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Design of a Protein Surface Antagonist Based on a-Helix Mimicry: Inhibition of gp41 Assembly and Viral Fusion

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Experimental Section:

All chemicals were obtained from Sigma/Aldrich unless otherwise noted. All peptides were purchased from the HHMI Biopolymer/Keck Foundation Biotechnology Resource Center at the Yale University School of Medicine (New Haven, CT). All solvents were appropriately distilled, all glassware was flame dried prior to use and all reactions were run under an inert (N_2) atmosphere unless otherwise noted. Column chromatography was performed using silica gel (230-400 mesh) and preparative thin layer chromatography was completed using 20 X 20 cm, 1000 micron precoated silica gel plates with fluorescent indicator (Analtech Inc., Newark DE). ^{1}H NMR spectra were recorded on Bruker Avance DPX-500 and DPX-400 spectrometers at 500 or 400 MHz. ^{13}C NMR spectra were recorded on a Bruker Avance DPX-500 spectrometer at 125 MHz. Chemical shifts are expressed as parts per million using solvent as the internal standard. All mass data were obtained from the mass spectroscopy facility at the University of Illinios at Urbana Champaign under the supervision of Dr. Steven Mullen.

Computation. Computational analysis was completed using Macromodel (W. C. Still, Columbia). MM2 energy minimizations performed on 3, 2', 2" -trimethylterphenyl indicate that the structure with 55 torsion angles to be the closest of several low energy conformers to the structure that presents i, i+4, i+7 side chain mimicry. The six carbon atoms of this conformation corresponding to the three Cα and the three Cβ carbons of the i, i+4, i+7 alanines (yellow in Figure 2) were overlayed on the helix. The resulting root mean squared difference (rmsd) between these atoms was calculated to be 0.90 Å.

Circular Dichroism. CD spectra were obtained on an Aviv Dichroism Model 202 spectrometer at 4 C, using a 1 nm bandwith, 1 nm resolution, 0.1 nm path length, and a 5.0 sec averaging time. Spectra were corrected by the subtraction of a blank corresponding to the solvent composition of each sample. All spectra were recorded in aqueous buffer (50 mM PBS, 150 mM NaCl, pH 7.0). Inhibitor stock solutions were composed of 1:1 buffer/trifluoroethanol (TFE). Overall TFE concentrations in the experiments never exceeded 0.5%. TFE had no effect on the CD spectra up to 5% (maximum tested). CD thermal denaturation experiments were completed by monitoring the Θ222 signal using a 4-90 C temperature range with a temperature step of 2 deg/min, dead band value of 0.2, equilibration time of 1 min, and an averaging time of 30 sec. The

T_m values for the unfolding transitions were estimated from the maximum of the first derivative with respect to a plot of CD signal at Θ222 versus T^{-1}.

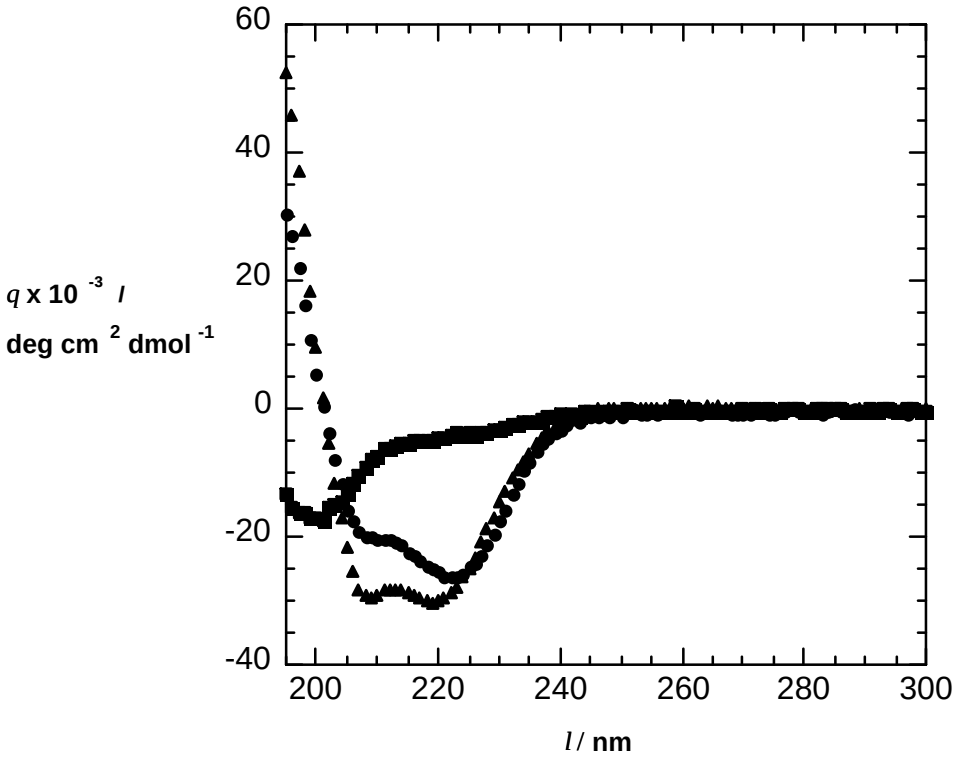


Figure 6. CD spectra of 10 μM C34 peptide (squares), 10 μM N36 peptide (circles), and 10 μM combination of C34 and N36 (triangles).

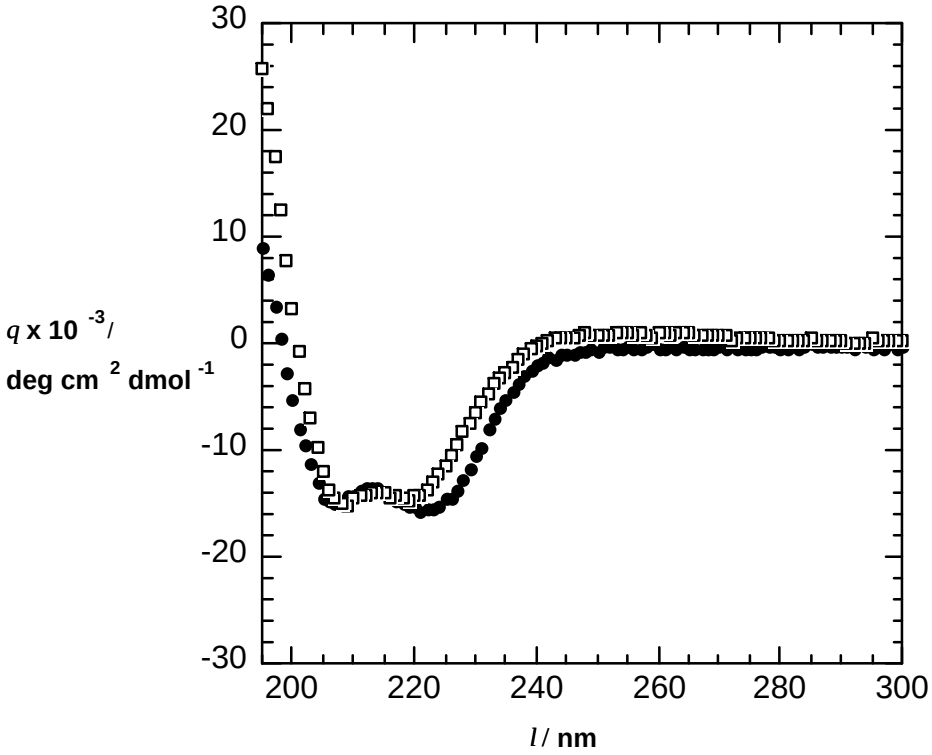
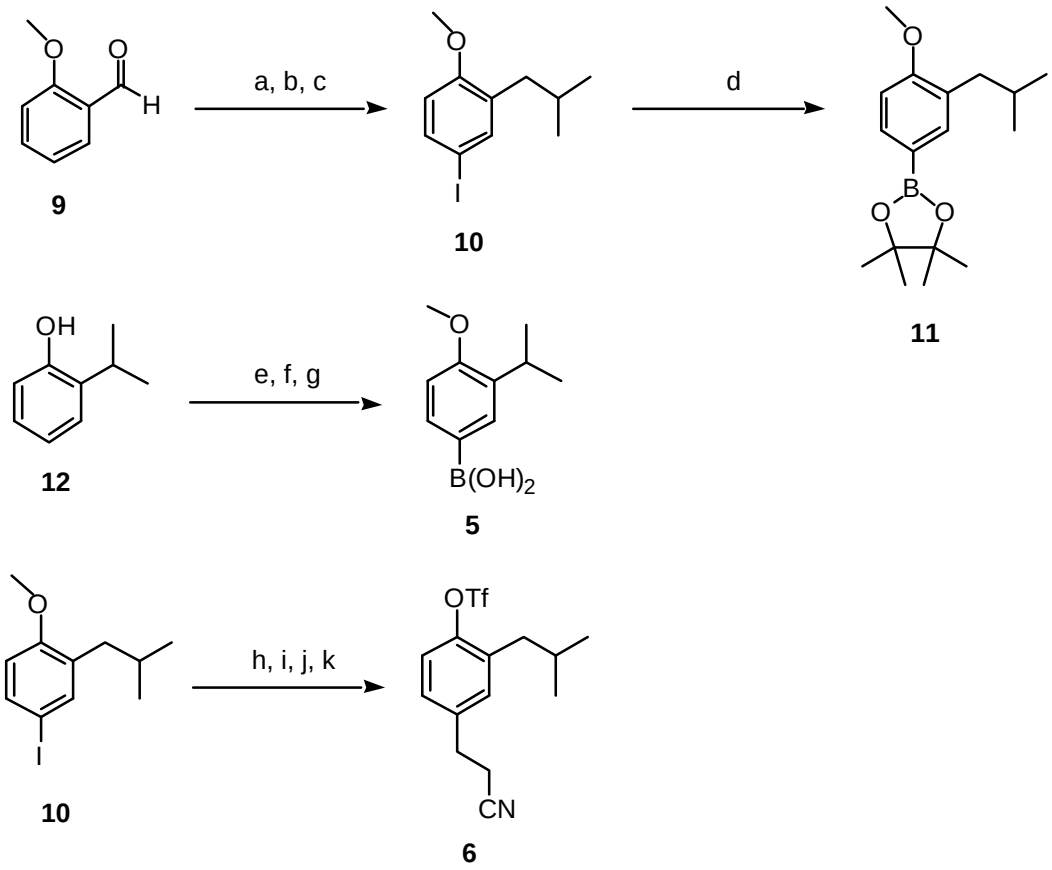
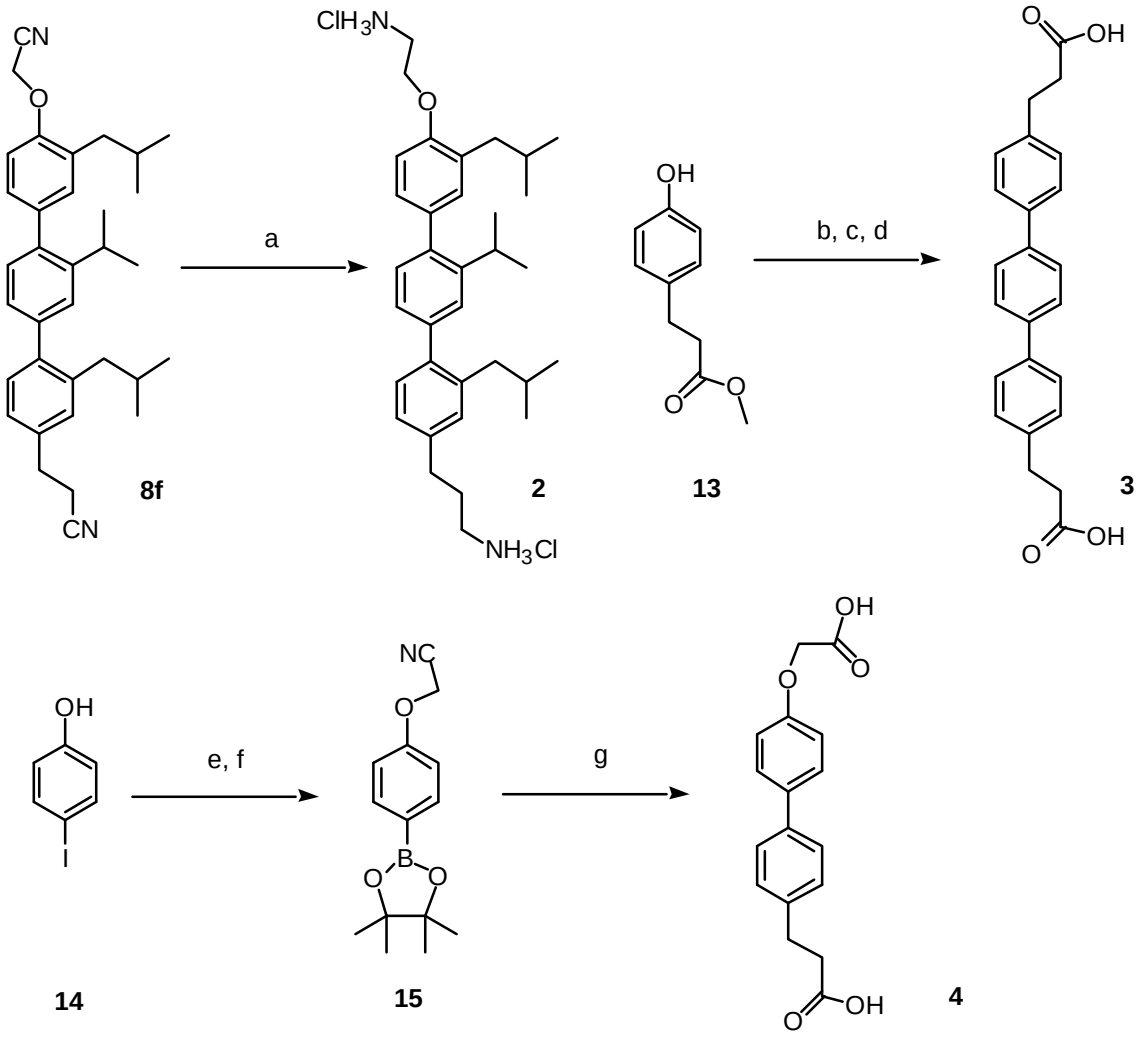


