Exploring the Structure Activity Relationship of the Ethylamine Portion of 3-Iodothyronamine for the Rat and Mouse Trace Amine Associated Receptor 1

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Materials and Methods

General. ^{1}H and ^{13}C NMR spectra were taken on a Varian 400 (400 MHz and 100 MHz respectively). Data reported are calibrated to internal TMS (0.0 ppm) for all solvents unless otherwise noted and are reported as follows: chemical shift, multiplicity (app = apparent, brd = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet), coupling constant, and integration. High resolution mass spectrometry (HRMS) using electrospray ionization was performed by the Mass Spectrometry Laboratory, School of Chemical Sciences, University of Illinois at Urbana-Champaign. Inert atmosphere operations were conducted under argon passed through a drierite drying tube in flame dried or oven dried glassware unless otherwise noted. Anhydrous THF, DCM, diethyl ether, pyridine, and diisopropyl ethyl amine were filtered through two columns of activated basic alumina and transferred under an atmosphere of argon gas in a solvent purification system designed and manufactured by Seca Solvent Systems. Anhydrous DMF was obtained by passing through two columns of activated molecular sieves. All other anhydrous solvents and reagents were purchased from Aldrich, Sigma-Aldrich, Fluka, Alfa Aesar or Acros and were used without any further purification unless otherwise stated. Final compounds were judged to be >95% pure by ^{1}H NMR analysis and confirmed HPLC. HPLC was performed on an Agilent 1200 Series LC system (using a Waters XTerra® Phenyl 3.5μm (3.0 x 50mm) column) with a gradient of 0-90% acetonitrile (0.1%TFA) over 8 min and 0-100% methanol (0.05% TFA) over 8 or 10 min.

General Procedure for *t*-Boc Protection. For amine hydrochloride or hydrobromide: To a solution of the amine hydrochloride or hydrobromide (4.57 mmol) in THF (33 mL) was added an aqueous solution of sodium bicarbonate (9.14 mmol in 10 mL of water) followed by addition of di-*tert*-butyl dicarbonate (4.57 mmol). After stirring at room temperature overnight, the reaction was quenched with water and extracted with diethyl ether. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product.

For amine: To a solution of amine (9.69 mmol) in THF (33 mL) was added an aqueous solution of $NaHCO_3$ (9.69 mmol in 21 mL of water) followed by addition of di-*tert*-butyl dicarbonate (9.69 mmol). After stirring at room temperature overnight, the reaction was quenched with water and diluted with diethyl ether. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product.

General Procedure for Alkylation of Phenols. To a suspension of sodium hydride (5.36 mmol) in DMF (30 mL) was added a solution of phenol (3.58 mmol) in DMF (5 mL). The reaction was stirred under argon at 0^oC for 15 minutes before adding a solution of alkyl halide (3.58 mmol) in DMF (5 mL). After stirring under argon at room temperature for 2 hrs, the reaction was quenched with water and extracted with diethyl ether. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product.

General Procedure for N-Methylation of *t*-Boc protected Amine. To a suspension of sodium hydride (0.75 mmol) in DMF (6 mL) was added *t*-Boc protected amine (0.60 mmol). The reaction was stirred under argon at 0^oC for 15 minutes before adding iodomethane (1.65 mmol) within 2-3 min. After stirring under argon at room temperature for 2 h, the reaction was quenched with water and extracted with diethyl ether. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product.

General Procedure for Amide Bond formation with an Acid Chloride. To a solution of thionyl chloride (0.97 mmol) and carboxylic acid (0.64 mmol) in dichloromethane (3 mL) was added a drop of DMF. After refluxing for 2 hrs, the reaction was concentrated under reduced pressure to give the acid chloride. A solution of the crude acid chloride (0.64 mmol) in dichloromethane (3 mL) was then added to a solution of amine hydrochloride (0.71 mmol) in pyridine (2 mL). After stirring under argon at room temperature for 2 h, the reaction was quenched with water and extracted with diethyl ether. The

organic layer was washed with brine, dried over MgSO4, filtered and concentrated under reduced pressure to give the crude product.

General Procedure for Amide Bond Formation with an Acid. To a solution of carboxylic acid (1.95 mmol) and HBTU (2.14 mmol) in dichloromethane (20 mL) was added dimethylaminopyridine (0.001 mmol). The solution was stirred under argon at 0^{o}C for 30 minutes before adding the amine hydrochloride (2.14 mmol) and Hunig's base (0.68 mL). The reaction was slowly warmed to room temperature and stirred under argon for 2 hrs. The reaction was diluted with ethyl acetate (40 mL), washed with 5% aqueous HCl (2 x 35 mL), saturated aqueous sodium bicarbonate (35 mL), and brine (35 mL). The organic layer was dried over MgSO4, filtered, and concentrated under reduced pressure to give the crude product.

General Procedure for Formation of Nitrile. A solution of thionyl chloride (10.80 mmol) and dibenzylic alcohol (7.20 mmol) in dichloromethane (2 mL) was stirred at room temperature for 2 h. The reaction was concentrated under reduced pressure to give the dibenzylic chloride. To a solution of the dibenzylic chloride (7.20 mmol) in dichloromethane (33.12 mL) was added trimethylsilyl cyanide (7.20 mmol) and titanium tetrachloride (7.20 mL, 1 M solution in dichloromethane). After stirring under argon at room temperature for 2 h, the reaction was quenched with methanol (13.90 mL) and water (41.62 mL) and diluted with dichloromethane (104 mL). The organic layer was washed with saturated, aqueous sodium bicarbonate (68.25 mL) and water (68.25 mL), dried over MgSO4, filtered and concentrated under reduced pressure to give the crude product.

General Procedure for Biaryl Ether Coupling. To a solution of phenol (1.37 mmol), phenyl boronic acid (2.75 mmol), copper (II) acetate (1.37 mmol) and dried 4Å molecular sieves (2.34 g) in dichloromethane (13.77 mL) was added pyridine (0.56 mL) and Hunig's base (1.20 mL). After stirring under dry air atmosphere at room temperature for 24 h, the reaction was filtered through celite and

silica gel, rinsed with ethyl acetate and washed with 0.5 M HCl, water and brine. The organic layer was dried over MgSO4, filtered, and concentrated under reduced pressure to give the crude product.

General Procedure for Nitrile Reduction and Subsequent *t*-Boc Protection of Amine. To a suspension of $LiAlH_4$ (195 mg, 5.1 mmol) in THF (10 mL) at 0°C was added aluminum chloride (682 mg, 5.1 mmol) in THF (5 mL). After stirring for 10 minutes at 0°C, a solution of nitrile (620 mg, 2.1 mmol) in THF (1 mL) was added, and the mixture was allowed to stir for 1 h at ambient temperature before quenching with water. The reaction mixture was then diluted with ether and filtered through celite. The filtrate was sequentially washed with brine, dried over $MgSO_4$, and concentrated in vacuo. To a stirred solution of the crude mixture in THF (5 mL) were added di-*tert*-butyl dicarbonate (492 mg, 2.3mmol) and an aqueous solution of potassium carbonate (190 mg in 2.5mL, 2.3 mmol). After overnight stirring, the reaction mixture was diluted with ether, washed with 1N HCl, water, brine, dried over $MgSO_4$ and concentrated to give the crude product.

