benzyl bromide, 2-bromobenzyl bromide, 3-bromobenzyl bromide, 4-bromobenzyl bromide, 4-*tert*-butylbenzyl bromide, 3-methoxybenzyl bromide, 3,5-dimethoxybenzyl bromide, 3-(trifluromethyl)benzyl bromide, 2-napthyl bromide.

Scheme S-9. Solution phase synthesis of derivatives region III .[a]



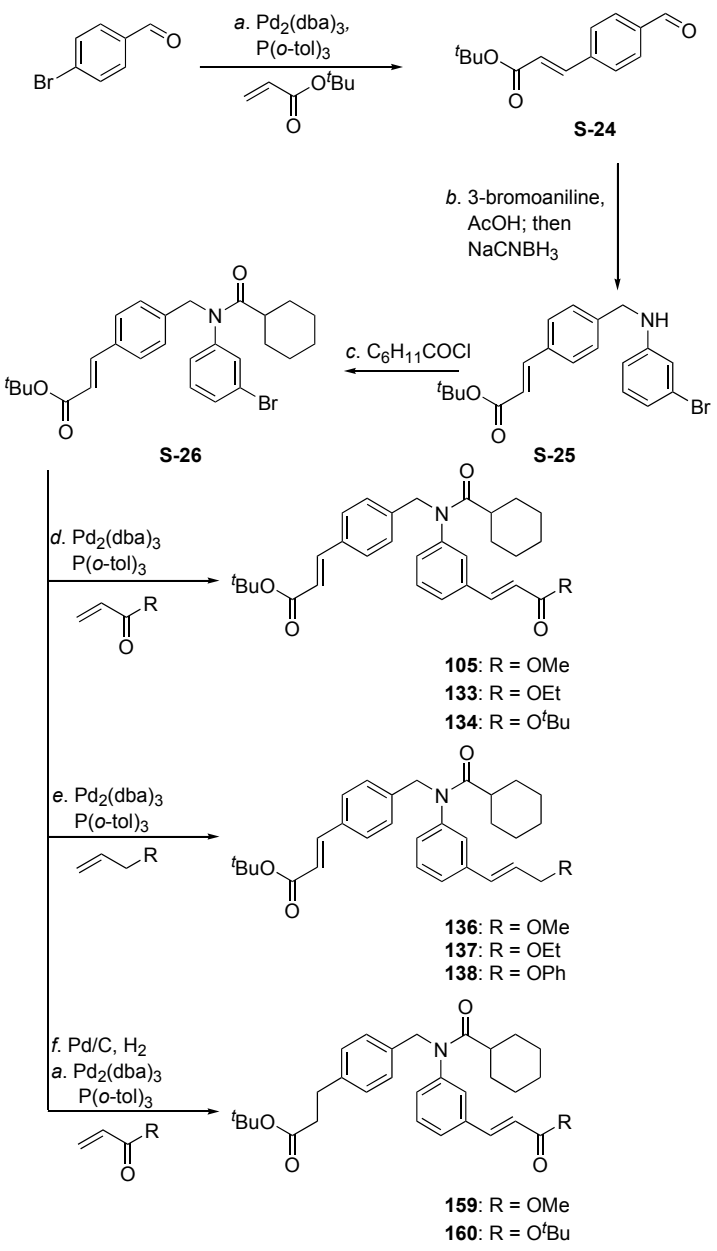
[a](a) 4.0 equiv of *tert*-butyl acrylate, 5.0 equiv of Et_3N, 0.05 equiv of $Pd_2(dba)_3$,, 0.15 equiv of P(*o*-tol)$_3$, DMF, 90°C, 12 h, 80%; (b) 20% TFA in CH_2Cl_2, 25°C, 1 h, 95%.