Figure 7. CD spectrum of 10 μM gp41 model complex in the presence of 50 μM **1** (squares) in comparison to the theoretical addition of the individual N36 and C34 spectra at 10 μM (circles).

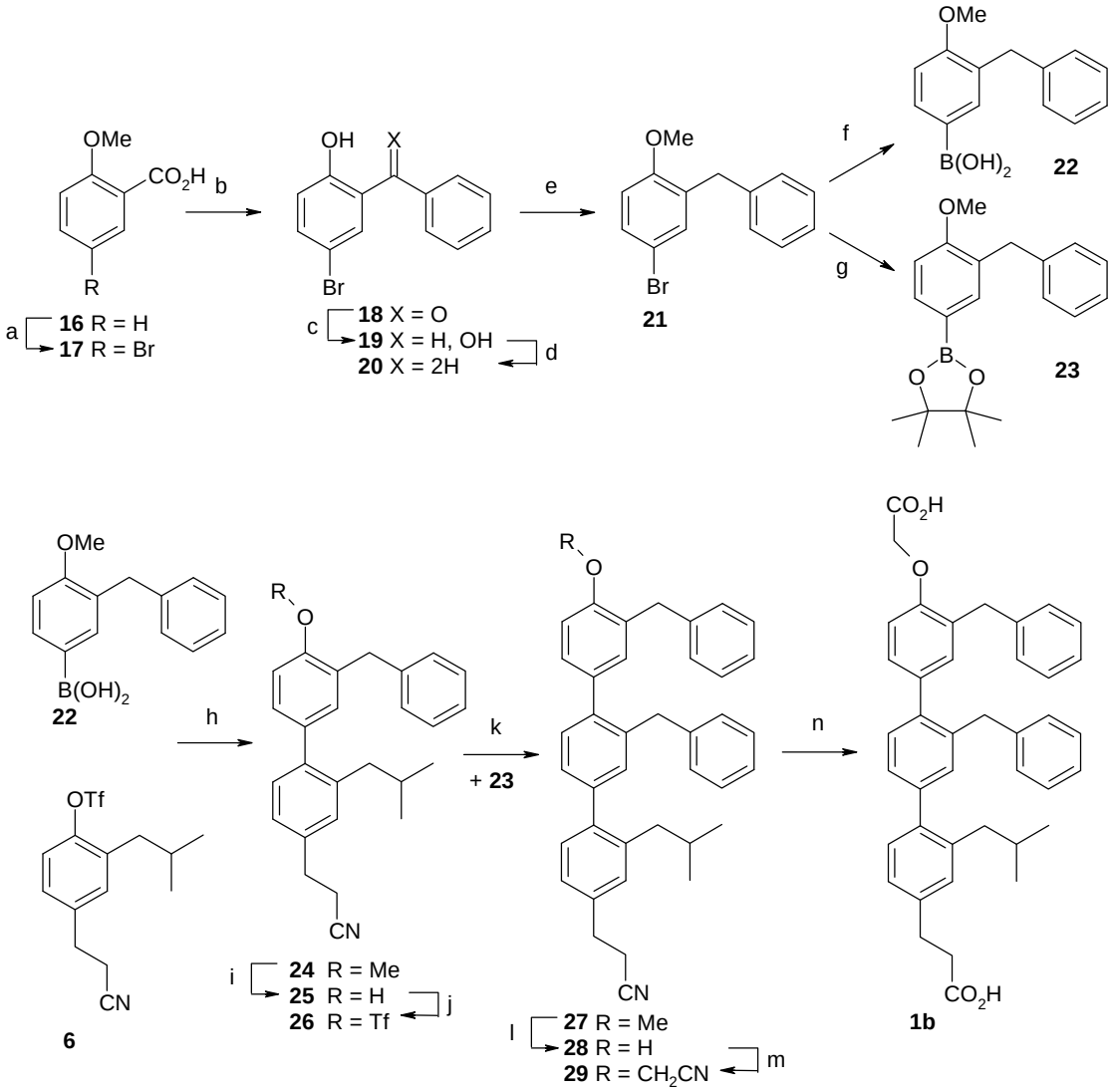
Synthesis.



Scheme 2. a) (i) isopropyl triphenylphosphonium iodide, BuLi, Et_2O, 0°C-rt, 35 min, (ii) **9**, rt, 20 h, 61%; b) H_2 (60 psi), 10% Pd/C, EtOH, rt, 9 h, 84%; c) Selectfluor reagent, I_2, CH_3CN, rt, 8 h, 73%; d) bis(pinacolato)diboron, KOAc, $PdCl_2$dppf, DMSO, 85°C, 3 h, 67%; e) dioxane dibromide, Et_2O, 0°C-rt, 30 min, 66%; f) MeI, K_2CO_3, acetone, 56°C, 24 h, 91%; g) (i) BuLi, THF, -78°C, 30 min, (ii) $B(OMe)_3$, rt, 24 h, (iii) NaOH, rt, 1 h, (iv) HCl, 95%; h) acrylonitrile, $Pd(OAc)_2$, tetra-n-butylammonium chloride, $NaHCO_3$, DMF, 40°C, 19 h, 74%; i) (i) Mg, MeOH, 0°C-rt, 5 h, (ii) 6M HCl, 96%; j) BBr_3, CH_2Cl_2, 10°C, 9 h, 99%; k) Tf_2O, pyridine, 0°C-rt, 17 h, 93%.



Scheme 3. a) H_2 (20 psi), 10% Pd/C, EtOH, rt, 12 h, 91%; b) Tf_2O, pyridine, 0°C-rt, 48 h, 92%; c) 1,4-phenylenebisboronic acid, $Pd(PPh_3)_4$, Na_2CO_3 (aq), DME/EtOH, 80°C, 36 h, 79%; d) (i) NaOH, dioxane/H_2O/HMPA, 110°C, 2 h, (ii) HCl, 95%; e) $ClCH_2CN$, K_2CO_3, acetone, 45°C, 24 h, 66%; f) bis(pinacolato)diboron, KOAc, $PdCl_2$dppf, DMSO, 85°C, 16 h, 80%; g) (i) 4-bromophenylhydrocinnamonitrile, $Pd(PPh_3)_4$, Na_2CO_3 (aq), DME, 80°C, 24 h, (ii) NaOH, MeOH/H_2O, 50°C, 24 h, (iii) HCl, 93%.