General Procedure for *t*-Butyldimethylsilyl or Triisopropylsilyl deprotection. To a stirred solution of *t*-butyldimethylsilyl protected phenol (155mg, 0.41 mmol) in THF (4 mL) cooled to 0°C was added dropwise TBAF (0.45 mL, 1M in THF, 0.45 mmol). The reaction mixture was stirred for 1 h at 0°C and then diluted with diethyl ether. The mixture was washed with water, brine, dried over $MgSO_4$, and concentrated under reduced pressure.

General Procedure for Acetal Deprotection and Subsequent Decarboxylation. To a solution of acetal (700 mg, 1.64 mmol) in dioxane (15 mL) was added 3N HCl (1 mL) and water (0.5 mL). After stirring at 100 °C for 2 h, the reaction was cooled to ambient temperature, diluted with ether, washed with water, brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was dissolved in dimethylacetamide (5 mL) and stirred at 135 °C for 1 h. After cooling to ambient temperature, the reaction was diluted with ether, washed with water, brine and dried over $MgSO_4$.

N-*t*-Boc-3-bromopropylamine (29). Refer to general procedure for *t*-Boc protection described above. The crude product was purified via flash SiO_2 chromatography (ethyl acetate/hexanes (10%/90%) to (15%/85%)) to give **29** as a white solid (0.85 g, 78% yield). ^{1}H-NMR (400 MHz, chloroform-*d*) δ 4.65 (s, 1 H), 3.44 (t, *J*=6.6 Hz, 2 H), 3.28 (q, *J*=6.4 Hz, 2H), 2.05 (m, 2 H), 1.46 (s, 9 H).

N-*t*-Boc-3-(4-phenoxyphenol)-propylamine (32). Refer to general procedure for alkylation of phenols described above. The crude product was purified via flash SiO_2 chromatography (ethyl acetate/hexanes (5%/95%) to (15%/85%)) to give **32** (1.02 g, 83% yield). ^{1}H-NMR (400 MHz, chloroform-*d*) δ 7.29 (app t, *J*=8.0 Hz, 2 H), 7.04 (t, *J*=7.6 Hz, 1 H), 6.95 (m, 4 H), 6.87 (app d, *J*=9.2 Hz, 2 H), 4.76 (brd s, 1 H), 4.01 (t, *J*=6.4 Hz, 2 H), 3.34 (brd q, *J*=6.0 Hz, 2 H), 1.98 (t, *J*=6.2 Hz, 2 H), 1.45 (s, 9 H)

N-*t*-Boc-3-(3-phenoxyphenol)-propylamine (33). Refer to general procedure for alkylation of phenols described above. The crude product was purified via flash SiO_2 chromatography (ethyl acetate/hexanes (5%/95%) to (15%/85%)) to give **33** (2.55 g, 91% yield). ^{1}H-NMR (400 MHz, chloroform-*d*) δ 7.34 (t, *J*=7.8 Hz, 2 H), 7.21 (t, *J*=8.2 Hz, 1 H), 7.11 (t, *J*=6.8 Hz, 1 H), 7.02 (d, *J*=8.4 Hz, 2 H), 6.62 (d, J=8.0 Hz, 1 H), 6.58 (d, *J*=8.0 Hz, 1 H), 6.55 (s, 1 H), 4.73 (brd s,1 H), 3.98 (t, *J*=6.0 Hz, 2 H), 3.30 (brd q, *J*=6.8 Hz, 2 H), 1.95 (t, *J*=6.2 Hz, 2 H), 1.43 (s, 9H)

N-methyl, N-*t*-Boc-3-(4-phenoxyphenol)-propylamine (34). Refer to general procedure for N-methylation of *t*-Boc protected amine described above. The crude product was purified via flash SiO_2 chromatography (ethyl acetate/hexanes (5%/95%) to (15%/85%)) to give **34** (0.21 g, 62% yield). ^{1}H-NMR (400 MHz, chloroform-*d*) δ 7.29(t, *J*=8.0 Hz, 2 H), 7.04 (t, *J*=6.8 Hz, 1 H), 6.96 (d, *J*=9.2 Hz, 2 H), 6.93 (d, *J*=8.4 Hz, 2 H), 6.86 (d, J=8.8 Hz, 2 H), 3.96 (t, *J*=6.2 Hz, 2 H), 3.41 (t, *J*=7.0 Hz, 2 H), 2.88 (s, 3 H), 2.00 (brd t, *J*=3.0 Hz, 2 H), 1.44 (s, 9 H).

N-*t*-Boc-2-(4-phenoxybenzamido)-ethylamine (40). Refer to general procedure for amide bond formation with an acid chloride described above. The crude product was purified via flash SiO_2 chromatography (ethyl acetate/hexanes (10%/90%) to (50%/50%)) to give **40** (0.30 g, 90% yield). ^{1}H-NMR (400 MHz, chloroform-*d*) δ 7.75 (d, *J*=8.8 Hz, 2 H), 7.34 (t, *J*=8.0 Hz, 2 H), 7.12 (t, *J*=7.4, 1 H), 6.98 (d, *J*=7.6 Hz, 2 H), 6.92 (d, *J*=8.8 Hz, 2 H), 3.37 (t, *J*=6.0, 2 H), 3.20 (t, *J*=6.0 Hz, 2 H), 1.35 (s, *3* H).

N-*t*-Boc-3-(4-phenoxybenzamido)-propylamine (41). Refer to general procedure for amide bond formation with an acid described above. The crude product was purified via flash SiO_2 chromatography (ethyl acetate/hexanes (10%/90%) to (50%/50%)) to give **41** (0.61 g, 64% yield). ^{1}H-NMR (400 MHz, chloroform-*d*) δ 7.83 (d, *J*=8.0 Hz, 2 H), 7.37 (t, *J*=7.8 Hz, 2 H), 7.17 (t, *J*=6.8, 1 H), 7.05 (d, *J*=8.0 Hz, 2 H), 7.01 (d, *J*=8.8 Hz, 2 H), 4.87 (brd s, 1 H), 3.50 (q, *J*=6.1 Hz, 2 H), 3.25 (q, *J*=5.2 Hz, 2 H), 1.72 (m, 2 H), 1.55 (s, 9 H).