Scheme S-10. Synthesis of region III cinnimate modifications .[a]



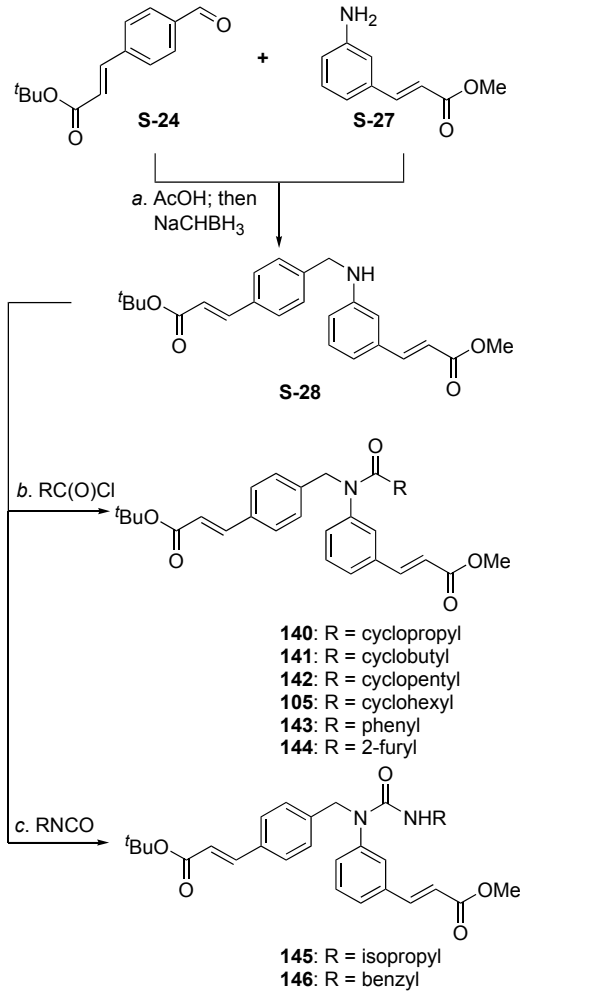
[a](a) 4.0 equiv of acrylate, 5.0 equiv of Et_3N, 0.05 equiv of $Pd_2(dba)_3$, 0.15 equiv of P(*o*-tol)$_3$, DMF, 90°C, 12 h, 50 - 80% ; (b) 20% TFA in CH_2Cl_2, 1 h, 25°C, 95%; (c) 1.2 equiv of DCC, 10.0 equiv of ^{i}PrOH, 0.2 equiv of 4-DMAP, DMF, 25°C, 12 h, 60%; (d) 1.2 equiv of DCC, 10.0 equiv of BnOH, 0.2 equiv of 4-DMAP, DMF, 25°C, 12 h, 60%; (e) 4.0 equiv of alkene, 5.0 equiv of Et_3N, 0.05 equiv of $Pd_2(dba)_3$,, 0.15 equiv of P(*o*-tol)$_3$, DMF, 90°C, 12 h, 35 - 75%; (f) 0.05 equiv of Pd/C, H_2 (1 atm), EtOAc, 25°C, 30 min, 100 %. DCC = 1,3-dicyclohexylcarbodiimide.

Scheme S-11. Synthesis of region I/region III cinnamate modifications.[a]