Scheme 4. a) Br_2, CH_2Cl_2/H_2O, rt, 19 h, 92%; b) (i) $SOCl_2$, toluene, DMF, 70°C, 1.5 h, (ii) $AlCl_3$, benzene, rfl., 5 h, 90%; c) $NaBH_4$, MeOH, rt, 2 h, 98%; d) (i) $LiAlH_4$, $AlCl_3$, Et_2O, rfl., 12 h, 62%; e) MeI, K_2CO_3, acetone, rfl., 24 h, 98%; f) (i) *n*-BuLi, THF, -78°C, 30 min, (ii) $B(OMe)_3$, rt, 24 h, (iii) H_2O, 10% aq. NaOH, rt, 1 h; g) bis(pinacolato)diboron, KOAc, $PdCl_2dppf*CH_2Cl_2$, DMSO, 85°C, 3 h, 55%; h) $Pd(Ph_3P)_4$, DME/EtOH (9+1), 2 M aq. Na_2CO_3, 80°C, 17 h, 52%; i) BBr_3, CH_2Cl_2, 0°C-rt, 9 h, 96%; j) Tf_2O, Py, 0°C-rt, 18 h, 85%; k) **23**, $Pd(Ph_3P)_4$, DME/EtOH (9+1), 2 M aq. Na_2CO_3, 80°C, 8 h, 91%; l) BBr_3, CH_2Cl_2, 0°C-rt, 6 h, 86%; m) K_2CO_3, acetone, $ClCH_2CN$, 55°C, 40 h, 97%; n) 25% aq. NaOH, MeOH/THF (1:1), rfl., 24 h, 11%.

1-(2-methoxyphenyl)-2-methylpropene (9a). Isopropyl triphenylphosphonium iodide (5.95 g, 13.7 mmol, 1.5 eqv) was suspended in 230 ml of Et_2O at 0°C. n-BuLi (8.6 ml of a 1.6 M solution in hexanes, 13.7 mmol, 1.5 eqv) was added via syringe. The subsequent red solution was allowed to stir for 35 min at rt. 2-Methoxybenzaldehyde (**9**) (1.25 g, 9.18 mmol) in 10 ml of Et_2O was added via syringe and the resulting solution was allowed to stir for 20 h at rt. The reaction mixture was filtered. The filtrate was diluted with H_2O and extracted with Et_2O. The organic fractions were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo. Column chromatography [Hexanes/Et_2O (9/1)] yielded 0.91 g of a clear oil (61%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.82 (s, 3H), 1.94 (s, 3H), 3.85 (s, 3H), 6.32 (s, 1H), 6.87 (d, *J* = 8.0 Hz, 1H), 6.63 (t, *J* = 7.5 Hz, 1H), 7.21 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.50, 26.60, 55.39, 110.27, 120.01, 120.51, 127.33, 127.50, 130.42, 135.51, 156.96; HRMS (EI) Calcd for $C_{11}H_{14}O$: 162.1044. Found 162.1044.

2-isobutylanisole (9b). A solution of 1-(2-methoxyphenyl)-2-methylpropene (**9a**) (3.37 g, 20.8 mmol) and 10% Pd/C (300 mg) in 100 ml of anhydrous EtOH at rt was hydrogenated at 60 psi until complete conversion was determined by GC/MS (9 h). The reaction mixture was filtered through celite and concentrated in vacuo to yield 2.87 g of a clear oil (84%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.90 (d, *J* = 6.6 Hz, 6H), 1.92 (m, 1H), 2.49 (d, *J* = 7.1 Hz, 2H), 3.82 (s, 3H), 6.88 (m, 2H), 7.10 (d, *J* = 8.9 Hz, 1H), 7.18 (t, *J* = 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.55, 28.64, 39.43, 55.22, 110.27, 120.07, 126.80, 130.22, 130.80, 157.70; HRMS (EI) Calcd for $C_{11}H_{16}O$: 164.1201. Found 164.1207.

4-iodo-2-isobutylanisole (10). 2-isobutylanisole (**9b**) (1.5 g, 9.14 mmol), 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo [2.2.2]octane bis(tetrafluoroborate) (3.24 g , 9.14 mmol, 1.0 eqv) and I_2 (1.18 g, 4.66 mmol, 0.51 eqv) were dissolved in 90 ml of CH_3CN. The solution was stirred for 8 h at rt, diluted with H_2O, and extracted with CH_2Cl_2. The organic fractions were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo. Column chromatography [Hexanes/CH_2Cl_2 (2/1)] yielded 1.93 g of a clear oil (73%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (d, *J* = 4.3 Hz, 6H), 1.88 (m, 1H), 2.42 (d, *J* = 7.2 Hz, 2H), 3.78 (s, 3H), 6.61 (d, *J* = 8.5 Hz, 1H), 7.38 (s, 1H), 7.45 (d, *J* = 10.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.45, 28.64, 39.02, 55.37, 82.58, 112.67, 133.20, 135.61, 139.21, 157.72; LRMS (EI) (M+, 290).

2-(3-isobutyl-4-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (11). A solution of 4-iodo-2-isobutylanisole (**10**) (0.150 g, 0.52 mmol), bis(pinacolato)diboron (0.144 g, 0.57 mmol, 1.1 eqv), KOAc (0.152 g, 1.55 mmol, 3 eqv), and $PdCl_2$dppf (21 mg, 5 mol%) in 3 ml of DMSO was stirred at 85°C for 3 h. The mixture was then added to H_2O and extracted with CH_2Cl_2. The organic fractions were combined, back extracted with H_2O, dried ($MgSO_4$), filtered, and concentrated in vacuo. Column chromatography [Hexanes/EtOAc (9/1)] yielded 0.100 g of a clear oil (67%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.84 (d, *J* = 6.5 Hz, 6H), 1.34 (s, 12H), 1.92 (m, 1H), 2.48 (d, *J* = 7 Hz, 2H), 3.84 (s, 3H), 6.84 (d, *J* = 8.5 Hz, 1H), 7.54 (s, 1H), 7.66 (d, *J* = 10 Hz, 1H); ^{13}C NMR (125 MHz,

$CDCl_3$) δ 22.59, 24.86, 28.84, 39.21, 55.15, 83.44, 109.58, 129.56, 134.31, 137.38, 160.39; HRMS (EI) Calcd for $C_{17}H_{27}BO_3$: 290.2053. Found 290.2052.

4-bromo-2-isopropylphenol (12e). To a solution of 2-isopropylphenol (**12**) (2.0 g, 14.6 mmol) in 15 ml of Et_2O at 0°C was added dioxane dibromide (3.62 g, 14.6 mmol, 1 eqv). The solution was allowed to stir for 30 min at rt. The reaction mixture was washed with sat. NaCl and 10% $NaHCO_3$. The Et_2O phase was concentrated in vacuo and then vacuum distilled (142-145°C, 20 mm Hg) to yield 2.07 g of a clear oil (66%) which solidified upon standing: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.23 (d, *J* = 3.7 Hz, 6H), 3.16 (m, 1H), 4.84 (s, 1H), 6.61 (d, *J* = 8.6 Hz, 1 H), 7.15 (d, *J* = 11.0 Hz, 1H), 7.28 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.33, 27.17, 113.24, 116.99, 129.34, 129.50, 136.91, 151.81; LRMS (EI) (M+, 214/216).

4-bromo-2-isopropylanisole (12f). A solution of 4-bromo-2-isopropylphenol (**12e**) (15.0 g, 69.8 mmol), K_2CO_3 (48.2 g, 349 mmol, 5.0 eqv), and CH_3I (99.0 g, 698 mmol, 10.0 eqv.) in 200 ml of acetone was refluxed for 24 h. The mixture was filtered and concentrated in vacuo. Column chromatography [Hexanes/Et_2O (9/1)] yielded 14.5 g of a clear oil (91%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.18 (d, *J* = 7.0 Hz, 6H), 3.27 (m, 1H), 3.79 (s, 3H), 6.70 (d, *J* = 8.6 Hz, 1H), 7.24 (d, *J* = 10.8 Hz, 1H), 7.28 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.46, 26.74, 55.52, 112.00, 113.02, 129.06, 129.10, 139.38, 155.85; LRMS (EI) (M+, 228/230).

3-(3-isobutyl-4-methoxyphenyl) propanenitrile (10i). 4-iodo-2-isobutylanisole (**10**) (1.92 g, 6.64 mmol), acrylonitrile (0.49 g, 9.29 mmol, 1.4 eqv), tetra-n-butylammonium chloride (1.85 g, 6.63 mmol, 1.0 eqv), $NaHCO_3$ (1.34 g, 15.9 mmol, 2.4 eqv), and $Pd(OAc)_2$ (10 mol %, 150 mg) were dissolved in 10 ml of DMF and the resulting solution was stirred at 40°C for 19 h. The mixture was diluted with Et_2O, filtered, and concentrated in vacuo. Column chromatography [Hexanes/EtOAc (4/1)] yielded 1.06 g of a clear oil (74%). GC/MS showed a 2:1 ratio of trans/cis isomers: The oil was dissolved in 40 ml of anhydrous MeOH and the soln was cooled to 0°C. Mg turnings (4.79 g, 19.7 mmol, 40 eqv) were added very slowly and the suspension was allowed to stir for 5 h at rt. The reaction was cooled to 0°C and 14 ml of 6 M HCl was added very slowly. The mixture was extracted with $CHCl_3$ and the organic fractions were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo. Column chromatography [Hexanes/EtOAc (5/2)] yielded 1.03 g of a clear oil (96%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.93 (d, *J* = 6.6 Hz, 6H), 1.94 (m, 1H), 2.50 (d, *J* = 7.2 Hz, 2H), 2.58 (t, *J* = 7.4 Hz, 2H), 2.89 (t, *J* = 7.4 Hz, 2H), 3.81 (s, 3H), 6.82 (d, *J* = 8.3 Hz, 1H), 6.97 (s, 1H), 7.05 (d, *J* = 10.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.52, 22.40, 28.51, 30.71, 39.28, 55.20, 110.42, 119.16, 126.39, 129.46, 130.52, 130.60, 156.76; HRMS (EI) Calcd for $C_{14}H_{19}NO$: 217.1467. Found 217.1468.