N-*t*-Boc-4-(4-phenoxybenzamido)-butylamine (42). Refer to general procedure for amide bond formation with an acid chloride described above. The crude product was purified via flash SiO_2 chromatography (ethyl acetate/hexanes (20%/90%) to (50%/50%)) to give **42** (0.35 g, 71% yield). ^{1}H-NMR (400 MHz, chloroform-*d*) δ 7.77 (d, *J*=8.4 Hz, 2 H), 7.37 (t, *J*=8.0 Hz, 2 H), 7.17 (t, *J*=7.4, 1 H), 7.04 (d, *J*=7.6 Hz, 2 H), 7.00 (d, *J*=8.8 Hz, 2 H), 6.42 (brd s, 1 H), 4.63 (brd s, 1 H), 3.48 (q, *J*=6.2 Hz, 2 H), 3.17 (app q, *J*=6.4 Hz, 2 H), 1.64 (m, 4 H), 1.44 (s, 9 H).

N-*t*-Boc-5-(4-phenoxybenzamido)-pentylamine (43). Refer to general procedure for amide bond formation with an acid described above. The crude product was purified via flash SiO_2 chromatography (ethyl acetate/hexanes (25%/90%) to (50%/50%)) to give **43** (0.78 g, 77% yield). ^{1}H-NMR (400 MHz, chloroform-*d*) δ 7.74 (d, *J*=8.8 Hz, 2 H), 7.37 (t, *J*=8.0 Hz, 2 H), 7.17 (t, *J*=7.6, 1 H), 7.04 (d, *J*=8.0 Hz, 2 H), 7.00 (d, *J*=8.8 Hz, 2 H), 6.14 (brd s, 1 H), 4.57 (brd s, 1 H), 3.45 (q, *J*=6.5 Hz, 2 H), 3.13 (app q, *J*=6.4 Hz, 2 H), 1.63 (m, 2 H), 1.52 (m, 4 H), 1.44 (s, 9 H).

4-Phenoxyphenyl-phenylmethanol (46). To a solution of 4-bromodiphenyl ether (2.0 g, 8.03 mmol) in THF (15 mL) at -78^{o}C was added *n*-butyllithium (3.85 mL, 2.6 M solution in hexanes). The reaction was stirred under argon for 2 h before a solution of benzaldehyde (0.85 g, 8.03 mmol) in THF at -78 ^{o}C was added. After stirring at 78^{o}C for 2 h, the reaction was quenched with water and extracted with ether. The organic layer was washed with brine, dried over MgSO4, filtered, and concentrated under reduced pressure to give the crude product. The crude mixture was purified via flash SiO_2 chromatography (ethyl acetate/hexanes (10%/90%) to (15%/85%)) to give **46** (2.22 g, 97% yield). ^{1}H-NMR (400 MHz, chloroform-*d*) δ 7.28-7.40 (m, 9 H), 7.10 (t, *J*=7.6, 1 H), 6.94-7.01 (m, 4 H), 5.84 (d, *J*=3.6 Hz, 1 H), 2.17 (d, *J*=3.6 Hz, 1 H).

3-Phenoxyphenyl-phenylmethanol (47). To a solution of 3-phenoxybenzaldehyde (2 g, 10.09 mmol) in THF (15 mL) at -78^{o}C was added dropwise phenyllithium (6.73 mL, 1.8M solution in cyclohexane-ether). After stirring under argon at -78^{o}C for 4 h, the reaction was quenched with water and extracted with diethyl ether. The organic layer was washed with brine, dried with MgSO4, filtered, and concentrated under reduced pressure to give the crude product. The crude mixture was purified via flash SiO_2 chromatography (ethyl acetate/hexanes (10%/90%) to (20%/80%)) to give **47** (2.79 g, 86% yield). ^{1}H-NMR (400 MHz, chloroform-*d*) δ 6.87-7.38 (m, 10 H), 7.09 (m, 1 H), 6.99 (app d, *J*=7.3 Hz, 1 H), 6.88 (m, *J*=8.6, 2.2 Hz, 1 H), 5.81 (s, 4 H).

2-(4-Phenoxyphenyl)-2-phenylacetonitrile (48). Refer to general procedure for formation of nitrile described above. The crude mixture was purified via flash SiO_2 chromatography (ethyl acetate/hexanes 5%/95%) to (10%/90%)) to give **48** (0.49 g, 90% yield). ^{1}H-NMR (400 MHz, chloroform-*d*) δ 7.25-7.40 (m, 9 H), 7.13 (t, *J*=7.4, 1 H), 6.99 (m, 4 H), 5.12 (s, 1 H).

2-(3-Phenoxyphenyl)-2-phenylacetonitrile (49). Refer to general procedure for formation of nitrile described above. The crude mixture of **49** (2.45 g, 98% yield) was not purified. ^{1}H-NMR (400 MHz,

chloroform-*d*) δ 7.27-7.42 (m, 10 H), 7.13 (app t, *J*=6.4 Hz, 1 H), 7.01 (app d, *J*=8.8 Hz, 1 H), 6.90 (m, 1 H), 6.08 (s, 1 H).

2-(3-Methoxyphenethylamino)-1-phenylethanol (51). A solution of 3-methoxyphenethylamine (2g, 13.23 mmol) and styrene oxide (1.539 g, 13.23 mmol) was heated @ 90-95^{o}C for 16 h. The hot reaction mixture was added to a 25% EtOAc/75% Hexanes and a fluffy precipitate formed. The solid filtered and washed with 25% ethyl acetate/75% hexanes to give **51** (31.30 g, 36% yield). ^{1}H-NMR (400 MHz, chloroform-*d*) δ 7.35 (m, 3 H), 7.32 (m, 1 H), 7.27 (m, 1 H), 7.22 (t, J=8.0 Hz, 1H), 6.79 (d, J=7.3 Hz, 1 H), 6.76 (m, 2 H), 4.67 (dd, J=9.0, 3.7 Hz, 1 H), 3.80 (s, 3 H), 2.90 (m, 3 H), 2.78 (m, 2 H), 2.70 (m, 1H).

7-Hydroxy-1-phenyl-2,3,4,5-tetrahydro-3-benzazepine hydrochloride (55). To a solution of **51** (1.30 g, 4.79 mmol) in trifluoroacetic acid (14.38 mL) was added dropwise sulfuric acid (0.36 mL, 7.19 mmol). The reaction was refluxed for ~3 h. After evaporating the trifluoroacetic acid under reduced pressure, the resulting crude mixture was poured into ~100 mL of ice cold water. The solution was made alkaline with 40% NaOH and extracted with EtOAc. The organic layers were washed with brine, dried over MgSO4, filtered and concentrated under reduced pressure to give a crude mixture of benzazepine **53** and an unknown product (0.91 g). To a solution of the crude mixture in dry $CHCl_3$ (30 mL) @ 0^{o}C was added BBr_3 (9.99 mL, 1.0 M solution in DCM). After stirring for 1 h at room temperature, the reaction was cooled to 0^{o}C and anhydrous MeOH (28.5 mL) was added. The reaction was refluxed in an open mouth flashed for 20 min before evaporating the solvent. The crude mixture was diluted with EtOAc and made alkaline with K_2CO_3. The organic layer was washed with water and brine, dried over MgSO4, filtered, and concentrated under reduced pressure. Treatment with 3N anhydrous HCl in ethyl acetate and exposure to diethyl ether precipitated the hydrochloride salts of **55** (0.35 g, 40%). (400 MHz, methanol-d_4) δ 7.41 (t, J=7.3 Hz, 2 H), 7.33 (t, J=7.3 Hz, 1 H), 7.20 (d, J=7.3 Hz, 2 H), 6.73 (d, J=2.4 Hz, 1 H), 6.61 (d, J=8.3 Hz, 1H), 6.57 (dd, J=8.8, 2.44 Hz, 1 H), 4.56

(dd, J=8.8, 2.0 Hz, 1 H), 3.77 (m, 1 H), 3.63 (dd, J=13.4, 2.2 Hz, 1 H), 3.42 (m, 1 H), 3.19 (m, 2 H), 3.03 (m, 1 H).