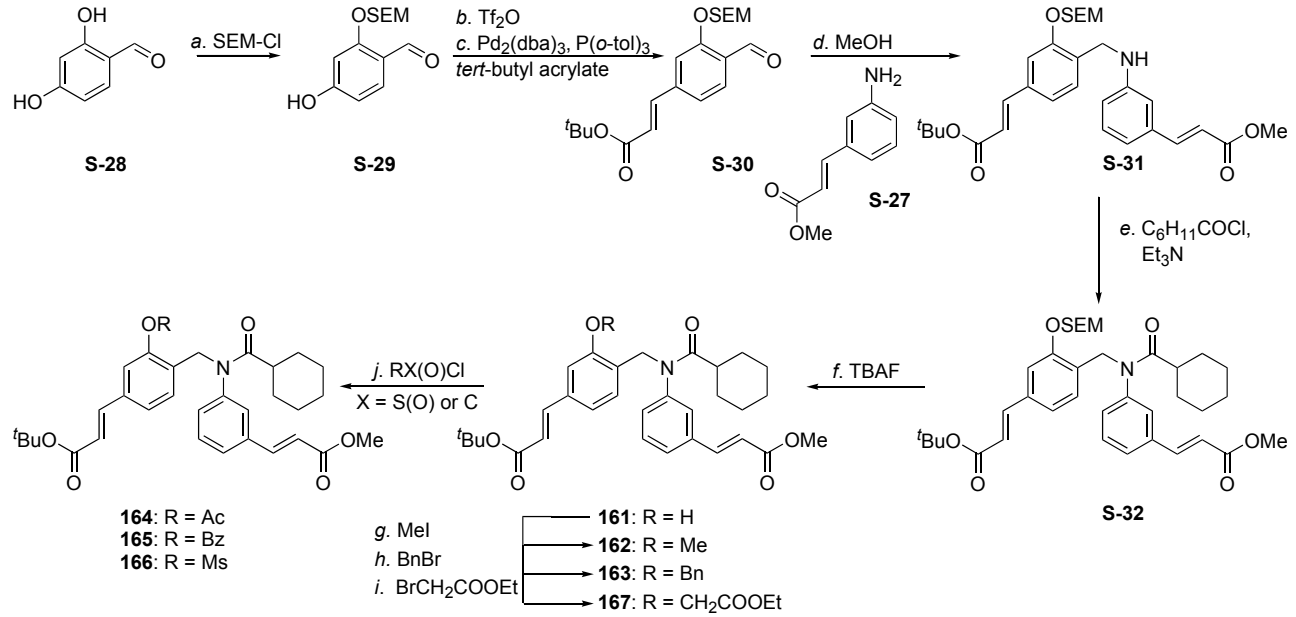
[a](a) 4.0 equiv of *tert*-butyl acrylate, 5.0 equiv of Et_3N, 0.05 equiv of $Pd_2(dba)_3$, 0.15 equiv of P(*o*-tol)$_3$, DMF, 90°C, 12 h, 85%; (b) 1.5 equiv of 3-bromoaniline, 0.05 equiv of AcOH, MeOH, 25°C, 30 min; then 1.7 equiv of $NaCNBH_3$, 1 h, 90%; (c) 1.1 equiv of $C_6H_{11}COCl$, 1.3 equiv of Et_3N, 0.05 equiv of 4-DMAP, CH_2Cl_2, 25°C, 3 h, 90%; (d) 4.0 equiv of acrylate, 5.0 equiv of Et_3N, 0.05 equiv of $Pd_2(dba)_3$, 0.15 equiv of P(*o*-tol)$_3$, DMF, 90°C, 12 h, 60 - 85%; (e) 4.0 equiv of alkene, 5.0 equiv of Et_3N, 0.05 equiv of $Pd_2(dba)_3$, 0.15 equiv of P(*o*-tol)$_3$, DMF, 90°C, 12 h, 35 - 80%; (f) 0.05 equiv of Pd/C, H_2 (1 atm), EtOAc, 25°C, 30 min, 100 %.

Scheme S-12. Synthesis of acyl group analogs in the bis cinnamate series.[a]