3-(4-hydroxy-3-isobutylphenyl) propanenitrile (10j). 3-(3-isobutyl-4-methoxyphenyl) propanenitrile (**10i**) (0.73 g, 3.36 mmol) was dissolved in 20 ml of CH_2Cl_2 and cooled to 0°C. BBr_3 (10.1 ml of a 1 M solution in CH_2Cl_2, 10.0 mmol, 3 eqv) was added slowly via syringe. The solution was allowed to stir for 9 h at 10°C. The reaction mixture was added to H_2O and extracted with CH_2Cl_2. The organic fractions were combined, dried

($MgSO_4$), filtered, and concentrated in vacuo. Column chromatography [Hexanes/EtOAc (2/1)] yielded 0.68 g of a clear oil (99%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.94 (d, *J* = 6.6 Hz, 6H), 1.93 (m, 1H), 2.47 (d, *J* = 7.0 Hz, 2H), 2.58 (t, *J* = 7.4 Hz, 2H), 2.87 (t, *J* = 7.4 Hz, 2H), 4.64 (s, 1H), 6.73 (d, *J* = 8.8 Hz, 1 H), 6.94 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.72, 22.50, 28.87, 30.87, 39.26, 115.62, 119.21, 126.81, 127.96, 130.09, 131.09, 152.84; HRMS (EI) Calcd for $C_{13}H_{17}NO$: 203.1310. Found 203.1306.

4-(2-cyanoethyl)-2-isobutylphenyltrifluoromethanesulfonate (6). 3-(4-hydroxy-3-isobutylphenyl) propanenitrile (**10j**) (0.67 g, 3.31 mmol) was dissolved in 3.5 ml of pyridine and cooled to 0°C. Triflic anhydride (1.12 g, 3.97 mmol, 1.2 eqv) was added slowly via syringe and the solution was allowed to stir for 17 h at rt. The reaction mixture was added to H_2O and extracted with Et_2O. The organic fractions were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo. Column chromatography [Hexanes/EtOAc (1/1)] yielded 1.03 g of a clear oil (93%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.94 (d, *J* = 7.3 Hz, 6H), 1.95 (m, 1H), 2.58 (d, *J* = 7.2 Hz, 2H), 2.64 (t, *J* = 7.3 Hz, 2H), 2.97 (t, *J* = 7.3 Hz, 2H), 7.17 (m, 2H), 7.25 (d, *J* = 15.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.17, 22.26, 29.17, 30.95, 39.33, 114.83, 117.37, 118.48, 119.91, 121.72, 122.46, 127.52, 131.99, 135.01, 138.07, 147.47; HRMS (EI) Calcd for $C_{14}H_{16}F_3NO_3S$: 335.0803. Found 335.0807.

3-(2-isobutyl-3'-isopropyl-4'-methoxy-1,1'-biphenyl-4-yl) propanenitrile (6a). A solution of 4-bromo-2-isopropylanisole (**12f**) (6.0 g, 26.2 mmol) in 200 ml of THF was cooled to -78°C. To this solution was added n-BuLi (16.4 ml of 1.6 M solution in hexanes, 26.2 mmol, 1 eqv) via syringe and the mixture was stirred for 30 min. $B(OMe)_3$ (8.17 g, 78.6 mmol, 3.0 eqv) was then added and the solution was stirred for 24 h at rt. Water (20 ml) and 10% NaOH aq (50 ml) were added and stirring was continued for 1 h. The pH was adjusted to 4-5 (1 M HCl) and most of the solvent was removed in vacuo. The residue was taken up in EtOAc and the layers separated. The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo to yield 4.81 g of a crude solid (95%). This material was used without further purification. The crude boronic acid (**5**) (0.081g, 0.417 mmol, 1.4 eqv), 4-(2-cyanoethyl)-2-isobutylphenyl trifluoromethanesulfonate (**6**) (0.10 g, 0.30 mmol), and $Pd(PPh_3)_4$ (10 mol%, 33 mg) were dissolved in 4 ml of 9/1 DME/EtOH. Na_2CO_3 (0.3 ml of 2 M aq solution, 0.59 mmol, 2 eqv) was added via syringe and the solution was stirred at 80 °C for 17 h. The reaction mixture was concentrated in vacuo and taken up in 2:1 H_2O/CH_2Cl_2. The layers were separated and the H_2O layer was extracted further with CH_2Cl_2. The combined organic fractions were dried ($MgSO_4$), filtered, and concentrated in vacuo. Column chromatography [Hexanes/EtOAc (3/1)] yielded 0.098 g of a clear oil (98%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.76 (d, *J* = 6.6 Hz, 6H), 1.22 (d, *J* = 6.9 Hz, 6H), 1.69 (m, 1H), 2.48 (d, *J* = 7.2 Hz, 2H), 2.67 (t, *J* = 7.5 Hz, 2H), 2.99 (t, *J* = 7.4 Hz, 2H), 3.37 (m, 1H), 3.88 (s, 3H), 6.88 (d, *J* = 8.3 Hz, 1H), 7.08 (m, 4H), 7.18 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.39, 22.44, 22.79, 26.65, 29.58, 31.41, 42.26, 55.46, 109.99, 119.18, 125.31, 127.26, 127.30, 129.83, 130.76, 133.97, 136.37, 136.50, 140.05, 141.61, 155.69; HRMS (EI) Calcd for $C_{23}H_{29}NO$: 335.2249. Found 335.2252.

3-(4'-hydroxy-2-isobutyl-3'-isopropyl-1,1'-biphenyl-4-yl) propanenitrile (6b). 3-(2-isobutyl-3'-isopropyl-4'-methoxy-1,1'-biphenyl-4-yl) propanenitrile (**6a**) (0.56 g, 1.67 mmol) was dissolved in 25 ml of CH_2Cl_2 and cooled to 0°C. BBr_3 (5.0 ml of a 1 M solution in CH_2Cl_2, 5.0 mmol, 3 eqv) was added slowly via syringe. The solution was allowed to stir for 9 h at 10°C. The reaction mixture was added to H_2O and extracted with CH_2Cl_2. The organic fractions were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo. Column chromatography [Hexanes/EtOAc (2/1)] yielded 0.49 g of a clear oil (92%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.76 (d, *J* = 6.6 Hz, 6H), 1.26 (d, *J* = 7 Hz, 6H), 1.68 (m, 1H), 2.48 (d, *J* = 7.2 Hz, 2H), 2.67 (t, *J* = 7.5 Hz, 2H), 2.98 (t, *J* = 7.4 Hz, 2H), 3.26 (m, 1H), 4.76 (s, 1H), 6.78 (d, *J* = 8.1 Hz, 1H), 6.95 (d, *J* = 8.1 Hz, 1H), 7.09 (m, 3H), 7.17 (d, *J* = 7.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.39, 22.43, 22.67, 27.01, 29.58, 31.39, 42.25, 114.93, 119.17, 125.32, 127.49, 127.61, 129.86, 130.73, 133.91, 134.48, 136.42, 140.02, 141.47, 151.60; HRMS (EI) Calcd for $C_{22}H_{27}NO$: 321.2093. Found 321.2095.

4'-(2-cyanoethyl)-2'-isobutyl-3-isopropyl-1,1'-biphenyl-4-yl trifluoromethanesulfonate (7). 3-(4'-hydroxy-2-isobutyl-3'-isopropyl-1,1'-biphenyl-4-yl) propanenitrile (**6b**) (0.48 g, 1.48 mmol) was dissolved in 7.0 ml of pyridine and cooled to 0°C. Triflic anhydride (0.502 g, 1.78 mmol, 1.2 eqv) was added slowly via syringe and the solution was allowed to stir for 17 h at rt. The reaction mixture was added to H_2O and extracted with Et_2O. The organic fractions were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo. Column chromatography [Hexanes/EtOAc (3/1)] yielded 0.639 g of a clear oil (95%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.75 (d, *J* = 6.6 Hz, 6H), 1.29 (d, *J* = 6.9 Hz, 6H), 1.64 (m, 1H), 2.45 (d, *J* = 7.2 Hz, 2H), 2.68 (t, *J* = 7.4 Hz, 2H), 2.99 (t, *J* = 7.3 Hz, 2H), 3.35 (m, 1H), 7.16 (m, 4 H), 7.28 (d, *J* = 8.4 Hz, 1H), 7.31 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.29, 22.27, 23.07, 27.07, 29.67, 31.22, 42.04, 114.79, 117.32, 119.02, 119.87, 120.73, 122.42, 125.57, 128.29, 128.83, 130.07, 130.27, 137.40, 139.67, 139.72, 140.64, 142,15, 145.89; HRMS (EI) Calcd for $C_{23}H_{26}F_3NO_3S$: 453.1586. Found 453.1594.

3-(2,3''-diisobutyl-3'-isopropyl-4''-methoxy-1,1':4',1''-terphenyl-4-yl) propane nitrile (7d). 2-(3-isobutyl-4-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**11**) (0.076g, 0.26 mmol, 1.2 eqv), 4'-(2-cyanoethyl)-2'-isobutyl-3-isopropyl-1,1'-biphenyl-4-yl trifluoromethanesulfonate (**7**) (0.099 g, 0.22 mmol), and $Pd(PPh_3)_4$ (15 mol%, 37 mg) were dissolved in 4 ml of 9/1 DME/EtOH. Na_2CO_3 (0.22 ml of 2 M aq solution, 0.44 mmol, 2 eqv) was added via syringe and the solution was stirred at 80°C for 20 h. The reaction mixture was concentrated in vacuo and taken up in 2:1 H_2O/CH_2Cl_2. The layers were separated and the H_2O layer was extracted further with CH_2Cl_2. The combined organic fractions were dried ($MgSO_4$), filtered, and concentrated in vacuo. Column chromatography [Hexanes/EtOAc (6/1)] yielded 0.089 g of a clear oil (87%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.79 (d, *J* = 6.6 Hz, 6H), 0.94 (d, *J* = 6.6 Hz, 6H), 1.17 (d, *J* = 6.9 Hz, 6H), 1.74 (m, 1H), 1.97 (m, 1H), 2.54 (m, 4H), 2.69 (t, *J* = 7.5 Hz, 2H), 3.01 (t, *J* = 7.4 Hz, 2H), 3.17 (m, 1H), 3.88 (s, 3H), 6.91 (d, *J* = 8.3 Hz, 1H), 7.17 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.37, 22.46, 22.58, 24.28, 28.62, 29.37, 29.65, 31.44, 39.59, 42.23, 55.39, 109.89, 119.15, 125.38, 126.21, 126.69, 127.63, 129.66,

129.79, 129.87, 130.64, 132.06, 133.68, 136.62, 139.54, 139.94, 140.52, 141.71, 146.13, 156.72; HRMS (EI) Calcd for $C_{33}H_{41}NO$: 467.3188. Found 467.3194.