N-*t*-Boc-8-hydroxy-1-phenyl-2,3,4,5-tetrahydro-3-benzazepine (56). Refer to general procedure for *t*-Boc protection of amine hydrochloride described above. The crude mixture was purified via flash SiO_2 column chromatography (ethyl acetate/hexanes (20%/80%)) to give **56** (0.76 g, 61% yield). ^{1}H-NMR (400 MHz, chloroform-*d*) δ 7.28 (m, 2 H), 7.21 (s, 1 H), 7.11 (app d, *J*=8.0 Hz, 2 H), 7.02 (d, *J*=8.4 Hz, 1 H), 6.63 (app d, *J*=9.6 Hz, 1 H), 6.40 (s, 1 H), 4.63 (brd s, 1 H), 3.61 (app q, *J*=10.0 Hz, 2 H), 3.02 (m, 2 H), 3.02 (m, 2 H), 2.83 (brd m, 2 H), 1.36 (s, 9 H).

N-*t*-Boc-7-hydroxy-1-phenyl-2,3,4,5-tetrahydro-3-benzazepine (57). Refer to general procedure for *t*-Boc protection of amine hydrochloride described above. The crude mixture was purified via flash SiO_2 column chromatography (ethyl acetate/hexanes (10%/90%) to (25%/75%)) to give **57** (0.41 g, 81% yield). ^{1}H-NMR (400 MHz, methanol-d_4) δ 7.27 (t, *J*=7.3, 2 H), 7.18 (t, J=7.3, 1 H), 7.10 (app t, *J*=9.3 Hz, 2 H), 6.75 (d, *J*=8.8 Hz, 1 H), 6.63 (s, 1 H), 6.54 (d, *J*=8.3 Hz, 1 H), 4.38 (brd s, 1 H), 3.83 (m, 2 H), 3.04 (m, 2 H), 2.80 (m, 2 H), 1.36 (s, 9 H).

N-*t*-Boc-8-phenoxy-1-phenyl-2,3,4,5-tetrahydro-3-benzazepine (58). Refer to general procedure for biaryl ether coupling described above. The crude mixture was purified via flash SiO_2 column chromatography (ethyl acetate/hexanes (20%/80%)) to give **58** (0.57 g, 100% yield). ^{1}H-NMR (400 MHz, chloroform-*d*) δ 7.37 (t, *J*=7.8 Hz, 4 H), 7.32 (d, *J*=7.3 Hz, 1 H), 7.10 (m, 4 H), 7.05 (t, *J*=7.3 Hz, 1 H), 6.92 (d, *J*=8.3 Hz, 1 H), 6.78 (dd, *J*=8.1, 2.7 Hz, 1 H), 6.66 (d, *J*=2.4 Hz, 1 H), 4.40 (brd d, *J*=35.2 Hz, 1 H), 3.90 (brd m, 2 H), 3.62 (brd m, 2 H), 2.95 (brd m, 2 H).

N-*t*-Boc-7-phenoxy-1-phenyl-2,3,4,5-tetrahydro-3-benzazepine (59). Refer general procedure for biaryl ether coupling described above. The crude mixture was purified via flash SiO_2 column chromatography (ethyl acetate/hexanes (0%/100%) to (5%/95%)) to give **59** (0.12 g, 94% yield). ^{1}H-NMR (400 MHz, chloroform-*d*) δ 7.26-7.35 (m, 4 H), 7.22 (app t, *J*= 8.4 Hz, 1 H), 7.12 (m, 4 H), 7.01

(d, *J*=7.6 Hz, 1 H), 6.88 (d, *J*=8.4 Hz, 1 H), 6.83 (d, *J*=2.4 Hz, 1 H), 6.74 (dd, *J*=8.4 Hz, 1 H), 4.41 (brd m, 1 H), 4.79 (brd d, *J*=36.4 Hz, 2 H), 3.62 (brd s, 2 H), 2.92 (brd m, 2 H).

2-(4-*tert*-Butyldimethylsilyloxyphenyl)acetonitrile (61). To a stirred solution of 4-hydroxybenzyl cyanide (2.0 g, 15.0 mmol) in DCM (10mL) was added *t*-butyldimethylsilyl chloride (2.5 g, 16.5 mmol). The reaction mixture was cooled to 0 ºC and imidazole (2.3 g, 33.0 mmol) was added. After warming to ambient temperature and stirring for 3 h, the reaction mixture was diluted with diethyl ether. The organic layer was washed with 0.5 M HCl, saturated aqueous $NaHCO_3$, water, brine, dried over MgSO4, filtered and concentrated under reduced pressure. The crude product was purified via flash SiO_2 chromatography (eluted with hexane/ethyl acetate (8:1)) to give **61** as a clear oil (3.6 g, 98% yield). ^{1}H-NMR (400 MHz, chloroform-*d*) δ 7.87 (d, *J* = 8.5 Hz, 2 H), 6.86 (d, *J* = 8.5 Hz, 2 H), 3.54 (s, 2 H), 0.98 (s, 9 H), 0.23 (s, 6 H).

2-(4-Triisopropylsilyloxyphenyl)acetonitrile (62). To a stirred solution of 4-hydroxybenzyl cyanide (1.3 g, 10 mmol) in DCM (5 mL) was added triisopropylsilyl chloride (2.1 mL, 10 mmol). The reaction mixture was cooled to 0 ºC and imidazole (1.7g, 25 mmol) was added. The mixture was stirred at 0 ºC for 30 minutes and then allowed to warm to ambient temperature over 24 hours. The reaction mixture was diluted with diethyl ether, washed with 1 N HCl, saturated aqueous $NaHCO_3$, brine, dried over MgSO4, filtered and concentrated under reduced pressure. The crude product was purified via flash SiO_2 chromatography (eluted with hexane/ethyl acetate (20:1)) to give **62** as a slightly yellow oil (2.4 g, 84 % yield). ^{1}H-NMR (400 MHz, chloroform-*d*) δ 7.16 (d, *J* = 8.4 Hz, 2 H), 6.87 (d, *J* = 8.4 Hz, 2 H), 3.67 (s, 2 H), 1.25 (m, 3 H), 1.10 (d, *J* = 8.4 Hz, 18 H); HRMS (EI+) for $C_{17}H_{27}NOSi$ calcd. 289.1862 found 298.1859.