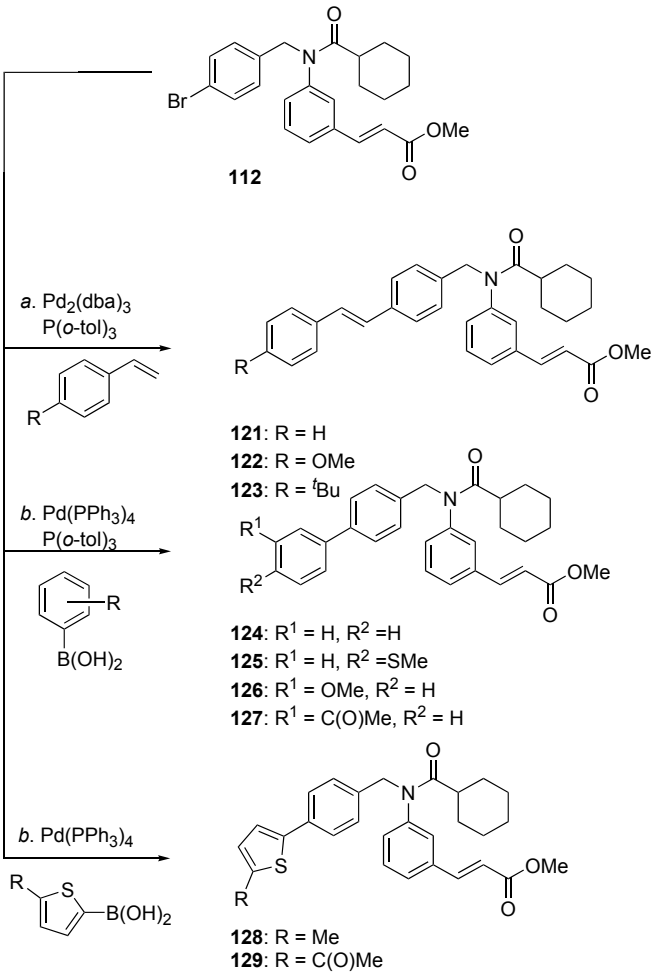
[a](a) 1.0 equiv of **S-24**, 1.0 equiv of **S-27**, 0.05 equiv of AcOH, MeOH, 25°C, 30 min; then 1.2 equiv of $NaCNBH_3$, 25°C, 1 h, 85%; (b) 2.0 equiv of acid chloride, 3.0 equiv of Et_3N, 0.05 equiv of 4-DMAP, CH_2Cl_2, 25°C, 1 h, 80 - 95%; (c) 2.0 equiv of isocyanate, 3.0 equiv of Et_3N, 0.05 equiv of 4-DMAP, CH_2Cl_2, 25°C, 1 h, 60 - 80%.

Scheme S-13. Synthesis of region III ring analogs.[a]



[a] (a) 1.0 equiv of SEMCl, 1.2 equiv of Et_3N, CH_2Cl_2, 25°C, 12 h, 75%; (b) 1.05 equiv of Tf_2O, 1.2 equiv of Et_3N, CH_2Cl_2, -78°C, 1 h, 95%; (c) 4.0 equiv of *tert*-butyl acrylate, 5.0 equiv of Et_3N, 0.05 equiv of $Pd_2(dba)_3$, 0.15 equiv of P(*o*-tol)$_3$, 90°C, 12 h, 76%; (d) 1.2 equiv of **S-27**, 0.05 equiv of AcOH, MeOH, 25°C, 1 h; then 1.5 equiv of $NaCNBH_3$, 2 h, 80%; (e) 1.2 equiv of $C_6H_{11}COCl$, 1.5 equiv of Et_3N, 0.05 equiv of 4-DMAP, CH_2Cl_2, 25°C, 4 h, 90%; (f) 7.0 equiv of TBAF, THF:HMPA (9:1), 55°C, 12 h, 65%; (g) 3.0 equiv of MeI, 5.0 equiv of K_2CO_3, DMF, 80°C, 12 h, 90%; (h) 3.0 equiv of BnBr, 5.0 equiv of K_2CO_3, DMF, 80°C, 12 h, 65%; (i) 3.0 equiv of $BrCH_2COOEt$, 5.0 equiv of K_2CO_3, DMF, 80°C, 12 h, 85%; (j) 3.0 equiv of AcCl, BzCl or MsCl, 5.0 equiv of Et_3N, CH_2Cl_2, 25°C, 2 h, 70-90%. HMPA = hexamethylphosphoramide, TBAF = tetrabutylammonium fluoride, SEMCl = 2-(trimethylsilyl)ethoxymethyl chloride.

Scheme S-14. Synthesis of region III modifications; cinnamate substitutions.[a]



[a](a) 4.0 equiv of styrene, 5.0 equiv of Et_3N, 0.05 equiv of $Pd_2(dba)_3$, 0.15 equiv of P(*o*-tol)$_3$, DMF, 90°C, 12 h, 65 - 80% ; (b) 2.5 equiv of boronic acid, 0.2 equiv of $Pd(PPh_3)_4$, toulene:MeOH:1 M Na_2CO_3 (10:3:1), 80°C, 12 h, 60 - 80%.