3-(4''-hydroxy-2,3''-diisobutyl-3'-isopropyl-1,1':4',1''-terphenyl-4-yl) propanenitrile (8). 3-(2,3"-diisobutyl-3'-isopropyl-4"-methoxy-1,1':4',1"-terphenyl-4-yl) propane nitrile (**7d**) (0.076 g, 0.16 mmol) was dissolved in 4 ml of CH_2Cl_2 and cooled to 0°C. BBr_3 (0.49 ml of a 1 M solution in CH_2Cl_2, 0.49 mmol, 3.0 eqv) was added slowly via syringe. The solution was allowed to stir for 9 h at 10 °C. The reaction mixture was added to H_2O and extracted with CH_2Cl_2. The organic fractions were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo. Column chromatography [Hexanes/EtOAc (3/1)] yielded 0.072 g of a clear oil (97%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.80 (d, *J* = 6.6 Hz, 6H), 0.99 (d, *J* = 6.6 Hz, 6H), 1.17 (d, *J* = 6.9 Hz, 6H), 1.74 (m, 1H), 2.00 (m, 1H), 2.54 (m, 4H), 2.69 (t, *J* = 7.5 Hz, 2H), 3.01 (t, *J* = 7.4 Hz, 2H), 3.16 (m, 1H), 4.70 (s, 1H), 6.83 (d, *J* = 8.6 Hz, 1H), 7.09 (m, 5H), 7.19 (d, *J* = 7.7 Hz, 1H), 7.25 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.42, 22.46, 22.56, 24.29, 28.81, 29.34, 29.67, 31.39, 39.42, 42.17, 114.86, 119.23, 125.39, 126.22, 126.69, 126.89, 128.01, 129.75, 129.89, 130.62, 132.33, 134.17, 136.63, 139.31, 139.89, 140.55, 141.61, 146.06, 152.58; HRMS (EI) Calcd for $C_{32}H_{39}NO$: 453.3031. Found 453.3025.

3-[4''-(cyanomethoxy)-2,3''-diisobutyl-3'-isopropyl-1,1':4',1''-terphenyl-4-yl] propanenitrile (8f). To a solution of 3-(4"-hydroxy-2,3"-diisobutyl-3'-isopropyl-1,1':4',1"-terphenyl-4-yl) propanenitrile (**8**) (18.6 mg, 0.04 mmol) and K_2CO_3 (28.0 mg, 0.20 mmol, 5.0 eqv) in 2.0 ml of acetone was added $ClCH_2CN$ (31.0 mg, 0.41 mmol, 10.0 eqv) via syringe. The solution was stirred for 40 h at 55°C and was then added to 20 ml of 1:1 H_2O/brine. The mixture was extracted with EtOAc and the combined organic fractions were washed (brine), dried ($MgSO_4$), filtered, and concentrated in vacuo. Column chromatography [Hexanes/EtOAc (3/1)] yielded 19.2 mg of a clear oil (95%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.80 (d, *J* = 6.6 Hz, 6H), 0.95 (d, *J* = 6.6 Hz, 6H), 1.18 (d, *J* = 6.8 Hz, 6H), 1.75 (m, 1H), 1.95 (m, 1H), 2.55 (m, 4H), 2.70 (t, *J* = 7.5 Hz, 2H), 3.01 (t, *J* = 7.4 Hz, 2H), 3.12 (m, 1H), 4.86 (s, 2H), 6.98 (d, *J* = 8.4 Hz, 1H), 7.18 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.43, 22.44, 22.49, 24.27, 28.87, 29.32, 29.66, 31.30, 39.27, 42.07, 53.65, 111.09, 115.41, 119.25, 125.39, 126.26, 126.73, 127.85, 129.60, 129.89, 130.49, 130.56, 132.76, 136.14, 136.65, 138.65, 139.81, 140.79, 141.37, 145.93, 153.58; HRMS (EI) Calcd for $C_{34}H_{40}N_2O$: 492.3140. Found 492.3131.

3-[4''-(carboxymethoxy)-2,3''-diisobutyl-3'-isopropyl-1,1':4',1''-terphenyl-4-yl] propanoic acid (1a). 3-[4"-(cyanomethoxy)-2,3"-diisobutyl-3'-isopropyl-1,1':4',1"-terphenyl-4-yl] propanenitrile (**8f**) (19.2 mg, 0.039 mmol) was dissolved in a solution containing 2 ml of 25% NaOH (aq) and 3.5 ml of MeOH. The mixture was stirred at 50°C for 24 h. The temperature was then reduced to 0°C and the solution was acidified to pH 2 with 1N HCl. The mixture was partitioned between EtOAc and brine and the organic layer was separated, dried ($MgSO_4$), filtered, and concentrated in vacuo. Prep TLC [Hexanes/EtOAc/AcOH (66/33/1)] yielded 15.3 mg of a white solid (74%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.77 (d, *J* = 6.6 Hz, 6H), 0.96 (d, *J* = 6.6 Hz, 6H), 1.15 (d, *J* = 6.8 Hz, 6H), 1.72 (m, 1H), 2.00 (m, 1H), 2.51 (d, *J* = 7.2 Hz, 2H), 2.60 (d, *J* = 7.1 Hz, 2H), 2.77 (t, *J* = 7.6 Hz, 2H), 3.01 (t, *J* = 7.4 Hz, 2H), 3.12 (m, 1H), 4.75 (s, 2H), 6.79 (d,

J = 8.9 Hz, 1H), 7.13 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.44, 22.57, 24.31, 28.78, 29.36, 29.65, 30.29, 35.33, 39.58, 42.17, 65.23, 110.89, 125.49, 126.32, 126.75, 126.83, 127.82, 129.67, 130.08, 130.26, 132.59, 135.28, 138.67, 138.81, 139.40, 140.64, 140.94, 145.90, 154.48, 172.99, 177.73; HRMS (EI) Calcd for $C_{34}H_{42}O_5$: 530.3032. Found 530.3031.

3-[4''-(2-aminoethoxy)-2,3''-diisobutyl-3'-isopropyl-1,1':4',1''-terphenyl-4-yl]propan-1-amine dihydrochloride (2). 3-[4"-(cyanomethoxy)-2,3"-diisobutyl-3'-isopropyl-1,1':4',1"-terphenyl-4-yl] propanenitrile (**8f**) (19.0 mg, 0.038 mmol) was dissolved in 5 ml of EtOH containing 10% Pd/C (15 mg) and 0.1 ml HCl (conc.). The solution was stirred overnight under 20 psi of H_2. The reaction mixture was filtered through celite and the filtrate was concentrated in vacuo to yield 20 mg of a white solid (91%): ^{1}H NMR (500 MHz, CD_3OD) δ 0.75 (d, *J* = 6.6 Hz, 6H), 0.93 (d, *J* = 6.9 Hz, 6H), 1.14 (d, *J* = 6.9, 6H), 1.68 (m, 2H), 1.96 (m, 1H), 1.99 (m, 1H), 2.54 (d, *J* = 6.6 Hz, 2H), 2.62 (d, *J* = 6.9 Hz, 2H), 2.76 (t, *J* = 7.4, 2H), 2.96 (t, *J* = 6.8 Hz, 2H), 3.11 (m, 1H), 3.41 (t, *J* = 4.5 Hz, 2H), 4.29 (t, *J* = 5.0 Hz, 2H), 7.13 (m, 9H); ^{13}C NMR (125 MHz, CD_3OD) δ 22.85, 22.96, 24.61, 30.15, 30.53, 30.54, 30.81, 33.34, 40.12, 40.53, 40.70, 43.42, 66.06, 112.90, 126.84, 127.50, 127.67, 129.06, 130.75, 131.25, 131.29, 131.33, 133.29, 136.26, 140.46, 140.49, 140.59, 141.95, 142.56, 147.13, 156.52; HRMS (FAB, M+H) Calcd for $C_{34}H_{49}N_2O$: 501.3845. Found 501.3845.

Methyl-3-(4-{[(trifluoromethyl)sulfonyl]oxy}phenyl)propanoate (13b). Methyl 3-(4-hydroxyphenyl)propanoate (**13**) (1.0 g, 5.5 mmol) was dissolved in 5 ml of pyridine at 0°C . Triflic anhydride (1.1 ml, 6.6 mmol, 1.2 eqv) was added and the solution was allowed to stir for 48 h at rt. The reaction mixture was added to H_2O and extracted with Et_2O. The organic fractions were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo. Column chromatography [Hexanes/EtOAc (2/1)] yielded 1.60 g of a clear oil (92%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.64 (t, *J* = 8.0 Hz, 2H), 2.98 (t, *J* = 7.2 Hz, 2H), 3.67 (s, 3H), 7.19 (d, *J* = 8.8 Hz, 2H), 7.28 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 30.12, 35.20, 51.66, 114.88, 117.43, 119.98, 121.29, 122.53, 130.07, 141.10, 148.04, 172.77; HRMS (EI) Calcd for $C_{11}H_{11}F_3O_5S$: 312.0279. Found 312.0275.