2-(4- *tert*-Butyldimethylsilyloxyphenyl)-2-methylpropanenitrile (63). To a solution of 2-(4-*tert*-butyldimethylsilyloxyphenyl)acetonitrile (**61**) (1.2 g, 5.0 mmol) in THF (10 mL) at -78 ºC was added dropwise LDA (2.75 mL, 2.0 M in heptane, THF, and ethylbenzene, 5.5 mmol). Iodomethane (0.37 mL,

6.0 mmol) was added dropwise and the mixture was stirred at -78 ºC for 30 minutes. After stirring at room temperature for 4h, the reaction was cooled to -78 ºC and LDA (2.75 mL, 2.0 M in heptane, THF, and ethylbenzene, 5.5 mmol) was added dropwise. Iodomethane (0.37 mL, 6.0 mmol) was added to the reaction dropwise and the mixture was stirred at -78 ºC for 30 minutes then allowed to warm to ambient temperature over 16 hours. The reaction mixture was diluted with ether and washed with 0.5 M HCl. The aqueous layer was extracted with ether and the combined organic layers were sequentially washed with water, brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified via flash SiO_2 chromatography (eluted with hexane/ethyl acetate (20:1)) to give **63** as a slightly yellow oil (1.3 g, 91% yield). ^{1}H-NMR (400 MHz, chloroform-*d*) δ 7.31 (d, *J* = 8.3 Hz, 2 H), 6.83 (d, *J* = 8.3 Hz, 2 H), 1.69 (s, 6 H), 0.98 (s, 9 H), 0.20 (s, 6 H).

2-(4-Triisopropylsilylphenyl)propanenitrile (64). To a solution of 2-(4-triisopropylsilyloxyphenyl)acetonitrile **(62)** (1.0 g, 3.5 mmol) in THF (30 ml) at -78 ºC was added dropwise LDA (2.9 mL, 1.8 M in heptane, THF, and ethylbenzene, 5.2 mmol). Iodomethane (0.24 mL, 3.8 mmol) was added dropwise to the reaction and the mixture was stirred at -78 ºC for 1 h. The reaction was diluted with ether and washed with 0.5 M HCl. The aqueous layer was extracted with ether and the combined organic layers were sequentially washed with water, and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified via flash SiO_2 chromatography (eluted with hexane/ethyl acetate (20:1)) to give **64** as a slightly yellow oil (930 mg, 89% yield). ^{1}H-NMR (400 MHz, chloroform-*d) δ* 7.16 (d, *J* = 8.8 Hz, 2 H), 6.83 (d, *J* = 8.8 Hz, 2 H), 3.82 (m,1 H), 1.63 (d, *J* = 7.3 Hz, 3 H), 1.26 (m, 1 H), 1.07 (d, *J* = 7.2 Hz, 18 H).

2-(4-Triisopropylsilylphenyl)-3-phenylpropanenitrile (65). To a solution of 2-(4-triisopropylsilyloxyphenyl)acetonitrile **(62)** (1.0 g, 3.5 mmol) in THF (30 ml) at -78 ºC was added dropwise LDA (2.9 mL, 1.8 M in heptane, THF, and ethylbenzene, 5.2 mmol). Benzyl bromide (0.45 mL, 3.8 mmol) was added dropwise to the reaction and it was stirred at -78 ºC for 1 h. The reaction

mixture was diluted with ether and washed with 0.5 M HCl. The aqueous layer was extracted with ether and the combined organic layers were washed with water, brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified via flash SiO_2 (eluted with ether/ethyl acetate (20:1)) to give **65** as a slightly yellow oil (985 mg, 75% yield). ^{1}H-NMR (400 MHz, chloroform-*d*) δ 7.26 (m, 4 H), 7.09 (m, 1 H), 7.06 (d, *J* = 8.4 Hz, 2 H), 6.83 (d, *J* = 8.4 Hz, 2 H), 3.93 (m, 1H), 3.17 (m, 1 H), 3.09 (m, 1 H), 1.24 (m, 1 H), 1.09 (d, *J* = 7.1 Hz, 12 H).

***tert*-Butyl 2-(4- *tert*-butyldimethylsilyloxyphenyl)-2-methylpropylcarbamate (66)** To a solution of 2-(4- *tert*-butyldimethylsilyloxyphenyl)-2-methylpropanenitrile (**63**) (1.0 g, 3.6 mmol) in THF (15 mL) at 0 ºC was added lithium aluminum hydride (207 mg, 5.5 mmol). The mixture was stirred at 0 ºC for 15 minutes and then refluxed for 2 h. The resulting solution was cooled to 0 ºC, quenched with 2 M NaOH and stirred for 15 minutes at 0 ºC. The crude mixture was filtered through celite and the filtrate was washed with brine, dried over $MgSO_4$, and concentrated to dryness. The crude mixture was dissolved in THF (10 mL) and it was added to a solution of $NaHCO_3$ (337 mg, 4.0 mmol) in water (5 ml) and di-*t*-butyldicarbonate (865 mg, 4.0 mmol). After stirring for 15 h, the reaction mixture was diluted with ether and washed with 0.5 M HCl. The aqueous layer was extracted with ether and the combined organic layers were sequentially washed with water, brine, dried over $MgSO_4$ and concentrated to dryness. The crude product was purified via flash SiO_2 (eluted with hexane/ethyl acetate (30:1)) to give **66** as a slightly yellow solid (627 mg, 46% yield). ^{1}H-NMR (400 MHz, chloroform-*d*) δ 7.33 (d, *J* = 8.4 Hz, 2 H), 6.85 (d, *J* = 8.4 Hz, 2 H), 3.28(s, 2H), 1.69 (s, 6 H), 1.41 (s, 9 H), 0.98 (s, 9 H), 0.20 (s, 6 H).

***tert*-Butyl 2-(4-triisopropylsilyloxyphenyl)propylcarbamate (67).** Refer to general procedure for nitrile reduction and subsequent *t*-Boc protection of amine described above. The crude product was purified via flash SiO_2 chromatography (eluted with hexane/ethyl acetate (10:1)) to give the pure product **67** as a slightly yellow solid (720 mg, 86 % yield). ^{1}H-NMR (400 MHz, chloroform-*d*) δ 7.03

(d, *J* = 8.1 Hz, 2 H), 6.82 (d, *J* = 8.1 Hz, 2 H), 4.38 (s, 1 H), 3.36 (m, 1 H), 3.12 (m, 1 H), 2.85 (m,1 H), 1.41 (s, 9H), 1.27 (m, 1 H), 1.22 (d, *J* = 7.0 Hz, 3 H),1.10 (s, *J* = 7.2 Hz,18 H).