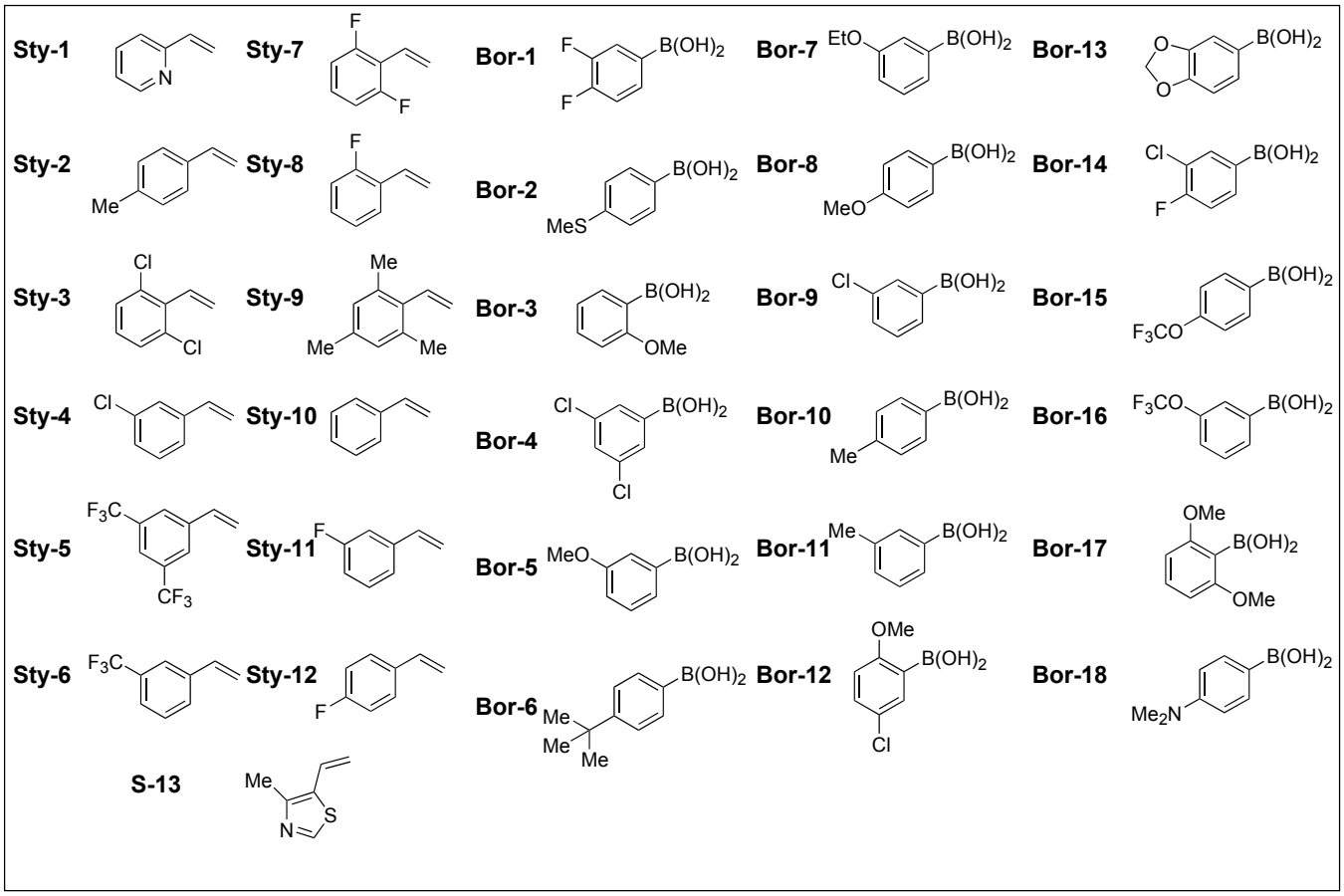


Figure S-15. Structures of styrenes and boronic acids used in library construction, see Scheme 4 and text for discussion.