Bis methyl 3-(1,1':4',1''-terphenyl-4,4''-yl)propanoate (13c). Methyl-3-(4-{[(trifluoromethyl)sulfonyl]oxy}phenyl)propanoate (**13b**) (188 mg, 0.60 mmol, 2.0 eqv), 1,4-phenylenebisboronic acid (50 mg, 0.30 mmol), and $Pd(PPh_3)_4$ (30 mol%, 100 mg) were dissolved in 7 ml of 6/1 DME/EtOH. Na_2CO_3 (0.6 ml of 2 M aq solution, 1.2 mmol, 4.0 eqv) was added via syringe and the solution was stirred at 80°C for 36 h. The reaction mixture was concentrated in vacuo. Column chromatography [Hexanes/EtOAc/CH_2Cl_2 (2/1/1)] yielded 0.095 g of a white solid (79%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.55 (t, *J* = 8.0 Hz, 4H), 2.88 (t, *J* = 7.2 Hz, 4H), 3.56 (s, 6H), 7.16 (d, *J* = 8.0 Hz, 4H), 7.43 (d, *J* = 7.6 Hz, 4H), 7.52 (s, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 30.54, 35.59, 51.64, 127.07, 127.28, 128.73, 138.68, 139.64, 139.66, 173.29; HRMS (EI) Calcd for $C_{26}H_{26}O_4$: 402.1831. Found 402.1832.

Bis methyl 3-(1,1':4',1''-terphenyl-4,4''-yl)propanoic acid (3). Bis methyl 3-(1,1':4',1"-terphenyl-4,4"-yl)propanoate (**13c**) (23 mg, 0.06 mmol) was dissolved in 5 ml of a 3/1/1

mixture of dioxane/HMPA/H_2O. NaOH (0.3 ml of a 25% aq solution) was added and the mixture was stirred at 110°C for 2 h. The reaction was cooled to rt, added to H_2O, and acidified to pH 1.0 with 1 N HCl. The mixture was extracted with EtOAc and the organics were combined, washed with H_2O, dried ($MgSO_4$), filtered, and concentrated in vacuo. The resulting solid was washed several times with CH_2Cl_2 and then sufficiently dried to yield 20 mg of the purified product as a white solid (95%): ^{1}H NMR (400 MHz, DMSO) δ 2.58 (t, *J* = 7.6 Hz, 4H), 2.87 (t, *J* = 7.2 Hz, 4H), 7.34 (d, *J* = 8 Hz, 4H), 7.63 (d, *J* = 8 Hz, 4H), 7.73 (s, 4H); ^{13}C NMR (125 MHz, DMSO) δ 29.86, 34.99, 126.35, 126.84, 128.79, 137.27, 138.68, 140.15, 173.64; LRMS (ESI) (M+, 374.4).

(4-iodophenoxy)acetonitrile (14e). 4-iodophenol (**14**) (2.0 g, 9.1 mmol), chloroacetonitrile (5.75 ml, 91 mmol, 10 eqv), and K_2CO_3 (6.28 g, 45.5 mmol, 5 eqv) were added to 20 ml of acetone. The mixture was stirred at 45°C for 24 h. The mixture was then added to 1/1 H_2O/brine and extracted with EtOAc. The organics were combined, washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. Column chromatography [Hexanes/EtOAc (2/1)] yielded 1.55 g of a white solid (66%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.74 (s, 2H), 6.77 (d, *J* = 7.2 Hz, 2H), 7.64 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 53.59, 85.85, 114.69, 117.25, 138.74, 156.38; HRMS (EI) Calcd for C_8H_6INO: 258.9494. Found 258.9505.

[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy]acetonitrile (15). A solution of (4-iodophenoxy)acetonitrile (**14e**) (0.30 g, 1.16 mmol), bis(pinacolato)diboron (0.32 g, 1.27 mmol, 1.1 eqv), KOAc (0.34 g, 3.47 mmol, 3.0 eqv), and $PdCl_2$dppf (5 mol%, 47 mg) in 4 ml of DMSO was stirred at 85°C for 16 h. The mixture was added to H_2O and extracted with CH_2Cl_2. The organic fractions were combined, back extracted with H_2O, dried ($MgSO_4$), filtered, and concentrated in vacuo. Column chromatography [Hexanes/EtOAc (2/1)] yielded 0.241 g of a white solid (80%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (s, 12H), 4.79 (s, 2H), 6.97 (d, *J* = 8.4 Hz, 2H), 7.81 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.85, 53.18, 83.80, 114.03, 114.89, 136.79, 158.89; HRMS (EI) Calcd for $C_{14}H_{18}BNO_3$: 258.1416. Found 258.1412.

3-[4'-(carboxymethoxy)-1,1'-biphenyl-4-yl)propanoic acid (4). [4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy]acetonitrile (**15**) (55 mg, 0.21 mmol), 4-bromophenylhydrocinnamonitrile (44 mg, 0.21 mmol, 1 eqv), and $Pd(PPh_3)_4$ (5 mol%, 12 mg) were dissolved in 3 ml of DME. Na_2CO_3 (0.21 ml of 2 M aq solution, 0.42 mmol, 2 eqv) was added via syringe and the solution was stirred at 80°C for 20 h. The reaction mixture was concentrated in vacuo and taken up in 2:1 H_2O/CH_2Cl_2. The layers were separated and the water layer was extracted further with CH_2Cl_2. The combined organic fractions were dried ($MgSO_4$), filtered, and concentrated in vacuo to yield a white solid. The crude solid was dissolved in 3/1 MeOH/dioxane. NaOH (1.5 ml of a 25% aq solution) was added and the mixture was stirred vigorously at 50°C for 24 h. The solution was acidified to pH 1.0 with 1N HCl and extracted with EtOAc several times. The organics were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo to yield a white solid. This material was washed several times with CH_2Cl_2 to yield 59 mg of purified product (93%): ^{1}H NMR (400 MHz, DMSO) δ 2.56 (t, *J* = 7.2 Hz, 2H), 2.84 (t, *J* = 7.2 Hz, 2H), 4.71 (s, 2H), 6.98 (d, *J* = 8.8 Hz, 2H), 7.28 (d, *J* = 8.4 Hz, 2H), 7.52 (d, *J*

= 8.0 Hz, 2H), 7.56 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (125 MHz, DMSO) δ 29.84, 35.07, 64.41, 114.75, 126.05, 127.46, 128.69, 132.66, 137.42, 139.37, 157.13, 170.10, 173.68; HRMS (EI) Calcd for $C_{17}H_{16}O_5$: 300.0998. Found 300.1003.

5-Bromo-2-methoxy-benzoic acid (17). 6.42 ml (125 mmol, 1.1 eqv) Br_2 was added to a solution of 17.50 g (115 mmol) 2-Methoxy-benzoic acid (**16**) in 220 ml CH_2Cl_2/H_2O (1:1) and the resulting mixture was stirred at rt for 19 h. After adding 1.32 g $NaHSO_3$ (12.7 mmol, 0.11 eq) the aq. layer was extracted with CH_2Cl_2. The comb. org. fractions were dried over $MgSO_4$ and the solvent was evaporated. The resulting white solid was suspended in 45 ml CH_2Cl_2 and treated with 450 ml ice-cold hexanes. The obtained white residue was filtered, washed with ice-cold hexanes and dried in high vacuum. This led to 24.53 g (106 mmol, 92%) **17**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.10 (s, 3H), 6.96 (d, 1H, *J* = 8.83 Hz), 7.67 (dd, 1H, J_1 = 8.83 Hz, J_2 = 2.52 Hz), 8.31 (d, 1H, *J* = 2.68 Hz), 11.91 (s, 1H), 10.50 (s, br., 1H).

(5-bromo-2-hydroxy-phenyl)-phenyl-methanone (18). 10.07 ml (138.8 mmol, 2.2 eqv) $SOCl_2$ was added to a solution of 14.77 g (63.9 mmol) 5-Bromo-2-methoxy-benzoic acid (**17**) in 140 ml dry toluene, followed by 0.5 ml (6.5 mmol, 0.1 eqv) DMF. After stirring this solution for 1.5 h at 70°C the solvent was evaporated and the the crude acyl chloride was dissolved in 75 ml of dry benzene. This solution was then added cautiously under stirring to a suspension of 10.30 g (77.3 mmol, 1.2 eqv) $AlCl_3$ in 80 ml dry benzene at 10°C. After complete addition the resulting mixture was refluxed for 5h and then quenched by adding H_2O and conc. hydrochloric acid. The aq. layer was extracted with EtOAc and the comb. org. fractions were dried over $NaSO_4$ and evaporated. Column chromatography (CH_2Cl_2) yielded 16.03 g (57.9 mmol, 90%) **18** as a yellow solid: R_f (CH_2Cl_2) 0.67; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.99 (d, 1H, *J* = 8.99 Hz), 7.52-7.68 (m, 6H), 7.70 (d, 1H, *J* = 2.36 Hz), 11.91 (s, 1H); LRMS (EI) *m/z* 278 (80), 277 (100), 276 (86), 275 (92), 201 (31), 200 (22), 199 (30), 198 (20), 105 (63), 77 (57), 63 (19); HRMS (EI) Calcd. for $C_{13}H_9BrO_2$: 275.978591. Found: 275.977717.

4-bromo-2-(hydroxy-phenyl-methyl)-phenol (19). 1.02 g (27 mmol, 3.9 eqv) $NaBH_4$ was added cautiously at rt to a solution of 1.92 g (6.9 mmol) (5-Bromo-2-hydroxy-phenyl)-phenyl-methanone (**18**) in 70 ml dry MeOH. After stirring this solution for 2 h at rt the solvent was evaporated and the residue was taken up in 70 ml water and 70 ml Et_2O. The aq. layer was extracted with Et_2O and the comb. org. fractions were washed twice with water, dried over Na_2SO_4 and evaporated. Column chromatography (Hexanes/EtOAc (1+1)) yielded 1.88 g (6.7 mmol, 98%) **19** as a white solid: R_f (Hexanes/EtOAc (1+1)) 0.57; mp 96-97°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.76 (d, 1H, *J* = 3.15 Hz), 5.98 (d, 1H, *J* = 3.00 Hz), 6.79 (d, 1H, *J* = 8.67 Hz), 6.98 (dd, 1H, J_1 = 2.21 Hz, J_2 = 0.47 Hz), 7.28 (dd, 1H, J_1 = 8.67 Hz, J_2 = 2.36 Hz), 7.33-7.41 (m, 5H), 7.92 (s, 1H); LRMS (EI) *m/z* 278 (5), 276 (4), 262 (56), 261 (100), 260 (46), 259 (95), 181 (21), 180 (12), 153 (12), 152 (33), 77 (16), 76 (16), 63 (10); HRMS (EI) Calcd. for $C_{13}H_{11}BrO_2$: 277.994241. Found: 277.993366.