***tert*-Butyl 2-(4-triisopropylsilyloxyphenyl)-3-phenylpropylcarbamate (68).** Refer to general procedure for nitrile reduction and subsequent *t*-Boc protection of amine described above. The crude product was purified via SiO_2 flash chromatography (eluted with hexane/ethyl acetate (15:1)) to give the pure product **68** as a slightly yellow solid (350 mg, 68 % yield). ^{1}H-NMR (400 MHz, chloroform-*d*) δ 7.14 (m, 4 H), 6.96 (d, *J* = 6.8 Hz, 1 H), 6.93 (d, *J* = 8.6 Hz, 2 H), 6.79 (d, *J* = 8.6 Hz, 2 H), 4.13 (s, 1 H), 3.55 (m, 1 H), 3.21 (m, 1 H), 2.96 (m, 1 H), 2.91 (m, 1 H), 2.79 (m, 1 H), 1.38 (s, 9 H), 1.21 (m, 1 H), 1.08 (d, *J* = 6.6 Hz, 12 H).

***tert*-Butyl 2-(4-hydroxyphenyl)-2-methylpropylcarbamate (69).** Refer to general procedure for *t*-butyldimethylsilyl deprotection described above. The crude product was purified via flash SiO_2 chromatography (eluted with hexane/ethyl acetate (10:1)) to give **69** as a white solid (107 mg, 98% yield). ^{1}H-NMR (400 MHz, chloroform-*d*) δ 6.97 (d, *J* = 8.4 Hz, 2 H), 6.77 (d, *J* = 8.4 Hz, 2 H), 3.25 (s, 2 H), 1.71 (s, 6 H), 1.44 (s, 9 H).

***tert*-Butyl 2-(4-hydroxyphenyl)propylcarbamate (70)**. Refer to general procedure for triisopropylsilyl deprotection described above. The crude product was purified via flash SiO_2 chromatography (eluted with hexane/ethyl acetate (5:1)) to give **70** as a white solid (405 mg, 91% yield). ^{1}H-NMR (400 MHz, chloroform-*d*) δ 7.06 (d, *J* = 8.2 Hz, 2 H), 6.79 (d, *J* = 8.2 Hz, 2 H), 4.45 (s, 1 H), 3.35 (m, 1 H), 3.14 (m, 1 H), 2.86 (m,1 H), 1.43 (s, 9H), 1.22 (d, *J* = 7.1 Hz, 3 H).

***tert*-Butyl 2-(4-hydroxyphenyl)-3-phenylpropylcarbamate (71).** Refer to general procedure for triisopropylsilyl deprotection described above. The crude product was purified via flash SiO_2 chromatography (eluted with hexane/ethyl acetate (4:1)) to give **71** as a white solid (215 mg, 91% yield). ^{1}H-NMR (400 MHz, chloroform-*d*) δ 7.18 (m, 2 H), 7.13 (d, *J* = 7.0 Hz, 1 H), 7.01 (d, *J* = 7.1

Hz, 2 H), 6.96 (d, *J* = 8.4 Hz, 2 H), 6.74 (d, *J* = 8.4 Hz, 2 H), 5.42 (s, 1 H), 4.38 (s, 2 H), 3.51 (m, 1 H), 3.22 (m, 1 H), 2.98 (m, 1 H), 2.91 (m, 1H), 2.82 (m, 1H), 1.39 (s, 9H).

***tert*-Butyl 2-methyl-2-(4-phenoxyphenyl)propylcarbamate (72).** Refer to general procedure for biaryl ether formation described above. The crude product was purified via SiO_2 flash chromatography (eluted with hexane/ethyl acetate (4:1)) to give **72** as a slightly yellow solid (63 mg, 46% yield). ^{1}H-NMR (400 MHz, chloroform-*d*) δ 7.32 (app t, *J* = 8.2 Hz, 2 H), 7.19 (d, *J* = 8.4 Hz, 2 H), 7.10 (app t, *J* = 8.2 Hz, 1 H), 6.97 (d, *J* = 8.2 Hz, 2 H), 6.89 (app d, *J* = 8.2 Hz, 2 H), 4.60 (brd s, 1H), 3.27 (s, 2 H), 1.70 (s, 6 H), 1.34 (s, 9 H).

***tert*-Butyl 2-(4-phenoxyphenyl)propylcarbamate (73).** Refer to general procedure for biaryl ether formation described above. The crude product was purified via SiO_2 flash chromatography (eluted with hexane/ethyl acetate (10:1)) to give **73** as a slightly yellow solid (130 mg, 41% yield). ^{1}H-NMR (400 MHz, chloroform-*d*) δ 7.33 (app t, *J* = 8.2 Hz, 2 H), 7.16 (d, *J* = 7.0 Hz, 2 H), 7.10 (app t, *J* = 8.2 Hz, 1 H), 7.01 (d, *J* = 8.2 Hz, 2 H), 6.96 (d, *J* = 8.2 Hz, 2 H), 4.45 (brd s, 1H), 3.39 (m, 1 H), 3.18 (m, 1 H), 2.91 (m, 1 H), 1.43 (s, 9 H), 1.26 (d, *J* = 7.0 Hz, 3 H).

***tert*-Butyl 2-(4-phenoxyphenyl)-3-phenylpropylcarbamate (74).** Refer to general procedure for biaryl ether formation described above. The crude product was purified via SiO_2 flash chromatography (eluted with hexane/ethyl acetate (10:1)) to give **74** as a slightly yellow solid (95 mg, 37 % yield). ^{1}H-NMR (400 MHz, chloroform-*d*) δ 7.33 (m, 2 H), 7.20 (d, *J* = 7.3 Hz, 2 H), 7.15 (d, *J* = 7.0 Hz, 2 H), 7.11 (m, 1 H), 7.08 (d, *J* = 8.4 Hz, 2 H), 7.03 (d, *J* = 6.8 Hz, 2 H), 6.98 (d, *J* = 7.9 Hz, 2 H), 6.93 (d, *J* = 8.2 Hz, 2 H), 4.38 (s, 1 H), 3.55 (m, 1 H), 3.26 (m, 1 H), 3.05 (m, 1 H), 2.94 (m, 1H), 2.85 (m, 1H), 1.40 (s, 9 H).

5-(4-Phenoxybenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (76). To a solution of 4-phenoxybenzaldehyde (3.9 g, 20 mmol) in benzene (50 mL) was added 2,2-dimethyl-1,3-dioxane-4,6-dione (2.9 g, 20 mmol), piperidine (35 mg, 0.4 mmol), and acetic acid (0.17 mL, 2.9 mmol). The

reaction was refluxed for 2 h using a Dean-Stark. After cooling to ambient temperature, the reaction mixture was diluted with ethyl acetate and sequentially washed with water, brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified via SiO_2 flash chromatography (eluted with hexane/ethyl acetate (4:1)) to give the pure product **76** as a yellow solid (4.6 g, 70 % yield). ^{1}H-NMR (400 MHz, chloroform-*d*) δ 8.39 (s, 1 H), 8.18 (d, *J* = 9.2 Hz, 2 H), 7.43 (m, 2 H), 7.23 (d, *J* = 6.4 Hz, 2 H), 7.10 (d, *J* = 7.5 Hz, 2 H), 7.01 (d, *J* = 8.8 Hz, 2 H), 1.79 (s, 6 H).