2-benzyl-4-bromo-phenol (20). A solution of 13.24 g (99.3 mmol, 4.1 eqv) $AlCl_3$ in 85 ml dry Et_2O was added cautiously under stirring to a suspension of 3.91 g (102.9 mmol,

4.2 eqv) $LiAlH_4$ in 100 ml dry Et_2O. After complete addition the resulting mixture was stirred for 30 min at rt and then a solution of 6.85 g (24.5 mmol) 4-Bromo-2-(hydroxy-phenyl-methyl)-phenol (**19**) in 80 ml dry Et_2O was added dropwise. The mixture was refluxed for 12 h and after that cooled to 0°C. After adding cautiously 60 ml of a mixture of Et_2O/MeOH (1:1), 170 ml 1 N HCl-solution was added and the mixture was extracted with Et_2O. The comb. org. fractions were washed with brine, dried over Na_2SO_4 and evaporated. Column chromatography (CH_2Cl_2) yielded 4.00 g (15.2 mmol, 62%) **20** as a colorless liquid: R_f (CH_2Cl_2) 0.41; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.95 (s, 2H), 4.64 (s, 1H), 6.67 (dd, 1H, J_1 = 8.04 Hz, J_2 = 0.79 Hz), 7.23 (m, 5H), 7.31 (m, 2H); LRMS (EI) *m/z* 265 (17), 264 (98), 263 (21), 262 (100), 186 (53), 184 (49), 183 (78), 182 (18), 181 (27), 165 (49), 153 (23), 152 (26), 91 (29), 84 (14), 78 (25), 77 (31), 76 (16), 63 (15); HRMS (EI) Calcd. for $C_{13}H_{11}BrO$: 261.999326. Found: 261.998568.

2-benzyl-4-bromo-anisole (21). 9.48 ml (152 mmol, 10 eqv) iodomethane was added to a suspension of 4.00 g (15.2 mmol) 2-Benzyl-4-bromo-phenol (**20**) and 10.50 g (76 mmol, 5 eqv) K_2CO_3 in 70 ml acetone and the resulting mixture was refluxed for 24 h. After adding water and aq. NH_3-solution, the aq. layer was extracted with Et_2O. The comb. org. fractions were washed with brine, dried over Na_2SO_4 and evaporated. Column chromatography (CH_2Cl_2) yielded 4.11 g (14.8 mmol, 98%) **21** as a colorless liquid: R_f (CH_2Cl_2) 0.77; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (s, 3H), 3.92 (s, 2H), 6.72 (d, 1H, J = 8.59 Hz), 7.18 (m, 4H), 7.27 (m, 3H); LRMS (EI) *m/z* 279 (17), 278 (95), 277 (18), 276 (96), 263 (14), 261 (17), 198 (18), 197 (65), 182 (34), 181 (31), 166 (20), 165 (56), 154 (19), 153 (24), 152 (29), 92 (11), 91 (100), 77 (13), 76 (16), 63 (13); HRMS (EI) Calcd. for $C_{14}H_{13}BrO$: 276.014976. Found: 276.014234.

3-benzyl-4-methoxy-benzene-1-boronic acid (22). 8.61 ml (13.8 mmol, 1 eqv) of a 1.6 M solution of *n*-BuLi in hexanes was added to a solution of 3.82 g (13.8 mmol) 2-Benzyl-4-bromo-anisol (**21**) in 100 ml dry THF at -78°C. After stirring this mixture for 30 min at –78°C, 4.70 ml (41.4 mmol, 3 eqv) $B(OMe)_3$ was added and the solution was stirred for 24 h at rt. Now 10 ml water and 25 ml of a 10% aq. NaOH-solution were added and stirring was continued for further 60 min. Then the pH was adjusted to 4-5 with 1-N-HCl-solution and most of the solvent was evaporated. The residue was extracted with EtOAc and the comb. org. fractions were dried over $MgSO_4$ and evaporated, which led after drying in high vacuum to 3.33 g (13.8 mmol, 100%) of an orange solid. This crude boronic acid **22** was used without further purification: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.81 (s, 3H), 3.98 (s, 2H), 6.89 (d, 1H, J = 8.20 Hz), 7.10-7.23 (m, 5H), 7.79 (d, 1H, J = 1.58 Hz), 7.96 (dd, 1H, J_1 = 8.20 Hz, J_2 = 1.73 Hz).

2-(3-benzyl-4-methoxy-phenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (23). A solution of 250.7 mg (0.91 mmol) 2-Benzyl-4-bromo-anisole (**21**), 243.1 mg (0.96 mmol, 1.1 eqv) bis(pinacolato)diboron, 269.3 mg (2.74 mmol, 3 eqv) KOAc and 37.7 mg (46 µmol, 0.05 eqv) $PdCl_2dppf*CH_2Cl_2$ in 5 ml DMSO was heated at 85°C for 3 h. After that, water was added and the mixture was extracted with CH_2Cl_2. The comb. org. fractions were washed with water, dried over $MgSO_4$ and evaporated. Column chromatography (Hexanes/EtOAc (9+1)) yielded 160 mg (0.49 mmol, 55%) **23** as a white solid: R_f (Hexanes/EtOAc (9+1)) 0.22; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (s, 12H), 3.74

(s, 3H), 3.90 (s, 2H), 6.80 (d, 1H, *J* = 8.21 Hz), 7.05-7.24 (m, 5H), 7.57 (d, 1H, *J* = 1.64 Hz), 7.62 (dd, 1H, J_1 = 8.21 Hz, J_2 = 1.64 Hz); LRMS (EI) *m/z* 325 (24), 324 (100), 323 (28), 309 (18), 238 (21), 225 (33), 224 (36), 223 (12), 209 (16), 191 (9), 165 (20), 147 (14), 117 (10), 91 (15), 83 (10); HRMS (EI) Calcd. for $C_{20}H_{25}BO_3$: 324.189675. Found: 324.188981.

3-(3'-benzyl-2-isobutyl-4'-methoxy-1,1'-biphenyl-4-yl)propanenitrile (24). 490 mg (1.46 mmol) Trifluoro-methanesulfonic acid 4-(2-Cyanoethyl)-2-isobutyl-phenyl ester (**6**), 505 mg (2.09 mmol, 1.4 eqv) crude 3-Benzyl-4-methoxy-benzene-1-boronic acid (**22**) and 169.4 mg (0.15 mmol, 0.1 eqv) $Pd(Ph_3P)_4$ were dissolved in 20 ml DME/EtOH (9+1). 1.46 ml (2.92 mmol, 2 eqv) of a 2 M aq. Na_2CO_3-solution was added to this yellow solution and the resulting mixture was heated at 80°C for 17 h. After concentrating the mixture in vacuo the residue was taken up in water and extracted with CH_2Cl_2. The comb. org. fractions were dried over $MgSO_4$ and evaporated. Column chromatography (Hexanes/EtOAc (3+1)) yielded 290.8 mg (0.76 mmol, 52%) **24** as a clear oil: R_f (Hexanes/EtOAc (3+1)) 0.34; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.63 (d, 6H, *J* = 6.70 Hz), 1.55 (m, 1H), 2.35 (d, 2H, *J* = 7.33 Hz), 2.57 (t, 2H, *J* = 7.45 Hz), 2.88 (t, 2H, *J* = 7.45 Hz), 3.79 (s, 3H), 3.92 (s, 2H), 6.82 (d, 1H, *J* = 8.34 Hz), 6.92 (d, 1H, *J* = 2.15 Hz), 6.96-7.20 (m, 9H); LRMS (EI) *m/z* 383 (13), 335 (15), 293 (23), 214 (17), 187 (21), 161 (20), 160 (100), 145 (35), 144 (35), 105 (50), 91 (58), 77 (11); HRMS (EI) Calcd. for $C_{27}H_{29}NO$: 383.224914. Found: 383.225267.

3-(3'-benzyl-4'-hydroxy-2-isobutyl-1,1'-biphenyl-4-yl)propanenitrile (25). 2.20 ml (2.20 mmol, 3 eqv) of a 1 M solution of BBr_3 in CH_2Cl_2 was added to a solution of 279 mg (0.73 mmol) 3-(3'-Benzyl-2-isobutyl-4'-methoxy-1,1'-biphenyl-4-yl)propanenitrile (**24**) in 12 ml dry CH_2Cl_2 at 0°C via syringe. After that, the solution was stirred for 2 h at 0°C and then for 7 h at rt. The reaction mixture was then added to water and extracted with CH_2Cl_2. The comb. org. fractions were dried over $MgSO_4$ and evaporated. Column chromatography (Hexanes/EtOAc (2+1)) yielded 258.5 mg (0.70 mmol, 96%) **25** as a pale yellow oil: R_f (Hexanes/EtOAc (2+1)) 0.53; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.65 (d, 6H, *J* = 6.62 Hz), 1.57 (m, 1H), 2.38 (d, 2H, *J* = 7.25 Hz), 2.57 (t, 2H, *J* = 7.41 Hz), 2.89 (t, 2H, *J* = 7.41 Hz), 3.95 (s, 2H), 4.62 (s, br., 1H), 6.74 (d, 1H, *J* = 8.04 Hz), 6.94-7.24 (m, 10H); LRMS (EI) *m/z* 369 (8), 335 (10), 293 (15), 161 (13), 160 (66), 91 (35), 86 (63), 84 (100); HRMS (EI) Calcd. for $C_{26}H_{27}NO$: 369.209264. Found: 369.209026.