2,2-Dimethyl-5-(1-(4-phenoxyphenyl)-3-phenylprop-2-ynyl)-1,3-dioxane-4,6-dione (77). To a solution of 5-(4-phenoxybenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**76**) (800 mg, 2.5 mmol) in THF (20 mL) at -78 ºC was added lithium phenylacetylide (3.0 mL, 1.0 M in THF, and 3.0 mmol) and the mixture was stirred at -78 ºC for 1 h. The reaction mixture was diluted with diethyl ether and washed with 0.5 M HCl. The aqueous layer was extracted with diethyl ether and the combined organic layers were sequentially washed with water, brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified via flash SiO_2 (eluted with hexane/ethyl acetate (3:2)) to give the pure product **77** as a white solid (810 mg, 77 % yield). ^{1}H-NMR (400 MHz, chloroform-*d*) δ 7.58 (d, *J* = 8.8 Hz, 2 H), 7.47 (m, 2 H), 7.32 (m, 5 H), 7.11 (t, *J* = 7.1 Hz, 2 H), 7.01 (d, *J* = 8.6 Hz, 2 H), 6.98 (d, *J* = 8.6 Hz, 2 H), 5.14 (d, *J* = 2.6 Hz, 1 H), 3.98 (d, *J* = 2.6 Hz, 1 H), 1.76 (s, 3 H), 1.66 (s, 3 H).

2,2-Dimethyl-5-(3-(trimethylsilyl)-1-(4-phenoxyphenyl)prop-2-ynyl)-1,3-dioxane-4,6-dione (78). To a solution of ethynyltrimethylsilane (0.4 mL, 2.29 mmol) in THF (20 mL) in -78 ºC was added butyl lithium (1.2 mL, 2.5 M in hexane, 3.0 mmol) and stirred for 30 minutes. 5-(4-phenoxybenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**76**) (800 mg, 2.5 mmol) in THF (5 mL) was then added and the reaction mixture was allowed to stir for 1 h. The reaction mixture was diluted with diethyl ether and washed with water, brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified via flash SiO_2 (eluted with hexane/ethyl acetate (3:2)) to give the pure product **78**

as a white solid (790 mg, 76 % yield). ^{1}H-NMR (400 MHz, chloroform-*d*) δ 7.49 (d, *J* = 9.0 Hz, 2 H), 7.34 (t, *J* = 7.6 Hz, 2 H), 7.32 (m, 5 H), 7.11 (t, *J* = 7.4 Hz, 2 H), 7.01 (d, *J* = 8.8 Hz, 2 H), 4.94 (d, *J* = 2.6 Hz, 1 H), 1.74 (s, 3 H), 1.67 (s, 3 H), 0.19 (s, 9 H).

3-(4-Phenoxyphenyl)-5-phenylpent-4-ynoic acid (79). Refer to general procedure for acetal deprotection and subsequent decarboxylation. The crude product was purified via flash SiO_2 chromatography (eluted with ethyl acetate) to give the pure product **79** as a yellow solid (577 mg, 98 % yield). ^{1}H-NMR (400 MHz, chloroform-*d*) δ 7.42 (m, 4 H), 7.34 (m, 1 H), 7.29 (m, 4 H), 7.10 (t, *J* = 7.2 Hz, 1 H), 7.02 (d, *J* = 7.7 Hz, 2 H), 6.98 (d, *J* = 8.6 Hz, 2 H), 4.37 (t, *J* = 7.3 Hz, 1 H), 2.97 (dd, *J* = 6.8, 16 Hz, 1 H), 2.86 (dd, *J* = 6.8, 16 Hz, 1 H).

5-(Trimethylsilyl)-3-(4-phenoxyphenyl)pent-4-ynoic acid (80). Refer to general procedure for acetal deprotection and subsequent decarboxylation. The crude product was purified via flash SiO_2 chromatography (eluted with hexane/ethyl acetate (3:1)) to give the pure product **80** as a slightly yellow solid (410 mg, 73 % yield). ^{1}H-NMR (400 MHz, chloroform-*d*) δ 7.35 (d, *J* = 6.6 Hz, 2 H), 7.32 (d, *J* = 6.8 Hz, 1 H), 7.11 (m, 1 H), 7.01 (dd, *J* = 1.1, 8.6 Hz, 2 H), 6.96 (d, *J* = 8.8 Hz, 2 H), 4.16 (t, *J* = 7.5 Hz, 1 H), 2.87 (dd, *J* = 7.1, 16 Hz, 1 H), 2.76 (dd, *J* = 7.1, 16 Hz, 1 H), 0.16 (s, 9 H).

3-(4-Phenoxyphenyl)pent-4-ynoic acid (81). To a solution of 5-(Trimethylsilyl)-3-(4-phenoxyphenyl)pent-4-ynoic acid **(80)** in methanol (5 mL) and water (2 mL) was added 10 % NaOH (5 mL) and stirred for 2 h at ambient temperature. The reaction mixture was concentrated and diluted with 3 N HCl. The aqueous layer was extracted with ether and the combined organic layers were sequentially washed with water, and brine, then dried over $MgSO_4$. The crude product was purified via flash SiO_2 (eluted with hexane/ethyl acetate (3:2)) to give the pure product **81** as a yellow solid (210 mg, 76 % yield). ^{1}H-NMR (400 MHz, chloroform-*d*) δ 7.34 (m, 4 H), 7.11 (t, *J* = 7.1 Hz, 1 H), 7.01 (d, *J* = 7.7 Hz, 2 H), 6.97 (d, *J* = 8.8 Hz, 2 H), 4.15 (m, 1 H), 2.90 (dd, *J* = 8.4, 16 Hz, 1 H), 2.79 (dd, *J* = 8.4, 16 Hz, 1 H), 2.32 (s, 1 H).

4-Phenoxynaphthaldehyde (83). Refer to general procedure biaryl ether coupling described above. The crude product was purified via flash SiO_2 chromatography (loaded with DCM, eluted with ethyl acetate/hexanes (0%/100%) to (5%/95%)) to give **83** (0.72 g, 39% yield). ^{1}H-NMR (400 MHz, chloroform-*d*) δ 10.15 (s, 1 H), 9.24 (d, *J*=8.3 Hz, 1 H), 8.34 (d, *J*=9.3 Hz, 1 H), 7.69 (m, 3 H), 7.63 (t, *J*=6.8 Hz, 1 H), 7.39 (app t, *J*=8.1 Hz, 2 H), 7.18 (t, *J*=7.3 Hz, 1 H), 7.06 (d, *J*=8.8 Hz, 1 H), 6.66 (s, 1 H).

4-Phenoxynaphthalenylmethanol (84). To a solution of **83** (0.28 g, 1.12 mmol) in ethanol (20 mL) was added sodium borohydride (0.042 g, 1.12 mmol). After stirring at room temperature for 15 min, the reaction was quenched with water and extracted with ethyl ether. The organic layer was washed with brine, dried over MgSO4, filtered, and concentrated under reduced pressure to give the crude product. The crude mixture was purified via flash SiO_2 chromatography (ethyl acetate/hexanes (25%/75%) to give **84** (0.28 g, 95% yield). ^{1}H-NMR (400 MHz, chloroform-*d*) δ 8.29 (d, *J*=8.3 Hz, 1 H), 8.17 (d, *J*=8.3 Hz, 1 H), 7.61 (m, 1 H), 7.53 (m, 1 H), 7.41 (d, *J*=7.8 Hz, 1 H), 7.35 (t, *J*=7.8 Hz, 2 H), 7.13 (t, *J*=7.3 Hz, 1 H), 7.05 (dd, *J*=8.6, 1.2 Hz, 2 H), 6.88 (d, *J*=7.8 Hz, 1 H), 5.12 (s, 2 H).

4-Phenoxynaphthalenylacetonitrile (85). Refer to general procedure for formation of nitrile described above. The crude mixture was purified via flash SiO_2 chromatography (loaded with DCM, eluted with ethyl acetate/hexanes (10%/90%)) to give **85** (0.21 g, 54% yield). ^{1}H-NMR (400 MHz, chloroform-*d*) δ 8.36 (d, *J*=7.8 Hz, 1 H), 7.67 (app t, *J*=7.1 Hz, 1 H), 7.59 (app t, *J*=8.1 Hz, 1 H), 7.47 (d, *J*=7.8 Hz, 1 H), 7.38 (app t, *J*=8.1 Hz, 2 H), 7.16 (t, *J*=7.6 Hz, 1 H), 7.07 (d, *J*=7.8 Hz, 2 H), 6.87 (d, *J*=7.8 Hz, 1 H), 4.11 (s, 2 H).

(1-Methoxynaphthalen-4-yl)(phenyl)methanol (87). To a solution of 4-methoxynaphthaldehyde (0.50 g, 2.69 mmol) in THF @ 0^{o}C was added PhMgBr (3.22 mL, 1.0 M in THF). After stirring at room temperature for 2 h, the reaction was quenched with MeOH and extracted with diethyl ether. The organic layer was washed with water, brine, dried over MgSO4, filtered and concentrated under

reduced pressure to give the crude product. The crude mixture was purified via flash SiO_2 chromatography (ethyl acetate/hexanes (5%/95%) to (15%/85%)) to give **87** as a slightly yellow oil (0.72 g, ~100% yield). ^{1}H-NMR (400 MHz, chloroform-*d*) δ 8.31 (m, 1 H), 8.03 (m, 1 H), 7.45 (m, 5 H), 7.33 (t, J=7.42 Hz, 2 H), 7.26 (m, 1 H), 6.79 (d, J=8.1 Hz, 1 H), 6.47 (d, J=4.0 Hz, 1 H), 4.01 (s, 3 H), 2.25 (d, J=4.0, 1 H).

(1-Hydroxynaphthalen-4-yl) phenylacetonitrile (88). Refer to general procedure for formation of nitrile described above. No purification was necessary. **88** was obtained as a yellowish solid (0.73 g, 97% yield). ^{1}H-NMR (400 MHz, chloroform-*d*) δ 8.34 (m, 1 H), 7.79 (m, 1 H), 7.51 (m, 3 H), 7.33 (m, 5 H), 6.82 (d, J=8.1 Hz, 1 H), 5.74 (s, 1 H), 4.03 (s, 3 H)

N-*t*-Boc-2-(1-hydroxynaphthalen-4-yl)-2-phenylethylamine (89). Refer to general procedure for *t*-Boc protection of amine hydrochloride described above. The crude mixture was purified via flash SiO_2 column chromatography (ethyl acetate/hexanes (5%/95%) to (15%/85%)) to give **89** as a yellow foam (0.12 g, 61% yield). ^{1}H-NMR (400 MHz, chloroform-*d*) δ 8.22 (m, 1 H), 8.02 (m, 1 H), 7.45 (m, 2 H), 7.26 (m, 4 H), 7.19 (d, J=8.1 Hz, 2 H), 6.81 (d, J= 7.9 Hz, 1 H), 5.70 (brd s, 1 H), 4.85 (t, J=7.5 Hz, 1 H), 4.62 (brd s, 1 H), 3.84 (m, 2 H), 1.15 (s, 9 H).

N-*t*-Boc-2-(1-phenoxynaphthalen-4-yl)-2-phenylethylamine (90). Refer to general procedure for biaryl ether coupling described above. The crude mixture was purified via flash SiO_2 column chromatography (ethyl acetate/hexanes (10%/90%)) to give **90** as a slightly yellow oil (0.08 g, 55% yield). ^{1}H-NMR (400 MHz, chloroform-*d*) δ 8.26 (d, J=7.9 Hz, 1 H), 8.11 (d, J=8.2 Hz, 1 H), 7.49 (m, 3 H), 7.35 (m, 2 H), 7.28 (m, 4 H), 7.21 (m, 1 H), 7.12 (t, J=7.4 Hz, 1 H), 7.06 (dd, J=8.6, 0.9 Hz, 2 H), 6.91 (d, J=7.9 Hz, 1 H), 4.94 (t, J=7.9 Hz, 1 H), 4.61 (brd s, 1 H), 3.88 (m, 2 H), 1.41 (s, 9 H).

Table S-1. Summary of HPLC purity data for final compounds 3-27.

	0-90% CH_3CN (0.1%TFA)			0-100% MeOH (0.05%TFA)		
Compound	Retention Time (min)	% Purity	Gradient Length (min)	Retention Time (min)	% Purity	Gradient Length (min)
3	4.68	96	8	7.21	96	10
4	4.82	96	8	5.54	96	10
5	4.68	96	8	5.49	95	8
6	4.75	100	8	5.49	100	8
7	4.44	100	8	6.69	100	10
8	4.46	100	8	6.82	100	10
9	4.50	100	8	6.96	100	10
10	4.57	96	8	7.22	97	10
11	4.53	95	8	6.98	95	10
12	4.56	100	8	7.09	100	10
13	4.59	97	8	4.90	96	8
14	4.66	97	8	5.46	98	8
15	4.99	95	8	5.32	95	8
16	4.97	95	8	5.29	95	8
17	5.10	99	8	5.37	99	8
18	5.18	95	8	5.52	100	8
19	4.71	100	8	5.01	98	8
20	4.63	95	8	4.90	99	8
21	5.07	97	8	5.39	99	8
22	5.26	98	8	5.67	100	8
23	4.65	99	8	4.91	98	8
24	4.89	95	8	5.28	95	8
25	4.47	94	8	4.70	95	8
26	4.76	95	8	5.13	97	8
27	5.33	99	8	5.72	100	8