Trifluoro-methanesulfonic acid 3-benzyl-4'-(2-cyano-ethyl)-2'-isobutyl-biphenyl-4-yl ester (26). 0.10 ml (0.59 mmol, 1.8 eqv) triflic anhydride was added to a solution of 116.8 mg (0.32 mmol) 3-(3'-Benzyl-4'-hydroxy-2-Isobutyl-1,1'-biphenyl-4-yl)propanenitrile (**25**) in 5 ml pyridine at 0°C. The resulting mixture was stirred at 0°C for 30 min and then at rt for 18 h. After that, water was added and the mixture was extracted with Et_2O. The comb. org. fractions were washed with brine, dried over $MgSO_4$ and evaporated. Column chromatography (Hexanes/EtOAc (1+1)) yielded 136.9 mg (0.27 mmol, 85%) **26** as a pale violet solid: R_f (Hexanes/EtOAc (1+1)) 0.59, ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.64 (d, 6H, *J* = 6.62 Hz), 1.51 (m, 1H), 2.31 (d, 2H, *J* = 7.25 Hz), 2.61 (t, 2H, *J* = 7.41 Hz), 2.93 (t, 2H, *J* = 7.41 Hz), 4.07 (s, 2H), 7.03-7.08 (m, 4H), 7.13-7.21 (m, 4H), 7.24-7.31 (m, 3H); LRMS (EI) *m/z* 503 (10), 502 (36), 501 (100), 369 (17),

368 (45), 326 (14), 91 (43); HRMS (EI) Calcd. for $C_{27}H_{26}F_3NO_3S$: 501.158551. Found: 501.158983.

3-(3',3''-dibenzyl-2-isobutyl-4''-methoxy-1,1':4',1''-terphenyl-4-yl)propanenitrile (27). 167.7 mg (0.33 mmol) 4'-(2-Cyanoethyl)-3-benzyl-2'-isobutyl-1,1'-biphenyl-4-yl-trifluoromethanesulfonate (**26**), 158.7 mg (0.49 mmol, 1.5 eqv) 2-(3-Benzyl-4-methoxy-phenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (**23**) and 58.8 mg (50.9 µmol, 0.15 eqv) $Pd(Ph_3P)_4$ were dissolved in 10 ml DME/EtOH (9+1). 0.33 ml (0.66 mmol, 2 eqv) of a 2 M aq. Na_2CO_3-solution was added to this yellow solution and the resulting mixture was heated at 80°C for 8 h. After concentrating the mixture in vacuo the residue was taken up in water and extracted with CH_2Cl_2. The comb. org. fractions were dried over $MgSO_4$ and evaporated. Column chromatography (Hexanes/EtOAc (3+1)) yielded 165.6 mg (0.30 mmol, 91%) (**27**) as a clear oil: R_f (Hexanes/EtOAc (3+1)) 0.30; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.69 (d, 6H, *J* = 6.62 Hz), 1.63 (m, 1H), 2.43 (d, 2H, *J* = 7.41 Hz), 2.61 (t, 2H, *J* = 7.57 Hz), 2.93 (t, 2H, *J* = 7.57 Hz), 3.82 (s, 3H), 3.93 (s, 4H), 6.85 (d, 1H, *J* = 8.36 Hz), 6.94 (m, 2H), 7.02-7.22 (m, 16H); LRMS (EI) *m/z* 549 (3), 501 (2), 446 (11), 383 (5), 335 (6), 293 (9), 256 (14), 215 (16), 214 (100), 199 (16), 160 (49), 91 (47); HRMS (EI) Calcd. for $C_{40}H_{39}NO$: 549.303164. Found: 549.302298.

3-(3',3''-dibenzyl-4''-hydroxy-2-isobutyl-1,1':4',1''-terphenyl-4-yl)propanenitrile (28). 0.90 ml (0.90 mmol, 3 eqv) of a 1 M solution of BBr_3 in CH_2Cl_2 was added to a solution of 164.3 mg (0.30 mmol) 3-(3',3''-Dibenzyl-2-isobutyl-4''-methoxy-1,1':4',1''-terphenyl-4-yl)propanenitrile (**27**) in 7 ml dry CH_2Cl_2 at 0°C via syringe. After that, the solution was stirred for 2 h at 0°C and then for 4 h at rt. The reaction mixture was then added to water and extracted with CH_2Cl_2. The comb. org. fractions were dried over $MgSO_4$ and evaporated. Column chromatography (Hexanes/EtOAc (2+1)) yielded 137.5 mg (0.26 mmol, 86%) **28** as a colorless oil: R_f (Hexanes/EtOAc (2+1)) 0.35; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.67 (d, 6H, *J* = 6.62 Hz), 1.61 (m, 1H), 2.40 (d, 2H, *J* = 7.09 Hz), 2.58 (t, 2H, *J* = 7.41 Hz), 2.91 (t, 2H, *J* = 7.41 Hz), 3.89 (s, 2H), 3.93 (s, 2H), 5.57 (s, 1H), 6.74 (d, 1H, *J* = 8.04 Hz), 6.90 (m, 2H), 6.99-7.26 (m, 16H); LRMS (EI) *m/z* 536 (19), 535 (46), 501 (10), 446 (9), 369 (21), 91 (100), 78 (12), 76 (10); HRMS (EI) Calcd. for $C_{39}H_{37}NO$: 535.287514. Found: 535.287420.

3-(3',3''-dibenzyl-4''-(cyanomethoxy)-2-isobutyl-1,1':4',1''-terphenyl-4-yl)propanenitrile (29). To a suspension of 136.8 mg (0.26 mmol) 3-(3',3''-Dibenzyl-4''-hydroxy-2-isobutyl-1,1':4',1''-terphenyl-4-yl)propanenitrile (**28**) and 184.9 mg (1.34 mmol, 5.2 eqv) K_2CO_3 in 12 ml acetone, 0.17 ml (2.69 mmol, 10.3 eqv) chloroacetonitrile was added. The resulting mixture was stirred for 40 h at 55°C and then added to 40 ml of a mixture of brine/water (1+1). After extraction with EtOAc the combined org. fractions were washed with brine, dried over $MgSO_4$ and evaporated. Column chromatography (Hexanes/EtOAc (2+1)) yielded 144.9 mg (0.25 mmol, 97%) **29** as a colorless oil: R_f (Hexanes/EtOAc (2+1)) 0.33; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.70 (d, 6H, *J* = 6.62 Hz), 1.64 (m, 1H), 2.44 (d, 2H, *J* = 7.41 Hz), 2.62 (t, 2H, *J* = 7.41 Hz), 2.94 (t, 2H, *J* = 7.41 Hz), 3.92 (s, 2H), 3.94 (s, 2H), 4.71 (s, 2H), 6.92 (m, 3H), 7.03-7.18 (m, 14H), 7.20-7.26 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.38, 21.04, 22.39, 29.53, 31.33, 35.96, 39.11, 42.02, 53.96, 111.86, 115.18, 119.18, 125.39, 125.79, 126.07,

127.27, 128.27, 128.41, 128.52, 128.64, 128.76, 129.86, 129.94, 130.31, 130.55, 131.64, 132.33, 136.32, 136.78, 137.69, 139.77, 140.19, 140.88, 140.89, 141.40, 149.00, 153.60; LRMS (EI) *m/z* 575 (2), 574 (5), 535 (1), 501 (1), 446 (2), 409 (15), 408 (50), 369 (13), 91 (100); HRMS (EI) Calcd. for $C_{41}H_{38}N_2O$: 574.298413. Found: 574.298309.

3-(3',3''-dibenzyl-4''-(carboxymethoxy)-2-isobutyl-1,1':4',1''-terphenyl-4-yl)propanoic acid (1b). 5 ml (41.5 mmol, 178 eqv) of a 25% aq. NaOH-solution was added to a solution of 134.0 mg (233.1 µmol) 3-(3',3''-Dibenzyl-4''-(cyanomethoxy)-2-isobutyl-1,1':4',1''-terphenyl-4-yl)propanenitrile (**29**) in 8 ml MeOH, 8 ml THF and 1 ml 1,4-dioxane. The resulting mixture was refluxed for 29 h and then cooled to 0°C. After adjusting the pH to 2 by adding 1 N aq. HCl-solution, which led to a white precipitate, brine was added and the mixture was extracted with THF. The comb. org. fractions were washed twice with brine, dried over $MgSO_4$ and evaporated. Column chromatography (first CH_2Cl_2/MeOH (10+1), then EtOAc/HOAc (95+5)) yielded 16.2 mg (26.4 µmol, 11%) **1b** as a white solid: R_f (CH_2Cl_2/MeOH (10+1)) 0.20; ^{1}H NMR (500 MHz, d_4-MeOH+d_4-HOAc) δ 1.06 (d, 6H, *J* = 6.62 Hz), 1.99 (m, 1H), 2.83 (d, 2H, *J* = 7.25 Hz), 3.03 (t, 2H, *J* = 7.57 Hz), 3.31 (t, 2H, *J* = 7.57 Hz), 4.31 (s, 2H), 4.40 (s, 2H), 5.09 (s, 2H), 7.27 (m, 3H), 7.41 (d, 1H, *J* = 2.21 Hz), 7.45-7.54 (m, 10H), 7.57-7.62 (m, 5H); ^{13}C NMR (100 MHz, d_4-MeOH+d_4-HOAc) δ 20.86, 22.84, 30.58, 31.59, 31.61, 36.67, 39.95, 43.23, 92.03, 112.62, 126.74, 126.80, 126.87, 128.35, 129.28, 129.31, 129.32, 129.74, 130.13, 131.04, 131.14, 131.18, 131.39, 132.69, 135.83, 139.17, 140.21, 140.77, 141.26, 141.47, 142.30, 142.38, 142.94, 176.09, 176.14; LRMS (FAB) *m/z* 658 (16), 635 (19), 331 (16), 329 (38), 309 (15), 297 (13), 193 (10), 179 (14), 177 (100), 155 (48), 154 (14), 153 (26), 152 (23), 135 (52), 121 (18), 119 (100); HRMS (FAB) Calcd. for $C_{41}H_{40}O_5Na$: 635.277345. Found: 635.277200.
Lyophilization of **1b** from NH_4OH led to the corresponding Bisammonia salt:
^{1}H NMR (500 MHz, d_4-MeOH) δ 0.67 (d, 6H, *J* = 6.62 Hz), 1.59 (m, 1H), 2.41 (d, 2H, *J* = 7.41 Hz), 2.46 (t, 2H, *J* = 8.04 Hz), 2.90 (t, 2H, *J* = 8.20 Hz), 3.90 (s, 2H), 4.05 (s, 2H), 4.43 (s, 2H), 6.85-6.91 (m, 3H), 6.94 (d, 1H, *J* = 1.89 Hz), 7.02-7.24 (m, 15H).